THE ALKALOIDS

Volume 1

R. H. F. Manske &
H. L. Holmes

THE ALKALOIDS

Chemistry and Physiology

VOLUME I

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Chemistry and Physiology

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PREFACE

Alkaloids occupy an important position in commerce and forensic chemistry, and in medicine they play a role that, in many instances, may be classed as indispensable. Because of their multiplicity of type and their unique and manifold reactions, alkaloids offer to the chemist a challenge shared by no other single class of organic compounds. There are few organic reactions that have not proved useful in the field of alkaloid chemistry, while in turn many of the reactions developed in this field of natural products have found extensive application in other branches of organic chemistry.

In view of the great volume of work already published in this field, it is felt that something in the nature of a "Handbuch" is both timely and warranted. Since it is our aim to assemble in five volumes all the pertinent knowledge of the chemistry and pharmacology of the alkaloids, we feel that such an ambitious scheme can only be consummated by the collaborative effort of many authorities. It is our hope that these publications will aid our colleagues in their researches on alkaloids and that they will collaborate with us in helping to keep the material up to date because it is planned to issue supplements at periodic intervals.

R. H. F. M.
H. L. H.

Guelph, 1949

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CHAPTER I

Sources of Alkaloids and their Isolation

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I. Natural Occurrence

The chemist who plans to work on the constitution of alkaloids is generally confronted with three main problems; first the location of a suitable plant source, second the isolation of the plant bases from this source, and third the resolution of this mixture of alkaloids into its pure components.

Alkaloid bearing plants have been found in virtually every habitat in which vascular plants grow, so no investigator need be short of plant material because of geographical limitations. There are, however, no taxonomic characteristics by which a plant may arbitrarily be assigned to a group suitable for alkaloid study. Well authenticated bases have been found to occur in some thirty-eight plant families and it may safely be said that the remaining families will provide only an occasional alkaloid bearing plant. As more plants are examined many more families will be included in the alkaloid bearing group for very recently two more genera (*Salsola* and *Anabasis*) in Chenopodiaceae have been found to yield alkaloids. This family along with others (Compositae, Boraginaceae, Convolvulaceae, etc.) is typical of those which only rarely yield such plants and it may safely be conjectured that the processes which gave rise to these genera or species

involved mutations which are abnormal to the group as a whole. An extreme is encountered in the Papaveraceae in which all species contain alkaloids and no mutations resulting in alkaloid free plants have yet occurred. The majority of plants occupy an intermediate position in which most species within a genus or closely related genera do or do not contain alkaloids. For example all *Aconitum* and *Delphinium* species elaborate them although most of the other genera (*Ranunculus*, *Trollius*, *Anemone*, etc.) in the same family (Ranunculaceae) do not. It has been observed that the structure of the alkaloids elaborated in various genera exhibit a degree of similarity of an order commensurate with the relationship of the genera from which they are derived. This is well exemplified by the occurrence of lycoctine in both *Delphinium* and *Aconitum*. When the relationship of the two genera within a family is remote (*Aconitum* vs. *Hydrastis*) the contained alkaloids (aconitines vs. hydrastine and berberine) may differ markedly in their nuclear type.

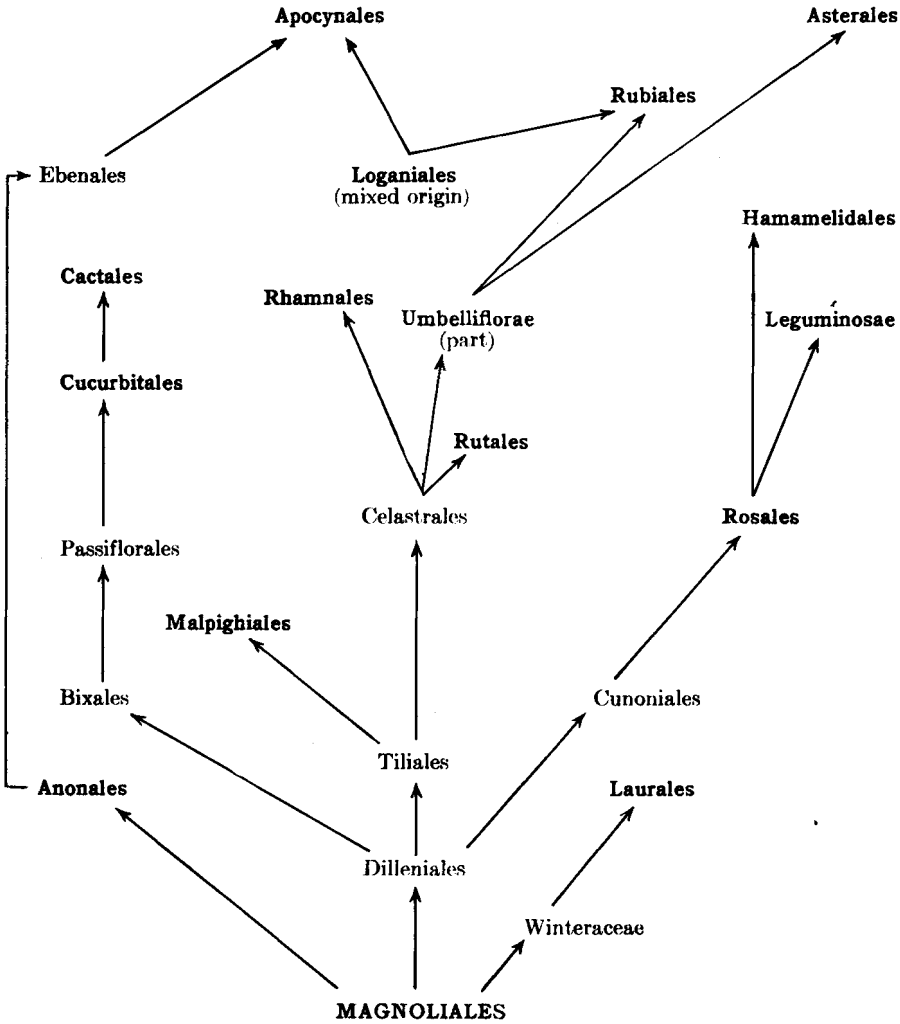
J. Hutchinson in his book, *The Families of Flowering Plants*, (MacMillan and Co. Ltd., London, 1926) has suggested a probable course of evolution of flowering plants based upon an original group of Archichlamydeae, which was assumed to evolve two basic orders, namely the Magnoliales, in which the arborescent habit is predominant, and the Ranales, in which the herbaceous habit is predominant. Both orders contain alkaloid bearing families and indeed many of the early descendant orders (Anonales, Laurales, Berberidales, Rhoeadales) retain this power of synthesis. On the other hand those orders which are near derivatives and do not yield alkaloids in the main give rise to orders which are equally impotent to elaborate them. For example, the Dilleniales are considered to have given rise to some forty orders of which less than fifteen are known to be alkaloid bearing. Charts I – III show Hutchinson's projected course of the evolution of the Gymnosperms. Only those orders which yield alkaloid bearing plants or give rise to such orders are shown. The orders and families are also given in Table 1. The alkaloid chemist is not likely to dispute such a course of evolution for although many apparent chemical anomolies do exist, they have been adequately accounted for. For example, the Anonales, the Laurales, and the Rhoeadales all elaborate aporphine alkaloids, yet the bases of the first two orders are secondary amines as opposed to the tertiary nature of members of the third order. Furthermore, the aporphines in the Rhoeadales are always accompanied by other types of alkaloids not contained in the first two orders.

The fact that berberine occurs in no less than six families has been the subject of frequent comment, and it is to be noted that three of these families (Berberidaceae, Ranunculaceae, and Papaveraceae) are either in the order Ranales or in orders derived therefrom and three (Rutaceae, Menisper-

maceae, and Anonaceae) are derived from Magnoliales. More remarkable still is the widespread distribution of nicotine. It is present not only in derivatives of the Ranales and Magnoliales but is to be found also in two

CHART I

ALKALOID BEARING DICOTYLEDONES DERIVED FROM MAGNOLIALES

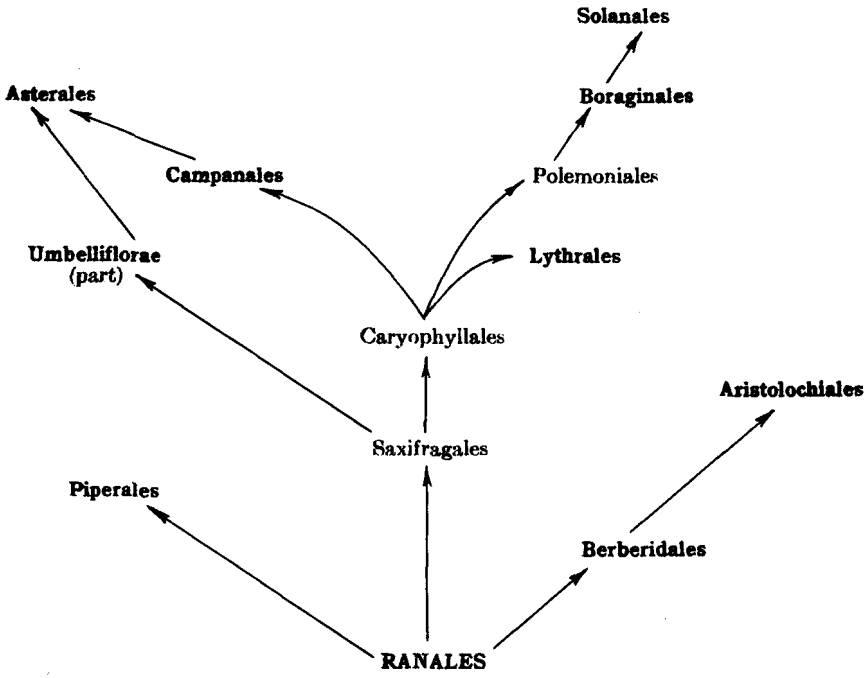


Cryptogamic orders, Lycopodiales and Equisetales. Since no reasonable taxonomic concessions could bring these orders into close relationship it must be assumed that parallel evolutions have occurred in plants that are

widely separated taxonomically. The occurrence of 3-methoxypyridine in *Equisetum* and in *Thermopsis*, and other closely related alkaloids occurring in widely separated families appear to give further support to the hypothesis of parallel mutation. In the main, the alkaloids of closely related

CHART II

ALKALOID BEARING DICOTYLEDONES DERIVED FROM RANALES

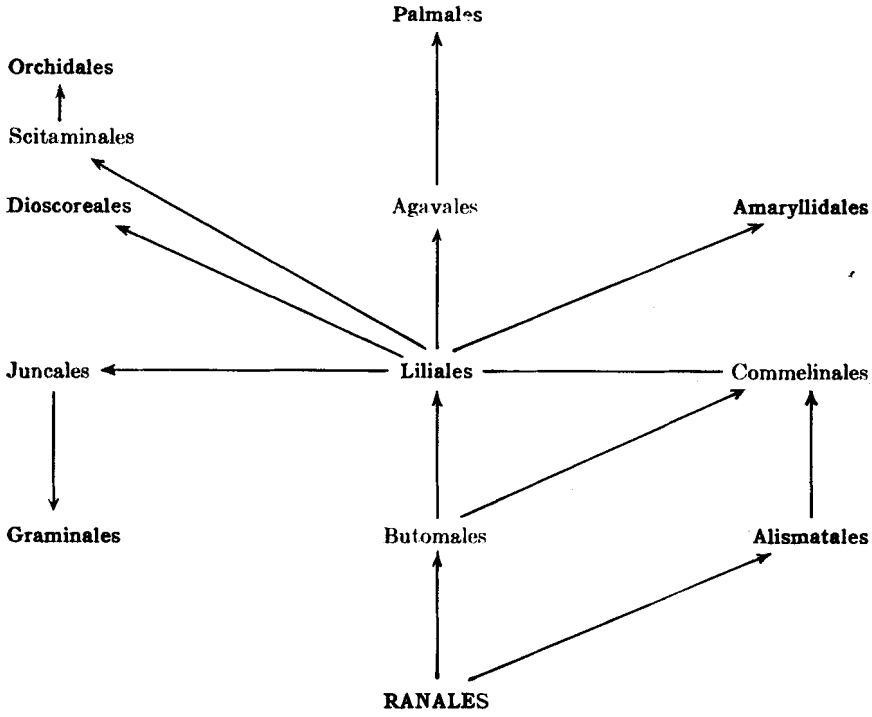


groups of plants show remarkably similar structural features. As this relationship becomes closer the contained alkaloids exhibit a greater similarity, but it is only in rare cases that two or more well defined species (*Stylophorum diphyllum* (Michx.) Nutt. and *Dicranostigma franchetianum* (Prain) Fedde) elaborate the same alkaloids. Elsewhere the author has pointed out that there is no justification chemically for establishing a new genus for the latter species since it was originally classified as *Stylophorum*. Within the divisions of a genus it is often possible by chemical methods to point to affinities and differences which taxonomic methods alone are unable to discern. The genus *Corydalis* has been subdivided into a number of sections by F. Fedde (Engler-Prantl, *Die Natürlichen Pflanzenfamilien*,

W. Engelmann, Leipzig, 1936) and a number of species in the section "Eucorydalis Prantl" have been examined chemically. In general, it was found that the alkaloids of the several species were closely related or identical while plants of other sections yielded alkaloids of different nuclear

CHART III

ALKALOID BEARING MONOCOTYLEDONES DERIVED FROM RANALES



structure. *Corydalis sempervirens* (L.) Pers., however, yielded alkaloids of a type foreign to those of other plants in the same section, e.g., *C. aurea* Willd., *C. caseana* A. Gray, *C. ophiocarpa* Hook. f. et Thoms., and others. The conclusion that *Corydalis sempervirens* (L.) Pers. is wrongly classified seems inescapable. Such inconsistencies of classification are slowly being recognized and it is highly probable that a reclassification of plants based upon their chemical constituents will be possible when their chemical assay becomes more all-inclusive. In this connection it should be pointed out that the chemical method of classification is not based on the choice of arbitrary characteristics without which taxonomic botany would not be systematic.

The orders which contain alkaloid bearing plants and the families in which these plants occur are listed in Table 1. Charts I and II are adapted

TABLE 1

ALKALOID BEARING ORDERS AND FAMILIES

Orders	Families
A. Dicotyledones	
Magnoliales	Magnoliaceae
Anonales	Anonaceae
Laurales	Lauraceae
	Monimiaceae
Ranales	Ranunculaceae
Berberidales	Berberidaceae
	Menispermaceae
Aristolochiales	Aristolochiaceae
Piperales	Piperaceae
Rhoeadales	Papaveraceae
Chenopodiales	Chenopodiaceae
Lythrales	Punicaceae
Cucurbitales	Caricaceae
Cactales	Cactaceae
Malpighiales	Erythroxylaceae
Rosales	Calycanthaceae
Leguminosae	Papilionaceae
Hamamelidales	Buxaceae
Rhamnales	Rhamnaceae
Rutales	Rutaceae
Umbelliflorae	Umbelliferae
Loganiales	Loganiaceae
Rubiales	Rubiaceae
Asterales	Compositae
Campanales	Lobeliaceae
Boraginales	Boraginaceae
Solanales	Solanaceae
	Convolvulaceae
B. Monocotyledones	
Liliales	Liliaceae
Amaryllidales	Amaryllidaceae
Dioscoreales	Roxburghiaceae (Stemonaceae)
	Dioscoreaceae
Palmales	Palmaceae
Graminales	Graminaceae
Orchidales	Orchidaceae
C. Gymnospermae	
Coniferae	Taxaceae
Gnetales	Gnetaceae
D. Pteridophytae	
Equisetales	Equisetaceae
Lycopodiales	Lycopodiaceae

from Hutchinson's classification and illustrate a possible course of evolution of the Magnoliales and Ranales, respectively, and their derived orders from the Archichlamydeae. Chart II schematically depicts a possible course

of evolution of the Monocotyledones from the Ranales. In these charts only those orders which contain alkaloid bearing plants (in bold-face type) or those orders (in light-face type) which are progenitors of orders containing such plants are shown.

II. Distribution in the Plant

The elaboration of alkaloids is not localized in certain specific organs but appears to be a characteristic of all organs (including the seeds) although it must be emphasized that not all organs of any one species possess such function. Noteworthy amongst organs which are devoid of alkaloids are the seeds of the tobacco plant and of the opium poppy. Although the seeds of these plants do not store detectable quantities of alkaloids yet on germination alkaloids are to be found in the very young seedling. On the other hand the author failed to detect alkaloids in the leaves and bark of *Calycanthus floridus L.* while the seeds contained 1% of basic products.

In the first year of growth alkaloids seem to be quite evenly distributed amongst the various organs, but with increased age (perennials) there appears to be a localization of these bases in a few organs. The bark of arborescent plants is generally richer in alkaloids than are the leaves or shoots (*Cinchona*) and this may be attributed to their accumulation in the bark year after year. The bark of old barberry roots may contain as much as 10% of berberine whereas that of very young plants contains little more than is found in the leaves. As in all generalizations there are exceptions to the statement that in biennials and perennials there is a preponderance of these nitrogenous products in the root. Notable amongst these exceptions are the aerial portions of *Dicentra, Aconitum,* and *Delphinium,* which in some instances prove to be a rich source of alkaloids. However, the difficulties attendant upon their extraction (due to fats and other extractives in the leaves) often offset the advantage of the abundance of these bases in the aerial portions.

While localization of the alkaloids in various organs does not appear to occur in the annuals yet there is a marked fluctuation of alkaloid content in all the organs throughout the growing season. The period of maximum output of these bases in *Papaver, Senecio, Corydalis,* etc. appears to be coincident with the early flowering stage. It is obvious then that the alkaloids are intermediates in plant metabolism though it is not possible to state the fate of the nitrogen. When radioactive nitrogen of sufficiently long life becomes available the problem may then be resolved by tracer techniques.

When plants elaborate more than one alkaloid their ratio in the plant need not necessarily be the same at all stages of growth. Isothebaine, for

example, is virtually absent in the young oriental poppy (*Papaver orientale L.*) but increases to isolable amounts as the plant approaches maturity. This observation may explain why different investigators report the isolation of different alkaloids from the same species. It is to be noted, however, that the cultivated oriental poppy may be in part a hybrid with *Papaver bracteatum Lindl.* In any case it is markedly heterozygous and discrepancies in alkaloid content may be attributable to variations in the source plants. In order that alkaloids with a transient existence in the plant (e.g., isothebaine) be not overlooked it is recommended that plant material at all stages of growth be examined. If this is not possible then the record of the investigation should include a statement of the stage of the growth of the plants examined.

Cultural and climatic conditions have only a moderate effect on the alkaloid content of plants. It is known that the amount of alkaloids in opium varies with the source, but some of this variation is undoubtedly due to varietal differences in the poppies in question. A lone example, frequently cited to illustrate the catastrophic effect of soil or climatic conditions upon the type of alkaloid elaborated, is the California poppy (*Eschscholtzia californica Cham.*). Records show that when this plant was grown in Brittany it yielded but a single base, ionidine, which, if correctly characterized, differed from those bases characteristic of the plant when it is grown in other habitats. In a systematic study of the true species and of cultivated varieties grown both in very rich and very poor soils, the author (unpublished results) failed to detect the presence of ionidine although several new alkaloids were found.

There are ample a priori reasons to suspect that different plants of a single species may elaborate different amounts of alkaloids. It is well known that strains of tobacco and of lupines can be selected to yield greater or lesser amounts of alkaloids. That mutants occur is also highly probable. In this connection it is not unreasonable to suspect that the opium poppy may in fact be a mutant which was selected and cultivated because of its unique alkaloids. Neither morphine nor codeine have been found in any other species of *Papaver* and the basic ring system in these alkaloids has been found in part only in alkaloids derived from plants of a family (Menispermaceae) whose affinities with Papaveraceae can only be remote.

III. Isolation

Work on the constitution of alkaloids is often prefaced by the problem of their isolation from plant material or from residues after commercially important constituents have been removed. While the isolation of each alkaloid ultimately proves to be an individual problem there are never-

theless a variety of procedures which may be entitled to generic rank.

There are very few plants which elaborate but a single alkaloid so that the main problem is the separation of mixtures. Fortunately, the isolation of the total alkaloids reasonably free from inorganic or other organic matter may be reduced to a simple procedure. The fact that most alkaloids are basic (rutaecarpine is a notable exception) and therefore soluble in aqueous acids (colchicine is non-basic but is soluble in water) suffices to separate them from the host of water insoluble products found in all plants. Although a number of procedures for preparing such solutions are available the simplest expedient is to extract the plant material with acidified water. Such extracts, however, are usually contaminated with organic and inorganic materials which render the solutions difficult to handle. They tend to foam, are often difficult to filter, and with immiscible liquids they generally form stubborn emulsions. These inconveniences, however, may often be circumvented if the alkaloids (sparteine and nicotine) are volatile in steam.

If an organic solvent is selected purification of the solvent before use is a prime prerequisite, for many such impurities as acetone in ethanol form condensation products which, in many instances, prove difficult to remove. When possible low boiling solvents (methanol) should be selected. Alcohol has many advantages over water as an extraction solvent but when the plant material (seeds) is very rich in fats, removal of these glycerides by a preliminary extraction with a petroleum solvent is often advantageous. In either case the alcoholic extract is concentrated to a small volume (reduced pressure is preferable if frothing can be avoided). The extract, largely free from solvent, may then be acidified to a pH of 2 or less and steam distilled to remove the adhering solvent. The aqueous solution remaining in the steam distillation flask is usually quite dark and contains suspended organic matter. Although it is desirable to keep the volume of this aqueous solution to a minimum yet it should be sufficiently dilute so that the further addition of water does not produce an appreciable turbidity. In general it is possible to get satisfactory solutions when 1 liter of water is used for every 1 – 3 kg. of plant material. Removal of the suspended matter from this aqueous solution in many instances offers serious difficulties which filter aids help little to overcome. In the writer's experience there is only one infallible procedure which has, as well, the added advantage of simplicity. If the boiling aqueous extract is set aside without being disturbed for 24 hours, and then is placed in a refrigerator for two to three days, the now clear aqueous solution can often be decanted from the separated resins and fats, and can be entirely freed from insoluble matter by filtering through a layer of charcoal or other material. Should this simple procedure fail, then in those cases where the foreign material

does not melt at 100°, paraffin may be added to entrap the suspended matter and the procedure followed as outlined above.

Removal of suspended matter is usually followed by extraction with an immiscible solvent to remove water soluble organic material which may interfere in subsequent operations. Addition of an organic solvent to this clear aqueous solution usually discharges a resin which collects at the interface of the two liquids (similar resins generally separate when these clear aqueous solutions stand for some time). The choice of organic solvent for such extractions is limited in practice almost entirely to ether or chloroform. The latter solvent offers the advantage that the extract can be drawn from the bottom of the separatory funnel, thus minimizing the manipulation of large volumes. Caution must be exercised since many alkaloid hydrochlorides as such are extracted from their aqueous solutions by chloroform but not by ether.

These aqueous solutions, when rendered alkaline with ammonia or sodium carbonate (sodium hydroxide when phenolic alkaloids are known to be absent), may yield the basic constituents in filterable form. However, experience has shown that it is more convenient to recover these by extraction with ether or chloroform. Chloroform is to be preferred for it extracts all alkaloids except the quaternary bases (curine), which in any case must be recovered in the form of an insoluble complex salt. This procedure fails when the alkaloids are unstable under the conditions of the experiment, and is conspicuously unsuccessful with the ergot bases. It is also probable that some alkamine esters suffer change under the conditions imposed.

A somewhat milder technique, and one occasionally preferred, is to extract the plant material with a water immiscible solvent (chloroform, ethylene dichloride, benzene, etc.) after it has been basified with ammonia or aqueous sodium carbonate solution. In this case too, prior defatting (petroleum solvent) is often advantageous. The alkaloids are extracted from the organic layer by the use of dilute solutions of acids.

At this stage a cursory test for the presence of alkaloids in the extract is in order. Mayer's reagent (potassium mercuric iodide solution) has proved very satisfactory, for it yields a precipitate with virtually all alkaloids. Unfortunately, the formation of precipitates by this reagent is not diagnostic for this group of natural products alone since plant extracts which are entirely free of alkaloids often give precipitates. Hence a positive test with this reagent must be interpreted with caution.

The residue of mixed alkaloids, after removal of the solvent, usually takes the form of a resinous mass and further purification is necessary before crystalline material is obtained. Towards this end the crude alkaloids may be dissolved in dilute acids, filtered from insoluble material, and

reprecipitated. Extraction of the aqueous acid solution with ether often proves advantageous, especially when the bases are dissolved in oxalic acid. Sparingly soluble salts often separate from the aqueous phase in a relatively pure and crystalline form during the ether extraction.

Many alkaloids may be only sparingly soluble in ether but, with the exception of pentane and hexane, their purification is more readily effected from this solvent than from any other. It is possible to prepare ether solutions of these bases of a concentration far in excess of their equilibrium value which then often yield a crystalline solid in reattaining a state of equilibrium. A supersaturated ethereal solution of these bases is readily prepared as follows: The relatively dilute aqueous acid solution of the alkaloids, in a separatory funnel, is covered with a layer of ether, *and* a layer of water interposed between the two layers by the cautious addition of water down the side of the funnel. Aqueous ammonia is run in, in a like manner, the stopper inserted in the funnel, and the mixture shaken very vigorously. Often the more insoluble alkaloids will crystallize from the ether layer before it can be separated. In any case the wet turbid ethereal solution can be brought to brilliant clarity by treatment with charcoal. Removal of the ether leaves a residue which is now amenable to fractional crystallization from other solvents, to fractional distillation, or to salt formation.

IV. Separation and Purification

There is no known procedure by which all mixtures of alkaloids can be separated into their components. Nevertheless a number of helpful methods of attack may be outlined.

Fractional crystallization should be the first mode of attack on the separation of these mixtures, but in the event that this method fails it may be necessary to resort to other methods. Virtually all solvents have proved useful. For most alkaloids the order of increasing solubility is the following: hexane, benzene, ether, ethyl acetate, methanol, acetone, and chloroform. An alkaloid that is too sparingly soluble in chloroform will generally dissolve quite easily in hot dioxane. When an alkaloid has solubilities in various solvents different from the order given its separation is relatively simple, as will be seen from the following example. Protopine and chelidonine are both readily soluble in chloroform and sparingly so in methanol, while their hydrochlorides are sparingly soluble in water. A naturally occurring mixture of these two bases is easily separated by extracting the mixture of bases with cold ether in which chelidonine is readily soluble and in which protopine is less soluble than in methanol. When the ether solution is evaporated to a thin sirup and treated with methanol pure chelidonine crystallizes. If the residual protopine is dis-

solved in chloroform and this solution is evaporated to a thin sirup, the addition of methanol yields a solution from which protopine crystallizes with great facility. If no single solvent should prove suitable for the separation, resort must then be made to a mixture of miscible solvents. The most satisfactory results are obtained by this method when the mixture of alkaloids is dissolved in the solvent in which it is more soluble, concentrated to a convenient consistency, and the second solvent (also hot) then added portionwise. For reasons not entirely obvious there are certain combinations of solvents that, in the writer's experience, are much more satisfactory than others in this field. Methanol or ethanol are the only solvents which work well in combination with chloroform. Acetone-methanol, ethyl acetate-methanol, dry ether containing only a few per cent of methanol, and hexane-dry ether are other useful combinations. Benzene, on the other hand, either alone or in combination with other solvents, rarely proves satisfactory. The use of methanol-water and acetone-water mixtures is limited to cases where large crystals of an already pure alkaloid are desired. It cannot be too strongly emphasized that only adequately purified and freshly distilled solvents should be used. Ether *must* be free from peroxides and alcohol free from acetone.

In the event that separation by fractional crystallization fails, and that one or more of the components of the mixture are volatile, then fractional distillation is recommended. In view of the relatively small losses in this method recent micro techniques may be applied conveniently to as little as 1 mg. of alkaloid. This method of separation has been applied with success to the *Lupine* and *Lycopodium* bases which crystallize only with difficulty.

Should both fractional crystallization and distillation fail in the resolution of these mixtures then they may be converted into any one of a number of salts in the hope that one of the component salts may be insoluble. There are a number of cases where certain special salts crystallize remarkably well but preliminary trials should be limited largely to the use of such acids as hydrochloric, hydrobromic, perchloric, picric, and oxalic, although sulfuric acid frequently affords acid or neutral sulfates that are sparingly soluble in alcohol or water. Instead of aqueous hydrochloric or hydrobromic acid absolute methanolic solutions of the reagents are recommended, since methanol is a good solvent for many bases. The methanolic solutions offer the added advantage that the excess hydrogen halide is readily removed by precipitating the salt with an excess of dry ether. Hydrochlorides, thus prepared, often crystallize readily from boiling acetone, or acetone containing just enough methanol to effect solution. Excesses of perchloric, picric, and oxalic acid may also be removed by precipitating the salts with dry ether and repeatedly triturating the gener-

ally pasty precipitate with fresh portions of the same precipitant. These salts are often appreciably soluble in acetone, from which they may be crystallized by the judicious addition of ethyl acetate (but not ether, benzene, or chloroform). In many instances perchlorates and oxalates crystallize satisfactorily from water but picrates, on the other hand, are generally too insoluble. Sparingly soluble nitrates (or iodides) are best prepared by dissolving the base in dilute acetic acid followed by the gradual addition of potassium nitrate (or potassium iodide) to the solution. The remarkable solubility of some alkaloid hydrochlorides in chloroform has formed the basis for an almost quantitative method for separating the Papaveraceous alkaloids into two groups. Some of these hydrochlorides (glaucine, bicuculline as well as some *Lobelia* alkaloids, and others) are so readily soluble in chloroform that this solvent readily extracts them, *as such*, even from dilute aqueous solutions. Methylene dichloride is almost equally good for this purpose, but no case has been reported of the solution of one of these hydrochlorides in carbon tetrachloride. Some alkaloid hydrochlorides (dicentrine and isocorydine), although they are readily soluble in chloroform saturated with water, are only sparingly soluble in the anhydrous solvent.

That phenolic alkaloids are soluble in aqueous solutions of fixed alkalies need not be stressed but it is important to note that some free bases (notably corydine and ochotensine) are extracted from such solutions by ether while others (bulbocapnine and hunnemanine) are not. A convenient method for recovery of these phenolic bases is to saturate their aqueous alkaline solutions with carbon dioxide or ammonium chloride. The latter reagent, however, is not invariably satisfactory (e.g., hunnemanine).

Separation of a mixture of secondary and tertiary amines is best accomplished by acetylation followed by trituration with dilute mineral acids. The acid soluble fraction contains the tertiary amine. The secondary amine may be regenerated from its insoluble acetyl derivative by mild acid hydrolysis. Benzoylation, however, cannot be applied with equal impunity for under the conditions for this reaction certain isoquinoline alkaloids (aporphines) suffer ring fission and benzoylation at the nitrogen atom.

The criteria for purity of alkaloids, as for other organic compounds, are constancy of melting point and of optical rotation. If, as is the case with many complex salts, melting is preceded by decomposition then a sharp melting point may often be obtained by the use of melting point tubes evacuated to oil pump vacua. The optical activity of an alkaloid may vary somewhat, depending upon solvent and concentration. Furthermore, many alkaloids, though otherwise pure, occur as partial racemates or may be partly or completely racemized during isolation (peganine).

The characterization of alkaloids has been limited, in most instances,

to the preparation of methiodides and a number of salts. Phenolic bases are best characterized as their methyl ethers (diazomethane), and secondary amines by their benzoyl derivatives (calycanthine is a notable exception).

Color and precipitation reactions may be quite helpful in forensic chemistry but as a means of identifying alkaloids they suffer from lack of specificity. Although the absence of certain colors with specific reagents shows the absence of a certain alkaloid, yet when the anticipated color is obtained confirmatory evidence for the alkaloid's presence is necessary.

Chapter II

Alkaloids in the Plant

W. O. JAMES, *Oxford, England*

I. Introduction

Comparatively little interest has been displayed in the past in the alkaloids as constituents of the plants that produce them. Their effects are not sensational, as are the results of introducing them into animal organisms, nor have they appeared to offer an opportunity to the plant physiologist comparable with their attractions for the pharmacologist and organic chemist. They have tended to be dismissed as difficult substances lying in a by-way, if not a blind alley, of nitrogen metabolism, whose study could contribute little to the general understanding of the plant. It is possible to produce a tobacco leaf without nicotine and a belladonna leaf without hyoscyamine, and in neither species do the alkaloid-free leaves differ in any obviously significant way from the normal. Conversely, tomato leaves and fruits containing foreign alkaloids to an extent that might make them dangerous to eat do not develop abnormally. This lack of demonstrable functional significance has relegated the alkaloids to a back place in plant studies. The neglect has been reinforced by the comparative lack of success of a large part of the work done with them. Much of the early investigation was vitiated by the sterility of its point of view, its authors being excessively concerned with the philosophic *Why* to the prejudice of the more attainable *How*. One method, the histochemical, was developed to a high level around the turn of the century, and yielded valuable results. The application of more modern methods of biochemistry to these problems may be said to be only now beginning, and, consequently, results are still sparse. Nevertheless, it seems clear that alkaloid formation is an integral part of the nitrogen metabolism of a very large number of plants. The formation of the simpler nitrogen bases is universal, and at the present time is receiving ever-increasing attention as their importance in vitamins, hormones, and coenzymes becomes more apparent. Although the impetus has come primarily from their systemic action, a further study of the alkaloids while still in the plant is likely to make valuable contributions to the general study of the plant's nitrogen metabolism.

Taking into account the extremely varied molecular structures that are included under the general heading of alkaloids, it is improbable that the behavior of all will be alike in the various species that produce them. A detailed treatment would no doubt necessitate breaking up the collection into a number of separate groups on physiological as well as chemical grounds. At the present time, adequate data for such a systematic treatment do not exist, and only a few groups have received serious attention. These must be taken as representing all we know of alkaloids in general. Among these limited groups, similarities and differences of physiological behavior are both evident. Among the similarities, which enable us to consider alkaloid metabolism a reasonable unity, are the following: All

alkaloids are associations of nitrogen with carbon and hydrogen, which places them in a rather definite category in metabolism. Heterocyclic and aromatic rings abound in their structures, indicating some degree of similarity in their formation, even though ring closure may take place at different stages and in different ways. Methylation must also be of frequent occurrence in the metabolism of different alkaloid groups, since many methylated and non-methylated forms exist side by side. Some of the simpler nitrogen bases can be thought of as methylated anhydrides of amino acids, and it by no means follows that methylation occurs as a sort of afterthought in the last stages of alkaloid synthesis. It may prove to be one of the ways in which amino acids, so to speak, take the wrong turning, and end up as alkaloids instead of proteins.

II. Distribution

1. Histology

Extensive examinations of the distribution of alkaloids through the plants' tissues were first made by the histochemical method. Its development and the considerable degree of success attained are particularly associated with the name of Errera and his school at Brussels. A number of general alkaloid precipitants, including phosphomolybdic acid, potassium mercuric iodide, picric acid, tannin, mercuric chloride, and platinic chloride were examined for their effectiveness in sections of plant tissues. For general reliability when applied to a range of materials, iodine in potassium iodide (frequently called Bouchardat's reagent) was preferred (1). The resistance of the protoplasm was observed to complicate the results even with so penetrating an agent as iodine, and it was often found advisable to follow the example of de Vries and destroy the membranes by heating. The iodine solution was found to throw down a brick-red, finely granular precipitate which tended to aggregate into larger clusters, and after a short time, to dissolve in the reagent. In the presence of much oil or protein, a red coloration only was obtained which resembled that given by glycogen. On gentle heating, the alkaloid coloration was found to be unchanged, but the glycogen color was reversibly bleached. Attempts to remove the oils by extraction with petroleum ether frequently led to loss of alkaloids. Confusion between alkaloid and protein reactions could be avoided by extracting the tissues with a 5% solution of tartaric acid in absolute alcohol. This removed all alkaloids and any iodine coloration obtained after such treatment was to be ascribed to the presence of proteins (2). Results obtained were checked by the use of further reagents, including, if possible, one more specific to the alkaloid concerned, such as dilute sulfuric acid for colchicine and methylal-sulfuric acid for morphine (3).

A very wide range of alkaloid-bearing plants was examined in researches spreading over about twenty years. All the organs of the plant and their individual tissues were carefully examined. The alkaloids covered included coniine (4, 5), nicotine (1, 5, 6), the hyoscyamine-hyoscine group (5, 6, 7), the opium alkaloids (3), solanine (6), colchicine (1), and the alkaloids of the Orchidaceae (8, 9), Leguminosae (10), Ranunculaceae (1, 5, 11), and Amaryllidaceae (1, 12). The Solanaceae were examined with special thoroughness. Subsequent work using similar methods has confirmed the original results with *Nicotiana* (13), *Atropa belladonna* L. (14), *Datura stramonium* L. (15), and *Hyoscyamus niger* L. (16).

The plants examined contained widely varying amounts of alkaloid. Among 104 species of orchids, 9 showed alkaloidal precipitations in differing degrees, and the rest none at all (9). Wherever such precipitations were found, their distributions possessed enough in common for a single example to suffice. *A. belladonna* may be taken as one of the most frequently and thoroughly investigated species (5, 6, 7, 15, 16). In the *stem*, the alkaloid is most abundant in the young regions that are still soft. With advancing age and accumulation of wood, the alkaloid precipitations become increasingly difficult to observe, and towards winter may be unobtainable. This observation can be checked by macroscopic analysis.

TABLE 1

LOWER STEMS OF *Atropa belladonna* L. (17)

Stage	G. *l*-hyoscyamine 100 g. dry weight
Before flowering	0.78
Flowering branches forming	0.70
Early flowering	0.26
Green berries	0.15
Berries ripe: leaves shed	<0.10

At the stem apex, alkaloids are present in all the young undifferentiated cells. According to Molle (6), the most recently formed cells have comparatively little, the precipitations increasing to a maximum density at a short distance behind the actual apex. The zone of tissue differentiation is also abundantly supplied, but as differentiation proceeds, alkaloids disappear from the vascular strands, and then from the central tissues of the pith. When differentiation is complete, the alkaloids are located principally in three concentric layers, in the epidermis and outer cortical layers just below it, in parenchyma within and adjacent to the phloem, and in the periphery of the pith just inside the xylem strands. The xylem parenchyma and medullary rays also possess alkaloids after they have disappeared from the conducting elements.

TABLE 2

THE DISTRIBUTION OF ALKALOID IN BELLADONNA STEMS (14)

	← Pith →		← Vascular bundles →					← Cortex →			
Organ	Central	Adjoining vascular bundle	Medullary rays	Xylem parenchyma	Trachea and fibers	Sieve tubes	Phloem parenchyma	Endodermis	Inner	Outer	Epidermis
		← Differentiating zone →									
Young stems	3	3			3			3	3	3	3
Mature stems	1	2	2	2	0	0	2	2	1	2	2
Old leafless stems	0	0–1	0	0	0	0	0	0	0	0	0

3 very abundant; 2 abundant; 1 present and detectable; 0 absent.

The epidermis is a site of alkaloid accumulation in the petiole, leaf blade, and the berry, as well as in the stem. Owing to the density of protein, starch, and chlorophyll present, a clear idea of the distribution of alkaloids in the internal tissues of the leaf blade is difficult to obtain, but they appear to be generally present in the mesophyll. Along the veins alkaloids are deposited in parenchyma adjacent to the phloem strands. The distribution in young belladonna roots resembles that in the young stem. The root cap and the young tissues just behind it show copious precipitations. Further back, alkaloids fade out from the central tissues and are found in the piliferous layer and outer cortex, in parenchyma around the outer phloem, and in the periphery of the pith. In the older fleshy roots (the belladonnae radix of commerce), the alkaloids lie mostly in parenchymatous cells of the outer tissues, in the vascular parenchyma, and in the regenerating phellogen and young cork derived from it.

The calyx and corolla show abundant alkaloids in the epidermis. The anthers possess them in the epidermis, the tapetal layers around the developing pollen sacs, and in the bundle sheath of the filament, but not in the vascular elements themselves. Carpels and ovules contain abundant alkaloids in all parts. During the development of the ovule into a seed, its alkaloids diminish and at the resting stage are confined to a single layer of crushed cells on the inside of the testa. The embryo itself and the endosperm are both devoid of alkaloid. The ripe berry has abundant alkaloid in the epidermis, mesocarp, and placenta.

Errera (18) drew attention to four tendencies of alkaloid distribution. Concentration is normally high in: (*a*) very active tissues, growing fruits, etc.; (*b*) epidermis, piliferous layer, and the layers just below them; (*c*) vascular sheaths and other perenchyma adjoining and penetrating the vascular tissue; (*d*) latex vessels, where present.

a. Active Tissues. In these may be included all tissues in which cell growth, nuclear division, and metabolic synthesis are all proceeding rapidly, or in which active secretion has succeeded to division. They are represented in the description of belladonna above by the stem and root apices, the tapetum of the anthers, the young tissues of the ovules and carpels, and the cork cambium of the older roots (Fig. 1). Similar observations have been made on many alkaloid-forming species, and examples of other active tissues are not lacking. The vegetative apex of *Colchicum autumnale* L. corms is particularly rich in colchicine (1) and the young sprouts of potatoes in solanine (6, 19, 20, 21). Lateral root apices forming in the pericycle of potato (6), (Fig. 2) and *Datura* roots give heavy alkaloid precipitations. It has been observed that wound cambia behave similarly (12). When a leaf of *Clivia miniata* Regel is cut, a wound cambium appears after several days, and the dividing cells develop alkaloids, although the sur-

rounding tissue at first has none. Alkaloids then gradually appear in a zone of normal cells spreading outwards from the cambium (Fig. 3). Similarly, in cut potatoes, the newly-forming cork forms abundant solanine without

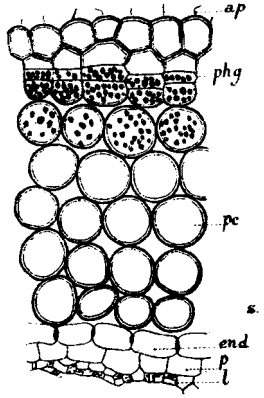


FIG. 1

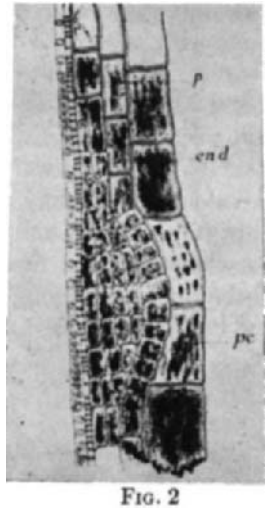


FIG. 2

FIG. 1. Part of transverse section of root of *Solanum dulcamara.*: *ap* remains of piliferous layer; *phg* phellogen; *pc* cortical parenchyma; *end* endodermis; *p* pericycle; *l* phloem. The heavy shading in the young phellogen (cork cambium) and the adjacent layer of cortex indicates the presence of solanine. From Molle (6).

FIG. 2. Part of a longitudinal section of young root of *Solanum tuberosum.* at the point of origin of a lateral root: *p* pericycle; *end* endodermis; *pc* inner layer of cortical parenchyma. Shading indicates the presence of solanine in the cells. From Molle (6).

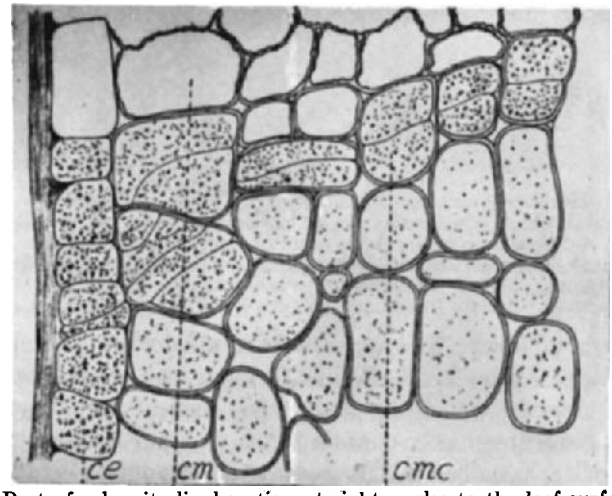


FIG. 3. Part of a longitudinal section at right angles to the leaf surface of *Clivia miniata* across a wound: *ce* epidermis; *cm* dead cells; *cmc* wound cambium. Shading shows the presence of alkaloid in the cells. x 270. From Molle (6).

depleting the deposit in the normal tissues (6). When a dormant lateral bud of *Nicotiana tabacum* L. sprouts, the underlying tissues regenerate and develop increasing quantities of nicotine (13). The normal cambium appears to be less vigorous in alkaloid production (7, 10, 13), but systematic observations with regard to the degree of cambial activity are lacking. It is, however, significant to notice that the enzymatic equipment of the cambium and its tissue initials may differ from that of primary meristems. In *Canavallia ensiformis* D. C., urease is absent from the former and present in the latter (22). The phloem and xylem initials in most instances rapidly develop alkaloids which may remain abundant in parenchyma cells; but soon disappear from vessel and sieve tube initials. According to Lotsy (23), the primary meristems of *Cinchona ledgeriana* Moens. and *C. succirubra* Pav., and the tissues adjoining them behave in the same way, the youngest cells of the meristems being at first alkaloid-free.

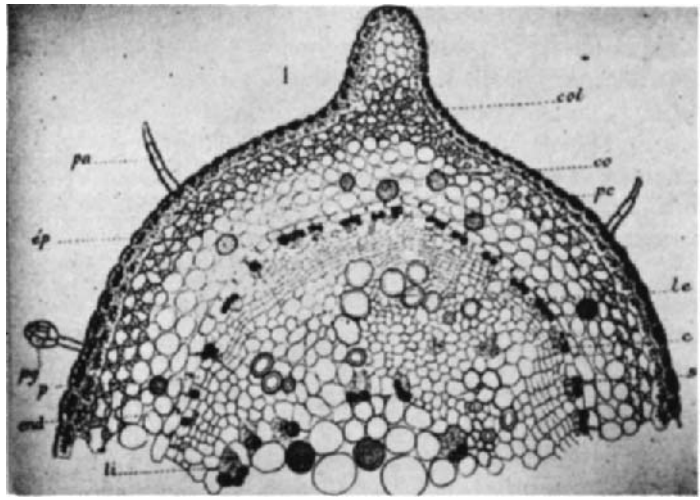


FIG. 4. Transverse section of a shoot of *Solanum tuberosum*: *ep* epidermis; *pa* hair; *pg* glandular hair; *c* collenchyma; *pc* cortical parenchyma; *co* cells with calcium oxalate; *end* endosperm; *p* pericycle; *le* outer phloem; *li* inner phloem. Heavy shading in the epidermis, outer cortex, pericycle, and pith near the internal phloem shows the presence of solanine. From Molle (6).

b. Surface Tissues. The appearance of alkaloids in the epidermis and piliferous layer occurs in all alkaloid-forming plants, and usually extends to one or more layers of the underlying cortical parenchyma (Fig. 4). Epidermal hairs frequently contain much alkaloid but the guard cells of the stomata are usually without it, even when young (Fig. 5). The root hairs of young tobacco plants contain nicotine, but lose it at an early stage. The hairs of its aerial parts may form a path by which nicotine is excreted

(24). The epidermis of *Cinchona* leaves is said to contain no alkaloids, but they accumulate in large cells to form a special hypodermal layer (23).

c. Tissues In and Near the Vascular Strands. Examples occur in bella-

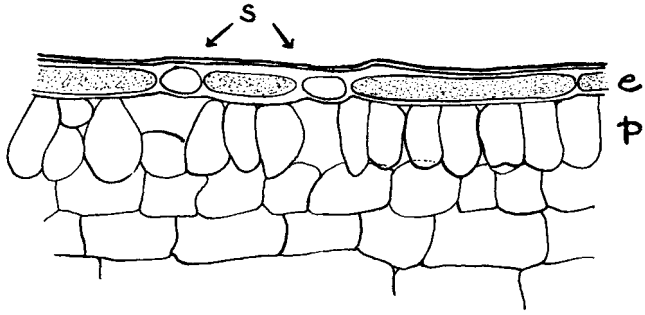


FIG. 5. Part of longitudinal section of flower stalk of *Narcissus rugulosus*: *e* epidermis; *s* young developing stomata; *p* parenchyma. Shading in the epidermal cells indicates the presence of alkaloids. x 110. After Errera, Maistriau and Clautriau (1).

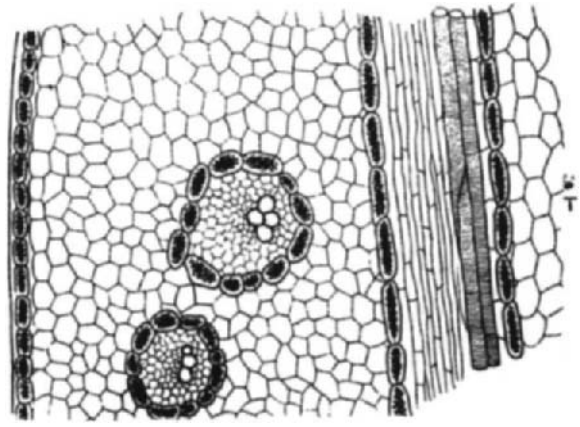


FIG. 6. Longitudinal section of active corm of *Colchicum autumnale* showing vascular bundles cut longitudinally and transversely. Deposits of colchicine are shown in epidermis and bundle sheath. x 130. From Errera, Maistriau and Clautriau (1).

donna in stems, roots, and petioles and in the corresponding positions of many other species as illustrated in Figs. 6, 7, and 8.

The cells concerned may occur as a bundle sheath (Figs. 6 and 7), or in the pericycle (Figs. 2 and 4), endodermis (Fig. 2), peripheral pith layers (Fig. 4), or even as phloem parenchyma as, for example, in *Scopolia japonica* Maxim. (6). Detectable quantities are never found in the vessels. Careful

examination has also invariably failed to show the presence of any alkaloids in the mature sieve tubes. Belladonna (6, 7, 14), tobacco, henbane (16), *Clivia* (12), narcissus, and *Cinchona* (23) have been examined with identical

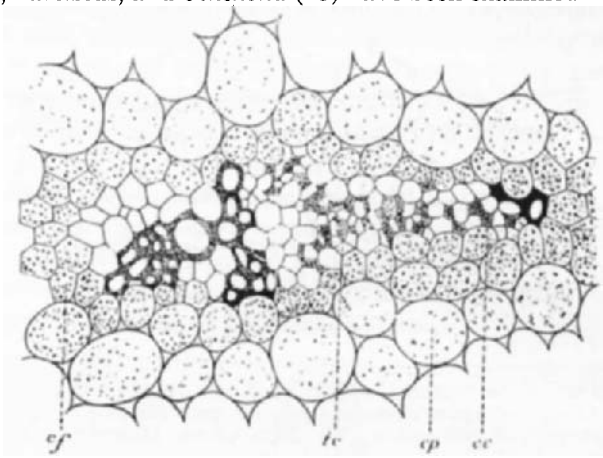


FIG. 7. Transverse section of vascular bundle in leaf of *Clivia miniata*: *cc* companion cells; *tc* sieve tube; *cf*, *cp* parenchyma around the bundle. x 270. From Molle (6).

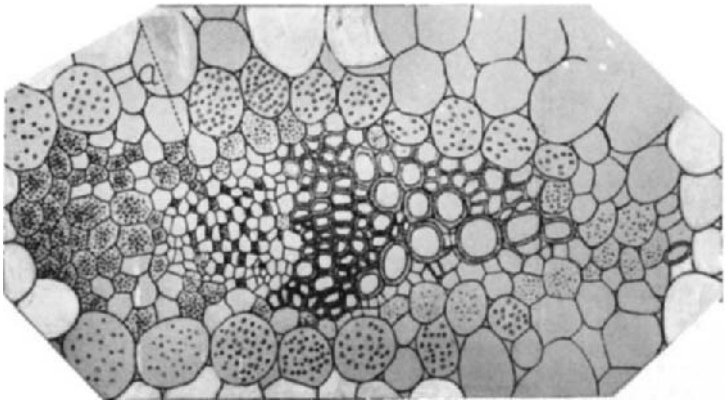


FIG. 8. Transverse section of vasuclar bundle in flower stalk of *Narcissus rugulosus*. Alkaloids precipitated in companion cells (a) and in the parenchyma around the bundle. x 160. From Errera, Maistriau and Clautriau (1).

results. In belladonna, henbane, and *Cinchona*, the companion cells are also devoid of alkaloids, but in *Clivia* and narcissus they have a rich content (Figs. 7 and 8). In *Rauwolfia canescens* L. (25) and British (16) and Indian (27) *Berberis* species, all phloem elements are devoid of alkaloids, although the neighboring cortex may be well supplied.

d. Latex Tubes. These are not represented in belladonna and the

classic example is the capsule of the opium poppy. The latex tubes extend throughout the plant and contain abundant alkaloids in all parts (3). The latex tubes are particularly numerous in the wall of the capsule, where they form an elaborate branching and anastomosing network.

Elongated cells with protoplasmic linings and large central vacuoles occur in the roots and leaves of *Clivia miniata*. They accumulate quantities of alkaloid (12).

e. Dead tissues. In the great majority of the tissues that have been examined, alkaloids have been found only in living cells. Even in the *Cinchona* barks, which accumulate quinine and its allies up to 10 or 12% of the dry weight, the alkaloids are confined strictly to the parenchyma and other living cells. None are found in the wood, cork, or phloem fibers (28). An interesting exception is provided by the dormant seeds of some of the Solanaceae, for example, *Datura*, examined by Clautriau (5) in careful detail. Shortly after fertilization, embryo and endosperm are enclosed in a well-developed tissue (perisperm) containing abundant quantities of all the alkaloids. Starch and protein reactions are given strongly. As the endosperm grows, this layer loses its starch and proteins, but the alkaloids remain, without any loss that can be determined by histochemical methods. The cells finally dry up and are crushed against the integument by the continuing growth of endosperm and embryo. At maturity, they form a thin membrane from whose dead cells the alkaloids, present as salts, are readily leached out because the semipermeable protoplasmic linings have perished. A similar development was observed in the seeds of aconite and belladonna (6).

The *Berberis* alkaloids, berberine and umbellatine, appear to behave somewhat differently from the solanaceous and other alkaloids. Instead of disappearing from the older woody tissues of the stem, they accumulate, and, in spite of the increasing mass of inert wood, the percentage of berberine increases as the season advances and from year to year. Part at least of this accumulation is in the wood. In a 30-year old plant of *Berberis darwinii* Hook., Cromwell (26) found 0.33% dry weight of berberine in the wood of young twigs and 1.53% in that of old stems at ground level. As the amount of wood increases, this must imply an active increase of alkaloid. Histochemical examination by means of the chlorine-hydrochloric acid reaction showed further that in mature stems and roots "penetration of the xylem" had occurred and that the lignified walls were impregnated with alkaloids. Nevertheless, the heaviest colorations were observed in the living cells adjacent to the vascular bundles, and evacuation was observable as usual in the aging pith. The umbellatine of Himalayan *Berberis* species (27) and rawolscine of *Rauwolfia canescens* (25) are said to occur similarly, but not exclusively, in dead cells of wood and bark.

2. Cytology

In dried tissues, such as occur in crude drugs, alkaloids may be found impregnating the cell walls. It happens, for example, in *Cinchona* barks, tissues that contain exceptionally large amounts of alkaloids. This is, however, a post-mortem effect due to the breakdown of the protoplasmic cell linings during drying. In living tissues, the alkaloids are invariably found as water-soluble salts dissolved in the cell vacuole. Even in *Cinchona* there is no precipitation of the alkaloids in less soluble forms (24). The localization of the alkaloid salts in the vacuole is readily demonstrated and was realized at an early stage. If a section of an alkaloid-containing tissue is cut thin enough to open the parenchymatous cells, the vacuolar contents escape and alkaloid reactions are no longer given by the cell residues. Such observations have been made with a sufficient variety of

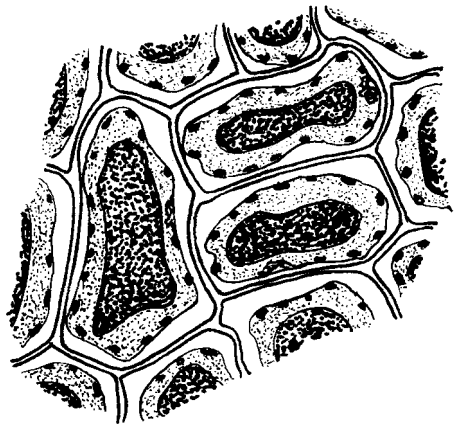


Fig. 9. Piece of the upper epidermis of a petal of *Dendrobium nobile* plasmolyzed and treated with iodine in potassium iodide. The heavy shading indicates alkaloid precipitated in the cell vacuoles, surrounded by the protoplasm (lighter shading) containing the pigmented chromoplasts. After Wildeman (8).

alkaloid-bearing species, e.g., *Colchicum*, *Narcissus*, belladonna (14), and other solanaceous plants (6), orchids (8, 9), *Clivia* (12), etc. to be taken as general. The retention of the alkaloids within the protoplasmic sac is clearly seen in cells plasmolyzed before applying the alkaloid precipitant (Fig. 9).

It is noteworthy that the cells just behind the shoot and root meristems, and adjacent to the cambium and phellogen, which are so frequently reported as accumulating alkaloids, are in a stage of active vacuolation. The most detailed study up to the present has been made by Chaze (13, 30). in the meristems and flower buds of the tobacco plant. In very young radicles at the outset of germination, the meristematic cells were observed

to contain aleurone grains which break down as germination begins. As their proteins disappear, the grains become fluid vacuoles which are characterized by their active absorption of neutral red. As soon as the grains are liquefied, alkaloids are formed and can be precipitated by the iodine-potassium iodide reagent. A little later, normal vacuoles arise in clusters in the cytoplasm, especially around the nucleus. These are at first exceedingly minute and are most readily demonstrated by their power to take

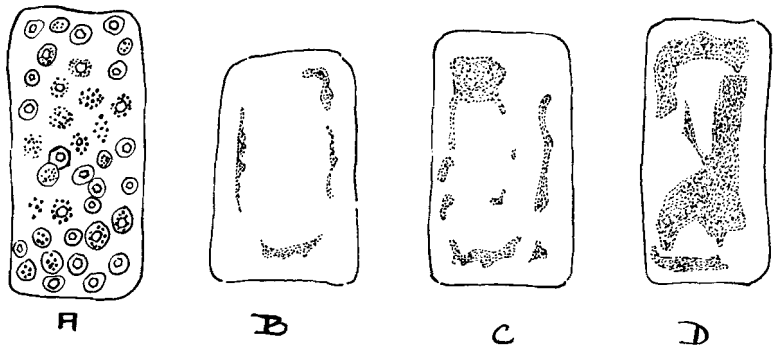


FIG. 10. A. Cell from germinating tobacco embryo treated with iodine in KI. The aleurone grains are breaking down and the protein reaction is replaced in some by the fine-grained alkaloid precipitate. B → D. Cells from the procambial strand similarly treated showing development of the alkaloid-containing vacuole. After Chaze (13).

up neutral red. They give alkaloid reactions from a very early stage (Fig. 10), and continue to do so as the vacuoles enlarge and run into one another, first in filamentous and other forms, and finally as one large central vacuole. Chaze was unable to demonstrate the presence of alkaloids in the mitochondria, and the site of their original formation in the cell, whether in mitochondria, plastids, the general body of the cytoplasm, at the vacuolar surface, or elsewhere, is at present uncertain.

III. Ontogeny

1. Individual Tissues

The investigators, who at the turn of the century developed the histochemical method, made repeated observations of the sequence of alkaloid development in specific tissues. In general, newly formed cells were observed to have but little alkaloid, although it accumulated rapidly as vacuolation set in. At cellular maturity, the large central vacuole contained an abundance of alkaloidal salts in solution. In tissues such as *Cinchona* bark the alkaloid content was maintained, so far as histochemical methods could determine, as long as the parenchyma remained alive. In

other tissues, as, for example, the pith, it was observed that a peak period was reached after which the alkaloid content of the vacuole appeared to decrease. Finally, in the cells at the center of the medulla, alkaloid reactions disappeared completely. Alkaloids disappear early from the procambial cells differentiating into vessels or sieve tubes. Although a slight change might easily be misconstrued, a complete failure of the reaction in a tissue formerly rich in alkaloids could only mean that there had unquestionably been a loss. This posed a question which has still to receive an unambiguous answer. Observing that, as the pith and other deep-seated tissues lost their alkaloids, the epidermis and circumvascular parenchyma appeared to be enriched, the earlier investigators seem to have assumed that a translocation of alkaloid was taking place. There was, and is, no conclusive evidence for this, and a breakdown of alkaloid *in situ* remains a possible alternative.

The leaf affords the most thoroughly investigated group of tissues from this point of view. During the development of the leaf primordia at the stem apex, the histochemical remains the only available method of investigation. Lotsy (23) found in *Cinchona ledgeriana* and *C. succirubra* that the youngest primordia were alkaloid-free, that a stage rich in alkaloids was soon reached, and that the cells of older leaves were relatively impoverished. Similar observations have been made in *Nicandra physaloides* Gaertn. (6).

When the leaf achieves a rather larger size, quantitative estimations of extracted alkaloids become possible, and a number of investigations have been carried out to determine the change in alkaloid quantity with time.

TABLE 3

COLCHICINE IN LEAVES OF *Colchicum autumnale*

Date of collection	G. colchicine in 100 g. dry weight*		Average length of leaf in cm.
	1944	1945	
March 10	...	0.88	17.0
April 15	...	0.75	30.0
May 12	0.48	0.12	45.0
May 25	0.32	...	...
June 3	...	0.26	45.0
July 6	0.04	...	...

*Method of the British Pharmacopoeia, 1932.

Klein and Pollauf (31), using a method of micro-extraction and estimation, obtained yields of colchicine from young and old autumn crocus leaves in the ratio of 5/3. The amounts of colchicine in a series of leaf samples picked at intervals throughout the growing season (32) are shown in Table 3.

From the stage when the leaves are large enough to be analyzed conveniently there is a steady falling away of the percentage alkaloid. The fall is most marked during the latter part of the season when growth has been completed and there can be no accumulation of inert matter to dilute the alkaloid. It seems clear that reduction in the actual amount of alkaloid per leaf must have occurred. More satisfactory data are available for belladonna. Analyses of leaves at different levels on the plant, and therefore of different ages, show an increasing series of both percentage and quantity of alkaloid per leaf. Maxima occur with the young, fully expanded leaves followed by a decline of both quantities in the aging leaves of the lower stems.

TABLE 4

TOTAL ALKALOIDS IN LEAVES OF *Atropa belladonna* (33)

	Dry weight per leaf in mg.	G. total alkaloid per 100 g. dry weight*	Mg. total alkaloid per leaf
Buds	20	0.18	0.04
Young opening leaves	60	0.22	0.13
Fully expanded leaves on young shoots	360	0.39	1.41
Leaves on top third of main stems below crown of young shoots	560	0.34	1.96
Leaves at middle of main stems	560	0.12	0.67
Leaves on bottom third of main stems	350	0.09	0.32

*Method of Allport and Wilson (34).

The position of a leaf on the plant may affect its alkaloid content quite apart from the question of the leaf's age. Thus Cromwell (26) observed that young barberry leaves contained no detectable berberine until the bush carrying the leaf had itself reached an advanced age; in other words, a leaf that is young when its parent plant is old is not an accurate index of the youth of a leaf borne when the plant itself was young.

Analyses carried out upon the basal leaves of belladonna throughout the second season of the plant's growth are summarized in Fig. 11 (33). The percentage alkaloid drops steadily from the beginning of the experiment. The actual accumulation of alkaloid, on the other hand, continues for some time, reaches a maximum when the leaf is fully expanded, and then drops away to a trifling value before leaf-fall, even in leaves which retain their green color more or less unimpaired. Yellowed leaves have an even lower alkaloid content per leaf.

2. SEEDLINGS

In every alkaloid-bearing plant that has been examined, the ovule bears an abundant supply at the time of fertilization. In this sense, all such plants begin life with a rich alkaloid equipment. During maturation

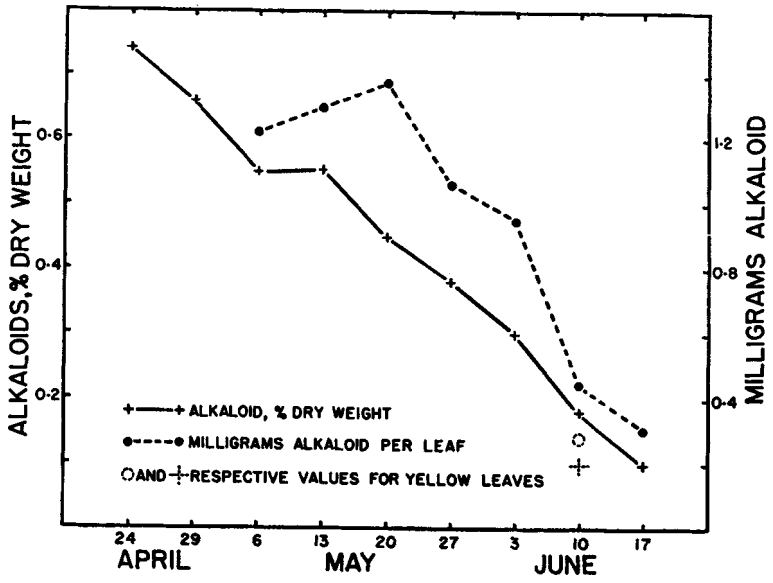


FIG. 11. Total alkaloids in the basal leaves of belladonna throughout their development. From Oxford Medicinal Plants Scheme (33).

of the seed, up to the phases of ripeness and dormancy, much of the alkaloid may disappear, with the result that resting seeds fall into three principal classes according to the degree of alkaloid loss or gain during maturation: (*a*) seeds with no alkaloids, (*b*) seeds with scanty alkaloids located only or mainly in surface membranes (testa and perisperm), and (*c*) seeds with relatively large amounts of alkaloid in reserve tissues (endosperm and cotyledons). The last class may also contain comparatively small amounts in the radicle and plumule. Table 5 gives examples of these classes.

Small quantities of alkaloid, not definitely located, occur in the seeds of *Cinchona spp.* (45, 46), *Strychnos quaqua* Gilg. (44), *Narcissus* (1), *Genista* spp., and *Ulex europaeus* L. (47). The behavior upon germination varies to some extent depending upon the class concerned, but the general tendency is for alkaloids to appear or increase in amount in the growing tissues and, where present, to disappear in the passive ones.

Class (a): The grass species forming hordenine are interesting as providing the simplest story. No alkaloid is present in any part of the

resting grain. After a few days of germination, when the radicle is put out, determinable amounts equal to about 0.5% of the dry weight are found in it (48, 49). The hordenine is limited to the meristematic cells

TABLE 5

ALKALOIDS IN SEEDS OF ALKALOID-FORMING SPECIES

(a) None	(b) Scanty; in Perisperm, Testa or Fused Pericarp	(c) Abundant; in Endosperm or Cotyledons
Nicotiana tabacum L. (5, 13)	*Atropa belladonna* L. (5, 6)	*Lupinus albus* L. (5)
Papaver somniferum L. (3, 5)	*Datura stramonium* L. (5, 6, 16)	*Lupinus luteus* L. (39, 40)
Nicandra physaloides Gaertn. (6)	*Hyoscyamus niger* L. (5, 6, 16)	*Phytostigma venenosum* Balf. (44)
Physalis alkekengi L. (6)	*Solanum tuberosum* L. (6)	*Areca catechu* L. (44)
Hordeum vulgare L. (35, 48, 49)	*Solanum dulcamara* L. (6)	*Strychnos nux-vomica* L. (41, 42, 44)
Hordeum murinum L. (35)	*Petunia violacea* Lindl. (6)	*Strychnos tieute* Lesch. (44)
Panicum miliaceum L. (35)	*Salpiglossis sinuata* Ruiz and Pav. (6)	*Strychnos ignatii* Berg. (44)
Strychnos potatorum L. (44)	*Conium maculatum* L. (4, 5, 44)	*Colchicum autumnale* L. (1)
Strychnos spinosa Lam. (44)	*Ricinus communis* L. (37, 36)	*Delphinium* (5)
	Peganum harmala L. (36)	*Sabadilla officinarum* Brandt and Ratzeb (44)
	Colchicum autumnale L. (44)	
	Erythroxylon coca Lam. (43)	

at the root tip (35, 50). A few days later it disappears and is apparently not formed in the adult plant. The same base has been isolated from the totally unrelated plant *Anhalonium fissuratum* Engl. (Cactaceae) (51) in the adult stage; the seedling stages do not yet seem to have been examined, but it is perhaps worth pointing out that the ontogenetic development of one and the same alkaloid obviously varies considerably with the plant.

Other members of class (a) develop alkaloids during their germination and afterwards continue to accumulate them throughout the subsequent

life of the plant. One of the most thoroughly investigated species is *Nicotiana tabacum*. Under ordinary conditions of germination no alkaloids are extractable for about 10 days (52). The careful histochemical examination carried out by Chaze (13) showed that the earliest appearances of alkaloids precipitable with iodine in potassium iodide are in the meristems of root and epicotyl. In seedlings only 3–5 mm. long, the root meristem, root cap, and piliferous layer, as well as the epicotyledonary bud gave heavy precipitations. The cotyledons gave little reaction and the hypocotyl an intermediate one. Seedlings grown on damp blotting-paper and starved at this stage lost their alkaloids first from the vacuolated cells and finally from the meristematic ones, while protein reactions were still strong.

During the germination of the opium poppy, alkaloids may first appear in seedlings which have attained a height of only 10–15 cm. (3), afterwards continuing to increase. Narcotine is said to be the first alkaloid to appear and may even be present in traces in the seed. Codeine, morphine, and papaverine may appear when the seedling is about 7 cm. high (53).

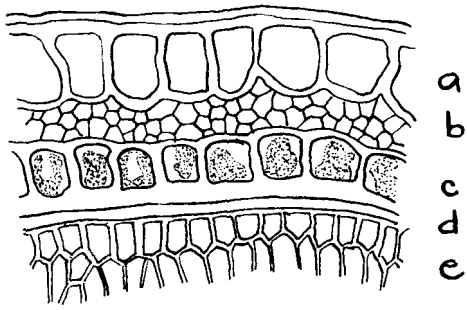


FIG. 12. Transverse section through testa and endosperm of seed of *Peganum harmala*: *a* epidermis; *b* small-celled layer; *c* alkaloid-bearing layer; *d* disintegrated perisperm; *e* endosperm. After Barth (44).

Class (*b*): In the early stages of germination of the *Atropa* — *Datura*— *Hyoscyamus* group the small quantities of alkaloid present in the peripheral tissues (Fig. 12) are reduced or may disappear completely (44, 54). It is possible that the losses are due at least in part to leaching out from the pervious dead cells containing them (37). Extractable quantities of alkaloid may reappear in the seedlings only after 14 or more days of germination. Using micro-extraction into ammoniated chloroform and precipitating as the aurichloride, Klein and Sonnleitner (54) considered that hyoscine was the first alkaloid to appear in *Hyoscyamus niger* and *Datura stramonium* seedlings, and that, more doubtfully, hyoscyamine was the first to appear in *Atropa belladonna*. Alkaloids precipitable with iodine appear in the

meristems at a very early stage (15). In several *Datura* varieties they appear with some suddenness when the radicle is no more than 2 or 3 mm. long. At this stage, they are limited to the root meristem and as soon as the cotyledons are expanded, they are demonstrable in the stem apex and leaf rudiments also. The cotyledons themselves and the hypocotyl and root intervening between the two meristems give little or no reaction at this stage. Starvation of these young plants causes the alkaloid to disappear even from the meristems. It is highly improbable that the alkaloids appearing in the *Datura* embryo are translocated thither from the dead tissues of the perisperm and testa, and it has been shown that complete removal of the alkaloid-bearing layers does not prevent normal development of the young seedling (5). The stage at which alkaloids can first be identifed in *Erythroxylon coca* is shown in Fig. 13.

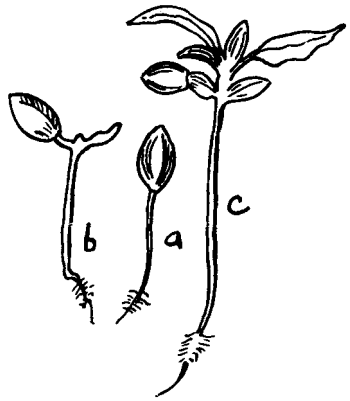


FIG. 13. Seedlings of *Erythroxylon coca*: *a* and *b* devoid of alkaloids demonstrable histochemically. Alkaloids can be detected in the leaves at stage *c*. After Tunmann (43).

The similarity of these observations to the results obtained with *Nicotiana* is evident.

In *Ricinus communis* seeds the deposits of ricinine occur to the extent of about 0.15% of the dry weight. The great bulk of this is located in the seed coat; 0.03% being recorded for the kernel (55). Owing to the great excess of fats (castor oil) present in the endosperm, there may be difficulty in satisfactorily extracting such small amounts for estimation, but Weevers (37) was unable to obtain more than trifling quantities of ricinine from endosperms previously defatted with ether, in which this alkaloid is not readily soluble. He found that, during germination in the dark, the ricinine nitrogen in 100 seeds without testas rose in 3 weeks from 4 to 72 mg. — a clear enough indication that synthesis had occurred. Examination of younger seedlings in which the cotyledons were still retained within the endosperm, showed that the ricinine at this stage was

present in extractable amounts only in the cotyledons and hypocotyl. There were only traces in the endosperm and in the young emerging root, 1–2 cm. long. Histochemical examination of the root tip does not seem to have been carried out, but the accumulation of alkaloid in the cotyledons and hypocotyl would appear to be due to translocation, with or without decomposition, from the endosperm.

Class (c): In the seeds of the Leguminosae, both the reserve tissues (cotyledons) and the embryonic (plumule and radicle) are well supplied with alkaloids (10). The integuments may be alkaloid-free. In this class the behavior of the alkaloids during germination can be satisfactorily examined only by quantitative methods. The most carefully investigated species has been *Lupinus luteus* grown in Europe for stock feed, and occasionally causing the death of sheep (56). Only the seeds are regarded as poisonous, neither the pods nor the leaves being thought dangerous.

Detailed investigation of the changes during germination has been made by Wallebroek (40). The alkaloids were extracted in etherchloroform after a previous defatting of the material. Failure to observe this precaution has made earlier results of doubtful value. In the resting seeds, alkaloid nitrogen was found to account for about 1.2% of the total nitrogen and to amount to about 120 mg. of alkaloid (calculated as lupinine) per 100 seeds, of which 1.00 mg. was in the plumules and radicles. The ratio of alkaloid in the cotyledons to alkaloid in the plumule plus radicle was thus more than 100:1. After three days germination, there was a tenfold increase of alkaloid in the embryonic tissues. At the same time there was a loss from the cotyledons more than sufficient to cover it. Consequently, it was impossible to say whether the increase in the plumule plus radicle was due to synthesis in their meristems or to translocation from the cotyledons.

In another batch of seed one of the two cotyledons was removed from each seedling after 9 days and germination allowed to proceed for a further 12 days with the depleted reserves still available from the other. The "lupinine" content of the plumule plus radicle fell, under this treatment, from 42.5 to 2.65 mg. per 100 seeds. There was also a loss from the surviving cotyledons, so it was evident that actual decomposition of alkaloid must have occurred. In a parallel experiment with normal seedlings, the gain of alkaloid between the ninth and twenty-first days exceeded the simultaneous loss from the cotyledons, and synthesis from the abundant "soluble nitrogen" was clearly taking place. Whether translocation occurs or not, it is therefore clear that, even in lupin seeds with an initial alkaloid content in the meristematic parts, actual synthesis takes place in the early stages of germination, accompanied by a decomposition in the reserve tissues. In these, as in the other classes of seedlings, the dependence of alkaloid formation upon active growth is very evident. The loss from the

reserve tissues is not due to shedding of the testa, which is alkaloid-free, or to leaching out into the seed-bed (39). A similar initial loss has also been recorded during the germination of *Strychnos nux-vomica* where it occurs in the active tissues of root and hypocotyl as well as in the reserve tissues (42). The exhaustion of the latter is not complete, and when they are discarded, they still contain about a fifth of the initial alkaloid content of the seed. The breakdown of the endosperm alkaloids occurs only under the influence of the embryo. Endosperms from which the embryos have been removed do not lose their alkaloids if kept under the conditions normal for germination (41). A similar behavior by the starch of cereal grains and the excretion of starch-degrading amylases from the embryo into the endosperm are well known (57). The initial disappearance and later reformation of alkaloids in the young embryo is also paralleled by the behavior of sucrose in barley grains (58). These alkaloids must therefore be regarded as metabolically labile substances, but that is not to say that their fluctuations are necessarily of significance to the plant comparable with those of the carbohydrates.

3. THE MATURING PLANT

After the first appearance of alkaloids in the seedling, steady accumulation goes on through the period of active vegetation, with a maximum at or about the time of flowering. The annual growth cycle has been carefully studied in two species, *Nicotiana tabacum* and *Lupinus luteus*.

TABLE 6

NICOTINE IN TOBACCO PLANTS (59)

Date	Weight of leaves*	Nicotine, %*	Total nicotine*
July 18	1.0	1.0	1.0
August 6	2.29	1.53	4.6
August 27	4.38	2.44	10.7
September 8	5.13	2.92	15.0
September 28	6.17	4.25	26.2
October 24	6.15	5.36	32.7

* Relative values; initial values taken as unity.

PERCENTAGE NICOTINE IN SEED-BEARING AND TOPPED PLANTS

Harvest	Alsace 1861	Havana 1861	Havana 1863
Seed-bearing plants	1.29	2.40	2.00
Topped plants	3.73	6.60	5.08

Schloesing (59) recorded that both the absolute and percentage amount of nicotine increased steadily in tobacco plants from July onwards until they reached their maximum weight in October. More recently, Deleano and Vladescu (60) have determined the total nicotine content of samples of 100 plants taken at frequent intervals through the growing season. The amount of protein formed was determined simultaneously and the two

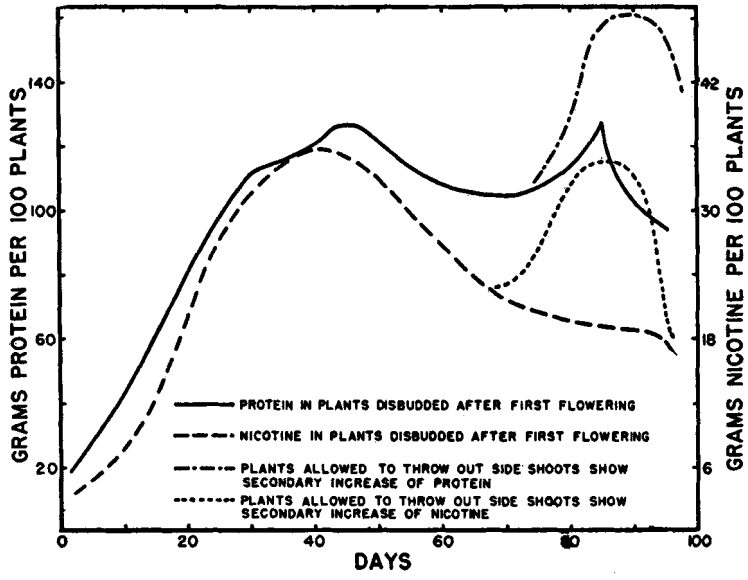


FIG. 14. Protein and nicotine in 100 tobacco plants throughout the growing period. From Deleano and Vladescu (60).

drifts are shown in Fig. 14. The two curves present an interesting parallel, both coming to a peak after 40–50 days at the time of the first flowering, maximum weight, and leaf maturity. A loss of both protein and alkaloid then sets in during the period of flowering and setting seed. Schloesing had already shown that plants prevented from flowering accumulated a higher percentage of nicotine than the normal (Table 6). When side shoots are formed, proteins and alkaloids accumulate again until these side shoots flower in their turn (Fig. 14). From the results of histological studies it is safe to assume that the newly formed alkaloids are present in the young vigorously growing side shoots. This is borne out by the fact that disbudded plants in which this secondary shoot development is suppressed show little or no secondary nicotine accumulation. It is important to note that accumulation of this kind in active tissues is not limited to substances that may be supposed to be synthesized in them, and the authors noted

similar behavior on the part of mineral salts in their tobacco plants. This is in line with general experience (see, for example, Steward (61) and Hoagland (62)). Whether it was nicotine as such or suitable material for its synthesis *in situ* that was attracted by the active tissues cannot be decided from these experiments. The disbudded plants lost nearly one half of their nicotine, but only a much smaller fraction of their protein by the end of the season (Fig. 14).

Some observations of Smirnov (63) also illustrate the accumulation of nicotine during the vegetation of the tobacco plant. He discarded stems and roots and analyzed only the leaves which contain 85–88% of the plant's alkaloids (52). Unfortunately, he did not indicate the amount of leaf present on each occasion but records his results per square meter of leaf surface. On this basis the nicotine content of normal plants increased steadily up to the time of flowering, and, since it is a safe assumption that leaf area increased or at least did not diminish up to this stage, there must have been an actual increase in the amount of nicotine formed. Protein

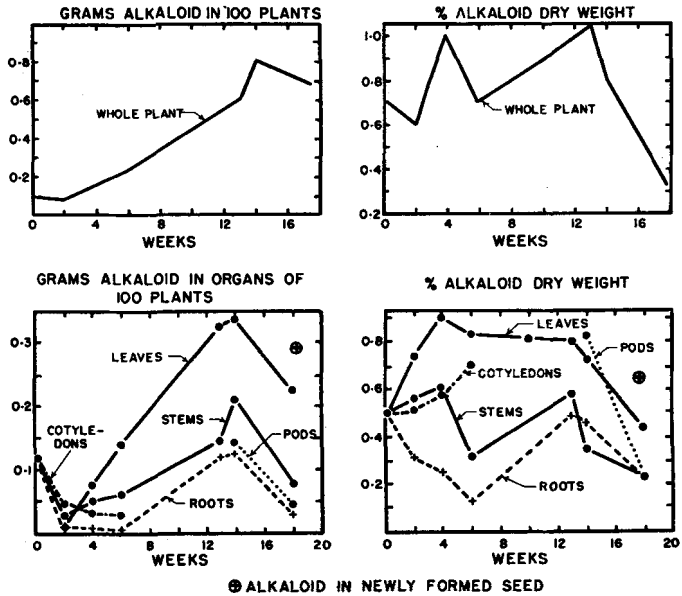


FIG. 15. Alkaloids in *Lupinus luteus* throughout the growing period. From Sabalitschka and Jungermann (65).

accumulation came to a stop somewhat earlier. After flowering there was some indication of a loss of nicotine, though the method of sampling makes the deduction rather uncertain. On plants which were cut down (topped) and which consequently sprouted a lot of young growth, the milligrams of

TABLE 7

Grafts: scion named above and stock below; scion alkaloid to left and stock alkaloid to right.

A. ALKALOID PROPER TO SCION SPECIES NOT FOUND IN SCION OR STOCK IN MORE THAN TRACES

Graft	Alkaloids in Scion	Alkaloids in Stock	References
Nicotiana tabacum *Solanum tuberosum* nicotine/solanine	a) Alkaloid ppt. just above graft.	a) Alkaloid ppt. just below graft. Amount of volatile alkaloid small.	73
	b)	b) No nicotine in tubers.	79
N. tabacum *Lycopersicum esculentum* nicotine/solanine	a) New growth free of nicotine. Amount originally present remained at base.	a) Alkaloid present apparently not nicotine.	74
	b) Initial nicotine lost in 44 days.	b)	91
	c) No volatile or non-volatile alkaloid.	c) No volatile alkaloid.	72
	d) Little nicotine.	d)	92
N. rustica *Ly. esculentum* nicotine/solanine	a) No volatile alkaloid.	a) No volatile alkaloid.	72
Datura stramonium *Solanum tuberosum* hyoscyamine/solanine	a)	a) Extremely small amounts of "atropine" in tubers.	66
	b)	b) No mydriatic alkaloid demonstrable in tubers.	69
	c)	c) No mydriatic alkaloid demonstrable in tubers.	70
	d)	d) Mydriatic alkaloid just below graft.	73

D. stramonium *Ly. esculentum* hyoscyamine/solanine	a) No mydriasis, Vitali reaction, or aurichloride. b) No mydriasis.	a) ..... b)	76 75
Atropa belladonna *S. tuberosum* hyoscyamine/solanine	a)	a) No mydriasis or Vitali reaction in tubers	79
A. belladonna *Ly. esculentum* hyoscyamine/solanine	a) Vitali reaction and mydriasis in fruits but not in leaves and stems. b) Very weak mydriasis. c) Traces of alkaloid giving Vitali reaction. Histo-chemical reaction near graft and in meristems.	a) ..... b) ..... c)	79 72 14, 32

TABLE 7 (*Continued*)

B. ALKALOID PROPER TO STOCK SPECIES FOUND IN SCION AND STOCK

Graft	Alkaloids in Scion	Alkaloids in Stock	References
Ly. esculentum *N. tabacum* solanine/nicotine	a) Nicotine isolated as picrate.	a) Nicotine isolated as picrate.	78
	b) Nicotine present.	b) Nicotine present.	74
	c) Nicotine present.	c) Nicotine present.	74
	d) Nicotine present.	d) Nicotine present.	77
Ly. esculentum *Nicotiana glutinosa* solanine/nicotine	a) Nicotine present.	a)	88
Ly. esculentum *Nicotiana rustica* solanine/nicotine	a) Nicotine present.	a) Nicotine present.	78
Solanum nigrum *N. tabacum* solanine/nicotine	a) Nicotine present equivalent to total alkaloid.	a) Nicotine present.	78
D. stramonium *N. tabacum* hyoscyamine/nicotine	a) Nicotine present	a)	82
D. stramonium *N. rustica* hyoscyamine/nicotine	a) Nicotine present, no mydriatics.	a)	72

Ly. esculentum *A. belladonna* solanine/hyoscyamine	a) Fruits: mydriasis and Vitali reaction. Leaves and stem; no reaction.	a)	79
	b) Mydriasis.	b)	72
	c) Alkaloids giving Vitali reaction.	c) Alkaloids present.	80
Ly. esculentum *D. stramonium* solanine/hyoscyamine	a) Strong mydriasis; Vitali reaction *l*-hyoscyamine isolated as aurichloride.	a)	76
	b) Mydriatics in fruit.	b)	75
	c) Atropine in all parts.	c)	81
	d) Strong mydriasis and Vitali reaction in leaves; none in fruit.	d)	80a.
Ly. esculentum *Nicotiana glauca* solanine/anabasine	a) Anabasine and a little nicotine.	a)	86
N. tabacum *N. glauca* nicotine/anabasine	a) Anabasine present, no nicotine.	a) Anabasine and trace of nicotine.	93
	b) Anabasine present and small amount of nicotine.	b)	90
Ly. esculentum *Duboisia myoporoides* solanine/hyoscine	a) Hyoscine, other non-volatile bases.	a)	83
N. tabacum *D. myoporoides* solanine/hyoscine	a) Nicotine (?), hyoscine, tropine.	a)	89

TABLE 7 (*Continued*)

C. ALKALOID PROPER TO SCION SPECIES FOUND IN SCION (AND STOCK?)

Graft	Alkaloids in Scion	Alkaloids in Stock	References
N. glauca *Ly. esculentum* anabasine/solanine	a) Anabasine present, no nicotine.	a) No alkaloids.	86, 88
N. glauca *N. tabacum* anabasine/nicotine	a) Anabasine and a small amount of nicotine.	a)	93
	b) Anabasine and nicotine both present.	b) Anabasine and nicotine both present.	90
	c) Anabasine and nornicotine.	c) Nicotine present. No nornicotine or anabasine.	88
N. glauca *N. rustica* anabasine/nicotine	a) Anabasine and nicotine both present.	a) Anabasine and nicotine both present.	90

D. TRIPLE GRAFTS

Graft	Alkaloids in Upper Scion	Alkaloids in Middle Scion	Alkaloids in Stock	References
Ly. esculentum (solanine) *A. belladonna* (hyoscyamine) *L. esculentum* (solanine)	No alkaloid.	No alkaloid.	No alkaloid.	94
Ly. esculentum (solanine) *N. rustica* (nicotine) *L. esculentum* (solanine)	No nicotine.	No nicotine.	.....	72
N. rustica (nicotine) *Ly. esculentum* (solanine) *N. rustica* (nicotine)	Nicotine.	Nicotine.	.....	72
Ly. esculentum (solanine) *N. glauca* (anabasine) *N. tabacum* (nicotine)	Nicotine.	Anabasine and nornicotine.	.....	88

nicotine per square meter of leaf surface, and, obviously, also the total nicotine formed, went on increasing. So far as a comparison can be made these results are therefore in agreement with those of Deleano and Vladescu. Mothes (64) determined the milligrams of nicotine in samples of 40 tobacco tops through the month of June. The fresh weights increased from 102 to 885 g. and the nicotine nitrogen from 3 to 40 mg., the equivalents of 1.1 and 6.6% of the total nitrogen. Accumulation of the alkaloid was therefore active. Accumulation of lupinine and associated alkaloids throughout the growth of the yellow lupin has been studied in detail by Sabalitschka and Jungermann (65). They determined the drift both in the plant as a whole and in each of its principal organs. After the initial loss of alkaloid during germination already described, accumulation went on steadily up to 14 weeks, when the plants were flowering and setting seed (Fig. 15A). Accumulation took place in leaves, stems and roots, and especially in the leaves (Fig. 15C). Only about 18% of the total alkaloid was below ground at the peak period. With the setting of the seed, a loss of alkaloid set in which was apparent in leaves, stems, and roots, and even in the pods. The newly formed seed contained more alkaloid than the matured seed from which the plants sprang, in agreement with direct observations on the maturation period in other species. The lupin cycle thus closely resembles that of tobacco up to the time of setting seed and its major phases of accumulation during vegetation and loss during seed formation may perhaps be taken as typical of annual plants. The secondary peak shown by tobacco under appropriate conditions is associated with a rejuvenation and growth not exhibited by lupins.

IV. Alkaloids in Grafts

In 1885 Strasburger (66) grafted thornapple cuttings upon potato stocks and afterwards had the tubers examined for alkaloids. They were found to contain "atropine" "though only in extremely small amounts." Normal potatoes yielded none. This experiment started a line of investigation that has since been applied to solanaceous plants on a large scale and has lead to important results (Table 7). Members of different species and genera of the family Solanaceae may be grafted together, usually without much difficulty, and good growth of both scion and stock obtained. The family produces a considerable range of alkaloids — individual alkaloids being restricted to definite groups of species. Thus nicotine is mainly restricted to the *Nicotiana spp.*; the tropane alkaloids to a group including *Atropa, Datura, Hyoscyamus,* and *Duboisia,* and solanine to species of *Solanum* and *Lycopersicum.* Even within these main groups there are important distinctions, such as the predominance of nicotine over allied alkaloids in

N. tabacum; of nornicotine in *N. glutinosa* and of anabasine in *N. glauca*. In the tropane group, *l*-hyoscyamine predominates in *A. belladonna* and *l*-hyoscine in *Datura metel* L. (68). The distribution of the alkaloids in a graft whose stock and scion produce different kinds may thus prove illuminating.

Strasburger's immediate successors in this field grafted tobacco, thornapple, belladonna, and henbane scions upon potato stocks. They were unable to discover in the tubers of plants with such grafts any alkaloids with mydriatic properties (69). Weak reactions observed with general alkaloid precipitants were probably due to solanine and its allies. Meyer and Schmidt (70) showed that, nearer to the scion, i.e., in the potato stem just below the graft, an alkaloid was present which, besides precipitating with potassium bismuth iodide and gold chloride, gave a strong mydriatic reaction. It was localized in the phelloderm. In the author's laboratory, alkaloid precipitations by iodine in potassium iodide have similarly been observed in the stems of tomato stocks just below belladonna scions, although normal tomato stems show none. Using grafts of *Nicotiana tabacum* on potato stocks, Meyer and Schmidt obtained heavy alkaloid precipitations just below the junction; again normal potato stalks gave none. The amount of volatile alkaloid found seems, however, to have been very small. In all these grafts relatively heavy precipitations were obtained in the swollen region *above* the graft.

It is probable that the difference between Strasburger and his followers was one of degree rather than kind. The mydriatic test for tropane alkaloids may be so carried out as to be highly sensitive, and may not be entirely specific. It has even been reported that the eating of leaves from normal potato plants may cause dilation of the pupil (71). In the more recent grafts of *Atropa belladonna* upon *Lycopersicum esculentum* Mill., made by Hieke (72), "barely detectable" quantities of mydriatics were found in the tomato stocks. The correct statement of these results seems to be that only traces of the alkaloids were to be found in the potato and tomato stocks.

Examination of the scions led to more startling results. Their leafy shoots were found as a whole to contain much reduced quantities of their normal alkaloids. *Nicotiana tabacum* on potato gave much lower assays for alkaloid than normal shoots (73); grafted upon tomato stocks the new growth yielded only a trace of nicotine that could be detected as a titratable base or as a dipicrate. Some of this was already present in the grafted material (74), and remained in the lower regions of the graft just above the stock. Similarly, *Datura stramonium* scions grafted upon tomato stocks develop little or no mydriatic alkaloid (75). As a result of mydriatic, Vitali, and aurichloride tests, Peacock, Leyerle, and Dawson (76) concluded that the concentration of alkaloids in such scions must be less than

$5x10^{-6}\%$. *Atropa belladonna* scions grown on tomato stocks cause barely detectable mydriasis (72), and yield only traces of tropane alkaloids giving the Vitali reaction (14, 32). These are, however, localized in the meristems where the concentration may be high.

The reciprocal grafts with tomato scions upon *Nicotiana tabacum* stocks show accumulation of nicotine in leaves and sometimes in fruits of the tomato scion (72, 74, 77). Shmuck, Smirnov, and Il'in (78) isolated nicotine as its picrate from tomato leaves and fruits raised on stocks of *N. tabacum* and *N. rustica* L. *Solanum nigrum* L. scions also grafted on tobacco yielded nicotine equivalent to the total alkaloid instead of the solanine normal for the species (78). Similar results were obtained when tomato was grafted upon species forming tropane alkaloids. Tomato scions on belladonna developed a strong capacity for mydriasis (72), a total alkaloid content estimated at 0.12% dry weight (80) and according to Javillier (79), a strong Vitali reaction in the fruits. In the author's laboratory positive results have also been obtained with the leaves of tomato scions; but the occurrence of alkaloids in the fruits has not been confirmed. A well-formed truss of ripe tomatoes grown on a belladonna stock caused no iodine precipitation in the tissues, and extracts yielded no Vitali reaction and no alkaloids as picrates. It is possible that alkaloids present in earlier stages had disappeared during ripening.

On *Datura stramonium* stocks similar results have been obtained, and *l*-hyoscyamine has been isolated from the tomato scions as the aurichloride (76). The fruits when eaten by humans caused dryness of the mouth, dilation of the pupils and other signs of hyoscyamine poisoning according to Krajevoj and Nachev (75); but Vincent and Dulucq-Mathou (80a) were able to find mydriatic alkaloids only in the leaves. Ripe fruits gave none.

Hieke, grafting thornapple upon *Nicotiana rustica*, found that it accumulated nicotine but no tropane alkaloids, as judged by the mydriatic test. The formation of nicotine was confirmed by Dawson, using *N. tabacum* (82). Tomato grafted upon *Duboisia myoporoides* R. Br. accumulated hyoscine to more than 1%, identified as the picrate by Hills, Trautner, and Rodwell (83).

From the above results it is clear that the alkaloid normally formed in the stock may also appear in the scion, to which it is a stranger, and that the reverse process occurs but little, if at all. At first sight, it seems easier to suppose that preformed alkaloid is translocated from the stock than that the scion develops an entirely new metabolic capability, and many investigators have taken this view. It is supported by the detection of alkaloids in the sap bleeding from decapitated thornapple (76), belladonna (80), and tobacco stumps (82). Dawson (82) was able to observe that the sap oozed

from the xylem, which would be expected if translocation occurred from stock to scion and not in the reverse direction. It would be unwise in seeking to explain the absence of scionic alkaloid from the stock to place too much stress upon the fact that alkaloids cannot be detected in the sieve tubes, the normal path of downward translocation.

Since the leaves and stalks of scions appear unable to form the alkaloids normal for their species when grafted upon foreign stocks, some workers suggest that alkaloid formation does not occur in leaves and stalks growing normally upon their own roots, and that their alkaloids are derived wholly by translocation from the roots. Even on the basis of grafting experiments alone, this could not be of general application. The results on which this opinion is based are derived principally from *Nicotiana tabacum* and *Datura stramonium*. Belladonna scions are not entirely devoid of mydriatic alkaloid when grown on foreign stocks. The experiments of Weevers and van Oort (84) suggest that quinine formation may take place in the leaves and it is therefore interesting that the grafting of *Cinchona ledgeriana* scions upon *C. succirubra* stocks is a common cultural practice (85). The aim is to combine the higher yield of *C. ledgeriana* with the more robust root development of *C. succirubra*. *Nicotiana glauca* Graeb., which normally forms not nicotine but the related alkaloid anabasine as its principal alkaloid, also gives a very different picture. In reciprocal grafts of this species with tomato, anabasine accumulated in the scions whether of *N. glauca* or tomato and was isolated in considerable quantity as the picrate (86). Grafts of the two *Nicotiana* species, *N. tabacum* and *N. glauca* contained anabasine in the scion, regardless of the way the graft was made (88, 90, 93). It is clear that the simple hypothesis of an alkaloid formation limited to the root is not supported by such results as these, and Dawson (86) suggests that whereas nicotine synthesis is thus restricted, the formation of anabasine can take place in the shoot as well. Further information was obtained by grafting *Nicotiana glutinosa* with *Nicotiana tabacum* and tomato (87, 88). On its own roots *N. glutinosa* L. produces relatively large amounts of nornicotine as well as nicotine. The same result is obtained when it is grafted upon *N. tabacum* stocks. In the reciprocal graft, or when tomato is grafted upon *N. glutinosa*, only nicotine appears in the scions. The suggestion is therefore made that *N. glutinosa* produces nornicotine because, unlike the other species, it demethylates nicotine in its leaves. The suggestion that different stages in the formation of an alkaloid may occur in different organs of the plant is confirmed by the results of Hills, Trautner, and Rodwell (89) with a tobacco-*Duboisia* graft. The *N. tabacum* scion was found to contain not only hyoscine, the normal alkaloid of the *Duboisia* used, but also relatively large amounts of tropine, although every precaution was taken to prevent hydrolysis of the alkaloids during extraction. It might therefore

be supposed that tropine formed in the roots of *Duboisia myoporoides* is normally oxidized and condensed to give hyoscine in the leaves.

Such simple interpretations of the results of grafting experiments, and to a large extent their value in studies of alkaloid metabolism, rest upon the assumption that the two partners in the graft do not materially alter one another. It implies, for example, that the metabolic potentialities of tomato leaves grown upon belladonna roots are precisely the same as those of tomato leaves upon their own roots; that there is no difference in the enzyme equipment, hormone controls, etc., of the two examples. At first sight it certainly seems simpler to suppose that soluble alkaloids, or their salts, pass a graft union readily than to postulate that radical changes take place in the cellular makeup of the stock or scion. The case for the upward movement of nicotine and tropane alkaloids from stock to scion appears to be satisfactorily made, but this does not in itself exclude the simultaneous occurrence of less obvious effects. The formation or non-formation of an alkaloid does not necessarily require a far-reaching alteration of metabolism. It is even possible that a change in the concentration of a single enzyme might deflect the direction of nitrogen synthesis at some key point. The conception of alkaloids, common at the present time, as trivial side products would fit easily with such an idea. Kusmenko and Tikhvinskaya (90) have put forward the view that stock and scion exert mutual influences upon one another to explain their results with various *Nicotiana* species, the influence of the stock usually being the greater. One is given pause, in dismissing this idea as unnecessary, by the fact that very considerable effects of stock upon scion are familiar in horticulture and are even turned to practical account. The dwarfing of apple trees upon Malling IX stocks is perhaps the most familiar of many differences of growth, longevity, fertility, and vigor induced by stocks in fruit-tree scions.

In the opinion of the present writer, more needs to be known about the stock-scion relationship before the results of grafting experiments can be applied to problems of alkaloid synthesis without reservations, and, important as they are, confirmation of their findings by other methods would be very welcome.

V. Translocation

Results of some of the grafting experiments described in the previous section suggest strongly that alkaloids, in particular those of the nicotine and tropane groups, are carried from the root and distributed throughout the aerial parts of the plant. The obvious agent of transport is the transpiration stream, and its participation has been confirmed by Dawson's (82) observations on the sap bleeding from cut stumps of Connecticut tobacco plants. The sap could be seen to exude from the xylem only and contained

0.24 mg. nicotine per ml. The sap exuding from the cut stumps of *Datura stramonium* plants gives a good Vitali-Morin reaction for tropane alkaloids (96). The alkaloids themselves, as distinct from soluble precursors, are therefore moved by this mechanism.

Counter movement outwards from the leaves presents a more difficult and doubtful problem the solution of which is urgently needed for any adequate understanding of alkaloid activities inside the plant. Until the possibilities of movements within the symplast, i.e., the whole body of living cells, is more fully understood, the site of actual alkaloid synthesis must remain difficult to determine with any exactness. Unfortunately, existing evidence still appears conflicting. All investigators are agreed upon one point: that it is impossible to demonstrate the occurrence of alkaloids in sieve tubes, the normal path of symplastic movements. Alkaloidal precipitations can be obtained in the companion cells of *Clivia miniata* and daffodil, and generally in parenchyma adjacent to or penetrating the phloem. Further, it has been agreed that many alkaloids are too insoluble to be translocated, but this cannot be applied to the frequently investigated nicotine and hyoscyamine, or even to the cinchona alkaloids. They have been shown cytochemically to exist in solution in the vacuoles associated with malic, citric and other acids (97). They are readily extractable with water and are soluble in weakly acid solutions such as vacuolar saps, to an extent far exceeding the very low concentrations in which they actually occur, (the concentration of nicotine in leaf fluids of tobacco is 0.012*M*.) (52).

Mothes (64) attempted to solve the problem by means of the half-leaf method originally used by Sachs to demonstrate the translocation of carbohydrates. After removal of one-half of the lamina for analysis, the other half was left attached by way of the midrib to the plant, which was kept in the dark for 6 or 7 days. The amount of nicotine per half-leaf had not changed appreciably at the end of the period, and Mothes concluded that no significant amount of translocation had occurred. This conclusion was obviously suggested by the analogy of carbohydrate behavior and Mothes forgot that the site of alkaloid formation was uncertain. If we suppose that nicotine was entering the leaves by means of the transpiration stream, as in normal plants, then the failure of the amount of nicotine per half-leaf to increase might indicate a corresponding rate of translocation outwards. Since, however, the plants were kept in the dark, the transpiration rate was probably subnormal and translocation may or may not have occurred. In similar experiments with *Cinchona succirubra*, Weevers and van Oort (84) found that attached half-leaves had not increased their total alkaloid after periods of 12 hours. Detached leaves kept in the dark did increase their amount of alkaloid per half-leaf, hence the authors concluded that translocation from the attached leaves had taken place.

It is a general observation that aging leaves lose at least a proportion of their alkaloids while attached to the plant. This could be due to a slow evacuation of soluble alkaloid salts into the stem. It could also be due to breakdown *in situ*, either with or without subsequent transport, of the degradation products. Detached belladonna leaves do break down their alkaloids after a more or less prolonged period of detachment, and similar destruction of nicotine has been observed by Mothes in old tobacco leaves, though Vickery *et al.* failed to observe it in leaves which were, perhaps, younger (99).

Some information may be derived from grafting experiments. When tomato stocks have belladonna (14) or thornapple (96) scions grafted upon them they acquire small but measurable quantities of alkaloids which give the Vitali-Morin reaction, even though the scions themselves form only small amounts of alkaloid. The accumulation of alkaloids, which can be precipitated in the tissues immediately above a graft union, has also been observed, and might be due to a partial interruption of translocation at this point. Cuttings taken from young belladonna shoots rooted in moist sand elaborate alkaloids at a very early stage in cortical tissues at the proximal end of the newly formed roots, adjacent to the original tissues with abundant alkaloids (96). Their early appearance here, as distinct from the more normal position at the tip, suggests a short translocation in the symplast rather than synthesis *de novo*. A rather similar observation has also been made during the germination of Ricinus seeds, where alkaloids disappear from the endosperm and appear in the cotyledons and hypocotyl embedded in it, instead of in the emerging radicle, as is usual in other species.

It is obvious that evidence for or against the movement within the symplast of alkaloids, as such, is still inconclusive. Movements accompanied by partial breakdown with subsequent resynthesis, as happens with proteins and polysaccharides, would also explain the above observations, but such a process appears chemically improbable in some instances.

VI. The Site of Formation

The histological distributions described in Section II suggest strongly that alkaloids are synthesized principally in young, actively growing tissues, whose cells are either completely filled with protoplasm or are rapidly vacuolating. This is shown most clearly during the germination of seeds such as those of barley, tobacco, and opium poppy, which contain no preformed alkaloids. Alkaloids, which can only have been formed *de novo*, appear at a very early stage in the meristematic tissues of the germinating radicle. A corresponding appearance of alkaloids can be observed in stem apices, but as these develop a little more slowly than the radicle, their alkaloid

formation usually lags somewhat behind that of the root. In young belladonna seedlings, however, copious deposits have been observed in the stem apex when the root tip had little or none (15). Belladonna scions grafted upon tomato stocks contain alkaloids which give the Vitali-Morin reaction and which are localized in the stem apices (96). It is conceivable that in these examples the stem tip collects alkaloids preformed in the root meristem or in the initial graft material. Up to the present, the tricky operation of growing excised stem apices in sufficient quantity for alkaloid determinations has not been achieved.

In passing, it is necessary to make clear what is meant by alkaloid formation. If the process is traced back to the entry into the plant of the carbon, hydrogen and nitrogen included in the alkaloid molecule, it is evident that practically every living part of the plant will have had a hand in the matter. It has been found possible to grow isolated *Nicotiana* roots without any shoots attached, and such roots accumulate nicotine (74). To accomplish this, the isolated roots have to be supplied with sucrose, normally provided by the shoot, and with growth substances which presumably also come ordinarily from the same source. Some part of the sucrose is probably required for incorporation via simpler nitrogenous substances into the nicotine molecule. Graft experiments suggest in some instances that alkaloid constituents may be built in different parts of the plant to a relatively late stage of the assembly, although we do not yet know whether this is to be regarded as common or exceptional. Since meristematic tissues are not primary importers of material into the plant, some kinds of nitrogenous and other materials must be transported to them from the absorbing tissues to account for their various syntheses. Supplies for protein formation reach them mainly in the form of sugars, amino acids and amides. Alkaloid synthesis possibly depends on similar materials, but amines and other simple nitrogen bases might also be involved. In referring to meristems as sites of alkaloid synthesis, it is probably with the final fitting together of such compounds that we are concerned, and in this sense it seems that metabolically active tissues such as meristems, glandular tissue, tissue initials, wound and cork cambia, and so on, may be potential alkaloid-formers in whatever organ of the plant — root, stem, flower, etc. — they occur. The actual occurrence of alkaloids in all such tissues has been described in Section II (a). When they fail to form alkaloids, as in *Nicotiana* and *Datura* scions on tomato stocks, we do not yet know whether it is because they fail to receive some essential precursor or because they have suffered some more radical change in their own constitution. In view of the histochemical data, it seems rather unlikely that in more normal circumstances they depend solely upon translocation for the alkaloids deposited in them. This is perhaps clearest in wound cambia arising in tissues

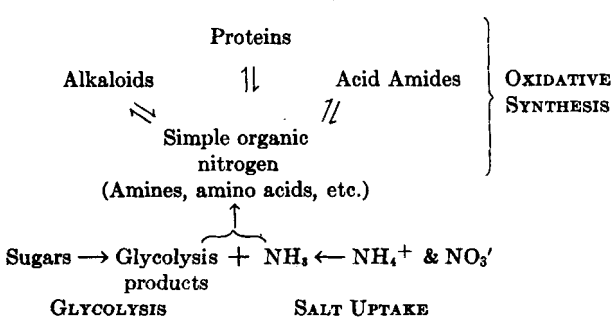
initially more or less free of alkaloids. As soon as local growth begins, the rejuvenated cells develop alkaloids which gradually become apparent in the surrounding cells to increasing distances, presenting a definite impression of new formation in the meristematic cells, followed by movement outwards from them rather than in the reverse direction. The accumulation of alkaloids in 'storage tissues' such as the bark of *Cinchona* spp. and the fleshy roots of belladonna is not an exception to the rule. Careful examination has shown that their alkaloids are found only in the living cells of the secondary growth, and it has never been found that alkaloid accumulation goes on after they have fully developed.

VII. Position in Nitrogen Metabolism

Since the alkaloids contain carbon, hydrogen and nitrogen, they must be ultimately of triple origin. Their carbon comes to them from the air, their hydrogen (and oxygen, if present) comes from the soil water, and their nitrogen comes from solutes of the soil solution. The complete story of their synthesis must include the bringing together of ammonia via the roots with derivatives of carbohydrates from the leaves. No doubt different alkaloids differ very much in the details of their synthesis, but this much they are likely to have in common, and it gears them to the plant's respiration as intimate members of its metabolism.

All plant tissues contain varying quantities of "soluble nitrogen," i.e., relatively simple nitrogenous compounds such as amines, amino acids, and simple nitrogen bases. These may arise by direct synthesis from ammonia and products of glycolysis, or indirectly via consecutive formation and decomposition of proteins. The term "soluble nitrogen" obviously covers a very extensive range of compounds which are likely to vary in kind and quantity within wide limits according to the nature, age, and experience of the tissue concerned. It is among the constituents of this fraction that the precursors of the alkaloids are to be sought.

These generalized relationships indicating the place of the alkaloids in the plant's metabolism are schematically presented in the following diagram.



The alkaloids have frequently been considered to arise through decomposition of the proteins (37, 100, 101). Since the heterocyclic rings characteristic of alkaloid structure do not exist preformed in proteins, this must imply an initial breakdown to soluble nitrogen, followed by a resynthesis. The evidence adduced is usually an observation that alkaloids have increased in amount at a time when protein is breaking down. Weevers (37) gives the following figures for castor oil seeds germinated in the dark.

TABLE 8

SEEDS AND SEEDLINGS OF *Ricinus communis* (37)

	100 Ungerminated seeds testas removed (mg.)	100 Etiolated 3-week seedlings (mg.)	Difference (mg.)
Total nitrogen	1164	1120	−44
Protein nitrogen	1044	750	−294
Ricinine nitrogen	4	72	+68
Residual nitrogen	116	298	+182

The loss of protein nitrogen could have accounted for the gain in ricinine nitrogen, but it is clear that there was also enough residual (soluble) nitrogen originally present in the seed to have done so, apart from that formed by protein breakdown. Weevers spoke of this second alternative as "very improbable." One may agree on the grounds that the residual nitrogen includes many and various substances not all, or even many, of which are likely to be able to serve as ricinine precursors. A clearer result was given by an experiment with young belladonna leaves (96) which were kept in the dark with their cut petioles dipping into a sucrose solution (Table 9 and Fig. 16).

TABLE 9

NITROGEN CONTENT OF 50 DETACHED LEAVES OF *Atropa belladonna* KEPT IN THE DARK AT 25°C.

Days from picking	Total nitrogen in mg.	Protein nitrogen in mg.	Soluble nitrogen in mg.	Alkaloid nitrogen in mg.	Color of leaves
0	200	183	15.4	1.04	Green
1	192	175	15.6	1.01	Green
2	194	179	13.8	1.00	Green
3	184	167	18.6	0.96	1 or 2 Yellow
4	179	126	51.9	1.02	6 or 7 Yellow
5	180	122	59.1	1.15	All yellow, Brown at edges.
7	164	93	73.6	1.10	All yellow, Half brown.

Total nitrogen by micro-Kjeldahl, protein nitrogen precipitated with trichloracetic acid, soluble nitrogen determined in the filtrate, alkaloid nitrogen by the method of Roberts and James (102), titration, and colorimetric assay gave good agreement. *l*-Hyoscyamine was isolated as picrate; m. p. 162° (Oxford Medicinal Plants Scheme, unpublished).

During the first 2–3 days the results show nothing except a small loss of alkaloid, but by the end of the third day a slight loss of protein was accompanied by a corresponding gain of soluble nitrogen. These changes became more rapid during the fourth day and the leaves began to turn

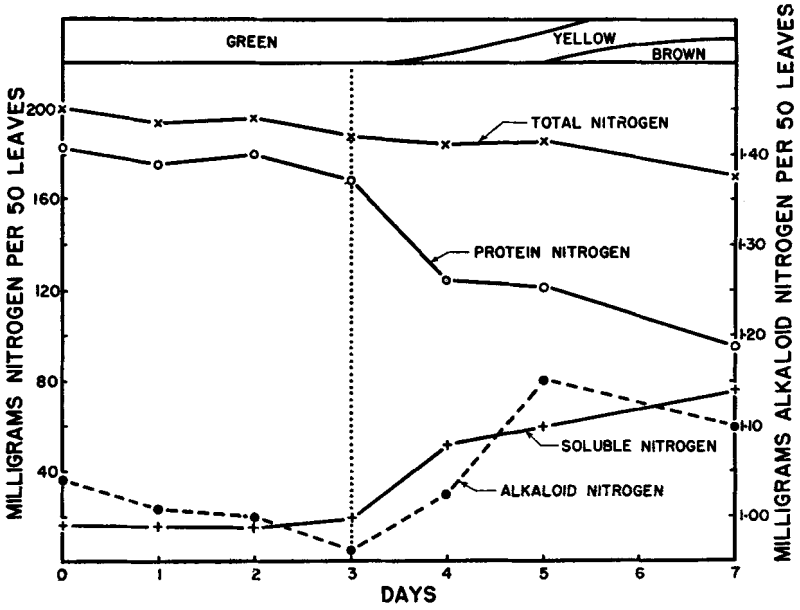


FIG. 16. Behavior of nitrogen fractions in detached belladonna leaves kept in the dark. See Table 9.

yellow. At the same time the amount of alkaloid present began to increase and reached a maximum on the fifth day when the leaves had become completely yellow. The leaves then began to turn brown, i.e., autolysis set in and alkaloid decomposition became apparent. Alkaloid formation coincided with protein breakdown in the living cell.

Although a considerable amount of "soluble nitrogen" was present from the start, no alkaloid synthesis took place until rapid protein breakdown set in. Although this was accompanied by simultaneous breakdown of chlorophyll, it seems unlikely that pyrroles and other decomposition products of chlorophyll are essential, since alkaloid formation occurs commonly in non-pigmented organs. The result indicates clearly that "soluble nitrogen" in general is not necessarily able to serve for alkaloid synthesis, which must have depended, in this experiment, upon a specific compound released by the protein degradation. The alternative possibility, that alkaloid formation could not take place until protein synthesis had ceased to monopolize supplies of available nitrogen, is ruled out by the simulta-

neous rapid formation of both proteins and alkaloids in meristems. Further experiments in which alkaloids have been found to increase in belladonna leaves kept on water or sugar solutions only have been carried out by the author and by Cromwell (103) who used the 'half leaf' method of sampling. While it may therefore be accepted that alkaloids can be formed from proteolytic products, it does not automatically follow that their production invariably requires protein degradation. Generally speaking, alkaloids are most vigorously formed in young tissues which are actively synthesizing proteins, but we do not know at present whether there is any simultaneous decomposition or not. If there were, a relatively low rate of protein breakdown would suffice, since only a very small proportion of the nitrogen present is ever found as alkaloid. Chaze's observations upon tobacco meristems, in which aleurone grains were found to break down to vacuoles containing nicotine, would suggest that in this example at least, the alkaloids arose by proteolysis, even in rapidly-growing cells. Similar observations have not yet been made with other materials. Until more is known of the actual nature of the nitrogenous precursors of alkaloids, it will probably remain impossible to say whether they are invariably derived from proteins or may also arise by direct synthesis.

Whether preceded by protein breakdown or not, the formation of alkaloids from simple soluble nitrogen is likely to be an endergonic synthesis with an overall increase of free energy. It is therefore likely to be integrated with some exergonic phase of respiration and to require the presence of oxygen. Such oxidative syntheses are commonly inhibited by narcosis, as shown by Mothes for the formation of amides (104). Detached *Phaseolus* leaves with an adequate carbohydrate content at first accumulated amides when kept in the dark, but leaves narcotized with chloroform vapor accumulated only amino acids and ammonia. The amides formed in non-narcotized leaves break down on further starvation (105). Protein breakdown occurs whether the leaves are narcotized or not. The similarity between the behavior of these amides (asparagine and glutamine), and the belladonna leaf alkaloids in Fig. 16 is obvious. The effect of narcosis on nicotine formation in tobacco leaves has also been examined by Mothes (64). Only very young leaves were found to accumulate nicotine when kept detached in the dark, and this formation was inhibited in those which were narcotized. Il'in (106) found that etiolated tobacco seedlings narcotized with toluene had also failed to accumulate nicotine after 3 or 4 days, or contained much less than the unnarcotized controls.

Adequate experiments on the effect of withdrawing oxygen do not seem to have been carried out yet. In a small experiment with detached belladonna leaves kept in the dark at 30°C., total alkaloids by the method of Allport and Wilson, were found to have increased slightly after 7 days

in air and to have diminished slightly after 7 days in nitrogen. The leaves in air were fully yellow, those in nitrogen still green, but softening.

A further indication that alkaloid formation from proteins involves a secondary synthesis is perhaps to be found in the fact that sugars appear to facilitate their formation in starving leaves.

VIII. Biosynthesis

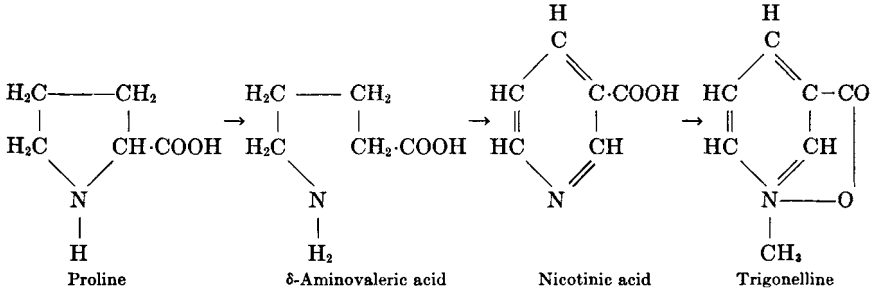
Since alkaloid synthesis in the living plant is frequently preceded by the breakdown of proteins, it is reasonable to assume that alkaloid precursors are to be found among the principal products of protein decomposition, the amino acids and amides. Alkaloid synthesis in the narrower sense may be considered to begin at amino acid level. Among the score of amino acids commonly obtainable from plant proteins, a few suggest themselves on chemical grounds as being particularly likely precursors of alkaloids. The reactions of some, notably proline and ornithine, have been investigated under mild conditions *in vitro* and some possible stages of alkaloid synthesis observed. Unfortunately, such investigations have been referred to as syntheses under physiological conditions, or even as physiological syntheses. To a biologist, the conditions imposed often appear remote from those of the living cell and the proposed reactions unlike the types of reactions already known to occur there. The value of such work in suggesting profitable lines for direct investigation has been considerable, but a final knowledge of the plant's method of alkaloid synthesis can only be derived from the plant itself. Such direct investigations will be referred to here as applied to biosynthesis, as distinct from the so-called physiological syntheses *in vitro*. They are at present in a very rudimentary state and have only been applied to a few of the simpler alkaloids, namely trigonelline, nicotine and *l*-hyoscyamine.

The most frequently used method has been that of the feeding experiment, in which the presumed precursor has been presented to the tissue and analysis made after an interval to detect any increase of the alkaloid. This theoretically simple technique is unfortunately beset with pitfalls, most of which are concerned with the details of sampling. Since alkaloid estimations invariably involve the destruction of the plant or tissue investigated, initial and final determinations cannot be carried out on the same material. The experimenter's ideal tissue, which contains no alkaloid but is capable of forming it under manipulation, has not yet been discovered. It is uncertain whether alkaloid-free scions of alkaloid-forming species come under this heading or not, since they have not yet been induced to form alkaloids in feeding experiments. Identical pairs of plants do not exist in sufficient numbers to be experimentally obtainable. Various bases of com-

parison considered applicable to particular cases have been tried and are best mentioned with the appropriate examples. Other difficulties are involved in securing access of the substance fed to the site of synthesis, in choosing a tissue suitable for handling and at the same time capable of alkaloid synthesis, in providing appropriate conditions, the optima being at present largely unknown, and in maintaining a reasonable degree of freedom from interfering microorganisms. Much preliminary work may also be necessary in working out quantitative methods of alkaloid determination which can be applied to the tissue in question, and in obtaining the often inaccessible compounds required. These purely chemical problems are usually capable of satisfactory solution, but those of sampling may be the cause of serious uncertainty in the results.

1. TRIGONELLINE

Trigonelline is the methylbetaine of nicotinic acid and, as such, is one of the simplest of the alkaloids. Both trigonelline and nicotinic acid are known from a large number of plant sources and may well be of general occurrence. On the basis of results obtained *in vitro*, Trier (101) suggested a synthesis of trigonelline from proline by way of δ-aminovaleric acid, (which has been identified as a product of proline decomposition), and nicotinic acid. Such a scheme, even if it were well founded, would tell us very little about the actual mechanism of the synthesis, but might serve as a starting point of investigation.



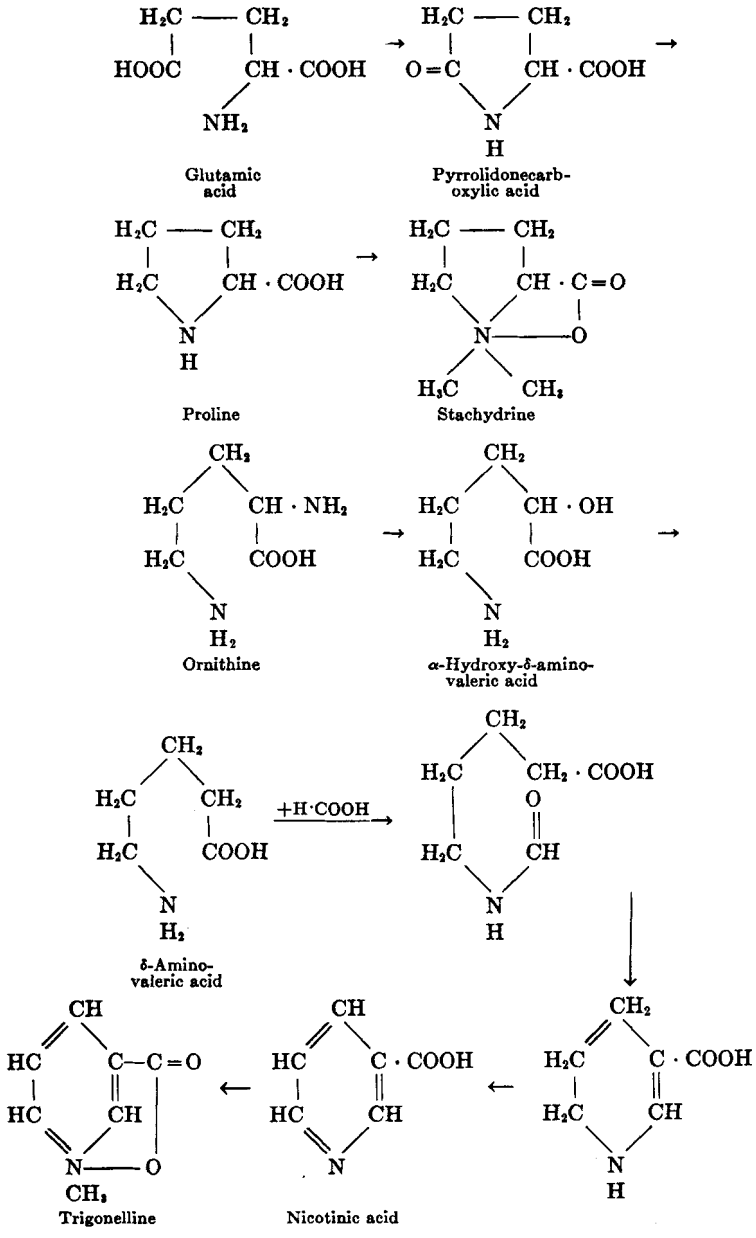
Klein and Linser (107) investigated the synthesis directly by injecting solutions of a number of different amino acids into the hollow stems of *Dahlia* var. Sieg. This they regarded as the most useful technique after trying a number of methods. They considered that their results showed an increased formation of trigonelline after feeding with proline, glutamic acid, pyrolidonecarboxylic acid, ornithine, δ-aminovaleric acid, α-amino-δ-hydroxyvaleric acid, and α-hydroxy-δ-aminovaleric acid. The formation with proline was much increased by addition of urotropine (hexamethylenetetramine) which may have acted as a source of formaldehyde. Negative

results were obtained with ammonium nitrate, alanine, *l*-leucine, citrulline, arginine, tyrosine, aspartic acid, and asparagine. Ornithine and the hydroxy acids might be regarded as alternative sources of δ-aminovaleric acid; and pyrrolidonecarboxylic acid as a transition stage between glutamic acid and proline. Klein and Linser, therefore, constructed the scheme on the opposite page which they regarded as based upon their results.

The conversion of proline to stachydrine was based on experiments with *Stachys palustris* L., *S. recta* L., and *Galeopsis ochroleuca* Lam. (108).

Closer examination of the results leads to serious doubts of the reality of the supposed increases. The method of injecting hollow stems has great advantages from the standpoint of manipulation, but raises serious difficulties in the selection of equivalent samples for treatment. Klein and Linser found it impracticable to select whole plants sufficiently alike for comparison. They were therefore obliged to take what they regarded as equal amounts of stem tissue at the beginning and end of the experiments which lasted 5 or 6 weeks. They point out that the water content of the tissue is subject to considerable fluctuations during periods of this length and that fresh weight is therefore an unsuitable basis for comparison. They therefore made their comparisons on a basis of 100 g. dry weight at the time of sampling, ignoring the possibilities of change in dry weight over the same period. Their comparisons are usually made between milligrams of trigonelline per 100 g. dry weight of stems injected with the chosen amino acid solution and from stems injected with water. It is, however, well known that amino acids frequently stimulate respiration which, by increased consumption of carbohydrate, would be likely to decrease the dry weight of any given piece of tissue. No data are offered by Klein and Linser bearing upon this point, but a simple calculation shows that the presumed increases of trigonelline in their *Dahlia* experiments could sometimes have arisen by rather small reductions of the dry weight. Thus the increased proportion of trigonelline obtained with ornithine could have arisen by a 4% greater loss of dry weight in one experiment and a 24% greater loss in a second experiment as compared with the water control, which, in the circumstances, seems only too possible. The differences observed with proline were greater, and could only have arisen in this way by a 21% greater loss of weight in one experiment and 33% greater loss in another. Except in the experiment with pyrrolidonecarboxylic acid, the final values for trigonelline were always lower than those determined at the start of the experiment, even though higher than the water controls. In one series, where an entirely untreated plant was sampled at the end of the experimental period, its proportion of trigonelline was also found to have fallen to about the same extent as that of the water-injected control. The authors assume that in these circumstances an excess of a treated sample

over the water control, which nevertheless falls short of the initial value, represents a synthesis from the precursor supplied superimposed upon a simultaneous loss. This is perhaps the simplest explanation, but obviously

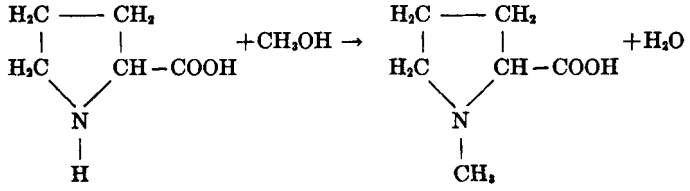


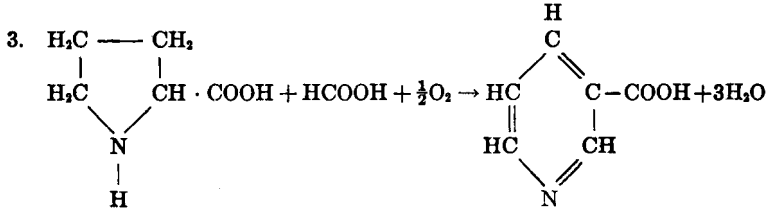
not the only possible one. Further investigation of these very interesting and suggestive results, with improved methods of handling the plant material, is much to be desired.

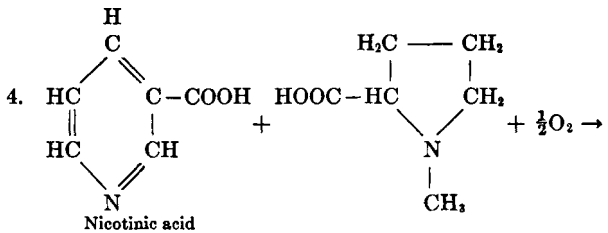
2. NICOTINE

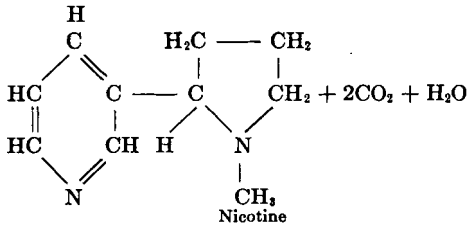
Trier (101) extended his hypothetical suggestions to the formation of nicotine, again taking proline as the amino acid starting point. The only other reactant postulated was formaldehyde, which was supposed to give rise by Cannizzaro reaction to formic acid and methyl alcohol. Proline was supposed to be methylated by the alcohol, and reaction of a second proline molecule with formic acid was presumed to provide nicotinic acid. Nicotinic acid and methylproline were presumed to give nicotine and CO_2 by oxidation.

1. $2HCHO + H_2O \rightarrow HCOOH + CH_3OH$

2. 

3. 

4. 



The feeding experiments of Ciamician and Ravenna (109) can now be considered as of merely historical interest on account of the crudities of their technique and the substances investigated. The only concrete result seems to have been to show that the wounding of tobacco plants might in itself lead to considerable formation of nicotine. Trier's speculations may therefore be considered to have afforded a starting point for subsequent experiments which have been concerned with the effect of proline and related substances.

Klein and Linser (110) applied to two tobacco species, *Nicotiana rustica* L. and *N. havanensis* the methods they worked out when investigating trigonelline and stachydrine formations. They injected 10% proline solutions into leafy stems and determined nicotine contents after 9 and 14 days. In two experiments the leaves wilted, but in the remaining eight experiments the shoots injected with proline remained turgid and had more nicotine per 100 g. dry weight than the corresponding water-injected controls. The differences rose as high as 190% so that they were unlikely to have resulted from simultaneous fluctuations of the dry weight. Single experiments with glutamic acid and ornithine gave more doubtful results. No data were given for the amounts of nicotine initially present in these experiments. Gorter (111) fed cut shoots of tobacco plants with 0.5% proline in diluted Knops solution. Finding in a preliminary experiment that the stems contained little nicotine, he analyzed only the leaves and expressed the results as milligrams of nicotine per square decimeter of leaf surface. He considered this the best basis of comparison in fully grown leaves over short periods such as the 4–5 days in direct sunlight which he employed. On this basis he found that proline-fed shoots gave slightly higher results than the controls, but that both were much lower than the initial value determined on untreated shoots at the start. This was a situation similar to that arrived at by Klein and Linser when considering trigonelline, and is obviously of rather doubtful significance. Gorter's methods of sampling do not really seem to be an improvement upon those of Klein and Linser; he does not present any data to show that leaf area remains any more constant than dry weight, and replicate determinations of milligrams of nicotine per square decimeter of leaf surface from five plants showed wide variations. Most serious of all, he seems to have lumped together leaves of all ages, although Mothes (64) had already shown that young and old tobacco leaves differ markedly in their capacity for alkaloid synthesis, the ability probably being lost at an early stage. It is not surprising, therefore, that expressed on a leaf area basis, Gorter failed to observe experimental increases.

More satisfactory experiments have been carried out by Dawson (112). He raised tobacco plants of commercial varieties and selected groups for

uniformity in height and leaf development. Each experimental unit consisted of 4–6 plants and results were expressed in terms of the milligrams of nicotine present in the total leaf material per plant. Feeding was carried out by allowing shoots to take up the solutions at their cut ends for 96 hours, and the solutions themselves were kept chilled to retard infections. Providing that sufficiently uniform plants can be selected, this represents a definite improvement in sampling technique. The principal results obtained in four successive experiments are summarized in Table 10.

TABLE 10

NICOTINE FORMATION IN LEAVES OF TOBACCO (112): MILLIGRAMS OF NICOTINE PER PLANT.

	a	*b*		*d*
Initial control	79	92	106	62
Water	72	90	94	—
Glucose	—	—	—	50
Glucose + ammonium nitrate	—	—	—	53
Glycine	—	103	—	45
Glutamic acid	74	99	—	—
Pyrrolidonecarboxylic acid	90*	121*	—	—
Arginine HCl	—	—	98	49
α-amino-*n*-valeric acid	—	—	98	—
Proline	—	—	115*	75*
Nicotinic acid HCl	—	—	123*	—
Final controls (rooted)	81	99	121	65
Hours	96	96	96	69

*Nicotine identified as the picrate m.p. 221–222°C.

Proline, pyrrolidonecarboxylic acid and nicotinic acid gave rise to considerably increased amounts of nicotine per plant, not only as compared with the water (or glucose solution) control, but over the amount initially present as well. In view of the later discovery that much of the shoot's nicotine content may normally be derived from the root system, it is impressive that these increases are comparable with and even greater than those found in the "final controls," i.e., in shoots which had remained attached to their roots during the period of the experiment. The evidence for the formation of nicotine from proline and pyrrolidonecarboxylic acid in these experiments seems therefore to be valid. Glutamic acid, arginine, α-amino-*n*-valeric acid and glycine, on the other hand, gave no clear indication of nicotine formation. A complication arises with nicotinic acid on

account of its being a growth hormone. In further experiments, it was noted that shoots exposed to sunlight increased their dry weight when kept on nicotinic acid solutions, instead of regularly losing weight, as on water or amino acid solutions. Proline and pyrrolidonecarboxylic acid caused increases both in the absolute amount of nicotine formed per plant and in its proportion to the general dry weight. A specific effect of these two acids seems therefore assured, but the increase due to nicotinic acid was related to the amount of growth and there was no increase relative to dry weight as compared with the water controls. Its effect might therefore be indirect in stimulating growth rather than direct as precursor. Dawson interprets his experiments done subsequently with tobacco grafts as showing that all the leaf alkaloids come from the roots. He has therefore concluded (112a) that the increases of alkaloid recorded in this experiment must be due to "something other than alkaloid synthesis," a change of mind that to the present writer seems unnecessary. The grafting experiments make it clear that tobacco leaves normally receive alkaloids from the roots; but they do not exclude the possibility that the leaves may themselves form alkaloids when provided with suitable precursors.

In the light of these results, proline appears at the present time to be the most probable amino acid precursor of nicotine. A further origin from glutamic acid via pyrrolidonecarboxylic acid and proline seems more doubtful even though the second step may be possible when the necessary pyrrolidonecarboxylic acid is supplied from outside. Concerning the intermediate stages lying between proline and nicotine, we still know nothing. It should be noted also that an increase of nicotine in tobacco leaves, due to proline, does not prove Trier's hypothesis that it is the only nitrogenous precursor necessary. The provision of any one of several necessary reagents may accelerate a synthesis in a tissue if its rate of formation happens to be normally one of the slowest.

One of the obvious shortcomings of Trier's hypothesis lies in the difficulty of producing the pyridine ring of nicotinic acid from the pyrrolidine ring of proline. No evidence supporting the transition has yet been brought forward. An alternative suggestion, avoiding this difficulty, has proposed that the pyrrolidine component of nicotine arises from the amino-acid ornithine, and the pyridine ring from acetonedicarboxylic acid, formaldehyde and ammonia (113).

Ornithine does not appear to exist as such in plant proteins, but arginine is always found, and might give rise to ornithine by a simple hydrolysis. According to the results described in the preceding pages, neither ornithine (110) nor arginine (112) increases nicotine formation, and the existing evidence gives a preference to proline as the amino acid precursor.

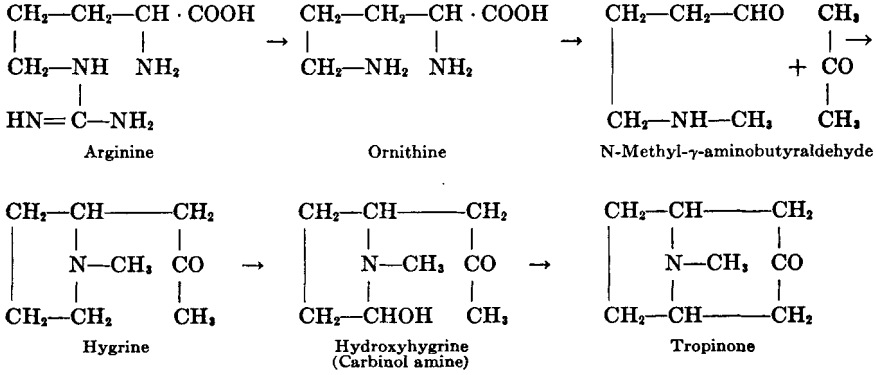
3. NORNICOTINE

Nornicotine, i.e., the non-methylated homolog of nicotine, might be expected to be closely related to nicotine in its method of synthesis. It has been shown that nornicotine accumulates in varieties of tobacco selected for low nicotine content (114) and the inference has been drawn that the productions of nicotine and nornicotine are complementary. This might arise by a simple conversion of one into the other, but according to Smith and Smith (67) who have examined a considerable number of *Nicotianas*, nornicotine tends to be associated with a low alkaloid content and nicotine with a high one. More significant is an observation drawn from grafting *Nicotiana glutinosa* with *N. tabacum* and tomato. Since nornicotine is only produced in any quantity in *N. glutinosa* leaves receiving a supply of nicotine, either from their own or from *N. tabacum* roots, it is suggested that it arises by demethylation of nicotine rather than by an independent synthesis (88). The ability to catalyze the demethylation seems, further, to be a specific property of the leaves and of the one species, *N. glutinosa*, since tobacco and tomato leaves on *N. glutinosa* stocks contain only nicotine.

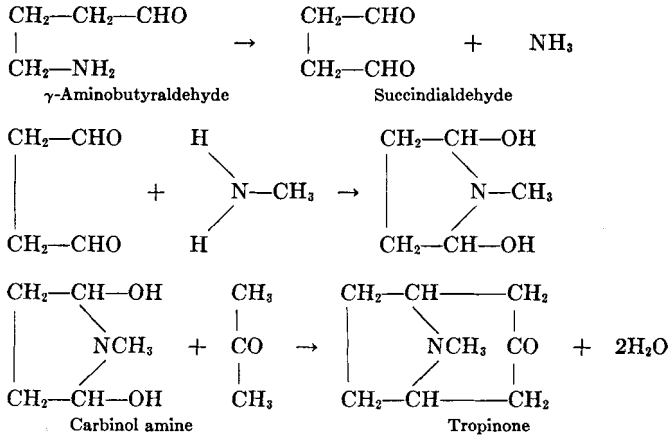
4. *l*-HYOSCYAMINE

Proline and ornithine would also appear to be the most probable amino acid precursors of *l*-hyoscyamine, and, as such, the source of the nitrogen of the tropane nucleus. The biosynthesis of the tropic acid half of the molecule has not yet received attention. Such investigations as have been made up to the present have been based upon Robinson's (113) proposed tropinone synthesis from ornithine plus acetone, and have been principally concerned with the identification of the original nitrogenous precursor.

The proposed synthesis supposes the following sequence of reactions:



Alternatively, further oxidation of the γ-aminobutyraldehyde to succindialdehyde is proposed, followed by condensation with methylamine and acetone.



Hygrine occurs in *Erythroxylon truxillense* Rusby leaves in extractable quantities, but not in those of other tropane-forming species. It could be equally well regarded either as an intermediate substance or an unmanageable side product. Difficulties in realizing its oxidation have led to the suggestion of yet another possible precursor of hyoscyamine in diaminoadipic acid. When this is done the difficulty of the intermediate oxidation disappears, but the origin of the diaminoacid puts another in its place.

Experiments in feeding *Atropa belladonna* with various nitrogenous substances have been carried out by Cromwell (80), who interpreted his results as showing a synthesis of *l*-hyoscyamine from arginine, putrescine, hexamine (hexamethylenetetramine), and formamol (hexamine anhydromethylenecitrate), and not from potassium nitrate, ammonium sulfate, asparagine, glycine, lysine, proline, cadaverine, choline, betaine, mono-, di-, and trimethylamines, succinimide, and urea. Putrescine and formamol were also considered to give positive results in *Datura stramonium*. The solutions were injected into adult plants through cut branches of the *Datura* and cut stems rising from the rootstocks of the belladonna. Stem and leaf samples were taken for analysis before and after the period of injection, which lasted 7 days, and the results were expressed as grams of alkaloid per 100 g. dry weight. No account is given of the means taken to secure comparable samples, or to avoid changes in the non-alkaloidal constituents of the dry weight. Most of the recorded increases of alkaloid relative to dry weight are small and could have arisen by minor differences, e.g., woodiness, in the latter. A rather different method has been employed in

the author's laboratory, in which large numbers of detached leaves were allowed to take up the desired solutions over periods usually lasting for three days. The leaves were selected for uniform age and size and divided into groups of equal number, usually about 30, and equal initial fresh weight. In this way the absolute amount of alkaloid per leaf as well as per 100 g. dry weight can be investigated before and after any desired treatment. Replication of the experiment under standard conditions permits statistical estimation of the experimental error to be made. For estimations of the total alkaloids, principally *l*-hyoscyamine, colorimetric methods (34, 102) have been employed which have been shown to be highly specific and to check well with the official method when applied to belladonna leaves (116). The cut leaves, allowed to take up pure water only, increase their total alkaloid content slightly if they are kept in the dark until they turn yellow (14). In a series of experiments, the increase found was small, but statistically significant, with a probability of more than 50 to 1. Two experiments, terminated before the leaves became yellow, showed no increase of alkaloid. The addition of various nitrogenous substances to the medium increased the amount of alkaloid formed even in experiments terminated before yellowing. The leaves used were fully expanded but still young and in a phase of increasing alkaloid content at the time when they were picked. Leaves picked late in the season showed no ability to form alkaloids even though of similar appearance. On the basis of these preliminary experiments, a further series was designed to test the ability of *l* (+) arginine to act as a *l*-hyoscyamine precursor. Sucrose solution (1–2%) was used as a control medium instead of water, to delay carbohydrate starvation, and because it was found to minimize the ammonia poisoning that developed with unbalanced arginine feeding. In a six-times repeated experiment (32), arginine (0.2 — 0.25%) plus sucrose was found to increase the absolute amount of alkaloid present per leaf or per 100 g. initial fresh weight both over the sucrose control and over the amount initially present. The chances against the result being fortuitous, as calculated by the standard statistical method (*z*-test), were more than 100 to 1. During the experimental periods, the leaves suffered a loss of dry weight, with the necessary result that the amount of alkaloid per 100 g. dry weight increased *a fortiori*. In the following season (96), young leaves injected with arginine plus sucrose solutions by vacuum infiltration showed similar increases of alkaloid. Arginine has been identified in the leaves and roots, both green and etiolated, of belladonna plants, by Cromwell (80). Arginine is hydrolyzed to ornithine and urea by the enzyme arginase. This has been shown to be present in the roots and shoots of belladonna, tomato, and tobacco, in the shoots of *Datura stramonium*, and in belladonna scions grafted upon tomato stocks. It releases urea from arginine itself and from agmatine, the amine produced

from arginine by decarboxylation, but not from arcaine in which the NH_2 is replaced by a second guanidyl group, or from free guanidine (32). Free ornithine has been demonstrated in the press juice of young belladonna sprouts by the paper chromatogram method and feeding young belladonna leaves with ornithine has led to significant increases in the amount of alkaloid per leaf (96).

The formation of γ-aminobutyraldehyde from ornithine involves oxidation and decarboxylation. According to the order in which these reactions took place, the principal intermediate compounds would most probably be α-keto-δ-aminovaleric acid (oxidation first) or putrescine (decarboxylation first). The second alternative has been investigated by Cromwell (117). Relatively large increases of alkaloid per unit dry weight were recorded in his feeding experiments with putrescine, and he was able to isolate it in small quantities from the young parts of *Atropa belladonna* and *Datura stramonium* shoots in August. Putrescine was isolated as the dihydrochloride (m.p. 289°). Benzoylation yielded a product which did not depress the melting point of authentic dibenzoylputrescine.

In a further experiment, it was shown that a 5% glycerol extract of belladonna roots released ammonia from putrescine on incubation at 25°C. for 24 hours in the presence of toluene as antiseptic. Boiling, or a $M/1000$ cyanide solution, completely inhibited the reaction which may therefore be ascribed to an oxidase. A simultaneous increase in carbonyl content in the digests was observed by formation of 2, 4-dinitrophenylhydrazones and estimation of the color produced on adding sodium hydroxide. Carbonyl formation was also suppressed by boiling or by a $M/1000$ cyanide solution. Positive results were obtained with etiolated shoots as well as roots, but not with green leaves.

The origin of the putrescine was not investigated, but attempts in the author's laboratory to decarboxylate ornithine with extracts and tissue slices of belladonna under a variety of conditions have hitherto been uniformly unsuccessful. Using the same methods, glutamic acid is decarboxylated vigorously, but not ornithine, alanine, or glycine. Decarboxylation of glycine would be of interest in connection with Robinson's alternative synthesis as providing a source of methylamine. Cromwell was unable to isolate methylamine from belladonna leaves and roots, either with or without injection of glycine or a variety of other possible sources. At present, there is no direct evidence in favor of its participation in hyoscyamine synthesis.

Oxidation of ornithine with consumption of atmospheric oxygen and release of ammonia is carried out by belladonna preparations (James and Beevers, 117a), and appears to be due to secondary oxidation by the quinones produced by the very active polyphenolase of belladonna tissues.

The oxidation product has been isolated as its 2,4-dinitrophenylhydrazone and corresponds with α-keto-δ-aminovaleric acid. Putrescine, arginine, Manske's *l* (+) acetylornithine (118) and other related amino acids are oxidized much less readily if at all. The same authors have extracted an ornithine dehydrogenase from the young roots of *Datura tatula*. It requires the coöperation of a coenzyme not yet identified, and appears unable to oxidize putrescine and amino acids other than ornithine and to a lesser extent glutamic. Either of these systems, or the two linked into a H-transfer chain, would seem able to catalyze the oxidation of ornithine in the living tissues. No carbon dioxide was released from ornithine by the polyphenolase system; but on addition of an unwashed belladonna tissue-suspension carbon dioxide was liberated, presumably by decarboxylation of the α-keto-δ-aminovaleric acid formed by the oxidation.

The evidence available at the present time suggests that the nitrogen of *l*-hyoscyamine and its allies may be derived from the δ-amino group of arginine and ornithine. Of the further stages of the conversion and of the sources of the other parts of the alkaloid molecule, nothing certain is yet known.

IX. Factors Affecting Alkaloid Formation

1. NUTRITION (119, 120)

a. General. Nutritional conditions affect the general growth of the plant as well as the actual formation of alkaloid. It was pointed out in Section II, 1 *a*, that accumulation of alkaloids occurs during the active growth of juvenile tissues, and it follows that any factor tending to increase its growth will be likely to increase the total formation of alkaloids by an individual plant. Growth is most commonly measured as an increase of dry weight. In considering the effect of plant nutrients upon alkaloid synthesis, it is desirable to give attention both to the effect on "assay," i.e., percentage alkaloid in the dry weight, and to the absolute amount of alkaloid per plant. Further information might be obtained by considering the effect of nutrients upon the ratio of alkaloid nitrogen to total nitrogen, but this has been done only infrequently as yet.

Early work was usually concerned with the effect of farmyard manure and other general fertilizers on the growth of drug plants and their alkaloid assay. Thus Mitlacher and Wasicki (121) found that the yield of *Datura stramonium* was raised from 23 kg. dry weight per 100 square meters to 33 by dunging field plots with farmyard manure, but that no considerable change took place in the assay. Increased formation of alkaloid must therefore have kept pace with the increased growth. This result seems to be of general application: balanced manuring, as with dung or a suitable mixture of artificials, increases growth and alkaloid formation without seriously

disturbing their normal relations. An old observation of Broughton's (122) is, however, of interest as suggesting that things may not always be so simple. He applied farmyard manure to six 3-year-old trees of *Cinchona officinalis* L. by digging it in freely around the roots. He subsequently assayed the bark of treated and untreated trees and found that, whereas the manuring had increased the percentage of quinine, it had markedly reduced the percentage of minor alkaloids. By contrast, manuring with nitrogenous fertilizers such as guano and ammonium sulfate increased the percentage of minor alkaloids as well as of quinine.

b. Nitrogen. Fertilizers that are rich in nitrogen usually produce marked increases of dry weight when applied to alkaloid plants such as *Atropa* (17, 33), *Datura* (123, 124), *Hyoscyamus* (125, 126, 127), *Aconitum* (128), *Lobelia* (129), *Nicotiana* (130), *Cinchona* (131), and *Solanum* (138). *Colchicum* (138) seems to be somewhat less responsive, and even with the other species, nitrogen manuring can be overdone, especially if given in a form which readily tends to liberate ammonia. First-year plants of *Atropa belladonna*, grown in pots containing a poor soil with moderate dressings of nitrogenous fertilizers yielded the following dry weights:

TABLE 11

DRY WEIGHT OF *Atropa belladonna* AFTER NITROGEN MANURING (17)

Treatment 0.75 g. N per pot	Dry weight in grams Leaf	Stem	Root
No added nitrogen	9.8	4.9	23.1
Nitrochalk	23.2	11.9	21.7
Ammonium sulfate	23.6	10.4	22.3
Sodium nitrate	20.9	11.9	35.1
Dried blood	23.2	10.7	25.0

Although all the fertilizers gave increased yields of leaf and stem, ammonium sulfate and nitrochalk (containing ammonium ion) failed to cause any corresponding increase of root growth. At higher concentrations, ammonium sulfate caused an actual stunting even of the shoot, as shown in the following results of a field plot experiment (17).

TABLE 12

Atropa belladonna MANURING WITH AMMONIUM SULFATE (17)

$(NH)_2SO_4$, cwt. per acre	0	1	2	4
Shoots: g. dry weight per plant	26.3	30.3	24.8	24.7

In both these experiments the soil used was calcareous and release of ammonia may have restricted root growth.

The effect of nitrogenous fertilizers upon the alkaloid assay is not quite so obvious, and the earlier results appeared contradictory. Reductions of assay were reported for *Lobelia* (133), and no significant change for *Datura stramonium* (120, 126) and *Aconitum* spp. (128). Various workers reported no change or small increases for *Atropa belladonna* (134, 135, 136, 137) and *Hyoscyamus niger* (126).

A possible reason for these variations emerges from the work of Salgues (138) who found that the response to nitrogen manuring was much affected by the nature of the soil concerned.

TABLE 13

ASSAY OF *Hyoscyamus niger* (BIENNIAL FORM) (138)

Soil	Fertilizer element added			
	None	N	K	P
Silica with lime	0.63	0.40	0.43	0.42
Silica with clay	0.46	0.67	0.45	0.43
Clay with lime	0.42	0.50	0.39	0.45
Silica only	0.55	0.52	0.48	0.44

It is noticeable that an increased assay due to addition of nitrogen is only shown on heavy soils containing clay.

In a considerable number of experiments carried out with *Atropa belladonna* on heavy clay soils near Oxford, increases both of assay and of total alkaloid per plant have been consistently observed following nitrogen manuring (17, 32, 33). On field plots dressed with ammonium sulfate at the rate of one and one-half cwt. per acre, the mean assay rose from 0.44% to 0.48% and in pot cultures with impoverished soils from 0.21% to 0.30% (means of 10). The total alkaloid per plant increased from 17 mg. to 60 mg. Similar increases were found to occur in all parts of the plant and with various sources of nitrogen.

TABLE 14

EFFECT OF VARIOUS NITROGEN TREATMENTS ON THE ALKALOID (AS *l*-HYOSCYAMINE) CONTENT OF *Atropa belladonna* POT CULTURES WITH IMPOVERISHED CLAY SOIL

Treatment	Assay			Mg. alkaloid per plant			
0.75 g. N per pot	Leaf	Stem	Root	Leaf	Stem	Root	Whole plant
No added nitrogen	0.21	0.21	0.31	20.8	10.3	71.6	102.7
Nitrochalk	0.29	0.24	0.45	67.7	28.3	94.6	190.6
Ammonium sulfate	0.30	0.27	0.42	70.8	28.1	93.8	192.7
Sodium nitrate	0.40	0.28	0.39	83.6	33.3	136.9	253.8
Dried blood	0.42	0.24	0.53	97.5	25.6	132.4	255.5

Perhaps the most interesting point in the above result is the contrast between ammonium sulfate and nitrochalk on the one hand and sodium nitrate on the other. All three increase the amount of alkaloid formed, but the nitrate is the most effective, especially in the root. This effect of the nitrate is associated with a considerable increase of root growth (see Table 11) rather than with a specific effect upon alkaloid formation. The effect of the ammonia-containing manures, on the other hand, is associated with a distinct rise in the assay (Table 14), although the growth is actually reduced. This effect becomes still more noticeable with heavier additions of ammonium sulfate even in the shoot, as illustrated by the results of a field-plot experiment given in Table 15.

TABLE 15

Atropa belladonna MANURING WITH AMMONIUM SULFATE (17)

$(NH_4)_2SO_4$ cwt. per acre	0	1	2	4
Shoots: g. dry weight per plant	26.3	30.3	24.8	24.7
Shoots: assay	0.29	0.30	0.35	0.47
Shoots: alkaloids: mg. *l*-hyoscyamine per plant	76.3	90.9	86.8	118.1

At the high levels of ammonium sulfate manuring, the plants were being stunted (reduced dry weight) and the young shoots showed signs of scorch. Nevertheless, the assay and even the total amount of alkaloid per plant were still increasing. Cromwell (103), after watering belladonna plants for 4 months with solutions of ammonium sulfate and nitrates, found that ammonium sulfate had increased the amount of alkaloid per unit of fresh weight in all parts of the plant, whereas the nitrates had not. Injecting ammonium sulfate solutions into growing belladonna plants was found to increase the assay (g. alkaloid per 100 g. dry weight) of leaves and roots by small amounts, whereas corresponding injections of potassium nitrate had no such results. As the behavior of the dry weight could not be determined during the experimental period it is uncertain whether there was any actual synthesis of alkaloids in Cromwell's last experiments or not.

A rather similar effect appears in Dawson's (130) results for Turkish tobacco plants in which higher percentages of nicotine were obtained in sand cultures with ammonium sulfate than in those with sodium nitrate, although the growth and total alkaloid production were greater with nitrate.

Mothes (64) added varying doses of ammonium sulfate to pot cultures of tobacco plants and estimated their nicotine-nitrogen content in relation to total nitrogen and protein-nitrogen. His results are given in Table 16.

From the tendency to increase both the total amount of alkaloid formed and the proportion of alkaloids relative to total solids, it would

appear that the readily available ammonia of ammonium sulfate can be used more or less directly in alkaloid synthesis. Mothes' figures appear to show that excess NH_3-nitrogen in soil tends to increase the percentage

TABLE 16

POT CULTURES OF TOBACCO. NICOTINE IN 50 TOPS (64)

Nicotine N	No added nitrogen	Ammonium sulfate		
		Little	Medium	Much
A. Mg. per 50 tops	3.05	13.8	12.6	11.1
Per cent total N	1.0	1.05	0.9	0.9
B. Mg. per 50 tops	3.05	26	28	18.1
Per cent total N	1.0	1.4	1.4	1.1
Per cent protein N	1.2	1.75	1.7	1.45

A. In culture media. B. In pots of soil.

of the total present in the nicotine molecule and the ratio of nicotine to protein. Nitrates, which are very slowly reduced in the plant, never give rise to an internal excess of ammonia, and so appear to affect alkaloid formation only indirectly through growth, i.e., perhaps by way of prior protein formation followed by degradation. In speaking of the direct effect of ammonia, one might quote the results of short-period experiments in which ammonium sulfate solutions have been fed to detached leaves in the dark. Under these conditions, growth and protein synthesis are reduced to a minimum. To avoid damage from excess free ammonia, it is advisable to add sugar to the medium and this has been done by most experimenters. Dilute solutions of ammonium sulfate and sucrose have been found to increase both the assay and the milligrams of alkaloid per leaf when supplied to cut belladonna leaves, both as compared with leaves sampled at the start and with leaves kept on corresponding solutions of sucrose only. Increases due to ammonium sulfate are never large and are not always observable in these short term experiments with isolated leaves (32, 96). Similar increases observed with *Nicotiana* leaves are so small as to be of doubtful significance also (64, 112).

A very elaborate series of experiments on the field scale manuring of opium poppies grown in India was carried out by Annett (139). Yields of alkaloid were determined by lancing the capsules to exhaustion and determining the total weight of opium (dry weight of the latex), and its percentage of morphine, codeine, and narcotine. Very large increases were recorded in the yield of opium per 1000 capsules on the plots dressed with nitrate of soda, but there was no change in the percentage of any of the three alkaloids in the opium obtained. The method of sampling was dic-

tated by the technical aims of the experiment, but, since the latex of the capsule is known to contain the great bulk of the alkaloids formed by the plant, it seems safe to conclude that, in this species also, the nitrate had increased the yield of alkaloids by way of increasing general growth rather than more directly.

c. Minerals. Improved growth of alkaloid-forming plants has been observed with potassium-, calcium-, and phosphorus-containing fertilizers. The increases are usually not so great as with nitrogen, but may be significant. The type of soil is important, potassium effects being, as usual, most noticeable on light silicious soils.

The influence of these elements on assay and total alkaloid production is more complex, especially with potassium. Changes of assay due to potassium are usually very small and may not reach a level of statistical significance in any one experiment. A number of independent authors have, however, reported small decreases of assay due to potassium fertilizers in the *Atropa — Datura — Hyoscyamus* group. It is noticeable in the data of Table 13 and especially in those for silicious soils. Further results for this group are summarized in Table 17. A reduction of alkaloid-content with rising potassium supply is also reported for *Lupinus luteus* and *L. angustifolius* grown in sand cultures (142). Maurin (143) found relatively large reductions in the assay of pelletierine alkaloids in the root and shoot cortex of pomegranates manured with potassium sulfate for 5 years on a sandy soil.

TABLE 17

EFFECT OF POTASSIUM FERTILIZERS ON MEAN ASSAYS

Species	With potassium	Without potassium	Difference	References
*Atropa belladonna**	0.352	0.345	+0.007	14
	0.464	0.507	−0.043	32
	0.365	0.380	−0.15	96
	0.313	0.330	−0.017	141
Datura stramonium	0.474	0.490	−0.016	126
Hyoscyamus niger				
(annual)	0.146	0.139	+0.007	126
(biennial)	0.147	0.147	0.000	126
Hyoscyamus niger	0.450	0.590	−0.140	138
	0.420	0.440	−0.020	138

* Boshart (124) also records a reduction of assay with potassium for this species.

Where potassium reduces the assay, it also appears to reduce the proportion of the nitrogen that is elaborated into alkaloid, although it increases, if anything, the percentage and total amount of nitrogen present in the plant.

TABLE 18

EFFECT OF POTASSIUM ON THE DISTRIBUTION OF TOTAL NITROGEN AND ALKALOID NITROGEN IN *Atropa belladonna*

	Dry weight g. per plant	Assay	Mg. *l*-hyoscyamine per plant	Total N % dry wt.	G. Total N per plant	*l*-Hyoscyamine-N % total N
Shoots						
With K	65.6	0.272	180	3.05	2.00	0.433
Without K	65.3	0.277	184	2.99	1.96	0.448
Difference	+0.3	−0.005	−4	+0.06	+0.04	−0.015
Thick Roots						
With K	25.4	0.352	81	1.95	0.49	0.900
Without K	24.2	0.395	93	1.87	0.45	1.030
Difference	+1.2	−0.043	−12	+0.08	+0.04	−0.130
Fine Roots						
With K	25.6	0.470	122	2.64	0.67	0.860
Without K	21.8	0.458	101	2.60	0.56	0.853
Difference	+3.8	+0.012	+21	+0.04	+0.11	+0.007

All figures represent means from four separate plants.
Oxford Medicinal Plants Scheme, unpublished data.

Even when potassium causes a reduction of assay, it may not cause a corresponding reduction in the amount of alkaloid per plant, because of the accompanying increase of growth.

In general practice, the *Atropa — Datura — Hyoscyamus* group are considered to need heavy liming to yield a satisfactory crop (144). *Atropa*

TABLE 19

EFFECT OF CALCIUM ON THE DISTRIBUTION OF TOTAL NITROGEN AND ALKALOID NITROGEN IN *Atropa belladonna*

	Dry weight g. per plant	Assay	Mg. *l*-hyoscyamine per plant	Total N % dry wt.	G. Total N per plant	*l*-Hyoscyamine-N % total N
Shoots						
With Ca	65.6	0.272	180	3.05	2.00	0.433
Without Ca	68.8	0.240	166	2.87	1.97	0.409
Difference	−3.2	+0.032	+14	+0.18	+0.03	+0.024
Thick Roots						
With Ca	25.4	0.352	81	1.95	0.49	0.900
Without Ca	28.2	0.299	85	1.63	0.46	0.883
Difference	−2.8	+0.053	−4	+0.32	+0.03	+0.017
Fine Roots						
With Ca	25.6	0.470	122	2.64	0.67	0.860
Without Ca	24.2	0.460	111	2.51	0.61	0.888
Difference	+1.4	+0.010	+11	+0.13	+0.06	−0.026

All figures represent the means from four separate plants.
Oxford Medicinal Plants Scheme, unpublished data.

belladonna is ecologically a rather strict calcicole. Experimental work on calcium under controlled conditions seems, however, to have been rarely carried out. In a series of pot experiments with *Atropa belladonna*, heavy additions of lime to a sandy soil caused increased growth in all parts of the plant and small increases of assay and hence of total alkaloid production (32). In a sand culture experiment with pure salts, the small increases of assay were again observed accompanied also by increases in alkaloid-nitrogen as percentage of total nitrogen except in the fine roots.

The apparent failure to increase growth (dry weight) is surprising at first sight, and may be due to sampling errors which were unfortunately high. On the other hand, it is possible that the effects of heavy dosages of lime, noted in the previous experiment, are due to their well-known physical effects upon the soil texture, and do not occur with the relatively small dosages of calcium salts in pure sand employed in the second experiment.

The contrast between the effects of potassium and calcium upon alkaloid formation suggested by the results summarized above is highly interesting and reaches a satisfactory level of statistical significance in the experiments summarized in Tables 18 and 19. The probability of the difference in assays for thick roots being fortuitous was about one in twenty-five. The interest of the result lies in the fact that potassium is known to favor protein synthesis (145) in plants and calcium to retard it (146), the converse of their effects upon alkaloid synthesis. We therefore arrive at the conception of a competitive formation of protein and alkaloids during

TABLE 20

EFFECT OF PHOSPHORUS ON THE DISTRIBUTION OF TOTAL NITROGEN AND ALKALOID NITROGEN IN *Atropa belladonna*

	Dry weight g. per plant	Assay	Mg. *l*-hyoscyamine per plant	Total N % dry wt.	G.Total N per plant	*l*-Hyoscyamine-N % total N
Shoots						
With P	65.6	0.272	180	3.05	2.00	0.433
Without P	55.7	0.242	135	2.80	1.56	0.419
Difference	+9.9	+0.030	+45	+0.25	+0.44	+0.014
Thick Roots						
With P	25.4	0.352	81	1.95	0.49	0.900
Without P	23.0	0.295	64	1.83	0.42	0.777
Difference	+2.4	+0.057	+17	+0.12	+0.07	+0.123
Fine Roots						
With P	25.6	0.470	122	2.64	0.67	0.860
Without P	18.1	0.500	90	2.60	0.47	0.930
Difference	+7.5	−0.030	+32	+0.04	+0.20	−0.070

All figures represent means from four separate plants.
Oxford Medicinal Plants Scheme, unpublished data.

the growth period with calcium favoring the diversion of nitrogen in the alkaloid direction and potassium in the protein direction.

Fertilization with phosphorus usually increases the formation of the dry weight in plants. In pot cultures of *Atropa belladonna* with sandy soil, small increases were observed in leaves, thick roots, and fine roots. These were accompanied by statistically significant increases of assay and of milligrams of alkaloid in each of the organs (32). The same results were obtained with sand cultures, except that there was a small lowering of the assay in the fine roots. In shoots and fleshy roots, the increased assay and total alkaloid were accompanied by an increase in the alkaloid nitrogen as a percentage of the total nitrogen. (Table 20).

Reductions of assay appear in the results of Salgues for *Hyoscyamus niger* on light soils (Table 13), and the conditions governing these fluctuations are not yet understood.

An increased production of opium (dry latex) per 1000 capsules and of its morphine percentage following additions of phosphorus as superphosphate has also been observed in large scale field experiments with opium poppies in India (147).

2. SOIL ACIDITY

Alkaloid-forming plants are found growing on soils of all acidities from pH 4 to pH 8, but, according to McNair (148), the pH and the percentage of alkaloid-forming genera fall off together. He interprets this as showing a greater ease of alkaloid synthesis under the more alkaline soil conditions, which he attributes in turn to a more efficient uptake of ammonium nitrogen.

TABLE 21

ALKALOID-FORMING PLANTS AND PH OF THE SOIL (148)

(a) pH range	4-5	5-6	6-7	7-8
(b) Number of genera investigated	51	129	54	100
(c) Number of alkaloid-forming genera	2	14	6	15
(d) $\frac{c \times 100}{b}$	3.9	10.8	11	15

McNair assumes also that ammonium nitrogen is more easily built into alkaloid molecules than nitrate nitrogen. Many plants have been found to absorb ammonium ions more effectively than nitrate ions at neutral or at faintly alkaline pH and to reverse the order in the acid range. Exceptions do not appear to be rare (149), however, and until the pH tolerance of alkaloid-formers has been directly investigated, the argument seems somewhat tenuous.

Mothes (64) was not able to observe any effect of pH upon nicotine formation by tobacco plants grown in sand cultures, but Ozerov (131), investigating *Cinchona* cuttings in a variety of soils, found those with alkaline reactions, pH 7.3 — 8.0, the best. He found that alkaline fertilizers, such as potassium phosphate and nitrate, increased growth and alkaloid production both as percentage and as absolute amount. Acid-generating fertilizers, such as ammonium salts uncorrected with lime, reduced alkaloid production. The beneficial effect of liming upon alkaloid formation in belladonna is not necessarily due only to its effect upon acidity, and Stillings and Laurie (141) found better growth and a somewhat higher assay on a series of plots with pH 5.5 — 6.5 than one with pH 6.5 — 7.5.

3. LIGHT

It is evident that light cannot be an essential for the final stages of alkaloid synthesis since alkaloids are habitually formed in roots, and have been found to accumulate in leaves kept in the dark. It is perhaps as well to point out that this does not in itself necessarily exclude formaldehyde as a possible methylating agent since the conditions of its formation in the plant are still uncertain.

Indirectly, light may have considerable influence upon the formation and/or distribution of alkaloids. It has been found by a number of independent investigators that the etiolation resulting from prolonged darkness may be accompanied by a marked increase in the percentage of alkaloid present in the dry matter. Unfortunately, this might result from a number of causes and does not by itself even mean that an increased synthesis has occurred. In darkness, there is rapid respiratory consumption of carbohydrates without any of the normal syntheses depending upon photosynthesis, so that, even if no change occurs in the alkaloids present, they would show a sharp increase as a percentage of the dry weight.

Ripert (150) covered young belladonna shoots sprouting from old rootstocks with dark but aerated boxes for 39 days, by which time they had developed to a flowering stage but become intensely etiolated. The alkaloid per cent dry weight rose from 0.445 to 0.752 in the leaves, whereas in normal leaves nearby it was 0.540. There were similar increases in the young stems. It was, however, significant that protein nitrogen showed an even larger response to etiolation and, if we suppose that owing to carbohydrate starvation the dry weight of the etiolated shoots had fallen 30% behind that of the normal ones, there would be no indication of extra synthesis. Ripert based an opinion that extra synthesis had, in fact, occurred, on histochemical observations. The epidermis of etiolated leaves contained "enormous amounts" of alkaloids even in cells most removed from the

veins, whereas the upper epidermis of normal leaves had none. It is not clear, however, whether this was due to redistribution or to new synthesis. That the effect is an indirect result of the interruption of photosynthesis also seems to be indicated by the observation that similar large increases of assay occur in illuminated belladonna shoots that are devoid of chlorophyll but otherwise apparently similar to normal shoots on the same stock (Author, unpubl.).

Relatively small reductions of light intensity tend to lower the alkaloid assay rather than to increase it. Stillings and Laurie (141) found that belladonna plants grown under aster cloth and under lath that reduced light intensity by 35 and 50% respectively, showed reduction of assay, dry weight, and total alkaloids produced per plant. Unger (151) had previously reported a decrease in assay of 0.35% in shade plants as against 0.40% in sun plants; a simultaneous rise of ash to 15.07% as against 13.34% suggests that in his plants also the dry weight was diminished, as would be expected, and that the total alkaloid formed per plant was therefore reduced as well. The Connecticut practice of shading tobacco fields with light cloth to produce a large thin leaf with low alkaloid assay shows that the same reduction operates in *Nicotiana* (see also Stutzer and Goy (152)). It is possible, but far from certain, that the effect here depends upon a reduced transpiration bringing up less alkaloid from the roots. The observation that in young leaves near the top of the stalk the amount of nicotine per unit dry weight may be increased by shading, may indicate that the reduction of photosynthesis may be more significant than control of transpiration at this level (152). The percentage of nicotine nitrogen in the total nitrogen is reduced by shading at all levels, so possibly some more direct effect of light is indicated.

More satisfactory methods of sampling can be employed with seedlings where the total amount of alkaloid in etiolated and greened seedlings can be compared, as well as the assay. Results available at present suggest that the light effect differs from species to species.

Etiolated *Ricinus* seedlings were found to have a higher percentage of ricinine than normal green ones (153). Weevers (159) realizing the ambiguity of this observation, determined the total amount of ricinine in batches of 300 seedlings three weeks old. He found the normal green seedlings to contain 273 mg. of ricinine and the etiolated ones 422 mg. Since both assay and absolute amount of ricinine are greater in the dark, it seems clear that light interferes in some way or other with its formation.

The formation of lupin alkaloids in the early days of growth seems, on the other hand, to be promoted by light, even though the assay falls on account of the more rapid simultaneous formation of carbohydrate. Thus Sabalitschka and Jungermann (39) recorded 86.2 mg. alkaloid in 2-week-old

seedlings kept in the light and 78.4 mg. in those kept in the dark. The corresponding assays were 0.60% dry weight in the light and 0.85% dry weight in the dark. The increased formation due to light has since been independently confirmed (40) (see Fig. 17).

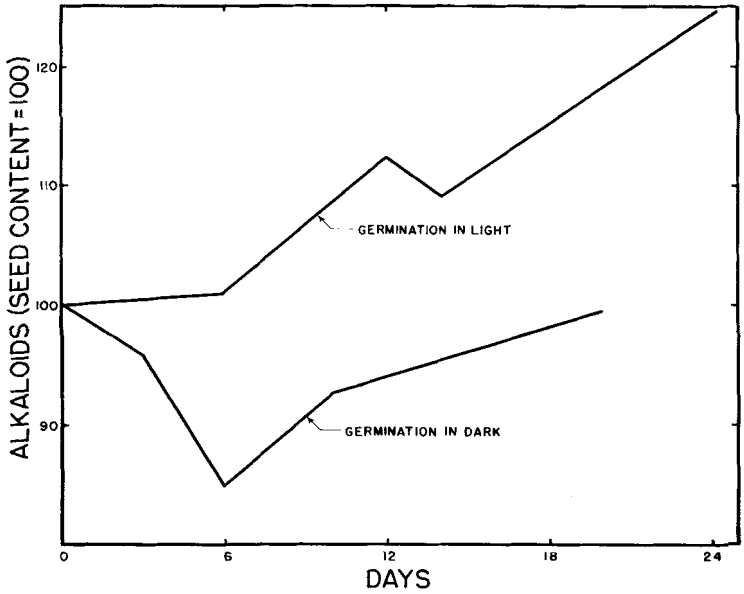


FIG. 17. Alkaloids in *Lupinus luteus* seedlings germinating in the light and in the dark. From Wallebroek (40).

The increased formation of solanine in potatoes exposed to light is a familiar fact and occurs over a wide range of wavelengths (20). Its glycoside constitution might appear to offer an explanation of the effect, but the most effective radiation appears to lie in the ultraviolet rather than in the photosynthetically efficient ranges. Conner (21) found 171% increase over controls with wavelengths around 300 mμ and relatively little with visible radiation.

4. LOCALITY

Many observations have been made upon the effect of locality on the production of alkaloids in plants. As these are mostly incapable of explanation at the present time, and of doubtful validity, only a few characteristic examples are given below. Differences of strain, soil, and climate may all come into the question, but it is rarely that any attempt has been made to evaluate their contributory effects.

Papaver somniferum. The opium poppy, a native of Asia Minor, has been grown at all latitudes from India to Sweden and Australia, and

at altitudes up to 6,500 feet. It has been successfully cultivated in tropical, subtropical, and temperate climates. In the more northern zones, e.g., in North Germany, it is usually grown for its oil rather than its alkaloids, and it is frequently supposed that it needs a warm and sunny climate to produce opium in quantity. Conversely, it has been stated that colder climates produce a more powerful opium, and that the hilly districts of the Himalayas, for example, produce opium richer in alkaloids than the plains of India. There is, however, little experimental basis for such statements.

Opium of high morphine content has been produced in Australia (11.5%, Southern U. S. A. (15.28%), China (11.27%), Japan (10.20%), India (20%), East Africa (14.3%), Algiers (14–17.8%), Egypt (?%), Turkey (12.18%), Persia (8–16%), France (12.1–22.9%), Germany (up to 16½%), and Sweden (12%) (139). The most serious attempt to decide whether locality affects the production of poppy alkaloids was carried out by Annett (139) who grew pure strains of *Papaver somniferum* at a number of stations in the hills up to 6,500 ft. and in the plains around Cawnpore in four successive seasons. He was unable to observe any consistent differences in percentage of morphine in the opium produced in the two types of station. An interesting observation was made by this author when trying to determine whether locality made any difference to the total flow of latex and thus to the total production of alkaloid. The weight per thousand capsules was found to be the same regardless of station, but it was noticed that in the cooler hill stations, more lancings — up to four — were necessary to obtain the full yield. In the plains, the yield of successive lancings of the same capsules fall off very rapidly, and it is therefore plausible to assume that the apparent difference is due to the method of sampling.

There is some evidence that the production of the minor alkaloids, such as narcotine and papaverine, is more dependent upon locality. Narcotine has been reported as absent from opium produced in France and to be particularly abundant (up to 7–11%) in that from Japan (139). It is present in opium from most of the usual sources derived from *Papaver somniferum var. album*, and it is absent from the latex of *P. somniferum var. nigrum*. It is possible that in this instance the locality difference is due to difference of strain. The presence or absence of papaverine, on the other hand, is said to be determined by locality in samples all derived from *var. album*. It has been found in samples from Asia Minor, China, America, France, Persia, and Egypt, and not in those from Bengal, Patna, and Benares. It is, of course, possible, though not in any way proved, that local strains may have been developed in these diverse sites.

Duboisia. Interesting observations have been made on the alkaloids of the *Duboisias* in recent years. *Duboisia myoporoides* contains alkaloids of the tropane group. It has a wide geographical range in Eastern Australia

through New South Wales and Queensland. North of Gosford, N. S. W., latitude 33°21′ S, natural stands produce hyoscine as the dominant alkaloid. Further south large admixtures of hyoscyamine come in (154). The more northerly groups with their almost pure hyoscine have become an important source of this previously rare drug. In a confined locality around Yarraman Queensland, specimens have been obtained which yielded norhyoscyamine in such large quantity as to have become the major alkaloid. Bushes in cultivation have sometimes retained the alkaloid characteristic of their origin, but others have adapted themselves to their locality. Season is also a factor, however, since a bush cultivated at Nambour, Queensland, produced 3% almost pure hyoscine in April and 2% almost pure hyoscyamine in October (155).

Duboisia hopwoodii F. Müll. is conspicuous among Duboisias as producing alkaloids of the nicotine group. Specimens from the central Australian desert have been found to produce almost pure nornicotine, whereas others obtained from Queensland have yielded 5% of almost pure nicotine (155). In Western Australia some stands have also yielded almost pure nicotine and others mixtures of nicotine and nornicotine (156).

X. Metabolic Status

The alkaloids are formed from simpler nitrogenous substances, either with or without the previous breakdown of proteins (see Section VII). Their formation involves a series of upgrade reactions of varying degrees of complexity from the relatively simple dehydrations and methylations suggested for trigonelline to the complexities of multiple ring formation in the higher members. In all of them, some small percentage (usually not more than 1–2%) of the plant's nitrogen is diverted into these elaborately specialized compounds. The causes of this specialization lie deep in the plant's physiology and genetics. The metabolic machinery of a plant producing any given alkaloid evidently differs slightly from that of any other, synthesizing some other alkaloid or none at all. One may speculate that it possesses, or lacks, a particular enzyme which catalyzes a side reaction leading to alkaloid formation. Such an enzyme would probably be itself developed as a result of processes set up by some controlling gene. How extensive such special features would need to be is quite uncertain, since it is possible that some stages of alkaloid formation — methylation for example — might be accidental properties of more normal (widely dispersed) systems. We do not yet know what reactions are involved in the formation of any single alkaloid so that speculations about their complexity are at present useless. The causes of alkaloid formation, i.e., the reasons why some plants form them and some do not, are correspondingly obscure in detail.

Whatever their precise nature may be, these metabolic specializations lead to the accumulation of alkaloids within the vacuoles of living cells in all the different organs of alkaloid-forming plants. There has been a good deal of debate in the past whether the alkaloids once formed can be broken down, or whether their production is irreversible, like that of cellulose. Satisfactory evidence of decomposition by the living plant has now been obtained for the alkaloids of lupin (40), *Strychnos* (42), and castor oil (37) seedlings, for detached leaves of belladonna, and for senescent plants of tobacco (60), lupin (65), and poppy (157, 158). Similar evidence can be brought forward for the purine base, caffeine (37). In view of such evidence, it has comforted some investigators to classify the alkaloids as reserve substances, i.e., as temporary accumulations capable of being returned to metabolic circulation. Before a substance can satisfactorily be called a reserve, it is necessary to show not only that it has been broken down, but also that it has been utilized for further synthesis or energy production. Weevers (159), found that detached leaves of *Ilex paraguayensis* A. St. Hil. increased the absolute amount of caffeine they contained in the dark, but reduced it in light. He inferred that the caffeine was utilized for further synthesis. Clautriau (157) found that when alkaloids were broken down during the ripening of poppy capsules, proteins also decreased. Alkaloid decomposition in detached leaves and during senescence is synchronized with a slow general breakdown. It is hardly likely to contribute to resynthesis at such a time, but could conceivably add its mite to the turnover of energy, which, in these late stages, already appears to be out of all proportion to requirement. Alkaloid decomposition in the reserve tissues of germinating seeds is accompanied by protein formation in the meristems of the embryo. It is, therefore, conceivable that their elements eventually become involved in protein synthesis. Since alkaloids only rarely account at any stage for more than a few per cent of the plant's nitrogen, it is evident that they cannot often be of much importance in this way. To avoid making a mountain out of such a metabolic molehill, most recent investigators, from Clautriau (97, 160) onwards, have preferred to classify the alkaloids as waste products, though only, as Chaze (13), for example, has been careful to say, "to give the thing a name," and not to imply any strictly defined sequence of events. At most stages of the life history the alkaloids are sufficiently stable in plant tissues to be safely regarded as end-products of synthetic sequences. These are by-roads of nitrogen metabolism and any importance they may have to the further existence of the plant must lie outside the strict limits of metabolism itself. Tschirch (162) has picturesquely likened them to flotsam thrown up on a beach. It is, perhaps, worth pointing out that they differ from the waste products of animal metabolism, to which they have been likened, not

merely in being retained within the body of the organism, but, more significantly, in being the final products of complex anabolic (upgrade) sequences.

XI. Consequences of Alkaloid Formation

To classify alkaloids as waste products of metabolism implies that their formation has no further consequences for the plant, and in the strict sense of the term, this implication involves all the difficulties of proving a negative. Towards such a proof it may be pointed out that 90 or more per cent of plants appear to manage very well without ever forming alkaloids and that even those that do form them show no obvious abnormalities when they are grown as alkaloid-free scions. The difficulties of the case become more apparent when it is realized that the full extent of alkaloid distribution is still uncertain, and that the scions may contain small amounts of alkaloid in their meristems.

The sensational effects of alkaloids when introduced into the animal organism operate for the most part upon highly specialized nervous tissue which has no counterpart in the plant. It would be profitless to look for analogous responses, but it does not follow that no others of different kinds exist. A variety of such possibilities have been probed; indeed, the earlier investigators seem to have been unduly preoccupied with such problems to the detriment of more profitable aspects of alkaloid studies.

1. PROTECTION

One of the first suggestions was that alkaloids might serve as a protection against herbivorous animals. Errera (1) upheld this notion because he observed that alkaloids are frequently deposited in relatively high concentrations in peripheral tissues. If alkaloid deposits could be shown to afford such protection in fact, they could be assigned a definite 'survival value' for the species forming them, but this amounts to supposing the elimination of most herbivores incapable of recognizing alkaloid-bearing tissues without eating them, rather a large assumption. Moreover, the toxicity of alkaloids, on which the presumption rests, has proved to be rather surprisingly specific.

Atropa belladonna is a convenient example. A few grams of the fresh tissues are a lethal dose in man, causing paralysis of numerous nerve endings, but farm animals may eat large quantities of the herbage with impunity (56). Rabbits and hares are equally immune (163) and insects thrive upon the young leaves whose alkaloid-content is high. Within the writer's own experience caterpillars of *Pieris rapae* and flea beetles have ravaged crops in cultivation. Caterpillars also freely eat the foliage of *Duboisia* containing 4% of the dry matter as hyoscine (155). The mite, *Tetranychus urticae*,

attacks young plants of *Duboisia myoporoides* and *Duboisia leichhardtii* F. Müll. and may cause serious damage. Greenfly (aphids) and blackfly suck the juices of belladonna stem apices and heavy infestations may destroy the plant if not controlled by vigorous spraying. The attractive berries are largely eaten by birds who, at least, survive long enough to act as very efficient agents of distribution. The introduction of belladonna into a suitable district has resulted in its rapid spread by bird carriage over a considerable area. It is difficult to observe the birds principally responsible, but in the neighborhood of water, the author has watched swans eating berries from the banks.

The effectiveness of quinine in controlling malaria depends upon its specific toxicity to protozoa. It is much less toxic to the host, and appears to be harmless to a variety of animals. *Cinchona* bark is eaten by *Helopeltis* spp. and the caterpillars of *Euproctis flexuosa* (165) and *Attacus atlas*. Examination of the last has revealed crystalline cinchonine in the body and amorphous alkaloids have been found in *Helopeltis bradyi* (165).

Nicotine, in the form of sprays, is a powerful insecticide, but strychnine (167) and the alkaloids of *Conium*, aconite, and cola seeds are said to have little effect. The alkaloids do not seem to be of any great value as fungicides. Moulds flourish on the over-ripe berries of belladonna and its seedlings are extremely easily damped off by *Pythium*. The germination of *Cladosporium fulvum* conidia is not inhibited by dilute solutions of berberine, chelidonine, atropine, or nicotine, although it is by solanine. The high resistance of *Solanum racemigerum* Zodda to attack by *Phytophthora* cannot be shown to be due to its relatively high content of solanine (168) and *Phytophthora* grows upon *Nicotiana* as well as upon tomato and potato tops. It has been shown that solanine accumulates in tissues where they have been infected by bacteria, and in *Solanum dulcamara* L. if attacked by dodder (169). This is also, however, a normal result of aseptic wounding. It does not cause the death of the parasite nor is there any evidence that its presence prevents the invasion of intact cells. Dodder successfully invades alkaloid-containing cells of *Conium* and *Delphinium* (163). In view of such facts, it is not possible to ascribe any great part to alkaloids in controlling the attacks either of animals or plant parasites.

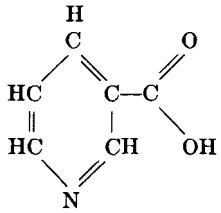
2. DETOXICATION

Since the alkaloids are not poisonous to the plants that synthesize them, it might be suggested that their formation uses up substances whose accumulation might otherwise cause damage. Pictet (170) suggested that the amino acids proline, histidine, and tryptophane fell under this heading, but apparently without showing that they were, in fact, toxic. More

recently, the acid amides, especially asparagine, have been alloted a similar role in "mopping up" free ammonia (171, 172, 173) which is readily shown to be toxic to cells in moderate amounts. Since free ammonia is convertible to some alkaloids, they may at least have some small significance in this way. Their efficiency must be very poor since growth may be stunted in spite of their formation.

3. REGULATION

A heterogeneous collection of substances has been found in recent years to have very marked effects in controlling plant growth. Many of them are indispensable, and if not synthesized by the organism itself, must be obtained from external sources. Nicotinic acid is interesting here because



of the now well-known need for it in plant growth (174) and its relation to nicotine synthesis. Dawson (112) found difficulty in deciding whether nicotinic acid was a precursor of nicotine in tobacco leaves because it so profoundly modified their growth. Nicotine itself does not seem to have any marked effect on the growth of the tobacco plant. The insertion of considerable quantities of nicotine tartrate had no perceptible result upon their growth, as compared with control plants lacerated without insertion of nicotine (189). Addition of nicotine hydrochloride to the culture solution of tobacco plants has been observed, on the other hand, to have a pronounced effect on the rate of uptake of nitrate and on the accumulation of nitrate, amide and ammonium nitrate in the shoots of the plant (97).

Since co-enzymes and prosthetic groups of enzymes include a number of heterocyclic rings, it is possible that the alkaloids are related to them or associated with their formation. Alkaloids might also act as enzyme activators or inhibitors.

Whatever possibilities of this kind exist — and they are many — it must not be forgotten that the majority of plants appear to carry on their existence without either forming alkaloids or obtaining them from external sources. Any part they play is, therefore, unlikely to be universal, although it is conceivable that they take over functions in alkaloid-forming plants which are performed by simpler bases or altogether different substances in other species. If they are to be labelled simply as waste products, it is

necessary to bear in mind that their formation implies the presence of complex synthetic mechanisms whose existence has no 'survival value' for the plant. They represent an unselected experimentalism in the handling of nitrogen which may be reflected in plant metabolism generally. When one recollects the almost infinite range of plant syntheses among polysaccharides, glycosides, pigments and tannins, to name only a few, it becomes difficult to believe that the formation of each of these variants is closely adapted to a specific need. It would appear more probable that we are witnesses to the wealth of possibility in a half-way stage of metabolic evolution, rather than of the end-point of a completed adaptation, where every existing compound is closely knit into an essential relation with every other. Alkaloids are perhaps waste products more in the manner of an experimental model than in the manner of urea in animals.

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CHAPTER III

The Pyrrolidine Alkaloids

LÉO MARION

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I. The Simple Bases

Comparatively few pyrrolidine alkaloids have been found to occur naturally. The parent substance is a constituent of *Daucus carota* L. (2) and is one of the minor alkaloids of tobacco. The presence of pyrrolidine in tobacco was established by characterization of this base (1) through its chloroaurate, $C_4H_9N \cdot HCl \cdot AuCl_3$, bright yellow plates, m.p. 206° (dec) and its chloroplatinate $(C_4H_9N \cdot HCl)_2PtCl_4$, as orange prisms which darken at 190° and melt with decomposition at 199°. It also forms a crystalline hydrochloride which sublimes on heating, and this in turn can be converted to a liquid nitrosamine by treatment with sodium nitrite.

Another minor alkaloid from tobacco (1) and *Atropa belladonna* L., (3) (yielding a chloroaurate, $C_5H_9N \cdot HCl \cdot AuCl_3$, yellow needles, m.p. 190–192°, a chloroplatinate $(C_5H_9N \cdot HCl)_2PtCl_4$, orange needles, and a picrolonate, m.p. 222° (dec) which crystallized in yellow prisms) proved to be *N*-methylpyrroline, identical with that obtained from the reduction of *N*-methylpyrrole with zinc and hydrochloric acid. A hygroscopic hydrochloride has been prepared but its conversion to a nitrosamine could not be realized.

Tobacco (4) and *Atropa belladonna* (3) have yielded a third member of this group. It is a component of the volatile tobacco alkaloids and was recovered from this fraction after the trimethylamine had been removed. Preparation of a number of its crystalline salts and comparison of their melting points by admixture with those from synthetic *N*-methylpyrrolidine completed the identification of this volatile amine. The salts used in this identification were the picrate, m.p. 223–225° (vac), the chloroaurate, m.p. 226° (vac), and the trinitro-*m*-cresolate, m.p. 171.5–172° (vac).

The volatile base, β-methylpyrroline, occurs in black pepper, (*Piper nigrum* L.) (5). The dextrorotatory ($[\alpha]_D = +2.77°$ (water)) hydrochloride crystallizes in long colorless needles and reacts with sodium nitrite yielding an oily nitrosamine. The base has also been converted to its chloroaurate $C_5H_9N \cdot HCl \cdot AuCl_3$, which crystallizes in yellow plates, m.p. 182° and into the chloroplatinate salt, $(C_5H_9N \cdot HCl)_2PtCl_4$, m.p. 216–217°. This base was converted by reduction with tin and hydrochloric acid into β-methylpyrrolidine, a base whose chloroaurate melts at 170–172°, chloroplatinate at 195° (dec), and picrate at 105°.

II. Hygrine

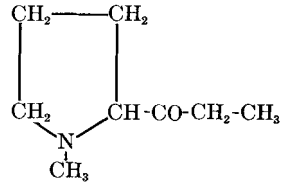
The volatile bases occurring in Peruvian Cusco leaves and those of the Coca plant contain hygrine, a fourth member of this series. An oily base first designated as hygrine by Wöhler and Lossen (6) proved to be inhomogeneous for it was later separated by Liebermann (7) into lower- and higher-boiling fractions. However the name hygrine was retained for the oily base with the lower boiling point (b.p. 193–195°). Hesse (8), another early worker, claimed to have isolated hygrine but the empirical formula which he assigned to his product leads one to doubt the homogeneity of this preparation.

Hygrine is a colorless oil, with a piperidine-like odor, distilling at 193–195° without decomposition, at 92–94°/20 mm., and at 111–113°/50 mm., d_4^{17} 0.935(10). It has always been reported as possessing a very small optical activity but this has recently been shown by Späth and Kittel (11) to be due to the presence of a small quantity of the optically active hygroline. Hygrine has the empirical formula $C_8H_{15}ON$. It forms a picrate, $C_8H_{15}ON \cdot C_6H_3O_7N_3$, yellow needles, m.p. 158° (corr.), and an oxime, (12, 13) $C_8H_{16}ON_2$, m.p. 124–125°, which itself yields a picrate, $C_8H_{16}ON_2 \cdot C_6H_3O_7N_3$, needles, m.p. 159–160°. It can, therefore, be concluded that the oxygen of hygrine is present in a carbonyl group.

1. Structure

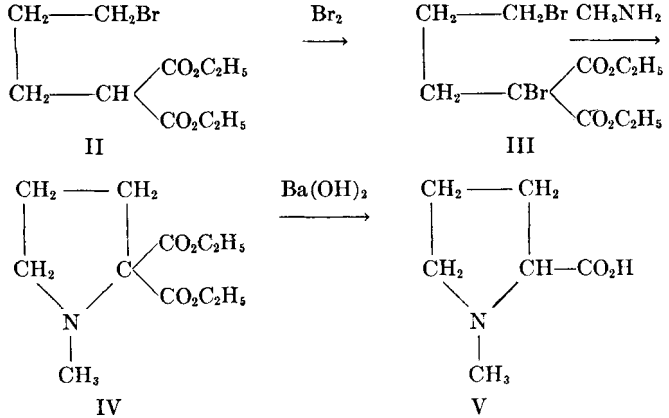
Hygrine when oxidized with chromic acid in sulfuric acid (14), yields hygrinic acid, $C_6H_{11}O_2N$, m.p. 164°, which forms a hydrochloride, m.p.

188°. This was first assumed to be a piperidinecarboxylic acid but comparison with the three synthetic piperidinecarboxylic acids (15) proved this view to be untenable. It was then found that on dry-distillation hygrinic acid gives rise to *N*-methylpyrrolidine(10) from which it was inferred that the C_6-acid is *N*-methylpyrrolidinecarboxylic acid. The ease with which hygrinic acid is decarboxylated placed it in the category of an α-amino acid which prompted the suggestion (10) that hygrine is ethyl α-*N*-methylpyrrolidyl ketone, (I).



I

The above structure for hygrinic acid has been confirmed by synthesis (16). The reaction in the cold of molar amounts of trimethylene bromide and ethyl sodiomalonate yielded ethyl bromopropylmalonate (II) which readily took up another atom of bromine to form ethyl α,δ-dibromo-



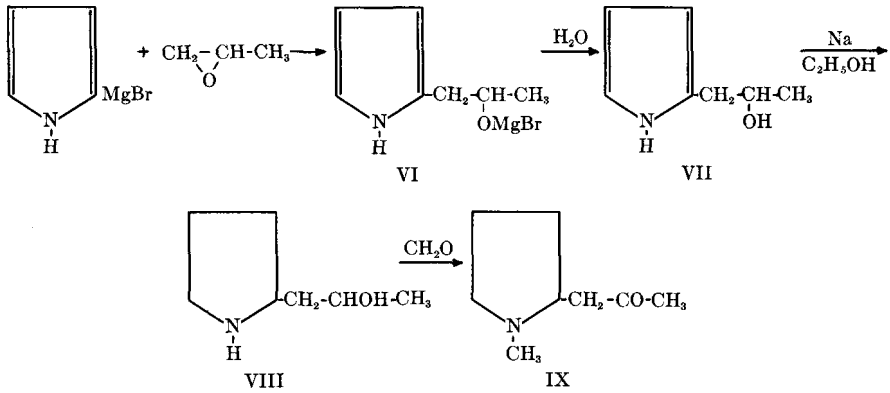
II III IV V

propylmalonate (III). When this was heated with methanolic methylamine it produced a 15% yield of ethyl *N*-methylpyrrolidine-α,α-dicarboxylate (IV) which on heating with barium hydroxide, lost carbon dioxide and gave rise to *N*-methylpyrrolidine-α-carboxylic acid (V), m.p. 164–166°, identical with hygrinic acid.

It is of interest here to note that *l*-hygrinic acid, m.p. 116°, $[\alpha]_D = -80°$ (H_2O), has been prepared by oxidation of *N*-methylnicotone with chromic acid in sulfuric acid (17).

2. Synthesis of Hygrine

The hitherto undetermined question whether the side chain, attached to the pyrrolidine ring in hygrine, is $-CH_2COCH_3$ or $-COCH_2CH_3$ was settled by the synthesis of these two bases by Hess (18). The required starting material for the synthesis of hygrine was obtained as a product of the reaction of α-pyrrylmagnesium bromide with propylene oxide. The main product, (VI), of the reaction when treated with water yielded



1-α-pyrrylpropan-2-ol (VII) which was reduced with sodium and ethanol to 1-α-pyrrolidylpropan-2-ol (VIII). The action of formaldehyde (13, 19) on an acidified aqueous solution of VIII simultaneously methylated the secondary amine and oxidized the secondary carbinol to a ketone. The resulting product, 1-α-*N*-methylpyrrolidylpropan-2-one (IX), b.p. 79–83°/14 mm., was identical with *dl*-hygrine. The picrate of synthetic *dl*-hygrine melts at 176° (corr.).

dl-Hygrine (13). A solution of 2.5 g. of 1-α-pyrrolidylpropan-2-ol in 5 cc. of water is made slightly acid with hydrochloric acid and is heated for 4 hours in a sealed tube at 115–120° with 6 cc. of 40% aqueous formaldehyde. The brown reaction mixture, when cold, is made strongly alkaline and the oily base recovered by steam distillation followed by extraction of the distillate with ether which is then dried over barium oxide. Distillation of the residual oil, after removal of the solvent, gives 2.0 g. of a colorless oil which boils at 79–83° (14 mm.) when distilled from barium oxide.

III. Hygroline

From the mother liquors obtained from the preparation of cocaine, Späth and Kittel (11) isolated a colorless liquid with a strong narcotic odor, which boiled at 78–82° (12 mm.). This, when fractionated, left a small undistilled oily residue which partially crystallized on cooling in dry ice. Recrystallization from petroleum ether yielded colorless needles

melting at 33–34°. This new base, hygroline, is soluble in the usual organic solvents and in water, and is volatile in steam.

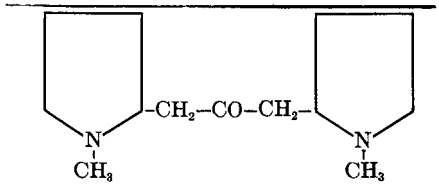
Analytical figures are in agreement with the formula $C_8H_{17}ON$ for this optically active base, ($[\alpha]_D^{23} = -63.2°$ (water)). The formation of acyl derivatives characterized this base as a secondary amine or one containing a hydroxyl group. The acyl derivatives prepared were the 3, 5-dinitrobenzoyl derivative, $C_{15}H_{19}O_6N_3$, m.p. 68°, and the oily benzoyl derivative, b.p. 105–110° (0.003 mm.), which was characterized through its crystalline chloroaurate, $C_{15}H_{21}O_2N \cdot HCl \cdot AuCl_3$, m.p. 114–115° and its chloroplatinate, m.p. 150–152° (dec). That it was a secondary alcoholic hydroxyl that underwent acylation and not a secondary amine was manifest by the chromic acid oxidation of an acetic acid solution of hygroline ($C_8H_{17}ON$) to hygrine ($C_8H_{15}ON$) (characterized as its picrate, m.p. 153–154°). The oxidized base also yielded an oxime, m.p. 124–125° and an oxime picrate, m.p. 159–160°, figures which are again in conformity with those for the respective derivatives of hygrine.

This oxidation of hygroline to optically inactive hygrine characterizes the former as 1-methyl-2-(β-hydroxypropyl)-pyrrolidine (the alcohol of *dl*-hygrine).

IV. Cuscohygrine

Liebermann (7) isolated a low-boiling fraction, hygrine, and a new high-boiling fraction (b.p. 185° (32 mm.)), cuscohygrine from leaves of the Peruvian Cusco and the Coca plant. In his early papers he assigned the formula $C_{14}H_{24}ON_2$ to this base but later revised it to the one accepted today, $C_{13}H_{24}ON_2$.

Cuscohygrine is an oil, b.p. 152° (14 mm.), d_4^{16} 0·9782, $n_D^{18·4}$ 1·48452, which forms a very hygroscopic dihydrochloride, $C_{13}H_{24}ON_2 \cdot 2HCl$, a dinitrate, m.p. 209°, a dihydrobromide, m.p. 234°, an amorphous chloroaurate and an amorphous chloroplatinate. With methyl iodide it produces a methiodide, m.p. 244°. Although pure cusohygrine has never been crystallized, it yields a hydrate, $(C_{13}H_{24}ON_2)_2 \cdot 7H_2O$, crystallizing from wet ether as colorless needles (20), m.p. 40–41°. The base contains a carbonyl group and two methylimino groups.

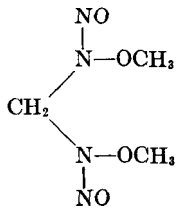


X

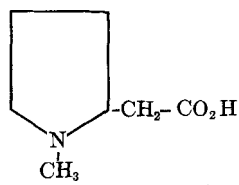
Like hygrine, when oxidized with chromic acid in sulfuric acid, 1 mole of cuscohygrine produces 0.3 moles of hygrinic acid (21) and hence is a

derivative of *N*-methylpyrrolidine. From the foregoing facts, Liebermann (21) assigned structure X to this alkaloid.

The above evidence does not establish the presence of the second pyrrolidine nucleus nor does it diagnose the nature of the oxygen atom in this base. This evidence was presented by Hess and Fink (22) who prepared the oxime, m.p. 53–54°, as well as an α-hydrazone, b.p. 182–183° (14 mm.), and a β-hydrazone, b.p. 119–120° (15 mm.). When treated with phosphorus pentachloride, the oxime does not undergo the Beckmann rearrangement but is recovered unchanged while under more vigorous conditions cuscohygrine is regenerated. The α-hydrazone, when heated with sodium in ethanol at 150–170°, produces an oxygen-free base (10% yield), b.p. 125° (16 mm.), isolated as a dipicrate, $C_{13}H_{26}N_2 \cdot 2C_6H_3O_7N_3$, crystallizing as long needles, m.p. 185°. On the other hand, the β-hydrazone when treated similarly gives rise to a strong base A, b.p. 95–99° (20 mm.), which yields a dipicrate crystallizing as needles, m.p. 203° and possessing the empirical formula of di-(α-*N*-methylpyrrolidyl)-methane, $C_{11}H_{22}N_2 \cdot 2C_6H_3O_7N_3$ which it was assumed to be. Base A was also obtained from cuscohygrine by an entirely different reaction. The degradation of cuscohygrine by Traube's reaction (23) (nitric oxide plus sodium ethoxide) produces a volatile base yielding a dipicrate, m.p. 203°, identical with the picrate of base A obtained from cuscohygrine β-hydrazone. The other products of the reaction are methylene di-isonitramine, characterized as its dimethyl ether XI, and homohygrinic acid, m.p. 95°, the ester of



XI



XII

which yielded a picrate, m.p. 113°. Homohygrinic acid was shown by synthesis to be α-*N*-methylpyrrolidylacetic acid, XII (24, 24a).

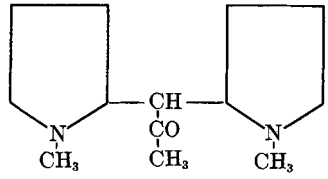
Base A (22). The reaction is carried out in a gas absorption apparatus as described by Traube (23). Thirty grams of cuscohygrine and a solution of 9.5 g. of sodium in 400 cc. of absolute ethanol are introduced into the apparatus and the air is swept out with hydrogen. The nitric oxide (free from water vapor and nitrogen dioxide) which is first introduced is reduced to nitrous oxide, and this is allowed to escape. When all the nitrous oxide has escaped the system is closed and the reaction mixture is cooled in an ice-water bath to maintain the temperature at 10–15°. At the outset the gas is rapidly absorbed (1 liter per minute) under vigorous agitation, but as the reaction proceeds the

rate of absorption becomes progressively slower and at the end of the reaction the mixture is yellow and quite gelatinous in nature. Twenty grams of nitric oxide may be introduced in this way which represents, after recovery of 4.3 g. of cuscohygrine (complete reaction of the cuscohygrine is never attained), about 5.8 mole equivalents of the reagent.

The addition of 30–40 cc. of water to the gelatinous reaction mixture causes separation of a brown, partly crystalline precipitate. To minimize decomposition, the precipitate is quickly filtered, pressed dry and taken up in ethanol. Upon the addition of a little water and gentle warming, the solution separates into a lower dark brown layer (the sodium salt of methylene di-isonitramine) and the upper pale yellow alcoholic solution of base A and the sodium salt of α-*N*-methyl pyrrolidylacetic acid.

The alcoholic solution, freed from the sodium salt of methylene di-isonitramine, is made acid with hydrochloric acid and the alcohol removed under vacuum. The residue is made alkaline, and base A is recovered by digestion of the residue with ether and separation of the ethereal solution which is in turn dried over potassium hydroxide. The residual brown oil, after removal of the solvent, is a mixture of base A and the higher boiling and unchanged cuscohygrine (usually about 4.3 g. (14.3%). Base A may be recovered from this mixture (which is very sensitive to air oxidation) by repeated fractional distillation when it is found to boil at 90–98° (16 mm.); yield, 3.7–4.0 g.

The failure of cuscohygrine to condense with benzaldehyde, ethyl oxalate and amyl nitrite is hard to accommodate on formula X. Because of the formation of two isomeric hydrazones, and on the erroneous assumptions that base A was di-(α-*N*-methylpyrrolidyl)-methane and that methylene di-isonitramine came from a methyl ketone group, Hess and Fink (22) altered Liebermann's formula X so as to represent cuscohygrine as an unsymmetrical di-(*N*-methylpyrrolidyl)-propan-2-one (XIII). It has since been found, however, that base A is not identical with di-(α-*N*-methylpyrrolidyl)-methane prepared by the action of phosgene on pyrrylmagnesium bromide followed by reduction and methylation (25). Moreover,

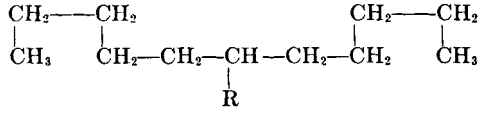


XIII

Sohl and Shriner (24) have refuted the hypothesis that the methylene di-isonitramine from Traube's reaction resulted from cuscohygrine and demonstrated that it arises from the solvent (ethanol), for when methanolic sodium methoxide was substituted for sodium ethoxide, no methylene di-isonitramine was formed.

Although he still adhered to formula XIII the strongest evidence against it was established by Hess himself (26). The reduction of cuscohygrine by means of sodium in ethanol produced a mixture of α- and

β-dihydrocuscohygrine separated by fractional crystallization of the picrates from methanol. α-Dihydrocuscohygrine is a colorless oil, b.p. 160° (16 mm.), d_4^{16}0.9750, n_D^{16}1.48876. It yields a dipicrate, m.p. 127° (less soluble than that of the β-isomer), a dimethiodide, m.p. 261–262°, a dinitrate, m.p. 176–177°, a dihydrobromide, m.p. 210°, a dihydrochloride, m.p. 222° (dec), and a benzoyl ester isolated as the picrate, m.p. 206°. β-Dihydrocuscohygrine is a colorless oil, b.p. 160–161° (16mm.), d_4^{15}0.9692, $n_D^{16.5}$1.48742. It yields a dipicrate, m.p. 215° (dec), a dinitrate, m.p. 209°, a dihydrobromide, m.p. 247°, and a dihydrochloride, m.p. 230° (dec) Oxidation of either α- or β-dihydrocuscohygrine with chromic acid in acetic acid produces cuscohygrine. Degradation of the mixture of the two forms of dihydrocuscohygrine by Hofmann's exhaustive methylation, the product being hydrogenated at each step of the degradation, gave rise to *n*-undecane (XIV, R=H), b.p. 194° (750 mm.) (corr.) $d_4^{16.5}$0.7455, $n_D^{20.2}$1.41842 and *n*-undecan-6-ol (XIV,R=OH), b.p. 111° (12 mm.), m.p. 16°, d_4^{20}0.8334, n_D^{20}1.43740. The identity of these products was established by comparison with synthetic specimens (27).



R=H, OH

XIV

A compound of formula XIII could not give rise directly to *n*-undecane (XIV, R=H) and *n*-undecan-6-ol (XIV, R=OH) and their formation affords the strongest support for Liebermann's formula (X) for cuscohygrine. A synthesis of cuscohygrine, confirming Liebermann's formula X, has recently been reported (27a). It consists in the dry distillation of the salt of (*N*-methyl-α-pyrryl)-acetic acid followed by the catalytic hydrogenation of the 1,3-di-(*N*-methyl-α-pyrryl)-propanone-(2) thus produced.

V. Carpaine

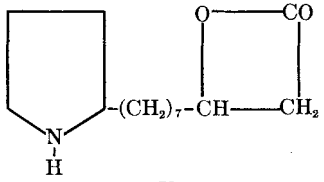
The alkaloid carpaine was discovered by Greshoff (28) in the leaves of the Papaw tree (*Carica papaya* L.) where it was found to occur to the extent of 0.07% in older leaves but is much more abundant (0.28%) in young leaves (29). Merck (30) assigned the formula $C_{14}H_{27}O_2N$ to this alkaloid but van Ryn (31) who investigated the base thoroughly, corrected this to $C_{14}H_{25}O_2N$. Carpaine, b.p. 215–235°, crystallizes from ethanol as colorless rhombs, m.p. 121° (corr.). It is soluble in ethanol, chloroform, and benzene, sparingly soluble in ether and insoluble in water; $[\alpha]_D^{21}+21.9°$

(ethanol). It forms a chloroaurate, $C_{14}H_{25}O_2N \cdot HCl \cdot AuCl_3$, m.p. 205°, and a hydrochloride which darkens but does not melt at 225°. Several other salts have been described (31) but their melting points were not recorded. Ethylation and methylation of carpaine afforded the respective tertiary bases and quaternary salts. Methylcarpaine melts at 71°, ethylcarpaine at 91°, and ethylcarpaine ethiodide at 235°. The formation by carpaine of a nitroso derivative, m.p. 145°, and an *N*-benzoyl derivative, m.p. 100°, demonstrates that it is a secondary amine.

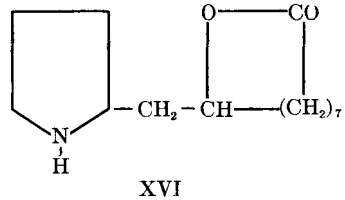
1. Carpamic Acid

Van Ryn's attempts (32) to gain further insight into the constitution of carpaine either by hydrolysis or oxidation failed. Barger (33) found that by heating the base at 130–140° in a sealed tube with 10% hydrochloric acid or on prolonged boiling with this acid that it was possible to isolate the hydrochloride of an amino acid, which crystallized in needles, m.p. 161°. Treatment of this hydrochloride with silver oxide produced the free carpamic acid, $C_{14}H_{27}O_3N$, m.p. 224°. Carpamic acid has been esterified and the ethyl ester forms a crystalline hydrochloride, m.p. 171–172°. Like carpaine, ethyl carpamate yields a nitroso derivative, hence the alkaloid is not a lactam but a lactone. This is further substantiated by the later discovery that carpamic acid is formed not only by the action of acids but also by alkalies in alcoholic solution (34). Since it has not been possible to regenerate carpaine from carpamic acid it is considered unlikely that carpaine is either a γ- or a δ-lactone.

Oxidation of carpamic acid with potassium permanganate or better, with nitric acid, produced an acid which, on the assumption that it was α,δ-dimethyladipic acid, led Barger (33) to the erroneous conclusion that carpaine contained a substituted cyclohexane ring. Subsequent characterization of this oxidation product as a mixture of azelaic and suberic acids (34) demonstrated the presence of a chain of seven methylene groups in this base. Since the dehydrogenation of carpaine with selenium gave rise to



XV



XVI

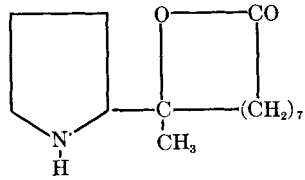
a substituted pyrrole (carpyrine) it was suggested that carpaine consisted of a pyrrolidine ring carrying a side chain terminated by a β-lactone ring (XV) or a much larger lactone ring (XVI). At that time the position of the side chain was not established directly, but was assumed to be attached

to the alpha position since carpamic acid failed to give the isatin color reaction diagnostic for pyrrolidines possessing two unsubstituted alpha positions (35).

Later work by Barger, Robinson, and Work (36) showed that ammonia was evolved when carpamic acid hydrochloride was heated to 320–330° for 7 hours with hydriodic acid, and red phosphorus, and a hydrocarbon, $C_{14}H_{28}$ or $C_{14}H_{30}$, n_D^{17} 1.4325, containing one *C*-methyl group was produced. Exhaustive methylation of carpaine followed by catalytic hydrogenation produces a lactone converted by hydrolysis to a hydroxyisomyristic acid, $C_{13}H_{26}(OH)CO_2H$, containing one *C*-methyl group (estimated by the Kuhn-Roth method). This acid was assumed to be *n*-9-hydroxy-9-methyltridecoic acid since its *p*-phenylphenacyl ester was different from that of the synthetic 8-hydroxy-8-methyltridecoic acid (37). These experiments support the location of the side chain of carpaine in the alpha position of the pyrrolidine ring, for otherwise, if located in the beta position, a second *C*-methyl group would appear in the product resulting from exhaustive methylation and reduction. These requirements of a *C*-methyl grouping and a chain of seven methylene groups make the β-lactone structure, XV, untenable for carpaine.

The successive treatment of carpamic acid hydrochloride with phosphorus pentachloride and potassium hydroxide produced an unsaturated acid, anhydrocarpamic acid which readily absorbed 1 mole equivalent of hydrogen yielding desoxycarpamic acid, m.p. 181°. Oxidation of anhydrocarpamic acid with potassium permanganate gave rise to azelaic acid as well as other small acidic fragments, while ozonolysis provided a minute amount of a monobasic acid which was assumed, on molecular weight determinations, to be $CH_3CO(CH_2)_7CO_2H$ (36).

That carpamic acid contains not a secondary, but a tertiary carbinol was indicated by the action of formaldehyde on this amino acid. Whereas pyrrolidylpropanols, containing a secondary carbinol, are invariably oxidized by this reagent to ketones (13) carpamic acid, on the other hand, yielded only *N*-methylcarpamic acid. The tertiary nature of the hydroxyl



XVII

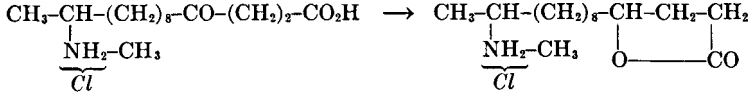
group was further supported by the resistance of carpamic acid to oxidation with chromic acid (36). In the light of the accumulated evidence, Barger, Robinson, and Work (36) favored structure XVII for carpaine.

2. The Synthesis of Carpaine-like Compounds

Although a compound of structure XVII has not been synthesized, several attempts have been made to prepare model compounds related to carpaine. The most interesting of these are 13-methylamino-4-hydroxytetradecoic acid and the corresponding lactone hydrochloride (XXI) (38). These were prepared by converting 4-keto-Δ^{13}tetradeconoic acid (XVIII) to the corresponding bromide (XIX) (hydrogen bromide in toluene). Interaction of XIX with methylamine and then hydrochloric acid gave the hydrochloride (XX) of 13-methylamino-4-ketotetradecoic acid. Re-

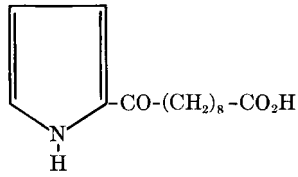
$$CH_2=CH-(CH_2)_8-CO-(CH_2)_2-CO_2H \longrightarrow CH_3-CHBr-(CH_2)_8-CO-(CH_2)_2-CO_2H \longrightarrow$$

XVIII XIX



XX XXI

duction of XX with sodium amalgam and lactonization of the resulting hydroxy acid with hydrochloric acid completed the synthesis of XXI. Whereas carpamic acid and the synthetic hydroxy acid are tasteless,



XXII

carpaine and the lactone, XXI, are intensely bitter. A second model, 2-(ω-carboxynonoyl)-pyrrole (XXII) has been synthesized from pyrrylmagnesium bromide and 9-carbethoxynonoyl chloride. All attempts to reduce the ketone of XXII to an alcohol failed (39).

VI. Stachydrine

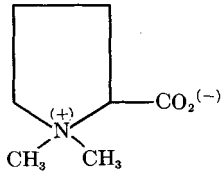
dl-Stachydrine ($C_7H_{13}O_2N$) was discovered in the roots of *Stachys tuberifera* Ndn. by v. Planta and Schulze 40, 41). It also occurs in the leaves of *Citrus vulgaris* Risso (42), in *Betonica officinalis* L. (43, 44) and in the blossoms and leaves of *Chrysanthemum sinense* Sabine (45). The alkaloid "chrysanthemine" which had been reported in *Chrysanthemum cinerariaefolium* Bocc. (46) has since been shown to be inhomogeneous and to consist of a mixture of choline and stachydrine (47). An optically active form of the base, *l*-stachydrine, has been isolated from the leaves of

Citrus aurantium L. (43) as well as from *Galeopsis grandiflora* Lam. (47), alfalfa hay (48), and *Medicago sativa* L. (49).

Stachydrine crystallizes with one mole of water, $C_7H_{13}O_2N \cdot H_2O$ as clear crystals possessing a sweet, unpleasant taste. It is readily soluble in water and alcohol, sparingly so in boiling chloroform, and insoluble in cold chloroform and ether. The anhydrous crystals melt at 235° with rearrangement to the isomeric methyl hygrinate (50). The salts of stachydrine crystallize readily. The hydrochloride, B · HCl, forms large, clear prisms melting at 235°; the chloroaurate, B · HCl · $AuCl_3$, crystallizes as four-sided rhombic plates melting at 225° on rapid heating; the chloroplatinate $(B \cdot HCl)_2PtCl_4 \cdot 4H_2O$ forms large orange crystals melting at 210–220° on rapid heating; the oxalate, B · $C_2H_2O_4$, melts at 105–107° and the picrate melts at 195–196° (50). The specific rotation of *l*-stachydrine hydrochloride in water is −26.5°.

Quaternary salts of hygrinic esters result from the esterification of stachydrine with alcohols and hydrogen chloride. For example ethyl hygrinate methiodide (51) results from the esterification of stachydrine in ethanol and hydrogen chloride followed by replacement of the chloride ion by iodine. Methyl chloride is lost when this intermediate ethyl hygrinate methochloride is pyrolyzed and ethyl hygrinate distils. The methochloroaurate of methyl hygrinate has been prepared from stachydrine in an analogous manner (42). This combined with the thermal isomerization of stachydrine to methyl hygrinate suggested the presence of a potential carboxyl group in stachydrine.

Some of the early reactions applied to stachydrine (42), although somewhat drastic, pointed to the presence of a dimethylamino grouping and a pyrrolidine nucleus in this alkaloid. Fusion of stachydrine with potassium hydroxide liberated dimethylamine while the vapors from the pyrolysis of this alkaloid gave a characteristic pyrrole test. This assumption of a pyrrolidine nucleus in the base is further confirmed by the above conversion of stachydrine into hygrinic acid. Schulze and Trier considered stachydrine to be the methylbetaine of hygrinic acid (XXIII). At about the same time Engeland, in elaborating his scheme for the isolation of



XXIII

amino acids by their conversion to betaines, suggested that the betaine obtained from proline was identical with stachydrine (53, 54, 55, 56). Confirmation of this structure for stachydrine is to be found in the preparation of this betaine from the action of moist silver oxide on the methiodide of ethyl hygrinate (50). An analogous synthesis of *l*-stachydrine was carried out by Karrer and Widmer (17) from *l*-hygrinic acid which was obtained by the oxidation of *N*-methylnicotone.

Experiments (although subject to some criticism) carried out by Klein and Linser (57) would indicate that stachydrine formation in the plant is markedly increased by injection into the hollow stalks of the possible precursor of the betaine. On the assumption that stachydrine could result from simple methylation of proline which in turn might be derived from glutamic acid via pyrrolidonecarboxylic acid, or from arginine via ornithine, injections were made of 1-2 % solutions of proline, ornithine dihydrochloride and sodium glutamate. The experiments carried out on *Stachys palustris* L., *Stachys recta* L., and *Galeopsis ochroleuca* Lam. revealed an apparent increase in stachydrine content as a result of these injections.

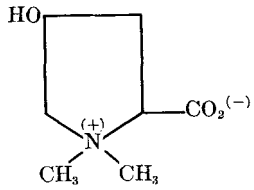
VII. Betonicine, Turicine and 4-Hydroxyhygrinic Acid

Schulze and Trier discovered betonicine, $C_7H_{13}O_3N$, in *Betonica officinalis* L. and in *Stachys sylvatica* L. (43, 58). This alkaloid has a sweet taste, a neutral reaction and is readily soluble in water but difficultly so in cold alcohol. Crystallization from this latter solvent yields short, four-sided, truncated pyramids containing a molecule of water of crystallization, $C_7H_{13}O_3N \cdot H_2O$. These crystals, after drying, melted at 252° (dec) (59) and at temperatures in excess of this produced a vapor which shows an intense pyrrole reaction. It is optically active, $[\alpha]_D - 36.6°$ (water), and forms salts readily. The hydrochloride separates from ethanol as colorless prismatic needles, m.p. 224° (dec) $[\alpha]_D^{15} - 24.8°$ (water), the chloroaurate, clusters of small yellow tablets, melts at 230–232° (dec) and the chloroplatinate, $(B \cdot HCl)_2PtCl_4$, melts at 225–226° (dec).

Betonicine is accompanied in the plant by a dextrorotatory isomeric base which can be separated owing to its lower solubility in alcohol. To designate this base Küng and Trier (60) suggested the name turicine. Turicine crystallizes from ethanol in flat prisms containing one mole of water. It is neutral to litmus, not hygroscopic, has a sweet taste, and gives an intense pyrrole reaction. The hydrated base melts at about 249° while the anhydrous form melts at 260° with frothing. The hydrated base has $[\alpha]_D + 36.26°$ (water) while the anhydrous base has $[\alpha]_D + 40.9°$ (water). It forms a hydrochloride which crystallizes from ethanol in six-sided tablets which melt at 224°; $[\alpha]_D + 25.7°$ (water). The chloroaurate crystallizes

from water in clusters of yellow prisms melting at 230–232° (dec) and the chloroplatinate, $(B \cdot HCl)_2PtCl_4$, melts at 223° (dec).

By using a modification of a reaction discovered by Traube and Lehmann (61, 62), Leuchs, Giua, and Brewster (63) synthesized 4-hydroxyproline from α-carbethoxy-α, δ-dichloro-γ-valerolactone from which Leuchs and Brewster (64) prepared *l*-hydroxyproline by resolution with the aid of quinine. On methylation of a sample of *l*-hydroxyproline thus prepared, Küng (65) obtained a mixture of optically active betaines which he separated by fractional crystallization into a levorotatory betaine identical with betonicine and a dextrorotatory betaine identical with turicine. Betonicine is, therefore, the methyl betaine of 4-hydroxyhygrinic acid (XXIV). Betonicine and turicine possess different solubilities and can be separated



XXIV

by fractional crystallization. They are, therefore, not enantiomorphs but diastereoisomers.

The amino acid of which betonicine is the methylbetaine has been found (59) to occur in the bark of *Croton gubouga* S. Moore, a small tree growing in the Eastern Transvaal. It is present in the bark to the extent of 0.2 to 0.4%. It crystallizes from hot alcohol as colorless needles, or prisms, containing water of crystallization, $C_6H_{11}O_3N \cdot H_2O$. The acid, which is not hygroscopic, melts at 242° (dec). It is optically active, $[\alpha]_D -$ 84.9° (water). When heated to its melting point it gives off a vapor which gives a strong pyrrole test. A boiling aqueous solution of this acid slowly dissolves copper oxide and forms a characteristic blue copper salt, $(C_6H_{10}O_3N_2) \cdot Cu(4–5\ H_2O)$. When methylated the acid gives rise to a mixture of betaines consisting of betonicine and turicine, which proves that it is 4-hydroxyhygrinic acid.

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CHAPTER IV

Senecio Alkaloids

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I. Occurrence and Constitution

Senecio, the largest genus belonging to the Compositae family, comprises over one thousand species, and most of these contain alkaloids. The closely related or perhaps synonymous genus *Erechtites* also consists of species rich in alkaloids. Within the family Boraginaceae, the *Heliotropium*, *Trachelanthus*, and *Trichodesma* genera contain alkaloids which are very similar to those extracted from the *Senecio* plants. *Crotalaria* plants, of the family Leguminosae, also contain alkaloids of the same type. Listed in Table 1 are these closely related alkaloids found in the three different botanical families. All are referred to as "*Senecio* alkaloids" for the sake of brevity. All contain only one nitrogen atom.

Although there are differences in the carbon content, the predominant alkaloids are those which contain eighteen carbon atoms. The hydrogen and oxygen contents of the alkaloids, considered as a series, are subject

TABLE 1

SENECIO ALKALOIDS

Alkaloid	Source	Melting point (°C.)	$[\alpha]_D$
Aureine (identical with Senecionine)			
Campestrine	*S. campestris* D. C. var. maritimus (1)	93	
$C_{13}H_{19}NO_3$			
Carthamoidine	*S. carthamoides* Greene (2, 3)	220–221	−109°[a]
$C_{18}H_{23}NO_5$			
Dicrotaline	*Crotalaria dura* (4)		
$C_{14}H_{19}NO_5$	*C. globifera* E. Mey. (4)	170 (d)	
Douglasiine	*S. douglasii* (2)	206–209 (d)	
Eremophiline	*S. eremophilus* Richards (2)	217–218 (d)	
Fuchsisenecionine	*S. fuchsii* C. C. Gmel. (5)		
$C_{12}H_{21}NO_3$			
Graminifoline	*S. graminifolius* Jacq. (6)		
$C_{18}H_{23}NO_5$			
Grantianine	*Crotalaria grantiana* Harv. (7)	204–205 (d)	50.6°[a]
$C_{18}H_{23}NO_7$			
Hastacine	*Cacalia hastata* L. (7a)	170–171	−72.3°
$C_{18}H_{27}NO_5$			
Heliotrine	*Heliotropium lasiocarpum*		
$C_{16}H_{27}NO_5$	Fisch. and Mey. (8, 9, 10, 11, 12, 13, 14, 15, 16, 17)	125–126	−75°[a]
Hieracifoline	*Erechtites hieracifolia* (L.) Rafin. (18)	227	−89.7°[a]
$C_{18}H_{25}NO_5$			
Integerrimine	*S. integerrimus* Nutt. (19)	172–172.5	4.3°[a]
$C_{18}H_{25}NO_5$			
Isatidine	*S. isatideus* D. C. (1, 6, 20, 21, 22, 23)	145	−8.25°[c]
$C_{19}H_{25}NO_7$	*S. retrorsus* Benth. (1, 20, 21, 22, 23, 24)		
	S. sceleratus (22, 25)		

[a] Chloroform, [b] methanol, [c] water, [d] ethanol — solvent used in determination of specific rotation.

TABLE 1 (*Continued*)

Alkaloid	Source	Melting point (°C.)	$[\alpha]_D$
Jacobine $C_{18}H_{25}NO_6$	*S. jacobaea* L. (1, 26, 27, 28) *S. cineraria* D. C. (1, 28) *S. paludosus* (1)	223–224	$-46.3°$[a]
Jacodine $C_{18}H_{25}NO_5$	*S. jacobaea* L. (26, 27, 28) *S. aquaticus* Hill (1) *S. cineraria* D. C. (28) *S. paludosis* L. (1)	217	$-109.6°$[c]
Jaconine $C_{18}H_{25}NO_8$	*S. jacobaea* L. (26, 27, 28)	146	
Lasiocarpine $C_{21}H_{33}NO_7$	*Heliotropium lasiocarpum* Fisch. and Mey. (8, 11, 13, 29)	94–95.5	$-4°$[d]
Longilobine $C_{18}H_{23}NO_5$	*S. longilobus* Benth. (19)	217–218	$-79.2°$[d]
Mikanoidine $C_{21}H_{29}NO_6$	*S. mikanioides* (Walp) Otto (28, 30) *S. kaempferi* D. C. (31, 32)		
Monocrotaline $C_{16}H_{23}NO_6$	*Crotalaria spectabilis* Roth. (33, 34) *C. retusa* L. (34, 35)	197–198	$-54.7°$[a]
Otosenine $C_{19}H_{27}NO_7$	*C. othonnae* Bieb. (36)	221–222	$20.8°$[a]
Platyphylline $C_{18}H_{27}NO_5$	*S. platyphyllus* D. C. (37, 38, 39, 40, 41) *S. adnatus* D. C. (6, 22, 23, 42) *S. hygrophilus* R. A. Dyer and C. A. Sm. (42, 43)	129	$-56°$[a], $-59°$[d]
Pterophine $C_{18}H_{23}NO_5$	*S. pterophorus* D. C. (6, 22, 23, 24) *S. ilicifolius* Thunb. (6, 22, 23, 24)	227–228	$-88.5°$[a]
Retrorsine $C_{18}H_{25}NO_6$	*S. retrorsus* (23, 26, 30, 43, 44, 45) *S. isatideus* (1, 22) *S. graminifolius* Jacq. (6) *S. glaberrimus* D. C. (1) *S. pterophorus* (6) *S. venosus* Harv. (1) *S. ilicifolius* (6, 23, 24) *S. sceleratus* Schweikerdt (22, 25)	215–216	$-18°$[d]

Riddelliine $C_{18}H_{23}NO_6$	*S. riddellii* Torr. and Gray (19, 46)	195–196	$-109.5°^a$
Rosmarinine $C_{18}H_{27}NO_6$	*S. rosmarinifolius* (6, 22, 23, 24, 47) *S. hygrophilus* R. A. Dyer and C. A. Sm. (43a) *S. brachypodus* D. C. (43a) *S. pauciligulatus* R. A. Dyer and C. A. Sm. (43a)	209	$-120°^a$, $-94°^d$
Sceleratine $C_{18}H_{27}NO_7$	*S. sceleratus* Schweikerdt (22, 25)	180	$54°^d$
Senecifolidine $C_{18}H_{25}NO_7$	*S. latifolius* D. C. (44, 48, 49, 50)	212	$-13.9°^d$
Senecifoline $C_{18}H_{27}NO_6$	*S. latifolius* D. C. (44, 48, 49, 50)	194–195	$28.1°^d$
Senecine	*S. vulgaris* L. (30, 43, 51, 52)	222	$-80.9°^a$
Senecionine $C_{18}H_{25}NO_5$	*S. vulgaris* L. (30, 43, 51, 52, 53) *S. viscosus* L. (43) *S. squalidus* L. (43) *S. aureus* L. (19, 26, 28, 30) *S. ilicifolius* Thunb. (6, 22, 23, 24, 47) *S. pseudo-arnica* Less. (19) *S. integerrimus* Nutt. (19)	232–233	$-56°^a$
Senecphylline $C_{18}H_{23}NO_5$	*S. platyphyllus* D. C. (37, 38, 39) *S. spartioides* T. and G. (19) *S. stenocephallus* Maxim. (37, 38, 39) *S. sylvaticus* L. (1, 5)	217–218 (d)	$-134.2°^a$
Silvasenecine $C_{12}H_{21}NO_4$ or $C_{13}H_{21}NO_3$			
Spartioidine $C_{18}H_{23}NO_5$	*S. spartioides* Torr. and Gray (19)	178	
Squalidine $C_{18}H_{25}NO_5$	*S. squalidus* (43)	169	$-26.9°^a$
Trachelanthamine $C_{15}H_{27}NO_4$	*Trachelanthus korolkovi* Lipsky (56, 56a, 56b, 56c)	92–93	$-18.1°^c$

TABLE 1 (*Continued*)

Alkaloid	Source	Melting point (°C.)	$[\alpha]_D$
Trachelanthine $C_{15}H_{27}NO_5$	*T. korolkovi* (56, 56a)	166–167	−22.5°[c]
Trichodesmine $C_{18}H_{27}NO_6$	*Trichodesma incanum* Bunge (13, 37, 54, 55)	160–161	38°[d]
C_5H_9NO	*S. sarracenicus* L. (1)		
$C_8H_{13}NO$	*S. sarracenicus* (1)		
$C_9H_{15}NO_2$	*S. fuchsii* (5)		
$C_{13}H_{21}NO_3$	*S. sarracenicus* (1)		
$C_{18}H_{25}NO_5$	*S. brasiliensis* (55a)	232–234	66.8°
$C_{18}H_{27}NO_5$	*S. erucifolius* L. (1)	222	
$C_{18}H_{27}NO_5$	*S. palustris* Hook. (1)	169	
$C_{18}H_{27}NO_6$	*S. hygrophilus* R. A. Dyer and C. A. Sm. (43)	175–176	−62.4°[b]
$C_{20}H_{17}NO_6$ or $C_{20}H_{19}NO_6$	*Erechtites hieracifolia* (18)	237 (d)	

to wide variation. In frequent cases, the same alkaloid has been isolated from different species within the same genus. For example, monocrotaline has been isolated from both *Crotalaria spectabilis* Roth. and *Crotalaria retusa* L. and the alkaloid retrorsine has been extracted from as many as

TABLE 2

NECINES

Necine	Parent Alkaloid	Melting point (°C.)	$[\alpha]_D$
$C_8H_{13}NO_2$	Heliotrine	116.5–118	31°[a]
Heliotridine	Lasiocarpine		
$C_8H_{13}NO_2$	Carthamoidine	121–122	50.2°[b]
Retronecine	Dicrotaline		
	Grantianine		
	Hieracifoline		
	Integerrimine		
	Jacobine		
	Jacodine		
	Longilobine		
	Monocrotaline		
	Pterophine		
	Retrorsine		
	Riddelliine		
	Sceleratine		
	Senecifoline		
	Senecionine		
	Seneciphylline		
	Squalidine		
	Trichodesmine		
$C_8H_{15}NO$	Trachelanthamine	liq.	−12.9°
Trachelanthamidine			
$C_8H_{13}NO_3$	Isatidine	212–215	22.4°[c]
Isatinecine			
$C_8H_{15}NO_2$	Hastacine	113–114	−9.1°
Hastanecine			
$C_8H_{16}NO_2$	Mikanoidine		
Mikanecine			
$C_8H_{15}NO_2$	Platyphylline	148–148.5	−56.8°[d]
Platynecine			
$C_8H_{15}NO_3$	Rosmarinine	171–172	−118.5°
Rosmarinecine			
$C_9H_{15}NO_3$	Otosenine		
Otonecine			

[a] Methanol, [b] ethanol, [c] water, [d] chloroform — solvent used in determination of specific rotation.

eight different species of *Senecio*. The *Senecio* alkaloids thus constitute a series of compounds, identical members of which are found in different species of plants within a genus, and related members of which are found in different genera within both the same and different botanical families.

In pharmacological behavior, most of the alkaloids are toxic and have been shown to be responsible for "dunsiekte" (liver cirrhosis) in animals and occasionally for bread poisoning in human beings (32). The plants containing the alkaloids responsible for the disease have been called, in common terminology, "poisonous ragwort" (England), and the disease has been variously termed "horse staggers" and "Molteno disease" (South Africa), "walking disease" (Nebraska, U. S. A.), "pictou" (Canada), "siraskaye" (Norway), and "Winton disease" (New Zealand).

In chemical constitution, most of the *Senecio* alkaloids are alkamine esters. They undergo alkaline hydrolysis to give an alkanolamine (necine) and an acid (necic acid). The nine necines which have been identified are included in Table 2. Not included is senecifolinine, which is probably identical with retronecine (44). Heliotridine has been obtained by cleavage of heliotrine and lasio carpine, alkaloids found in the same plant, *Heliotropium lasiocarpum*. Retronecine has been obtained in the alkaline hydrolysis of many of the parent alkaloids, in fact, in the hydrolysis of alkaloids extracted from plants of different genera: *Senecio, Crotalaria, Erechtites,* and *Trichodesma,* whereas the same parent alkaloid has been obtained only from plants of different species within the same genus. Thus, it is in consideration of the necines that the close alkaloidal relationship of these different genera becomes apparent. Since retronecine is an optical isomer of heliotridine (of which proof will be described in due course) the further relationship of the *Senecio* and other genera with the genus *Heliotropium* is also indicated.

When the *Senecio* alkaloids undergo alkaline hydrolysis, an acid is also formed. The necic acids, as they are called, have been obtained in greater variety than have the necines. One individual necine may constitute the basic moiety of many different alkaloids, but there are only three necic acids which have been shown to constitute the acid moiety of more than one *Senecio* alkaloid. Platynecic acid (also called senecic acid lactone) has been obtained by alkaline hydrolysis of the alkaloids platyphylline and senecionine, jaconecic acid, by hydrolysis of jacobine (from *Senecio* species) and otosenine (from *Senecio othonnae*), and trachelanthic acid, by hydrolysis of trachelanthine and trachelanthamine. The necic acids which have been isolated are listed in Table 3. The majority of the acids contain eight or ten carbon atoms, and a number of these are isomeric but apparently not identical. Hydrolytic cleavage of certain of the alkaloids gave necic acids and other acids as well: simple, low-molecular-weight acids of known structure. *Racemic* lactic acid was obtained by alkaline hydrolysis of trichodesmine (55). Angelic acid (*trans*-2-methyl-2-butenoic acid) was obtained by alkaline hydrolysis of lasiocarpine (29). Senecioic acid (3-methyl-2-butenoic acid) was isolated during the extraction of mika-

TABLE 3

NECIC ACIDS

Necic acid	Parent alkaloid	Melting point (°C.)	$[\alpha]_D$
C_6 Acids			
$C_6H_{10}O_5$ Dicrotalic	Dicrotaline	109	
C_7 Acids			
$C_7H_{12}O_2$	Trichodesmine		
$C_7H_{14}O_4$ Trachelanthic	Trachelanthine Trachelanthamine	93–95	
C_8 Acids			
$C_8H_{12}O_5$ Monocrotalic	Monocrotaline	181–182	−5.3°[a]
$C_8H_{16}O_4$ Heliotrinic	Heliotrine	92.5–94.5	−12°[a]
$C_8H_{16}O_5$ Lasiocarpinic	Lasiocarpine	95–97	10.6°[b]
C_{10} Acids			
$C_{10}H_{14}O_4$ Senecic acid lactone *or* Platynecic acid	Platyphylline Senecionine	154–155	41.8°[b]
$C_{10}H_{14}O_4$ Squalinecic	Squalidine	129	
$C_{10}H_{14}O_5$ Carthamoidinecic	Carthamoidine	117–118	−10.8°[a]
$C_{10}H_{14}O_5$ Longinecic	Longilobine	126	
$C_{10}H_{14}O_5$ Sceleranecic	Sceleratine	156	−9.3°[a]
$C_{10}H_{14}O_5$ Seneciphyllic	Seneciphylline	140–141	0.0°[b]
$C_{10}H_{14}O_6$ Riddellic	Riddelliine	102–103	−2.6°[b]
$C_{10}H_{14}O_7$ Grantianic	Grantianine		
$C_{10}H_{16}O_5$ Hastanecinic	Hastacine	148–149	4.6°
$C_{10}H_{16}O_5$ Hieracinecic	Hieracifoline	132	
$C_{10}H_{16}O_5$ Integerrinecic	Integerrimine	151	
$C_{10}H_{16}O_5$ Senecic	Rosmarinine	151	11.8°[b]
$C_{10}H_{16}O_5$	Jacodine	136–137	
$C_{10}H_{16}O_6$ Isatinecic	Isatidine	148.5	88.2°[a]

[a] Water, [b] ethanol — solvent used in determination of specific rotation.

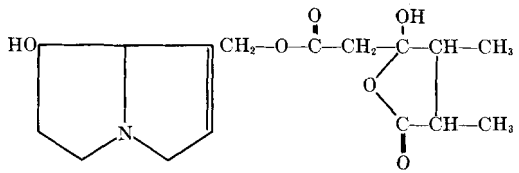
TABLE 3 (*Continued*)

Necic acid	Parent alkaloid	Melting point (°C.)	$[\alpha]_D$
$C_{10}H_{16}O_6$ Jaconecic	Jacobine Otosenine	182	31.7°
$C_{10}H_{16}O_6$ Pterophnecic lactone	Pterophine	166.5	−17.7°[a]
$C_{10}H_{16}O_6$ Retronecic	Retrorsine	177	−11.4°[b]
$C_{10}H_{16}O_6$ Senecifolic	Senecifoline	198–199	28.4°[b]
C_{13} Acids			
$C_{13}H_{16}O_5$ Mikanecic	Mikanoidine	240	

noidine (28, 30), but it appears not to have been in ester combination with the alkanolamine portion. This acid, as its common name would indicate, has long been known to be present in Senecio plants (31, 32). It has not been found in combination with a necine but has always been isolated independent of the plant alkaloid.

II. Extractive and Degradative Procedure

Of all the *Senecio* alkaloids, the structure of monocrotaline is known with most certainty as a result of the work of Adams and his co-workers over a period of five years or more. The alkaloid monocrotaline (I) is the ester of retronecine with monocrotalic acid. The structure of the necine portion has been proved conclusively, while the structure of the necic acid portion is considered the most likely of three possible configurations. The position of attachment of the two portions is known with certainty. The



I

extraction of monocrotaline from *Crotalaria spectabilis* (34) will serve as an example of the general type of extractive procedure used successfully with most of the *Senecio* alkaloids.

Extraction of monocrotaline from Crotalaria spectabilis

Two kilograms of Florida grown *Crotalaria spectabilis* seed ground to 16-mesh was extracted continuously for 72 hours with 95% ethanol. The extract was acidified to congo paper with citric acid, the solvent was removed *in vacuo*, and the residue was taken

up in 400 cc. of water. The suspended fat was extracted with successive portions of ether until the ether extracts were colorless, and finally with two 100-cc. portions of chloroform. The aqueous solution was then treated with 200 cc. of chloroform and with saturated aqueous sodium carbonate solution until the aqueous layer was distinctly alkaline to litmus. After exhaustive extraction of the aqueous layer with chloroform, the combined chloroform extracts were evaporated to dryness *in vacuo*. The crude alkaloid residue was recrystallized twice from absolute ethanol to obtain monocrotaline in pure form; yield, 65 g. (3.2%).

Alkaline hydrolysis of the alkaloids has been employed as a useful degradative tool in the study of most of the alkaloids of the *Senecio* type, since hydrolysis gives the necine and necic acid (or modified necic acid) portions which constitute the parent alkaloid. The other general degradative procedure which has been exceedingly useful is that of hydrogenolysis of the alkaloid to give a modified necine and necic acid. The alkaline hydrolysis and the hydrogenolysis of monocrotaline by Adams and Rogers (34) will serve as examples of these two general types of cleavage reactions employed in the study of the *Senecio* alkaloids. Alkaline hydrolysis of monocrotaline gave retronecine, monocrotic acid, and carbon dioxide; hydrogenolysis gave retronecanol and monocrotalic acid.

Alkaline hydrolysis of monocrotaline

Monocrotic acid, $C_7H_{12}O_3$. A mixture of 20 g. of monocrotaline and 40 g. of barium hydroxide octahydrate in 250 cc. of water was refluxed for one hour. After cooling, the solution was saturated with carbon dioxide and the barium carbonate was filtered. The filtrate was made just acid to congo red with hydrochloric acid and was then submitted to continuous extraction with ether for twelve hours. The ether extract was dried, the ether was removed, and the residue was distilled *in vacuo* at 145–146° (18 mm.); yield, 4.2 g. (48%).

Retronecine hydrochloride, $C_8H_{13}NO_2 \cdot HCl$. The aqueous solution obtained after ether extraction of monocrotic acid was evaporated to dryness *in vacuo*. The sirup thus obtained was dissolved in 100 cc. of absolute ethanol and the solvent was removed by evaporation. A crystalline mass resulted and this was extracted with three 30-cc. portions of boiling absolute ethanol to separate the alkaloid salt from barium salts. The combined ethanolic extracts were concentrated to 20 cc. and allowed to cool. The salt, retronecine hydrochloride, separated and the filtrate yielded an additional amount by the addition of ether. Recrystallization from absolute ethanol gave white prisms, m.p. 161–162°; yield, 10.3 g. (87%).

Hydrogenolysis of monocrotaline

Monocrotalic acid, $C_8H_{12}O_5$. A solution of 10.8 g. of monocrotaline in a mixture of 10 cc. of glacial acetic acid and 40 cc. of ethanol was hydrogenated at 2–3 atm. with 0.1 g. of platinum oxide catalyst. Two moles of hydrogen were absorbed in 5 hours. The solution was filtered from the catalyst and evaporated *in vacuo*. The remaining sirup was taken up in 34 cc. of 1 *N* hydrochloric acid and the aqueous solution thus obtained was extracted continuously with ether for 24 hours. The ether solution was dried, the ether was removed, and the crystalline residue of monocrotalic acid was purified by recrystallization from acetone-petroleum ether (b. p. 30–60°); white plates, m.p. 181–182°.

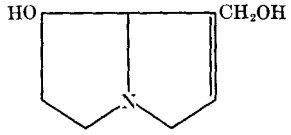
Retronecanol, $C_8H_{15}NO$. After extraction of the monocrotalic acid with ether, the aqueous solution was clarified with norite, filtered, and made strongly alkaline with sodium hydroxide. The solution was then extracted with five 50-cc. portions of ether. The combined ether extracts were dried. When the ether was removed, the oily basic residue solidified. It was best purified by distillation; b.p. 140° (30 mm.); white crystals, m.p. 95–96°.

These illustrations may be regarded as typical experimental procedures for the extraction, hydrolysis, and hydrogenolysis of a *Senecio* alkaloid. In order to assign a structure to a particular *Senecio* alkaloid, it is first necessary to prove the structure of the portions obtained on hydrolysis and hydrogenolysis of the alkaloid. Accordingly, the structure of the necines and necic acids will be considered before that of the parent alkaloid, which is necessarily represented by their combination.

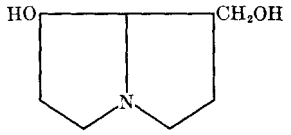
III. Structure of the Necines

1. Heliotridine, Retronecine, and Platynecine

These three necines will be considered together because their structures have been thoroughly established and because they are so closely related. Heliotridine and retronecine are stereoisomers and both are represented by the structure II. Platynecine has the structure III. The necine isolated



II



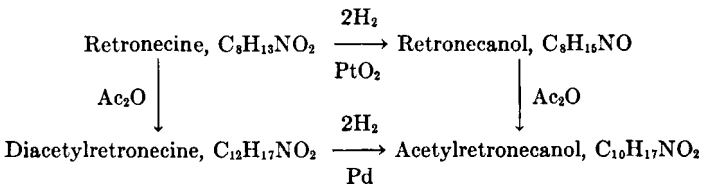
III

on hydrolysis of the alkaloid senecifoline (from *Senecio latifolius*) and first named senecifolinine (48) has since been identified as retronecine (44). The comparison was not direct, but the identity was established on the basis of the identity of the melting points of the hydrochloride and aurichloride salts, the specific rotations of the hydrochloride salts, and the correct elementary analyses. Similarly, trichodesmidine was originally regarded as a new necine when it was isolated from the hydrolytic cleavage of trichodesmine (from *Trichodesma incanum*) (55). It was later shown to be identical with retronecine by means of a direct comparison of retronecine and "trichodesmidine" and by the observation that the melting points of mixtures of the bases or of their respective salts were not depressed (37).

Retronecine was first obtained from the hydrolysis of senecifoline by Watt in 1909 (48) (named senecifolinine) and from the hydrolysis of jacobine by Manske in 1931 (26). The optical isomer, heliotridine, was first isolated

from the hydrolytic cleavage of heliotrine by Men'shikov in 1932 (8). The other alkaloids which gave these necines on hydrolysis are included in Table II. The elucidation of the structure of these isomeric necines will be considered historically in terms of the determination of the functional groups present, the basic ring structure, and the positions of the functional groups in the molecule.

a. Functional Groups Present. The molecular formula of retronecine and heliotridine (II) was determined as $C_8H_{13}NO_2$. Both formed salts with acids (retronecine hydrochloride, m.p. 161–162°; heliotridine hydrochloride, m.p. 122–124°; retronecine aurichloride, m.p. 150°) (8, 44), were soluble in water and ethanol, and less soluble in acetone and benzene. The presence of a basic nitrogen atom was thus established. A Zerewitinoff active hydrogen determination disclosed the presence of two active hydrogen atoms. The tertiary nature of the amino nitrogen in retronecine was established by the absence of a reaction with nitrous acid and by the formation of a methiodide, $C_8H_{13}NO_2 \cdot CH_3I$. Analysis also showed the absence of an *O*-methyl group and an *N*-methyl group. Retronecine formed no substituted phenylhydrazone derivative and gave a negative test with Fehling's solution. The presence of two alcoholic hydroxyl groups in the molecule, suggested by the evidence which precluded the presence of carbonyl, carboxyl, and secondary amine groups, was further indicated by the formation of dibenzoylheliotridine (9) (hydrochloride, m.p. 180°) and diacetylretronecine (44) (picrate, m.p. 146°; methiodide, m.p. 118–120°). Reduction of retronecine with zinc and acetic acid or with sodium and alcohol was unsatisfactory, but catalytic hydrogenation over platinum oxide resulted in the formation of retronecanol, $C_8H_{15}NO$, m.p. 95–96°, $[\alpha]_D^{28} - 91.1°$ (ethanol) (methiodide, m.p. 193°; picrate, m.p. 210°; hydrochloride, m.p. 210°; picrolonate, m.p. 184–185°) after the absorption of two moles of hydrogen. Diacetylretronecine was hydrogenated more readily than retronecine over palladium catalyst, with the absorption of two moles of hydrogen and the formation of acetylretronecanol, $C_{10}H_{17}NO_2$ (picrate, m.p. 176°). Both reductions evidently involved hydrogenolysis. Barger



and his co-workers (44) showed that the acetylretronecanol produced by hydrogenolysis of diacetylretronecanol was identical with that formed by the action of acetic anhydride on retronecanol. Barger also obtained

retronecanol by hydrogenolysis of the parent alkaloid, retrorsine (44). This reaction was parallel to Men'shikov's hydrogenolysis of heliotrine to give the isomer of retronecanol, namely, oxyheliotridane, $C_8H_{15}NO$, m.p. 61–65° (methiodide, m.p. 296°; picrate, m.p. 196°) (10). Men'shikov also found that hydrogenolysis of dibenzoylheliotridine over platinum oxide gave benzoyloxyheliotridane, which yielded oxyheliotridane on saponification. Therefore, it appeared that retronecine and the isomeric base, heliotridine, contained one remarkably labile hydroxyl group, since room temperature hydrogenolysis of carbon-oxygen linkages are not common. The evidence thus far presented indicated the presence of a tertiary amine group, two alcoholic hydroxyl groups, one of which was labile to hydrogenation, and unsaturation in the molecule (II).

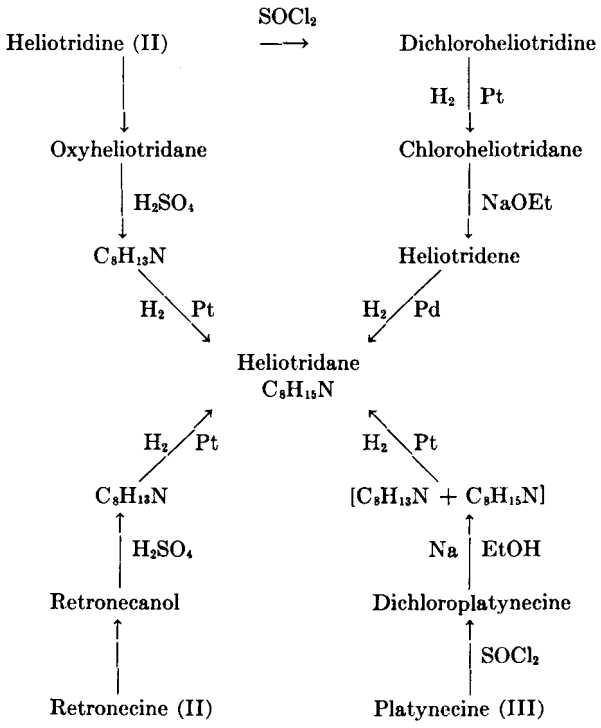
Heliotridine, when treated with thionyl chloride, formed a dichloro compound, which was not isolated (9). Dichloroheliotridine hydrochloride absorbed two moles of hydrogen over platinum oxide catalyst with the formation of chloroheliotridane, $C_8H_{14}ClN$, b.p. 84–85° (10 mm.), $[\alpha]_D$ −133.5°. This colorless, water-soluble oil contained no unsaturation which could be detected by permanganate. Treatment with sodium ethoxide brought about dehydrochlorination and the formation of heliotridene, $C_8H_{13}N$, b.p. 54–55° (12 mm.), $[\alpha]_D$ − 10.5°, a colorless, unsaturated, water-soluble base. Hydrogenation over palladium converted heliotridene to the saturated base heliotridane, $C_8H_{15}N$, b.p. 169–170° (760 mm.), $[\alpha]_D$ − 68° (methiodide, m.p. 240–250°; picrate, m.p. 236°). When chloroheliotridane was treated with sodium and ethanol, a mixture of heliotridene and heliotridane was formed. The intermediate mixture was converted wholly to heliotridane by further reduction with hydrogen over palladium.

Oxyheliotridane, $C_8H_{15}NO$, was also converted to the saturated, oxygen-free base, heliotridane (10). Treatment of oxyheliotridane with sulfuric acid at 170–175° gave the unsaturated base, $C_8H_{13}N$, b.p. 165–166° (760 mm.) (picrate, m.p. 222°) which had a specific rotation ($[\alpha]_D$ − 160°) greater than that of the heliotridene obtained from chloroheliotridane. The base $C_8H_{13}N$ absorbed a mole of hydrogen over platinum oxide catalyst to give $C_8H_{15}N$, b.p. 167–168.5° (760 mm.). This compound possessed a higher *levo* rotation ($[\alpha]_D$ − 99.5°) than heliotridane, but the picrate had the same melting point as the original heliotridane picrate and there was no depression of melting point when the two picrates were mixed. Both $C_8H_{15}N$ compounds were considered identical, but one had probably undergone some racemization during its formation.

Retronecanol, $C_8H_{15}NO$, was converted to heliotridane by Konovalova and Orékhov (53). Their method of conversion was identical with that of Men'shikov for the isomeric oxyheliotridane. An unsaturated base, $C_8H_{13}N$

was formed when retronecanol was dehydrated with sulfuric acid. Although the specific rotation of the base differed slightly from that of heliotridene, the corresponding derivatives of the two bases gave no depression in melting point when mixed. The base $C_8H_{15}N$, formed on catalytic hydrogenation of $C_8H_{13}N$ over platinum oxide, was considered identical with heliotridane since the salts (picrate, m.p. 237–238°; picrolonate, m.p. 152–153°; aurichloride, m.p. 199–200°) were identical with those of heliotridane as shown by mixed melting points.

Retronecanol was later converted to heliotridane by Adams and Rogers (57) by a method not involving the rather vigorous conditions necessary for forming heliotridene from retronecanol. This was done in order to insure that rearrangement of the nucleus during dehydration to heliotridene, which rearrangement would persist in heliotridane, had not occurred. Retronecanol was converted to chlororetronecane, $C_8H_{14}ClN$, b.p. 112° (32 mm.), $[\alpha]_D^{30}$53.8°, by treatment with thionyl chloride. The



chlorine was replaced smoothly by hydrogen, using Raney nickel and hydrogen at room temperature. The product was heliotridane and its properties agreed in boiling point and rotation ($[\alpha]_D^{25}$ − 92.1°), with a

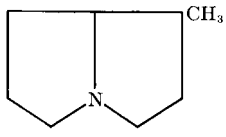
sample of heliotridane ($[\alpha]_D^{34}$ − 91.3°) prepared by dehydration of retronecanol followed by hydrogenation. Their picrates were identical.

The formation of heliotridane from oxyheliotridane and retronecanol proved that both alkaloid hydrogenolysis products have the same basic skeleton (13). It further showed the interrelation of all alkaloids that give heliotridine on hydrolysis with all those alkaloids that give retronecine.

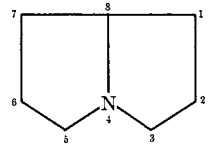
Platynecine (III), $C_8H_{15}NO_2$, first obtained by Orékhov and Tiedebel (38) on alkaline hydrolysis of platyphylline (from *Senecio platyphyllus*), was degraded to heliotridane by Konovalova and Orékhov (40). The method was as follows: Dichloroplatynecine, $C_8H_{13}Cl_2N$, m.p. 63–64° (hydrochloride, m.p. 186–187°; picrate, m.p. 205–206°) was obtained in low yield when platynecine was treated with thionyl chloride. When dichloroplatynecine was reduced with sodium and ethanol followed by hydrogen over platinum oxide catalyst, heliotridane was the product. Identity was established by specific rotation and mixed melting points of all derivatives (54). The formation of heliotridane from platynecine proved that this alkaloid hydrolysis product also has the same basic skeleton that is present in heliotridine and retronecine.

A determination of the structure of heliotridane would establish the basic skeleton present in the necines: heliotridine, retronecine, and platynecine, and in their conversion products. Accordingly, the main effort of the alkaloid chemists was directed next toward establishing the structure of heliotridane.

b. Ring Structure. Heliotridane, because of its elementary composition and the presence of a tertiary nitrogen not a part of an *N*-methyl grouping, was considered by Men'shikov to be bicyclic, with the nitrogen common to both rings (9). Subsequent degradative and synthetic research proved that heliotridane was an optically active form of 1-methylpyrrolizidine (IV).



IV



V

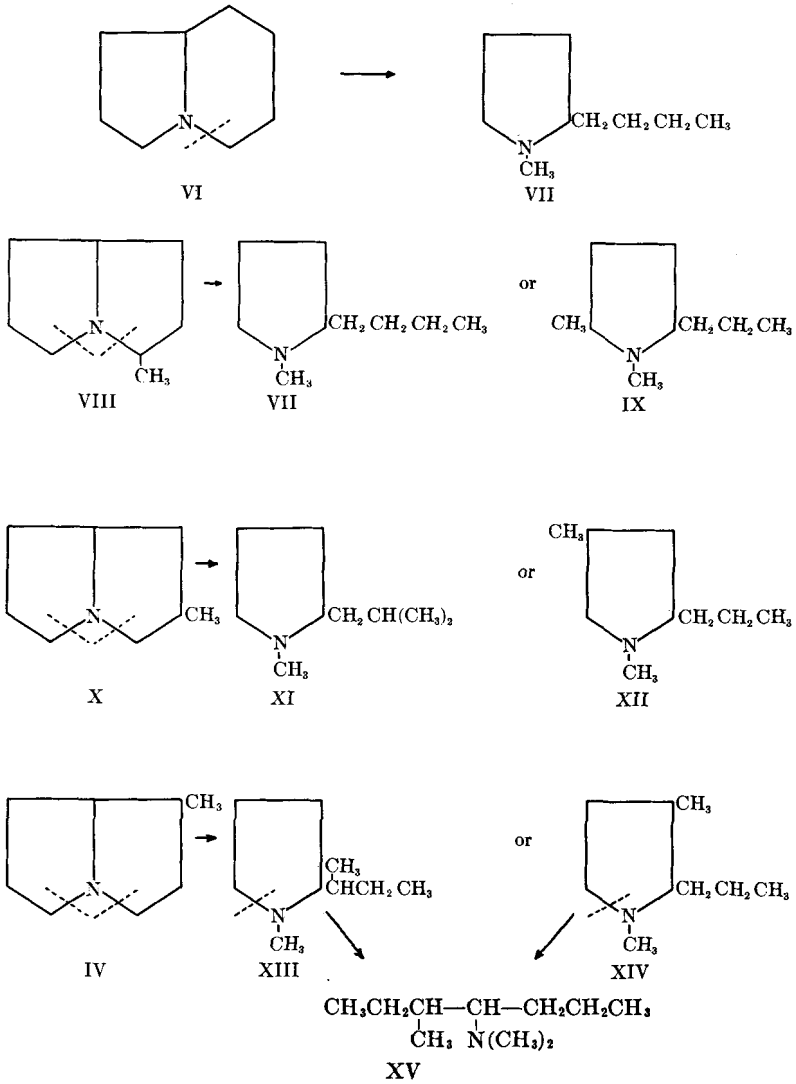
The pyrrolizidine ring structure (V) was not known prior to the discovery of its presence in the *Senecio* alkaloids.

Neither Hofmann degradation of benzoylretronecine nor oxidation of retronecanol with chromic acid disclosed information which was helpful in deciding the ring structure of the base (30, 44). The presence of a five-membered, nitrogen-containing ring was suggested by the fact that a positive pine splint test for pyrrole was observed when retronecine was distilled with zinc dust (44). The absence of a six-membered, nitrogen-

containing ring was presumed because the dehydrogenation of heliotridane yielded no pyridine bases (13). Certain proof of the presence of at least one five-membered, nitrogen-containing ring in heliotridane was provided by Men'shikov (12). Exhaustive methylation of heliotridane, followed by reduction, gave a substance which he called *l*-dihydro-des-N-methylheliotridane, $C_9H_{19}N$, b.p. 165° (760 mm.), $[\alpha]_D$ − 1.5° (methiodide, m.p. 137–138°, picrate, m.p. 125–126°). This product was demonstrated to be a pyrrolidine by its smooth dehydrogenation to an optically inactive pyrrole base, $C_9H_{15}N$, b.p. 189–191° (760 mm.). Subsequent reduction of the pyrrole regenerated the pyrrolidine in optically inactive form (*dl*-dihydro-des-*N*-methylheliotridane) and thus provided an advantageous substance for comparison with synthetic products (14, 15).

The structure of *dl*-dihydro-des-*N*-methylheliotridane was deduced by Men'shikov after comparison of several synthetic pyrrolidines with those which could possibly be obtained by Hofmann degradation of octahydropyrrocoline (VI) and from various monomethyl derivatives of pyrrolizidine (V). Octahydropyrrocoline (VI), on exhaustive methylation and subsequent reduction, could yield only one pyrrolidine, 1-methyl-2-*n*-butylpyrrolidine (VII). There are four *monomethyl* pyrrolizidines, 1, 2, 3, and 8; of these, 8-methylpyrrolizidine can be eliminated since the des-base could not be dehydrogenated to a pyrrole without loss of carbon. 3-Methylpyrrolizidine (VIII) would yield by this degradation procedure either 1-methyl-2-*n*-butylpyrrolidine (VII) or 1,5-dimethyl-2-*n*-propylpyrrolidine (IX); 2-methylpyrrolizidine (X) would yield 1-methyl-2-isobutylpyrrolidine (XI) or 1,4-dimethyl-2-*n*-propylpyrrolidine (XII); 1-methylpyrrolizidine (IV) would yield 1-methyl-2-*s*-butylpyrrolidine (XIII) or 1,3-dimethyl-2-*n*-propylpyrrolidine (XIV). The pyrrolidines with structures VII (17), IX (13), XI (17), XII (16), and XIII (15) were synthesized by Men'shikov and Zhdanovich. Since these compounds were all liquids which boiled in the same range, the picrates of each were made and compared in melting point with the picrate of *dl*-dihydro-des-*N*-methylheliotridane. It was stated that 1-methyl-2-*n*-butylpyrrolidine (VII) was different from this base, although the picrates melted at the same point. The synthesis of VII was repeated later by Adams and Rogers (57), who reported that the picrate of VII showed a sharp depression in melting point when mixed with *dl*-dihydro-des-*N*-methylheliotridane picrate. This result excludes the possibility of heliotridane being octahydropyrrocoline (VI). Since the picrates of the synthetic compounds IX, XI, XII, and XIII were also not identical with the picrate of the product from heliotridane, Men'shikov concluded that *dl*-dihydro-des-*N*-methylheliotridane must be 1,3-dimethyl-2-*n*-propylpyrrolidine (XIV), and therefore that heliotridane must be 1-methylpyrrolizidine (IV) (13).

The pyrrolidine XIV was not synthesized by Men'shikov, but in order to confirm his postulated structure, he degraded *dl*-dihydro-des-*N*-methylheliotridane by a second exhaustive methylation followed by reduction.

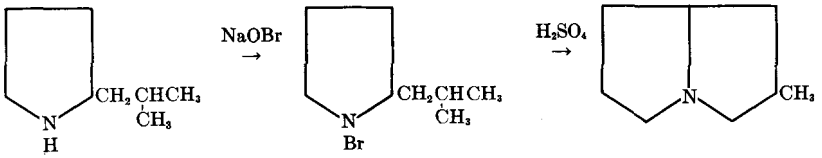


XV

For the resulting compound, which he called tetrahydro-des-*N*-dimethylheliotridane, he proposed the structure XV (14). The same base (XV), as shown by identity of the picrates and picrolonates, was prepared by similar treatment of 1-methyl-2-*s*-butylpyrrolidine (XIII). The isolation

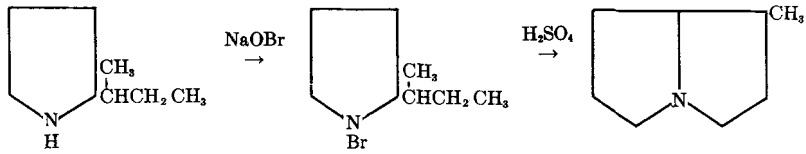
of an identical base by these two degradations established the structure of the product as 4-dimethylamino-3-methylheptane. Since the pyrrolidine XIII had been shown previously to give a picrate not identical with that from *dl*-dihydro-des-*N*-methylheliotridane, this was further indirect proof that *dl*-dihydro-des-*N*-methylheliotridane was 1,3-dimethyl-2-*n*-propylpyrrolidine (XIV) and that heliotridane was 1-methylpyrrolizidine (IV).

The synthesis of *dl*-2-methylpyrrolizidine and *dl*-1-methylpyrrolizidine was carried out by Men'shikov (14, 16) in order to compare these products with the optically active heliotridane. 2-Methylpyrrolizidine (X) was formed in low yield by the action of sulfuric acid on the bromamine (XVII)



XVI XVII X

derived from 2-isobutylpyrrolidine (XVI) and sodium hypobromite. The boiling point of 2-methylpyrrolizidine was 162–163° (760 mm.), in the same range as that of heliotridane, but the melting points of its derivatives (picrate, m.p. 182–184°; methiodide, m.p. 225–226°) were very different from those of the corresponding heliotridane salts. 1-Methylpyrrolizidine (IV) was synthesized with difficulty in a similar manner, starting with 2-*s*-butylpyrrolidine (XVIII) and proceeding through the bromamine (XIX). Only sufficient product was obtained for formation of a picrate



XVIII XIX IV

which had a melting point (m.p. 236°) identical with that of optically active heliotridane picrate and which gave no melting point depression when mixed with it. While suggestive, the same melting-decomposition points and no depression in the mixed melting point of Men'shikov's synthetic *dl*-1-methylpyrrolizidine picrate and *levo*rotatory heliotridane picrate did not constitute convincing evidence for structural identity of the two. Since in most cases the active forms of a substance melt at a different temperature from the racemic, and since mixed melting points of closely related but non-identical salts often show no depression in mixed melting point determinations, identity of heliotridane with 1-methylpyrrolizidine was not yet conclusive.

In reviewing the results of Men'shikov, Adams and Rogers (57) pointed out that the formation of 4-dimethylamino-3-methylheptane (XV), as previously described, definitely excluded the pyrrolidines VII, IX, XI, and XII from consideration as the structure for *dl*-dihydro-des-*N*-methylheliotridane, and therefore excluded 3- and 2-methylpyrrolizidine from consideration as the structure for heliotridane. However, their critical evaluation questioned the deduction of Men'shikov in ruling out formula XIII as the possible structure for *dl*-dihydro-des-*N*-methylheliotridane on the basis of the non-identity of their picrates. Two diastereoisomers of XIII are possible, and Adams and Rogers argued that the synthetic 1-methyl-2-*s*-butylpyrrolidine might have been a diastereoisomer of *dl*-dihydro-des-*N*-methylheliotridane. If this were the case, the picrates of the two most probably would not melt at the same temperature. Thus, both formula XIII and XIV still had to be considered as possible representations of *dl*-dihydro-des-*N*-methylheliotridane.

Adams and Rogers were able to decide between XIII and XIV by a synthesis of 1,3-dimethyl-2-*n*-propylpyrrolidine (XIV) and proof of its identity with *dl*-dihydro-des-*N*-methylheliotridane. The picrates had the same melting point (116°) and a mixed melting point showed no depression. The picrolonates and methiodides of the synthetic and natural bases also had identical melting points and showed no depression in mixed melting point determinations. Two racemic mixtures of XIV were actually obtained in the synthesis. The picrates had different melting points: 116° and 126°. The picrate with a melting point 126° was nonidentical with *dl*-dihydro-des-*N*-methylheliotridane picrate. These results showed that where two diastereoisomers are possible in the pyrrolidine degradation products, each should be synthesized before structural deductions, by comparison of the melting points of the picrates, are justified. More important, the results proved conclusively the identity of heliotridane with 1-methylpyrrolizidine (IV). Once the carbon skeleton of heliotridine, retronecine, and platynecine had been established, attention was turned effectively toward determination of the types and positions of the alcohol groups and of the unsaturation in the necines.

c. Integration of Functional Groups and Ring Structure. Of the two hydroxyl groups in retronecine (or heliotridine), one was labile and was lost on hydrogenation. In the parent alkaloids, it must have been this hydroxyl which was bound as an ester group. In the diacyl derivatives of the necines, the ester group on this labile hydroxyl was also lost on hydrogenation. If the hydroxyl groups in retronecine (or heliotridine) were replaced by chlorine and the resulting dichloro compounds subjected to hydrogenation over platinum, the chlorine corresponding to the labile hydroxyl was removed. The ease of hydrogenolysis of the groups decreases

in the order: Cl>OOCR>OH (58). Both retronecine and heliotridine could be esterified to give mono- and diesters (9, 26). In all cases the labile hydroxyl was the more readily esterified.

Adams and Rogers (58) contributed further to the knowledge of the character of the hydroxyl groups by catalytic hydrogenation studies on monocrotaline and retronecine under various conditions. From monocrotaline in the presence of either platinum oxide or Raney nickel, if the reduction was stopped after the absorption of one mole equivalent of hydrogen, monocrotalic acid and a base, $C_8H_{13}NO$, m.p. 77–78°, were obtained. The name desoxyretronecine was suggested for the base since a hydroxyl group had been lost although the double bond was retained (hydrochloride, m.p. 182–183°; picrate, m.p. 157–158°). The double bond was easily reduced with the formation of retronecanol. If retronecine (II), instead of an ester of the base (monocrotaline) was reduced catalytically with Raney nickel, only one mole of hydrogen was absorbed with saturation of the double bond and formation of platynecine (III). The product agreed in all its properties with the base obtained by saponification of the alkaloid platyphylline (39), as follows: m.p. 148–149°, $[\alpha]_D^{30} - 57.7°$ (chloroform); methiodide, m.p. 207–207.5°; monobenzoylplatynecine, m.p. 119–120°, $[\alpha]_D^{29} - 88.6°$ (ethanol). The identity in position of the hydroxyl groups in retronecine and platynecine, which was suspected when Orékhov and Tiedebel (38) found esters of both in *Senecio platyphyllus*, was therefore confirmed. With the relationship of retronecine and platynecine proved, an earlier observation of Konovalova and Orékhov (40) became significant. It was that platynecine forms a mono- or dibenzoyl derivative depending upon the conditions, and therefore that one hydroxyl is esterified much more readily than the other. It thus became evident that the presence of the double bond in retronecine was not the primary cause for the difference in the reactivity of the two hydroxyls in that molecule. The cause evidently persisted in the saturated molecule.

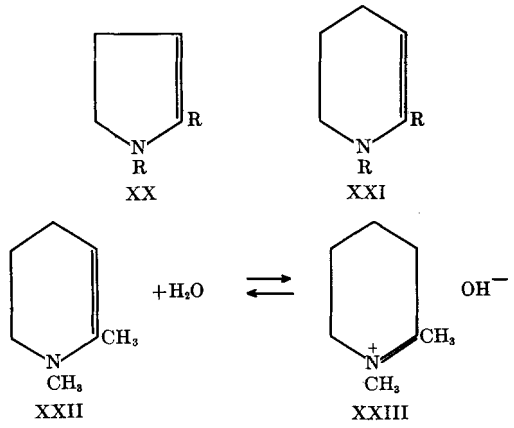
Platynecine was not further reduced by hydrogen and nickel catalyst or platinum catalyst (58). Hydrogenolysis of monobenzoylplatynecine was not possible in the presence of nickel or platinum, whereas monobenzoylretronecine was readily hydrogenolyzed under the same conditions. These results indicated that hydrogenation of the labile hydroxyl and of groups replacing it (OOCR, Cl) was dependent upon the presence of the double bond, and that the labile hydroxyl was probably allylic.

Further relation between the hydroxyl groups was discovered by Orékhov and his co-workers (39, 40). When platynecine was treated with a variety of reagents (sulfuric acid, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, or phosphorus oxychloride), it underwent the loss of a molecule of water to form anhydroplatynecine, $C_8H_{13}NO$, b.p.

194–195° (750 mm.) (picrate, m.p. 265–270°; picrolonate, m.p. 226–227°; methiodide, m.p. 211–213°). The indifferent character of the oxygen in anhydroplatynecine showed that both hydroxyls must have been involved in the formation of an ether, and the ease with which the linkage was formed suggested that the hydroxyls were in a position 1,4 or 1,5 to each other.

A detour from the correct road to the structure of retronecine was made (58) on the basis of the belief of Men'shikov (13) that one of the hydroxyls of the isomeric heliotridine was tertiary. Starting with oxyheliotridane, he performed a series of exhaustive methylations and reductions until a nitrogen-free compound was obtained. The final product was described as a tertiary octanol. However, no detailed description of the procedure was published, no intermediates were isolated or purified, and the characterization of the tertiary octanol was doubtful. It was not until the hydroxyls were regarded as primary and secondary (59) that progress was again made in the direction of the correct structure for retronecine. Also important to such progress were the clarifying fundamental studies of Adams and Mahan (60) on the basic strength of tertiary vinyl amines.

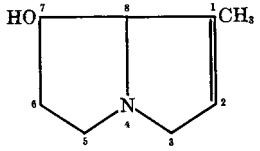
It had been known for some time that the introduction of a double bond into a primary or secondary amine lowers the basic strength constant (by 2.4–3.3 pK_H units). The normal assumption would seem to be that vinyl tertiary amines should be weaker bases than the corresponding saturated amines. Aston (61, 62), in an investigation of substituted dihydropyrazonium hydroxides, indicated that this assumption might not be valid. Adams and Mahan showed that vinyl tertiary amines of



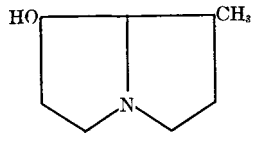
the type XX and XXI were actually more basic than the corresponding saturated amines. The possible mechanism suggested was one of hydration and rearrangement to a quaternary ammonium base (XXII → XXIII).

Vinyl primary and secondary amines, if they underwent similar rearrangement, would form ammonium bases rather than the strong quaternary ammonium bases. The former would have lower basicity than their saturated analogs, which is as observed.

That retronecine could be a vinyl amine was regarded as improbable because of the marked stability of retronecine toward acid and alkali. Basicity studies on retronecine and related bases bore out this assumption, since the unsaturated amines (all tertiary) were less basic than the corresponding saturated molecules (59) — the reverse of the condition which should obtain if they were vinyl tertiary amines. Thus, retronecine (II) was less basic than platynecine (III) and desoxyretronecine (XXIV) was less basic than retronecanol (XXV). Structures II, III, XXIV, and XXV



XXIV



XXV

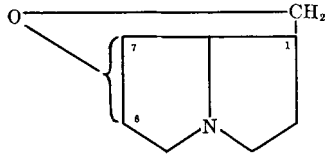
were assigned to these compounds by Adams, Carmack and Mahan (59), although they suggested that the secondary hydroxyl group might be attached at either the 6- or the 7-position of the pyrrolizidine nucleus. The structures were assigned on the basis of the following pertinent facts:

(1) Basicity studies showed that the unsaturated amines were not vinyl amines.

(2) Esterification rates indicated that the hydroxyl groups are primary and secondary. The postulation of a primary hydroxyl limits its position to the side-chain 1-methyl group.

(3) The ease of hydrogenolysis of one hydroxyl indicated that it is allylic. (Platynecine does not undergo hydrogenolysis.) The allylic hydroxyl is probably the primary hydroxyl since —

(4) Retronecanol can be dehydrated readily and therefore has a secondary hydroxyl rather than a primary hydroxyl group.



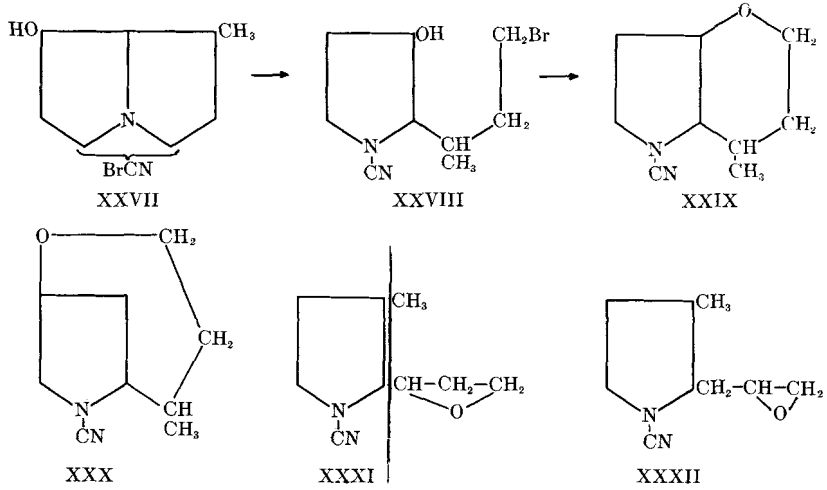
XXVI

(5) The ease of dehydration of platynecine to anhydroplatynecine (XXVI) indicated that the hydroxyl groups are probably located so that a 5- or 6-membered cyclic ether may be formed by the dehydration.

(6) Retronecine has no readily enolized ketone as demonstrated by the inability to isolate a ketone derivative and the absence of a color with ferric chloride.

(7) Carbon-methyl determinations indicated one methyl group present in retronecanol (XXV) and in desoxyretronecine (XXIV), none in retronecine (II), platynecine (III), or anhydroplatynecine (XXVI).

Construction of models indicated that the structures represented by XXVI involved very little strain whether the secondary hydroxyl was in the 6- or the 7-position. The 7-position was favored on the basis of experiments involving the degradation of retronecanol (XXV) by cyanogen bromide (59). An addition compound (XXVII) was formed with this reagent which, on rearrangement (XXVIII) and treatment with alkali yielded a halogen-free compound, $C_9H_{14}N_2O$, m.p. 94.5–95°, postulated as an ether (XXIX). Only the cyanide group was removed on hydrolysis with hot sulfuric acid; there was no cleavage of the cyclic ether. The ring opening was believed to occur in the ring containing the methyl group;



assuming the 7-position for the hydroxyl group a six-membered ether (XXIX) would be produced, or assuming the 6-position a much less likely structure (XXX) would result. Cleavage of the unmethylated ring in XXVII would yield an ether of structure XXXI or XXXII, depending upon the position of the hydroxyl group. Either of these would be expected to hydrolyze upon treatment with hot sulfuric acid.

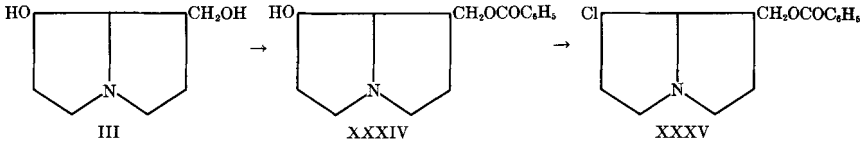
The points concerning the structure of retronecine which remained to be proved unequivocally were the presence of a secondary hydroxyl, the presence of a primary hydroxyl, the position of the double bond, and the position of the secondary hydroxyl.

d. Presence of a Secondary Hydroxyl. Adams and Hamlin (63) proved that retronecanol (XXV) contains a secondary hydroxyl group since aluminum *t*-butoxide in the presence of cyclohexanone oxidized the molecule without degradation to a ketone, retronecanone (XXXIII). The ketone

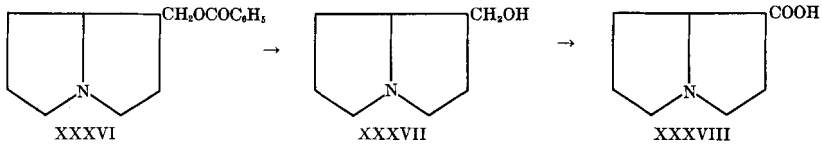
XXV XXXIII

analyzed correctly for $C_8H_{13}NO$. It was a colorless, mobile liquid, b.p. 95–96° (15 mm.), $[\alpha]_D^{30}$ − 96.7° (ethanol) (picrate, m.p. 195°). The ketone function was identified by the formation of an oxime (m.p. 167–168°, $[\alpha]_D^{26}$ − 76.0° (ethanol)) and a semicarbazone (m.p. 209–210°).

e. Presence of a Primary Hydroxyl. Retronecine was converted to platynecine (III) and the secondary hydroxyl was removed in order to facilitate oxidation of the primary hydroxyl group alone. Monobenzoylplatynecine (XXXIV) was converted to the corresponding chloride (XXXV



III XXXIV XXXV

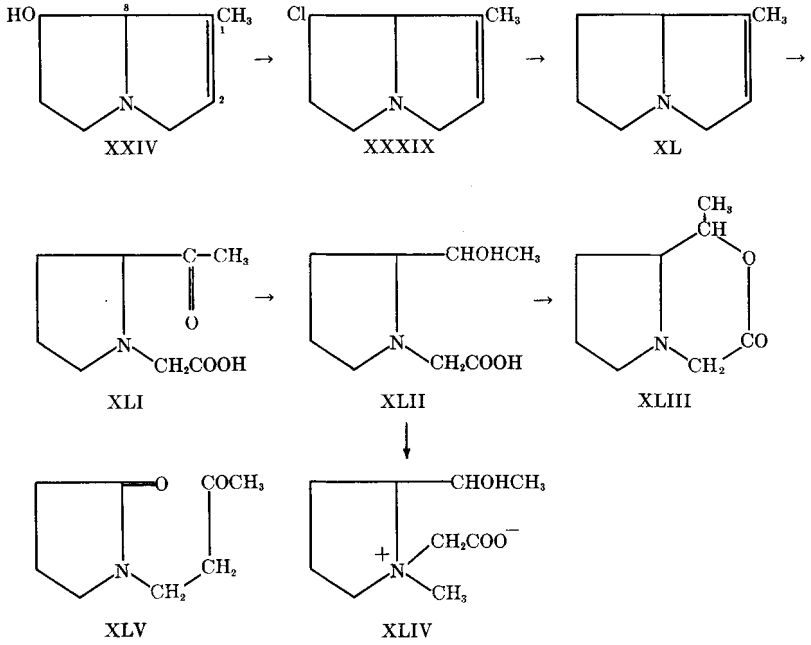


XXXVI XXXVII XXXVIII

(40). The chlorine could not be replaced by hydrogen when a variety of agents were tried (40), but Adams and Hamlin found no difficulty in bringing about this replacement by the use of Raney nickel and hydrogen in ethanol solution (63). The name assigned to the chlorine-free base was benzoylisoretronecanol (XXXVI) (m.p. 56–57°, $[\alpha]_D^{28}$ − 60.8° (ethanol); picrate, m.p. 130–131°). Hydrolysis of this base furnished isoretronecanol (XXXVII), $C_8H_{15}NO$ (m.p. 39–40°, $[\alpha]_D^{27}$ − 78.2° (ethanol); methiodide, m.p. 281–282°; picrate, m.p. 194–195°). Isoretronecanol was oxidized by means of chromic anhydride to an optically active amino acid, $C_8H_{13}NO_2$ (m.p. 228–229°, $[\alpha]_D^{28}$ − 65.8° (ethanol); picrate, m.p. 220–221°). The fact that the oxidation product was an amino acid was established by its form-

ation of a betaine with diazomethane. The betaine was identified as such by analyses of the aurichloride and picrate. The acid group, and therefore the original primary alcohol group, could only occupy position 1 on the pyrrolizidine nucleus.

f. Position of the Double Bond. The double bond of retronecine was proved conclusively to be in the 1,2-position by Adams and Mahan (64). Desoxyretronecine (XXIV) was converted by thionyl chloride to $C_8H_{12}ClN$ (b.p. 59.5–60.5° (4.5 mm.), $[\alpha]_D^{32}$ 50.1°; picrate, m.p. 179.5–180°), which was designated as chloroisoheliotridene (XXXIX). The chlorinated product was reduced with chromous chloride to the unsaturated base, isoheliotridene (XL), $C_8H_{13}N$ (b.p. 73° (30 mm.), $[\alpha]_D^{28}$ − 45.8°; picrate,



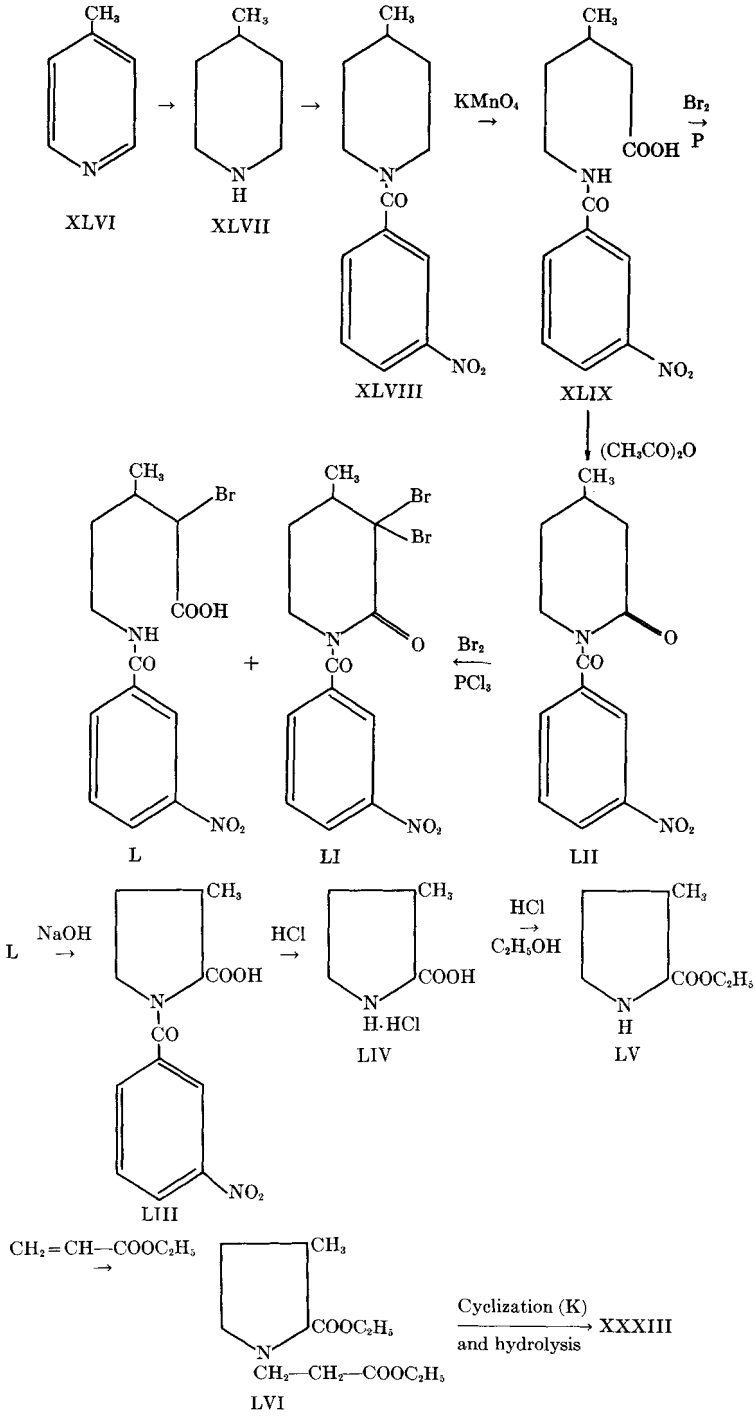
m.p. 198.5–199.5°). When isoheliotridene was hydrogenated over platinum oxide at room temperature and atmospheric pressure, it absorbed a mole of hydrogen rapidly to give heliotridane, characterized by comparison of the picrate with an authentic sample of heliotridane picrate. The hydrochloride of isoheliotridene was subjected to ozonolysis in aqueous solution. A product was obtained which was postulated as the hydrochloride of 2-acetyl-1-pyrrolidine acetic acid (XLI), $C_8H_{14}ClNO_3$ (m.p. 180–181°, $[\alpha]_D^{27}$ − 4.4° (methanol)). Compound XLI was characterized as a ketone by the formation of a 2,4-dinitrophenylhydrazone, and as a methyl ketone by a strong positive iodoform test. This delimits the double bond to

either the 1,2- or the 1,8-position. With the double bond at 1,2, ozonization should yield an amino acid; at 1,8, a pyrrolidone (XLV). Proof of the presence of a carboxylic acid group should be ample to place the double bond definitely at 1,2. Reduction of XLI yielded a carbinol, XLII, which was stable both as the free amino acid (m.p. 186.5–187.5°, $[\alpha]_D^{28} - 63.5°$ (water)) and as the hydrochloride (m.p. 147–148°, $[\alpha]_D^{32}$ 54.3° (ethanol)). A by-product of the reduction was a basic oil, $C_8H_{13}NO_2$, characterized by means of the methiodide (m.p. 242–243°, $[\alpha]_D^{29} - 15.0°$ (methanol)) and picrate (m.p. 169–170°). The basicity and molecular formula suggested that the compound was the lactone (XLIII) of the carbinol XLII. This was confirmed by direct conversion of the carbinol to the lactone by means of acetic anhydride. The presence of a carboxylic acid group was further confirmed by the formation of a betaine (XLIV) when the carbinol XLII was treated with diazomethane in moist ether. The hydrochloride of the betaine, m.p. 176–177°, had the expected analysis.

The formation of these carboxylic acid derivatives, lactone and betaine, and the presence of the methyl ketone group confirmed the structure of XLI as 2-acetyl-1-pyrrolidine acetic acid. This established the 1,2-position of the retronecine double bond unequivocally.

g. Position of the Secondary Hydroxyl. On the basis of the relative strain in models of anhydroplatynecine (XXVI) and on the basis of the cyanogen bromide degradation of retronecanol, the 7-position for the secondary hydroxyl was favored. Therefore, the synthesis of an optically active 1-methyl-7-ketopyrrolizidine was carried out by Adams and Leonard (65). The product was found to be identical with retronecanone (XXXIII) by showing the identity of the oximes (m.p. 166–167°, $[\alpha]_D^{32} - 77.3°$ (ethanol)), and the picrates (m.p. 188–190°) and picrolonates (m.p. 209–211°) of the oximes. The unequivocal synthesis was executed in the manner shown on following page, starting with γ-picoline (XLVI).

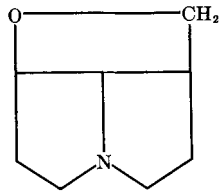
In the first experiments, the synthesis was carried out on the racemic β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (XLIX) with the resultant formation of optically inactive 1-methyl-7-ketopyrrolizidine (XXXIII) as a colorless mobile liquid, b.p. 96.5–98° (18 mm.). The picrate (m.p. 189–190°), methiodide (m.p. 149.5–150.5°) and oxime (m.p. 128–130°) of inactive compound XXXIII were prepared. Although theoretically two racemic modifications might be present in the liquid XXXIII as synthesized, only single derivatives were isolated in each case. An attempt was made to isolate an optically active 1-methyl-7-ketopyrrolizidine from the possible mixture of four forms by the use of *l*-menthydrazide. A pure *l*-menthydrazone was obtained but it proved to have a different melting point and specific rotation from the *l*-menthydrazone of retronecanone. Moreover, hydrolysis of the 1-methyl-7-ketopyrrolizidine *l*-menthydrazone and


XLVI
XLVII
XLVIII
XLIX
L
LI
LII
LIII
LIV
LV
LVI
KMnO4
Br2
P
(CH3CO)2O
NaOH
HCl
C2H5OH
Cyclization (K)
and hydrolysis
XXXIII

conversion of the ketone to the oxime gave an optically inactive product.

In order to decrease the stereochemical possibilities in the final product as a result of working with racemic modifications, the acid XLIX was resolved through the quinidine salt. Both forms of the acid were obtained and a similar series of reactions was carried out using the *levo*rotatory β-methyl-δ-*m*-nitrobenzoylaminovaleric acid. There was thus obtained optically active 1-methyl-7-ketopyrrolizidine (XXXIII) which could not consist of a mixture of more than two forms. Like the product from the racemic acid, this was an oil. When treated with hydroxylamine, however, a single, pure optically active oxime was isolated. This proved to be identical in melting point, crystalline form as observed under the microscope, and specific rotation with retronecanone oxime, and the melting points of mixtures of the two compounds showed no depression. The picrates of the aminoketoximes obtained from natural and synthetic sources were also found to be identical and showed no depression of melting-decomposition point when mixed. Likewise, the picrolonates of the oximes were identical.

Since the keto group in retronecanone occupies the same position as the secondary hydroxyl group in its parent, retronecanol, this hydroxyl group was located definitely at the 7-position, and the precise structure of retronecanol was proved to be represented by XXV. Retronecine, therefore, has structure II; platynecine, structure III; desoxyretronecine, structure XXIV;



XXVIa

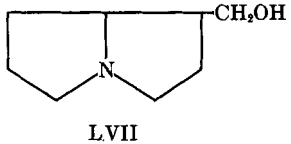
and anhydroplatynecine, structure XXVIa. Owing to the fact that heliotridine and oxyheliotridane are merely stereoisomers, respectively, of retronecine and retronecanol, it was also established that these molecules have the secondary hydroxyl group in the 7-position.

It was also shown by Adams and Leonard that in the reduction of desoxyretronecine, retronecine, and esters of retronecine to give retronecanol, asymmetric reduction takes place with the exclusive formation of one stereochemical configuration of the C_1-CH_3.

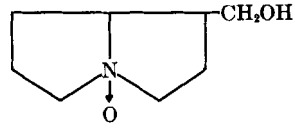
2. Trachelanthamidine

Trachelanthamidine, $C_8H_{15}NO$, (LVII) appears to be related to the necines, heliotridine, retronecine, and platynecine, since it is a diastereoisomer of isoretronecanol (XXXVII) (56b). Unlike most of the necines

it is a liquid, b.p. 114–115° (3 mm.), but solid derivatives have been obtained (hydrochloride, m.p. 110–112°; picrate, m.p. 174°; picrolonate, m.p. 182°) (56a). With the structure of trachelanthamidine established as LVII, the structure of the necine, trachelanthidine, $C_8H_{15}NO_2$ (hydro-



LVII



LVIII

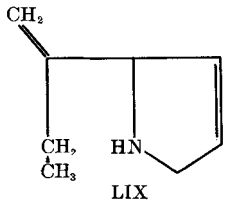
chloride, m.p. 107–108°) (56), is that of the *N*-oxide (LVIII) of trachelanthamidine. This relationship in the necine structures depends upon the fact that the parent alkaloids, trachelanthamine and trachelanthine, which bear the relationship of tertiary base and tertiary base *N*-oxide (56a), give the same acid on hydrolysis along with necines differing by one oxygen, respectively, trachelanthamidine and trachelanthidine.

Trachelanthamidine was shown by Men'shikov (56b) to be a methylolpyrrolizidine by oxidation to an amino acid, $C_8H_{13}NO_2$ (m.p. 214–215.5°, $[\alpha]_D$ − 43.3°; picrate, m.p. 176–177.5°), and by subsequent decarboxylation of this amino acid to pyrrolizidine. Assignment of the 1-position as the point of attachment of the methylol group was made on the basis of analogy to the necines of established structure, all of which possess a 1-CH_2OH group, and also on the basis of the similarity of certain degradation products to those from the necines discussed previously. The primary hydroxyl of trachelanthamidine, $C_8H_{15}NO$, was replaced by chlorine to give $C_8H_{14}ClN$ (b.p. 86–88° (8 mm.), $[\alpha]_D$ − 16.5°; picrate, m.p. 180°), and the chlorine was subsequently removed by reduction, first with sodium and isoamyl alcohol, then with hydrogen over platinum catalyst, to give $C_8H_{15}N$ (b.p. 159–160°, $[\alpha]_D$ − 8.25°; picrate, m.p. 232–233°; picrolonate, m.p. 162–163°; aurichloride, m.p. 183–184° (56a). The latter compound was named pseudoheliotridane and was considered, on analogical grounds, to be a diastereoisomer of heliotridane.

3. Isatinecine

Isatinecine, $C_8H_{13}NO_3$, isolated as one of the hydrolysis products of isatidine (from *Senecio isatideus*) by Blackie (1), apparently differs from the necines of $C_8H_{13}NO_2$ constitution because there is evidence that it is not a pyrrolizidine type base (22). Isatinecine has two carbon-carbon double bonds since de Waal (6, 20) found that hydrogenation over platinum

catalyst gave tetrahydroisatinecine, $C_8H_{17}NO_3$ (m.p. 174.5°, $[\alpha]_D^{20}$ − 88.0° (H_2O)). The same hydrogenated necine was obtained by hydrolysis of hexahydrodesoxyisatinecine, formed by catalytic hydrogenation of isatidine. Tetrahydroisatinecine was unstable toward alkaline permanganate. Isatinecine was found to have no tertiary nitrogen, no C-CH_3 group, and no N-CH_3 group. It was insoluble in chloroform, which is unusual for a necine. The presence of a pyrrolidine ring was suggested by de Waal (22), who postulated the skeleton structure LIX. The three oxygen atoms are probably present as hydroxyl groups although the number of hydroxyls in the molecule has not yet been determined.



LIX

4. Mikanecine

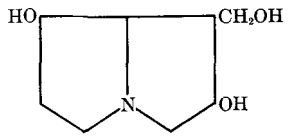
When mikanoidine (from *Senecio mikanioides*) was hydrolyzed by Manske (30) with methanolic potassium hydroxide, an uncrystallizable base was obtained to which was assigned the name mikanecine. The picrate was obtained crystalline, and analysis of the picrate suggested the formula $C_8H_{15}NO_2$ for the necine itself. Manske suggested that the compound might be a dihydroretronecine. It is noteworthy that the mikanecine picrate melts at 186°, which is the region where the picrate of platynecine (also $C_8H_{15}NO_2$) melts.

5. Rosmarinecine

Both the hydrolysis (22) and hydrogenolysis (6) of rosmarinine (from *Senecio rosmarinifolius*) resulted in the formation of rosmarinecine, $C_8H_{15}NO_3$ (picrate, m.p. 175°; methiodide, m.p. 195°). The basic portion of the alkaloid therefore remains unchanged during hydrogenation; accordingly, rosmarinecine must be a saturated necine base.

The formation of a methiodide indicated the tertiary character of the amine, and lack of any oxidation with periodic acid showed that a 1, 2-glycol grouping of two of the oxygens had to be excluded (43). Attempted condensation with nitromethane did not proceed and no reduction product was obtained by the use of sodium amalgam or hydrogen over platinum catalyst. Richardson and Warren also suggested that rosmarinecine was

a saturated base. They postulated 1-hydroxymethyl-2,7-dihydroxypyrrolizidine (LX) as a likely structure for the necine, but provided no further experimental justification for their postulate.



LX

6. Otonecine

The necine portion of otosenine (from *Senecio othonnae*) was obtained by acid hydrolysis of the alkaloid after Zhdanovich and Men'shikov (36) discovered that alkaline hydrolysis resulted in tar formation. Hydrolysis of otosenine with dilute hydrochloric acid yielded otonecine hydrochloride, $C_9H_{15}NO_3 \cdot HCl$ (m.p. 146–148°, $[\alpha]_D - 18.5°$ (ethanol)). The base is unusual in that it contains nine rather than eight carbon atoms and because it has an *N*-methyl group, which precludes the possibility of its having a pyrrolizidine nucleus. Hydrogenation of otonecine hydrochloride over platinum catalyst produced $C_9H_{17}NO_2$, b.p. 105–107° (9 mm.) (picrate, m.p. 231.5°). A Zerewitinoff determination indicated that reduced otonecine had one active hydrogen. Oxime formation ($C_9H_{18}N_2O_2$) indicated that reduced otonecine contained a carbonyl group.

Of the necines known and partially characterized thus far, apparently only isatinecine and otonecine do not possess a pyrrolizidine nucleus. The synthesis of this nucleus and of substituted pyrrolizidines has been the subject of recent review (66).

IV. Structure of the Necic Acids

The necic acids are those acids which are bound in ester combination with the hydroxyl group of the necines. Due to the wide divergencies in composition, properties, and structure, they will be treated individually in the order of increasing carbon content.

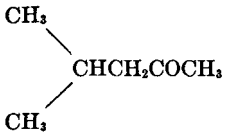
1. C_6 Acids

The only representative of this category is dicrotalic acid, $C_6H_{10}O_5$, from dicrotaline, which was found by titration with standard alkali to be a dibasic acid (4).

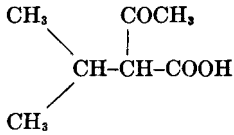
2. C_7 Acids

Alkaline hydrolysis of most of the *Senecio* alkaloids results in the formation of a necine and a necic acid. Certain of the alkaloids, however, hydrolyze to form the necine, an acid (usually), and carbon dioxide. Tri-

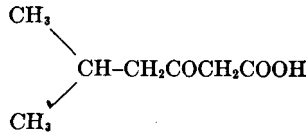
chodesmine produced retronecine, *dl*-lactic acid, a compound of formula $C_6H_{12}O$, and carbon dioxide — all these, when treated with aqueous sodium hydroxide (55). The lactic acid was not obtained free, but it gave the typical color reactions with guaiacol and codeine. The quinine salt gave no melting point depression when mixed with the quinine salt of *racemic* lactic acid. The compound $C_6H_{12}O$ was identified as methyl isobutyl ketone (LXI) since the semicarbazone gave no depression of melting point when mixed with an authentic sample of methyl isobutyl ketone semicarbazone. Since carbon dioxide was obtained in the saponification, the ketone must



LXI



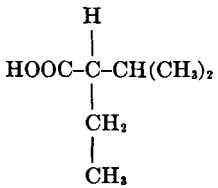
LXII



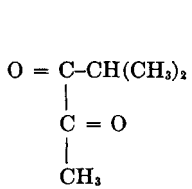
LXIII

have been formed by the ketonic split of a β-keto acid, $C_7H_{12}O_3$, which could have been either α-isopropylacetoacetic acid (LXII) or isovalerylacetic acid (LXIII). It was not possible to tell whether both acids (lactic acid and $C_7H_{12}O_3$) esterify the alcohol groups of retronecine or whether one esterifies the alcohol group of the other. However, Men'shikov and Rubinstein (55) found that the parent alkaloid, trichodesmine, gave no color with ferric chloride, which permitted them to conjecture that the lactic acid had esterified the enolic hydroxyl of the tautomeric form of the β-keto acid.

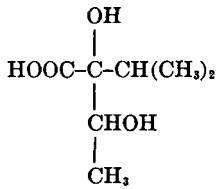
Trachelanthic acid, $C_7H_{14}O_4$, was obtained by Men'shikov and Borodina (56) in the hydrolytic cleavage of trachelanthine and trachelanthamidine, and was found to be a monobasic acid having two hydroxyl groups. The hydroxyl groups were replaced by hydrogen through treatment with phosphorus and hydriodic acid followed by zinc and hydrochloric acid. The product was identified as ethylisopropylacetic acid (LXIIIa). The product of mercuric oxide oxidation of trachelanthic acid was identified as methylisopropylglyoxal (LXIIIb). On the basis of these conversions, Men'shikov (56c) assigned the structure 2-methyl-3,4-dihydroxy-3-pentanecarboxylic acid (LXIIIc) to trachelanthic acid.



LXIIIa



LXIIIb

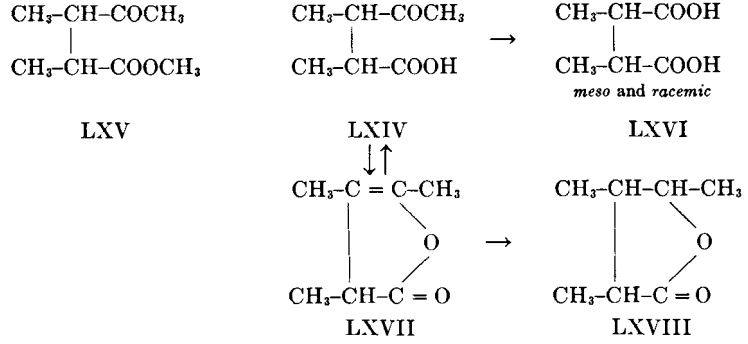


LXIIIc

3. C_8 Acids

a. Monocrotalic Acid. The key to the structure of monocrotalic acid, $C_8H_{12}O_5$, the hydrogenolysis product of monocrotaline, was found in the structure of monocrotic acid, $C_7H_{12}O_3$, the hydrolysis product of the same alkaloid. Monocrotic acid was also formed when monocrotalic acid was treated with aqueous alkali.

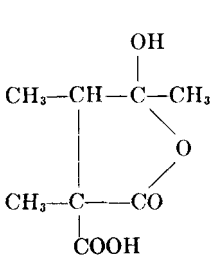
Monocrotic acid was found to be optically inactive and monobasic. It formed a monomethyl ester with diazomethane: methyl monocrotate, b.p. 94–96° (18 mm.) (67). The character of the third oxygen was determined by condensation of the methyl ester with 2,4-dinitrophenylhydrazine. Since the ester showed no reducing action with Tollens' reagent or Fehling's solution, the presence of a ketone group was inferred. The designation of the ketone as a methyl ketone followed from the positive iodoform test. Oxidation of monocrotic acid with sodium hypobromite resulted in a mixture of two products which were shown by Adams, Rogers, and Sprules (67) to be *meso* and racemic α,α'-dimethylsuccinic acids (LXVI) by direct comparison with authentic samples of the acids and



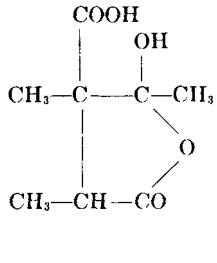
their derivatives. On the basis of these data, the structure assigned to monocrotic acid was that of α,β-dimethyllevulinic acid LXIV and to the ester, LXV. When monocrotic acid was heated at atmospheric pressure, a molecule of water was lost to give a neutral compound, $C_7H_{10}O_2$, b.p. 121° (20 mm.), which could be reconverted to the acid by hydrolysis. This compound was shown to be the unsaturated lactone, α,β-dimethyl-Δ^{β}-angelicalactone (LXVII), by its conversion to the saturated lactone, α,β-dimethyl-γ-valerolactone (LXVIII).

The establishment of the structure of monocrotic acid as α,β-dimethyllevulinic acid (LXIV) and its formation from monocrotalic acid by loss of carbon dioxide limits very definitely the possible structures of the latter. Monocrotalic acid was known to contain one carboxyl group and the presence of a lactone group was indicated on back titration of the acid

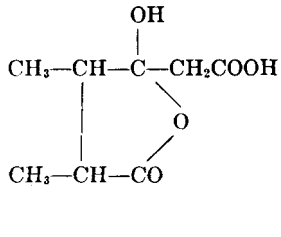
with excess alkali (34). The crystalline monomethyl ester could be prepared by the action of diazomethane (68), methanol containing 10% of dry hydrogen chloride (69), or by the action of thionyl chloride followed by treatment with methanol (70). The solid methyl monocrotalate (m.p. 79–80°, $[\alpha]_D^{30}$ − 16.24° (ethanol)) was distilled in high vacuum by Wicks (b.p. 162–165° (1 mm.)). Methyl monocrotalate showed one active hydrogen in a Zerewitinoff determination. Thermal decomposition of monocrotalic acid gave α,β-dimethyl-Δ^{β}-angelicalactone (LXVII), identical with that formed from monocrotic acid. The same lactone was also obtained by a two-step procedure which clarified the reaction. Methyl monocrotalate on heating *in vacuo* lost water to form an unsaturated ester, $C_9H_{12}O_4$ (b.p. 115–116° (3 mm.), $[\alpha]_D^{30}$ 25.74°) which was named methyl anhydromonocrotalate. When methyl anhydromonocrotalate was hydrolyzed with concentrated hydrochloric acid, α,β-dimethyl-Δ^{β}-angelicalactone was produced. The formation of the latter from monocrotalic acid therefore involved a dehydration and a decarboxylation (68). These observations showed that monocrotalic acid contains a lactone group which is stable to heat and strong acid, but which cleaves readily with alkali to give an unstable, easily decarboxylated acid (not isolated). The ease of dehydration and decarboxyla-



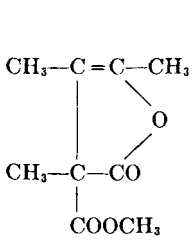
LXIX



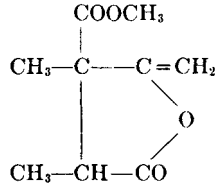
LXX



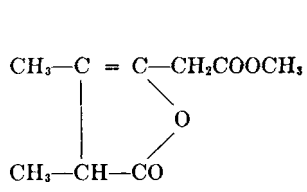
LXXI



LXXII



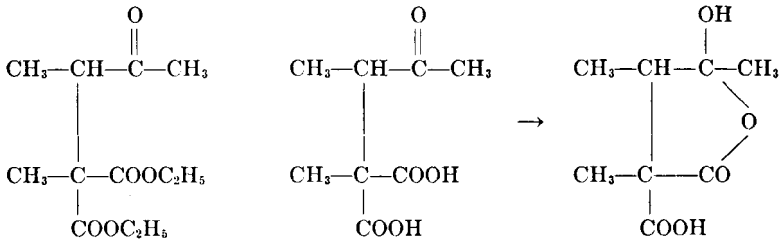
LXXIII



LXXIV

tion suggested structures LXIX, LXX, LXXI as possible for monocrotalic acid. The structures of methyl anhydromonocrotalate corresponding to these would be represented by LXXII, LXXIII, and LXXIV.

After Adams and Long (71) had established the structure of monocrotic acid unequivocally by the synthesis of α,β-dimethyllevulinic acid (LXIV), these workers established some grounds for the elimination of the unsatisfactory structures among those three postulated for monocrotalic acid. One of the intermediates prepared in the synthesis of α,β-dimethyllevulinic acid was the substituted malonic ester LXXV. By acid hydrolysis, the malonic acid derivative (LXXVI), which would be formed first, might then isomerize spontaneously to LXIX, one of the possibilities for mono-



LXXV LXXVI LXIX

crotalic acid. Acid hydrolysis of compound LXXV, however, resulted in an acid which lost carbon dioxide to form α,β-dimethyllevulinic acid. In contrast to this is natural monocrotalic acid, which is stable to boiling hydrochloric acid without the loss of carbon dioxide. Alkaline saponification of compound LXXV followed by acidification gave an oily acid which was titrated and shown to be dibasic, thus indicating no lactonization, and which upon heating to 80° was decarboxylated to α,β-dimethyllevulinic acid (LXIV). Monocrotalic acid, on the other hand, loses carbon dioxide in alkaline solution even at room temperature to give α,β-dimethyllevulinic acid (monocrotic acid). Structure LXIX was therefore not favored for monocrotalic acid (71).

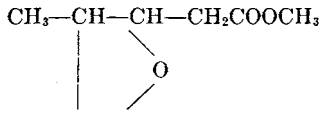
If the structure of monocrotalic acid were LXX, then the structure of methyl anhydromonocrotalate would be represented by LXXIII. However, no methylene group could be detected in methyl anhydromonocrotalate. Other evidence was found which mitigated against structure LXX for monocrotalic acid by Adams and Long. Upon alkaline hydrolysis of

LXXVII LXXVIII

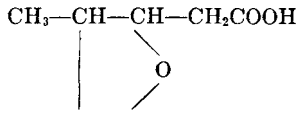
ethyl β-carbethoxy-α,β-dimethyllevulinate (LXXVII), carbon dioxide was lost and α,β-dimethyllevulinic acid was isolated. Boiling hydrochloric acid

gave similar results. However, cold hydrochloric acid yielded the half ester, unquestionably of structure LXXVIII. Compound LXXVIII gave a normal neutral equivalent and thus apparently showed no tendency to isomerize to a cyclic molecule. Methyl monocrotalate, on the other hand, hydrolyzes by means of hydrochloric acid to monocrotalic acid which is stable in this medium and does not lose carbon dioxide.

These reactions indicated indirectly that LXXI must be considered the most preferable of the three possible structures. The structure of methyl anhydromonocrotalate would then be LXXIV. This ester was



LXXIX



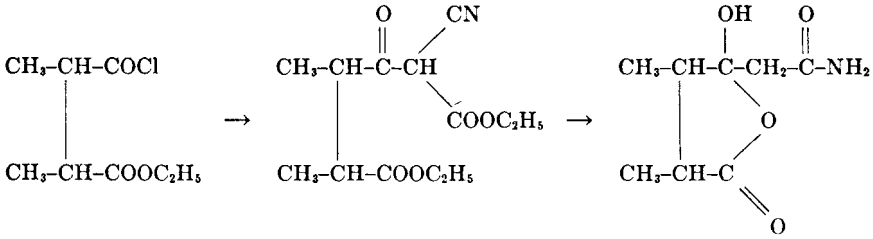
LXXX

hydrogenated at high temperature and pressure over Raney nickel. A mole equivalent of hydrogen was absorbed and methyl dihydroanhydromonocrotalate, $C_9H_{14}O_4$ (b.p. 115–117° (1 mm.), $[\alpha]_D^{29}$ 5.60°), was formed, the structure of which would be designated as LXXIX. This ester was hydrolyzed by boiling acid or alkali to the corresponding acid, $C_8H_{12}O_4$ (m.p. 131–132°, $[\alpha]_D^{30}$ 3.80° (ethanol)) (68). Dihydroanhydromonocrotalic acid (LXXX) showed no tendency to lose carbon dioxide (71).

Adams and Wilkinson (70) found other evidence which favored structure LXXI for monocrotalic acid. This is the only one of the three possible structures in which the carboxyl group is primary. In the other two possibilities, this group is tertiary. Methyl monocrotalate and its derivatives were converted with ease to the corresponding monoamides by treatment with aqueous or ethanolic ammonia at room temperature. The amide from methyl anhydromonocrotalate crystallized almost immediately upon the addition of aqueous ammonia. Methyl monocrotalate and methyl dihydroanhydromonocrotalate were converted to their amides by standing for several hours at room temperature. Such ease of ammonolysis would be expected of a primary carbomethoxyl group. The formation of methyl monocrotalate from the acid by treatment with methanol and hydrogen chloride is also consistent with the behavior of a primary carboxylic acid on esterification. Oxidation studies favored structure LXXI since nitric acid oxidation of monocrotalic acid gave dimethylmaleic anhydride and traces of acetic acid. Oxidation with acid permanganate also gave acetic acid.

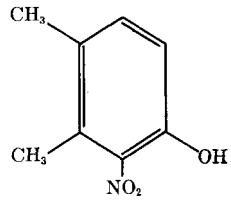
Numerous attempts to convert monocrotalic acid to an open chain compound which could be identified by synthesis were not successful (69, 70). A number of promising, but not yet successful, methods of synthetic approach

to monocrotalic acid have been studied. β-Carbethoxy-α,β-dimethylpropionyl chloride (LXXXI) was condensed with sodio ethyl cyanoacetate in ether to give ethyl δ-carbethoxy-δ-cyano-α,β-dimethyllevulinate (LXXXII),

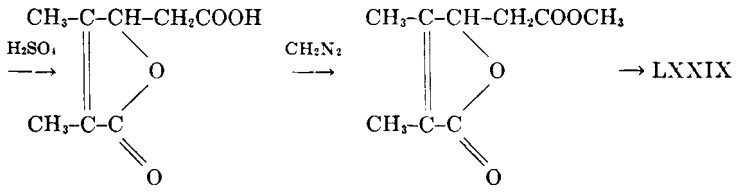


LXXXI LXXXII LXXXIII

but LXXXII could not be converted by acid or alkaline hydrolysis to the amide of inactive monocrotalic acid (LXXXIII) (70). A more unusual synthetic approach was that leading to optically inactive methyl dihydroanhydromonocrotalate (LXXIX) for comparison with the active material (69). The substituted phenol LXXXIV was treated with sulfuric acid to give slightly contaminated α,β-dimethyl-$\Delta^{\alpha,\beta}$-crotonolactone-γ-acetic acid (LXXXV). The methyl ester LXXXVI, formed by reaction with diazo-



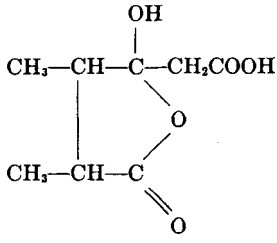
LXXXIV



LXXXV LXXXVI

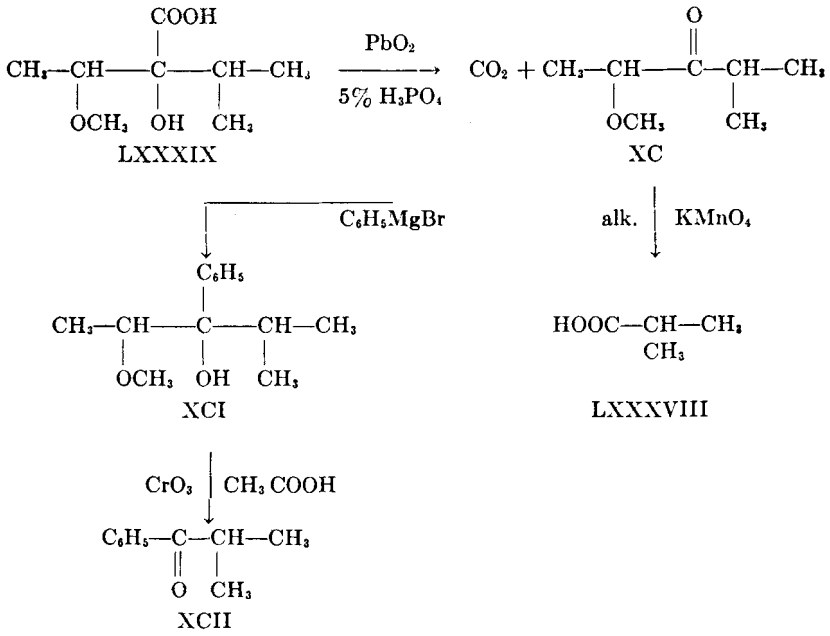
methane, contained 0.7% nitrogen. Hydrogenation of LXXXVI over Raney nickel at high pressure produced material which had the correct carbon and hydrogen analysis for the saturated ester LXXIX, but still contained a trace of nitrogen. Nevertheless, there was close correspondence between the physical properties of the synthetic ester (b.p. 114–115° (1 mm.), n_D^{20} 1.4578) and those of methyl dihydroanhydromonocrotolate (b.p. 115–117° (1 mm.), n_D^{20} 1.4510). Despite the nitrogenous impurity

which was carried along through this reaction scheme, it appears to be one of the most promising approaches toward the synthesis of a compound which would definitely establish the structure of monocrotalic acid as LXXXVII.



LXXXVII

b. Heliotrinic Acid. This acid, $C_8H_{16}O_4$, was obtained on hydrolysis of the alkaloid heliotrine. The presence in the molecule of a carboxylic acid group was demonstrated by titration; a hydroxyl group, by a Zerewitinoff determination; a methoxyl group, by a Zeisel determination (8). The structure postulated for heliotrinic acid by Men'shikov (11) was that of an optically active form of 2-methyl-3-hydroxy-4-methoxypentane-3-carboxylic acid (LXXXIX) on the basis of the following degradation reactions:



LXXXIX XC XCI LXXXVIII XCII

The loss of carbon dioxide and oxidation to a ketone was typical of the reaction of an α-hydroxy acid with lead dioxide and mineral acid. A ketone was obtained (b.p. 144–146° (760 mm.); $[\alpha]_D$ 22.5°; semicarbazone, m.p. 146–147°; oxime, b.p. 108.5–109.5° (16 mm.)) the structure of which was postulated as 2-methyl-4-methoxy-3-pentanone (XC). The ketone was oxidized by alkaline permanganate to isobutyric acid, which established the probable presence of the isobutyryl group in the ketone. Reaction of the ketone with phenylmagnesium bromide, followed by hydrolysis, gave a tertiary alcohol XCI. Oxidation of XCI by chromic anhydride in acetic acid gave isopropyl phenyl ketone (XCII), which was identical with synthetic isopropyl phenyl ketone. This proved that the ketone XC was an isopropyl ketone since the phenyl group could add only to the carbonyl group of an isopropyl ketone to produce isopropyl phenyl ketone as the subsequent oxidation product. Decision as to the position of the methoxyl group in the radical, $C_2H_2(OCH_3)$, also attached to the carbonyl group of the ketone XC was facile because of the requirement that this ketone be optically active. That the structure of this radical is α-methoxyethyl rather than β-methoxyethyl would also account for the ready cleavage of the 1,2-glycol monomethyl ether (XCI) by chromic anhydride in acetic acid. Therefore, the structure postulated by Men'shikov for heliotrinic acid (LXXXIX) has been verified on the basis of degradation but still awaits incontrovertible proof by synthesis.

c. Lasiocarpinic Acid. Of the C_8 necic acids — in fact, of all the necic acids — the structures of monocrotalic and heliotrinic are known with most certainty. Little is known about the structure of lasiocarpinic acid, $C_8H_{16}O_5$, which was obtained by Men'shikov and Zhdanovich (29), except that the oxygen content is accounted for by the fact that it is a monobasic acid having two hydroxyl groups and one methoxyl group. Lasiocarpinic acid was not isolated from the alkaline hydrolysis of the parent alkaloid, lasiocarpine, but it could be isolated following hydrogenolysis of the alkaloid. Angelic acid was isolated and identified as one of the hydrolytic cleavage products of lasiocarpine; therefore, this acid is also present in the alkaloid in ester combination.

4. C_{10} Acids

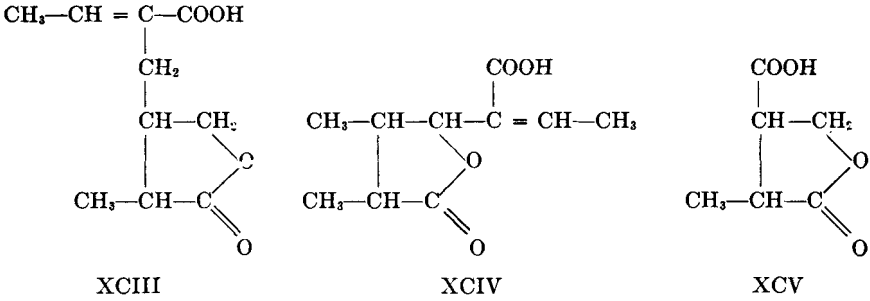
a. Platynecic Acid or Senecic Acid Lactone ($C_{10}H_{14}O_4$) and Senecic Acid ($C_{10}H_{16}O_5$). Platynecic acid, first isolated upon alkaline hydrolysis of platyphylline by Orékhov and Tiedebel (38), was found later by de Waal (6, 42) to be identical with senecic acid lactone (also $C_{10}H_{14}O_4$). The nomenclature of senecic acid lactone is confusing since sometimes it is called simply senecic acid, although the name senecic acid ($C_{10}H_{16}O_5$) also

refers to the dicarboxylic acid from which the lactone is derived. The $C_{10}H_{16}O_5$ dicarboxylic acid should be called "senecic acid," and the $C_{10}H_{14}O_4$ monocarboxylic acid monolactone should be called "senecic acid lactone." Such a convention will be observed in the present discussion.

Senecic acid lactone was first isolated upon hydrolysis of senecionine by Barger and Blackie (43). It was compared directly and was found identical with platynecic acid by de Waal. Senecic acid lactone was also isolated upon hydrolysis of rosmarinine (6, 22) but Richardson and Warren (43a) found that senecic acid was obtained under certain conditions of hydrolysis and isolation. These workers proceeded to convert senecic acid to senecic acid lactone. They further indicated that differences in recorded physical properties and difficulties in the purification of this lactonic acid were probably due to the presence of mixtures of senecic acid and senecic acid lactone.

Senecic acid was converted to the pure senecic acid lactone by repeated evaporation with a drop of hydrochloric acid (43a). The presence of the carboxylic acid and lactone groups in senecic acid lactone (or platynecic acid) was indicated by molecular weight determination and by titration with standard alkali (6, 38, 43). The presence of a carbon-carbon double bond was indicated by the catalytic hydrogenation of senecic acid lactone to dihydrosenecic acid lactone, $C_{10}H_{16}O_4$, m.p. 120° (24). The saturated lactone was also obtained by hydrogenolysis of rosmarinine. Oxidation studies provided useful information as to the structure of senecic acid lactone. Chromic acid oxidation yielded more than two equivalents of acetic acid, which served as an indication of the presence of up to three C-CH_3 groups (43). Nitric acid oxidation yielded $C_6H_8O_4$, m.p. 142°, an acid in which the lactone grouping was still present but which contained only two C-CH_3 groups. Alkaline permanganate oxidation in the cold gave acetic acid but no acetone or formaldehyde (19). Manske pointed out that, since senecic acid possesses a hydroxyl group which lactonizes readily, the hydroxyl group must be γ- with respect to one of the carboxyl groups but not to both of them; otherwise two senecic acid lactones would exist. He also suggested that the double bond must be present in a $CH_3{-}CH{=}C\begin{matrix}/\\ \\ \backslash\end{matrix}$ grouping, since acetic acid but no acetone or formaldehyde was formed on permanganate oxidation. With this accumulated information and the bold assumption of the presence of two isoprene units, Manske suggested two possible structures for senecic acid lactone, XCIII and XCIV. The structure XCIII was favored because nitric acid oxidation of such a compound might result in the loss of four carbons with the formation of a methylparaconic acid, $C_6H_8O_4$, of the type XCV. Such a product would not be

expected from XCIV. Final assignment of the correct structure for senecic acid lactone awaits further degradative and synthetic study.



XCIII XCIV XCV

b. Squalinecic Acid ($C_{10}H_{14}O_4$). Isomeric but not identical with senecic acid lactone is squalinecic acid, $C_{10}H_{14}O_4$, which was obtained by Barger and Blackie (43) upon hydrolysis of squalidine. Analysis indicated that the acid was not pure. The material isolated may well be a mixture of acid and lactone since the analytical figures lay between those calculated for $C_{10}H_{14}O_4$ and $C_{10}H_{16}O_5$. Squalinecic acid is similar to senecic acid lactone in that it was found to contain unsaturation and probably three C-methyl groups.

c. Carthamoidinecic, Longinecic, Sceleranecic, and Seneciphyllic Acids ($C_{10}H_{14}O_5$). These isomeric necic acids are not identical, as may be observed from the differences in physical properties recorded in Table 3.

Carthamoidinecic acid was studied in Adams' laboratory, where Phillips (3) isolated the acid upon alkaline hydrolysis of carthamoidine. The acid proved to be dibasic. It lactonized readily and formed a diester when treated with diazomethane. The presence of a double bond was detected and it was assigned a position α,β to one of the carbomethoxy groups because of the exaltation in the molar refraction of dimethyl carthamoidinecate (b.p. 135° (5 mm.); $[\alpha]_D^{29}4.3°$ (ethanol)). Hydrogenolysis of the parent alkaloid, carthamoidine, produced a sirupy acid which was probably saturated.

Longinecic acid was assigned the molecular formula $C_{10}H_{14}O_5$ on the basis of the formulas for the parent alkaloid, longilobine, and for the necine, retronecine, which is the other product of hydrolysis of the alkaloid (19). The analysis of longinecic acid gave poor agreement with the formula assigned.

Sceleranecic acid was obtained by de Waal and Pretorius (25) from sceleratine by hydrolysis or hydrogenolysis. The compound had no free carboxyl group but was a dilactone; one lactone ring was very stable. The first lactone was opened by treatment with sodium hydroxide in the cold. The second ring was opened only by refluxing with sodium hydroxide.

Catalytic hydrogenation returned the unchanged sceleranecic acid. A more stable form of the dilactone was also obtained. It was less soluble in water, melted at 213°, but was similar otherwise.

Seneciphyllic acid, isolated upon alkaline hydrolysis of seneciphylline by Konovalova and Orékhov (37), is unusual among the necic acids in that it showed no optical activity. Titration with standard alkali indicated that it is a dibasic acid. A Zerewitinoff determination indicated the presence of two active hydrogens.

d. Riddellic Acid ($C_{10}H_{14}O_6$). Saponification of riddelliine yielded retronecine and riddellic acid (46). The acid was obtained by Adams and his co-workers in both anhydrous and hydrated forms. Direct titration showed that riddellic acid was dibasic; addition of excess alkali followed by back titration gave evidence for a third carboxyl group, probably occurring as a lactone linkage in the necic acid. Hydrogenation of the acid over platinum oxide catalyst indicated the absorption of two mole equivalents of hydrogen, but no product was obtained in the pure state. The acid formed a dimethyl ester on treatment with diazomethane. Dimethyl riddellate (b.p. 144–145° (1 mm.); $[\alpha]_D^{32}$ − 2.84° (ethanol)) was hydrogenated over platinum oxide with the absorption of one mole equivalent of hydrogen to give a nearly quantitative yield of dimethyl dihydroriddellate (b.p. 146–147° (1 mm.); $[\alpha]_D^{32}$ − 15.3° (ethanol)). Both carboxyl groups of riddellic acid appear to be esterified with the necine hydroxyls in the parent alkaloid.

e. Grantianic Acid ($C_{10}H_{14}O_7$). Saponification of grantianine yielded retronecine and a necic acid which was not obtained in a pure state. However, the hydrolysis and hydrogenation experiments of Adams, Carmack, and Rogers (7) indicated that the acid would have the molecular formula $C_{10}H_{14}O_7$ and that both of its carboxylic acid groups would be in ester combination in the alkaloid molecule.

f. Hastanecinic, Hieracinecic, and Integerrinecic Acids ($C_{10}H_{16}O_5$). These acids are isomeric with senecic acid, $C_{10}H_{16}O_5$, and with a dibasic acid, m.p. 136–137°, which was obtained on hydrolysis of jacodine by Barger and Blackie (28). Hastanecinic acid, found to be a dibasic hydroxy acid, was obtained by Konovalova and Men'shikov (7a) on hydrolysis of hastacine. Hieracinecic acid was obtained as one of the alkaline hydrolysis products of hieracifoline by Manske (18), who also isolated integerrinecic acid (19) in the same manner from the alkaloid integerrimine. Although the melting points of integerrinecic acid and senecic acid were identical, the acids were not.

g. Isatinecic, Jaconecic, Retronecic, Senecifolic Acids and Pterophnecic Lactone ($C_{10}H_{16}O_6$). All of these isomeric necic acids differ in melting point and specific rotation, as may be seen in Table 3.

Isatinecic acid, which was obtained by Blackie (1) on hydrolysis of isatidine, is the most unusual of these necic acids since it contains a peroxygen atom within a percarboxylic acid group. de Waal (20) found that this acid, obtained on hydrolysis of isatidine with barium hydroxide under mild conditions, oxidized potassium iodide. If greater heat was applied during the hydrolysis, a monolactone was formed, $C_{10}H_{14}O_5$ (m.p. 197–198°, $[\alpha]_D^{20}$108.8°), which contained the peroxide oxygen in the lactone ring (24). This was indicated because the $C_{10}H_{14}O_5$ compound liberated iodine only from acidified potassium iodide solution (6). The same applies to isatidine, which has one peroxygen atom easily removed by catalytic hydrogenation, so that both carboxylic and percarboxylic groups must be esterified with the hydroxyl groups of the necine fragment. When isatidine was split with alcoholic potassium hydroxide, a migration of the peroxygen atom must have taken place because a dicarboxylic acid, $C_{10}H_{16}O_6$, was formed which was isomeric with isatinecic acid (22). This acid, to which the name "dewalinecic acid" was assigned (21), was an ordinary dicarboxylic acid that had physical constants (m.p. 181°, $[\alpha]_D^{22}$ 56° (water)) different from those of isatinecic acid. Dewalinecic acid and isatinecic acid each consumed two moles of hydrogen on catalytic reduction to give oily dihydro acids.

Jaconecic acid, $C_{10}H_{16}O_6$, is somewhat unusual since it was obtained on alkaline hydrolysis of two different alkaloids, jacobine, by Manske (26), and otosenine, by Zhdanovich and Men'shikov (36). When otosenine was heated with 15% hydrochloric acid for 30 hours, $C_{10}H_{12}ClO_4$ was formed (m.p. 111–113°, $[\alpha]_D$ − 25.2° (chloroform)). Evidently this reaction involved the loss of a molecule of water from jaconecic acid and replacement of a hydroxyl group by chlorine. The only other available information on jaconecic acid consists in the *C*-methyl determination on the acid by Barger and Blackie (28), which indicated the presence of three or more such groups.

Retronecic acid was first obtained by Manske (26) upon alkaline hydrolysis of retrorsine. It was found to be a dibasic acid which formed a lactone, $C_{10}H_{14}O_5$ (m.p. 186°), with ease. The acid was stable in the presence of reducing and mild oxidizing agents (44) and was found to have two *C*-methyl groups (43) and one hydroxyl (44).

Senecifolic acid was found to be a product of the hydrolysis of senecifoline by Watt in 1909 (3). Watt suggested that the compound was probably a monocyclic dihydroxydicarboxylic acid. The sodium salt gave no reaction with potassium permanganate.

Pterophnecic lactone was isolated and studied by de Waal (6, 24), who obtained the compound as a hydrolysis product of pterophine. Evidently no free carboxyl group is present. The lactone group was indicated

by titration, but the molecular formula and the true nature of the compound remain in doubt.

5. C_{13} Acids

Little is known concerning the only necic acid containing thirteen carbon atoms which has been isolated. Mikanecic acid was one of the hydrolysis products of mikanoidine (30), along with mikanecine. Senecioic acid was also obtained from the plant extract, but it does not appear to have been in combination with the alkaloid (28).

V. Structure of the Alkaloids

With a knowledge of the structures of the hydrolysis and hydrogenolysis products of the *Senecio* alkaloids, it is possible to combine the necines and necic acids in formulas to represent the parent alkaloids. Where the chemistry of the alkaloid provides information concerning its structure which is not provided by the chemistry of the two fractions, such additional information has been included in the discussion, along with the pertinent hydrolysis and hydrogenolysis reactions. Where nothing is known about the alkaloid except its molecular formula and physical properties as outlined in Table 1, the alkaloid will not be discussed. For information concerning the physical properties of derivatives of the alkaloids, the reader should consult the references listed in Table 1. The structure of the alkaloid is given when it has been established with some degree of certainty. A number of alkaloids which appear in Table 1 are probably not pure chemical individuals but are mixtures of two or more alkaloids. They have been included with the best information available to date as to their physical and chemical properties.

1. Carthamoidine

Carthamoidine was obtained in 0.52% yield from *Senecio carthamoides*; no other alkaloid was found in this source.

Hydrolysis (3): $\underset{\text{Carthamoidine}}{C_{18}H_{23}NO_5} + 2H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Carthamoidinecic acid}}{C_{10}H_{14}O_5}$

Hydrogenolysis (3): $C_{18}H_{23}NO_5 + 3H_2 \xrightarrow{Pt} \underset{\text{Retronecanol}}{C_8H_{15}NO} +$ Sirupy acid

2. Dicrotaline

Dicrotaline was isolated in 0.27% yield from *Crotalaria dura* and in 0.18% yield from *Crotalaria globifera.*

Hydrolysis (4): $\underset{\text{Dicrotaline}}{C_{14}H_{19}NO_5} + 2H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Dicrotalic acid}}{C_6H_{10}O_5}$

3. Grantianine

Extraction of the seeds of *Crotalaria grantiana* gave grantianine in 0.34% yield.

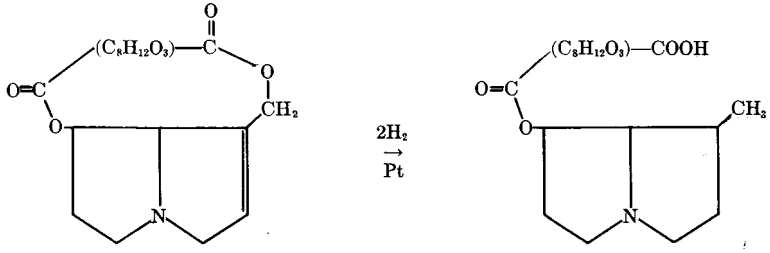
Hydrolysis (7): $C_{18}H_{23}NO_7 + 2H_2O \xrightarrow[CH_3OH]{KOH} C_8H_{13}NO_2 +$ Grantianic acid

Grantianine — Retronecine

Hydrogenation (7): $C_{18}H_{23}NO_7 + 2H_2 \xrightarrow{Pt} C_{18}H_{27}NO_7$

Tetrahydrograntianine (m.p. 242.5°)

Adams, Carmack, and Rogers (7) suggested that grantianine might be retronecine esterified on both hydroxyls with one mole of the dibasic acid, grantianic acid, or a cyclic diester. The first molecule of hydrogen would cleave the less stable ester grouping and the second molecule of hydrogen would reduce the double bond in the nucleus of the base. The tetrahydrograntianine would then be an amino acid. Its solubility characteristics — slightly soluble in water, insoluble in ethanol, soluble in cold dilute hydrochloric acid and cold dilute aqueous ammonia — tend to confirm this assumption. On the basis of the structure which has been proved correct for retronecine (65), the formula for grantianine would be XCVI and that for tetrahydrograntianine, XCVII, following the suggestions of Adams and his co-workers (7).



XCVI XCVII

4. Hastacine

Hastacine was extracted from *Cacalia hastata* in 0.085% yield.

Hydrolysis (7a): $C_{18}H_{27}NO_5 + 2H_2O \xrightarrow[C_2H_5OH]{KOH} C_8H_{15}NO_2 + C_{10}H_{16}O_5$

Hastacine — Hastanecine — Hastanecinic acid

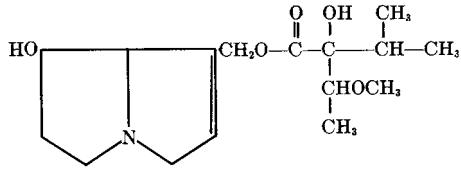
5. Heliotrine

Heliotrine was obtained in a yield of 0.25%, along with lasiocarpine, as the main alkaloid in *Heliotropium lasiocarpum.*

Hydrolysis (8): $C_{16}H_{27}NO_5 + H_2O \xrightarrow{Ba(OH)_2} C_8H_{13}NO_2 + C_8H_{16}O_4$
Heliotrine — Heliotridine — Heliotrinic acid

Hydrogenolysis (10): $C_{16}H_{27}NO_5 + 2H_2 \xrightarrow{Pt} C_8H_{15}NO + C_8H_{16}O_4$
Oxyheliotridane — Heliotrinic acid

Structure:



XCVIII

6. Hieracifoline

Hieracifoline was obtained in 0.016% yield from *Erechtites hieracifolia,* commonly called "fireweed."

Hydrolysis (18): $C_{18}H_{25}NO_5 + 2H_2O \xrightarrow[CH_3OH]{KOH} C_8H_{13}NO_2 + C_{10}H_{16}O_5$
Hieracifoline — Retronecine — Hieracinecic acid

7. Integerrimine

Integerrimine was found as a minor constitutent, obtained from the mother liquor of senecionine, in *Senecio integerrimus* when the plant was mature and seed was beginning to form.

Hydrolysis (19): $C_{18}H_{25}NO_5 + 2H_2O \xrightarrow[C_2H_5OH]{KOH} C_8H_{13}NO_2 + C_{10}H_{16}O_5$
Retronecine — Integerrinecic acid

8. Isatidine

Isatidine was obtained from *Senecio isatideus* in 1.3% yield, along with retrorsine; from *Senecio retrorsus* in 0.3% yield; from *Senecio sceleratus* in 0.05% yield. Compared with the other *Senecio* alkaloids, isatidine is unusual in its possession of a peroxygen atom which is easily removed by cat-

alytic hydrogenation. This atom is present in the isatinecic acid portion of the molecule as a free percarboxylic acid group.

Hydrolysis: (a)(20) $C_{18}H_{25}NO_7 + 2H_2O \xrightarrow{Ba(OH)_2}$ $C_8H_{13}NO_3$ (Isatinecine) + $C_{10}H_{16}O_6$ (Isatinecic acid)
Isatidine

(b)(22) $C_{18}H_{25}NO_7 + 2H_2O \xrightarrow[C_2H_5OH]{KOH}$ $C_8H_{13}NO_3$ (Isatinecine) + $C_{10}H_{16}O_6$ (Dewalinecic acid)

Hydrogenation (20, 21, 24): $C_{18}H_{25}NO_7 + 4H_2 \xrightarrow{Pt}$ $C_{18}H_{31}NO_6$ (Hexahydrodesoxyisatidine (m.p. 183–184°)) + H_2O

$C_{18}H_{31}NO_6 \xrightarrow{Ba(OH)_2} C_8H_{17}NO_3$ (Tetrahydroisatinecine)

9. Jacobine

Jacobine was extracted from *Senecio jacobaea* in 0.03% yield from plants which had been collected in June and in 0.05–0.06% yield from plants which had been collected in July and August. It was also obtained, in 0.05% yield, along with jacodine, from *Senecio cineraria* collected in June.

Hydrolysis (26): $C_{18}H_{25}NO_6 + 2H_2O \rightarrow C_8H_{13}NO_2 + C_{10}H_{16}O_6$
Jacodine — Retronecine — Jaconecic acid

10. Jacodine

Senecio aquaticus collected in July gave 0.04% of jacodine; that collected in September, 0.018%.

Hydrolysis (28): $C_{18}H_{25}NO_5 + 2H_2O \rightarrow C_8H_{13}NO_2 + C_{10}H_{16}O_5$
Jacodine — Retronecine

11. Lasiocarpine

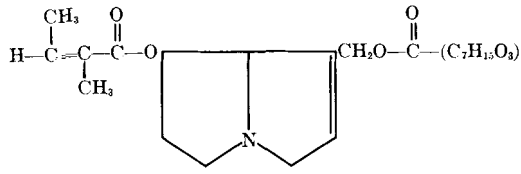
Lasiocarpine was obtained in 0.025% yield, along with heliotrine, from *Heliotropium lasiocarpum*.

Hydrolysis (29): $C_{21}H_{33}NO_7 + H_2O \xrightarrow{NaOH}$ $C_8H_{13}NO_2$ (Heliotridine) + $C_5H_8O_2$ (Angelic acid)
Lasiocarpine

Hydrogenolysis (29): $C_{21}H_{33}NO_7 + 3H_2 \xrightarrow{Pt}$ $C_{13}H_{23}NO_2$ (b.p. 123–125°/8 mm.) + $C_8H_{16}O_5$ (Lasiocarpinic acid)

$C_{13}H_{23}NO_2 \xrightarrow[H_2O]{KOH,\ C_2H_5OH} C_8H_{15}NO$ (Oxyheliotridane) + $C_5H_{10}O_2$ (2-Methylbutanoic acid)

Structure:



XCIX

Lasiocarpinic acid was considered to be esterified with the allylic hydroxyl of heliotridine because of its isolation in the hydrogenolysis of the alkaloid. The angelic acid was considered to be esterified with the 7-hydroxyl of heliotridine since this linkage was not easily reduced.

12. Longilobine

Senecio longilobus collected in September, at and past the flower stage, yielded 0.058% of longilobine.

Hydrolysis (19): $C_{18}H_{23}NO_5 + 2H_2O \rightarrow \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Longinecic acid}}{C_{10}H_{14}O_5}$

13. Mikanoidine

The alkaloid was obtained impure from *Senecio mikanioides* in 0.02% yield. The molecular formula of mikanoidine was assigned by Manske and was based upon the formulas of the hydrolysis products.

Hydrolysis (30): $\underset{\text{Mikanoidine}}{(C_{21}H_{29}NO_6} + H_2O \xrightarrow[CH_3OH]{KOH} \underset{\text{Mikanecine}}{C_8H_{15}NO_2} + \underset{\text{Mikanecic acid}}{C_{13}H_{16}O_5}$

14. Monocrotaline

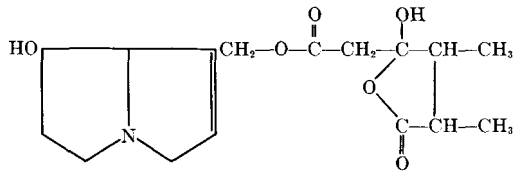
Monocrotaline was extracted from the seeds of *Crotalaria spectabilis* in 3.2% yield and from those of *Crotalaria retusa* in 1.89% yield.

Hydrolysis (34): $\underset{\text{Monocrotaline}}{C_{16}H_{23}NO_6} + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Monocrotic acid}}{C_7H_{12}O_3} + CO_2$

$\uparrow$ NaOH

Hydrogenolysis (34): $C_{16}H_{23}NO_6 + 2H_2 \xrightarrow{Pt} \underset{\text{Retronecanol}}{C_8H_{15}NO} + \underset{\text{Monocrotalic acid}}{C_8H_{12}O_5}$

Structure:



I

15. Otosenine

Extraction of *Senecio othonnae* gave otosenine in 0.07% yield. The presence of one hydroxyl and one *N*-methyl group was indicated by analysis.

Alkaline hydrolysis (36): $C_{19}H_{27}NO_7 + H_2O \xrightarrow{Ba(OH)_2} C_{10}H_{16}O_6$
Otosenine — Jaconecic acid

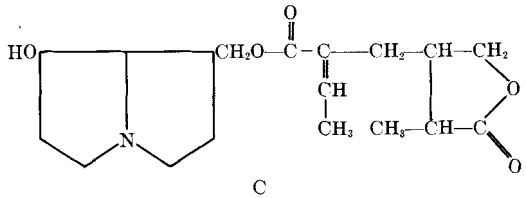
Acid hydrolysis (36): $C_{19}H_{27}NO_7 + HCl \xrightarrow{\Delta} C_9H_{15}NO_3 + C_{10}H_{13}ClO_4$
Otonecine

16. Platyphylline

Platyphylline was obtained together with seneciphylline from *Senecio platyphyllus*, with rosmarinine from *Senecio hygrophilus*, and in 0.5% yield from *Senecio adnatus* in the flowering stage. Platyphylline can be separated from a mixture with seneciphylline by precipitation when the mixture is heated with an ethanolic solution of tartaric acid (72). On the basis of the structure postulated by Manske (19) for platynecic acid (senecic acid lactone), the structure of platyphylline would be C.

Hydrolysis (38): $C_{18}H_{27}NO_5 + H_2O \xrightarrow[C_2H_5OH]{NaOH} C_8H_{15}NO_2 + C_{10}H_{14}O_4$
Platynecine — Platynecic acid

Structure (?):



C

17. Pterophine

Pterophine was obtained in 0.18% yield, together with retrorsine, from *Senecio pterophorus* in the preflowering and flowering stages, and it was obtained, together with retrorsine and senecionine, from *Senecio ilicifolius* collected in the postflowering stage.

Hydrolysis (6, 24): $C_{18}H_{23}NO_5 + 3H_2O \xrightarrow[C_2H_5OH]{KOH} C_8H_{13}NO_2 + C_{10}H_{16}O_6$
Pterophine — Retronecine — Pterophnecic lactone

18. Retrorsine

Retrorsine was extracted from the sources indicated in the following yields: *Senecio retrorsus*, 1.3%; *Senecio isatideus*, 0.15%; *Senecio glaberrimus*, 0.027%; *Senecio venosus*, 0.01%.

Hydrolysis (26): $C_{18}H_{25}NO_6 + 2H_2O \xrightarrow{NaOH} C_8H_{13}NO_2 + C_{10}H_{16}O_6$
Retrorsine — Retronecine — Retronecic acid

Hydrogenolysis (44): $C_{18}H_{25}NO_6 + 2H_2 \xrightarrow{Pt} C_8H_{15}NO$
Retronecanol

19. RIDDELLIINE

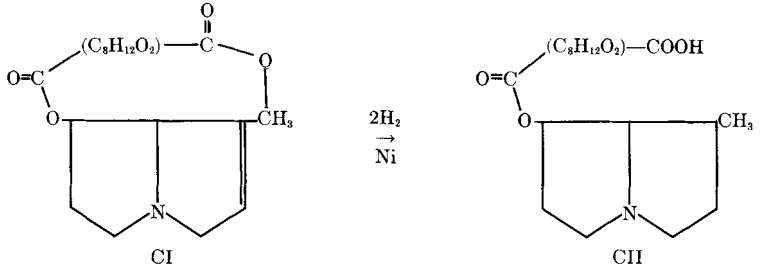
The alkaloid from *Senecio riddellii* was obtained in yields of 0.45–0.67%.

Hydrolysis (46): $C_{18}H_{23}NO_6 + 2H_2O \xrightarrow{Ba(OH)_2} C_8H_{12}NO_2 + C_{10}H_{14}O_6$
(Riddelliine → Retronecine + Riddellic acid)

Hydrogenation (46): (a) $C_{18}H_{23}NO_6 + 2H_2 \xrightarrow{Ni} C_{18}H_{27}NO_6$
(Tetrahydroriddelliine (m.p. 205°))
$\xrightarrow{H_2O \mid Ba(OH)_2} C_8H_{15}NO + C_{10}H_{14}O_6$
(Retronecanol + Riddellic acid)

(b) $C_{18}H_{23}NO_6 + 4H_2 \xrightarrow{Pt} \xrightarrow[NaOH]{H_2O} C_8H_{15}NO$
(Retronecanol)

Tetrahydroriddelliine was found to possess the physical properties of an amino acid. Since retronecanol and riddellic acid were obtained as hydrolysis products of tetrahydroriddelliine, one mole of hydrogen must have been used in the hydrogenolysis of the allylic ester grouping and one mole for the saturation of the pyrrolizidine ring. On the basis of this evidence, Adams and his co-workers (46) suggested that riddelliine exists as a cyclic diester (CI), in which one molecule of the dibasic riddellic acid is linked to the two hydroxyls of a molecule of retronecine. The alkaloid is similar in general structure to grantianine. Tetrahydroriddelliine would then be represented by CII, an amino acid, which would account for retronecanol and riddellic acid as its hydrolysis products.



CI CII

If hydrogenation of riddelliine was carried out over platinum oxide, four mole equivalents of hydrogen were rapidly absorbed but the octahydroriddelliine was not isolated. Alkaline hydrolysis of the crude reaction product yielded retronecanol and an acid which resisted purification. The additional two moles of hydrogen must have reacted with the acid portion of the molecule, a fact which agrees with the hydrogenation of riddellic acid itself.

20. Rosmarinine

Rosmarinine was obtained from *Senecio rosmarinifolius* in 0.1% yield, from *Senecio brachypodus* in 0.24–0.36% yield, and from *Senecio pauciligulatus* in 1.0% yield. The alkaloid content of *Senecio hygrophilus* varies. Rosmarinine, platyphylline, and an alkaloid $C_{18}H_{27}NO_6$ have been isolated as the sole constituents or as mixtures depending upon the stage of growth, season and district. Rosmarinine was found alone (1.5%) or in combination with platyphylline (0.03–0.3%). The plant appeared to be richest in alkaloid prior to budding and when growing in the shade.

Hydrolysis: (a)(43a) $C_{18}H_{27}NO_6 + 2H_2O \xrightarrow{Ba(OH)_2} C_8H_{15}NO_3 + C_{10}H_{16}O_5$
Rosmarinine — Rosmarinecine — Senecic acid

$\xrightarrow{\Delta \mid HCl}$

(b)(6) $C_{18}H_{27}NO_6 + H_2O \xrightarrow[C_2H_5OH]{KOH} C_8H_{15}NO_3 + C_{10}H_{14}O_4$
Rosmarinecine — Senecic acid lactone

$\xrightarrow{H_2 \mid Pt}$

Hydrogenation (6): $C_{18}H_{27}NO_6 + H_2 \xrightarrow{Pt} \xrightarrow[H_2O]{Ba(OH)_2} C_8H_{15}NO_3 + C_{10}H_{16}O_4$
Rosmarinecine — Dihydrosenecic acid lactone

21. Sceleratine

Senecio sceleratus, collected in early summer, yielded 0.11% sceleratine, 0.17% retrorsine, and 0.05% isatidine.

Hydrolysis (25): $C_{18}H_{27}NO_7 + H_2O \xrightarrow{Ba(OH)_2} C_8H_{13}NO_2 + C_{10}H_{14}O_5$
Sceleratine — Retronecine — Sceleranecic acid

Hydrogenolysis (25): $C_{18}H_{27}NO_7 + 2H_2 \xrightarrow{Pt} C_8H_{15}NO + C_{10}H_{14}O_5$
Retronecanol — Sceleranecic acid

22. Senecifoline

The source of senecifoline is uncertain since Barger and his co-workers (44) were not able to isolate any senecifoline from *Senecio latifolius* when they repeated the work of Watt (48) on carefully identified plant material.

Hydrolysis (48): $C_{18}H_{27}NO_8 + H_2O \rightarrow C_8H_{13}NO_2 + C_{10}H_{16}O_6$ (?)
Senecifoline — Retronecine — Senecifolic acid

It will be noted that these formulas are incompatible, so that the formula of either senecifoline or senecifolic acid must be in error. Carbon and hydrogen analyses of senecifoline and gold analysis of its aurichloride

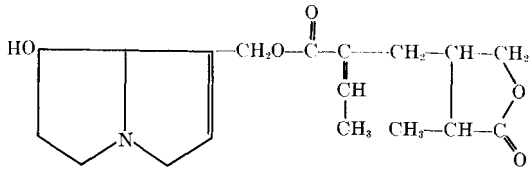
support the formula $C_{18}H_{27}NO_8$. The carbon and hydrogen analyses of senecifolic acid support the formula $C_{10}H_{16}O_6$, but molecular weight determinations on the sodium and silver salts disagree with this formula for the acid.

23. Senecionine

Senecionine was extracted from the sources indicated in the following yields: *Senecio vulgaris* L., 0.17%; *Senecio viscosus*, 0.075%; *Senecio squalidus*, 0.06%; *Senecio aureus* L., 0.006%; *Senecio ilicifolius*, 0.02%; *Senecio pseudo-arnica*, 0.02%; *Senecio integerrimus*, 0.3%. On the basis of the structure postulated by Manske (19) for senecic acid lactone (platynecic acid), the structure of senecionine would be CIII.

Hydrolysis (43): $\underset{\text{Senecionine}}{C_{18}H_{25}NO_5} + H_2O \rightarrow \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Senecic acid lactone}}{C_{10}H_{14}O_4}$

Structure (?):



CIII

24. Seneciphylline

Seneciphylline was obtained together with platyphylline in a total crude yield of about 1.0% from *Senecio platyphyllus*. It was obtained together with a small amount of spartioidine in a total crude yield of 0.54%. It was found to be the only alkaloid present (0.04%) in *Senecio stenocephalus*.

Hydrolysis (37): $\underset{\text{Seneciphylline}}{C_{18}H_{23}NO_5} + 2H_2O \xrightarrow{NaOH} \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Seneciphyllic acid}}{C_{10}H_{14}O_5}$

25. Squalidine

Squalidine was obtained in 0.005% yield, along with the main alkaloidal constituent, senecionine, from *Senecio squalidus*.

Hydrolysis (43): $\underset{\text{Squalidine}}{C_{18}H_{25}NO_5} + H_2O \rightarrow \underset{\text{Retronecine}}{C_8H_{13}NO_2} + \underset{\text{Squalinecic acid}}{C_{10}H_{14}O_4}$

26. Trachelanthamine

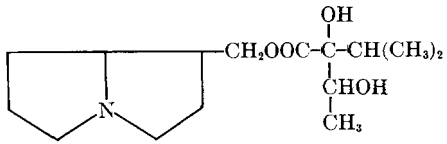
From *Trachelanthus korolkovi*, 0.25–0.30% of trachelanthine was obtained along with a small quantity of trachelanthamine. Trachelanthine is the *N*-oxide of trachelanthamine.

Hydrolysis: (a) (56a, 56c) $C_{15}H_{27}NO_4 + H_2O \xrightarrow{Ba(OH)_2}$ Trachelanthamine → $C_8H_{15}NO$ Trachelanthamidine + $C_7H_{14}O_4$ Trachelanthic acid

$H_2O_2 \downarrow \quad \uparrow H_2SO_3$

(b) (56) $C_{15}H_{27}NO_5 + H_2O \xrightarrow{Ba(OH)_2}$ Trachelanthine → $C_8H_{15}NO_2$ Trachelanthidine + $C_7H_{14}O_4$ Trachelanthic acid

Structure (?):



CIIIa

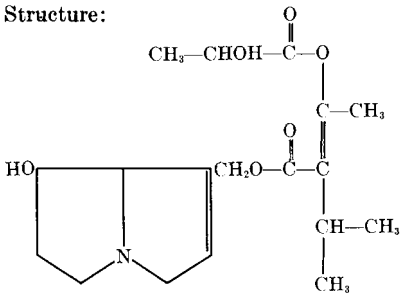
27. Trichodesmine

Extraction of *Trichodesma incanum* gave trichodesmine in 0.075% yield. A Zerewitinoff determination indicated the presence of two active hydrogens. No color was obtained with ferric chloride. The probable structure of trichodesmine is either CIV or CV.

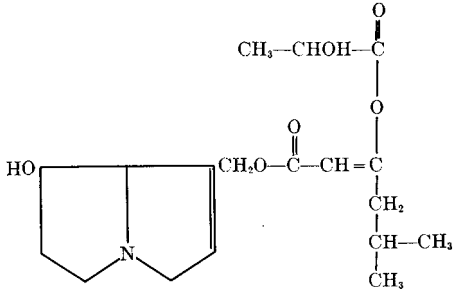
Hydrolysis (55): $C_{18}H_{27}NO_6 + 2H_2O \xrightarrow{NaOH}$ Trichodesmine → $C_8H_{13}NO_2$ Retronecine + $C_3H_6O_3$ *dl*-Lactic acid + $C_6H_{12}O$ Methyl isobutyl ketone + CO_2

Hydrogenolysis (55): $C_{18}H_{27}NO_6 + H_2 \xrightarrow{Pt} C_8H_{15}NO$ Retronecanol

Structure:



CIV



CV

VI. Common Sources of Different Senecio Alkaloids

From the foregoing discussion, it will be observed that a number of plants contain more than one of the *Senecio* alkaloids. Those plants which

serve as a common source of different *Senecio* alkaloids are listed in Table 4. The molecular formulas of alkaloids found in the same plant appear to be

TABLE 4

COMMON SOURCES OF DIFFERENT SENECIO ALKALOIDS

Plant	Alkaloids	Formulas
Senecio fuchsii	Fuchsisenecionine	$C_{12}H_{21}NO_3$
	—	$C_9H_{15}NO_2$
S. graminifolius	Graminifoline	$C_{18}H_{23}NO_5$
	Retrorsine	$C_{18}H_{25}NO_6$
S. integerrimus	Integerrimine	$C_{18}H_{25}NO_5$
	Senecionine	$C_{18}H_{25}NO_5$
S. isatideus	Isatidine	$C_{18}H_{25}NO_7$
	Retrorsine	$C_{18}H_{25}NO_6$
S. retrorsus	Isatidine	$C_{18}H_{25}NO_7$
	Retrorsine	$C_{18}H_{25}NO_6$
S. sceleratus	Isatidine	$C_{18}H_{25}NO_7$
	Retrorsine	$C_{18}H_{25}NO_6$
	Sceleratine	$C_{18}H_{27}NO_7$
S. jacobaea	Jacobine	$C_{18}H_{25}NO_6$
	Jacodine	$C_{18}H_{25}NO_5$
	Jaconine	$C_{18}H_{25}NO_8$
S. cineraria	Jacobine	$C_{18}H_{25}NO_6$
	Jacodine	$C_{18}H_{25}NO_5$
S. paludosus	Jacobine	$C_{18}H_{25}NO_6$
	Jacodine	$C_{18}H_{25}NO_5$
S. platyphyllus	Platyphylline	$C_{18}H_{27}NO_5$
	Seneciphylline	$C_{18}H_{23}NO_5$
S. hygrophilus	Platyphylline	$C_{18}H_{27}NO_5$
	Rosmarinine	$C_{18}H_{27}NO_6$
	—	$C_{18}H_{27}NO_6$
S. pterophorus	Pterophine	$C_{18}H_{23}NO_5$
	Retrorsine	$C_{18}H_{25}NO_6$
S. ilicifolius	Pterophine	$C_{18}H_{23}NO_5$
	Retrorsine	$C_{18}H_{25}NO_6$
	Senecionine	$C_{18}H_{25}NO_5$
S. latifolius	Senecifolidine	$C_{18}H_{25}NO_7$
	Senecifoline	$C_{18}H_{27}NO_8$
S. vulgaris	Senecine	—
	Senecionine	$C_{18}H_{25}NO_5$
S. squalidus	Senecionine	$C_{18}H_{25}NO_5$
	Squalidine	$C_{18}N_{25}NO_5$

TABLE 4 (*Continued*)

Plants	Alkaloids	Formulas
S. spartioides	Seneciphylline	$C_{18}H_{23}NO_5$
	Spartioidine	$C_{18}H_{23}NO_5$
S. saracenicus	—	C_5H_9NO
	—	$C_8H_{13}NO$
	—	$C_{13}H_{21}NO_3$
Erechtites hieracifolia	Hieracifoline	$C_{18}H_{25}NO_5$
	—	$C_{20}H_{17}NO_6$ or $C_{20}H_{19}NO_6$
Heliotropium lasiocarpum	Heliotrine	$C_{16}H_{27}NO_5$
	Lasiocarpine	$C_{21}H_{33}NO_7$
Trachelanthus korolkovi	Trachelanthamine	$C_{15}H_{27}NO_4$
	Trachelanthine	$C_{15}H_{27}NO_5$

very closely related in most cases. *Crotalaria usaramoensis* and *Crotalaria incana* have been found to contain crystallizable alkaloids (2), but the crystalline material obtained appeared to be a mixture of two or more alkaloids. Finally, Orékhov and Tiedebel (38) reported that the following species of *Senecio* also contain a certain amount of alkaloidal material: *Senecio candollianus, platyphylloides, thyrsophorus, brachychaetus, orientalis, pedunculosus, grandidentatus, jacquinianus,* and *massagetovii* (sp. nova).

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CHAPTER V

The Pyridine Alkaloids

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I. Introduction

Two facts concerning tobacco are significant. Although the growing of tobacco was restricted in Europe and Asia by the need for food crops, the world production for the season 1945–46 was estimated at 6,654,000,000 lbs. One of the factors forcing the economics of Britain into an unfavorable position is the import of tobacco into that country from the dollar areas. These two facts clearly illustrate that at least one of the pryidine alkaloids occupies a unique position of economic and industrial importance, commensurate with its theoretical interest.

There are isolated instances where the parent bases, pyridine and piperidine, have been found to occur in nature. However, it is the more complex members of this series of bases that have attracted the attention of alkaloid chemists. Pyridine occurs in the rayless goldenrod, *Aplopappus hartwegi* (Gray) Blake (2.04% of the dry weight)(1), while 3-methoxypyridine has been isolated in small quantity from *Equisetum arvense* L. (2), and *Thermopsis rhombifolia* (Nutt.) Richards (3). Piperidine on the other hand is one of the basic constituents in pepper (*Piper nigrum* L.) (4, 5) and tobacco (8), as well as in *Psilocaulon absimile*, N. E. Br. (Aizoaceae; 4.5%) (6) and in *Petrosimonia monandra* (Pall.) Bge. (Chenopodiaceae; 1.33%) (7). *N*-Methylpiperidine constitutes 1% of the green parts of *Girgensohnia diptera* Bge. (Chenopodiaceae) where it is associated with the alkaloid dipterine (9).

The distribution of the more complex pyridine alkaloids in the plant kingdom is more widespread. For presentation in this chapter, the various groups of alkaloids will be classified according to the position of the substituents and the degree of substitution in the pyridine nucleus (the term "pyridine" is used loosely in this classification scheme to include also those alkaloids with a piperidine nucleus) of the index compound or main member of each group of alkaloids. The index compounds with substituents at position 1 will be in group I, those with substituents at position 2 of the nucleus will be in group II, while those with substituents at 3 will constitute group III. Group I will be further extended to accommodate those alkaloids with substituents at (a), 2, (b), 3, (c), 2, 6 and (d), 3, 4 as well as in position 1. Hence, the order of presentation will be: 1) the pepper alkaloids, 2) the alkaloids of Areca nut, 3) trigonelline, 4) the alkaloids of the pomegranate bark, 5) the Lobelia alkaloids, 6) the *Ricinus* alkaloids, 7) leucaenine, 8) the alkaloids of the hemlock, 9) the tobacco alkaloids, 10) the tobacco smoke alkaloids, and 11) ammodendrine.

II. The Pepper Alkaloids

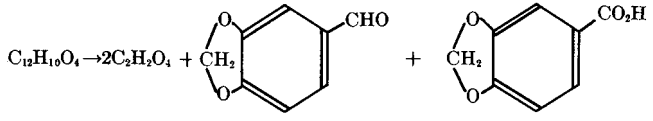
1. Piperine

Piperine, $C_{17}H_{19}O_3N$ (17), occurs in the unripe fruit (black pepper), in the kernel of the ripe fruit (white pepper) of *Piper nigrum* (10), and in the fruit of Aschanti (*P. clusii* C. DC. 5%) (12, 13). It is also found in long pepper (*P. longum* L. 4.98%), in *P. lowong*, Bl. (1.5%) (13), and in the seeds of *Cubeba censii* (14). The piperine content of black pepper varies from 6–9% although some may contain as much as 11% (15).

Piperine is prepared by extraction of the ground black pepper and evaporation of the extract. After removal of the resin (see chavicine) in aqueous sodium hydroxide, the residue is dissolved in hot ethanol from which the base crystallizes on cooling. Although the solid is tasteless (16), an ethanolic solution of the base has quite a sharp taste. This alkaloid is a very weak base which forms salts with one mole of a strong mineral acid (18). The hydrochloride is a yellow crystalline solid soluble in ethanol, chloroform, and hot benzene while the hydrobromide is a yellow crystalline powder melting to a red liquid at ca. 170°. Under special conditions a dihydrochloride can be obtained as an orange powder which decomposes spontaneously, losing hydrogen chloride in the air. All these salts are readily hydrolyzed by water. With 1, 3, 5-trinitrobenzene, piperine forms a compound which crystallizes as red needles, m.p. 130° (19).

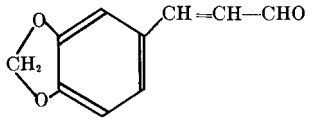
As early as 1849, piperine was hydrolyzed with aqueous sodium hydroxide (20, 23) or nitric acid (21) to a new volatile base, piperidine, $C_5H_{11}N$ (22, 23). The acidic product of hydrolysis, piperic acid ($C_{12}H_{10}O_4$, m.p. 216–217°) (24, 25), when fused with potassium hydroxide, gave protocatechuic acid (27), while addition occurred when bromine was added to the C_{12}-acid. One mole of bromine entered the molecule ($C_{12}H_{10}Br_2O_4$) (26) by the direct addition of the reagent, while tetrabromopiperic acid ($C_{12}H_{10}Br_4O_4$, m.p. 160–165°, dec) resulted when bromine in carbon disulfide was the reagent. Further evidence for the presence of two ethylenic linkages in piperic acid was derived from its reduction (NaHg) (28) to a dihydropiperic acid (m.p. 70.5–71.5°), which in turn absorbed one mole of bromine. Moreover, piperic acid was regenerated by the action of potassium hydroxide on this dibromodihydropiperic acid ($C_{12}H_{12}Br_2O_4$, m.p. 135–136°) (29). Tetrahydropiperic acid resulted from the catalytic reduction of either piperic acid (34, 35) or its dihydroderivative (33). Furthermore, tetrahydropiperine was obtained by the catalytic hydrogenation of piperine (34, 35, 36). Hot sodium hydroxide converted the tetrabromo acid to piperonal while replacement of two bromines by hydroxyls and subsequent elimination of water to yield a lactide-anhydride is induced either by boiling water alone or in combination with sodium carbonate (29).

The structure of piperic acid was deduced from oxidative experiments. Piperic acid when oxidized with potassium permanganate gave oxalic acid and two new products, piperonal and piperonylic acid (26) (the structures of which were subsequently established (31)) according to the following equation:

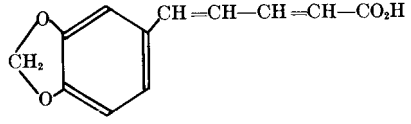


Piperic acid — Oxalic acid — Piperonal — Piperonylic acid

From this, piperic acid was considered to be represented by II (29) a structure accommodated by the subsequent observation that the acid is converted by careful oxidation ($KMnO_4$ in basic solution) to piperonal, piperonylic acid, and tartaric acid (32). The acid of structure II, obtained by condensing piperonal with acetaldehyde followed by the action of sodium acetate and acetic anhydride on the resulting aldehyde I, was identical with piperic acid (38).

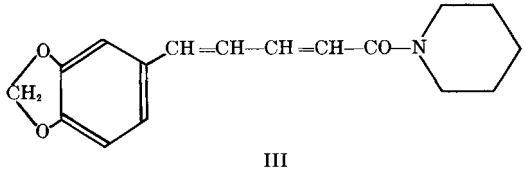


I



II

After the structure of piperidine had been established (30), it was possible to confirm the early assumption that piperine is the piperidine amide of piperic acid (29). Piperine resulted when the acid chloride of II (PCl_5) was treated with piperidine (37). Hence, piperine must be represented by III. Methyl, ethyl and phenyl analogs of piperine have been prepared by similar syntheses (39).



III

By comparison with a number of compounds closely related to piperine, it has been concluded (16, 40) that the peculiar taste of the alcoholic solution of piperine is dependent upon the presence of the phenyl group, the 4-carbon chain, and the amide group of piperine, but is independent of the methylenedioxy group, the double bonds, and the piperidine nucleus.

2. Chavicine

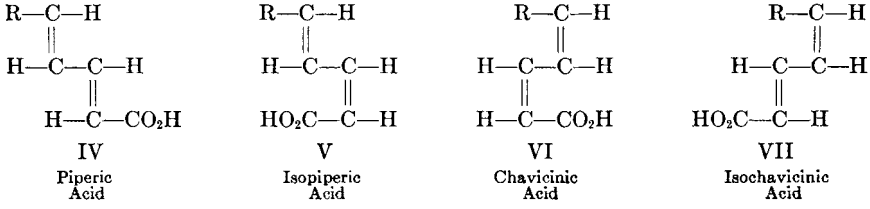
Since piperine is tasteless, Pelletier (41) and later Buchheim (42) concluded that the component (*chavicine*, $C_{17}H_{19}O_3N$ (43)), responsible for the particular taste of pepper must be in the resin. Chavicine was isolated as follows (43):

Ground pepper was extracted with ethanol and the extract evaporated to dryness. The residue was thoroughly extracted with ether and the ethereal solution washed successively with 10% potassium hydroxide and with water. Removal of the ether and steam distillation of the residue expelled the essential oils. The nonvolatile residue was dissolved in ether, the solution filtered to remove small amounts of piperine which separated, and the filtrate was evaporated to dryness. Subsequent digestion of the residue with petroleum ether, solution in ethanol, and decoloration with charcoal afforded the amorphous chavicine.

Hydrolysis of chavicine with alcoholic potassium hydroxide yielded piperidine and isochavicinic acid (43), m.p. 200–202° (earlier workers (42) reported the isolation of an isomer, chavicinic acid). Isochavicinic acid is isomeric with piperic acid and the catalytic hydrogenation of both acids

$$\underset{\text{Chavicine}}{C_{17}H_{19}O_3N} + H_2O \longrightarrow \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Isochavicinic acid}}{C_{12}H_{10}O_4}$$

yield the same tetrahydro derivative. Since unsymmetrical dienes like piperic acid can exist in four possible forms (IV–VII, where R is a methylene dioxyphenyl radical), it is considered that isochavicinic acid is a geometrical isomer of piperic acid (IV, m.p. 217°). The condensation of 3, 4-methylenedioxycinnamaldehyde (I) with malonic acid followed by decarboxylation of



the product afforded isopiperic acid, m.p. 145°, which is considered to be V. Hence, VI or VII must represent chavicinic acid and isochavicinic acid. Chavicine is the piperidine amide of isochavicinic acid.

3. Piperovatine

Piperovatine, $C_{16}H_{21}O_2N$ (44), occurs in *Piper ovatum* Vahl. It crystallizes from aqueous methanol or from petroleum ether in colorless needles, m.p. 123° (corr.). It is devoid of basic properties and is insoluble in dilute mineral acids and alkali, but it is hydrolyzed by hot dilute hydrochloric acid or concentrated potassium hydroxide solution into an acid and a vola-

tile base which is assumed to be related to pyridine. It has been suggested without much apparent experimental evidence, that piperovatine may be identical with or closely related to pellitorine (45), an alkaloid occurring in *Anacyclus pyrethrum* DC.

III. The Alkaloids of Areca Nut

The areca nut or betel nut is the fruit of *Areca catechu* L., a palm tree of the far East. The nut is consumed in large quantities by the natives. Adams (74) describes a limestone quarry at Getembe, near Kandy, Ceylon, from which the quarried stone is burnt and the resulting quicklime when slaked is all sold to the Singhalese to mix with ground areca nuts. The mixture is wrapped in betel leaves (*Piper betle* L.) and chewed by the natives.

As early as 1886, it was discovered that the active principle of the areca nut was alkaloidal in nature (75) and since then six alkaloids from that source have been characterized: they are arecoline (76), arecaidine (76), (arecaine (78)), guvacine (78), guvacoline (81), isoguvacine (79), and arecolidine (80). The structure of the first four of these has been completely elucidated, but little is known of that of arecolidine, and the homogeneity of isoguvacine is uncertain.

1. Isolation of Arecoline

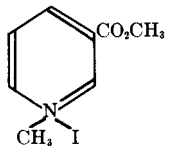
Chemnitius (82) has described a process for the large-scale extraction of arecoline as follows:

The ground areca nut (in 500-kg. lots) is moistened with 250 kg. of 10% aqueous potassium hydroxide, dried and successively refluxed for 2 hours with three portions of ether. The combined extract is concentrated to 80 l. and the water that separates is removed. The concentrate is then divided into portions of convenient volume and to each 50% acetic acid is added with stirring until a turbidity appears. After vigorous stirring, water (1 l.) is added and the ether removed by distillation. After the last trace of ether has been removed, the warm aqueous solution is allowed to cool overnight in evaporating dishes. The solid fat which rises to the surface is collected, melted, and stirred with several 1-l. portions of water, each time allowing it to cool and decanting the water to recover the base retained by the fat. The combined acidic aqueous extract is filtered and extracted with ether to remove suspended and nonbasic material, then saturated with potassium carbonate, shaken with three portions of ether, and dried over anhydrous potassium carbonate. The mixture of bases, recovered after removal of the ether, is sufficiently pure to be used directly for the isolation of pure arecoline as its hydrobromide. The bases are dissolved in twice their weight of absolute ethanol, the solution filtered, cooled, and made slightly acid by the addition, with stirring, of a 50% ethanolic solution of hydrogen bromide. The crystalline hydrobromide separates on the addition of ether to incipient turbidity followed by clarification with a few drops of ethanol. The solution is cooled for 24 hours and the crystalline salt is filtered and washed first with an ethanol-ether mixture, and then with ether. The arecoline hydrobromide thus obtained, when dried at 60°, melts at 170°.

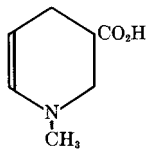
The aqueous solution separated from the original ether extract is acidified with acetic acid, filtered, extracted with ether, saturated with potassium carbonate, and worked up as above. The other bases are isolated from the mother liquors left from the crystallization of arecoline hydrobromide.

2. Arecoline and Arecaidine

Arecoline, $C_8H_{13}O_2N$, a colorless oil with a strongly alkaline reaction, is volatile in steam and forms well-defined salts (Table 1). Hydrolysis of arecoline with hydrochloric acid under pressure or boiling hydriodic acid or hot alkalies, eliminates a methyl group and produces crystalline *arecaidine*, $C_7H_{11}O_2N$ (77), a product which also occurs as such in the plant. Arecaidine forms crystalline salts; it forms aqueous solutions with a neutral reaction that are colored red by a trace of ferric chloride. Arecaidine contains a carboxyl group and, when esterified with methanol, is converted back to arecoline. When heated with a solution of barium hydroxide under pressure, arecaidine yields methylamine (83) and when reduced it is converted to dihydroarecaidine which, in turn, can be esterified to dihydroarecoline. Hence, as well as a carboxylic group, the base contains one double bond and a methylimino group. To both arecoline and arecaidine, Jahns assigned the structure of tetrahydropyridines and proved the validity of these formulas by synthesis. The methiodide of methyl nicotinate (VIII) was reduced with tin and hydrochloric acid and the product, on hydrolysis, produced a mixture of *N*-methylhexahydronicotinic acid and *N*-methyltetrahydronicotinic acid separated by means of their different solubility in chloroform. The hexahydro acid was identical with dihydroarecaidine while the tetrahydro acid was identical with arecaidine, and was considered to be *N*-methyl-Δ^5-tetrahydropyridine-3-carboxylic acid (IX) although the nature of this synthesis did not prove the position of the double bond.



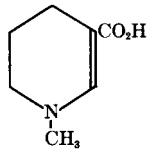
VIII



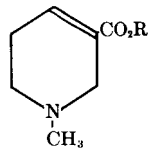
IX

Since naturally occurring arecaidine is optically inactive and since neither synthetic arecaidine nor its methyl ester (arecoline) can be resolved, it was concluded that the double bond in arecaidine could not occupy the Δ^5-position because such a molecule (IX) includes an asymmetric C-atom (84). Structures with the double bond in either the Δ^2-position (X) or the Δ^3-position (XI) are the only two which do not involve a center of asymmetry. Structure XI (Δ^3-position) was shown to be correct by an

unambiguous synthesis (85). β-methyliminodipropionaldehyde tetracetal (XII) obtained by the condensation of two moles of β-chloropropionalde-

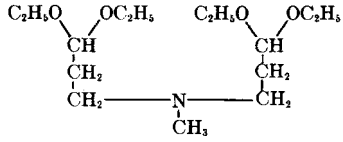


X

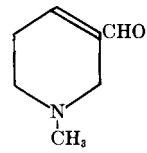


XI

hyde acetal with methylamine, underwent ring closure when treated with cold hydrochloric and produced *N*-methyl-Δ^3-tetrahydropyridine-3-alde-



XII

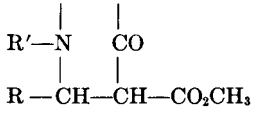


XIII

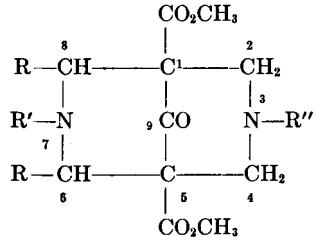
hyde (XIII). Successively, the aldehyde was converted to the oxime, dehydrated to the nitrile, hydrolyzed to the acid (XI; R = H) (identical with arecaidine) and esterified to the methyl ester (arecoline).

Although it has been claimed (87) that arecoline is obtained from methyl *N*-methylpiperidine-3-carboxylate by bromination and treatment of the product with hot sodium methylate, this has since been shown to be incorrect (88).

Piperidonedicarboxylic esters (XIV) react with formaldehyde and primary amines to form compounds of structures XV designated as bispidines (89). Furthermore hydrolysis of dimethyl 9-keto-3, 6, 7, 8-tetra-



XIV



XV

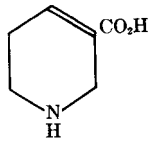
methylbispidine-1, 5-dicarboxylate (XV, R = R′ = R″ = CH_3) with hydrochloric acid produces methyl 4-keto-1-methylpiperidine-3-carboxylate (90). This compound affords a route to arecaidine since it can be reduced in aqueous ethanol with a nickel catalyst to methyl 4-hydroxy-1-methylpiperidine-3-carboxylate, which is dehydrated and hydrolyzed by the action

of hydrogen chloride and acetic acid with formation of the base (XI, R = H) (91). A number of homologs of arecoline have been prepared by this method (92).

A simpler synthesis of arecaidine consists in heating a mixture of methylamine hydrochloride, 35% formalin, water, and acetaldehyde at 70° for 15 hours (93). The product of the reaction, *N*-methyl-Δ^3-tetrahydropyridine-3-aldehyde (XIII), is converted via the oxime and nitrile to arecaidine.

3. Guvacine

Guvacine, $C_6H_9O_2N$ (78), small, lustrous crystals, m.p. 271–272° (dec.) is insoluble in ether, chloroform, benzene, and absolute ethanol, but is soluble in water. It is neutral to litmus but forms well crystallized salts (Table 1). The action of barium hydroxide on the alkaloid gives rise to ammonia while distillation with zinc dust produces β-picoline (83). The base yields a nitrosoguvacine, m.p. 167–168° (83, 94), and an acetyl derivative, m.p. 189–190° (94). Furthermore it is hydrogenated catalytically to dihydroguvacine, $C_6H_{11}O_2N$, m.p. 252°, identical with hexahydronicotinic acid. Hence guvacine is a tetrahydronicotinic acid and its properties are in agreement with those of synthetic Δ^3-tetrahydronicotinic acid (XVI) (95). That guvacine is des-*N*-methylarecaidine is confirmed by the action of methyl iodide in methanol which converts it into arecaidine methylbetaine (94, 96, 97). The betaine forms a hydrochloride, m.p. 256–258°, a picrate, m.p. 224–225°, a chloroplatinate, m.p. 253°; and an aurichloride, m.p. 224–226°.



XVI

For many years after Jahns' work (77) numerous papers appeared concerning the alkaloid arecaine which, according to Jahns, was isomeric, but not identical, with arecaidine. Eventually, the two bases were shown to be identical (98), but the confusion had again brought into question the structure of guvacine (87). However, structure XVI for guvacine was later confirmed by Freudenberg (99, 100).

4. Guvacoline

Guvacoline, $C_7H_{11}O_2N$ (81), is an oil, b.p. 114° (corr.)/13–14 mm., m.p. 27°, which forms crystalline salts (Table 1). It is hydrolyzed by barium hydroxide to guvacine (81) and is identical with the methyl ester of

that base (98). Guvacoline is best purified by recrystallization of its hydrobromide. Hence, guvacoline is the methyl ester of guvacine while arecoline is the methyl ester of arecaidine which, in turn, is *N*-methylguvacine.

5. Isoguvacine

Jahns (83) reported the presence in areca nut of an alkaloid, m.p. 265–270°, which was later named *isoguvacine* ($C_6H_9O_2N$) (79) and assumed to be Δ^2-tetrahydronicotinic acid. From the mother liquors left after the isolation of arecoline, Winterstein and Weinhagen (94) isolated a base, m.p. 220°, also claimed to be isoguvacine. It was acid to litmus, optically inactive, and formed crystalline salts (Table 1). It was reduced by hydrogen over a platinum catalyst, but the product was not homogeneous. When methylated, it gave rise to a dimethyl derivative which appeared to be a betaine and formed a chloroplatinate, m.p. 252°. Distillation of the base with zinc dust produces a distillate giving a positive pyrrole reaction. It was concluded that isoguvacine must have a structure quite different from that of guvacine (94). However, a comparison of the melting points of isoguvacine and its salts with those of arecaidine and its corresponding salts (Table 1) leads one to suspect that the base may be impure arecaidine

6. Arecolidine

Arecolidine, $C_8H_{13}O_2N$ (80), which is isomeric with arecoline, was isolated in small quantity from the mother liquors from the technical preparation of arecoline hydrobromide (80). It crystallizes from ether as colorless needles, m.p. 105°, but after sublimation the base melts at 110°. It forms stable salts (Table 1) and a methiodide, yellow needles, m.p. 264° (dec.) which behaves towards alkalies as a quaternary ammonium salt. The methiodide may be transformed to a methaurichloride, m.p. 252° (dec.). Arecolidine is not hydrolyzed by alkalies and it was suggested by Emde (80) that it is probably 3,4-dimethoxy-1-methyl-1,2-dihydropyridine. However, the evidence is inadequate to support such a structure.

TABLE 1

ARECA NUT ALKALOIDS

Base	Formula	Melting points, °C.				
		Base	Chloroplatinate	Chloroaurate	B·HBr	B·HCl
Arecoline	$C_8H_{13}O_2N$	B.p., 209	176	Oil	170–1	157–8
Arecaidine	$C_7H_{11}O_2N$	223–4	234–5	200	248–9	257–8
Guvacine	$C_6H_9O_2N$	271–2	233	197–9	280	316
Guvacoline	$C_7H_{11}O_2N$	27	211		144–5	121–2
Isoguvacine	$C_6H_9O_2N$	220	235	198–200		231
Arecolidine	$C_8H_{13}O_2N$	110	222–3	219–220	268–71	250

IV. Trigonelline

Trigonelline, $C_7H_7O_2N$, was discovered in the seeds of *Trigonella foenum-graecum* L. (63) but it has since been found in a wide variety of plants such as the seeds of *Pisum sativum* L. and *Cannabis sativa* L. (64) in the seeds of *Strophanthus kombe* Oliver (65), and in coffee (66, 67); also in the soybean (69), in potatoes (70) and in the tubers of *Dahlia variabilis* Des. and *Scorzonera hispanica* L. (73). The content of the base in known coffees is fairly constant (0.228–0.245%) (68).

Trigonelline consists of colorless flat prisms which gradually carbonize when heated. It is soluble in water, sparingly so in cold alcohol, insoluble in ether, chloroform, and benzene. It forms a hydrochloride, m.p. 248° and two aurichlorides, $B \cdot HAuCl_4$, m.p. 198°, and $4B \cdot 3HAuCl_4$, m.p. 186° (51). Heating trigonelline with barium hydroxide at 120° produces methylamine while heating with hydrochloric acid at 260–270° gives rise to nicotinic acid and a gas, probably methyl chloride (71). The assumption based on these facts that trigonelline is the methylbetaine of nicotinic acid was confirmed by comparison of the base with the synthetic betaine (72).

V. The Alkaloids of the Pomegranate Root Bark

The bark of the pomegranate tree (*Punica granatum* L.) was first investigated by C. Tanret who isolated from it four alkaloids which he named pelletierine (204), isopelletierine, methylpelletierine, and pseudopelletierine (205, 206). Methylpelletierine and pelletierine were observed to be optically active while isopelletierine and pseudopelletierine were inactive. Later, Piccinini (207) found a fifth alkaloid, isomethylpelletierine in the mother liquors obtained from the preparation of pseudopelletierine. Eventually, however, Hess (208) while reinvestigating the bark obtained pseudopelletierine, Piccinini's isomethylpelletierine and a third, optically inactive base, but found no trace of Tanret's optically active methylpelletierine. He could not find any optically active alkaloids and, considering his third base identical with Tanret's isopelletierine (185) renamed the latter base pelletierine. Further, Hess and Eichel (209) considered Tanret's methylpelletierine and Piccinini's isomethylpelletierine as identical but different from methylated pelletierine and named it methylisopelletierine (185).

To these three alkaloids, two more were subsequently added: isopelletierine (210) and α-*N*-methylpelletierine-β-one (209). The latter was subsequently shown to be methylisopelletierine (188, 211). Altogether, there are therefore four alkaloids present in the bark: pelletierine, $C_8H_{15}ON$ (Tanret's isopelletierine); pseudopelletierine, $C_9H_{15}ON$, isopelletierine,

$C_8H_{15}ON$ and methylisopelletierine, $C_9H_{17}ON$ (Tanret's methylpelletierine, Piccinini's isomethylpelletierine).

Methods of detection of these alkaloids have been described by van Itallie (212) and by Chaze (213), while a method for their quantitative estimation has been outlined by Ewers (214). According to G. Tanret (215) commercial samples of pelletierine sulfate and tannate show wide divergencies in character and amount of total alkaloids. Many are complex mixtures containing no pelletierine.

The separation of the alkaloids is effected as follows:

Pseudopelletierine is separated by freezing the mixture of crude alkaloids while the bulk of the pelletierine is crystallized as its hydrobromide. The base recovered from the mother liquors is distilled under reduced pressure and the distillate treated with ethyl chloroformate. Repeated fractional distillation of the product affords a first fraction consisting of pure methylisopelletierine and a second fraction, b.p. 150–165°/13 mm. consisting of the urethanes of pelletierine and isopelletierine. Hydrolysis of this last fraction resinifies the liberated pelletierine whereas the isopelletierine is recovered and purified by distillation. One hundred kilograms of the bark yields 179 g. of pseudopelletierine, 52.5 g. of pelletierine, 23 g. of methylisopelletierine, and ca. 1.5 g. of isopelletierine.

1. Pelletierine

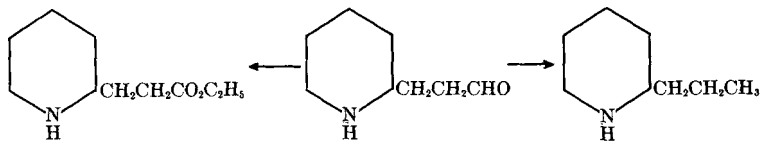
Pelletierine, $C_8H_{15}ON$ (185, 205) as isolated from the bark is the *dl*-modification although it is not certain that this is the form in which it occurs in the plant since the isolation of the *l*-form and its facile racemization have been reported (216). A similar observation made concerning *l*-pelletierine obtained from the *dl*-base by resolution (217) confirms the last statement. However, the optical activity of Tanret's *l*-pelletierine is much greater than that reported for the resolved base. Hess and coworkers (217, 218) claim that they never succeeded in detecting optical activity in the bases either before or after distillation.

Pelletierine is a colorless oil, b.p. 106°/21 mm., which is rapidly discolored and eventually resinified by atmospheric oxygen. It is soluble in the usual solvents and forms crystalline salts with ease: the hydrobromide, feathery needles, m.p. 140°, the hydrochloride, needles, m.p. 143–144°, and the picrate, m.p. 150–151°. The base can be resolved through its tartrates, yielding *l*-pelletierine-*l*-tartrate, m.p. 129°, $[\alpha]^{20} - 20.94°$ and *d*-pelletierine-*d*-tartrate, m.p. 129°, $[\alpha]^{20} + 20.93°$. *d*-Pelletierine sulfate has $[\alpha]^{18} + 6.1°$ and *l*-pelletierine sulfate has $[\alpha]^{18} - 5.89°$. As a source of light for the determination of the optical rotation, Hess and Eichel (217) used an incandescent gas light.

Although it does not yield a nitroso derivative, pelletierine is a secondary base since it forms an *N*-acetyl derivative, b.p. 173–174°/18 mm., and an *N*-benzoyl derivative, prisms or plates, m.p. 75°. Both derivatives

yield aurichlorides, m.p. 95–96° and 139° (dec) respectively. The base is converted to *N*-methylpelletierine by the action of formaldehyde at 135–143°. The methylated base, b.p. 98–102°/14 mm., which is more subject to aerial oxidation than pelletierine, forms a hydrobromide, long prismatic needles, m.p. 152°, and a semicarbazone, the hydrochloride of which crystallizes in prismatic rods, m.p. 168–169° (dec). Pelletierine itself forms a semicarbazone hydrochloride crystallizing in clusters of prisms, m.p. 188° and an oxime, b.p. 173°/21 mm., crystallizing in two forms, m.p. 96–97° (from petroleum ether) and m.p. 80° (from ether). Hence the oxygen in pelletierine is present either in a ketonic or an aldehydic group and this is confirmed by the presence of an active methylene group evidenced by (a) the formation of benzylidenepelletierine, the hydrochloride of which, $C_{15}H_{19}ON \cdot HCl$, melts at 187° and (b) the formation from *N*-benzoylpelletierine of an isonitroso derivative, m.p. 192–193°.

Pelletierine oxime can be converted (PCl_5) to a nitrile ($C_8H_{18}N_2$, b.p. 104–106°/15 mm.; picrate, m.p. 175–176°) hydrolyzable to an acid, $C_8H_{19}O_2N$, the ethyl ester of which is identical (163) with synthetic ethyl β-2-piperidylpropionate (XVIII) (143). This acid which, however, cannot be derived by the direct oxidation of the base,



XVIII XVII XIX

shows that the oxygen atom of pelletierine is present in an aldehyde group and pelletierine is β-2-piperidylpropionaldehyde (XVII). The reduction with sodium ethoxide of pelletierine hydrazone (a liquid, b.p. 150°/20 mm.) to *dl*-coniine (XIX) confirms structure XVII.

An elegant synthesis of pelletierine acetal has been reported (497) although it has not yet been possible to synthesize the alkaloid itself. β-(2-pyridyl)-propionaldehyde diethylacetal, obtained in 28–29% yield from lithium picolyl and bromoacetal, is hydrogenated in glacial acetic acid over a platinum catalyst to β-(2-piperidyl)-propionaldehyde diethylacetal. It is of interest to note that if the hydrogenation be carried out in dilute solution, the product is δ-coniceine (498). However, hydrolysis of the acetal succeeds only if the secondary nitrogen is first blocked (497, 518).

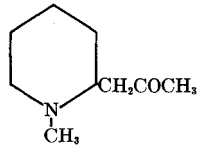
2. Methylpelletierine

The methylation of pelletierine yields *dl*-methylpelletierine ($C_9H_{17}ON$) (206), b.p. 98–102°/14 mm. (208). C. Tanret (206) described an oily base, b.p. 215°, 106–108°/45 mm. which is optically active, $[\alpha]_D$ + 27.7° (216).

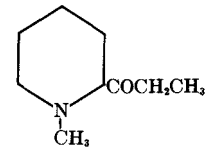
This base forms the following crystalline salts: the hydrochloride, m.p. 168–170°, $[\alpha]_D$ + 41.2°, the hydrobromide, m.p. 165–167°, $[\alpha]_D$ + 33.5°, the sulfate, $[\alpha]_D$ + 38°, the picrate, m.p. 157–159°, and the chloroplatinate, m.p. 206–208°. However, no other worker has succeeded in isolating optically active methylpelletierine from the plant (185) and its occurrence is uncertain.

3. Methylisopelletierine

Methylisopelletierine, $C_9H_{17}ON$, is a strongly alkaline oil, b.p. 114–117°/26 mm., miscible with water and optically inactive (209). It gives rise to a hydrochloride, m.p. 158°, a hydrobromide, m.p. 151–153°, a picrate, m.p. 158°, and a methiodide, m.p. 156°. The base is resolvable into its optical antipodes through the tartrates: *d*-methylisopelletierine-*d*-bitartrate has $[\alpha]_D^{20}$ + 22.77°, *d*-methylisopelletierine sulfate, $[\alpha]_D^{18}$ + 7.64° while the *d*-hydrochloride has $[\alpha]_D^{18}$ + 11.08°. *l*-Methylisopelletierine-*l*-tartrate has $[\alpha]_D^{18}$ − 20.83°, the sulfate, $[\alpha]_D^{18}$ − 8.03° and the hydrochloride, $[\alpha]_D^{18}$ − 10.64°. Methylisopelletierine forms (a) a semicarbazone, $C_{10}H_{20}ON_4$, m.p. 169°, the hydrochloride of which melts at 208–209° (207); (b) an oxime, b.p. 160°/12 mm., yielding a picrate, m.p. 106°, and (c) a hydrazone, $C_9H_{19}N_3$, a limpid oil, b.p. 154–155°/29 mm. Just as pelletierine hydrazone is reduced to *dl*-coniine by sodium ethoxide, so methylisopelletierine hydrazone is similarly converted to *dl*-*N*-methylconiine. Furthermore, oxidation of the base with chromic acid in sulfuric acid produces 1-methylpiperidine-2-carboxylic acid, m.p. 214–215° (184). Hence, since the base is not identical with methylpelletierine, it is either α-2-*N*-methylpiperidylpropan-



XX



XXI

β-one (XX) or α-2-*N*-methylpiperidylpropan-α-one (XXI). Methylisopelletierine was first claimed to be different from the synthetic compound of structure (XX) (187) and must be represented by XXI so that the alkaloid was considered to be an isomer of methylconhydrinone. Since methylisopelletierine and methylconhydrinone are not identical, the stereoisomerism was attributed to the asymmetry of the tervalent nitrogen atom. Subsequently, however, the differences in the chemical reactivity of these two alkaloids were pointed out and it was further definitely established that α-(2-*N*-methylpiperidyl)-propan-β-one (XX) prepared from the methosulfate of α-(2-pyridyl)-propan-β-ol by catalytic hydrogenation followed

by oxidation of the product with chromic acid in acetic acid, is identical with methylisopelletierine (XX) (188, 211). The synthesis was also achieved by the catalytic reduction of α-(2-pyridyl)-propan-β-ol, methylation of the product with formaldehyde and formic acid, followed by oxidation with chromic acid.

Methylisopelletierine is also obtained when α-(2-pyridyl)-propan-β-one, prepared from lithium picolyl and ethyl acetate (501), is converted to the methosulfate and hydrogenated over a platinum catalyst (500).

4. Isopelletierine

Isopelletierine, $C_8H_{15}ON$ (210), is an optically inactive oil, b.p. 102–107°/11 mm., which forms a picrate, m.p. 147–149°, a hydrobromide, m.p. 135° and a hydrochloride, m.p. 143°. It is a secondary base which reacts with ethyl chloroformate to form an *N*-carbethoxy derivative. This property is used in the method of isolation since the derivative on hydrolysis yields the unchanged base. Isopelletierine is not methylated by formaldehyde and formic acid, but is converted to methylisopelletierine with the aid of methyl sulfate. Hence, the base is α-(2-piperidyl)-propan-β-one.

When lithium picolyl reacts with acetic anhydride, there is formed a mixture of α,γ-(bis-2-pyridyl)-β-methylpropan-β-ol and α-(2-pyridyl)-propan-β-one. The latter on hydrogenation in acetic acid solution over platinum gives rise to *dl*-isopelletierine (499).

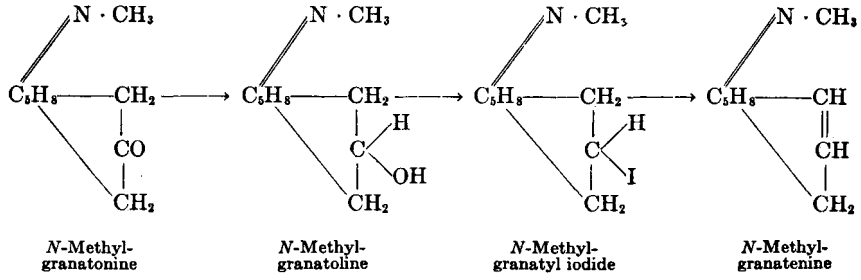
5. Pseudopelletierine

Pseudopelletierine, $C_9H_{15}ON$ (205), also designated *N*-methylgranatonine, is an optically inactive base crystallizing from petroleum ether in prismatic plates, m.p. 53–54°, b.p. 246°. It is very soluble in alcohol, chloroform, water, and ether, but less so in petroleum ether. It is a strong base and forms crystalline salts: an aurichloride, yellow crystals, m.p. 162° (dec), a picrate, yellow needles from water, m.p. 252–253° (dec). A trace of potassium dichromate added to a solution of the base in sulfuric acid produces a bright green coloration. The best color test, however, is supplied by the dipiperonylidene derivative which is highly characteristic. This derivative crystallizes from ethanol in glistening yellow microscopic plates having an equilateral triangular outline. Its salts with mineral acids are all sparingly soluble, deep yellow substances and in this it resembles the closely related tropinone derivative. The solution of dipiperonylidene-pseudopelletierine in concentrated sulfuric acid is intensely royal blue and becomes green and then yellow on dilution with water (219).

a. Structure. Pseudopelletierine is a tertiary base. It forms an oxime, $C_9H_{16}ON_2$, m.p. 128–129° and it is reduced by sodium amalgam or by sodium in ethanol to a dihydro base, $C_9H_{17}ON$, b.p. 251°, m.p. 100°

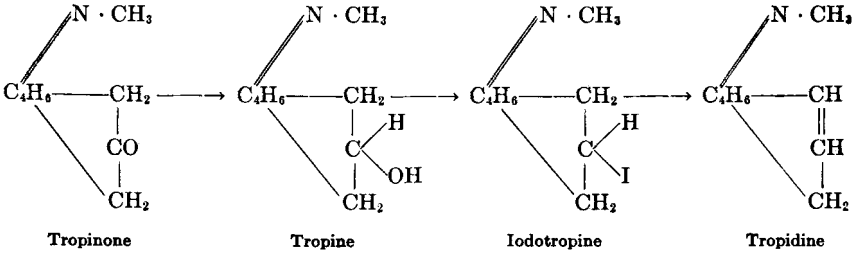
(aurichloride, yellow needles, m.p. 213°) which no longer forms an oxime, but can be oxidized back to pseudopelletierine (220). The dihydro base also exists in another form, m.p. 69°; both forms can be obtained by the fractional crystallization of their hydrochlorides or their benzoyl derivatives (221). The formation of a benzoyl derivative indicates the presence in the dihydro base of a hydroxylic group formed by reduction of the carbonyl group of pseudopelletierine. The presence of a ketonic group is confirmed by the formation of dibenzylidenepseudopelletierine, small yellow prisms, and a diisonitroso derivative, yellow prisms deflagrating when heated (hydrochloride, m.p. 240–250°) (207). Hence, the grouping —CH_2—CO—CH_2— is present in the base.

As the reactions of pseudopelletierine are reminiscent of those of tropinone, the former was renamed *N*-methylgranatonine in order to bring the nomenclature of its derivatives into conformity with those of the latter (223). Dihydropseudopelletierine (*N*-methylgranatoline) is converted by hot hydriodic acid and red phosphorus either to *N*-methylgranatyl iodide, $C_9H_{16}NI$, or to *N*-methylgranatenine, $C_9H_{15}N$, depending on the temperature. The latter is a viscid liquid, b.p. 136°/751 mm., forming an aurichloride, m.p. 220° (dec) and a methiodide crystallizing in cubes which do not melt at 315°. The above series of reactions may be represented thus:



N-Methylgranatonine — *N*-Methylgranatoline — *N*-Methylgranatyl iodide — *N*-Methylgranatenine

which is entirely parallel with the results of a similar series of experiments carried out with tropinone (224):



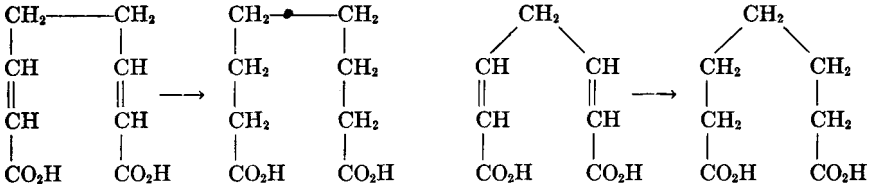
Tropinone — Tropine — Iodotropine — Tropidine

The electrolytic reduction of *N*-methylgranatonine in dilute sulfuric acid (225) produces an almost quantitative yield of *N*-methylgranatanine,

b.p. 192–195°, which forms an aurichloride, m.p. 243–244°, a picrate, m.p. ca. 300°, and a methiodide which does not melt at 330°. On the other hand, when *N*-methylgranatoline is heated with hydriodic acid and red phosphorus for 6–8 hours at 260°, there is formed a base which is isolated as its *N*-carbethoxy derivative, m.p. 135–136°. The base, granatanine, $C_8H_{15}N$, recovered by hydrolysis of the *N*-carbethoxy derivative, crystallizes in colorless needles, m.p. 50–60°, and gives rise to a chloroplatinate, yellow plates, m.p. 255°, a nitroso derivative, $C_8H_{14}N \cdot NO$, m.p. 148°, and an *N*-benzoylgranatanine, colorless needles, m.p. 111°. Hence, in the formation of granatanine, the reduction of —CO— to —CH_2— is accompanied by the elimination of the imino methyl. Dry distillation of granatanine hydrochloride with zinc dust produces α-propylpyridine. It is also possible to remove the imino methyl of *N*-methylgranatoline by mild oxidation with potassium permanganate, or by conversion to the *N*-oxide, treatment with acetic anhydride and saponification of the product (235). Granatoline, $C_8H_{15}ON$, thus obtained crystallizes as colorless needles or prisms, m.p. 134°; it forms a hygroscopic hydrochloride, an aurichloride, m.p. 215°, and a nitroso derivative, colorless plates, m.p. 125°. Distillation of granatoline hydrochloride with zinc dust gives rise to pyridine. The action of hydriodic acid and red phosphorus at 140° converts granatoline to granatenine; an *N*-carbethoxy-derivative, m.p. 104–106°, a hydriodide, m.p. 221°, a hydrochloride, m.p. 250°, and an aurichloride, m.p. 186°, have been prepared from the latter (226). The foregoing transformations lead to the conclusion that an α-substituted piperidine ring forms part of the pseudopelletierine molecule and this conclusion is supported by the oxidation of granatoline with chromic acid in sulfuric acid to granatic acid, $C_8H_{13}O_4N$, a substance which when first treated with mercuric acetate and subsequently distilled with barium hydroxide, is converted to α-methylpyridine (227).

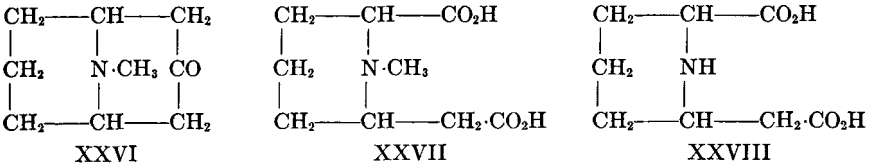
N-methylgranatoline is oxidized by potassium permanganate to *N*-methylgranatic acid, $C_9H_{15}O_4N$, just as tropine is oxidized to tropinic acid (228). The methiodide of the dimethylester of *N*-methylgranatic acid ($C_{11}H_{19}O_4N \cdot MeI$, colorless prisms, m.p. 167°) is converted by hot alkali carbonates to dimethyl *N*-dimethylgranatenate, $COOCH_3—CH_2 \cdot CH—N(CH_3)_2—CH_2—CH_2—CH = CH—COOCH_3$. This ester is an oil, the crystalline methiodide ($C_{12}H_{21}O_4N \cdot CH_3I$, thin leaflets, m.p. 143–144°) of which, when boiled with concentrated aqueous sodium hydroxide solution gives rise to trimethylamine and homopiperylenedicarboxylic acid (XXII). Reduction of this unsaturated acid with sodium amalgam produces suberic acid (XXIII). Tropinic acid when treated similarly yields piperylenedicarboxylic acid (XXIV) which can be reduced to pimelic acid (XXV). The persistent parallelism between the reactions of pseudopelletierine and

those of tropinone has led to the suggestion at various times of formulas for the former similar to those adopted for tropinone. Eventually Piccinini



XXII XXIII XXIV XXV

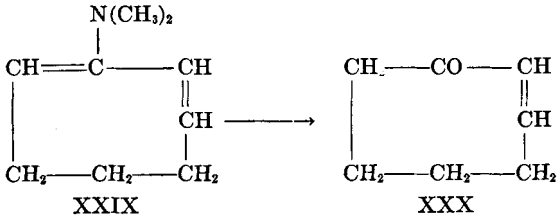
(229) suggested a formula (XXVI) similar to Willstätter's tropinone formula, which was finally adopted. On the basis of this formula (XXVI) for pseudopelletierine the structures of *N*-methylgranatic acid (XXVII) and granatic acid (XXVIII) become obvious.



XXVI XXVII XXVIII

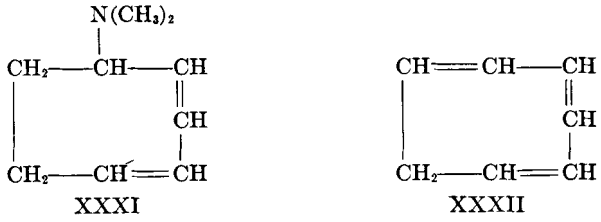
The close similarity between pseudopelletierine and tropinone is further exemplified by the formation of the isomeric methylgranatylamines. When methylgranatonine (pseudopelletierine) oxime is reduced by means of sodium amalgam in acetic acid (230), methylgranatylamine, $C_9H_{18}N_2$, is formed as a dense, colorless liquid, b.p. 160–170°/60 mm. It is very soluble in water and absorbs carbon dioxide from the air with formation of the solid carbonate. It gives rise to a deliquescent hydrochloride, an aurichloride, yellow needles, m.p. 226°, a chloroplatinate, golden yellow spangles, m.p. 260–261°, and a picrate, yellow leaflets, m.p. 239–240°. With phenylthiocarbimide it is converted into methylgranatylphenylthiocarbamide, $C_9H_{16}N \cdot NH \cdot CS \cdot NHC_6H_5$, m.p. 132–133°. If, on the other hand, methylgranatonine oxime is reduced by sodium in amyl alcohol, ψ-methylgranatylamine results as a dense, colorless oil, b.p. 232–236°. It absorbs carbon dioxide from the air forming a carbonate, m.p. 123°. Its aurichloride melts at 231–232°, its chloroplatinate at 265°, and its picrate at 239–240°. By the action of phenylthiocarbimide it is converted into ψ-methylgranatylphenylthiocarbamide, $C_{16}H_{23}N_3S$, slender, colorless needles, m.p. 176°. Furthermore, methylgranatylamine when boiled for a long time with a 30% caustic soda solution or with sodium in amyl alcohol is transformed into ψ-methylgranatylamine. The relation between the two methylgranatylamines is the same as that found to exist between the two tropylamines (231).

b. Hofmann Degradation of Bases Derived from Pseudopelletierine. The degradation of *N*-methylgranatic acid and of granatic acid to pyridine derivatives together with the formation of suberic acid by the exhaustive methylation of the dimethyl ester of *N*-methylgranatic acid (228) support Piccinini's formula (XXVI) for pseudopelletierine. This structure also received confirmation from the results of the Hofmann degradation of the alkaloid which again are in close parallelism with those obtained by the similar degradation of tropinone. The base β-des-methyltropidine, obtained by the methylation of tropinone, is formed from an isomeric α-des-methyltropidine first produced, through the migration of a double bond (237). β-Des-methyltropidine (XXIX) does not undergo exhaustive methylation and on treatment with methyl iodide splits off tetramethylammonium iodide; furthermore the action of acids causes scission of the molecule into dimethylamine and Δ^2-cycloheptenone (the so-called tropilene) (XXX).



XXIX XXX

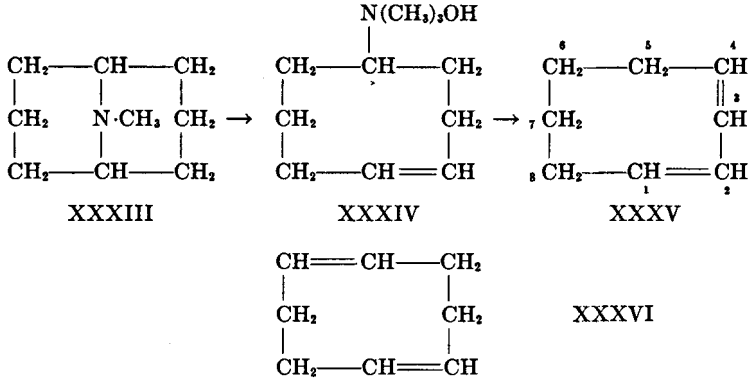
The α-base (XXXI) on the other hand, when exhaustively methylated, readily yields cycloheptatriene (tropilidine) (XXXII).



XXXI XXXII

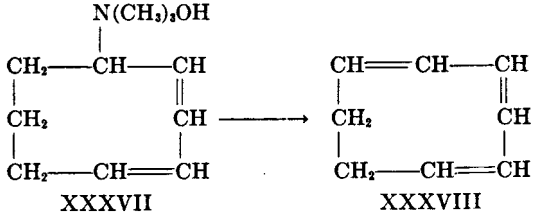
The application of Hofmann's degradation to *N*-methylgranatanine (XXXIII) gives rise in the first step to a des-dimethylgranatanine, b.p. 89.5–92°/14.5 mm., d_4^0 0.916, which forms a picrate, m.p. 155°, a chloroplatinate, m.p. 178–180° (dec), and a methiodide, m.p. 264° (dec) (221). The quaternary hydroxide (XXXIV) corresponding to des-dimethylgranatanine methiodide is decomposed by heat into trimethylamine and $\Delta^{1,3}$-cyclooctadiene (XXXV), b.p. 39.5°/16.5 mm. Although the sole product of the ozonization of the hydrocarbon is succindialdehyde (232), which indicates $\Delta^{1,5}$-cyclooctadiene (XXXVI), it has been shown to consist of a tautomeric mixture of the two forms. It absorbs bromine readily, but,

although the process is accompanied by the elimination of some hydrogen bromide, the product can be separated into a homogeneous fraction, b.p. 93.5–94.5°/17 mm., having the composition of monobromocyclooctadiene and a fraction, b.p. 142–143°/14 mm., which appears to be a mixture of



XXXIII XXXIV XXXV XXXVI

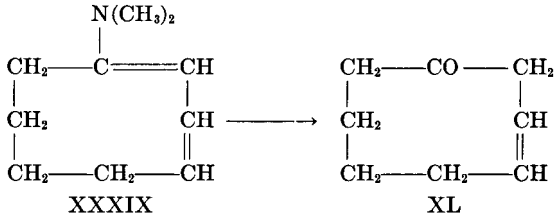
stereoisomeric dibromo derivatives. When the dibromo derivative of cyclooctadiene is heated with quinoline, it gives rise to a product which appears to be a mixture of cyclooctadiene and cyclooctatriene. Nevertheless, when the mixture of dibromo- and bromocyclooctadiene is heated with dimethylamine, there is obtained a base, $C_8H_{11}N(CH_3)_2$, designated α-des-dimethylgranatenine. The quaternary hydroxide (XXXVII) of this base, like that of the corresponding α-des-methyltropidine, produces trimethylamine and cyclooctatriene (XXXVIII) on pyrolysis (233). This triene is a colorless oil, b.p. 31.2–31.8°/8 mm., which is reduced catalytically over platinum to cyclooctane.



XXXVII XXXVIII

On the other hand, the methiodide of pseudopelletierine is converted by distillation with baryta into an oily base which does not undergo the Hofmann degradation and is split by the action of hydrochloric acid into dimethylamine and "granatal," a compound which contains no nitrogen (236). Furthermore, the methiodide of *N*-methylgranatenine, when distilled at atmospheric pressure with potassium hydroxide, gives rise also to an oily base which is decomposed by hydrochloric acid into dimethyl-

amine and "granatal" (26, 222). Since "granatal" yields cyclooctanone on reduction and adipic acid on oxidation, it is Δ^3-cyclooctenone (XL) and hence the base that gives rise to it is β-des-dimethylgranatenine (XXXIX) analogous to β-des-methyltropidine (234). Just as β-des-methyltropidine



XXXIX XL

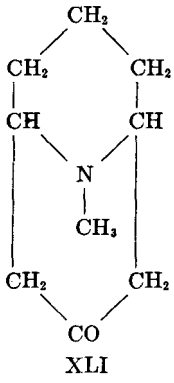
is a rearrangement product of its α-isomer, so is β-des-dimethylgranatenine (XXXIX) a rearrangement product of α-des-dimethylgranatenine. The latter is isolated in 90% yield when the quaternary ammonium base derived from the methiodide of *N*-methylgranatenine is distilled at 100–110°/10 mm. It is a colorless oil, b.p. 71–71.5°/8 mm., that dissolves in hydrochloric acid to give a solution, which, when heated, does not produce Δ^3-cyclooctenone. It forms a chloroplatinate $(C_{10}H_{17}N \cdot HCl)_2PtCl_4$, m.p. 168–169° and a methiodide, m.p. 172–173°. If, however, the α-base is distilled under atmospheric pressure, it is isomerized into β-des-dimethylgranatenine.

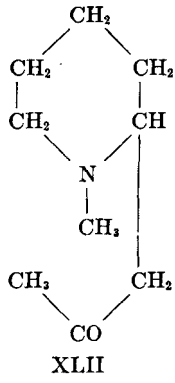
c. Cyclooctatetraene. These results fully elucidate the structure of pseudopelletierine and prove the validity of Piccinini's formula (XXVI). It is nevertheless of interest to note the reactions of cyclooctatriene studied by Willstätter. This hydrocarbon on bromination gives rise to a dibromo derivative, b.p. 129.5–130°/9 mm., which when treated with dimethylamine in cooled benzene yields tetramethyldiaminocyclooctadiene, $(C_8H_{10}(N(CH_3)_2)_2)$, a yellow oil, b.p. 126–127°/14 mm., forming a chloroplatinate, m.p. 220°. The dibasic product on exhaustive methylation yields cyclooctatetraene in 10–12% yield. This hydrocarbon is a yellow oil, b.p. 42.2–42.4°/17 mm., d_4^{20} 0.925, n_D^{20} 1.5389, converted by catalytic reduction to cyclooctane. On treatment with bromine, cyclooctatetraene gives rise to a dibromo compound crystallizing as glistening needles, m.p. 70–71.5° (corr.). If more bromine is allowed to react, hydrogen bromide is eliminated and there is formed a tribromo derivative, $C_8H_7Br_3$, m.p. 53–55° (238). This synthesis of cyclooctatetraene has been repeatedly questioned but is entirely vindicated by a recent repetition of the work (502).

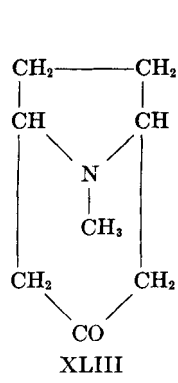
In view of the extremely laborious method employed by Willstätter to obtain cyclooctatetraene, it is noteworthy that a very simple synthesis has been discovered by Reppe (239). A solution of acetylene in tetrahydrofuran is heated to a pressure of 20 atmospheres in the presence of a cat-

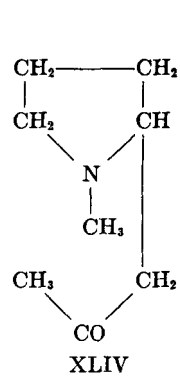
alyst which may be nickel cyanide, nickel acetoacetate, or nickel rhodanide. A rather high yield of cyclooctatetraene is obtained. This product boils at 45.5–45.8°/17 mm., and melts at −7.4°. It has d_4^{20} 0.9206 and n_D^{20} 1.5290.

An examination of the structure assigned to pseudopelletierine (XLI) reveals that it is related to methylisopelletierine (XLII) in precisely the same way as tropinone (XLIII) is to hygrine (XLIV):

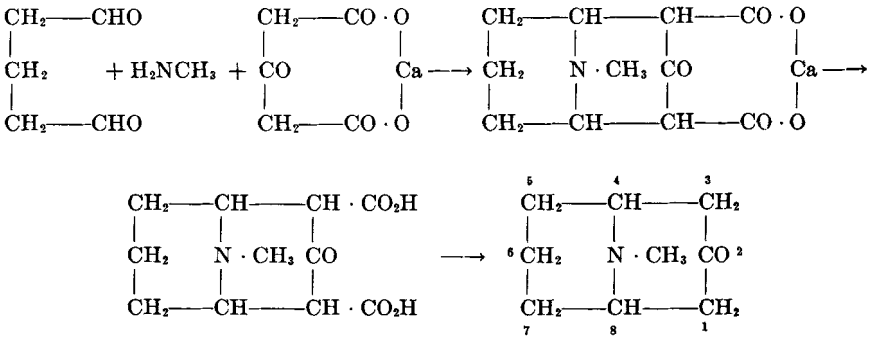

XLI


XLII

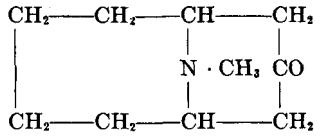

XLIII


XLIV

d. Syntheses of Pseudopelletierine. The structure of pseudopelletierine has been confirmed by two syntheses which are remarkable because they were both carried out under mild conditions and with materials that could occur in plants. In the first of these, an aqueous solution containing calcium acetone-dicarboxylate, glutardialdehyde and methylamine is kept at room temperature for 24 hours, after which the solution is acidified with hydrochloric acid, boiled to decarboxylate the primary product and treated with ammonium oxalate to remove the calcium. The base obtained from the filtered aqueous solution is purified by crystallization of its picrate. The recovered base crystallizes as soft, colorless flakes, m.p. 48.5°, identical with pseudopelletierine (219). The reactions can be expressed thus:

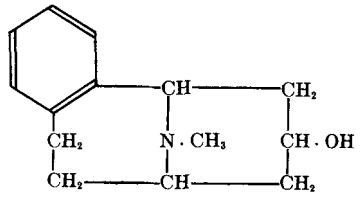


By substituting adipicdialdehyde for glutardialdehyde in the same series of reactions, *N*-methylhomogranatonine (XLV) is obtained (240), and application of the same type of synthesis to thiobisacetaldehyde, to selenobisacetaldehyde, and to methyliminobisacetaldehyde yields compounds



XLV

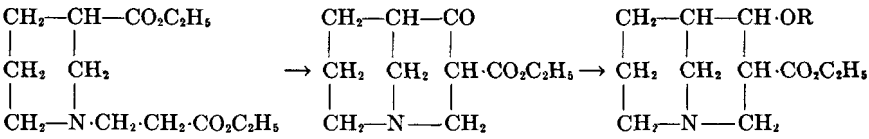
similar to pseudopelletierine in which the CH_2 at 6 is replaced by S, Se and N.Me respectively (241). The substitution of *o*-formylhydrocinnamaldehyde for glutardialdehyde in the same synthesis yields 8-9-benz-$\Delta^{8\cdot9}$-homogranaten-3-one which can be reduced to the corresponding alcohol (XLVI) (242). Benzoylation of this alcohol gives rise to an analog of tropacocaine possessing properties of a local anaesthetic. Similarly α-phenylglutardialdehyde condenses with calcium acetonedicarboxylate and



XLVI

methylamine and the product on decarboxylation proved to be 6-phenylpseudopelletierine (243) the dipiperonylidene derivative of which melts at 210°.

The second synthesis of pseudopelletierine involves throughout only conditions approximating those which could exist in the plant. An aqueous, buffered solution of glutardialdehyde, methylamine hydrochloride and acetonedicarboxylic acid is kept at 25° for 8 days. The ether extract of this solution gives a 72% yield of pseudopelletierine which crystallizes readily. Good yields of the alkaloid are obtained at pH 3–13 but the best yields are produced at pH 5–7 (244).



XLVII XLVIII XLIX

A bicyclic nitrogen ring structure which is a derivative of a nucleus isomeric with pseudopelletierine has been prepared by McElvain and

Adams (245). Ethyl β-(3-carbethoxypiperidine)-propionate (XLVII) is converted by the action of sodium in xylene into ethyl isogranatonine-carboxylate (XLVIII) which is reduced to the corresponding alcohol (XLIX, R = H). The benzoyl derivative of this alcohol (XLIX, R = C_6H_5CO) is closely related to cocaine in structure.

VI. Lobelia Alkaloids

Many species of *Lobelia* have been examined and several reported as containing alkaloids. However, all the known alkaloids of this group have been isolated from *Lobelia inflata* L., with the exception of lobinaline which occurs in *L. cardinalis* L. (465). *L. sessilifolia* Lamb. contains a base which forms a crystalline hydrochloride, m.p. 180–190°, but it has not been further characterized (466). An assay method based on precipitation with silicotungstic acid has been developed by Mascré and Caron (467, 468); but this has been followed by the publication of numerous procedures for the determination of the alkaloid content of *Lobelia*. Although these procedures include further gravimetric methods (473, 474), titrimetric methods seem to be preferred (475, 476, 477). However, Lynch and Evers (478) who have reviewed all the published methods, recommend a procedure involving the careful isolation of the total alkaloid and titration with 0.02 *N* sulfuric acid. Good results are also obtained by treating the total alkaloid with dimethylaminoazobenzene and titrating with 0.05 *N* *p*-toluenesulfonic acid (479). By means of the silicotungstic acid method, the alkaloid content of *L. inflata* has been found to be 0.585% in the leaves and 0.21–0.235% in the seeds although the quantity of alkaloid varies with the conditions of growth (0.134–0.635%) (470). The other species of *Lobelia* assayed are the following: *L. cardinalis* (0.445%), *L. urens* L. (0.752%), *L. syphilitica* L. (0.535% (468) but also given as 0.152% (470)), *L. erinus* L. (traces) (469), and *L. dortmanna* L. (traces) (470).

Of the alkaloids of *L. inflata* the major and most important one is lobeline. The content of lobeline increases very rapidly in the young plant, reaching a first maximum shortly before blooming, a second maximum at the time blooming ceases, and a rapid decrease as the plant withers. Lobeline is distributed unequally in the different parts of the plant (471), the blossoming apex containing 0.9–1.1%, the unripe capsule 0.88–1.05%, the leaves 0.42–0.43%, the stems 0.35–0.38%, and the roots 0.54–0.56%. Heavy fertilization with potassium sulfate increases the alkaloid content (472).

Methods for the isolation of the alkaloids of *L. inflata* have been described in many patents (480). The isolation of these alkaloids and the elucidation of their chemical structure is due to Heinrich Wieland and his

students who, in the period 1921–1939, published on this subject a series of remarkable papers. The fourteen alkaloids known from this source can be classified into three groups:

Lobeline group	*l*-Lobeline
	dl-Lobeline
	Lobelanine
	Lobelanidine
	Norlobelanine
	Norlobelanidine
Lelobine group	*dl*-Lelobanidine
	l-Lelobanidine-I
	l-Lelobanidine-II
	d-Norlelobanidine
Lobinine group	Lobinine
	Isolobinine
	Lobinanidine
	Isolobinanidine

1. Lobeline

Lobeline, $C_{22}H_{27}O_2N$ (481), is a monoacidic, tertiary base, m.p. 130–131°, $[\alpha]_D^{15} - 42.85°$. It is soluble in chloroform, hot benzene, and hot alcohol but only very sparingly soluble in water and petroleum ether; it forms a crystalline hydrochloride, m.p. 182°, an amorphous chloroplatinate and a benzoyl derivative, m.p. 155–157°. Hence one of its oxygen atoms is present in a hydroxyl group.

2. Lobelanine

Lobelanine, $C_{22}H_{25}O_2N$ (482), crystallizes from ether in rosettes of needles, m.p. 99°. It readily forms crystalline salts such as the hydrochloride, m.p. 188° (dec), the hydrobromide, m.p. 188°, the hydriodide, m.p. 169–172°, the nitrate, m.p. 153–154°, and the perchlorate, m.p. 173–174°. The base is optically inactive and reacts neither with nitrous acid nor with benzoyl chloride so that it is a tertiary base containing no hydroxyl groups.

3. Lobelanidine

Lobelanidine, $C_{22}H_{29}O_2N$, which accompanies lobeline and lobelanine, is also a tertiary and monoacidic base. It crystallizes from ethanol as colorless prisms, m.p. 150°, is readily soluble in acetone, benzene, and pyridine, less soluble in cold ethanol, sparingly in ether and petroleum ether, and insoluble in water. The base forms crystalline salts and derivatives: a hydrochloride melting at 138°, a hydrobromide, m.p. 188–190°, a diacetyl derivative, the acetate of which melts at 75°, and a dibenzoyl

derivative, $C_{36}H_{37}O_4N$, m.p. 109–110°. The base, therefore, contains two hydroxyl groups. It further forms a methiodide, m.p. 173–175°, which, on treatment with silver oxide, yields a crystalline ammonium base, m.p. 152°, from which lobelanidine is regenerated by heating. When lobeline in weak acetic acid solution is reduced with sodium amalgam, it takes up two atoms of hydrogen whereas lobelanine under the same conditions takes up four atoms of hydrogen. In each case the product is the dihydroxy base, lobelanidine. Hence, the three alkaloids are closely related.

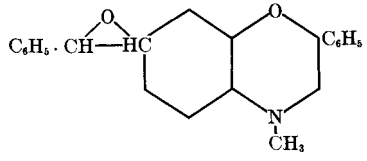
4. Structure of Lobeline, Lobelanine and Lobelanidine

Lobelanine on oxidation with potassium permanganate produces 2 moles of benzoic acid and, therefore, must contain two monosubstituted benzene rings. When lobelanine is heated to 140° with molten benzoic acid or at 125° with excess dilute hydrochloric acid, it gives rise to acetophenone, a product also characteristic of the decomposition of lobeline. Heating with hydrochloric acid also produces methylamine and fluorene whereas heating under pressure with alcoholic potassium hydroxide yields a mixture of methylamine, benzhydrol, and phenylmethylcarbinol. The

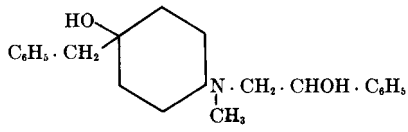
$$C_{22}H_{25}O_2N \xrightarrow[KOH]{HCl} C_8H_8O + C_{13}H_{10} + CH_3NH_2 + H_2O$$

$$C_{22}H_{25}O_2N \longrightarrow C_8H_8O + C_{13}H_{12}O + CH_3NH_2$$

formation of fluorene and benzhydrol combined with the fact that initially Wieland did not succeed in preparing any of the usual derivatives characteristic of the hydroxyl and the keto group from either lobeline or lobelanine led to an erroneous conclusion. Wieland assumed that the oxygen atoms present in these two bases form part of ether linkages and that the production of the dihydroxy base lobelanidine by the reduction of lobeline and lobelanine involves the scission of the ether linkages (482). He suggested that lobelanine and lobelanidine might be represented by formulas (L) and (LI) respectively. The two hydroxyl groups of lobelani-



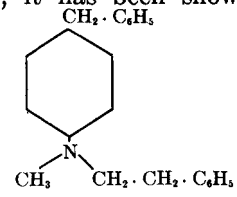
L



LI

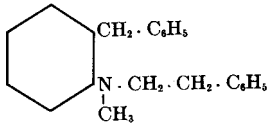
dine are substituted by chlorine when the base is heated with phosphorus trichloride and the resulting compound ($C_{22}H_{27}NCl_2$) when reduced with nascent hydrogen gives rise to a base designated as lobelan. For this parent alkaloid, a structure consistent with formula (LI) for lobelanidine

was suggested, i.e., 4-benzyl-*N*-methyl-*N*-phenylethylcyclohexylamine (LII). Lobelan methiodide, however, does not undergo the Hofmann degradation and heating the corresponding quaternary hydroxide merely regenerates lobelan. Further, it has been shown (483) that the two



LII

synthetic isomers (*cis-* and *trans-*) of 2-benzyl-*N*-methyl-*N*-phenylethylcyclohexylamine (LIII) both readily undergo the Hofmann degradation



LIII

giving rise to a tertiary amine and styrene, in accordance with the rule stated by v. Braun and Cahn (484) that phenylethylammonium bases when degraded always yield the phenylethyl portion as styrene. Formula (LII) for lobelan is therefore untenable.

Subsequently, it was found (485) that both lobelanidine and lobeline, by mild oxidation with chromic acid in acetic acid, are converted into lobelanine. Therefore, lobelanine is a diketone while lobeline is a keto alcohol and this is confirmed by the fact that lobelanine yields a dioxime, $C_{22}H_{27}O_2N_3$, m.p. 209°, and a diphenylhydrazone, $C_{34}H_{41}O_2N_5$, m.p. 187°. Furthermore, lobelanine undergoes the Hofmann degradation. When the methiodide of this base is degraded, about half the quantity reverts to lobelanine, but there is also formed the salt of a quaternary base which is isolated only with difficulty. This quaternary base is so sensitive that when it is liberated from its salt by means of moist silver oxide, it immediately gives off trimethylamine and forms a nitrogen-free compound which still contains the twenty-two C-atoms of the original base less one due to the loss of the N—CH_3 group. This compound, on mild catalytic hydrogenation in alcoholic solution, absorbs two moles of hydrogen and is converted to a crystalline compound, $C_{21}H_{24}O_2$, m.p. 56–57°, identified as 1:7-dibenzoylheptane. If the catalytic hydrogenation is carried out in acetic acid solution, four moles of hydrogen are absorbed and the product is a glycol which by mild oxidation with chromic acid is readily converted to 1:7-dibenzoylheptane. Energetic oxidation converts the last compound

to benzoyl-*n*-heptanoic acid, $C_6H_5CO(CH_2)_6CO_2H$. These reactions can be represented thus:

$$C_{22}H_{25}O_2N \rightarrow C_6H_5COCH{=}CH{-}CH_2 \cdot CH_2 \cdot CH_2 \cdot CH{=}CHCOC_6H_5 + CH_3NH_2$$

$$\downarrow 2H_2$$

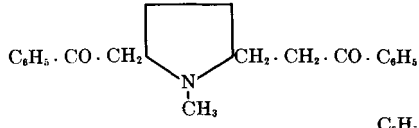
$$C_6H_5COCH_2CH_2CH_2CH_2CH_2CH_2CH_2COC_6H_5$$

$$\downarrow O$$

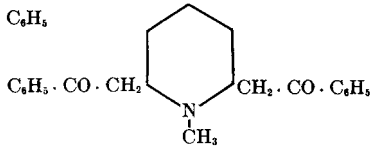
$$C_6H_5COCH_2CH_2CH_2CH_2CH_2CH_2 \cdot CO_2H + C_6H_5CO_2H$$

The results of this degradation of lobelanine, together with the ready interconversions of lobeline, lobelanine, and lobelanidine by mild oxidation or reduction, indicate the structure of these three alkaloids.

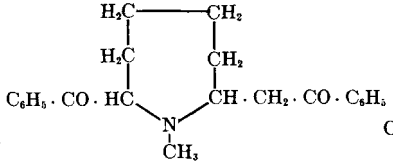
Lobelanine contains a tertiary nitrogen and by the action of both acids and alkalies yields methylamine. Therefore the nitrogen which carries a methyl group forms part of a heterocyclic ring which must be formed of from five to eight atoms so that the alkaloids could be derivatives of pyrrolidine (LIV), piperidine (LV), hexamethyleneimine (LVI) or heptamethyleneimine (LVII).



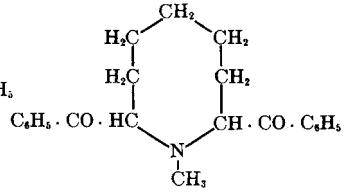
LIV



LV



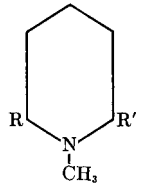
LVI



LVII

Lobelanine, which is optically inactive, can be obtained by oxidation of optically active lobeline and also by oxidation of optically inactive lobelanidine. This makes it possible to eliminate some of the above formulas although all four would be consistent with the results of the Hofmann degradation. Because of the relationship of the three alkaloids, it is evident that the optical activity of lobeline must be attributed to the asymmetry of the C-atom involved in the secondary alcohol group in this keto-alcoholic base. The optical activity of lobeline is lost when the

hydroxyl group is oxidized to a keto group in the transformation of the base into lobelanine. On the other hand, hydrogenation of lobeline converts the keto group into a new secondary alcohol group and transforms the base to lobelanidine which is optically inactive. This is possible only if the newly formed center of asymmetry in the resulting lobelanidine compensates the activity already existent. Consequently, there are two similarly substituted asymmetric C-atoms on the two carbinol groups and lobelanidine is a *meso* compound. Unsymmetrical formulas (LIV) and (LVI) can then be deleted and so can formula (LVII), since it is extremely unlikely that such a structure could give rise to acetophenone on hydrolysis. Hence, formula (LV) represents the only possible structure left for lobelanine which is the diketone $\alpha\alpha'$-diphenacyl-*N*-methylpiperidine. Lobeline is, therefore, the keto alcohol (LVIII, R = $C_6H_5 \cdot CO \cdot CH_2$; R′ = $C_6H_5 \cdot CHOH \cdot CH_2$), while lobelanidine is the dialcohol (LVIII, R = R′ = $C_6H_5 \cdot CHOH \cdot CH_2$). These structures for the three alkaloids are further supported by the fact that the dioxime of lobelanine, when treated with



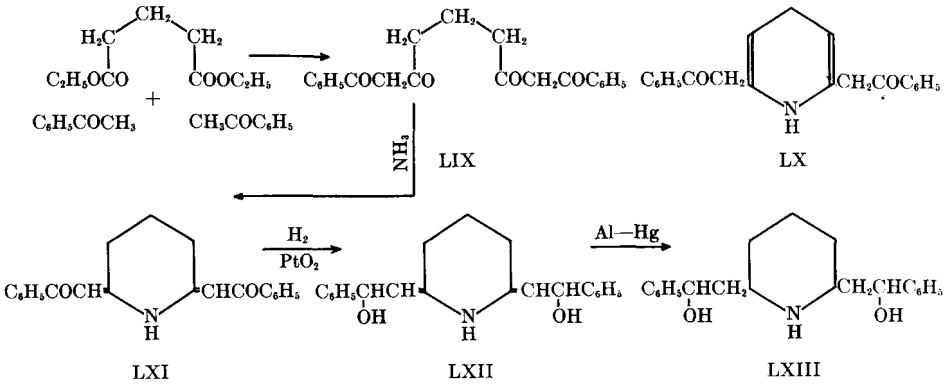
LVIII

thionyl chloride, undergoes the Beckmann transformation and gives rise to the dianilide (LVIII, R = R′ = $C_6H_5 \cdot NH \cdot CO \cdot CH_2$). Hydrolysis with hydrochloric acid produces aniline and lobelinic acid, $C_{10}H_{17}O_4N$, identical with *N*-methylpiperidine-$\alpha\alpha'$-diacetic acid (LVIII, R = R′ = $CH_2 \cdot CO_2H$). Furthermore, the vigorous oxidation of lobelanine with chromic acid yields scopolinic acid (LVIII, R = R′ = CO_2H). The formulas of lobelanine (LV), lobeline (LVIII, R = $C_6H_5 \cdot CO \cdot CH_2$; R′ = $C_6H_5CHOH \cdot CH_2$) and lobelanidine (LVIII, R = R′ = $C_6H_5 \cdot CHOH \cdot CH_2$) do not appear consistent with the formation of fluorene and of benzhydrol when lobelanine is treated with acid and alkali respectively (482). It is admittedly difficult to explain the formation of such compounds although an ingenious explanation has been suggested (485). Whatever the value of this explanation, the structure of lobelanine and that of the other two bases have been definitely confirmed by synthesis.

Synthesis of Lobelan and the Three Bases. The simpler desoxy-compound lobelan was first synthesized (486). $\alpha\alpha'$-Distyrylpyridine obtained by the condensation of $\alpha\alpha'$-dimethylpyridine (lutidine) with benzaldehyde, gives

rise when hydrogenated with sodium in alcohol, to 2:6-diphenethylpiperidine which is norlobelan. Both the *cis*- and *trans*-forms are obtained in this reaction. The *cis*-form, on treatment with methyl iodide, is converted into a product identical with lobelan methiodide. Lobelan itself is obtained when 2:6-diphenethyl-1-methylpyridinium *p*-toluenesulfonate (m.p. 232–4°) is hydrogenated over Adam's catalyst (487). Because of the asymmetry of C-atoms 2 and 6 of the piperidine ring *cis* (*meso*) and *trans*-(*dl*) stereoisomers are theoretically possible but lobelan (the *meso* form) alone (hydrochloride, m.p. 195–6°) is obtained.

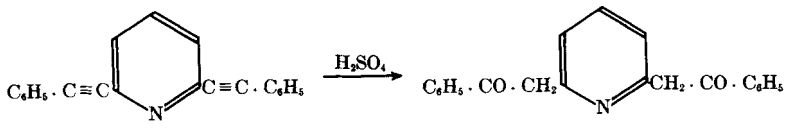
For the synthesis of lobelanidine (486), ethyl glutarate is condensed with acetophenone in the presence of sodamide and the resulting 1:7-dibenzoylheptadione-2:6 (LIX) treated with ammonia at 100°. The product, however, is not the expected dihydropyridine derivative (LX) but



the piperidine derivative (LXI). Catalytic hydrogenation of the latter over platinic oxide produces a glycol (LXII) isolated in two isomeric forms: α-norlobelanidiene, m.p. 148°, and β-norlobelanidiene, m.p. 173°. Reduction of β-norlobelanidiene in ether solution with aluminum amalgam gives rise to a base, $C_{21}H_{27}ON$, m.p. 120°, isolated as its hydrochloride, identical in every respect with naturally occurring norlobelanidine (LXIII) (488). Mild oxidation of this synthetic norlobelanidine with chromic acid produces norlobelanine, identical with the naturally occurring base (488). Methylation of norlobelanidine gives rise to synthetic lobelanidine.

The foregoing synthesis has been considerably simplified by the discovery that 2:6-distyrylpyridine rapidly adds two moles of bromine and the resulting compound on treatment with alcoholic potash gives rise to 2:6-diphenethinylpyridine (LXIV). Hydration of this diacetylenic compound with sulfuric acid yields 2:6-diphenacylpyridine (LXV) which can be hydrogenated in methanol over a platinic oxide-barium sulfate catalyst

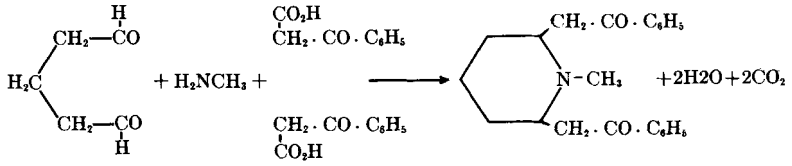
first to the corresponding disecondary alcohol and then to norlobelanidine (LXIII). The reduction, however, is not quite complete and the product is accompanied by some norlobelanine and some *dl*-norlobeline. If 2:6-



LXIV LXV

diphenacylpyridine (LXV) is treated with methyl *p*-toluenesulfonate and the product reduced catalytically, a 49% yield of lobelanidine is obtained or, if the reduction is interrupted at an intermediate stage, lobelanine is the product. The hydrogenation of *N*-methyl-2:6-diphenacylpyridinium-toluenesulfonate has been further studied by Gurevich (490) who claims to have obtained lobeline directly.

The synthesis of lobelanine has also been achieved by an elegant method which affords a beautiful example of a synthesis carried out under so-called physiological conditions (491). A mixture of glutaric dialdehyde, methylamine hydrochloride and benzoylacetic acid kept in a buffered solution at pH 4 and 25° for 8 hours gives a 90% yield of lobelanine thus:



At numerically higher or lower pH values, the yield is decreased. It has been shown that in the synthesis of tropine under similar conditions, the first step in the reaction is the production of tropinone (491). Likewise in the above synthesis the diketone lobelanine is first formed, but as the time of the reaction is increased, lobeline and lobelanidine are produced by the partial or complete reduction of the diketone. The formation of lobelanine in this synthesis takes place only in an acid medium and it is noteworthy that the range of pH at which good yields are obtainable is very narrow.

It is interesting to note that the substitution of succinic dialdehyde for the glutaric dialdehyde in the foregoing reaction gives rise to a lower homolog of lobelanine, *N*-methyl-2:5-diphenacylpyrrolidine. This base, which has not been found in nature, is obtained in 94% yield as beautiful crystals, m.p. 205–206°. Like lobelanine, it forms a hydrochloride, m.p. 205–206°, which is sparingly soluble in water.

5. *dl*-Lobeline

dl-Lobeline, $C_{22}H_{27}O_2N$. In the course of his original isolation of *l*-lobeline, Wieland (481) also isolated another base which he termed lobelidine. Subsequently, this base (488) was found to yield lobelanine when oxidized with chromic acid. Its optical inactivity indicates that it is racemic lobeline and this was confirmed by resolution of the base. Repeated crystallization of the *d*-tartrate from hot water yielded *l*-lobeline-*d*-tartrate from which the *levo*-rotatory lobeline was obtained. The firm of Boehringer, Nieder-Ingelheim, Germany, have been preparing *d*-lobeline by resolution of synthetic *dl*-lobeline with the aid of both *d*- and *l*-dibenzoyltartaric acid.[1]

6. Norlobelanine

Norlobelanine, $C_{21}H_{23}O_2N$, is isolated from crude lobelanidine nitrate (488). It had earlier been designated as isolobelanine. It melts at 117–118° and contains a secondary nitrogen since it yields a nonbasic benzoyl derivative, m.p. 125–126°. It can be reduced with sodium amalgam to norlobelanidine which in turn can be reoxidized to norlobelanine. On methylation it gives rise to lobelanine.

7. Norlobelanidine

Norlobelanidine, $C_{21}H_{27}O_2N$. Lobelanidine is separated from the other *Lobelia* alkaloids by crystallization of its sparingly soluble hydrochloride (488), and the alcoholic mother liquors contain the hydrochloride of a secondary base. This base, which is optically inactive, melts at 120° and forms a hydrochloride, m.p. 244°, a nitrate, m.p. 179–180°, and a hydriodide, m.p. 211°. Since it is converted by methyl *p*-toluenesulfonate to lobelanidine and by oxidation with chromic acid to norlobelanine, the base is norlobelanidine. It is obtained as an intermediate product in the synthesis of lobelanidine (486).

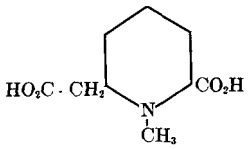
In the course of a search for compounds possessing the particular physiological activity exhibited by lobeline, Warnat (492) prepared many substances. Among these, phenylpropanol-phenylpropanone-methylamine was found to possess a physiological activity very similar to that of lobeline although it is less toxic.

8. *dl*-Lelobanidine

dl-Lelobanidine, $C_{18}H_{29}O_2N$. In the process of working up the main alkaloids of *Lobelia*, the minor bases are obtained as a yellowish brown

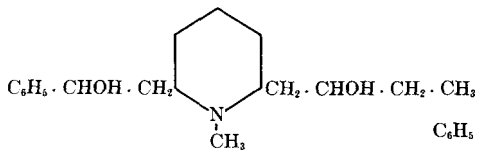
[1] Personal communication from Dr. G. Scheuing to Prof. Paul Gagnon of Laval University, Quebec, who visited Ingelheim in 1945 as a scientific investigator.

sirup. A number of these minor bases are isolated by fractional crystallization of their hydrochlorides or hydrobromides which are more soluble than the corresponding salts of the main alkaloids. One of these minor bases, *dl*-lelobanidine (493), m.p. 68°, forms a hydrochloride, m.p. 79°, a hydriodide, m.p. 159°, and a perchlorate, m.p. 152°. It is a tertiary dialcoholic base which forms a dibenzoyl derivative, $C_{32}H_{37}O_4N$, the hydrochloride of which melts at 178°. Vigorous oxidation of the alkaloid with chromic acid gives rise to a mixture of benzoic acid and methylgranatic acid (LXVI). Since the similar oxidation of the main alkaloids of this group produces benzoic acid and scopolinic acid (LVIII, R = R′ = CO_2H), it can be con-

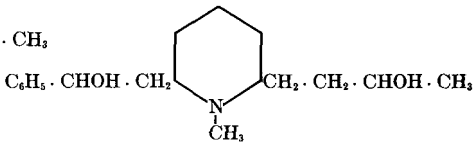


LXVI

cluded that there is a group $C_6H_5 \cdot CHOHCH_2$ present on one side of the piperidine ring in the molecule which is split off as benzoic acid, leaving a carboxylic group in the α-position. The molecule, therefore, carries the residual four-carbon side chain ($CH_2CHOH \cdot C_2H_5$) or ($CH_2CH_2CHOH \cdot CH_3$) in the α'-position of the ring, so that lelobanidine must be represented either by formula (LXVII) or (LXVIII), since methylgranatic acid (LXVI) could be formed from either. A choice between (LXVII) and (LXVIII)



LXVII



LXVIII

is made possible by the results of the Hofmann degradation of lelobanidine. The dialcoholic base lends itself to the degradation no better than lobelanidine, but on mild oxidation it gives rise to a diketo base, lelobanine, $C_{18}H_{25}O_2N$, m.p. 142°, whose methiodide is amenable to the Hofmann degradation. The reaction brings about the elimination of the nitrogen as dimethylamine and the formation of a doubly unsaturated diketone, $C_{17}H_{20}O_2$, which can be reduced catalytically to a glycol, $C_{17}H_{28}O_2$, and this in turn, when oxidized with chromic acid, gives rise to a saturated diketone, $C_{17}H_{24}O_2$, m.p. 53°, identical with synthetic 1-benzoyl-7-propionylheptane, $C_6H_5CO(CH_2)_7COCH_2CH_3$. Lelobanidine must therefore be represented by formula (LXVII).

9. *l*-LELOBANIDINE-I

l-Lelobanidine-I, $C_{18}H_{29}O_2N$. Among the minor alkaloids, there occurs a small quantity of a base which has the same composition as *dl*-lelobanidine but is levorotatory and is designated *l*-lelobanidine. It forms a hydrochloride, m.p. 86°, $[\alpha]_D$ − 41.5° (ethanol), a hydriodide, m.p. 171°, and a perchlorate, m.p. 176°. Resolution of *dl*-lelobanidine with *d*-camphorsulfonic acid yields the pure *d*-lelobanidine, the hydrochloride of which has $[\alpha]_D$ + 40.7° (ethanol). The melting points of the salts of the *d*-component agree exactly with those of the corresponding salts of *l*-lelobanidine (493). Furthermore, a mixture of equal parts of the hydrochlorides of the two enantiomorphs has the same properties as *dl*-lelobanidine hydrochloride. Since the methylgranatic acid produced by the oxidation of *dl*-lelobanidine is identical with the acid derived from the oxidation of *N*-methylgranatoline, it must consist of the racemic mixture of the two possible *cis*-forms. The inactive base is, therefore, *dl*-lelobanidine, while the naturally-occurring levo-base is designated *l*-lelobanidine-I, where I designates that the alkaloid is one of the optical isomers of the *cis*-form.

10. *l*-LELOBANIDINE-II

l-Lelobanidine-II, $C_{18}H_{29}O_2N$. There also occurs in the lelobanidine (lelobine) group another levorotatory alkaloid which is remarkably similar to *l*-lelobanidine-I but is definitely different since the melting points of the hydrochlorides of the two bases differ by about 20°. It is designated *l*-lelobanidine-II. It forms a hydrochloride, $B \cdot HCl \cdot 1.5H_2O$, m.p. 102–105°, $[\alpha]_D$ − 41.7° (ethanol), a hydriodide, m.p. 165°, and a perchlorate, m.p. 158°. On mild oxidation with chromic acid, it is converted to the same *l*-lelobanine obtainable from *l*-lelobanidine-I. Therefore, the two bases must be identical insofar as the two asymmetric C-atoms of the ring are concerned, so that their difference must rest in the different configuration of one or both asymmetric C-atoms in the side chains. This conclusion is supported by the fact that the optical activity of the hydrochlorides of both bases is identical. If the four asymmetric C-atoms are numbered, 1 and 4 for the two in the side chains, 2 and 3 for the two in the ring, then Wieland (493) suggests that *l*-lelobanidine-I and *l*-lelobanidine-II might be represented thus:

(1)	(2)	(3)	(4)		(1)	(2)	(3)	(4)
l	*l*	*d*	*d*		*d*	*l*	*d*	*l*

11. *d*-NORLELOBANIDINE

d-Norlelobanidine, $C_{17}H_{27}O_2N$, is an optically active secondary base which crystallizes from petroleum ether as colorless rosettes, m.p. 90°, $[\alpha]_D$ + 62.8°. It forms a hydrochloride, m.p. 193°, a hydrobromide, m.p.

202°, a hydriodide, m.p. 193° and a perchlorate, m.p. 141°. It forms a di-*m*-nitrobenzoyl derivative, m.p. 212° and therefore contains two hydroxyl groups. Methylation with methyl *p*-toluenesulphonate converts the base to *d*-lelobanidine, whereas oxidation with chromic acid yields *d*-norlelobanine. The latter forms a methiodide which, when subjected to the Hofmann degradation, yields a diketone convertible by hydrogenation to 1-benzoyl-7-propionylheptane which confirms the structure of the alkaloid as *d*-norlelobanidine.

12. Lobinine

Lobinine, $C_{18}H_{25}O_2N$, is obtained as follows (494):

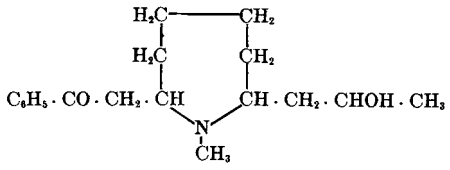
The minor bases obtained after removal of the main alkaloids are precipitated with acetic acid from their solution in ether. A further separation is effected by treating the precipitated bases with petroleum ether which dissolves the lobinine together with some of the other bases. The impure lobinine recovered from the petroleum ether solution is converted to its perchlorate in alcoholic solution.

Lobinine perchlorate, after recrystallization, melts at 143°, but the free base recovered from it has not been crystallized. Besides the perchlorate, it forms readily crystallizable salts such as the hydrochloride, m.p. 144°, $[\alpha]_D$ − 106.1° (alcohol), the hydriodide, m.p. 130°, and a chloroplatinate, $(B \cdot HCl)_2PtCl_4$, m.p. 190° (dec). Lobinine was first assigned the formula $C_{18}H_{27}O_2N$, but this was later corrected (493) to $C_{18}H_{25}O_2N$. It gives rise to both an oxime forming a crystalline hydrochloride, $C_{18}H_{27}O_2N_2Cl$, m.p. 182°, and a benzoyl derivative crystallized as the hydrochloride, $C_{25}H_{30}O_3NCl$, m.p. 146–147°, so that it is both a ketone and an alcohol.

Careful oxidation of lobinine removes two hydrogen atoms with the resulting formation of an optically active diketone, lobinanine, $C_{18}H_{23}O_2N$ (designated earlier as lobinone, perchlorate, m.p. 133°, hydrochloride, m.p. 94°, $[\alpha]_D$ − 18.6°) whereas vigorous oxidation with chromic acid produces benzoic acid and an unidentified acid which is identical neither with scopolinic acid nor with methylgranatic acid.

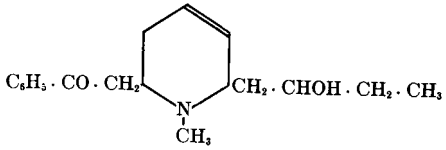
The diketone lobinanine forms a methiodide which under the action of sodium bicarbonate undergoes scission into dimethylamine and an intensely yellow, nitrogen-free compound originally assigned the empirical formula $C_{17}H_{20}O_2$, later corrected to $C_{17}H_{18}O_2$. This compound, on catalytic reduction, gives rise to a saturated glycol $C_{17}H_{28}O_2$ which can be converted by mild oxidation to a crystalline, saturated diketone $C_{17}H_{24}O_2$, m.p. 53°. More vigorous oxidation splits the diketone into benzoic acid, suberic acid and acetic acid, and these acids account for all the C-atoms present in the original molecule except that of the methylimino group. Wieland and Ishimasa (494) had not detected the double bond originally

present in the molecule and had obtained neither scopolinic acid nor methylgranatic acid as a product of the oxidation of lobinine. They, therefore, interpreted the results of the Hofmann degradation in which the unsaturated diketone was assumed to be $C_{17}H_{20}O_2$ instead of $C_{17}H_{18}O_2$ as meaning that the alkaloid contains a seven-membered heterocyclic ring and they assigned to lobinine structure (LXIX) which appeared to be the only formula consistent with the formation of suberic acid. However,



LXIX

reinvestigation of lobinine (493) revealed the presence of one double bond in the molecule and also that vigorous oxidation gives rise to benzoic acid and an acid, $C_9H_{13}O_4N$, m.p. 207–208°, which is unsaturated and therefore could not be formed from a structure such as (LXIX). The catalytic hydrogenation of lobinine hydriodide causes the absorption of four H-atoms and the formation of a dihydroxy compound, $C_{18}H_{29}O_2N$, which is an isomer of lelobanidine although it is identical neither with *l*-lelobanidine-I nor with *l*-lelobanidine-II. This reduced base, designated *β*-lelobanidine, forms a hydriodide, m.p. 181°, $[\alpha]_D$ − 39.2° (ethanol) and a perchlorate, m.p. 152°. In the light of these reactions, lobinine is an unsaturated keto alcohol which is converted by hydrogenation to an alkaloid of the lelobanine (lelobine) group. For the sake of consistency with the nomenclature used for the Lobelia alkaloids, since lobinine is a keto alcohol, the corresponding diketone (originally named lobinone) is designated as lobinanine whereas the corresponding dialcohol is named lobinanidine.



LXX

$$C_6H_5 \cdot CO \cdot CH_2 \cdot CH = CH \cdot CH = CH \cdot CH = CH \cdot CO \cdot CH_2 \cdot CH_3 \qquad \text{LXXI}$$

$$C_6H_5C(OH) = CH \cdot CH = CH \cdot CH = CH \cdot CH = CH \cdot C(OH) = CH \cdot CH_3 \qquad \text{LXXII}$$

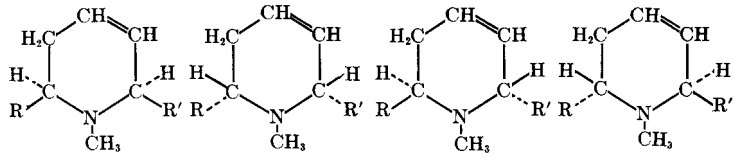
Since the double bond of lobinine must be located in the heterocyclic ring, Wieland (493) suggested formula LXX to represent it. The results of the

Hofmann degradation of lobinanine support formula (LXX) rather than the abandoned formula (LXIX). As already mentioned, lobinanine methiodide is decomposed, by merely stirring with alkali, into dimethylamine and a deep-yellow, unsaturated ketone, m.p. 81–82°, first assigned the empirical formula $C_{17}H_{20}O_2$, later corrected to $C_{17}H_{18}O_2$. This ketone dissolves in alkalies with the development of an extraordinarily intense violet coloration. The color reaction is so sensitive that it can be used for the detection of small traces of lobinine. If structure (LXX) be assumed for lobinine, then the unsaturated diketone must be 1-benzoyl-7-propionylheptatriene (LXXI) which by the action of alkalies is converted to the dienol (LXXII). The saturated ketone, $C_{17}H_{24}O_2$, obtained from the dienol by hydrogenation followed by mild oxidation is identical with 1-benzoyl-7-propionylheptane, the end product of the Hofmann degradation of lelobanine. Hence a close relationship exists between the lobinine and lelobine groups and the nuclear structure for lobinine (LXX) is definitely confirmed although the exact location of the double bond in the heterocyclic ring has not been established.

13. Isolobinine

Isolobinine, $C_{18}H_{25}O_2N$, an isomer of lobinine, was discovered and characterized by Thomä (495). When the total minor bases of *Lobelia* are removed from an ether solution by extraction with the calculated amount of acid previously divided into ten portions and used successively, fractions 5 and 6 thus obtained contain the base isolobinine. This base is purified by crystallization of its dibenzoyl tartrate, m.p. 156°, from ethanol. The free base, $C_{18}H_{25}O_2N$, crystallizes from petroleum ether, m.p. 78°. It is readily soluble in ether but sparingly so in petroleum ether. Its hydrochloride monohydrate melts at 132° but after drying, at 154°, $[\alpha]_D$ − 76.0° (water). Isolobinine forms an oily oxime which yields a crystalline hydrochloride, $C_{18}H_{25}O_2N_2 \cdot HCl$, m.p. 186°. When oxidized vigorously with chromic acid, the base yields benzoic acid and acetic acid, but no scopolinic acid although, if the alkaloid is first hydrogenated and subsequently oxidized, scopolinic acid is found amongst the products (495). On the other hand, mild oxidation with chromic acid yields the corresponding diketo base, $C_{18}H_{23}O_2N$, isolobinanine which forms a hydrochloride, m.p. 151°, $[\alpha]_D$ − 11.0° (ethanol) (494). Isolobinanine is not identical with lobinanine produced similarly from lobinine, but its methiodide undergoes the Hofmann degradation, giving rise to the same triene diketone, $C_{17}H_{18}O_2$, obtainable similarly from lobinanine, the oxidation product of lobinine. The triene diketone forms the characteristic deep-violet sodium salt mentioned above. Discarding the possibility that isolobinanine could differ from lobinanine because the double bond in the former might occupy

a different position in the heterocyclic ring than it does in the latter, Wieland concludes that the two bases are stereoisomers. In the stereoisomerism of the lobinanines, it is the two asymmetric C-atoms of the heterocyclic ring that are considered to be involved. Four optically active configurations are possible and these are illustrated in formulas LXXIII to LXXVI. On the basis of the known facts, it is possible provisionally to say only that lobinanine and isolobinanine cannot be LXXIII and LXXIV, nor LXXV and LXXVI because both bases are active in the same direction, i.e., both are levorotatory. They can be either LXXIII and LXXV, or LXXIV and LXXVI.



LXXIII LXXIV LXXV LXXVI

Since the product of the hydrogenation of isolobinine is identical with *l*-lelobanidine-I and since the latter is one of the two optically active *cis*-forms (corresponding to LXXIII or LXXIV), both isolobinine and isolobinanine must have the *cis*-configuration and, therefore, lobinine should have the *trans*-configuration. The lelobanidine obtained by the catalytic hydrogenation of lobinine is identical with neither of the two known *cis*-antipodes, *l*-lelobanidine-I and *l*-lelobanidine-II and it is designated *β*-(*trans*)-lelobanidine.

14. Lobinanidine

Lobinanidine, $C_{18}H_{27}O_2N$, like lobinine occurs with the alkaloids of *Lobelia* and, like it, is levororatory. The hydrochloride of this base is more soluble than the hydrochlorides of the accompanying alkaloids and the base is purified by crystallization of the hydriodide or perchlorate. Lobinanidine crystallizes from petroleum ether as small plates, m.p. 95°, $[\alpha]_D$ − 120° (in alcohol). It forms a hydrochloride, m.p. 169°, and a hydriodide, m.p. 200°. The base is a di-secondary alcohol which by mild oxidation with chromic acid is converted to lobinanine, the corresponding diketo base. The perchlorate of this lobinanine, m.p. 130°, is identical with that of the lobinanine obtained by oxidation of lobinine. This identity is further confirmed by the observation that the Hofmann degradation of the lobinanine obtained from lobinanidine yields the same yellow diketone, m.p. 81–82°, which shows a deep purple color with alkali. The vigorous oxidation of the base with chromic acid yields the same acid, $C_9H_{13}O_2N$, m.p. 207–208°, already obtained by the oxidation of lobinine. Hydrogenation of lobinanidine yields a base isomeric with *β*-lelobanidine obtained

from lobinine but different from it; it is designated α-lelobanidine. It yields a hydriodide, m.p. 174°, $[\alpha]_D$ − 37°, and a perchlorate, m.p. 142°. Naturally-occurring lobinanidine is not identical with the product of the reduction of lobinine and the latter product is designated β-lobinanidine.

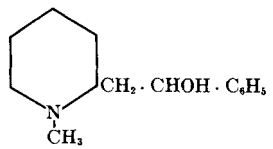
15. Isolobinanidine

Isolobinanidine, $C_{18}H_{27}O_2N$, is separated as its perchlorate and purified by crystallization of its hydrochloride. It is an amorphous base which forms crystalline salts. The hydrochloride, $B \cdot HCl \cdot 2H_2O$, m.p. 111°, $[\alpha]_D$ − 28.3° (water), the hydriodide, m.p. 164°, have been described. The structure of isolobinanidine is established by the catalytic hydrogenation of the base which converts it to *l*-lelobanidine-I and by oxidation which yields isolobinanine (493).

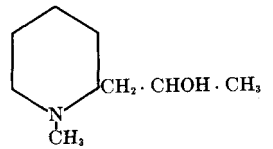
16. Other Minor Bases

Wieland and his coworkers (493) have also reported the isolation of a base $C_{19}H_{23}O_3N_2$, m.p. 232°, which forms a hydrochloride, m.p. 299–300°, a hydriodide, m.p. 279°, and a perchlorate, m.p. 254–255°. It gives rise to a methiodide, m.p. 244° (dec) and a monobenzoyl derivative, $C_{26}H_{30}O_4N_2$, m.p. 220°. It is unsaturated but on hydrogenation produces a heterogeneous product.

Three other minor bases, $C_9H_{19}ON$, m.p. 85–87°, $C_{14}H_{21}ON$, m.p. 103°, and $C_{14}H_{21}ON$, m.p. 81° have also been isolated. The last of these bases yields a benzoyl derivative isolated as its crystalline hydrochloride, m.p. 118°, so that its oxygen is present in a hydroxyl group. On mild oxidation it yields a ketone, $C_{14}H_{19}ON$, the hydrochloride of which melts at 109°, while on vigorous oxidation with chromic acid it produces benzoic acid and an acid $C_7H_{13}O_2N$, m.p. 235°, which is not identical with the *N*-methylpiperidine-α-carboxylic acid of Hess and Leibbrandt (87) but is assumed to be a stereoisomer of it. Structure LXXVII is suggested for the base $C_{14}H_{21}ON$ of melting point 81° and structure LXXVIII for the simpler base $C_9H_{19}ON$, although no experimental proof is submitted to support the structure of the latter (493).



LXXVII



LXXVIII

17. Lobinaline

Lobinaline, $C_{28}H_{38}ON_2$, has been isolated from *Lobelia cardinalis* L. by Manske (496). It is the main and possibly only base present in the plant.

TABLE 2

INTERRELATION OF MINOR LOBELIA ALKALOIDS

	Natural base	Derivative	$[\alpha]_D$	Melting points, °C. Base	B·HCl	B·HI	B·$HClO_4$
Lelobine group	*dl*-Lelobanidine	Oxidation → *dl*-Lelobanine	Inact.	68	79	159	152
			Inact.		142		
		Resolution → *d*-Lelobanidine	+40.7[a]		86	171	176
	l-Lelobanidine-I	Oxidation ↑	−41[a]		86	171	176
	Norlelobanidine	Methylation → *l*-Lelobanine	+63[b]	90	193	193	141
			+20[a]		186		
	l-Lelobanidine-II		−41[a]		102–5	165	158
Lobinine group	Lobinine	Reduction → β-Lobinanidine	−130[a]		144	130	143
					180		
		Hydrogenation → β-Lelobanidine	−39.2[c]			181	152
		Oxdation → Lobinanine	−18.6[d]		94		133
	Lobinanidine	Oxidation ↑	−120[b]	95	169	200	
		Hydrogenation → α-Lelobanidine	−37[c]			174	142
	Isolobinine	Oxidation → Isolobinanine	−76[d]	78	154		
			−11[a]		151		
		Reduction → β-Isolobinanidine			161		
		Hydrogenation → *l*-Lelobanidine-I ↑					
	Isolobinanidine	Hydrogenation ↑	−28.3[d]		111	164	169

[a] Hydrochloride in alcohol.
[b] Free base in alcohol.
[c] Hydriodide in alcohol.
[d] Hydrochloride in water.

Lobinaline crystallizes from dry ether as fine, colorless prisms, m.p. 94–95° (corr.), $[\alpha]_D^{24} + 22.3°$ (chloroform). It forms a monohydrochloride, $C_{28}H_{38}ON_2 \cdot HCl \cdot 1.5H_2O$, which crystallizes from chloroform-acetone as fine, colorless needles, m.p. 200° (corr.). The salt is readily soluble in dilute acids, but is decomposed by boiling with water into the readily soluble dihydrochloride and the base from both of which the monohydrochloride can be regenerated. Lobinaline dihydrochloride has not been obtained in crystalline form. From its empirical formula it is obvious that lobinaline is different from the alkaloids of *Lobelia inflata* which are all derivatives of piperidine. There appears, however, to be one point of similarity in the occurrence of a *C*-benzoyl group (or the corresponding carbinol) in lobinaline as in all the alkaloids of *L. inflata*. Oxidation of lobinaline with potassium permanganate yields benzoic acid although in amount insufficient for the presence of two monosubstituted benzene nuclei. The constitution of lobinaline has not been further elucidated.

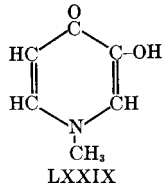
VII. The Ricinus Alkaloid

Ricinine

Ricinine, $C_8H_8O_2N_2$ (51), was discovered in 1864 in the seeds of *Ricinus communis* L. (48) the pressed seeds containing 0.3% and the total plant yielding 1.1%. The alkaloid, which sublimes at 170–180°/20 mm., crystallizes from alcohol or water as glistening plates or colorless prisms, m.p. 201.5° (corr.). It dissolves in cold pyridine to the extent of 2% and in the boiling solvent 34%. It is optically inactive and gives certain color reactions. The addition of potassium dichromate to a solution of ricinine in concentrated sulfuric acid produces a yellowish green to green color (46). A red color develops around the drop when ricinine is heated with concentrated nitric acid, the diluted solution concentrated and a drop of dilute ammonia added to the yellowish residue. If the solution is evaporated to dryness and the residue dissolved in water, a red solution is produced (47). The base also gives a positive Weidel reaction: a mixture of ricinine, a few drops of hydrochloric acid, and some potassium chlorate is evaporated to dryness on the steam bath and moistened with dilute ammonia when a red color is produced (47). Although the presence in castor seeds of a second base, ricidine, has been reported (49), this has since been shown to be ricinine (47, 50).

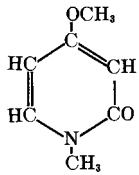
Ricinine forms a compound with mercuric chloride, $C_8H_8O_2N_2HgCl_2$, m.p. 204°. It also gives a chloro derivative, m.p. 240°, and a bromo derivative, m.p. 247° (46). Saponification of the base with sodium hydroxide produces methyl alcohol and ricininic acid, $C_7H_6O_2N_2$, m.p. 320° (dec) (46, 51). Heating ricininic acid at 150° with fuming hydrochloric acid

decomposes it to carbon dioxide, ammonium chloride, and a base hydrochloride, $C_6H_7O_2N \cdot HCl \cdot H_2O$, crystallizing from water in large prisms. The hydrochloride, after losing its water of crystallization, melts at 155–160° (chloroplatinate, m.p. 184–186°). The free base ($C_6H_7O_2N$) after crystallization from water or alcohol, becomes liquid at 80°, solidifies, and melts again at 170–171°. It produces a red coloration with ferric chloride, reduces hot Fehling's solution and, when treated with bromine, gives rise to a series of crystalline bromo derivatives, $C_6H_6O_2NBr$, m.p. 265°, $C_6H_7O_2NBr_2$, m.p. 170° and $C_6H_7O_2NBr_4$, melting with decomposition. Furthermore, the action of phosphorus pentachloride on this base removes a methyl group and produces a dichloro compound, $C_5H_3NCl_2$, b.p. 98°/18 mm. which when heated with hydriodic acid and phosphorus gives rise to pyridine. Pyridine is also obtained by the distillation of ricinine with zinc dust (53). The base ($C_6H_7O_2N$) was therefore regarded as 1-methyl-3-hydroxy-4-pyridone (LXXIX) (52). That the alkaloid contains

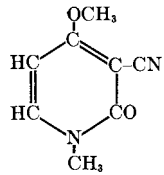


LXXIX

two double bonds is confirmed by the results of the hydrogenation over platinum of ricinine hydrochloride to tetrahydroricinine hydrochloride, $C_8H_{12}O_2N_2 \cdot HCl$, m.p. 212–215° (chloroplatinate, m.p. 222–225° (dec); aurichloride, m.p. 160°) (53). However, refluxing ricinine with 57.4% sulfuric acid converts it to a product ($C_7H_9O_2N$) melting at 55–57° and after drying at 112–114°. This product which forms a chloroplatinate, m.p. 198–199° (dec) and an aurichloride, m.p. 129–131°, has a neutral reaction, is unsaturated and shows a red color with ferric chloride. It was subsequently shown to be identical with synthetic 4-methoxy-*N*-methyl-2-pyridone (LXXX) and to be converted by heating with hydrogen chloride



LXXX

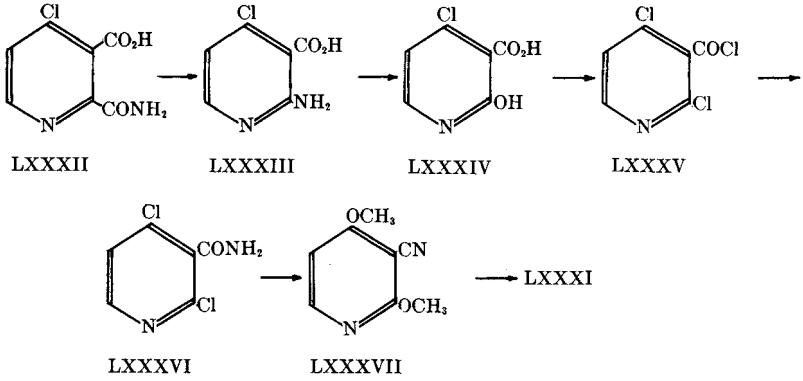


LXXXI

at 140°, to the compound, $C_6H_7O_2N$, previously obtained from ricininic acid. The compound $C_6H_7O_2N$ is therefore 4-hydroxy-*N*-methyl-2-pyridone and it follows that the methyl group of ricinine which is so easily

lost is present not in a carbomethoxy group but in a methoxy group attached to the 4-position of a 2-pyridone ring (LXXX) (55). The so-called ricininic acid (which is not an acid but a substituted 4-hydroxy-pyridone) produces, when heated with phosphorus oxychloride, a chloro compound which is converted by the action of sodium methylate to ricinine (56). If, however, the chloro compound is reduced catalytically, a desmethoxy-ricinine is produced which, on warming with potassium hydroxide, gives rise to ammonia and, not the expected 1-methyl-2-pyridone, but 1-methyl-2-pyridone-3-carboxylic acid. This observation and the fact that the oxidation of ricinine with chromic acid gives rise to hydrocyanic acid (54) lead to the conclusion that ricinine contains a CN group located in position 3 of the pyridone ring. The conclusion is confirmed by the fact that the chloride of 1-methyl-2-pyridone-3-carboxylic acid on treatment with ammonia is converted to the amide which by dehydration ($POCl_3$) gives rise to desmethoxyricinine (56). Hence, ricinine is 1-methyl-3-cyano-4-methoxy-2-pyridone (LXXXI).

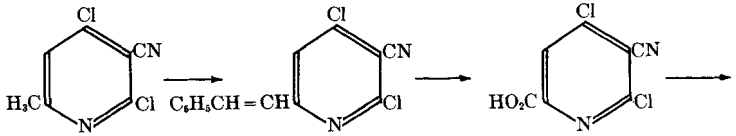
Syntheses. The structure (LXXXI) of ricinine has been confirmed by several syntheses. The anhydride of 2,3-dicarboxy-4-chloropyridine, obtained by the oxidation of 4-chloroquinoline, is converted by means of ammonia to the monoamide (LXXXII). This is converted by the Hofmann reaction to the amine (LXXXIII) from which the hydroxy compound (LXXXIV) is obtained by diazotization. The action of phosphorus oxychloride and phosphorus pentachloride on the hydroxy compound



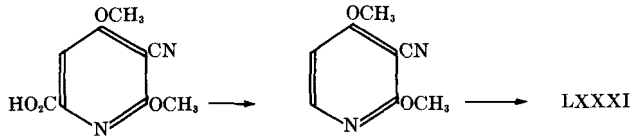
(LXXXIV) gives rise to 2:4-dichloronicotinic acid chloride (LXXXV) which is converted to the amide (LXXXVI) and this in turn with the aid of sodium methylate to 2:4-dimethoxy-3-cyanopyridine (LXXXVII). When this last compound is treated with methyl iodide a reaction takes place, probably through the intermediate formation of an unstable methio-

dide, which gives rise to ricinine (LXXXI), identical in all its properties with the natural alkaloid (57).

A second route to ricinine was suggested by the observation that ethyl 2:4-dihydroxy-6-methyl-nicotinate is obtained from the condensation of ethyl malonate and ethyl β-aminocrotonate in the presence of sodium ethylate (59). This substituted ethyl nicotinate when converted to the amide by means of alcoholic ammonia and dehydrated with phosphorus oxychloride gives rise to 2:4-dichloro-3-cyano-6-methylpyridine (LXXXVIII). Condensation of LXXXVIII with benzaldehyde followed by oxidation yields the acid (LXXXIX) and this on treatment with sodium methylate



LXXXVIII LXXXIX



XC LXXXVII LXXXI

produced 2-carboxy-4:6-dimethoxy-5-cyanopyridine (XC) which is decarboxylated to 2:4-dimethoxy-3-cyanopyridine (LXXXVII) (58). This last product also obtained in the previous synthesis is converted to ricinine as before.

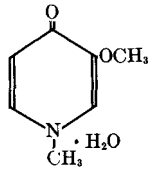
A third synthesis (60) uses as starting material 3-nitro-4-pyridone which via 3-nitro-4-chloropyridine and 3-amino-4-methoxypyridine is converted to 3-cyano-4-methoxypyridine. The product of the reaction of this last compound with methyl sulfate is oxidized with potassium ferricyanide to ricinine.

A fourth and interesting route to ricinine (61) is based on the observation that the spontaneous polymerization of cyanoacetyl chloride gives rise to 2:4-dihydroxy-6-chloronicotinonitrile (6-chloronorricinine) (62). When the product of the reaction of the disodium salt of this compound with methyl sulfate is reduced with zinc and sulfuric acid, the so-called ricininic acid is produced. Conversion to the corresponding chloro compound and replacement of the halogen by a methoxyl completes the synthesis.

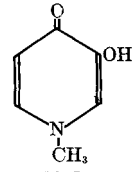
VIII. Leucaenine

Leucaenine (leucenol), $C_8H_{10}O_4N_2$ (506), is the active principle of the seeds of *Leucaena glauca* Benth. (503). It is prepared from an aqueous

extract of the seeds by precipitation with alcohol, filtration and evaporation of the filtrate (yield 1.1%) (505). Leucaenine, m.p. 240–245° (dec, ev. tube, corr.), is optically inactive and it is practically insoluble in all organic solvents except methanol and ethanol. It forms crystalline salts such as the hydrochloride, m.p. 174.5–5° (dec), the hydrobromide, m.p. 179.5° (dec) and the hydriodide, m.p. 183–3.5° (dec). The ninhydrin test indicates that it is an α-amino acid and this is confirmed by the following facts: (a) 50% of its nitrogen is contained in a primary amino group; (b) it is recovered unchanged from dilute acidic or basic solutions by adjusting the pH to 3.8–5.4; (c) it forms a hydroxy acid when diazotized with barium nitrite; (d) refluxing with methanolic hydrogen chloride converts it to the methyl ester dihydrochloride, m.p. 180–181° (dec). Furthermore, the color tests with ferric chloride show the presence of a phenolic hydroxyl (504). The distillation of leucaenine with zinc dust gives rise to pyridine (506). Methylation with dimethyl sulfate in alkaline medium produces a compound, $C_7H_{11}O_3N$, m.p. 92–92.5°, which no longer shows the ferric chloride test. The hydrochloride of this compound on heating loses methyl chloride and is converted to a new substance, $C_6H_7O_2N$, m.p. 242–244°, showing the ferric chloride test (506). The latter proved to be identical with synthetic *N*-methyl-3-hydroxypyridone-4 (XCII) (507, 508) while the compound $C_7H_{11}O_3N$ from which it is derived is identical with *N*-methyl-

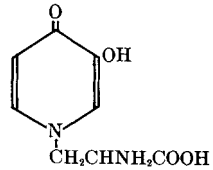


XCI



XCII

3-methoxypyridone-4 monohydrate (XCI) prepared by heating an aqueous solution of 3-methoxypyrone-4 and methylamine (509). Furthermore, the pyrolysis of leucaenine produces 3,4-dihydroxypyridine (3-hydroxypyridone-4) (506, 510, 511, 512). Hence leucaenine is a 3-hydroxypyridone-4 substituted with an α-aminopropionic acid side chain (XCIII) which is



XCIII

considered attached to the nitrogen atom since leucaenine is not affected by boiling hydrobromic acid (511), and this structure is supported by infrared absorption spectra (513).

The alkaloid mimosine, $C_8H_{10}O_4N_2$, m.p. 228°, $[\alpha]_D^{22} - 21°$ (516) isolated from the sap of the sprouts and roots of *Mimosa pudica*, Benth. (515, 516) is probably levorotatory leucaenine (505, 514).

IX. The Alkaloids of Hemlock

The toxic properties of the poison hemlock (*Conium maculatum* L.) were known in antiquity and the Greeks administered an extract of the plant to criminals. These toxic properties are due to the presence in the plant of a group of alkaloids, the major one of which is coniine. The occurrence of coniine has been reported in many other plants such as fool's parsley (*Aethusa cynapium* L., 0.00023%) (101), *Arum maculatum* L., *Arum italicum* Mill., *Arisarum vulgare* Targ., *Amorphophallus rivieri* Dur., and *Caladium bulbosum* Hort. (102), but does not seem to have been definitely nor sufficiently characterized, so that the only definite natural source of coniine is the poison hemlock. It occurs in all parts of the plant and the content of total alkaloid, which varies with the season, ranges from 0.01 to 0.06% in the stem, 0.03–0.18% in the leaves and 0.73–0.98% in the green fruit. The quantity of total alkaloid in the leaves before blooming increases from 0.096% to 1.49% and falls during the blooming season to 0.35–0.47%. The content of the seed also decreases as the seed ripens: it is 1.62% in the green seed, 1.26% in the half-ripe seed and 1.00% in the ripe seed (103). It has been reported that *Conium maculatum* in British Columbia has a larger habit than that in Great Britain and that the coniine content is above the average (104).

Although coniine is the major alkaloid of *C. maculatum* where it occurs in both its optically active forms, it is known to be accompanied by four other alkaloids: *N*-methylconiine (both *d*- and *l*-), γ-coniceine, conhydrine, and pseudoconhydrine. Several color tests for the detection of coniine have been described. The addition of a dilute solution of sodium nitroprusside to a very dilute solution of coniine causes the slow formation of an intense red color which develops more rapidly on shaking and gradually changes to yellow. On boiling the solution its color fades but reappears on cooling. A small quantity of an aldehyde added to the red solution changes the color to violet or blue while a large excess destroys the color (105). Boiling a mixture of coniine, a little sodium carbonate, a few drops of alcohol and carbon disulfide, and then adding water and a few drops of an uranium nitrate solution produces a red solution which, when shaken with toluene, colors the latter red (106). The test described by Melzer (107) consists in diluting coniine with alcohol and adding a few drops of dilute aqueous copper sulfate. The solution is colored brown, and after dilution with water and shaking with ether the latter becomes brown.

1. Isolation of the Alkaloids

A method for the large-scale isolation of coniine has been described by Chemnitius (108).

The ground seed (300 kg.) moistened with 10% of its weight of 15% aqueous sodium hydroxide is placed in layers separated by wood shavings into an extraction cylinder equipped with a heating coil and a condenser. Ether is forced in under nitrogen pressure in sufficient quantity to cover the charge and heat is applied until the evaporated ether condenses back into the extractor. After 3–4 hours, the extract is drawn into a kettle and the ether distilled and returned to the extractor. This process is repeated three times, but the first extract, because of its water content, is further worked up. The concentrated extract is poured into several 15-l. flasks and 50% acetic acid is added to each until a turbidity is produced and then the ether is distilled. The residues are combined in an earthenware container and allowed to cool. The solid floating layer of fat is removed and heated twice with 10% acetic acid, cooled, and the aqueous layers added to the main solution. The aqueous solution is then extracted with ether, basified with a large excess of 35% sodium hydroxide and again extracted with ether. The extract containing the alkaloid is dried over potassium carbonate, filtered, and the solvent removed by distillation. Fractional distillation of the crude alkaloid in a stream of hydrogen yields a fraction, b.p. 165°, which can be used without further purification for conversion into the various salts of coniine. The rest of the distillate is refractionated.

Schorm (109) recommended fractional distillation for the separation of the remaining hemlock alkaloids, but this has been shown to be insufficient. According to Wolffenstein (110) the fraction, b.p. 173–174°, contains mostly *N*-methylconiine with a little coniine which is separated either by nitrosation or by fractional crystallization of the hydrobromides. The γ-coniceine contaminated with coniine is contained in the fraction, b.p. 169–173°, and the two bases are separated by making use of the different solubilities of their hydrochlorides in acetone. A method for the quantitative separation of the bases has been outlined by v. Braun (112) which involves fractional distillation to remove most of the lower boiling coniine. The minor alkaloids are in the next fraction, while conhydrine and pseudoconhydrine are left in the residue. The minor alkaloids are benzoylated and the tertiary *N*-methylconiine separated. γ-Coniceine is obtained by fractional distillation of the benzoylated mixture and saponification.

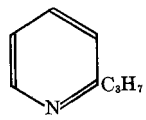
2. Coniine

Coniine, $C_8H_{17}N$, the major alkaloid of *Conium maculatum*, was discovered in 1827 (113) and has since been the subject of many studies. Ortigosa (114) suggested for it the empirical formula $C_8H_{16}N$. Later, Blyth (115) altered this to $C_{17}H_{17}N$, and in the same year Gerhardt (116) suggested the formula $C_8H_{15}N$ which was adopted by v. Planta and Kekulé (117), but was altered by Hofmann (118) to the formula $C_8H_{17}N$ finally adopted. Coniine is a colorless, strongly alkaline oil of mild piperidine-like odor, b.p.[2] 168° (119), d_4^{23} 0.8440 (120), n_D^{23} 1.4537 (121, 122), which is dextrorotatory, $[\alpha]_D$ + 15.7° (110), and is readily soluble in alcohol, ether, acetone, benzene and petroleum ether. It forms well-crystallized salts such as the hydrochloride, rhomboids, m.p. 221°, the hydrobromide, prisms,

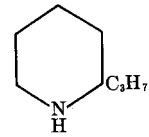
[2] The boiling point more usually given is 166.5°

m.p. 211°, the hydriodide, plates, m.p. 165°, the aurichloride, yellow plates, m.p. 77°, the chloroplatinate, orange crystals, m.p. 175–176°, and the picrate, m.p. 75°. Coniine combines with carbon disulfide and forms the coniine salt of coniylthiocarbamic acid, $C_8H_{16}N \cdot CSSH \cdot NC_8H_{17}$ crystallizing as colorless needles, m.p. 71–72° (107). A 2:4-dinitrobenzoylconiine, m.p. 139–140° and a 3:5-dinitrobenzoylconiine, m.p. 108–109°, have also been prepared (123).

Oxidation of coniine with chromic acid produces butyric acid (115, 124), while dehydrogenation of the alkaloid with silver acetate converts it to a base, conyrine (125), which is also obtained from coniine hydrochloride by distillation with zinc dust (126). Conyrine, $C_8H_{11}N$, is a colorless, fluorescent oil, b.p. 166–168°, which forms a chloroplatinate and an aurichloride; it can be converted back to coniine by reduction with hydriodic acid, it behaves on methylation like a pyridine base, and further, it gives rise on oxidation to α-pyridinecarboxylic acid. Therefore, conyrine is a 2-propylpyridine (XCIV) while coniine is a 2-propylpiperidine (XCV) (126), in which the side chain is normal since conyrine is not identical with 2-isopropylpyridine (127).



XCIV

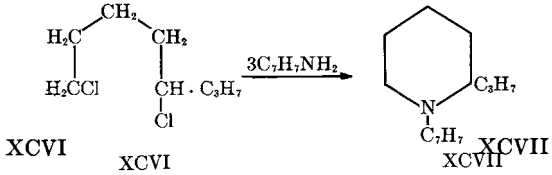


XCV

The exhaustive methylation of coniine gives rise to an unsaturated hydrocarbon, conylene, which is also obtained from nitrosoconiine, $C_8H_{16}N \cdot NO$, by the action of phosphoric acid (128, 129). These results support the view that coniine is a secondary base and a simple derivative of piperidine, a view which is confirmed by the conversion of coniine to *n*-octane by heating it with hydriodic acid and phosphorus at 300° (130). Furthermore, the action of an alkaline solution of bromine on coniine gives rise to a bromoconiine, $C_8H_{16}NBr$, which, on treatment with acid, produces a tertiary base, $C_8H_{15}N$, b.p. 158°, containing two H-atoms fewer than coniine whereas treatment with alkalies converts bromoconiine to an isomeric base, $C_8H_{15}N$, b.p. 173°, which, however, is secondary. Both bases give back coniine on mild reduction, but when the reduction is more vigorous, give rise to octylamine and *n*-octane (131). The base obtained by the action of acid was named α-coniceine and later renamed δ-coniceine (132). The isomer obtained by the action of alkalies was named γ-coniceine.

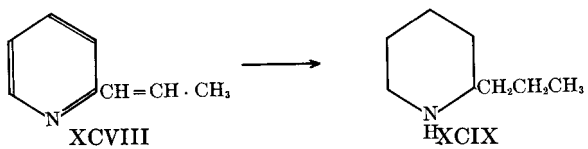
The structure (XCV) of coniine has been established by numerous

degradation experiments and finally by several syntheses. Coniine in acetone solution is oxidized by hydrogen peroxide (133) to a δ-amino-octaldehyde, $NH_2 \cdot CH(CH_2CH_2CH_3)CH_2CH_2CH_2CHO$, a colorless sirup, b.p. 103–105°/10 mm., which is optically active, $[\alpha]_D + 59.95°$. Other products of oxidation are acetic acid and butyrylbutyric acid. The aldehyde, when distilled with potassium hydroxide, loses water and gives rise to a mixture of *d*-coniine and a little coniceine. Reduction of the aldehyde with zinc and hydrochloric acid also reconverts it to coniine. The coniceine, which is different from γ-coniceine, can also be obtained directly by the action of a larger quantity of hydrogen peroxide on coniine, but it has not been further characterized. Distillation of *N*-benzoylconiine with phosphorus pentachloride causes scission of the ring with elimination of the nitrogen atom and formation of dichlorooctane (XCVI) which, by reaction with benzylamine, produces *N*-benzylconiine (XCVII) (134).



XCVI XCVI XCVII XCVII

Schiff (135) reported a synthesis of coniine involving the action of alcoholic ammonia on butyraldehyde, but it was later shown that the resulting tertiary amine was not identical with coniine. The first synthesis of coniine and the first synthesis of an alkaloid is that of Ladenburg (136) who condensed 2-methylpyridine with paraldehyde at 250° and reduced the resulting 2-allylpyridine (XCVIII) with sodium in ethanol, thereby obtaining an inactive base (XCIX) very similar to coniine in properties. The



XCVIII XCIX XCIX

synthetic base can be resolved by repeated crystallization of the hydrogen-*d*-tartrate (137, 138, 139). The yield is very low but may be improved by heating 2-methylpyridine and acetaldehyde with water at 150° (141) and converting the 2-(β-hydroxypropyl)-pyridine (C) thus obtained to a mixture of allylpyridine and 2-(β-chloropropyl)-pyridine (CI) by treatment with hydrochloric acid at 185°. The mixture is then reduced with sodium in ethanol (140). The yield may be further improved when 2-(β-hydroxypropyl)-pyridine (C) is heated at 125° with hydriodic acid and phosphorus

and the product subsequently treated with zinc dust and water. The 2-propylpyridine thus obtained is converted to *dl*-coniine by reduction with sodium in ethanol (142). A better yield of 2-(β-hydroxypropyl)-

C CI

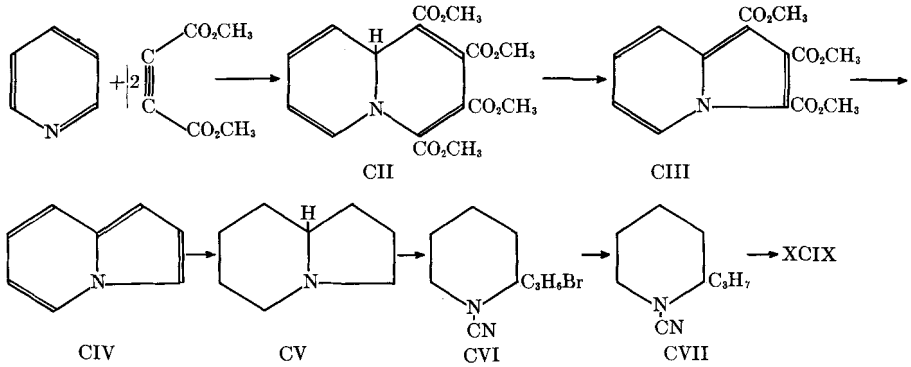
pyridine is obtained by heating the mixture of 2-methylpyridine and acetaldehyde with a fourfold quantity of concentrated hydrochloric acid at 175–180° (143).

It was found by Ladenburg (144) that when coniine hydrochloride is distilled with zinc dust, the conyrine and unaltered coniine obtained are accompanied by a quantity of a base isomeric with the latter which he named isoconiine. He claimed that it forms a chloroplatinate insoluble in ethanol-ether whereas coniine chloroplatinate is soluble in that solvent; further that this salt exhibits dimorphism, one form melting at 175°, the other at 160° (145). Since there are three forms of coniine known already, i.e., *d*-, *l*-, and *dl*-coniine, Ladenburg sought to explain the isomerism of isoconiine by the presence of an asymmetric nitrogen atom (146, 147). Wolffenstein (148) showed that Ladenburg's higher melting isoconiine chloroplatinate is *d*-coniine chloroplatinate, whereas the lower melting salt is *dl*-coniine chloroplatinate (149). A polemic ensued (150, 151) and Ladenburg claimed that isoconiine was also present in his synthetic coniine ($[\alpha]_D$ + 19°). The last modification that Ladenburg made to his synthesis also yielded a *d*-coniine of high rotation, $[\alpha]_D$ + 17.85° which he concluded must be due to isoconiine (142). Ladenburg's last synthesis was repeated by Hess and Weltzien (152) who also obtained a high rotation for the synthetic product, but solved the difficulty by a further modification of the synthesis. The catalytic hydrogenation of 2-(β-hydroxypropyl)-pyridine gives rise to 2-β-hydroxypropylpiperidine which is converted to coniine by heating with hydriodic acid and phosphorus and subsequent reduction with zinc and sulfuric acid. The *d*-coniine obtained by resolution of the resulting inactive base has $[\alpha]_D^{17}$ + 14.96° which is in good agreement with the value obtained with natural *d*-coniine.

Still a further modification of Ladenburg's synthesis involves the preparation of α-propenylpyridine by condensing 2-methylpyridine with chloral to α-pyridyl-γ-trichloro-β-hydroxypropane which is then reduced in aqueous alcoholic solution with zinc dust. α-Propenylpyridine is further reduced with sodium in ethanol and the resulting *dl*-coniine resolved as the

tartrate (153). Furthermore, the reduction with sodium amalgam of 2-propionylpyridine obtained by fusion of the calcium salts of picolinic and propionic acids, yields 2-α-hydroxypropylpyridine and further reduction of this last compound with sodium and ethanol gives rise to a small quantity of *dl*-coniine and much 2-α-hydroxypropylpiperidine (154). 2-α-Hydroxypropylpyridine can be obtained directly by reacting pyridine-α-aldehyde with ethyl magnesium bromide (155).

An ingenious synthesis of coniine has been obtained by an adaptation of the Diels-Alder type of reaction thus: the reaction of pyridine with methyl acetylene dicarboxylate in ether gives rise to methyl quinolizine-1:2:3:4-tetracarboxylate (CII), m.p. 187–188°, and this, on oxidation either



with dilute nitric acid or sodium dichromate in acetic acid is converted to methyl indolizinetricarboxylate (CIII), m.p. 151–152°. Hydrolysis of the triester (CIII) with aqueous potassium hydroxide produces a salt $C_{11}H_6O_6NK$ which is decarboxylated by boiling dilute hydrochloric acid to indolizinemonocarboxylic acid, m.p. 240–242°. Complete decarboxylation is performed by distillation with lime and the indolizine (CIV), m.p. 75°, picrate, m.p. 101°, thus obtained is converted by catalytic hydrogenation to octahydroindolizine (CV) (156). Octahydroindolizine (CV) by treatment with cyanogen bromide gives rise to the bromocyanide (CVI) which is converted to the cyanide (CVII) by reduction with hydrogen over a palladium-calcium carbonate catalyst. Hydrolysis of the cyanide (CVII) with concentrated hydrochloric acid produces *dl*-coniine (XCIX). Octahydroindolizine can also be prepared by different routes (143, 158). A method of preparing indolizine has been described (159), which has since been reinvestigated (160) and generalized (161). The structure of the product thus obtained has definitely been confirmed by reduction to octahydroindolizine and conversion to *dl*-coniine by means of cyanogen bromide (162).

3. *dl*-Coniine

dl-Coniine has been obtained by reduction of the hydrazone of pelletierine with sodium and ethanol (163) and also by the reduction of γ-coniceine (164). *l*-Coniine occurs in *Conium maculatum* in small quantities and is isolated as racemic coniine which forms a hydrochloride, m.p. 211°. It is prepared by the reduction of β-coniceine obtainable from conhydrine (165). *l*-Coniine, b.p. 166–166.5°, d_4^{15} 0.845, has $[\alpha]_D$ − 15.3°; it forms a hydrochloride, m.p. 220–221°, a hydrobromide, m.p. 205°, and a *l*-coniine-*l*-tartrate, m.p. 56°. Its chloroplatinate melts at 175–176°. The dependence of the optical rotation of (+)-piperidine-2-carboxylic acid (pipecolinic acid), its hydrogen-*d*-tartrate and the corresponding hydantoin on the concentration and the solvent leads to the conclusion that the (+)-form of the acid belongs to the *d*-series (166). Since the steric relationship of (+)-conhydrine to (−)-coniine is established (165) and (+)-conhydrine can be oxidized to (−)-pipecolinic acid, it follows that (+)-coniine and (+)-2-methylpiperidine (α-pipecoline) must like (+)-piperidine-2-carboxylic acid belong to the *d*-series and possess the same spatial configurations.

4. *N*-Methyl-*d*-Coniine

4. *N-methyl-d-coniine*, $C_9H_{19}N$, has been found in *Conium maculatum* (110); it is obtained by treating the hydrochloride of the higher boiling fraction of crude coniine with sodium nitrite to remove the coniine as the insoluble nitroso compound. The base is an oil, b.p. 173–174°, $d^{24.3}$ 0.8318, $[\alpha]_D^{24.3}$ + 81.33°, which forms a hydrochloride, m.p. 188–189°, an aurichloride, m.p. 79°, and a chloroplatinate, m.p. 158–160°. It is identical with *N*-methyl-*d*-coniine prepared by methylation of *d*-coniine with potassium methyl sulfate (167). Von Braun (112) recommends separating *N*-methylconiine from the secondary bases by benzoylation of the latter. v. Braun's base, however, had a low optical rotation and was eventually shown to contain a little *N*-methyl-*l*-coniine (168).

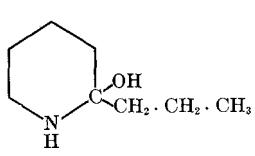
5. *N*-Methyl-*l*-Coniine

N-Methyl-l-coniine, $C_9H_{19}N$, was first isolated from *C. maculatum* by Ahrens (169) who obtained it from a residue left from the manufacture of *d*-coniine. It is separated from coniine by fractional crystallization of the hydrobromides, coniine hydrobromide being the less soluble of the two. The coniine which is thus separated is a mixture of *d*- and *dl*-coniine. *N*-Methyl-*l*-coniine is a colorless oil, b.p. 175–176°, d_{20}^{20} 0.8349, $[\alpha]_D^{20}$ − 81.92°. It forms a hydrochloride, colorless leaflets, m.p. 189–190°, a hydriodide, m.p. 147°, a chloroplatinate, orange crystals, m.p. 153–154°, an aurichloride, m.p. 77–78°, a mercurichloride, B · HCl · $3HgCl_2$, m.p. 152–153°, and a picrate, m.p. 121–122°.

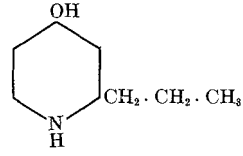
6. Conhydrine

Conhydrine, $C_8H_{17}ON$, was discovered in *Conium maculatum* in 1856 and was then assigned its correct empirical formula (170). It is a solid crystallizing as colorless leaflets from ether, m.p. 120.6°, b.p. 224.5°/720 mm., $[\alpha]_D$ + 10 (c = 10 in ethanol) (171), and is soluble in ethanol or chloroform but only moderately so in water and in ether. It forms an aurichloride, m.p. 133°, and a benzoyl derivative. An *N*-ethylconhydrine has also been prepared (172) as well as an *N*-methyl derivative (173) so that the base contains a secondary nitrogen atom.

Since conhydrine differs from coniine by containing one oxygen atom and since it can be transformed into an iodoconhydrine convertible by reduction to *l*-coniine (165, 174, 175), the base is a hydroxyconiine (130). Structural formulas have been suggested for conhydrine such as (CVIII) (176) containing a quaternary C-atom and (CIX) which is α-propyl-γ-

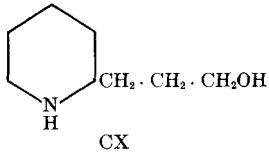


CVIII

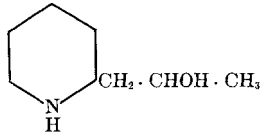


CIX

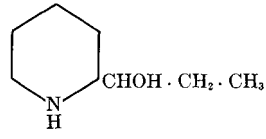
hydroxypiperidine (177). Both, however, had been suggested on purely speculative bases and were later shown to be untenable because conhydrine is oxidized with chromic acid to *l*-2-piperidine-carboxylic acid (*l*-pipecolinic acid) so that the presence of the hydroxyl group in the heterocyclic ring is precluded (178). Of the three possibilities, (CX), (CXI) and (CXII), for



CX



CXI

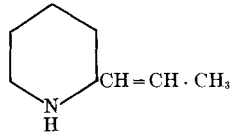


CXII

conhydrine, formula (CX) is eliminated because oxidation of the primary alcohol group should give rise to 2-piperidylpropionic acid whereas 2-piperidinecarboxylic acid is obtained. Conhydrine must then be represented by either (CXI) or (CXII). The racemic form of compound CXI was synthesized (179) and found to be very similar to conhydrine, but the comparison remained inconclusive because of the optical activity of the alkaloid. The isomeric 2-(α-hydroxypropyl)-piperidine (CXII) was synthe-

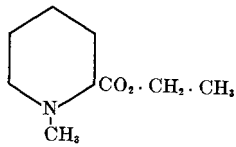
sized by Engler and Bauer (154) who obtained both racemic forms pure and held the view that the compound was identical not with conhydrine but with inactive pseudoconhydrine so that the latter was represented by (CXII). Willstätter (178) regarded pseudoconhydrine as a diastereoisomer of conhydrine and represented the two bases by (CXII), but Engler later altered his views (180, 181) and challenged this formulation of conhydrine.

When conhydrine is treated with a dehydrating agent, it loses water and a mixture of coniceines is obtained. Dehydration with phosphorus pentoxide (170) or with fuming hydrochloric acid (130) gives rise to β-coniceine (CXIII), to the isomeric iso-α-allylpiperidine (165) and some γ-coniceine. With fuming hydrochloric acid, however, the products are accompanied by some α-coniceine, the constitution of which is not yet established. Finally, the elimination of hydrogen iodide from iodoconhydrine (182) generates a bicyclic ϵ-coniceine which is a mixture of two stereoisomeric methylconidines. Although a great deal of importance has been given in the older literature to the coniceines (130, 165, 170, 182, 183), it is obvious that both compounds (CXI) and (CXII), by loss of water can be converted to β-coniceine (CXIII) and that γ-coniceine on the other hand can be obtained neither from (CXI) nor (CXII) by direct dehydration but must involve a wandering of the double bond (183). Hence the coniceines are not suitable to establish a choice between formulae (CXI) and (CXII). However, the resolution of racemic β-coniceine obtained from synthetic 2-(β-hydroxypropyl)-piperidine (CXI) into its optical



CXIII

antipodes and the addition of hydrogen iodide to the *l*-form followed by decomposition with silver acetate and saponification, yields the two optically active diastereoisomeric compounds of formula (CXI), neither of which is identical with conhydrine (183). Furthermore, synthetic 1-(α-*N*-methylpiperidyl)-propan-1-one (CXIV) is identical with racemic *N*-methyl-

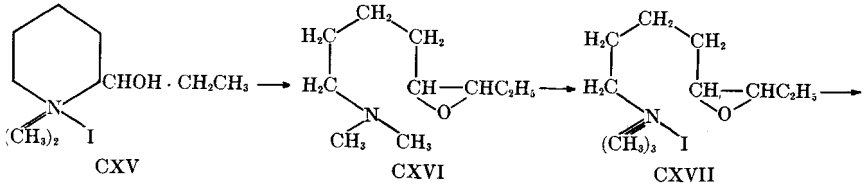


CXIV

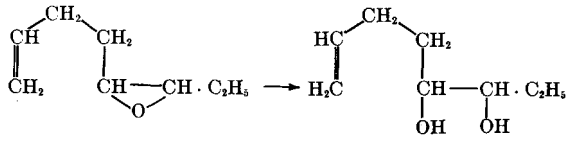
conhydrinone previously prepared from conhydrine (184, 185), and racemic conhydrine is identical with the β-form of synthetic 1-(α-piperidyl)-propan-1-ol (CXII) of Engler and Bauer (154, 185). Hence, conhydrine

has structure (CXII) and this is confirmed by the fact that both conhydrine and conhydrinone, when dehydrogenated over platinum or palladium and treated N_2O_3, produce α-pyridyl ethyl ketone and inactive α-pyridyl ethyl carbinol identical with the corresponding synthetic products (186). The structure of conhydrine (CXII), however, remained uncertain until the structure of methylisopelletierine was settled (184, 185, 187, 188) and until it was unequivocally confirmed by a study of the Hofmann degradation of the alkaloid (175).

The optically active *N*-methylconhydrine methiodide (CXV), m.p. 221–223°, on treatment with moist silver oxide yields an ammonium base which, by decomposition *in vacuo*, gives rise to an ether-soluble dextro base, $C_{10}H_{21}ON$ (conhydrinemethine), b.p. 91°/10 mm. This base absorbs no hydrogen in the presence of palladium and therefore is fully saturated; it does not contain a hydroxyl group and does not react with reagents for carbonyl groups. On long standing in water, the methine is converted back to the quaternary base from which it arises and on addition of sodium iodide, it is converted to *N*-methylconhydrine methiodide. Hence the oxygen atom of conhydrine methine is present in an ether linkage (CXVI). Conhydrine methine methiodide (CXVII), m.p. 134–135°, yields a quaternary ammonium base from which two compounds are obtained by heating *in vacuo:* an oil, b.p. 157–159°/744 mm., $C_8H_{14}O$, and a crystalline, less volatile compound, m.p. 75–76°, $C_8H_{16}O_2$. This crystalline dihydroxy compound absorbs 1 mole of hydrogen on catalytic hydrogenation (Pd+C) and forms a substance, m.p. 94–96°, while on oxidation with potassium permanganate and sulfuric acid it undergoes scission into succinic acid and propionaldehyde. Since the dihydro compound of m.p. 94–96° is converted to *n*-valeric acid on oxidation, it is 3:4-dihydroxyoctane and the unsaturated



CXV CXVI CXVII



CXVIII CXIX

compound of m.p. 75–76° is dihydroxy-5,6-octene-1 (CXIX). The oil obtained besides the crystalline compound in the Hofmann degradation can, by heating with water at 170°, be converted into the crystalline com-

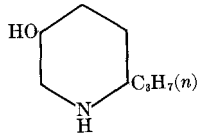
pound, m.p. 75–76°, so that it must be the unsaturated oxide (CXVIII). The various steps of the Hofmann degradation definitely establish formula (CXII) for conhydrine.

7. Pseudoconhydrine

Pseudoconhydrine, $C_8H_{17}ON$ (189), is an isomer of conhydrine discovered by Merck in the residues from the preparation of coniine and studied by Ladenburg and Adam (189). It is a strong base, b.p. 236–236.5°, which crystallizes as a monohydrate from wet ether in plates, m.p. 58–60°, or from dry ether as colorless needles, m.p. 105–106°. It is optically active, $[\alpha]_D$ + 11.0 (c = 10, in ethanol) and forms a hydrochloride, m.p. 213–214°, an aurichloride, m.p. 133–134°, and a chloroplatinate, m.p. 185–186°. Pseudoconhydrine is a secondary base which yields an oily nitrosoamine (189) and a crystalline *N*-benzoyl derivative, m.p. 132–133° (123). Like conhydrine, pseudoconhydrine contains a hydroxyl group and when heated with phosphorus pentoxide at 110° it is converted to a strongly dextrorotatory base, $C_8H_{15}N$ (pseudoconiceine) and thence by hydriodic acid to an iododerivative, m.p. 155°, which on reduction yields *d*-coniine (191). The same transformation is brought about by treating pseudoconhydrine with hydriodic acid and red phosphorus and reducing the resulting iododerivative (191). *d*-Coniine is also obtained when pseudoconhydrine is dehydrated with phosphorus pentoxide and reduced catalytically (123). It is obvious from these results that pseudoconhydrine is a hydroxyconiine.

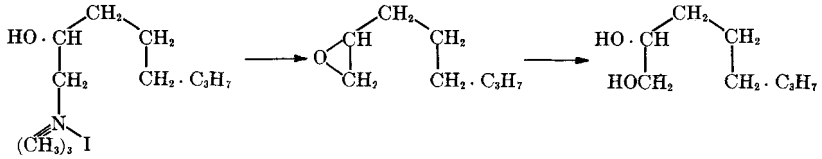
The hydroxyl group was first assumed to be in the side chain (180) and later, in analogy with the structures of tropine and of *N*-methylgranatoline, it was assigned to position 4 of the piperidine ring (191). It cannot, however, be in the side chain since the oxidation of the base with chromic acid does not yield pipecolinic acid as originally claimed (178), but an amino acid, m.p. 205–207° (benzoyl derivative, m.p. 150–152°) (123). This amino acid is also obtained together with another amino acid, $C_7H_{15}O_2N$ (benzoyl derivative, m.p. 130–131°), as a product of the oxidation of *N*-benzoylpseudoconhydrine. Hydrolysis of the benzoyl derivative of the latter acid does not yield the amino acid as such, but in the form of its lactam, $C_7H_{13}ON$, m.p. 45–47°. The hydrochloride of the acid, formed by heating the lactam with hydrochloric acid in a sealed tube, is converted by treatment with nitrous acid into the optically active lactone, $C_7H_{12}O_2$, of the corresponding hydroxy acid. This lactone is oxidized with chromic acid to a keto acid, $C_7H_{12}O_3$, identical with synthetic 1-heptan-4-one-carboxylic acid and, therefore, the original amino acid, $C_7H_{15}O_2N$, is 4-amino-oenanthic acid. The amino acid, $C_6H_{13}O_2N$, which does not form a lactam, is assumed to be 3-amino-*n*-caproic acid. Consequently, the alkaloid contains an *n*-propyl side chain in the α-position of a hydroxy-

piperidine nucleus (123). The position of the hydroxyl group in the piperidine nucleus is indicated by the results of the Hofmann degradation of the alkaloid. The methiodide of pseudoconhydrine, when treated with silver oxide and distilled *in vacuo*, yields a methine, $C_{10}H_{21}ON$, b.p. 101.5–103.5°/14 mm., $[\alpha]_D^{15}$ + 18.7° which on catalytic hydrogenation takes up two atoms of hydrogen and is converted to dihydropseudoconhydrine methine, b.p. 99–100.5°/11 mm., $[\alpha]_D^{15}$ + 12.2°. Furthermore, oxidation of the dihydro-methine, $C_{10}H_{23}ON$, with potassium permanganate yields *n*-heptylic acid (oenanthic acid), thus confirming the fact that the alkaloid contains an unbranched chain of eight C-atoms and showing that the hydroxyl group cannot be in the side chain nor in positions 2, 3, or 4 of the piperidine ring. Position 6 can also be eliminated because dihydropseudoconhydrine methine should then be the addition product of dimethylamine and *n*-octylaldehyde and, whereas aldehyde-ammonia compounds are readily hydrolyzed by acids, the methine is stable towards acids. The hydroxyl group of pseudoconhydrine, therefore, can occupy only position 5 of the piperidine ring and the alkaloid is represented by formula (CXX).



CXX

Such a formula explains best the further results of the Hofmann degradation. Dihydropseudoconhydrinemethine methiodide (CXXI) when treated with silver oxide and decomposed thermally, gives rise to a neutral oil which is the optically active octylene oxide-1,2 (CXXII). Distillation of the crude oil with 5% hydrochloric acid produces a chlorinated substance, probably a chlorhydrin, while heating with water at 180° converts it in good yield to the optically active octanediol-1,2 (CXXIII). In the

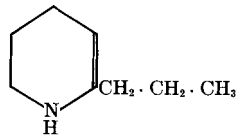


CXXI CXXII CXXIII

last two steps of the degradation, the trimethylammonium group is replaced by a hydroxyl group which undergoes ring closure with the α-hydroxyl group already present to form an ethylene oxide ring. In one particular instance, the degradation yielded octan-2-one. The formation of a ketone is also in accordance with the normal reaction and results from the elimination of water followed by tautomerization of the derived enol.

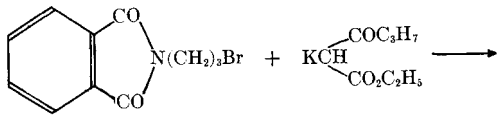
8. γ-Coniceine

γ-Coniceine, $C_8H_{15}N$, is isolated from crude coniine and is separated from coniine by fractional crystallization of the hydrochlorides in acetone (111). It is an optically inactive colorless oil, b.p. 171–172°, $d^{22.5}$ 0.8825, which forms a hydrobromide, m.p. 139°, a hydriodide, m.p. 102°, a zinc chloride double salt, m.p. 215° and other salts (Table 3). It is identical with the γ-coniceine obtained by the action of alkalis on bromoconiine (130) and with that resulting from the action of alcoholic potassium hydroxide on chloroconiine (164). γ-Coniceine also accompanies conyrine formed by the distillation of coniine hydrochloride with zinc dust (164) and it can be obtained from conhydrine (183). It is a secondary base which on reduction yields *dl*-coniine (164). Since the base is optically inactive and since on

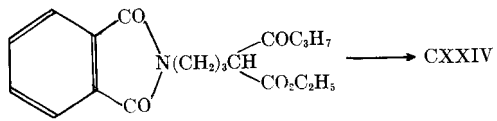


CXXIV

dehydrogenation it yields 2-propylpyridine, it has been assigned structure (CXXIV) (164). This is confirmed by the benzoylation (Schotten-Baumann reaction) which opens the ring of γ-coniceine and gives rise to benzoyl-δ-aminobutyl propyl ketone $C_6H_5CONH(CH_2)_4COC_3H_7$. It had been observed previously that Δ^2-tetrahydro-α-picoline does not react normally with benzoyl chloride (193) but gives rise to a benzoylamino ketone, $C_6H_5CONH(CH_2)_4COCH_3$; that this facile opening of the ring is attributable to the influence of the ethylene linkage in the neighborhood of the amino group and that *N*-methyltetrahydro-α-picoline is hydrolyzed even by water to methylaminobutyl methyl ketone, $CH_3NH(CH_2)_4COCH_3$ (194). Hence, γ-coniceine contains a double bond in the Δ^2-position as in structure



CXXV CXXVI



CXXVII

(CXXIV), a conclusion later confirmed by the synthesis of the base (195). γ-Bromopropylphthalimide (CXXV) reacts with the potassium derivative of ethyl butyroacetate (CXXVI) affording δ-phthalimino-α-carbethoxy-

butyl propyl ketone (CXXVII) which when heated with dilute sulfuric acid causes hydrolysis of the carbethoxy group, loss of carbon dioxide, hydrolysis of the phthalic acid residue and cyclization to γ-coniceine (CXXIV).

9. Coniceines

Coniceines, $C_8H_{15}N$. Altogether six isomeric coniceines are obtained from the alkaloids of *Conium maculatum* only one of which, γ-coniceine, actually occurs in the plant.

Hofmann (130) has described three methods for the preparation of α-coniceine, but these yield different products. The action of fuming hydrochloric acid on conhydrine produces the tertiary base α-coniceine, whereas the effect of alkali on iodoconhydrine and that of sulfuric acid on bromoconiine produce ε-coniceine and δ-coniceine respectively (132). If, on the other hand, bromoconiine is treated with alkali, γ-coniceine is obtained. β-Coniceine is the main product of the dehydration of conhydrine with phosphoric anhydride and pseudoconiceine is obtained as a product of the dehydration of pseudoconhydrine (191).

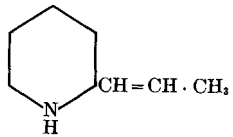
β-Coniceine boils at 168–169° and melts at 41°, d_4^{30} 0.8519, $[\alpha]_D^{45} - 50.64°$. It forms crystalline salts such as the bitartrate, m.p. 62–63° and others (Table 3). It readily reduces potassium permanganate and when a solution of its hydrochloride is treated with sodium nitrite, it gives rise to a nitroso derivative so that it is an unsaturated secondary base. Since the

TABLE 3

PROPERTIES OF THE HEMLOCK ALKALOIDS AND THE CONICEINES

Base	Melting points, °C.					$[\alpha]_D$
	B.p. °C.	B·HCl	$(B\cdot HCl)_2$ $PtCl_4$	B·HCl $AuCl_3$	Picrate	
d-Coniine	166.5	221	175–6	77	75	+15.7°
l-Coniine	166	220–1	175–6			−15.6°
N-Methyl-*d*-coniine	173–4	188–9	158–60	79		+81.3°
N-Methyl-*l*-coniine	175–6	190	153–4	77–8	121–2	−81.9°
Conhydrine	m. 121			133		+10°
Pseudoconhydrine	m. 105–6	213–4	185–6	133–4		+11.0°
α-Coniceine	158	Deliq.		196–8	224	+18.4°
β-Coniceine	m.p. 41	206–7	184	107–8	113–4.5	−50.6°
γ-Coniceine	171–2	143		69–70	62	Inact.
δ-Coniceine	158			207	226	−7.8°
ε-Coniceine	150–1	Deliq.	198–200	178	223–4	+42°
2-Methylconidine	151–4		184–5	167–8		+67.4°
Iso-2-methylconidine	143–5	Deliq.	185	198–9		
Pseudoconiceine	171–2	205–6	153–4	Oil		+122.6°

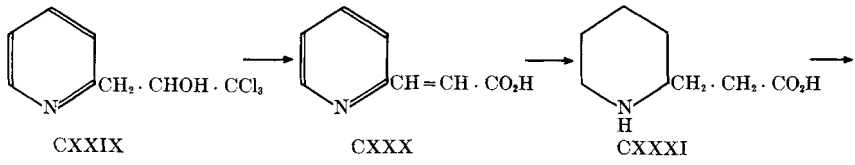
treatment of β-coniceine with hydriodic acid yields an iodo derivative converted by the action of silver acetate into 2-(β-hydroxypropyl)-piperidine, it is assigned formula (CXXVIII). This structure is confirmed by conversion of the base into *l*-coniine and by synthesis. When 2-(β-hydroxypropyl)-



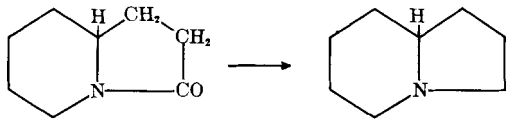
CXXVIII

piperidine is heated with phosphoric anhydride, it gives rise to a mixture of two isomeric bases, one of which, α-allylpiperidine, is a solid melting at 18° while the other, iso-α-allylpiperidine remains oily. The bases are separated by fractional crystallization of the picrates and the solid base is resolved by crystallization of the tartrates. The *l*-α-allylpiperidine obtained is identical with β-coniceine (CXXVIII) (165). Iso-α-allylpiperidine, b.p. 166.5–168.5°, d_4^{15} 0.8695, forms an oily picrate, a hydrochloride, m.p. 186–187°, and a chloroplatinate, m.p. 138–139°. It can also be resolved into its optical isomers, one of which, *d*-iso-α-allylpiperidine, $[\alpha]_D^{15}$ + 24.81°, forms a hydrochloride, m.p. 189–190°. β-Coniceine obtained from conhydrine is accompanied by an oily base which has $[\alpha]_D$ − 25.5° and forms a hydrochloride, m.p. 189–190°, so that it is likely *l*-iso-α-allylpiperidine. This base can be partly transformed into β-coniceine by saturation with hydrogen chloride at −16° and removal of hydrogen chloride by Ladenburg's method.

δ-Coniceine (Hofmann's α-coniceine) is obtained by the action of sulfuric acid on bromoconiine (132). It is a fully saturated tertiary base



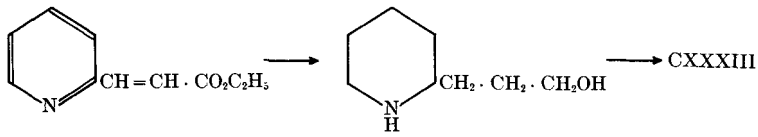
CXXIX CXXX CXXXI



CXXXII CXXXIII

which has been assigned a bicyclic structure (CXXXIII) (174) since confirmed by synthesis (143). The aldol, 2-(β-hydroxy-γ-trichloropropyl)-pyridine (CXXIX), obtained from the reaction of chloral with α-picoline, is converted by alcoholic potassium hydroxide to the substituted acrylic

acid (CXXX) and this is reduced with sodium in ethanol to 2-piperidyl-propionic acid (CXXXI). This acid readily loses water to form the lactam (CXXXII) which is reduced with sodium in ethanol to octahydroindolizine (CXXXIII) (piperolidine) identical with δ-coniceine prepared from *dl*-coniine. δ-Coniceine is also obtained when ethyl β-2-pyridylacrylate (CXXXIV) is reduced by Bouveault's method to 2-(γ-hydroxypropyl)-piperidine (CXXXV), this is heated with fuming hydriodic acid and phosphorus at 125°, and subsequently treated with alkali (197). Furthermore,



CXXXIV CXXXV

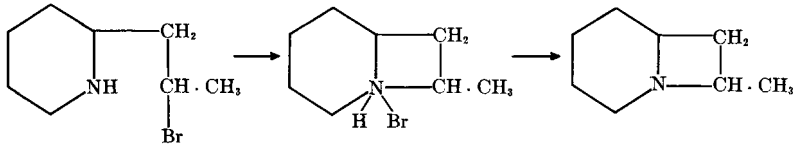
when 2-(γ-hydroxypropyl)-piperidine is heated with phosphoric anhydride at 135° for 3 hours, or with glacial acetic and concentrated sulfuric acids at 160–165° for 3–4 hours, a mixture of δ-coniceine with some 2-allyl-piperidine (*dl*-β-coniceine) is produced (197).

Incidentally, the naming of δ-coniceine and the synthetic base affords a striking example of the confusion that can be created by the lack of a proper nomenclature. While the synthetic δ-coniceine prepared by Löffler and Kaim (143) was named piperolidine, the same bicyclic structure had been named pyrindole by Angeli (198). It was later synthesized by Scholtz (159) who named it pyrrocoline although he subsequently adopted Angeli's designation (199). Later again, Tschitschibabin (161) designated the corresponding unsaturated compound as indolizine and the saturated product indolizidine and this terminology was also adopted by Diels and Alder (156) although more recently Clemo and Ramage (158, 200) used Scholtz's original designation of pyrrocoline.

In the course of a study of a synthesis of *dl*-pelletierine, Beets and Wibaut (498) discovered a new mode of preparation of δ-coniceine. The catalytic hydrogenation of β-(2-pyridyl)-propionaldehyde diethyl acetal in glacial acetic acid solution over platinum leads to different products, depending on the concentration used. If the hydrogenation be carried out in concentrated solution, the product is *dl*-pelletierine diethyl acetal, but if a dilute solution is used, δ-coniceine is obtained. Solutions of medium concentration afford mixtures of the two products.

ε-Coniceine is most readily obtained by the action of alkalies on iodoconiine and also by the action of hydriodic acid on conhydrine (132). It is a dextrorotatory oil, $[\alpha]_D$ + 42°, b.p. 150–151°, which forms crystalline salts (Table 3). Alpha-substituted pyridine containing a halogen atom in the side chain can rearrange to pyridinium compounds (201). This same

transformation takes place in 2-(β-bromopropyl)-piperidine (CXXXVI), obtained by the action of hydrobromic acid on 2-(β-hydroxypropyl)-piperidine, with the resulting formation of the piperidinium compound



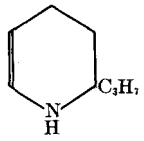
CXXXVI CXXXVII CXXXVIII

(CXXXVII) which, on treatment with a base such as diethylamine (or an alkali), is converted to a bicyclic tertiary base identical with ε-coniceine. ε-Coniceine, therefore, is (CXXXVIII) (202), but it is not homogeneous and consists of a mixture of two stereoisomerides (182). A base of structure (CXXXVIII) contains two asymmetric C-atoms and the two isomerides of ε-coniceine correspond to the (− −) and (− +) compounds. The same two isomerides are formed by the action of hydrobromic acid or hydriodic acid on 2-(β-hydroxypropyl)-piperidine. The bicyclic system involved in this molecule has been termed conidine (203) and the two bases of which ε-coniceine is composed are called 2-methylconidine and iso-2-methylconidine. The isomers are separated by fractional crystallization of the optically active tartrates (2-methyl-conidine-*d*-tartrate is more readily soluble in water than the corresponding salt of its isomer). Its dihydrate crystallizes in long needles, m.p. 72–73°. The base, b.p. 151–154°, d_4^{15} 0.8856, has $[\alpha]_D^{15}$ + 67.4° and forms crystalline salts (Table 3). Iso-2-methylconidine is a clear, strongly refractive liquid, b.p. 143–145°, d^{15}0.8624, which also forms crystalline salts (Table 3).

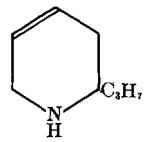
α-Coniceine ($[\alpha]_D$ + 18.4°) is obtained by the action of fuming hydrochloric acid on conhydrine and also by the action of fuming hydrochloric acid on 2-(β-hydroxypropyl)-piperidine (196). It is considered as a stereoisomer of 2-methylconidine and, therefore, as a stereoisomer of the two components of ε-coniceine. However, the structure of α-coniceine has never been demonstrated satisfactorily.

Pseudoconiceine is a product of the dehydration of pseudoconhydrine with phosphoric anhydride (191). It is a strongly basic, colorless oil, b.p. 171–172°, d_4^{15} 0.8776, $[\alpha]_D^{15}$ + 122.6°, which forms salts (Table 3). It reduces potassium permanganate readily and on treatment of its hydrochloride with nitrous acid gives rise to a nitrosoamine so that it is an unsaturated secondary amine. It readily absorbs hydrogen iodide with the formation of an iodoconiine hydriodide, m.p. 182°, which is different from the derivative obtained by the direct action of fuming hydriodic acid on pseudoconhydrine since the hydriodide of the latter melts at 216–217°. Pseudoconiceine when reduced either via its iodo derivative (191) or

directly (123) gives rise to *d*-coniine. From the constitution of pseudoconhydrine (CXX) it follows that pseudoconiceine must be represented



CXXXIX



CXL

either by (CXXXIX) or (CXL), although insufficient evidence is available to permit a choice between the two.

X. The Tobacco Alkaloids

The main alkaloids of this group have long been considered as characteristic constituents of *Nicotiana* species. The occurrence of *d*-nornicotine (246, 247) in *Duboisia Hopwoodii* F. Muell. (Solanaceae) and of anabasine (248), an alkaloid of tobacco in *Anabasis aphylla* L. (Chenopodiaceae) were thought to be remarkable exceptions. However, in recent years it has been repeatedly shown that *l*-nicotine is a rather widespread alkaloid and its occurrence in very small quantities has been reported in *Asclepias syriaca* L. (249), in *Equisetum arvense* L. (250), in *Lycopodium flabelliforme* L. (251), *Lycopodium tristachyum* Pursh. (252), *Lycopodium clavatum* L. (253), *Lycopodium lucidulum* Michx. (254), *Lycopodium sabinaefolium* Willd. (255), and *Sedum acre* L. (256). The presence of nicotine has also been recorded in Indian hemp (*Cannabis sativa* L. var. indica) by Preobraschensky (256) and although some doubt has been cast on his work (258), it now seems unwise to reject his results without a reinvestigation of the plant. Hence, nicotine can no longer be considered as the diagnostic alkaloid for *Nicotiana* species. It is noteworthy that nicotine is the only alkaloid that has bridged the gap between the flowering plants (Spermatophyta) and the vascular cryptogams (Pteridophyta) to which the *Lycopodium* species belong.

Although *l*-nicotine is the major alkaloid of tobacco, a number of other bases have been reported as occurring with it such as nicotimine, nicoteine, and nicotelline (259, 260, 261) to which Noga later added two more: isonicoteine and nicotoine (261). It is now known that nicoteine was a mixture (262) and the homogeneity of nicotimine is extremely doubtful. The latter was considered to be 3′-pyridyl-2-piperidine, but its properties do not agree with those of that compound now known to be identical with anabasine. Furthermore, isonicoteine has been shown to be identical with 3′,2-dipyridyl (263).

However, the systematic reinvestigation of the tobacco alkaloids by Späth and his students has considerably lengthened the list of bases known to occur in tobacco. Besides ammonia and trimethylamine (264) the follow-

ing twelve bases have been definitely found in tobacco and characterized:

l-Nicotine	Piperidine	3',2-Dipyridyl
Nicotyrine		Anabasine
l-Nornicotine	Pyrrolidine	*N*-Methylanabasine
		Anatabine
d-Nornicotine	*N*-Methylpyrrolidine	*N*-Methylanatabine

To these may be added nicotelline and nicotoine, neither of which has been characterized nor further studied. *d*-Nicotine has not been found in nature but has been prepared by the methylation of *d*-nornicotine (247).

These alkaloids were mostly found in crude nicotine obtained commercially by treating the leaves of cultivated tobacco (*Nicotiana tabacum* L. and sometimes *N. rustica* L.) with an aqueous solution of an alkali and distilling with steam (265). The total nicotine content of the tobacco plant is distributed as follows: flowers, 5%, stems 18%, roots 13%, and leaves 64% (266). There is considerable variation in the nicotine content of different varieties of tobacco, but there is a close parallelism in the plant between nicotine and citric acid. Nicotine in the plant, however, is not always combined with an organic acid. The glucoside tabacilin yields glucose, nicotine, and other substances (267) when hydrolyzed while the tobacco glucoside tabacin yields nicotine when treated with alkalis (268).

1. Detection and Determination

Numerous methods have been devised for the estimation of minute amounts of nicotine as well as for some of the alkaloids that accompany it. Nicotine can be determined gravimetrically as nicotine tetrachloroiodide (269) or by means of reactions with chlorodinitrobenzene for detection of the pyridine nucleus, with *p*-dimethylaminobenzaldehyde after dehydrogenation with silver acetate for detection of the pyrrole nucleus, and with quinone for detection of the iminomethyl group of the pyrrol nucleus (270). Spies (271) uses a micromethod for the determination of the alkaloid by precipitation with silicotungstic acid, while a nephelometric method (272) and a microtitrimetric method (273) have also been described. Nicotine in smoke can be determined as follows: the tobacco is burned, the base in the smoke absorbed in solutions (274) and the nicotine determined gravimetrically as its dipicrate (275). The more rapid the combustion, the greater the quantity of nicotine in the smoke. A simplified method of determining nicotine in tobacco smoke has been published by Wenusch (276, 277). Analytical methods applicable to mixtures of nicotine, nornicotine, and anabasine have been developed by Shmuk and Borozdina (278) and by Smith and Smith (279) and used by them for the investigation of the alkaloid content of numerous species of *Nicotiana*.

TABLE 4

ALKALOIDS OF *Nicotiana* SPECIES

Species	Main alkaloid	Secondary alkaloid	References
N. acuminata Hook.	Nicotine		278
N. alata Link & Otto	Nicotine	None	278, 279
N. angustifolia Mill.[a]	Nicotine		278
N. attenuata Torr.	Nicotine		283
N. benavidesii Goodspeed	Nicotine	Nornicotine	279
N. bigelovii S. Wats.	Nicotine		278, 279
N. bonariensis Lehm.	Nicotine		278
N. colyzina	Nicotine		278
N. chinensis Fisch.	Nicotine		278
N. clevelandi A. Gray	Nicotine		278
N. gossei Domin	Nicotine	None	279
N. inglubra	Nicotine	Nornicotine	278
N. langsdorffii Schrank	Nicotine	Nornicotine	278, 279
N. macrophylla Spreng.[a]	Nicotine		278
N. paniculata L.	Nicotine	Nornicotine[b]	278, 279
N. petiolaris Schlecht.	Nicotine		278
N. quadrivolvis Pursh	Nicotine		278
N. raimondii Macbr.	Nicotine	Nornicotine[b]	278, 279
N. rustica L.	Nicotine		278
N. sanguinea Link & Otto	Nicotine	Nornicotine	278
N. solanifolia Walp.	Nicotine	Nornicotine	278
N. stocktoni	Nicotine	Nornicotine	279
N. tabacum L.	Nicotine	Nornicotine	278
N. wigandioides C. Koch & Fint.	Nicotine	None	278, 279
N. benthamiana Domin	Nornicotine		278
N. caudigera Phil.	Nornicotine		278
N. cavanillesii Dun.	Nornicotine	Nicotine[c]	279
N. eastii	Nornicotine		278
N. exigua Wheeler	Nornicotine	Nicotine	279
N. glutinosa L.	Nornicotine	None[d]	278, 279
N. goodspeedii Wheeler	Nornicotine	Nicotine	279
N. maritima Wheeler	Nornicotine	None	278, 279
N. megalosiphon Heurck & Muell.	Nornicotine	Nicotine	278, 279
N. nesophila I. M. Johnston	Nornicotine	Nicotine	279
N. nudicaulis S. Wats.	Nornicotine	Nicotine	279
N. otophora Griseb.	Nornicotine		279
N. palmeri A. Gray	Nornicotine		278
N. plumbaginifolia Viv.	Nornicotine	Nicotine	278, 279
N. repanda Willd.	Nornicotine	Nicotine	278, 279
N. rosulata Domin	Nornicotine	Nicotine	278
N. rusbyi Britton	Nornicotine		278
N. sanderae Hort.	Nornicotine		278
N. suaveolens Lehm.	Nornicotine	Nicotine	278, 279, 284
N. silvestris Speg. & Comes	Nornicotine	Nicotine	279
N. tomentosa Ruiz & Pav.	Nornicotine	None[d]	278, 279

TABLE 4 (*Continued*)

Species	Main alkaloid	Secondary alkaloid	References
N. tomentosiformis Goodspeed	Nornicotine	Nicotine[c]	279
N. trigonophylla Dun.	Nornicotine	None	278, 279
N. undulata Ruiz & Pav.	Nornicotine	Nicotine[b]	278, 279
N. velutina Wheeler	Nornicotine		278
N. debneyi Domin	Anabasine	Nicotine	278, 279
N. glauca R. Grah.	Anabasine	Nicotine[e]	278, 279, 282
N. rotundifolia Lindl.[f]	Anabasine	Nornicotine Nicotine	278

[a]Synonymous with *N. tabacum* L.
[b]Smith & Smith (279) disagree with Shmuk & Borozdina (278) as to the major alkaloid.
[c]Present as a trace only. [d]Shmuk & Borozdina (278) report nicotine.
[e]Depending on the strain nicotine or nornicotine may accompany the anabasine.
[f]Synonymous with *N. suaveolens* Lehm.

In the first of these methods, a quantity of ground dry material (20–50 g.) is mixed with 10–30 cc. of a 40% solution of sodium hydroxide and extracted with ether in a Soxhlet. Aqueous alcohol is added to the extract, the ammonia removed by aeration, and the residual liquid titrated with 0.10*N* acid in the presence of a lacmoid indicator to obtain the total alkaloid content. The neutral liquor is then extracted twice with dilute sulfuric acid. The combined acid extract is used for the determination of the alkaloids. A portion is treated with nitrous acid, almost neutralized, and poured into aqueous picric acid. The dipicrate of nicotine is thus obtained. After removal of nicotine dipicrate, the secondary bases are recovered, converted to the picrates and methylated. The nicotine dipicrate obtained by fractional crystallization corresponds to nornicotine (280).

In the method used by Smith and Smith (279), a 50-g. sample is digested with water for 2 hours at 100°, the insoluble material filtered and washed with several portions of boiling water. The combined extract and washings are evaporated to a small volume on the steam bath, made strongly alkaline with sodium hydroxide and extracted repeatedly with ether. The combined ether extract is washed with dilute hydrochloric acid. The acid solution is made strongly alkaline and again repeatedly extracted with ether. The ether extract is dried over potassium hydroxide pellets and evaporated in a tared flask. This procedure gives the total alkaloid content. The nicotine is separated from the mixture by mixing with water and distilling through a Widmer column. This separation is based on the fact that nicotine forms an azeotropic mixture with water at the boiling temperature in which 2.5 g. of the base is contained in 100 cc. of water (281). Neither anabasine nor nornicotine forms a similar mixture. The nonvolatile alkaloids are precipitated with picric acid. It is apparent that a combination of both methods should be better than either. Methylation of the picrates of the residue left after distillation of the nicotine followed by liberation of the bases and removal as the azeotrope of the nicotine arising from nornicotine would give a positive determination of the latter. Such a combination of both methods was indeed applied by Dawson (282) who further elaborated on the method of analyzing mixtures of nornicotine and anabasine.

By the use of one or the other of the described methods, a total of fifty-two species of *Nicotiana* have been studied and it has been demonstrated that the wild species have a lower alkaloid content than the two cultivated species, i.e., *N. tabacum* and *N. rustica*. The results obtained

are assembled in Table 4 in which the main alkaloid is mentioned together with the secondary alkaloid whenever it was determined.

An examination of the tabulated results will make it apparent that the *Nicotiana* species can be classified into four groups: group A, comprising those species in which nicotine is the main alkaloid and a secondary alkaloid is either absent or present in insignificant quantity; group B, comprising species in which nornicotine is the main alkaloid and a secondary alkaloid is either absent or present in very small quantity; group C includes those species in which both nicotine and nornicotine are present in appreciable quantities; finally, group D includes those species in which anabasine is the chief alkaloid. The examination of these wild species has not been as thorough as that of *N. tabacum* and it is probable that a more detailed study with much larger quantities of material might reveal the presence in them of many more bases. It is significant, however, that nicotine is not the main alkaloid in all *Nicotiana* species. It should be mentioned also that the minor alkaloid can vary in content or even be absent, depending on the particular strain of a species used (282) and this may account for the contradictory statements found in the literature (278, 279).

In order to study what mutual effect the mechanism of the formation of two alkaloids in two different species would have on each other, a number of hybrids were prepared by cross-pollination between species belonging to each of the groups mentioned and the alkaloid content of the leaves of the hybrids of the F_1 generations was then determined (279). The results obtained are given in Table 5.

TABLE 5

ALKALOIDS OF *Nicotiana* INTERSPECIFIC HYBRIDS

Nicotiana cross	Main alkaloid	Secondary alkaloid	Total alkaloid content, %
F_1 (*tabacum* × *sylvestris*)	Nornicotine	Nicotine	2.26
F_1 (*tabacum* × *tomentosa*)	Nornicotine	Nicotine	1.20
F_1 (*tabacum* × *glutinosa*)	Nornicotine	Nicotine	1.92
F_1 (*tabacum* × *glauca*)	Anabasine	Nicotine	0.96
F_1 (*glauca* × *tomentosa*)	?	?	0.24
F_1 (*glutinosa* × *sylvestris*)	Nornicotine	Nicotine	1.36

The genetic factors for anabasine formation are considered by Smith and Smith (279) to be partly dominant over those controlling nicotine formation in the F_1 generation since the total percentage of anabasine was higher in the *N. tabacum* × *N. glauca* hybrid than in *N. glauca*. It is not considered dominant because the ratio of anabasine to total alkaloid is

lower in the hybrid than in *N. glauca*. This work, however, has been repeated by Dawson (293) who showed that the supposed anabasine of the hybrid is actually a mixture of anabasine and nornicotine with usually more nornicotine than anabasine. In the F_1 hybrid *N. glutinosa* × *N. sylvestris*, in which the parents are two predominantly nornicotine species, the alkaloid is mostly nornicotine with a small percentage of nicotine. On the other hand, in crosses between *N. tabacum* which contains mostly nicotine, and species with an alkaloid content made up largely or entirely of nornicotine, the hybrids contain mostly nornicotine together with small quantities of nicotine.

Concerning the mechanism of formation of the alkaloids in the plant, investigations of grafts between nonalkaloid-bearing plants and *Nicotiana* species have yielded much more information than the study of interspecific hybrids. A large part of the present knowledge in this connection is due to the ingenious experimental work of R. F. Dawson. Excised tobacco shoots cultured in solutions of nicotine hydrochloride absorb the alkaloid and, of the nicotine absorbed, about 80% is located in the leaf tissues, although a study of the nitrogen balance in the tobacco shoots indicates that none of the nicotine appears to enter into the course of protein metabolism. The known accumulation of nicotine in the tobacco leaf had given rise to the opinion that the alkaloid was synthesized *in situ*. However, although tobacco leaves and shoots in various stages of development have been removed from the roots and cultured under a variety of conditions, only in isolated and unusual cases has there been an apparent increase in the nicotine content of the detached aerial part of the plant (285, 286). Furthermore, recent experiments with reciprocal grafts of tomato (*Lycopersicum esculentum* Mill.) and tobacco (*Nicotiana tabacum*) show not only that when tomato scions are grown upon tobacco stocks, small quantities of nicotine are found in the tomato stems and fruits and large quantities in the leaves (287), but that tobacco scions grown on tomato stocks are devoid of alkaloid. Incidentally, since the growth of a tobacco scion upon a tomato stock is quite normal, it appears that appreciable quantities of nicotine are not essential for the development of the aerial portions of the plant. The foregoing results indicate that the root system is responsible for the synthesis of nicotine and this is positively demonstrated by the growth of excised roots of *Nicotiana tabacum* in sterile cultures. In the course of a total period of ten months, nicotine can be repeatedly isolated in reasonably good yields from the excised roots and from the residual culture medium. The bulk of the alkaloid always occurs in the culture medium while only very small amounts remain in the roots and continued subculturing does not destroy the ability of the root to synthesize nicotine (288). It is, therefore, the root of the plant that synthesizes nicotine

which is then translocated into the leaves, and this translocation takes place through the xylem since the cut stumps of tobacco plants bleed a sap rich in nicotine; it is not the pith or the cortical tissue but only the xylem which exudes (289). Similarly, in reciprocal grafts of *Datura stramonium* L. and *N. tabacum*, it is the root of *D. stramonium* that synthesizes hyoscyamine (299). However, although it is the root which is the exclusive organ of the tobacco plant capable of synthesizing nicotine, this does not hold for the other two of the three predominant alkaloids of *Nicotiana* species. Anabasine occurs only as a very minor component of the total alkaloids of *N. tabacum*, but it is the predominant alkaloid and in some strains the only alkaloid of *N. glauca*. A study of reciprocal grafts of *N. glauca* and tomato reveals that anabasine accumulates in appreciable amounts in both tomato scions grown on *N. glauca* roots and in *N. glauca* scions grown on tomato stocks. Also, nicotine is found in small quantities in the former, although it cannot be detected in the intact *N. glauca* nor in *N. glauca* scions grown on tomato roots (291). Hence, anabasine is synthesized in both root and shoot and the total anabasine content of the shoot of *N. glauca* is derived in part from synthesis *in situ* and in part from the accumulation of the alkaloid translocated from the root (291, 292).

The leaves of *N. glutinosa* contain only, or predominantly, nornicotine, but although nornicotine is undoubtedly formed *in situ*, it has been established that the leaves of *N. glutinosa* do not carry out the entire alkaloid synthesis. The leaves of *N. glutinosa* scions grown on tomato roots contain none of the three major alkaloids of *Nicotiana* species. Yet, *N. glutinosa* roots produce not nornicotine as one might have expected, but nicotine, so that the roots of this species are equivalent to the root system of *N. tabacum*. In fact, these roots can be interchanged by grafting without the alkaloid composition of the leaves being materially altered (293). *N. glutinosa* scions grown on *N. tabacum* stocks still contain nornicotine as well as nicotine, whereas *N. tabacum* scions on *N. glutinosa* stocks have the same alkaloidal composition as the intact *N. tabacum*. If both an *N. glutinosa* scion and an *N. tabacum* scion are grafted to the same *N. tabacum* stock, the leaves of the glutinosa scion contain nornicotine while those of the tabacum scion contain nicotine. When an *N. glauca* scion is grafted on an *N. tabacum* root and a tomato scion in turn is grafted on the *N. glauca* scion, the root is found to contain nicotine, the *N. glauca* scion, anabasine and nornicotine, while the tomato scion contains nicotine alone (282). By cross pollination, Dawson (282) obtained a hybrid of *N. glauca* $\times$ *N. tabacum* which contained nicotine and nornicotine as well as anabasine. When tomato scions are grafted onto the hybrid stocks, it is found after a certain growth period that the tomato leaves contain about equal parts of anabasine and nicotine but no nornicotine. On the other hand, hybrid

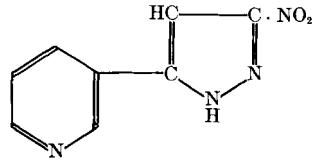
scions grown on *N. tabacum* stocks have a total alkaloid content made up mostly of nicotine, of one-sixth of nornicotine, and but a very small quantity of anabasine. It is evident from these experiments that no organ of the plant is capable of carrying out a primary synthesis of nornicotine. This alkaloid is formed in the leaves, from nicotine translocated from the roots, by a mechanism of transmethylation probably involving a methyl acceptor. It is believed that it is the mechanism of transmethylation that is an inheritable character. The transmethylation reaction is rather slow and when the root, such as that of *N. glauca*, does not produce much nicotine, the alkaloid is all converted to nornicotine after translocation to the leaves. On the other hand, the roots of *N. tabacum* produce nicotine at a rate which greatly exceeds that of the transmethylating mechanism and, therefore, *N. glutinosa* scions grown on *N. tabacum* roots contain both nornicotine and nicotine.

2. Nicotine

Nicotine, $C_{10}H_{14}N_2$, was first observed by Vauquelin (294) in 1809 and isolated in a pure form nineteen years later by Posselt and Reimann (295). The correct empirical formula, $C_{10}H_{14}N_2$, was determined by Melsens (296) and confirmed by Barral (297) and by Schloesing (298) who determined the molecular weight. Nicotine is a colorless liquid, b.p. 246.1–246.2°, 124–125°/18 mm., d_4^{20} 1.0099 (303), n_D^{20} 1.5282 (302), which becomes discolored in the air; it possesses a narcotic odor, is very hygroscopic and can be distilled with steam. It is miscible in all proportions with water below 60° and above 210°, but it is less soluble between these temperatures (299). As previously mentioned, it forms an azeotropic mixture with water at the boiling temperature (281). Nicotine is *levo*rotatory, $[\alpha]_D - 169.3°$, $[\alpha]_{5461} - 204.1°$ (300), but its salts are *dextro*rotatory. The hydrochloride, B · HCl, has $[\alpha]_D + 102.2°$, the sulfate $[\alpha]_D + 84.4°$, the acid *d*-tartrate, $C_{10}N_{14}N_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$, m.p. 88–89°, has $[\alpha]_D^{27} + 26.6°$ (calculated for the dry salt) and the neutral *d*-tartrate, $C_{10}H_{14}N_2 \cdot C_4H_6O_6 \cdot 2H_2O$, m.p. 68.5°, has $[\alpha]_D^{27} + 29.5°$ (calculated for the dry salt). The dipicrate, m.p. 226° (corr.), and dipicrolonate, m.p. 228° (corr.) are characteristic salts. It also forms a dihydriodide, colorless needles, m.p. 195°, and an aurichloride, B · 2HCl · $2AuCl_3$, yellow warts which darken at 150° and melt at 180° (dec). The tetrachloroiodide, $C_{10}H_{14}N_2 \cdot 2HICl_4$, orange prisms, m.p. 150° (dec) (301) and the zincichloride, B · 2HCl·$ZnCl_2 \cdot H_2O$, crystallize well (302, 303). Nicotine normally functions as a monoacidic base when titrated with acids in the presence of various indicators (304). The base and its derivatives show a strong absorption band at 2650 A. which is twice as strong in the zincichloride and in the methiodide but ten times weaker when the base is dissolved in water. This is interpreted (305) as

showing that the aqueous solution may contain an unionized hydrate or pseudobase of the type investigated in the isoquinoline series (306). A study of the index of refraction of aqueous nicotine solutions of various concentrations has led to a similar conclusion (307, 308). The physical properties of nicotine have been extensively studied and a mass of data accumulated. A comprehensive review of the physical properties of nicotine, such as that of Jackson (309) should be consulted.

a. Structure. That nicotine is a derivative of pyridine was established long ago. When oxidized with chromic acid in sulfuric acid, nicotine gives rise to an amino acid, $C_6H_5O_2N$, which on decarboxylation yields pyridine (310). This acid, named nicotinic acid by Weidel (311), was shown to be pyridine-β-carboxylic acid (312, 313). Oxidation of nicotine with potassium permanganate (314), with hydrogen peroxide (315, 316, 317), or with nitric acid (311, 318, 259) yields nicotinic acid which is also obtained by the anodic oxidation of the base (319). It has been observed, but too late to be of help in the elucidation of the structure of the base, that the oxidation of nicotine with nitric acid produces besides nicotinic acid about 5% of a pyrazole (320, 321, 322) eventually shown to be 3-nitro-5-(3′-pyridyl)-pyrazole (323) (CXLI) the structure of which confirmed by synthesis (324). It is evident from these reactions that nicotine is a 3-substituted pyridine



CXLI

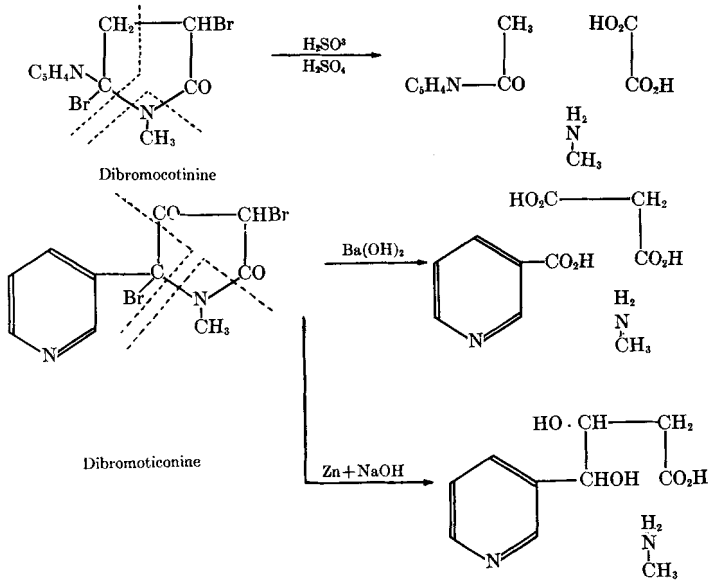
and that the substituent is a saturated group containing five C-atoms and one N-atom. It had been shown that the distillation of nicotine with lime gives rise to pyrrole and methylamine (314), that the formation of nicotinic acid by oxidation with potassium permanganate (314) is accompanied by the formation of methylamine and finally that nicotine behaves towards ethyl iodide like a ditertiary base (325). However, against this evidence pointing to an *N*-methylpyrrolidine ring was the fact that the action of strong hydrochloric acid (326) or even of hydriodic acid (327) fails to split off a methyl group. Furthermore, the mild oxidation of nicotine with potassium ferricyanide in alkaline solution yields a dehydro product claimed by Cahours and Etard (328, 329) to be a dipyridyl but subsequently shown by Blau (330) to be *N*-methyl-(3-pyridyl)-pyrrole (or 3′,2-nicotyrine). The reduction of nicotine with sodium and alcohol was first studied by Liebrecht (331) and by Oliveri (332). Both isolated a product which they claimed to be dipiperidyl. Eventually, this product was shown by Blau not to be

identical with synthetic dipiperidyl (333) but to consist of a mixture of two amines which he designated as hexahydronicotine and octahydronicotine (334, 335). Pinner (327), who repeated this work, obtained mostly hexahydronicotine although Overhoff and Wibaut (337), who again reinvestigated the reduction nearly forty years later, obtained chiefly the octahydro compound. It appears that the nature of the reduction product is greatly dependent upon the conditions of the reaction, a conclusion which has been substantiated by recent work (338, 339, 340).

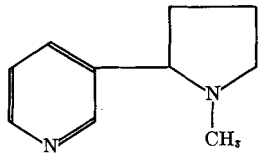
The nature of the $C_5H_{10}N$ residue was finally established by a study of the action of bromine on nicotine. This reaction, which had been tried previously by several investigators (328, 341, 342, 343), was more thoroughly investigated by Pinner (344). Although the action of bromine on nicotine results in the formation of a large quantity of resinous products, bromine when allowed to react on a solution of nicotine in acetic acid or hydrobromic acid affords an oily perbromide which is converted to a free base by treatment with sulfurous acid. In acetic acid solution, however, the reaction quickly proceeds further and hydrogen bromide is eliminated, resulting in a mixture of two compounds: dibromoticonine, $C_{10}H_8O_2N_2Br_2$ and dibromocotinine, $C_{10}H_{10}ON_2Br_2$. Dibromocotinine is also obtained as a perbromide, $C_{10}H_{10}ON_2Br_2 \cdot HBr_3$, by the addition of bromine to an aqueous solution of nicotine hydrobromide while the free base is best prepared by reducing the perbromide with sulfurous acid and precipitating with potassium carbonate. Dibromocotinine crystallizes from dilute alcohol in colorless prisms, m.p. 125°, forms a methiodide, $C_{10}H_{10}ON_2Br_2 \cdot CH_3I$, prisms, m.p. 175° (dec), but reacts neither with benzoyl chloride nor hydroxylamine. When heated with a mixture of sulfurous and sulfuric acids at 130–140°, it is decomposed into methylamine, oxalic acid and methyl-β-pyridyl ketone (chloroplatinate, $(C_7H_7ON \cdot HCl)_2PtCl_4$, yellowish red needles, m.p. 193° (dec)). Reduction of dibromocotinine perbromide with zinc dust and hydrochloric acid removes the bromine and yields cotinine, $C_{10}H_{12}ON_2$, a base, b.p. 250°/150 mm. which melts at 50° and forms a chloroplatinate, yellowish red prisms, m.p. 220°.

The second bromo derivative, dibromoticonine, forms a hydrochloride crystallizing as colorless needles which darken at 200° without melting, a chloroplatinate, yellow prisms, which darkens at 230°, sinters at 240° and does not melt at 250°, and a picrate, small yellow needles, m.p. 235° (dec). Reduction of dibromoticonine in cold alkaline solution with zinc dust yields monobromoticonine, $C_{10}H_9O_2N_2Br$, small rhombohedra, which forms a hydrochloride, small prisms, decomposing without melting (336). If, however, the reduction is carried out in hot alkaline solution, methylamine and pyridyl-β,γ-dihydroxybutyric acid, $C_5H_4N(CHOH)_2CH_2CO_2H$, are obtained. Finally, when dibromoticonine is heated in a sealed tube at

100° with barium hydroxide, it is decomposed into methylamine, nicotinic acid and malonic acid. Pinner (344) represented the reactions thus:



and deduced for nicotine the structure, *N*-methyl-(3′-pyridyl)-2-pyrrolidine

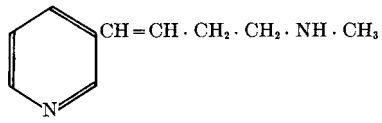


CXLII

The oxidation of nicotine with hydrogen peroxide yields, besides nicotinic acid and nicotine-*N*-oxide (345), an oxynicotine (315), which is also produced when an aqueous solution of nicotine is oxidized by air under the influence of sunlight (346) or ultraviolet radiation (347). Formula (CXLII) for nicotine enabled Pinner (316) and Wolffenstein (317) to show that oxynicotine is not a primary product of oxidation, but a condensation product consisting of two substances, nicotine and nicotol.

To Pinner's formula (CXLII) there remained an objection in the existence of a benzoyl-derivative of nicotine. This derivative had been observed by Will (348) and by Pinner and Wolffenstein (349), but it was purified and characterized by Etard (350) who also prepared an acetyl derivative of nicotine (351). The formation of these derivatives seemed to

indicate the presence of a secondary amino group in nicotine, and this was inconsistent with Pinner's formula (CXLII). It was shown by Pinner (352), however, that Etard's benzoylnicotine is in reality benzoylmetanicotine, i.e., the benzoyl derivative of a secondary base isomeric with nicotine which he named metanicotine. Benzoylmetanicotine is best purified through its picrate, $C_{17}H_{18}ON_2 \cdot C_6H_3O_7N_3$, m.p. 128°. The benzoylated base recovered from the picrate crystallizes as needles, m.p. 83°. Metanicotine obtained by hydrolysis of the benzoyl derivative is an oil, b.p. 275–278°, which is optically inactive. It forms a dihydrochloride, $C_{10}H_{14}N_2 \cdot 2HCl$ (hygroscopic crystals), a chloroplatinate, m.p. 255° (dec), an aurichloride, m.p. 160°, and a dipicrate melting first at 114°, then solidifying and melting again at 163°. Pinner (352) concluded that metanicotine was 4-(β-pyridyl)-1-methylaminobut-Δ^3-ene (CXLIII) and this was confirmed by reduction of metanicotine to dihydrometanicotine, b.p. 131–



CXLIII

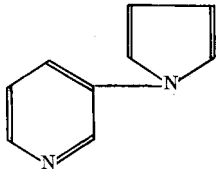
132°/8 mm., (picrate, m.p. 161–162°), treatment of the latter with sodium hypobromite and conversion of the resulting *N*-bromo derivative to *dl*-nicotine by the action of concentrated sulfuric acid (353). Metanicotine is a secondary base and forms a nitroso derivative (354), silky needles, m.p. 116°.

The production of metanicotine explains the formation of two reduction products from nicotine. Hexahydronicotine is 3′,2-piperidyl-*N*-methylpyrrolidine, whereas hydrogenolysis of the pyrrolidine nucleus is involved in the formation of octahydrometanicotine, i.e., 4-(β-piperidyl)-1-methylaminobutane, $C_5H_{10}N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NH \cdot CH_3$. Hexahydrometanicotine is prepared by the reduction of metanicotine with sodium in alcohol (355): it is an optically inactive oil, b.p. 251–252°. Dihydrometanicotine is converted to octahydrometanicotine by reduction with sodium in alcohol (356).

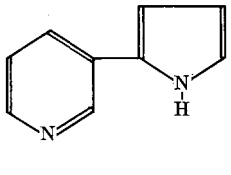
Pinner's formulation of nicotine received support from the discovery that the nicotyrine (3′-pyridyl-*N*-methyl-2-pyrrole) formed by the oxidation of nicotine with silver oxide is accompanied by a small quantity of *N*-methylpyrrolidine (357), and from the methylation of nicotine which gives rise to two isomeric quaternary methiodides (358). One of these, nicotine isomethiodide, yields a quaternary hydroxide which on oxidation with potassium permanganate produces trigonelline, the methylbetaine of nicotinic acid. Nicotine isomethiodide, therefore, has a quaternary pyridine nitrogen, $C_5H_4N \cdot CH_3I \cdot C_4H_7N \cdot CH_3$ while nicotine methiodide has

a quaternary pyrrolidine nitrogen, $C_5H_4N \cdot C_4H_7N(CH_3)_2I$. Nicotine isomethiodide has been used for the preparation *l*-hygrinic acid from which it has been obtained in 25% yield on oxidation (359). The presence of an *N*-methyl group in nicotine received confirmation by Herzig and Meyer who determined it directly with the aid of their now well-known analytical method (360).

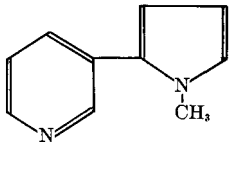
b. Synthesis. The constitution of nicotine was finally confirmed by a synthesis based on the discovery (361) that *N*-acetylpyrrole is transformed by heat to a *C*-acetylpyrrole shown to be α-acetylpyrrole (362). Pictet and Crépieux (363) applied this reaction to *N*-β-pyridylpyrrole (CXLIV) obtained by the reaction of β-aminopyridine with mucic acid. The oily compound (CXLIV) is transformed by heat into 3′-pyridyl-2-pyrrole (CXLV). It was later shown that in this transformation (CXLV) is accompanied by some 3′,3-pyridylpyrrole (364). An attempt to methylate



CXLIV

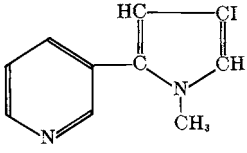


CXLV

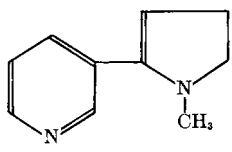


CXLVI

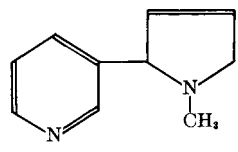
the pyrrole nitrogen by heating the potassium derivative with methyl iodide produced the methiodide of 3′-pyridyl-*N*-methyl-2-pyrrole, identical with the methiodide of Blau's nicotyrine obtained by the oxidation of nicotine with silver oxide (330). Distillation of this methiodide with lime yields nicotyrine (CXLVI) (365). The direct methylation of the potassium derivative of 3′-pyridyl-2-pyrrole (CXLV) (nornicotyrine), however, has since been carried out (366). Pictet and Crépieux (367) did not succeed in their attempts to reduce nicotyrine directly, but achieved this object by means of an ingenious device. Nicotyrine methiodide is converted into iodonicotyrine (CXLVII), m.p. 110°, by shaking with a solution of iodine in dilute sodium carbonate and the resulting iodonicotyrine reduced with zinc and hydrochloric acid to dihydronicotyrine, b.p. 248° (corr.), (chloro-



CXLVII



CXLVIII

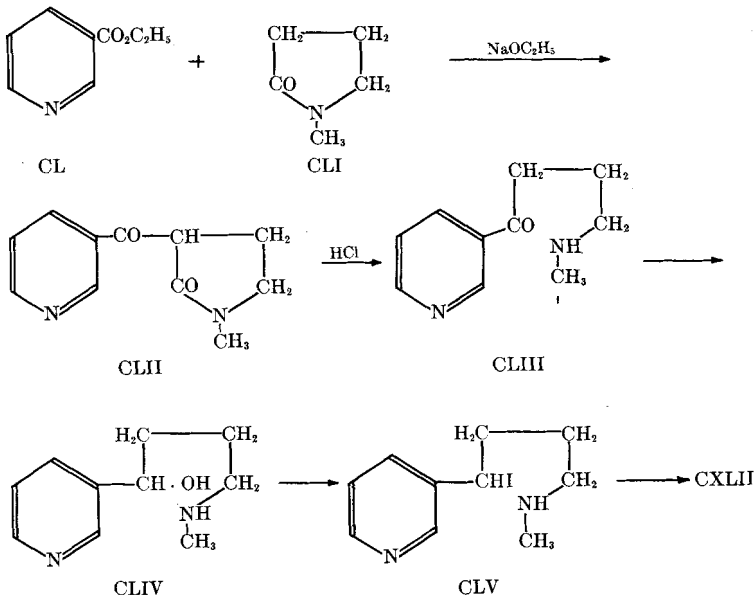


CXLIX

platinate, $C_{10}H_{12}N_2 \cdot H_2PtCl_6$, m.p. 240–242°). Dihydronicotyrine was assigned formula CXLVIII which Pictet (260) later altered to CXLIX. More recently, it has been shown that the dihydronicotyrine of Pictet and

Crépieux is correctly represented by (CXLVIII) and that it is identical with *N*-methylmyosmine (262). Dihydronicotyrine treated in acetic acid solution with a solution of bromine in the same solvent yields a perbromide which was reduced by tin and hydrochloric acid to *dl*-nicotine (368), identical with that obtained by racemization of an aqueous solution of *l*-nicotine hydrochloride at 180–250° (369). Pictet and Rotschy (370) subsequently resolved *dl*-nicotine by crystallization of the *d*-tartrate from water. The laborious conversion of nicotyrine (CXLVI) to nicotine has been very materially simplified by the selective hydrogenation of the pyrrole nucleus with a palladium-carbon catalyst (371) to give a 25% yield.

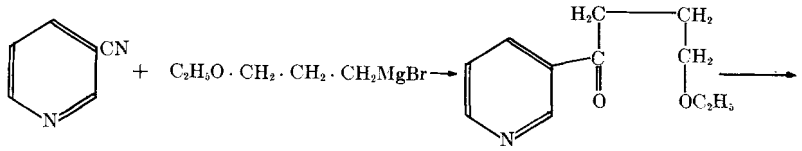
While Pictet's classical synthesis of nicotine is extremely ingenious, it involves two steps at high temperature, one of which is a rearrangement, so that it cannot be considered as a rigid proof of the correctness of Pinner's formula. Späth and Bretschneider (372) have carried out a synthesis of nicotine which involves no rearrangement at high temperature. Ethyl nicotinate (CL) was condensed with *N*-methylpyrrolidone (CLI) in the presence of sodium ethylate and the resulting β-pyridyl-β′-(*N*′-methyl-α′-pyrrolidonyl)-ketone (CLII) hydrolyzed with fuming hydrochloric acid at 130°. The derived amino ketone (CLIII) was reduced with zinc in alcoholic sodium hydroxide to the corresponding alcohol (CLIV) which was



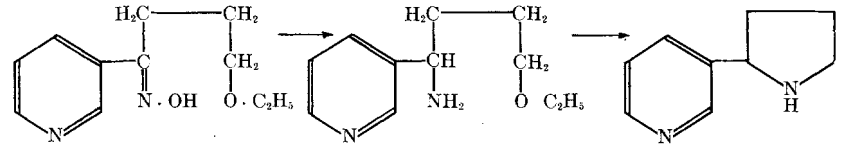
converted to the iodo derivative (CLV) by heating with fuming hydriodic acid at 100°. The last compound was not isolated but the reaction mixture was made alkaline and steam distilled, an operation which closed the ring

and yielded *dl*-nicotine (CXLII) (dipicrate, m.p. 218–219° (vac), dipicrolonate, m.p. 238° (vac)).

In a third synthesis of nicotine (373), nicotinonitrile (CLVI) was reacted with γ-ethoxypropylmagnesium bromide (CLVII). The product of the reaction, 3-pyridyl-γ-ethoxypropylketone (CLVIII) formed an oxime (CLIX) which was reduced to α-(3-pyridyl)-α-amino-δ-ethoxy-*n*-butane (CLX) and this amino derivative, on heating to 150–155° with 48% hydrobromic acid was converted to *dl*-nornicotine (CLXI) which in turn has been methylated to *dl*-nicotine:



CLVI CLVII CLVIII



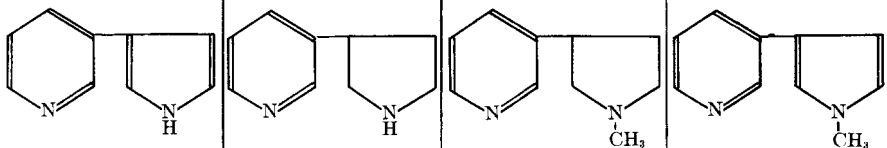
CLIX CLX CLXI

A claim has been made in patents issued to Auzies (374) that nicotine can be prepared on an industrial scale from ammonia and butadiene. This process is reported to involve the production of pyrrole by the catalytic interaction of ammonia and butadiene, the methylation and hydrogenation of pyrrole, the conversion of *N*-methylpyrrolidine to β-chloropyridine by heating over a thorium catalyst with chloroform, and the interaction of β-chloropyridine with *N*-methylpyrrolidine over the same catalyst. The process, however, does not seem to have been put into practice and the reactions described have never been confirmed by a precise chemical investigation.

Bhargava and Dhar (375) claimed that nicotine could be obtained in an aqueous solution containing formaldehyde, ammonia, and copper carbonate by irradiation either with sunlight or a mercury vapor lamp, but Watson and Vaidya (376) were unable to confirm this.

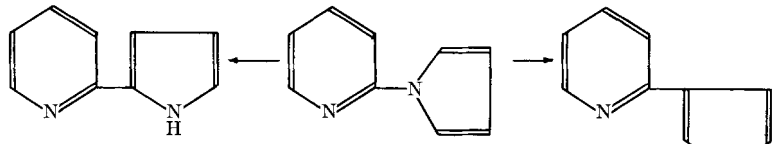
c. Synthetic Isomers. Synthetic structural isomers of nicotine have been described. In their reinvestigation of Pictet's nicotine synthesis, Späth and Kainrath (364) found that the 3′,2-nornicotyrine is accompanied by a small quantity of 3′,3-nornicotyrine (CLXII) and this has been confirmed (366). 3′,3-Nornicotyrine, on hydrogenation, is converted to 3′-pyridyl-3-pyrrolidine (CLXIII) which on methylation yields 3′,3-nicotine (CLXIV). The potassium derivative of 3′,3-nornicotyrine can also be

methylated directly to 3′,3-nicotyrine (CLXV). The constitution of 3′,3-nicotine follows from its behavior as a diacidic base. Had the reduction taken place in the pyridine ring, the resulting base would have been monoacidic (364).



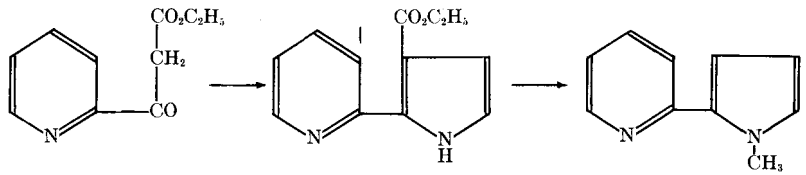
CLXII CLXIII CLXIV CLXV

The dry distillation of 2-aminopyridine mucate yields 1-(2-pyridyl)-pyrrole (CLXVI) from which by thermal rearrangement a 50% yield of 2′,2-nornicotyrine (CLXVI,a), m.p. 90°, accompanied by a varying quan-



CLXVI(a) CLXVI CLXVII

tity of 2′,3-nornicotyrine (CLXVII), m.p. 132°, is obtained (377). If, however, the thermal transformation is carried out at a higher temperature, only the 2′,2-isomer (CLXVI,a) is obtained (378). The structures of the two products are evident from their mode of formation and the fact that both yield picolinic acid on oxidation, but the structure of 2′,2-nornicotyrine was confirmed by synthesis (379). Ethyl picoloylacetate (CLXVIII) is condensed with chloroacetaldehyde and ammonia and the product, ethyl 2-(2′-pyridyl)-pyrrol-3-carboxylate (CLXIX), saponified and decarboxy-



CLXVIII CLXIX CLXX

lated. The base thus obtained is identical with the 2′,2-nornicotyrine melting at 90°; it is transformed to 2′,2-nicotyrine (CLXX) by treatment of its potassium derivative with methyl iodide. The isomeric base, 2′,3-nornicotyrine (CLXVII) differs from 2′,2-nornicotyrine in that its methylation is always accompanied by the formation of some methiodide (380). Although 2′,2-nicotyrine (CLXX) is reduced with zinc and hydrochloric acid to 2′,2-nicotine, 2′-2-nornicotyrine (CLXVI) cannot be similarly reduced to 2′,2-nornicotine (381). It is noteworthy that the hydrogenation

of 2′,2-nornicotyrine over Adam's catalyst reduces only the pyrrole ring (283).

A synthesis of 2′,2-nornicotine and 2′,2-nicotine was accomplished by Craig (383) from picolinonitrile in a series of reactions exactly paralleling those used in his synthesis of nicotine (373).

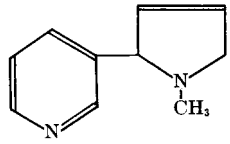
3. Nicotyrine

Nicotyrine, $C_{10}H_{10}N_2$, a base found in tobacco (384, 392, 385), is a colorless oil, b.p. 280–281°, 150°/15 mm., d^{13} 1.124. It forms a dipicrate, m.p. 170–171°, a chloroplatinate, m.p. 160° (dec) and a methiodide, m.p. 211–213°. It had been prepared synthetically long before its occurrence in tobacco was discovered. 3′,2-Nicotyrine is an intermediate in Pictet's synthesis of *l*-nicotine (365). The methylation of the potassium salt of nornicotyrine yields nicotyrine (366), which is 2-(3′-pyridyl)-*N*-methylpyrrole. It is obtained as the product of the dehydrogenation of nicotine with silver oxide (330). The dehydrogenation of nicotine with sulfur in boiling toluene yields thiodinicotyrine and 2.5% of nicotyrine (386). Nicotine when passed over platinized asbestos at 320° yields a mixture of nicotyrine and dihydronicotyrine (387).

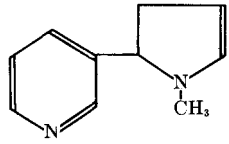
Nicotyrine can be hydrogenated catalytically directly to nicotine (371) or it can be partially reduced with zinc and hydrochloric acid to a dihydronicotyrine (388) identical with that obtained when nicotine is dehydrogenated over platinized asbestos. This partially hydrogenated nicotyrine cannot be resolved (389) and it was eventually shown to be identical with *N*-methylmyosmine and, therefore, to be 4,5-dihydronicotyrine (CLXXIII) (262). Dihydronicotyrine is also prepared by the reduction of iodonicotyrine (367). It has been shown that dihydronicotyrine is unstable and on standing undergoes disproportionation, giving rise to a mixture of nicotine and nicotyrine (262). Structural isomers of nicotyrine such as 3′,3-nicotyrine (364), 2′,3-nicotyrine, and 2′,2-nicotyrine (377) have already been described in the course of the discussion of the corresponding isomers of nicotine. Certain azo derivatives of 3′,2-nicotyrine have been prepared (390).

Pictet and Rotschy (259) and later Noga (261) described a base which they obtained from an aqueous extract of tobacco and named nicoteine. It is a colorless oil, b.p. 266–267°, miscible with water and soluble in ether, $[\alpha]_D$ − 46.41°. It forms a dihydrochloride which is amorphous and has $[\alpha]_D$ − 8.27°, a chloroplatinate, which does not melt at 280°, an aurichloride which is discolored at 150° and melts at 180° (dec) and a picrate, m.p. 165°. It was assigned the formula $C_{10}H_{12}N_2$. On oxidation, it yields nicotinic acid and its acid solution shows a pyrrole color test. As it has the empirical formula of dihydronicotyrine and it is identical neither with the dihydro-

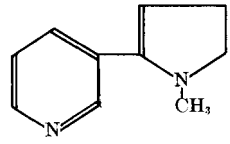
nicotyrine synthesized by Pictet and Crépieux (367) nor with Pinner's dehydronicotine (316), it was assigned the structure (CLXXI). Later it was found that nicoteine on treatment with silver oxide is not oxidized, but is converted to dihydronicotyrine, and it was assumed that the reduction of nicotyrine to dihydronicotyrine was a 1,4-addition of hydrogen to the pyrrole conjugated double bonds and that the isomerization of nicoteine



CLXXI



CLXXII



CLXXIII

to dihydronicotyrine was due to a rearrangement of a double bond (260). Consequently, structure CLXXI was assigned to dihydronicotyrine and structure CLXXII to nicoteine. The structure of dihydronicotyrine, however, was eventually proved to be CLXXIII. The hydrochloride of nicoteine is said to be *levo*rotatory, but of the definitely characterized tobacco bases *l*-anatabine is the only one which is *levo*rotatory both in the free state and in its salts. In an extract from Kentucky tobacco, Ehrenstein (391) isolated a base, b.p. 269–270° which corresponds to Pictet's nicoteine and contains no methylimino group. Further, by the fractional crystallization of the picrates, Ehrenstein succeeded in separating "nicoteine" into two alkaloids and, therefore, Pictet's nicoteine should be considered as nonexistent. One of these bases Ehrenstein named nornicotine while to the other he assigned the structure of 3′,2-pyridylpiperidine.

4. *l*-Nornicotine

l-Nornicotine, $C_9H_{12}N_2$ (391), is a colorless oil, b.p. 120°/0.5 mm., $[\alpha]_D^{20}$ − 88.8°, which forms a dipicrate, m.p. 190–191°, a dipicrolonate, m.p. 253°, a trinitro-*m*-cresolate, m.p. 200°, and a diperchlorate, m.p. 183–186° (392). Its constitution (CLXI) is obvious from the following facts: the base does not contain a methylimino group, it is oxidized to nicotinic acid, and by catalytic dehydrogenation it is converted to nornicotyrine (391). *l*-Nornicotine is obtained from *l*-nicotine by heating with hydrocinnamic acid, but the product is mostly racemized (393). The same difficulty is encountered when it is obtained from nicotine-*N*-oxide (396). The successful demethylation of *l*-nicotine was achieved by oxidation with potassium permanganate or with silver oxide. In both cases optically pure *l*-nornicotine was obtained through crystallization of its perchlorate (394).

5. *d*-Nornicotine

d-Nornicotine occurs in *Duboisia hopwoodii*, F. v. Muell, an Australian Solanaceae (395, 247, 517). It has $[\alpha]_D^{20}$ + 88.8° and it forms a dipicrate,

dipicrolonate, and trinitro-*m*-cresolate, the respective melting points of which are identical with the corresponding derivatives of the *levo* base. *dl*-Nornicotine has been isolated from tobacco (403) and, therefore, both optical isomers of nornicotine are elaborated by the plant. Racemic nornicotine is obtained as an intermediate in Craig's synthesis of *dl*-nicotine (373), and by the catalytic hydrogenation of nornicotyrine (364). The racemic base is resolved with the aid of *l*- and *d*-6,6′-dinitro-2,2′-diphenic acid (397). Although the quantity of *l*-nornicotine present in the tobacco alkaloids is very small, it is the main alkaloid in quite a large group of *Nicotiana* species (see Table 4). In *Nicotiana glutinosa*, for instance, it seems to be the only alkaloid present.

As in the case of nicotine and nicotyrine, several structural isomers of nornicotine have been synthesized. 2′,2-Nornicotine is obtained as an intermediate in the synthesis of 2′,2-nicotine (383).

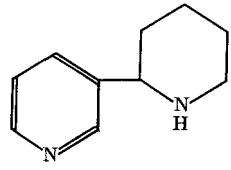
6. 3′,2-Dipyridyl

3′,2-Dipyridyl, $C_{10}H_8N_2$, was isolated from tobacco as follows (398): the lower-boiling fractions of crude nicotine yield one boiling at 120–140°/1 mm. This was dissolved in ether and fractionated by shaking with 10 portions of saturated salt solution each containing a small quantity of hydrochloric acid. The tenth extract yielded a base whose dipicrate, m.p. 167–168° and trinitro-*m*-cresolate, m.p. 190–191°, were identical with the corresponding derivatives of 3′,2-dipyridyl. Noga (261) had isolated from a tobacco extract a base that he designated isonicoteine, for which he suggested the empirical formula $C_{10}H_{12}N_2$, and the structural formula which is now assigned to *N*-methylmyosmine (262). Like dipyridyl, it is not volatile in steam and the boiling point of dipyridyl is very close to that reported for isonicoteine. Späth and Biniecki (263) subsequently obtained the isonicoteine of Noga. Although 3′,2-dipyridyl is normally scarcely distillable with steam, it can be distilled readily from concentrated sodium hydroxide solution. Noga's isonicoteine thus purified proved to be 3′,2-dipyridyl.

7. Anabasine

Anabasine, $C_{10}H_{14}N_2$. One of the two bases obtained by Ehrenstein (391) in his fractionation of Pictet's nicoteine was described as an oil, isomeric with nicotine, giving rise to *levo*rotatory salts, but containing no methylimino group. On oxidation it yields nicotinic acid and on catalytic dehydrogenation, 3′,2-dipyridyl. It was but a short step to conclude that this base is 3′,2-pyridylpiperidine (CLXXIV). The nicotimine of Pictet and Rotschy (259) has also been assigned structure (CLXXIV). This same structure (CLXXIV) has been shown (399) to be that of an alkaloid, *l*-anabasine, discovered by Orechoff (248, 400) in *Anabasis aphylla* (Cheno-

podiaceae) and of a synthetic product designated neonicotine (401). Nicotimine, which is different in properties from anabasine, cannot be represented



CLXXIV

by structure (CLXXIV) and the structure of Ehrenstein's base (391) has been shown to be different (402, 398).

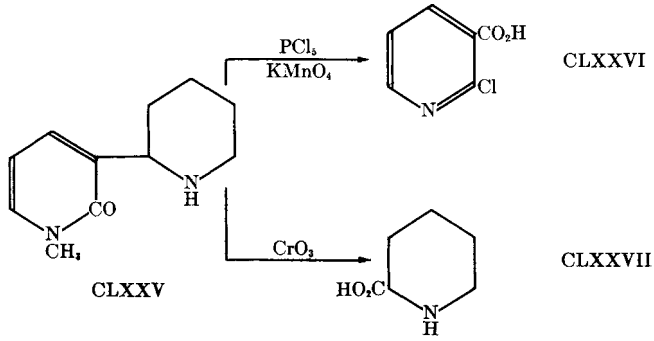
Anabasine is the chief alkaloid of *Anabasis aphylla*, a mid-Asiatic plant, but it is accompanied by appreciable quantities of lupinine, aphyllidine, and aphylline (248, 400). It has been identified as one of the alkaloids of tobacco by Späth and Kesztler (403). The quantity found in tobacco is extremely small, but in some species of *Nicotiana* anabasine supplants nicotine as the chief alkaloid (Table 4). Owing to its significance as an insecticide the large scale isolation of anabasine has been extensively studied (405, 406, 407). Many tests have been described for the detection of anabasine, such as the color tests based on the Miltzer reagent (carbon disulfide, ethanol, and dilute aqueous copper sulfate) or the Mecke reagent (selenic acid and concentrated sulfuric acid) (408), or that used by Shmuk and Borozdina (409). The gravimetric determination of anabasine as the fluorosilicate (410) is said to be affected by amino acids, proteins, and fats so that a method of determination based on acetylation is preferred (411). A method has been developed of estimating anabasine in the presence of nornicotine based on the methylation of the mixed picrates (412). Anabasine can be distinguished from nicotine in that its ethereal solution, when added to an ethereal solution of iodine, does not, like nicotine, cause the precipitation of an iodo derivative (413). According to Burkat (414) anabasine can be estimated by distillation from a sodium hydroxide sodium chloride solution into standard phosphomolybdic acid. A microscopic test has also been described for the qualitative estimation of anabasine in the presence of nicotine (415). It makes use of the fact that the crystal form of anabasine aurichloride is quite distinct from that of nicotine aurichloride (416).

a. Isolation of Anabasine. The crude alkaloid isolated from *Anabasis aphylla* L. is a thick oil which constitutes 2.33% of the dried plant. It can be fractionated by distillation *in vacuo* into a fraction (85%), b.p. 136–138.5°/12 mm. and a fraction (15%), b.p. ca. 200°/12 mm. The low boiling fraction is separated by benzoylation and fractional distillation of the product into lupinine and benzoylanabasine, b.p. 222°/2 mm., m.p. 83–84°, $[\alpha]_D^{20} = 127.23°$ (alcohol). Anabasine can also be separated from lupinine by the addition of sodium to a solution of the basic mixture in liquid ammonia. The

sodium salt of lupinine is filtered off and anabasine recovered from the filtrate (417). In this separation, toluene can be substituted for liquid ammonia (418).

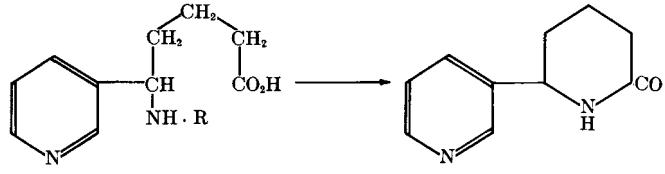
b. Structure. *l*-Anabasine obtained either by separation by means of sodium or by hydrolysis of the benzoyl derivative, is an oil, b.p. 104–105°/2 mm., freezing at 9°, d_{20}^{20} 1.0455, n_D^{20} 1.5430, $[\alpha]_D^{15}$ − 81.7° (403). For the resolved synthetic anabasine, Späth and Kesztler (430) report $[\alpha]_D^{18}$ − 92.45°. It has been observed that the optical rotation of anabasine depends a great deal on the method of isolation since some racemization may result (404). It is strongly basic, is miscible with water in all proportions (415), and is only slightly volatile with steam. It forms a hydrochloride which deliquesces and is *dextro*rotatory, $[\alpha]_D^{20}$ + 9.23°, a dipicrate, m.p. 205–207°, a dipicrolonate, m.p. 235–237° and a fluorosilicate, $C_{10}H_{14}N_2 \cdot H_2SiF_6 \cdot H_2O$, m.p. 239° (dec) (410). *l*-Anabasine is racemized when the aqueous solution of its salt is heated under pressure for 120 hours, but because of the long heating period required about half of it is converted to tar. *N*-Nitrosoanabasine and *N*-aminoanabasine, obtained from the former by reduction, are more readily racemized (419).

The formation of a monobenzoyl derivative and a mononitroso derivative, b.p. 176°/4 mm., $[\alpha]_D$ − 155° (no solvent) shows that anabasine is a secondary-tertiary diacidic base. This conclusion is substantiated by the formation of an *N*-methylanabasine, b.p. 268°, when the base is heated with formaldehyde and formic acid (420). With potassium permanganate anabasine is oxidized to nicotinic acid whereas dehydrogenation either with silver acetate or with zinc dust causes the loss of six hydrogen atoms and the formation of 3′,2-dipyridyl, b.p. 293–294° (picrate, m.p. 151–152°)(423). These experiments support structure CLXXIV previously applied to anabasine (399), a formulation that is confirmed by the following experiments. When *N*-benzoylanabasine methiodide is oxidized with potassium ferricyanide, the *N*-benzoyl derivative of the corresponding pyridone,



N-methylanabasone (CLXXV) is obtained. Treatment of *N*-methylanabasone with phosphorus pentachloride converts it to α-chloroanabasine,

light yellow oil, b.p. 159–164°/10 mm., m.p. 98–99°, which is oxidized by potassium permanganate to α-chloronicotinic acid (CLXXVI). On the other hand, oxidation of *N*-methylanabasone with chromic acid in sulfuric acid produces pipecolinic acid (CLXXVII), m.p. 252–254° (424). Moreover, oxidation of *N*-benzoylanabasine with potassium permanganate produces the expected δ-benzoylamino-δ-(β′-pyridyl)-valeric acid, m.p. 146° (CLXXVIII, R = COC_6H_5) which, on hydrolysis with hydrochloric acid

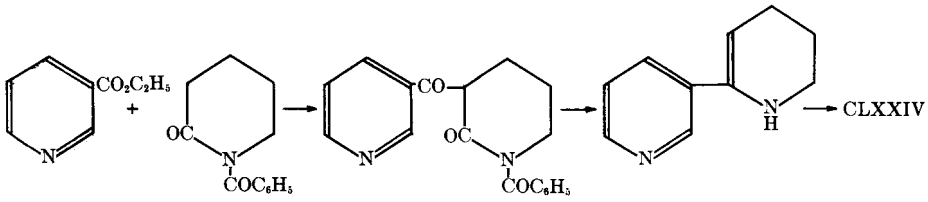


CLXXVIII CLXXIX

liberates the free amino acid (CLXXVIII), R = H). This acid is unstable and is readily converted to the lactam, α′-(β″-pyridyl)-α-piperidone (CLXXIX) (425). Finally, the reduction of anabasine either with sodium in ethanol or catalytically over Adam's catalyst yields a mixture of bases from which *l*-3′,2-dipiperidyl, m.p. 66–68° can be isolated (426, 427, 428).

c. Synthesis. When pyridine is heated with sodium and the product slowly oxidized with a stream of air, there is obtained a mixture of bases from which Smith (401) isolated a pyridylpiperidine which he named "neonicotine." It was suggested that "neonicotine" is probably *dl*-anabasine (423) and this is indicated by a comparison of the synthetic base with *l*-anabasine, but definite confirmation by comparison with *dl*-anabasine is still lacking.

Although the preparation of "neonicotine" is a synthesis of the alkaloid, it is not of much value as a confirmation of structure. The structure (CLXXIV) assigned to anabasine, however, was confirmed by an unambiguous synthesis (429). *N*-Benzoylpiperidone (CLXXX) was condensed with ethyl nicotinate and the resulting ketone (CLXXXI) heated with

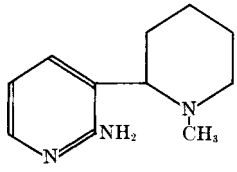


CLXXX CLXXXI CLXXXII

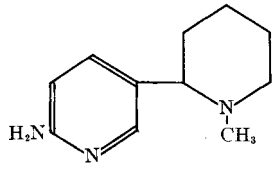
concentrated hydrochloric acid in a sealed tube. Treatment with acid caused hydrolysis, decarboxylation, and ring closure with the formation of the unsaturated anabaseine (CLXXXII). Anabaseine was hydrogenated

catalytically to *dl*-anabasine (CLXXIV) identified by comparison of its dipicrate, m.p. 214°, dipicrolonate, m.p. 258–259°, and 2.4.6.-trinitro-*m*-cresolate, m.p. 140–142°, with the corresponding derivatives of the naturally occurring anabasine after complete racemization (419, 429). Later, it was found that synthetic *dl*-anabasine may be resolved with the aid of *l*- and *d*-6,6′-dinitro-2,2′-diphenic acid (430). The *l*-anabasine salt of *l*-6,6′-dinitro-2,2′-diphenic acid, m.p. 264.5–265° has $[\alpha]_D^{16} - 76.92°$ (c. 0.52 in methanol). The preparation of *dl*-anabasine by partial hydrogenation of 3′,2-dipyridyl or by partial dehydrogenation of 3′,2-dipiperidyl has not been realized (431).

With the object of improving the pharmacological action of anabasine, numerous derivatives of the alkaloid have been prepared. *N*-Amino-anabasine is prepared by reducing *N*-nitroso anabasine with zinc dust in acetic acid. It is partially racemized during distillation and on subsequent benzoylation it yields a mixture of two compounds: one melting at 150–151° and having $[\alpha]_D - 31°$, the other melting at 170–171° and optically inactive (419). By boiling a solution of anabasine in xylene with sodamide, there is obtained a 5% yield of an aminoanabasine, m.p. 111°, first assumed to be α-aminoanabasine (433), but later shown to be α′-aminoanabasine (434, 437). *N*-Methylanabasine when treated similarly yields 45–50% of a mixture of two amino-*N*-methylanabasines, the one melting at 95–95.5° and forming a picrate, m.p. 238–239.5° (dec), the other, m.p. 91.5–92.3° (402), an oil, b.p. 140–163°/6 mm., forming a picrate, m.p. 227.5–228°. The first was assigned the structure of α-amino-N-methylanabasine (CLXXXIII) since on treatment with hydrogen chloride and sodium nitrite it is converted into an oily α-chloro-*N*-methylanabasine which



CLXXXIII



CLXXXIV

on oxidation yielded α-chloronicotinic acid. The second is, therefore, α′-amino-*N*-methylanabasine (CLXXXIV) (433), a structure confirmed by an analogous degradation to α′-chloro-*N*-methylanabasine and 6-chloronicotinic acid (432).

If in the amination of anabasine with sodamide, the xylene is replaced by dimethylaniline and the reaction is carried out at 140°, a 30% yield of aminoanabasine is obtained (435). There are, however, two isomers in the product, the one, m.p. 85.5–90°, is an α-aminoanabasine since on treatment with hydrogen chloride and sodium nitrite it is converted to α-chloroanabasine, m.p. 58.5–59.5°, which yields α-chloronicotinic acid on

oxidation (436). The other, m.p. 109°, is α′-aminoanabasine since it yields α′-chloroanabasine, m.p. 99.5–100° and then on oxidation 6-chloronicotinic acid identical with a synthetic specimen (434). Treatment of *N*-methylanabasone with phosphorus pentachloride yields a chloroanabasine, m.p. 98–99°, first assumed to be α-chloroanabasine (424), but later shown to be the α′-derivative (434, 437). The α-position of the substituent in the aminoanabasines is further confirmed by the similarity of behavior of α′-aminoanabasine (437) with the α-aminopyridines (438). It gives rise to α′-nitraminoanabasine which is converted by acetic anhydride to α′-hydroxyanabasine. This last compound is identical with that obtained by diazotizing α′-aminoanabasine (439).

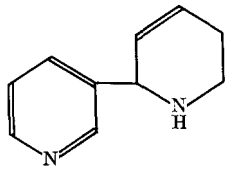
8. *N*-Methylanabasine

N-Methylanabasine, $C_{11}H_{16}N_2$. *l*-Anabasine can be methylated by heating with formaldehyde and formic acid (420) or by treatment with methylmagnesium iodide (421). *l*-*N*-Methylanabasine is a colorless oil, b.p. 127–128°/12 mm., $[\alpha]_D^{15}$ − 85.1° which forms a dipicrate, m.p. 237–238° (dec), a dipicrolonate, m.p. 234–236° (dec), and a trinitro-*m*-cresolate, m.p. 231–232° (385). The claim that the base is present in *Anabasis aphylla* (422) is rather doubtful (421), but it does occur in small quantity in the more basic fractions of crude nicotine (385).

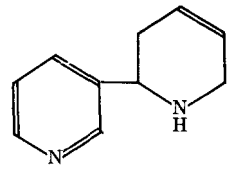
9. Anatabine

Anatabine, $C_{10}H_{12}N_2$ (440). In the lower-boiling fractions of crude nicotine there is one boiling at 120–140°/1 mm. (398) which, when dissolved in ether, can be fractionated by shaking with ten successive portions of saturated salt solution each containing a small quantity of hydrochloric acid. The tenth fraction, as already mentioned, yields 3′,2-dipyridyl (398). The sixth fraction contains a base which, after purification by recrystallization of its picrate and dinitrodiphenate, resembles the base obtained by Ehrenstein (391) from Pictet's "nicoteine" to which he erroneously assigned the formula now known to represent anabasine. It differs from anabasine, as Ehrenstein himself had found, in that both it and its hydrochloride are *levo*rotatory. This new alkaloid is *l*-anatabine, a colorless oil, b.p. 145–146°/10 mm., $[\alpha]_D^{17}$ − 177.8° (no solvent); $[\alpha]_D^{17}$ − 65.4° (in two equivalents of hydrochloric acid), d,1.091; n_D^{20} 1.5676. It forms an *l*-6,6′-dinitro-2,2′ diphenate, m.p. 238–238.5°, a dipicrate, m.p. 191–193°, a dipicrolonate, m.p. 234–235°, and a trinitro-*m*-cresolate, m.p. 191–192°. On benzoylation, *l*-*N*-benzoylanatabine, b.p. 160–170°/0.01 mm. is obtained, so that anatabine is a secondary-tertiary base. Dehydrogenation over palladium-asbestos converts it to 3′,2-dipyridyl, while absorption of two atoms of hydrogen (Pd + C) converts it to *l*-anabasine. Hence, *l*-anatabine is a 3′-pyridyl-2-tetrahydropyridine.

The benzoylation of anatabine does not open the tetrahydropyridine ring with addition of water (Lipp-Widmann reaction) and this eliminates the possibility of the double bond being in an α, β-position to the N-atom. One of these two positions is already eliminated by the fact that the alkaloid is optically active and furthermore, since the nitrogen is secondary the double bond cannot be next to it. Hence the double bond can occupy one or the other of the two positions as in formulas CLXXXV and CLXXXVI. A choice between these two formulas is made possible by



CLXXXV



CLXXXVI

the result of the mild oxidation of benzoylanatabine which gives rise to a little benzoic acid, to nicotinic acid (which confirms the 3-pyridyl half of the molecule) and to hippuric acid, $C_6H_5CO \cdot NH \cdot CH_2CO_2H$. The formation of hippuric acid eliminates CLXXXV since the oxidation of such a molecule would produce 3-benzoylaminopropionic acid. Hence, the structure of anatabine is CLXXXVI. It seems likely from the properties of *l*-anatabine that Pictet's nicoteine was essentially nornicotine containing some *l*-anatabine and that one of the bases isolated from nicoteine by Ehrenstein was impure anatabine.

In the acid fractionation of the low-boiling portion, b.p. 120–140°/1 mm., of crude nicotine, the third fraction contains optically impure *l*-anatabine which is purified by crystallization of the perchlorate. The mother liquor from the perchlorate (403) contains an optically inactive base which on dehydration produces 3′,2-dipyridyl, while oxidation of its benzoyl derivative gives rise to hippuric acid. Since the base has been resolved with *l*-6,6′-dinitro-2,2′-diphenic acid to *l*-anatabine it is *dl*-anatabine.

10. *N*-Methylanatabine

N-Methylanatabine, $C_{11}H_{14}N_2$. From the strongly basic fractions of crude nicotine which contain *N*-methylanabasine, there is also obtained a second ditertiary base (385). It is an oil, b.p. 120°/1 mm., $[\alpha]_D^{18} - 171.4°$ (in methanol) which forms a dipicrate, $C_{11}H_{14}N_2 \cdot 2C_6H_3O_7N_3$, m.p. 207–208°, and a trinitro-*m*-cresolate, $C_{11}H_{14}N_2 \cdot 2C_7H_5O_7N_3$, m.p. 228–229°. Since these two derivatives are identical with the corresponding derivatives prepared from the product of the methylation of *l*-anatabine with formaldehyde and formic acid, the base is *N*-methylanatabine.

11. Noncharacterized Alkaloids

In 1915, Noga (261) reported the presence in tobacco extracts of a base which he named nicotoine. This base is a colorless oil, b.p. 208°, $C_8H_{11}N$, possessing an odor resembling that of pyridine, d_4^{21} 0.9545, n_D^{20} 1.5105. It is said to form well crystalized salts. Another alkaloid, nicotelline, was described by Pictet and Rotschy (259) who isolated it from a tobacco extract. It is a solid melting at 147–148° and boiling above 300°; this was confirmed by Noga (261). The properties of nicotelline, $C_{10}H_8N_2$, are different from those of the other tobacco alkaloids. Its aqueous solution is neutral to litmus and it is not volatile with steam. It forms a sparingly soluble dichromate and does not give a pyrrole reaction. It has been considered as a dipyridyl, but all the isomers of dipyridyl have since been synthesized and all are different from nicotelline.

From a tobacco extract, Pictet and Rotschy (259) isolated still another base, nicotimine, which forms nitroso and benzoyl derivatives and, therefore, contains a secondary nitrogen atom. It is separated from nicotine by fractional distillation of the benzoyl derivative. It is isomeric but not identical with nicotine or with metanicotine. It is miscible with water and forms a picrate, m.p. 163°. No one seems to have isolated nicotimine again, although Vickery and Puchner (441) obtained a base from tobacco which they thought might be nicotimine, but the melting point of the picrate (m.p. 179.5–180.5°) of their base is much higher than that of Pictet's base, and the empirical formula $C_{10}H_{14}N_2$ was derived only from the N-analysis of the dipicrate. Pictet (260) assigned to nicotimine the structure now known to represent anabasine, but the recorded properties of nicotimine are widely divergent from those of anabasine.

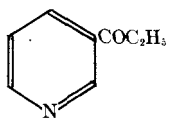
XI. Tobacco Smoke Alkaloids

The first recorded investigation of tobacco smoke seems to be Zeise's (442) reported failure to find any basic components in it. Later, Vohl and Eulenberg (443) claimed that tobacco smoke contains a number of pyridine bases, but no nicotine although this was later refuted by Melsens (296). In more recent years, tobacco smoke has been carefully investigated and shown to contain a large number of bases including nicotine (447, 448). (Most of the work concerning the tobacco smoke bases has been published in *Fachlich Mitteilungen der österreichischen Tabak-Regie*, all of which has not been abstracted. Since this technical journal is not available, a review article written by Späth and Kuffner (449) and the introduction to a paper by Späth, Wenusch, and Zajic (450) have been used both as a source of information and of reference to supplement *Chemical Abstracts*.) It is important to differentiate between basic and acid smoke (444). Smoke

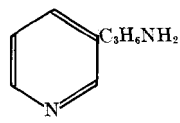
from dark cigars is alkaline, whereas cigarette smoke is acid (445) as shown by the quantitative determination of the volatile acids and bases present in the two types of smoke (446). The smoke of cigars made from Brazilian, Cuban, and Havana tobacco contains, besides relatively large quantities of nicotine and small quantities of a base yielding a picrate, m.p. 185°, not further investigated, two groups of bases, one of which is volatile with steam (448). The first group (452) contains myosmine, obeline, pyridine, poikiline (451), and three difficultly separable bases. These three bases do not yield crystallizable picrates but are obtained as their picrolonates: α-socratine (picrolonate, m.p. 104°), β-socratine (picrolonate, m.p. 130°) and γ-socratine (picrolonate, m.p. 256°). The picrate of obeline can be sublimed without decomposition and the base is said to occur also in certain tobaccos (452). The second group of bases, not distilled with steam, contains anodmine, lathreine, and lohitam. Of these bases, myosmine and the socratines are responsible for the aroma of tobacco, whereas the others are odorless (448). In cigarette smoke, myosmine and lohitam are absent, but the socratines are present (453), together with obeline, nornicotine, pyridine, and anodmine. Cigarette smoke has since been found to contain another base named gudham. In general, cigarette smoke contains fewer bases than cigar smoke.

Both cigar and cigarette smoke contain a base which can be extracted with ether from an acid solution (pH 3.0–3.5) (454). It proved to be identical with 3-pyridyl ethyl ketone (CLXXXVII) already synthesized by Engler (455).

The acid equivalents and, therefore, the molecular weight of a number of the tobacco smoke bases have been determined by a titrimetric process (454). The molecular weights found are, for myosmine, 149, for poikiline, 166, for obeline, 146. From the results of color tests designed to indicate certain constitutional groups in the molecule, Wenusch and Schöller (456, 457) concluded that none of the socratines contain a pyrrole nucleus and the strong odor of these bases led them to assume that they are closely related to pyridyl ethylketone (CLXXXVII). There is some evidence that α- and β-socratine might be 3-pyridyl alkyl carbinols and so would



CLXXXVII



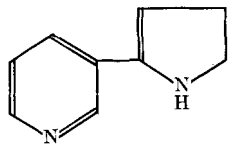
CLXXXVIII

be closely related to conhydrine, while the more basic γ-socratine was considered to be an aminopropylpyridine (CLXXXVIII) (199). Of the tobacco smoke alkaloids, myosmine only has been assigned a structure that has been verified by synthesis, although 3-pyridyl ethyl ketone has

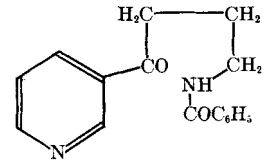
also been definitely identified. The alkaloid poikiline seems to be closely related to myosmine.

1. Myosmine

Myosmine, $C_9H_{10}N_2$, was discovered by Wenusch and Schöller (448) among the bases of tobacco smoke which are volatile in steam and it has been studied by Späth, Wenusch, and Zajic (450) who purified it and elucidated its structure. Myosmine which is a weaker base than nicotine, is crystalline, m.p. 45°, and forms a picrate, m.p. 185°, and a picrolonate, m.p. 213°. It is optically inactive and is not a racemic base. When heated with palladium sponge, it is dehydrogenated to 3′,2-pyridylpyrrol, m.p. 98–99°, picrate, m.p. 200°, obtained in a similar manner from *l*-nornicotine. Hence, myosmine is a dihydronornicotine and since it does not contain an asymmetric C-atom it is represented by structure CLXXXIX. Its structure is confirmed by the fact that when heated with benzoic anhydride in absolute ether, the base does not yield a simple derivative, but a compound $C_{16}H_{16}O_2N_2$, m.p. 118°, the formation of which involves ring scission

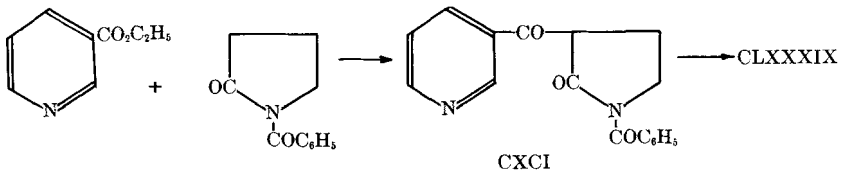


CLXXXIX



CXC

and addition of water. Such a reaction takes place in compounds having a double bond in an α,β-position to a secondary nitrogen atom; it is well-known and has been observed with tetrahydropicoline (458) and 2-phenylpyrroline (459). Hence, this benzoyl derivative has structure (CXC). The structure of myosmine has finally been established by a synthesis. *N*-Benzoylpyrrolidone and ethyl nicotinate were condensed in the presence of sodium ethylate and the resulting ketone (CXCI) was heated with fuming hydrochloric acid in a sealed tube at 130° for 6–7 hours. This treatment resulted in debenzoylation, ring fission and decarboxylation, followed by ring closure and formation of a product identical with myosmine (CLXXXIX).



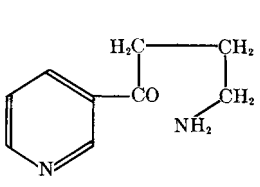
CXCI

The elucidation of the structure of myosmine enabled Späth, Wibaut, and Kesztler (262) to determine the structure of the dihydronicotyrine obtained by partial dehydrogenation of nicotine or the partial hydrogena-

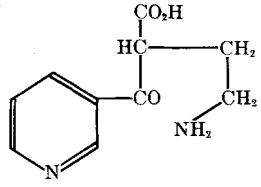
tion of nicotyrine (388) since dihydronicotyrine is identical with *N*-methylmyosmine. It is of interest to note that nicotine in buffered aqueous solution can be dehydrogenated to *N*-methylmyosmine by certain bacteria (461). Furthermore, it has been shown that the pyrolysis of nicotine over crushed quartz in an iron pot at 555–570° gives rise to an 18.1% yield of myosmine together with β-picoline, 3-ethylpyridine, 3-vinylpyridine and 3′,2-nicotyrine (462).

2. Poikiline

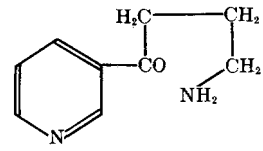
Poikiline, $C_9H_{12}ON_2$, was obtained by Wenusch and Schöller (451) as its picrolonate, m.p. 150°. When either picric acid or styphnic acid is added to a solution of poikiline, no precipitation occurs. However, from such solutions salts lowly separate which seem to be identical with the corresponding salts of myosmine. Hence poikiline must be closely related to myosmine and probably has structure CXCII. Substances such as CXCIII obtained as intermediates in syntheses of nicotine (372) evince a



CXCII



CXCIII



CXCIV

similar tendency towards cyclodehydration and the parallelism of their behavior with that of poikiline supports the suggested formula (CXCII).

XII. Ammodendrine

Ammodendron Conollyi Bunge (Leguminosae) is a small tree found in the deserts of Central Asia. Although its stem and branches are almost devoid of alkaloids, its leaves contain a considerable quantity (1.8% of the dry weight). The crude, oily alkaloid may be separated by vacuum distillation into three fractions and a residue (463). The lower boiling fraction consists of *d*-sparteine while the fraction b.p. 185–200°/4 mm., consists mostly of a new alkaloid which is named ammodendrine. The ratio of *d*-sparteine to ammodendrine varies with the time of harvesting (464). In plants collected in July, this ratio was 5:1, while in material collected in August and September, it was 2:3.

Structure of Ammodendrine

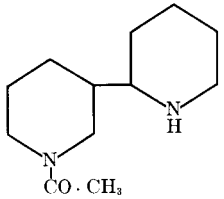
Ammodendrine, $C_{12}H_{20}ON_2$, crystallizes from wet ether in colorless prisms containing one mole of water of crystallization which is lost *in vacuo* at 70–80°. Hydrated ammodendrine melts at 73–74° while the anhydrous base melts indefinitely at 50–60°. It is an optically inactive monoacidic

TABLE 6

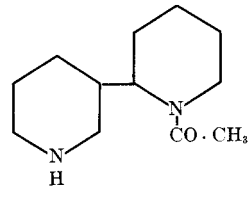
PROPERTIES OF TOBACCO AND TOBACCO SMOKE ALKALOIDS

Name	Formula	B. p. °C.	$[\alpha]_D$	Density	n_D	Picrate	Picrolonate	Chloro-platinate	Trinitro-*m*-cresolate	References
Trimethylamine	C_3H_9N	4				216°	256°	245°		398
Pyrrolidine	C_4H_9N	88		0.8520		112°		200°		
Pyridine	C_5H_5N	115		0.9808	1.5107	164°		242°		451
N-Methylpyrroline	C_5H_9N	80					222°			
Piperidine	$C_5H_{11}N$	106		0.8615	1.4535	152°	248°	201°		398
Nicotoine	$C_8H_{11}N$	208		0.9545	1.5105					261
Pyridylethylketone	C_8H_9ON	232					159°			454
Myosmine	$C_9H_{10}N_2$	m.p. 45				185°	213°			452
l-Nornicotine	$C_9H_{12}N_2$	267	−88.8°	1.0737	1.5378	192°	253°		200°	391, 392
d-Nornicotine	$C_9H_{12}N_2$		+88.8°	1.0757	1.5490	194°	240°			247, 395
dl-Nornicotine	$C_9H_{12}N_2$	267		1.044						403
3′,2-Dipyridyl	$C_{10}H_8N_2$	294				168°				398
Nicotelline	$C_{10}H_8N_2$	m.p. 148								259
Nicotyrine	$C_{10}H_{10}N_2$	280		1.124		171°		160°	172°	392, 385
l-Anatabine	$C_{10}H_{12}N_2$	146/10 mm.	−177.8	1.091	1.5676	193°	235°		192°	440
dl-Anatabine	$C_{10}H_{12}N_2$			1.086	1.5655	202°	235°		141°	403
l-Nicotine	$C_{10}H_{14}N_2$	246	−169.3	1.0099	1.5282	224°	226°	280°	208°	295
dl-Nicotine	$C_{10}H_{14}N_2$	243		1.0081	1.5289	229°	239°	250°	205°	
l-Anabasine	$C_{10}H_{14}N_2$	276	−82.4°	1.0455	1.5430	207°	237°			403
dl-Anabasine	$C_{10}H_{14}N_2$	282				214°	259°		142°	403
"Nicotimine"	$C_{10}H_{14}N_2$	255								259
N-Methyl-*l*-anatabine	$C_{11}H_{14}N_2$	120/1 mm.	−171.4°	1.036		208°			229°	385
N-Methyl-*l*-anabasine	$C_{11}H_{16}N_2$	268	−143.8°	1.003	1.5328	238°	236°		232°	385
Obeline						272°	270°			452
Lathreine							150°			452
α-Socratine							104°			452
β-Socratine						150°	130°			452
γ-Socratine							256°			452
Anodmine						254°	320°			452
Lohitam										452
Gudham							160°			454
Poikiline							150°			451

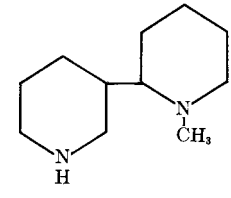
base which forms amorphous salts with hydrochloric, sulfuric, and hydrobromic acids, but its hydriodide (m.p. 218–220°) and its perchlorate (m.p. 199–200°) are crystalline. With methyl iodide it forms *N*-methylammodendrine hydriodide, m.p. 183–185°, from which the free methylated base, $C_{13}H_{22}ON_2$, is obtained as colorless needles, m.p. 65–66°. *N*-Methylammodendrine forms a methiodide, $C_{13}H_{22}ON_2 \cdot CH_3I$, m.p. 163–165°. The behavior of ammodendrine towards methyl iodide shows that it contains a secondary nitrogen. The other nitrogen and the oxygen are chemically inert and hydrolysis with alkali gives rise to acetic acid and a di-secondary base, $C_{10}H_{18}N_2$, so that ammodendrine contains an *N*-acetyl group. The base, $C_{10}H_{18}N_2$, is amorphous and becomes resinous on standing. If, however, ammodendrine is hydrogenated catalytically, it takes up one mole of hydrogen and gives rise to dihydroammodendrine, $C_{12}H_{22}ON_2$, an oil which on hydrolysis yields acetic acid and a crystalline base, $C_{10}H_{20}N_2$, m.p. 65–67°, which forms a dipicrate, m.p. 225–226°, and a dinitroso derivative, m.p. 86–87°. This hydrolytic base, when dehydrogenated with silver acetate, loses six moles of hydrogen and is converted to 3′,2-dipyridyl. Hence, the hydrogenated hydrolytic base $C_{10}H_{20}N_2$ is 3′,2-dipiperidyl. Consequently, dihydroammodendrine is represented either by CXCV or CXCVI. Ammodendrine, however, when first methylated and hydrogenated and subsequently hydrolyzed, gives rise to an *N*-methyl-3′,2-



CXCV



CXCVI



CXCVII

dipiperidyl (picrate, m.p. 232–234°, picrolonate, m.p. 246–247° (dec) hydrochloride, m.p. 264–266°) which is identical with the product of hydrogenation of *dl*-*N*-methylanabasine and, therefore, is CXCVII. Hence, dihydroammodendrine is represented by formula CXCV, but there still remains the problem of assigning a position to the double bond in ammodendrine.

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Chapter VI

The Chemistry of the Tropane Alkaloids

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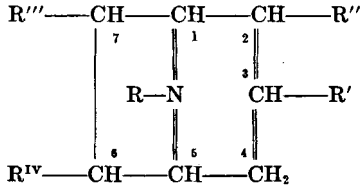
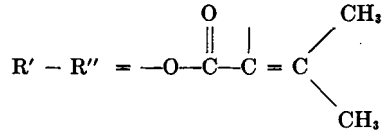
I. Introduction

The tropane alkaloids, which have been isolated from various species of the plant families, Convolvulaceae, Dioscoraceae, Erythroxylaceae, and Solonaceae, all exhibit common structural features. They are all esters of organic acids (atropic, benzoic, cinnamic, isovaleric, *d*-α-methylbutyric, tiglic, tropic, truxillic and veratric) combined with one of a series of bicyclic hydramines (methylecgonine, nortropine, pseudotropine, scopine, tropine and others) which may be conveniently represented in general form by I[1].



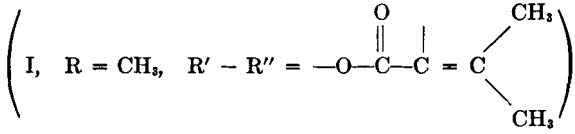
R = H, CH_3 R''' = H, OH
R' = H, OH R^{IV} = H, OH
R'' = H, $COOCH_3$



$R''' - R^{IV} = R' - R''' = -O-$

I

The work in this branch of alkaloid chemistry has been extensive and, although a number of these bicyclic hydramines have been isolated, it must be emphasized that all possible combinations of I have not as yet been found in nature. Dioscorine, although it does fulfill the requirements of the above generalized formula, is a lactone:



In many instances a useful purpose is served by presenting the chemistry of the alkaloids according to their occurrence in various plant families, genera and species (254). However, it is the opinion of the author that a more direct route to a knowledge of the chemistry of the tropane alkaloids is through (1) the presentation of the chemistry of the alkaloids whose structure is known with certainty (e.g., atropine, *l*-cocaine, *l*-hyoscyamine

[1] All R groups in formula I will be considered to be hydrogen unless otherwise stated.

and related products) followed by (2) a discussion of those alkaloids whose structure is, as yet, more speculative in nature (e.g., *l*-scopolamine or *l*-hyoscine[2] and dioscorine). This order has been adopted in the descriptive part of this chapter and will be followed by a table of the physical constants of the alkaloids and their products of transformation and degradation.

II. Identification and Separation

Atropine and the allied bases present a close general resemblance in their physical, chemical, and physiological characters so that the methods for their isolation follow the same general pattern (40, 187, 238, 239, 240). The qualitative identification of these alkaloids, as a class, is not difficult for many spot tests and diagnostic color reactions have been developed; however, separation and identification of the individual bases present a difficult problem for the alkaloid chemist.

By far the most sensitive test for atropine, *l*-hyoscyamine, and *l*-scopolamine is their ability to produce mydriasis of the pupil of the eyes of young cats, dogs and rabbits (1). An aqueous, alcohol-free solution of the alkaloid, its sulfate or acetate which must be almost neutral is used. It is dropped into the conjunctival sac of the eye and held so that none is lost by overflow of tears (252). It has been reported (1) that 1 part in 40,000 or that 0.000,000,427 g. of atropine sulfate will cause a distinct dilation of the pupil of the eye in 1 hour. Besides the tropane alkaloids certain digitalis preparations and the volatile base, coniine, possess this same property. Tropine, the basic cleavage product of atropine and *l*-hyoscyamine, has no effect upon the eye if administered in the normal way but does possess mydriatic properties when administered internally (252).

The most frequently used color reactions are those developed by Vitali and Gerrard and may be briefly described as follows: *The Vitali Reaction* (1). A minute quantity (as little as 0.0001 mg. is sufficient) of solid atropine, *l*-hyoscyamine or *l*-scopolamine, on a watch glass, is treated with a drop of fuming nitric acid and the liquid evaporated to dryness at 100°. The residue when treated with a drop of freshly prepared solution of ethanolic potassium hydroxide develops a bright purple coloration which slowly fades to a dark red and finally to a colorless liquid. The color sequence can be reproduced by the addition of more potassium hydroxide reagent.

The same color display is observed in the case of the modified Vitali test. The alkaloid is ground with sodium nitrate and moistened with sulfuric acid, and subsequently treated with potassium hydroxide reagent. This color reaction has been applied to sixty alkaloids and only veratrine

[2] *l*-Scopolamine will be used throughout this chapter in preference to *l*-hyoscine so as to avoid any possibility of confusion of this alkaloid with *l*-hyoscyamine.

could be considered to interfere with this as a class reaction for these alkaloids. Even veratrine can be eliminated by a slight modification of the procedure (1). *The Gerrard Reaction* (1). A deep red color develops when 1 cc. of a 2% solution of mercuric chloride in 50% aqueous ethanol is added to 0.006 g. of atropine. With hyoscyamine the red color does not develop until the mixture is warmed.

These alkaloids also give distinctive micro-crystals with Wormley's reagent (1) (bromine in hydrobromic acid) and Wagner's reagent (196) (iodine in potassium iodide).

Dioscorine gives a diagnostic color reaction with potassium iodate and sulfuric acid (188). The brownish-yellow color, first formed, slowly changes to a bluish-violet.

The separation of atropine, *l*-hyoscyamine and *l*-scopolamine has been effected by the fractional crystallization of their aurichlorides. It has been pointed out, however, that the solubility relations of these derivatives are dependent upon impurities and the relative amounts of each present in the mixture (50). The bases may be recovered by decomposing an aqueous solution of the aurichloride with hydrogen sulfide and filtering to remove the gold sulfide. The base is liberated by addition of potassium carbonate to the filtrate and extraction with chloroform. An alternate method for the separation of atropine and *l*-hyoscyamine (25) is by fractional crystallization of their oxalates from acetone and ether in which the *l*-hyoscyamine derivative has the greater solubility. *l*-Scopolamine and dioscorine on the other hand are purified through their insoluble hydrobromides.

These alkaloids react readily with picric and aurichloric acids to give nicely crystalline derivatives which, because of the wide spread in their melting points, are the most satisfactory derivatives for the identification of the individual members of this group of alkaloids. There is also a characteristic difference in the aurichloride crystals of atropine and *l*-hyoscyamine (20). Atropine aurichloride is a dull lusterless powder which melts in boiling water while *l*-hyoscyamine aurichloride crystallizes in glistening golden-yellow leaflets which do not melt in boiling water.

III. *l*-Hyoscyamine and Atropine

l-Hyoscyamine is the most commonly occurring alkaloid in plants of the Solonaceae family and is usually found associated with varying amounts of *l*-scopolamine and in rare cases (50, 60, 225) with small amounts of atropine.

l-Hyoscyamine (20) and atropine are isomers having the formula $C_{17}H_{23}O_3N$. Atropine is optically inactive and proved to be the racemic form of *l*-hyoscyamine. Such diverse conditions as heating under vacuum

(96, 97), caustic alkalies in cold alcoholic solution (60, 96), ammonia (96), the presence of tropine (60), and even boiling chloroform (187, 238) or cold water (205) are sufficient to cause racemization of *l*-hyoscyamine to atropine. It is therefore highly probable that, in most cases (60), atropine is not present in the plant but results from the racemization of *l*-hyoscyamine (50, 63, 96) during isolation. Water must be kept to a minimum in the racemization of this *levo*rotatory base by alkali to minimize hydrolysis (60). Early workers considered the hydrolyzable linkage to be an amide (11) but subsequent work has shown that it is an ester group that is hydrolyzed. Both *l*-hyoscyamine and atropine are readily hydrolyzed by aqueous solutions of mineral acids (13, 14, 15, 16) as well as by sodium hydroxide (11) and barium hydroxide (12, 14, 16, 19) to form an optically inactive base, tropine, and an acid, *dl*-tropic acid. Depending upon the conditions, *dl*-tropic acid may suffer dehydration and the resulting atropic acid (17) in turn may dimerize to isatropic acid. The insolubility of the more polar tropic acid in petroleum ether or benzene (16, 17) provides an easy method for the separation of this acid from atropic acid. These conversions may be represented as follows:

(a) $\underset{\text{Atropine}}{C_{17}H_{23}O_3N} + H_2O \longrightarrow \underset{\text{Tropine}}{C_8H_{15}ON} + \underset{\textit{dl}\text{-Tropic acid}}{C_9H_{10}O_3}$

(b) $C_9H_{10}O_3 \longrightarrow \underset{\text{Atropic acid}}{C_9H_8O_2} + H_2O$

(c) $2C_9H_8O_2 \longrightarrow \underset{\text{Isatropic acid}}{(C_9H_8O_2)_2}$

When hydrochloric acid or hydrobromic acid is the hydrolytic agent the replacement of the alcoholic hydroxyl of tropine respectively by chlorine or bromine has been observed to occur (186), while sulfuric acid causes dehydration to the unsaturated base, tropidine (192a).

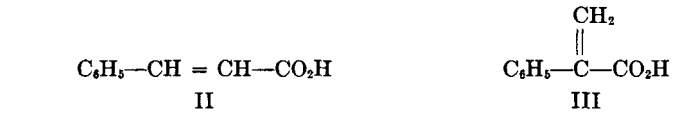
$$C_8H_{15}ON + HX \longrightarrow C_8H_{14}NX + H_2O \qquad X = Cl, Br$$

$$C_8H_{15}ON + H_2SO_4 \longrightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + H_2O$$

The ease with which *l*-hyoscyamine is racemized by alkali would suggest (235) that atropine is the intermediate in the hydrolysis of *l*-hyoscyamine to tropine and *dl*-tropic acid. If *l*-hyoscyamine is hydrolyzed in water (60) tropine and *l*-tropic acid are formed. From this it would appear that the optical activity of this *levo*rotatory alkaloid may be attributed to the asymmetry of the tropic acid residue or that racemization of the tropine during hydrolysis has occurred. This last assumption apparently is not valid for all attempts to resolve tropine have failed (205).

1. Atropic and Tropic Acids

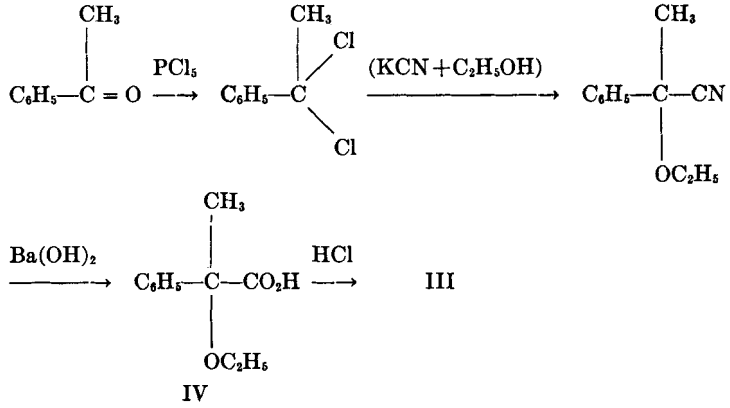
The unsaturated nature of the monobasic acid, atropic acid, which results from the dehydration of tropic acid, is readily established by the ease with which it absorbs two atoms of bromine (14) or hydrogen (sodium amalgam) (18). From the oxidation of atropic acid to benzoic acid it may be characterized as an unsaturated C_9-monocarboxylic acid with one phenyl group as a substituent. Only two structures (II and III) account for these facts. The isolation of formic acid and phenylacetic acid from the alkaline



II III

(KOH) cleavage of atropic acid is evidence in favor of III for this acid (18), yet it was the synthesis of cinnamic acid in 1877 that effectively disposed of II.

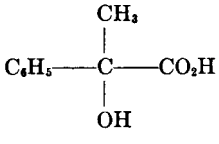
Several syntheses from acetophenone have definitely established structure III for atropic acid. In the first instance the ethyl ether (IV) of atrolactic acid was synthesized and the atropic acid was derived from this by splitting the ether and dehydrating (HCl) the resulting atrolactic acid (83). The synthesis of atrolactic acid ethyl ether involved the conversion of acetophenone to α,α-dichloroethylbenzene (PCl_5), thence to α-ethoxy-α-cyanoethylbenzene (alcoholic KCN) followed by hydrolysis ($Ba(OH)_2$) to IV. This may be illustrated by the following reaction sequence:



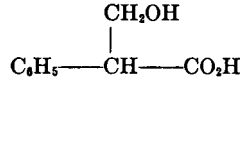
An alternative and more favorable route to the same acid lies in the synthesis and dehydration of atrolactic acid (V) (213). Atrolactic acid is obtained in good yield (73%) by the hydrolysis (HCl) of acetophenone cyanohydrin. Various reagents (82) have been used for the dehydration

but the most practical method is by the rapid distillation of atrolactic acid at pressures between 10 and 15 mm. (213).

The addition of hydrogen chloride to atropic acid, followed by the replacement of the chlorine atom (Na_2CO_3) by a hydroxyl group (213), or the addition of hypochlorous acid to the unsaturated acid followed by the reductive elimination of the chlorine (Zn-Fe + NaOH) (82) completed the synthesis of tropic acid but gave no clear insight into the position of the hydroxyl in the tropic acid molecule (V or VI). Although both V and VI



V



VI

are possible structures for tropic acid, yet the previous synthesis of atrolactic acid precludes a consideration of V for tropic acid. A direct proof for the structure of tropic acid was afforded by the synthesis of VI from phenylacetic esters (166, 168, 171, 213). The yields in the condensation of formic esters with esters of the above acid and the subsequent reduction (aluminum amalgam) of the α-formylphenylacetic esters to the esters of *dl*-tropic acid are good. An alternate route to the same acid is through the action of the organo-zinc compound from ethyl α-bromophenylacetate upon formaldehyde (192). The resolution of *dl*-tropic acid by the fractional crystallization of the quinine (61, 108), quinidine (212), or morphine (213) salts gave an optically active acid identical with *l*-tropic acid from the hydrolysis of *l*-hyoscyamine (60). Tropic acid being a hydroxy acid, it is readily converted to an acetyl derivative which in turn may be converted to acetyltropyl chloride.

2. Tropine and Related Products

a. Tropine, $C_8H_{15}ON$ (13), occurs to a limited extent in *Atropa Belladonna* L. (225) but is obtained more readily from the hydrolysis (acidic or basic) of *l*-hyoscyamine or atropine. The base obtained by hydrolysis even under the mildest conditions is optically inactive (60), while all attempts (205) to resolve it have failed.

The tertiary nature of the nitrogen in this strong base is demonstrated by its quantitative reaction with one mole of alkyl halide (methyl iodide (21), ethyl iodide (14)) with the formation of quaternary salts. Secondly, the isolation of methylamine as one of the products of fusion of tropine with alkali (sodium hydroxide (22), barium hydroxide (14)) suggests the presence of the grouping in this base. Tropine, by virtue of

the nature of its formation from atropine, is an alcohol (22) which has been esterified by a number of aliphatic and aromatic acids (see Table II). These esters are collectively known as the tropeines. The alcohol is readily dehydrated (HCl or H_2SO_4 in HOAc (22)) to an oily, unsaturated base, tropidine, with a coniinelike odor. Like tropine, tropidine reacts with

$$\underset{\text{Tropine}}{C_8H_{15}ON} \longrightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + H_2O$$

but one mole of methyl iodide (22) and the resulting methiodide, when digested with moist silver oxide and heated, is decomposed to α-methyltropidine, a base very prone to isomerization (heat to 150°) to β-methyltropidine. β-Methyltropidine, in contrast to the α-isomer, is very sensitive

$$[C_8H_{13}N - CH_3]^+OH \longrightarrow \underset{\alpha\text{-Methyltropidine}}{C_9H_{15}N} + H_2O$$

to alkali or acid, for in aqueous potassium hydroxide solution the nitrogen complex is eliminated as dimethylamine, with the formation of a carbonyl-containing compound (sodium bisulfite addition product (121)), tropilene.

$$\underset{\beta\text{-Methyltropidine}}{C_9H_{15}N} + H_2O \xrightarrow{KOH} (CH_3)_2NH + \underset{\text{Tropilene}}{C_7H_{10}O}$$

A second exhaustive methylation and Hofmann degradation eliminates the nitrogen of α-methyltropidine as trimethylamine. These last two reactions demonstrate that the tertiary nitrogen of tropidine (and hence of tropine) contains the grouping $\diagdown\!\!\diagup N\text{–}CH_3$ and at the same time is a component of a ring. The non-basic product from the degradation of α-methyltropidine is a highly unsaturated hydrocarbon, tropilidene.

$$\underset{\substack{\alpha\text{-Methyltropidine}\\ \text{methohydroxide}}}{[C_9H_{15}N - CH_3]^+OH} \longrightarrow (CH_3)_3N + H_2O + \underset{\text{Tropilidene}}{C_7H_8}$$

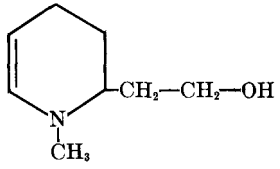
Hydriodic acid and phosphorus (22), like hydrochloric or hydrobromic acid replaces the hydroxyl of tropine by a halogen atom. The reductive elimination of this iodine atom from iodotropane by nascent hydrogen (Zn + HCl) provided the first preparation of the parent substance, tropane (dihydrotropidine) (I, R = CH_3). (A more direct preparation of tropane is by the catalytic reduction of tropidine over platinum black (159a)). Tropane reacts readily with hydrogen chloride at an elevated temperature eliminating methyl chloride with the formation of a new saturated base, nortropane (94). The methyl group eliminated from tropane must have been attached to the nitrogen, for nortropane, in contrast to tropane, forms a well defined *N*-nitroso derivative. The isolation of methyl chloride and the secondary amine, nortropane, confirms the earlier assumption of the

presence of an $\diagup\!\!\diagdown N{-}CH_3$ grouping in both tropidine and tropine. Nortropane (I) is isomeric but not identical with α-ethylpiperidine, but a close relationship between these two isomers was sensed when the former was converted to α-ethylpyridine by zinc dust distillation of its hydrochloride salt (94). The dehydrogenation of tropidine (bromine) to 3,5-dibromopyridine and ethylene dibromide as well as some methyldibromopyridine further suggested the presence of a piperidine nucleus in these alkaloids.

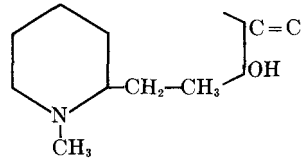
$$\underset{\text{Tropane}}{C_7H_{12}N-CH_3} + HCl \longrightarrow \underset{\text{Nortropane}}{C_7H_{12}N-H} + CH_3Cl$$

$$\underset{\text{Tropidine}}{C_8H_{13}N} + 4Br_2 \longrightarrow \underset{\text{3,5-Dibromopyridine}}{C_5H_3Br_2N} + C_2H_4Br_2 + 3HBr + CH_3Br$$

It appeared to Ladenburg but a short step from ethylene dibromide and dibromopyridine to the structure for tropidine. From the high hydrogen content tropidine must be an *N*-methylhydropyridine with a vinyl side chain, and hence tropine would be VII, in which the double bond has been arbitrarily (128) assigned to the position $\Delta^{5\text{-}6}$. Fischer (86) on the other hand suggested that the hydroxyl of tropine might be attached to the piperidine nucleus (VIII). Subsequently it was shown that this formula was inadequate to account for the oxidation of tropine to tropinic acid, a

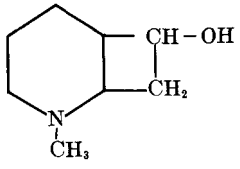


VII

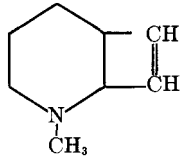


VIII

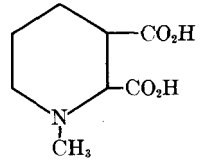
dicarboxylic acid (21), or to account for the saturated nature of tropine (146), unless an abnormal and subdued type of unsaturation is assumed. Merling saw that it was possible to dispense with the troublesome ethenoid linkage of Ladenburg's formula and at the same time maintain agreement



IX



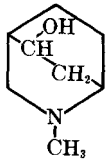
X



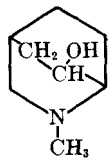
XI

with analytical figures by cyclization of the side chain of VII to IX. If tropine is IX then tropidine and tropinic acid are respectively X and XI. Merling (121) subsequently modified his tropine formula from an *N*-methylpiperidine with an *ortho*-bridge to one with a *para*-bridge (XII or XIII).

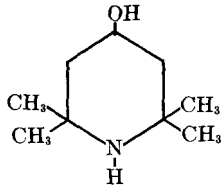
Structure XII was favored by Merling, for like Fischer's triacetonealkamine, XIV (the mandelic ester possesses mydriatic properties (86)), the hydroxyl is gamma with respect to the nitrogen. Tropidine would then have an unsaturated *trans*-bridge while tropinic acid would be *N*-methyl-



XII



XIII



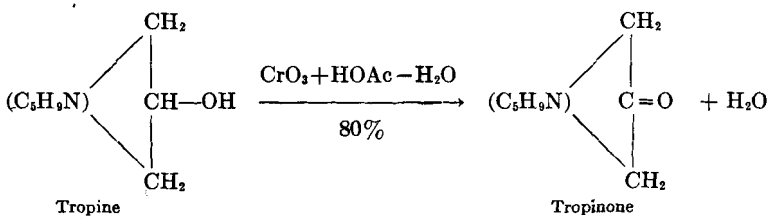
XIV

piperidine-2,5-dicarboxylic acid. This formula for tropine failed in two respects: (1) XII, with three centers of asymmetry, should be either optically active or resolvable into optically active forms, and (2) tropine has

been shown to contain the system $-CH_2-CH-CH_2-$. It has already been stated that tropine is optically inactive and that it has not been resolved.

Evidence for the grouping $-CH_2-CH-CH_2-$ is based on condensation reactions of the corresponding ketone, tropinone, with aldehydes, esters, and amyl nitrite.

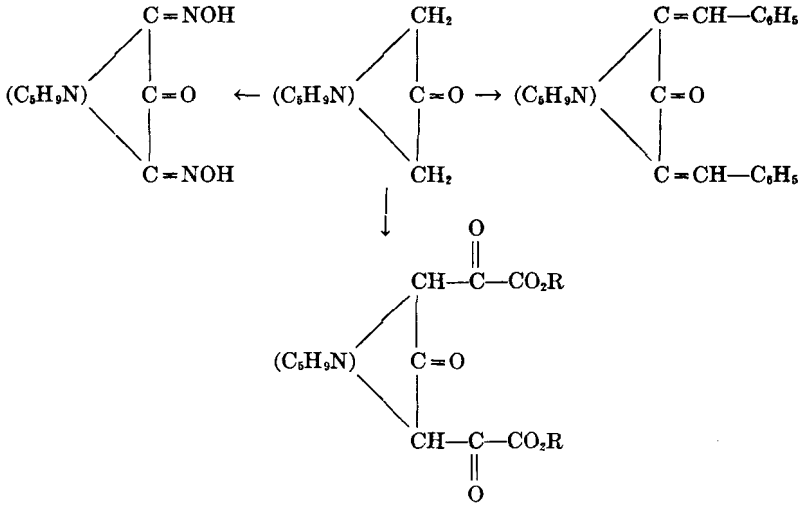
Tropine is oxidized to the ketone (oxime), tropinone, by chromic acid under rigidly controlled conditions (128). Two methylene groups alpha to

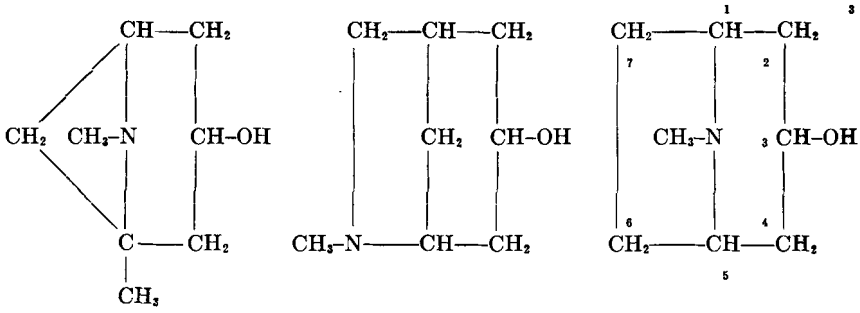


Tropine Tropinone

the carbonyl group of tropinone were unquestionably established when a dibenzylidine derivative (condensing agent HCl (140) or dilute alkali (141)), a diisonitroso derivative, and a diglyoxylic ester (condensing agent $NaOC_2H_5$) were isolated. Three formulas (XV, XVI, XVII) fulfill the requirements imposed above, but two of these (XV, XVI) proved to be inadequate on other grounds. The tropine molecule, as represented by XV and XVI, is asymmetric and should be resolvable. Furthermore these two formulas fail to account for the results of exhaustive methylation and degradation of both tropinone and tropinic acid. The oxidation of tropine ($C_8H_{15}ON$) to the optically inactive tropinic acid ($C_8H_{13}O_4N$), XVIII, by

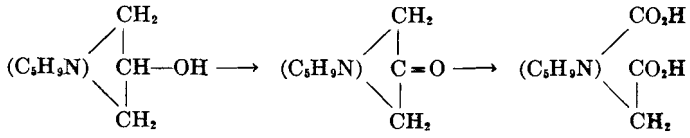
chromic acid (21) probably involves tropinone as an intermediate. Since the oxidation of tropine to the dicarboxylic acid (dimethyl ester, etc. (21,





XV XVI XVII

116, 127)) does not involve the loss of carbon, then this oxidation may be represented by partial formulas as follows:



XVIII

[3] The number systems adopted in this chapter are those recommended by A. M. Patterson and L. T. Capell, *The Ring Index*, Reinhold, New York, 1940.

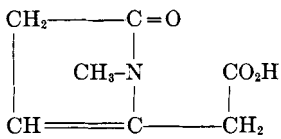
dl-Tropinic acid is saturated (acid permanganate (146)) and the dimethyl ester is but weakly basic; however, reaction with methyl iodide does occur with the formation of a crystalline methiodide. On warming this methiodide with alkali (127) the corresponding des-base (dimethyl methyltropinate) results. A repetition of this degradation upon the methohydroxide of dimethyl methyltropinate eliminates the nitrogen as trimethylamine, and upon saponification a doubly unsaturated dicarboxylic acid can be isolated. The double bonds of this piperylenedicarboxylic acid must be as shown in XIX, for by reduction (4% NaHg) in carbonate solution the dihydro acid, XX, is obtained, while in strongly alkaline solution the second ethylene migrates into a position of conjugation with one of the carboxyls and is then reduced. The isolation of *n*-pimelic acid (143) imposes a further restriction

$HO_2C-CH_2-CH = CH-CH = CH-CO_2H$ XIX

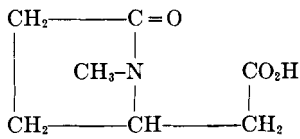
$HO_2C-CH_2-CH = CH-CH_2-CH_2-CO_2H$ XX

on the tropine formula. The carbon atoms of tropine lie in an unbranched chain, a requirement satisfied only by Willstätter's formula containing fused piperidine and pyrrolidine nuclei (XVII).

Tropine and tropinic acid both give the Runge pine splinter test (140), yet the oxidation of tropine to ecgoninic acid supplied the first evidence for a pyrrolidine ring in this alkaloid. (3,5-Dibromopyridine from the dehydrogenation of tropidine and α-ethylpyridine from the zinc dust distillation of nortropane offered support for the piperidine nucleus in tropine.) Ecgoninic acid ($C_7H_{11}O_3N$), which accompanies *dl*-tropinic acid in the oxidation of tropine, represents a further stage in the oxidation of this alkaloid by chromic acid (119). That ecgoninic acid is *N*-methyl-2-pyrrolidone-5-acetic acid (XXII) has been demonstrated by various syntheses. This acid has been obtained by condensing methylamine with β-bromoadipic acid fol-



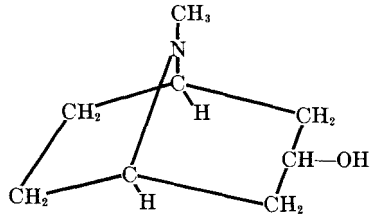
XXI



XXII

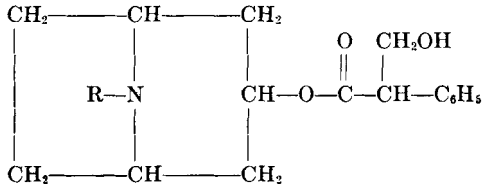
lowed by lactamization of the resulting β-methylaminoadipic acid (34a, 152). An alternate synthesis is the condensation of methylamine with the ester of β-ketoadipic acid followed by reduction of the product (XXI) over Adam's platinum oxide catalyst (193). Ecgoninic acid (as its ester) does not form a nitrosamine but a Herzig-Meyer determination establishes the presence of one $\diagdown\!\!\diagup N-CH_3$ grouping in the acid (149). Although indications are that there is a piperidine and a pyrrolidine nucleus in tropine, yet,

before XVII can be unequivocally accepted for tropine, the presence of a seven-membered carbocyclic ring in this alkaloid must be established. The most direct proof for this ring system in tropine is by the Hofmann degradation of tropidine and related products (p. 285). Finally, tropine must be the relatively strain-free cis modification (XXIII) of Willstätter's tropine formula, for only then is there a symmetry in the molecule to account for the non-resolvable nature of this alkaloid.



XXIII

b. The Tropeines. A number of tropine esters (tropeines, see tables p. 315) of aliphatic, aromatic, and heterocyclic acids have been prepared for the study of their mydriatic activity. In general, they are formed from the action of an acyl chloride upon tropine hydrochloride. For example (158), when acetyltropyl chloride is heated on a water bath with tropine hydrochloride, followed by hydrolysis of the acetyl group with water and liberation of the base with alkali, tropyltropeine (XXIV, R = CH_3) results, identical with atropine. The *levo* form of this *dl*-base, obtained by resolution of the *d*-camphorsulfonate, proved to be *l*-hyoscyamine (205). Hyos-



R = H, CH_3

XXIV

cyamine has also been prepared by the repeated evaporation of a hydrochloric acid solution of tropine with *l*-tropic acid (61).

Apoatropine results from the dehydration (27) (nitric acid, sulfuric acid, acetic or benzoic anhydrides, or phosphorus pentoxide) of atropine. It was proved to be atropyltropeine, for it results from the repeated evaporation of a hydrochloric acid solution of tropine with atropic acid (22) or by the action of tropine with α-phenyl-β-chloropropionyl chloride and elimination of hydrogen chloride from the primary tropeine (158).

Belladonnine (78) is obtained by heating apoatropine at 110° for 48

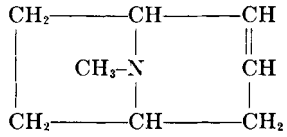
hours. It is saturated towards bromine and potassium permanganate but gives a positive Vitali color reaction. Molecular weight measurements indicate that it is a dimer and, as might be expected, it proved difficult to crystallize. It is isatropylditropeine.

Veratroyltropeine, appearing in the literature under the name convolamine (176), has been isolated from *Convolvulus pseudocantabrica* Schrenk. This alkaloid is identical with that prepared from tropine and veratroyl chloride.

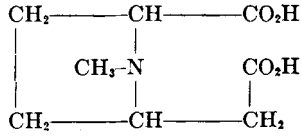
Homatropine (239a) or mandelyltropeine, a common synthetic substitute for atropine, can be distinguished from the natural product by its failure to give a positive Vitali test (1).

c. Pseudotropine. The relation of tropine to tropinone as alcohol and ketone appears to be well established, yet on reduction (sodium amalgam, or sodium in alcohol, or moist ether (130)) tropinone gave pseudotropine ($C_8H_{15}ON$), an isomer of tropine. On the other hand, when tropinone was electrolytically reduced, or when zinc dust and hydriodic acid were used, a mixture of tropine and pseudotropine was formed which was separated by fractionation of the picrates. The isomerism of tropine and pseudotropine must be due to the steric position of the hydroxyl group for both isomers are readily converted to tropidine (XXV), tropinone, and tropinic acid (XXVI) but at different rates (130). Pseudotropine is the stable isomer because boiling sodium amylate (130, 205) converts tropine to pseudotropine, but the reverse is only possible by oxidation to tropinone and reduction with zinc dust and hydriodic acid.

The hydroxyl of pseudotropine has been esterified with various aliphatic and aromatic acids. These esters are known as the pseudotropeines. Of these, tiglylpseudotropeine is known under the name tigloidine and has been isolated from *Duboisia myoporoides* R. Br. (222), while benzoylpseudotropeine or tropacocaine has been isolated from the leaves of a species of coca grown in Java (120). Tropacocaine (120) and the pseudotropeines (211), unlike atropine and the tropeines, show no mydriatic properties.



XXV



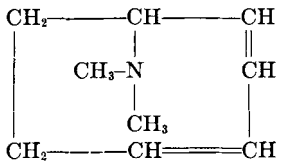
XXVI

d. The Tropylamines. A type of isomerism similar to that of tropine and pseudotropine obtains for the amines (I, R = CH_3, R′ = NH_2) from the reduction of tropinone oxime with sodium amalgam. Like tropine, tropylamine is converted to the stable pseudotropylamine by boiling sodium amylate (142).

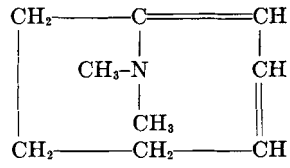
3. Tropidine and Related Products

Tropidine, ($C_8H_{13}N$) (80), a strong oily base with a coniinelike odor results from the dehydration of tropine and pseudotropine. While sulfuric acid has proved to be one of the most suitable dehydrating agents, fuming hydrochloric acid has also been used (80). However, under certain conditions, replacement of the hydroxyl of tropine by a chlorine atom accompanies dehydration and the resulting 3-chlorotropane (186) (I, R = CH_3, R′ = Cl) for a time was erroneously called bellatropine (186). Tropidine is unsaturated, readily decolorizes acid permanganate and is catalytically reduced (159a) to the saturated base, tropane (I, R = CH_3). Further evidence for the double bond in tropidine is derived from its controlled oxidation ($KMnO_4$) (124a) to dihydroxytropane (I, R = CH_3, R′ = R″ = OH) and the subsequent oxidation (chromic acid) of this glycol to tropinic acid (126).

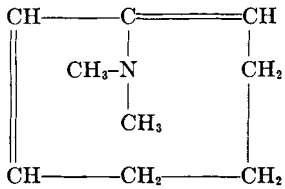
Tropidine readily forms a methiodide. When the methiodide is treated with moist silver oxide and the aqueous solution distilled the doubly unsaturated α-methyltropidine (XXVII) is obtained in good yield. The purification of this oil proved difficult for isomerization to β-methyltropidine occurs at 140–150° (121). The isomerism involves a shift of the double bonds. The β-isomer is soluble in cold hydrochloric acid but on warming an insoluble and unsaturated ketone (oxime, phenylhydrazone), tropilene, settles out (121). Oxidation of tropilene gives adipic acid, while cycloheptanone is formed by its catalytic reduction (160). The preparation of



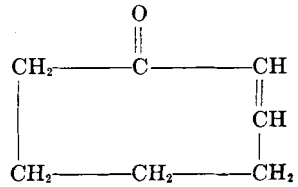
XXVII



XXVIIIA



XXVIIIB



XXIX

tropilene by the elimination of hydrogen chloride from α-chlorocycloheptanone located the double bond αβ- to the ketone. Hence, β-methyltropidine and tropilene must be *XXVIIIA or B* and *XXIX* respectively.

Exhaustive methylation of α-methyltropidine followed by a Hofmann degradation eliminates the nitrogen as trimethylamine and the low boiling cycloheptatriene (tropilidene) was isolated in good yield (22, 121). Tropane may be converted through the intermediate methyltropane to $\Delta^{1,3}$-cycloheptadiene (hydrotropilidene) by a similar process. In the conversion of methyltropane methohydroxide to cycloheptadiene (139), 20% of the methyltropane is reformed by the loss of methanol, a side reaction which occurs in most Hofmann degradations to a greater or lesser extent. Cycloheptatriene and cycloheptadiene have been reduced to cycloheptane (194) which in turn has been oxidized (nitric acid) to pimelic acid.

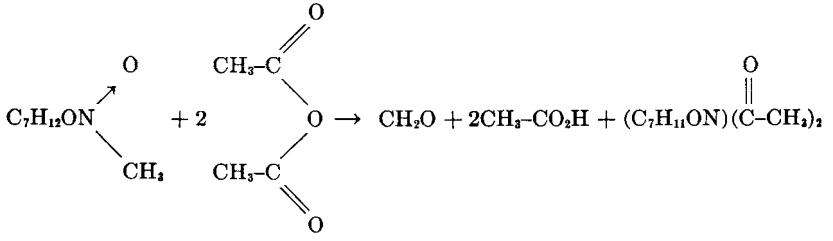
4. Oxidation Products of Tropine

The point of attack of oxidizing agents in the tropine molecule is largely dependent upon the acidity or alkalinity of the oxidizing medium.

a. Alkaline Media. In alkaline solution the *N*-methyl group is oxidized to carbon dioxide and a secondary amine (nitrosamine) nortropine (tropigenine) (21) is obtained. (Under similar conditions norpseudotropine is obtained from pseudotropine (136)). Methylation (21) of nortropine (I, R′ = OH) to tropine clearly establishes the relation between these two bases. An alternate method for the demethylation of the tertiary amines of this series (tropine, pseudotropine, tropinone, hyoscyamine, atropine and apoatropine) is by the action of acetic anhydride (or other anhydrides) upon the amine oxides of the above-mentioned tertiary amines (182, 184). In general, the method is as follows:

An excess of acetic anhydride is added dropwise to the dried and well-stirred amine oxide. The reaction flask is cooled in an ice bath until the vigorous reaction has subsided and the flask is then heated for 4 hours on a steam bath. The excess acetic anhydride in the brown reaction mixture is decomposed with ethyl alcohol and after the addition of some water the mixture is evaporated to a sirup, made alkaline, and extracted several times with boiling ether.

For the amine oxide of tropine the reaction may be expressed by the following equation:



Hydrolysis (20% H_2SO_4) of the *O*,*N*-diacetylnortropine yields nortropine.

The reactions of the alcoholic hydroxyl of nortropine parallel those of the hydroxyl in tropine. Nortropine is oxidized (chromic acid) to nortro-

pinone (131) which in turn is reduced (sodium + ethanol) to norpseudotropine. The latter isomer, like pseudotropine, is the stable one since nortropine is isomerized to norpseudotropine (225) by boiling sodium amylate. Nortropine is dehydrated (H_2SO_4) to nortropidine (227) or may be reduced by phosphonium iodide and hydriodic acid to nortropane (167).

A number of esters of nortropine, some of which occur naturally, are known. *l*-Tropylnortropeine or norhyoscyamine (209) (XXIV, R = H) has been isolated from *Scopolia japonica* Maxim., *Datura metel* L., *Datura meteloides* D. C., *Duboisia myoporoides, Mandragora vernalis* Bertol (209) and *Solandra longiflora* Tussac (245, 246) and has been referred to as pseudohyoscyamine (53) and solandrine (245, 246).

The *O,N*-diacetylnorhyoscyamine has been prepared by the action of acetic anhydride upon the amine oxide of hyoscyamine (182). In acid the *O*-acetate is hydrolyzed but in cold alkali, water is eliminated as well with the formation of *N*-acetylnorapoatropine (acetic anhydride upon the amine oxide of atropine reacts in an analogous fashion). Norhyoscyamine, like hyoscyamine, is easily racemized in alcoholic sodium hydroxide to the optically inactive noratropine (XXIV, R = H). Noratropine and norhyoscyamine are converted with methyl iodide respectively to atropine or *l*-hyoscyamine and their methiodides (209).

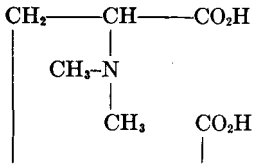
Veratroylnortropeine or convolvine (178) occurs in *Convolvulus pseudocantabrica* along with convolamine to which it has been converted by methyl iodide.

Another pair of difficultly separable nortropeines, poroidine and isoporoidine, have been isolated from *Duboisia myoporoides* (222). These two alkaloids have been shown by syntheses to be respectively isovaleryl- and *d*-α-methylbutyryl-nortropeine.

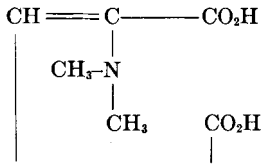
b. Acidic Media. In acid media (chromic acid (128, 129), lead peroxide and sulfuric acid (146) or potassium permanganate in sulfuric acid (146)) it is the secondary hydroxyl of tropine that is oxidized under controlled conditions to tropinone, and under more vigorous conditions to *dl*-tropinic acid (XXVI) and *dl*-ecgoninic acid (XXII).

Tropinone is a low melting tertiary base which readily forms a methiodide. The decomposition of this methiodide in alkali, in contrast to that of tropine and tropidine, does not give the expected des-base. With potassium hydroxide resinification of the primary product occurs (129); however, with silver oxide (128) or sodium bicarbonate (129) a product thought to be $\Delta^{4,6}$-dihydrobenzaldehyde (oxime and phenylhydrazone (117)) was isolated in good yield. (This sensitivity towards alkali is a general characteristic of β-aminocarbonyl compounds.) Silver oxide oxidizes this aldehyde to a dihydrobenzoic acid, while at elevated temperatures benzoic acid is formed.

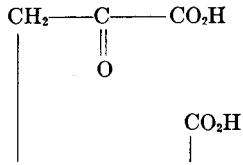
dl-Tropinic acid is a dibasic acid (21, 116) which, by crystallization of its cinchonine salt, has been resolved into the two optically active enantiomorphs. The *dl*-acid forms both mono- and diesters, the latter being weakly basic. The methiodide (127), when digested with an aqueous suspension of silver oxide and warmed, gives the normal des-base. The nitrogen of this dimethyl methyltropinate is eliminated as trimethylamine by a repetition of this decomposition, the nitrogen-free fragment being piperylenedicarboxylic acid (XIX). If sodium hydroxide is substituted for silver oxide in the decomposition of dimethyl *dl*-tropinate methiodide then dimethylamine, formic acid, and adipic acid are the products of degradation. These degradation products might be accounted for by the isomerization of the normal product of the Hofmann degradation (XXX) to XXXI which in alkali, like β-methyltropidine, might be expected to yield dimethylamine and the keto acid XXXII. The fission of XXXII would account for the formation of both formic and adipic acids.



XXX



XXXI



XXXII

5. Syntheses in the Tropine Series

From analytical data the structure for tropine appears to be well established and this has been confirmed by synthesis. The classical synthesis of this alkaloid by Willstätter was followed in rapid succession by the shorter and more direct methods both of Robinson and of Willstätter.

The long and laborious synthesis of Willstätter may be conveniently divided into the following three phases:

(*a*) the synthesis of tropidine (29, 30, 31, 148),

(*b*) the conversion of tropidine to pseudotropine (33, 153),

(*c*) the oxidation of pseudotropine to tropinone and its reduction to tropine (130).

(*a*) *First phase* (XXXIII–XXV). The reduction (sodium and ethanol) of cycloheptanone oxime provided most of the starting material; however, a portion of the cycloheptylamine (XXXIV) was prepared by the degradation of hydroecgonidine. Exhaustive methylation converted the cycloheptylamine to cycloheptene which in turn was brominated and the dibromocycloheptane treated with a benzene solution of dimethylamine. A dimethylamino group substituted for one bromine atom while the second

halogen atom was eliminated as hydrogen bromide. By exhaustive methylation the Δ^2-dimethylaminocycloheptene was converted to $\Delta^{1,3}$-cycloheptadiene (identical with that from tropane). The conversion to cycloheptatriene (identical with that from tropidine) was effected in two ways; (a) by the 1,4 addition of bromine to XXXVII followed by the elimination (quinoline) of two moles of the hydrogen bromide, or (b) by replacement of the two bromine atoms by dimethylamino groups, followed by a double Hofmann degradation. The bridge nitrogen atom of tropidine was introduced by the addition of one mole of hydrogen bromide to cycloheptatriene and the replacement of the halogen atom by a dimethylamino group. The completion of the nitrogen bridge of this α-methyltropidine (XXVII) was effected by intramolecular alkylation of XXVII. Prior to this time (24) it had been demonstrated that, when hydrogen chloride was bubbled into 5-dimethylaminopentene-1, it added to the ethylene in such a manner that the product from the subsequent intramolecular alkylation was 1,2-dimethylpyrrolidine methochloride or, if a high enough temperature was attained, methyl chloride was evolved and 1,2-dimethylpyrrolidine resulted. It has been reported (31, 121) that tropidine methochloride results in 72% yield from the addition of one mole of hydrogen chloride to XXVII, but it is more probable that the very similar isotropidine methochloride (XLVIII) is formed. This difficulty was circumvented by the addition of one mole of hydrogen to the conjugated system of XXVII followed by bromination of the double bond of XL. Internal alkylation by either bromine atom of XLI led to 2-bromotropane methobromide (XLII). The conversion of XLII to tropidine involved the elimination of hydrogen bromide and the pyrolysis of the resultant tropidine methochloride. At best the overall yield from cycloheptanone was 3.8%.

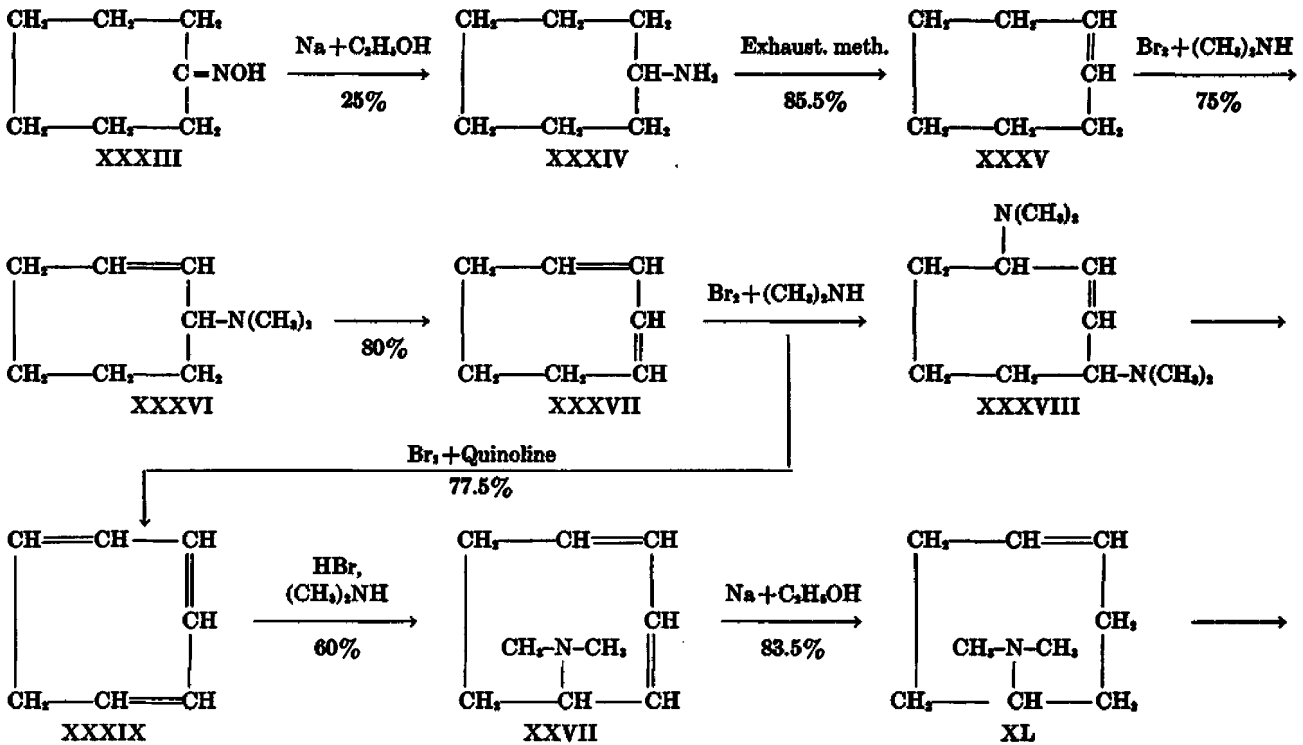
(*b*) *Second phase* (XXV–XLV). It has been stated in several short communications that tropidine may be converted to tropine by warming with hydrogen bromide followed by treatment with aqueous alkali, but this has been refuted (31, 147). However, the conversion of tropidine to pseudotropine has been effected by two methods.

(i) The more direct method for this conversion was by the addition of hydrogen bromide to an acetic acid solution of tropidine followed by hydrolysis of the resulting 3-bromotropane (I, R = CH_3, R′ = Br) with 10% sulfuric acid at 200–210°. The overall yield was 24%.

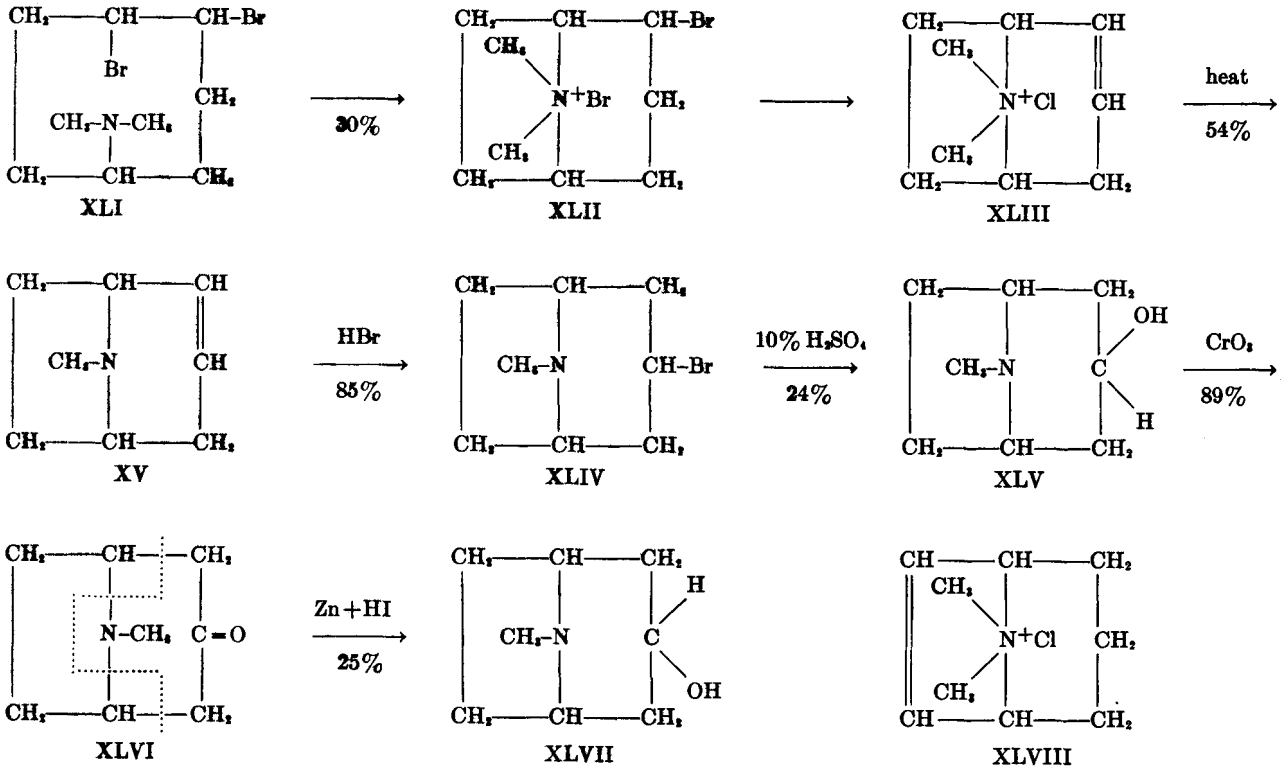
(ii) The alternative procedure (32) involved the addition of hydrogen chloride to the Δ^2-ethylene of α-methyltropidine (21, 22) and the replacement of the halogen by a hydroxyl group (sodium carbonate). This unsaturated alcohol proved to be identical with methylpseudotropine, the Hofmann degradation product of pseudotropine. Bromination of the double bond of methylpseudotropine followed by intramolecular alkylation

CHART I

THE SYNTHESIS OF PSEUDOTROPINE



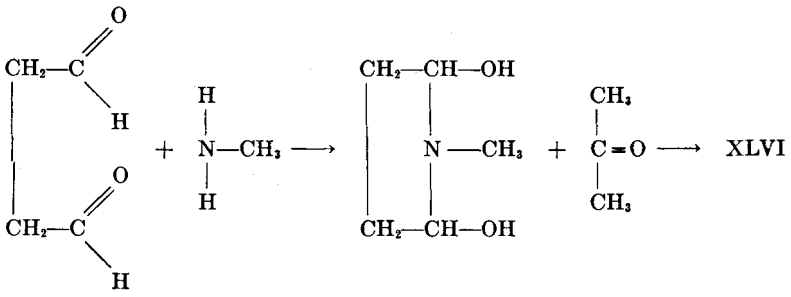
XXXIII XXXIV XXXV XXXVI XXXVII XXXVIII XXXIX XXVII XL


XLI
30%
XLII
heat
54%
XLIII
XV
HBr
85%
XLIV
10% H2SO4
24%
XLV
CrO3
89%
XLVI
Zn+HI
25%
XLVII
XLVIII

afforded the bromopseudotropine methobromide. The reductive elimination (zinc and hydriodic acid) of the bromine atom of bromopseudotropine methobromide was also accompanied by dehydration. Conversion of the tropidine methiodide to the methochloride (silver chloride) and pyrolysis of the latter completed the alternate synthesis of tropidine.

(*c*) *Third phase* (XLV–XLVII). The reactions in the conversion of pseudotropine to tropine have already been dealt with so that an outline of the methods used will be sufficient at this point. The oxidation of pseudotropine to tropinone proceeded smoothly (84%), while the reduction of this ketone (zinc and hydriodic acid) and its separation from the pseudotropine afforded only a 24% yield of tropine. This synthesis of tropine represents one of the high-water marks in organic syntheses and, although with but few exceptions the yield in each individual step was of the order of 80%, the overall yield of tropine from cycloheptanone was 0.19%.

Robinson's synthesis of tropine (210) on the other hand was as direct (two steps) as Willstätter's was long but it involved the use of the very sensitive succinic dialdehyde (from pyrrole) (157, 219). The fragments from the hypothetical fission of the symmetrical tropinone (XLVI) suggested to Robinson the possibility of obtaining this ketone by the condensation of succinic dialdehyde and methylamine with acetone. The primary reaction was considered to be the combination of succinic dialdehyde with methylamine and the resulting biscarbinolamine (XLIX) in turn condensed with acetone. This synthesis was realized when these reactants, in aqueous



XLIX

solution, were allowed to stand for 30 minutes. The yield of the ketone was estimated from the weight of the dipiperonylidene derivative recovered. The yield was improved (42%) by substitution of the more reactive calcium acetonedicarboxylate or its ester for acetone. This, combined with the previous reduction of tropinone to tropine, constitutes a complete synthesis of tropine.

The Robinson method has been applied to the synthesis of a number

of tropinonelike compounds by replacing the succinic dialdehyde by various aldehydes (acetaldehyde (76), glutaric dialdehyde (215), adipic dialdehyde (218), *o*-aldehydo-phenylpropionic aldehyde (220), methylaminobisacetaldehyde (219), selenobisacetaldehyde (219), and thiobisacetaldehyde (219)) and keto aldehydes (laevulinic aldehyde (221)). Acetonylacetone failed to react normally with methylamine and calcium acetonedicarboxylate (221). Other amines (ethylamine, isopropylamine, benzylamine and ethanolamine) have been substituted successfully (195a) for the methylamine in the above synthesis. The synthesis of "open" tropinone, which would result from a hypothetical hydrogenolysis of the C_6–C_7 bond of tropinone, has been realized by substituting two moles of acetaldehyde for succinic dialdehyde in the above synthesis (76). The fission of the C_6–C_7 bond of tropinone removed the strain and the open tropinone has been isolated pure in the nonresolvable *cis* form, but difficulty was encountered in the purification of the *trans* modification. *Cis* open tropinone is reduced (sodium amalgam, catalytic reduction, electrolytic reduction, and Zn + HI) to the open pseudotropine, for it is stable to boiling sodium amylate. The benzoyl ester (open tropacocaine) shows anaesthetic properties and the tropyl ester is a mydriatic agent. Other modifications of this synthesis have also been reported (175, 177).

The yield of tropinone by Robinson's synthesis has been demonstrated to be markedly dependent upon experimental conditions (39). Table 1 illustrates the variation in the yield of tropinone with changes of temperature and pH (time of reaction 72 hours). The yield of tropinone at a pH of 13 is 5% or less but an additional 65% may be recovered by decarboxylation of the tropinonedicarboxylic acid formed under these conditions.

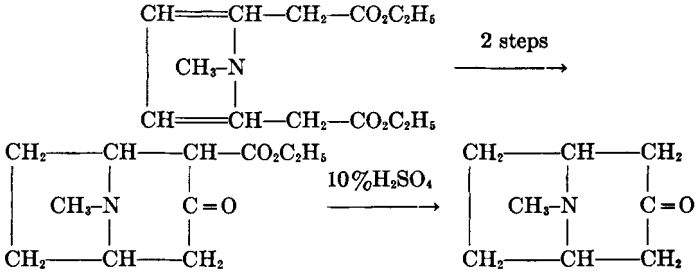
TABLE 1

YIELD OF TROPINONE AT pH 3–13

pH	3	5	7	9	11	13
Yield of tropinone at 20° (%)	51	58	70	71	92.5	3.2
Yield of tropinone at 25° (%)	73	89	84	65.5	69	5.4

Willstätter's second synthesis (36) involved the condensation of methylamine with succinyldiacetic ester (Kolbe electrosynthesis on the monopotassium salt of the monoethyl ester of acetonedicarboxylic acid (35)), reduction (H_2 + Pt) of the resulting diethyl *N*-methylpyrrolediacetate and cyclization (Na + *p*-cymene) of the *cis* form of diethyl *N*-methylpyrrolidinediacetate to ethyl tropinone-2-carboxylate. Hydrolysis of the ester to tropinone and its reduction (Zn + HI) to tropine (147) completed the

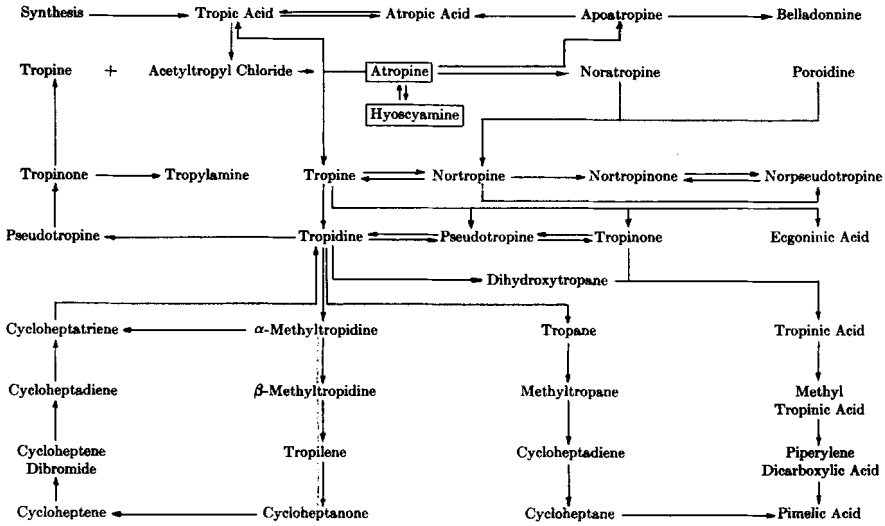
synthesis. The yield of tropinone from diethyl *N*-methylpyrrolidinediacetate was 24%.



The relation of the various transformation products of *l*-hyoscyamine and atropine is summarized schematically in Chart II.

CHART II

TRANSFORMATION PRODUCTS OF HYOSCYAMINE AND ATROPINE



IV. Cocaine

l-Cocaine was first isolated in 1862 (10, 15) and assigned the formula $C_{16}H_{20}O_4N$, but this was later revised to $C_{17}H_{21}O_4N$. It is the principal alkaloid of the various species of the genus *Erythroxylon*. The alkaloid content of the species grown in South America is 0.2–0.8% of the total plant weight and of this 90% is cocaine. The remainder is cinnamylcocaine, cinnamylecgonine, and hygrine. In Java and Peruvian coca leaves α- and β-truxilline and tropacocaine occur to a limited extent.

The by-products in the crude extract from South American coca are removed by oxidation (below 5°) of a solution of the extract in 3% sulfuric acid with saturated permanganate solution. After filtration the base is liberated and crystallized from ether (239). The *l*-ecgonine, formed by hydrolysis of the esters in the preliminary extraction, may be converted to *l*-cocaine by esterification (CH_3OH) and benzoylation of the ecgonine methyl ester. A process has been developed whereby cinnamylcocaine and the truxillines are converted to *l*-ecgonine methyl ester which in turn is converted by benzoylation to *l*-cocaine.

Cocaine, a levorotatory crystalline base, is a tertiary amine that forms a methiodide with one mole of methyl iodide (100). Methyl bromide is eliminated from *l*-cocaine by cyanogen bromide (165a) in the formation of cyanonorcocaine. *l*-Cocaine must therefore contain the characteristic $\rangle N{-}CH_3$ grouping of atropine and *l*-hyoscyamine. *l*-Cocaine also contains

$$\underset{\text{l-Cocaine}}{C_{16}H_{18}O_4N{-}CH_3} + CNBr \xrightarrow[63\%]{} \underset{\text{Cyanonorcocaine}}{C_{16}H_{18}O_4N{-}CN} + CH_3Br$$

two hydrolyzable groups for acid hydrolysis (H_2SO_4 (15), HCl (10, 15)) yields equimolar amounts of *l*-ecgonine, benzoic acid, and methanol, thus accounting for all the carbon atoms. The hydrolysis may be arrested at

$$\underset{\text{l-Cocaine}}{C_{17}H_{21}O_4N} + 2H_2O \xrightarrow{H_2SO_4} \underset{\text{l-Ecgonine}}{C_9H_{15}O_3N} + C_7H_6O_2 + CH_3OH$$

an intermediate stage, boiling water (95) yielding benzoyl-*l*-ecgonine and methanol (benzoyl-*l*-ecgonine has been isolated from Peruvian coca leaves).

$$\underset{\text{l-Cocaine}}{CH_3O_2C{-}(C_7H_{10}N{-}CH_3){-}O_2C{-}C_6H_5} + H_2O \longrightarrow \underset{\text{Benzoyl-l-ecgonine}}{HO_2C(C_7H_{10}N{-}CH_3){-}O_2C{-}C_6H_5} + CH_3OH$$

The stepwise hydrolysis is completed by boiling benzoyl-*l*-ecgonine with dilute hydrochloric acid.

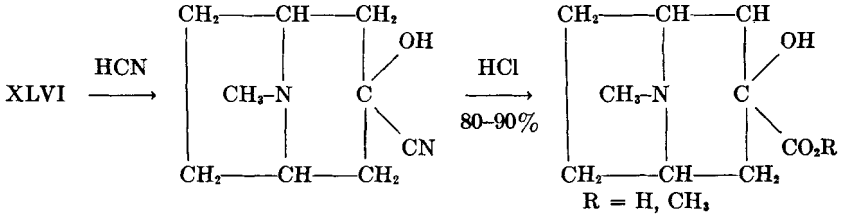
1. *l*-Ecgonine

l-Ecgonine ($C_9H_{15}O_3N$) (15) crystallizes as the monohydrate and the water of crystallization is notlost until temperatures of 120–130° are reached. *l*-Ecgonine is an acid which has been converted to an amide (123) and to a number of esters by the Fischer method (*l*-ecgonine methyl ester occurs in Java coca leaves (250)). These alkylecgonines react with one mole of methyl iodide with the formation of crystalline methiodides.

The preparation of a number of *O*-acyl derivatives of *l*-ecgonine prove the presence of an alcoholic hydroxyl in this base. Furthermore, the original base may be dehydrated to anhydroecgonine, a product which is unsaturated towards permanganate and bromine. Dihydroanhydroecgonine

is formed from anhydroecgonine by the addition of one mole of hydrogen in the presence of a catalyst. Since anhydroecgonine is readily esterifiable the carboxyl group of the parent base is still present. (The methyl ester has been isolated from the seeds of *Erythroxylum Coca* Lam. and *Erythroxylon novogranatense* Morris (195), while the ethyl ester, found in the mother liquors from the preparation of *l*-cocaine, is considered to be of secondary origin, resulting from the ethanol and hydrochloric acid used in the process (156)). The degradation of anhydroecgonine to an acid and methylamine (chloroplatinate (100)) by heating with water under pressure suggests the presence of the characteristic tropine $\diagdown\!\!\diagup N\text{–}CH_3$ grouping in this base (and hence in *l*-ecgonine and *l*-cocaine).

An insight into the nuclear structure of l-ecgonine and of the position of the hydroxyl and carboxyl grnups in the molecule has been gained from the oxidation and dehydration of *l*-ecgonine. The oxidation of *l*-ecgonine by chromic acid to the optically active acids, *d*-tropinic acid (XXVI) (116, 119) and *l*-ecgoninic acid (XXII) (116, 119, 149) (these acids, obtained from tropine in an analogous manner, are optically inactive), suggested the presence of a tropane nucleus with a hydroxyl and a carboxyl group attached either separately or collectively to C_2 and/or C_3. This relationship of the coca bases to tropane was confirmed by decarboxylation of anhydroecgonine to tropidine (115) by hydrochloric acid at 280°. Attachment of the hydroxyl and carboxyl groups to C_3 has been excluded by the synthesis of α-ecgonine (LI, R = H) from tropinone (131, 134). This acid and its

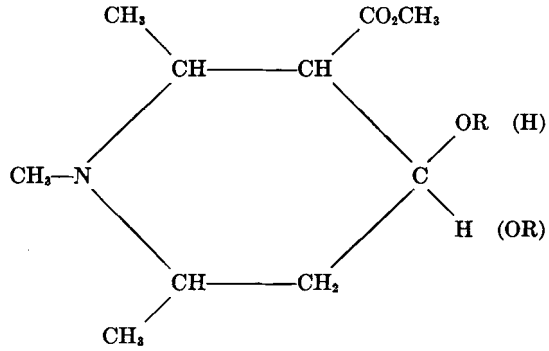


methyl ester resulted in good yield from the hydrolysis of tropinone cyanohydrin (L). The most outstanding difference between *l*-ecgonine and α-ecgonine was the marked stability of the methiodide of α-ecgonine methyl ester towards alkali (134). Were the carboxyl of ecgonine at C_3, then this series of bases could be related to those of the tropine series by degrading hydroanhydroecgonine (hydroecgonidine) to tropylamine or pseudotropylamine. The conversion of the carboxyl of hydroecgonidine to an amine has been achieved by the Hofmann and Curtius methods. The resulting isotro-

pylamine (LVI) differed from both tropylamine and pseudotropylamine and it was not convertible into either of these amines by acid or alkali (145). Conversion of isotropylamine by nitrous acid to an isotropine failed, but some tropidine was formed in this reaction which would suggest that the amine of isotropylamine and hence the carboxyl of hydroecgonidine and *l*-ecgonine is at C_2. The oxidation (CrO_3 + H_2SO_4) of *l*-ecgonine (LII) to a keto acid (LIII, R = H) which spontaneously decarboxylated to tropinone (145) located the hydroxyl at C_3 and the carboxyl at C_2. The oxidation of *l*-ecgonine to tropinone (XLVI) completed the conversion of *l*-cocaine to atropine.

The seven-membered carbocyclic ring of *l*-ecgonine and hydroecgonidine was established through the conversion of the latter to cycloheptanone (LVII) (144) by a series of mild reactions. This involved the conversion of hydroecgonidine (LV) to cycloheptadienecarboxylic acid (hydrotropilidinecarboxylic acid, two exhaustive methylations), the reduction (Na + C_2H_5OH) of the latter to cycloheptanecarboxylic acid, and the conversion of this saturated acid to cycloheptanone. The last phase in this conversion was effected by bromination of the carbon alpha to the carboxyl (Hell-Volhard) of the saturated acid, substitution of a hydroxyl for the bromine ($Ba(OH)_2$), and oxidation of the hydroxy acid with lead peroxide.

The synthesis of LII supplied the confirmatory evidence for the structure of ecgonine (38). The methyl esters of *dl*-ecgonine and of the stereoisomeric *dl*-pseudoecgonine are formed in the reduction (NaHg + HCl) of methyl tropinone-2-carboxylate (LIII, R = CH_3) (by a Robinson synthesis from the monomethyl ester of acetonedicarboxylic acid, methylamine, and



R = H, C_6H_5—CO—

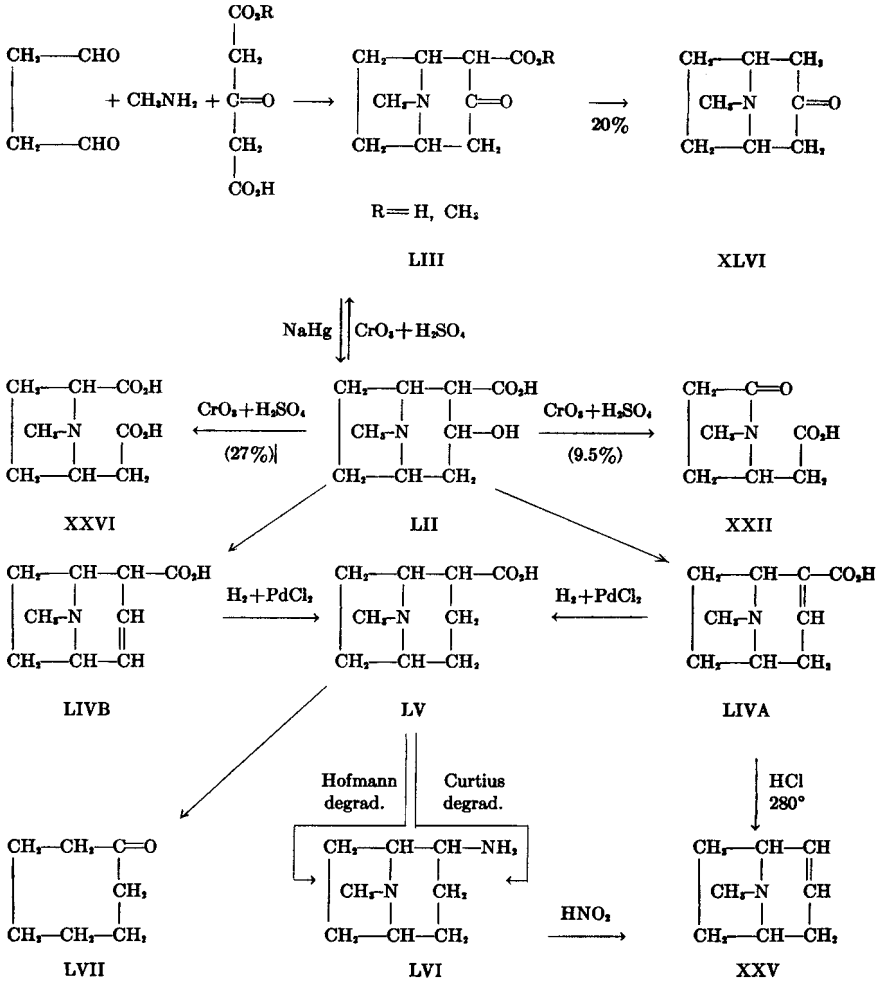
LVIII

succinic dialdehyde). The separation of these two diastereomeric esters proved difficult but was accomplished by way of the benzoates. The chemical properties of the more soluble benzoate were very similar to those

of natural *l*-cocaine. The *l*-form (resolved by crystallization of the bitartrate) of this synthetic benzoyl-derivative was *l*-cocaine.[4]

CHART III

ECGONINE SYNTHESIS AND TRANSFORMATION PRODUCTS



[4] The methyl esters of "open" *dl*-ecgonine (LX, R = H) and "open" *dl*-pseudoecgonine resulted from a similar synthesis (76). The ketoester, resulting from the condensation of two moles of acetaldehyde with methylamine and the monomethyl ester of acetonedicarboxylic acid, was reduced (H_2 + PtO_2) to a mixture of the methyl esters of open *dl*-ecgonine and of open *dl*-pseudoecgonine. Benzoylation of open *dl*-ecgonine methyl ester gave open *dl*-cocaine (*LVIII*, R = C_6H_5–CO–) which, like cocaine, possessed pronounced anaesthetic properties.

The methyl ester of *dl*-pseudoecgonine is formed in preponderant amount in the reduction of methyl tropinone-2-carboxylate (likewise in the reduction of sodium tropinone-2-carboxylate (151)). The *dl*-pseudoecgonine must be the stable form (like pseudotropine) since *dl*-ecgonine and its esters are converted to the pseudoisomer by alkali (38). The *d*-form of pseudoecgonine[5] (by resolution of the α-bromocamphor-β-sulfonate) is identical with that obtained by the isomerization of *l*-ecgonine with alkali (111). The steric position of the hydroxyl is the only configurational change involved in this isomerization because both isomers are dehydrated (HOAc + HCl) to anhydroecgonine (111) (there is a marked difference in the ease of dehydration of the two isomers) and oxidized to *l*-ecgoninic acid (149).

The $\diagdown\!\!\diagup N\text{–}CH_3$ groups of *l*-ecgonine (100) and of *d*-pseudoecgonine (124) can be oxidized by alkaline permanganate and the secondary amines, nor-*l*-ecgonine and nor-*d*-pseudoecgonine, thus obtained. The nor-*d*-pseudoecgonine has been esterified (CH_3OH, C_2H_5OH) and the ethyl ester benzoylated (124) (the hydrochloride is as strong an anaesthetic and equally as toxic as that of *l*-cocaine). Methyl iodide converted nor-*d*-pseudoecgonine ethyl ester to the methiodide of *d*-pseudoecgonine ethyl ester.

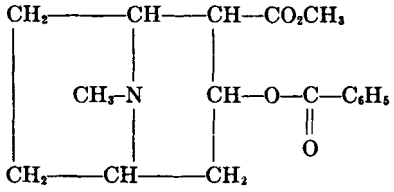
3. Synthesis of the Cocaines

The first synthesis of *l*-cocaine, in poor yield (4%), was by heating benzoyl-*l*-ecgonine and methyl iodide with sodium methylate. Later natural cocaine was synthesized directly from *l*-ecgonine in 80% yield by heating a mixture of *l*-ecgonine, benzoic anhydride, and methyl iodide (90) at 100°. The quantitative conversion of *l*-ecgonine to *l*-cocaine has been achieved in a stepwise manner. *l*-Ecgonine was esterified with methanol and the methyl ester benzoylated with benzoyl chloride (102, 125, 239, 249) or *l*-ecgonine was benzoylated first and then esterified with methanol (95, 101, 125). *l*-Cocaine, therefore, is benzoylmethylecgonine (LIX). The ethyl ester of benzoyl-*l*-ecgonine is cocethyline or methylcocaine (90, 95).

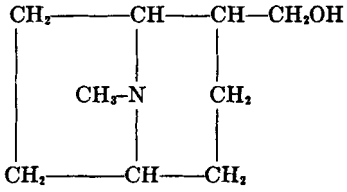
Cinnamyl-*l*-ecgonine has been obtained by acylation of *l*-ecgonine with cinnamic anhydride. Esterification of this cinnamyl-derivative with methanol gave cinnamylcocaine (103). After the physical properties of cinnamylcocaine had been established it was subsequently isolated from Java coca leaves (109) and from *Erythroxylum monogynum* Roxb. (77). It has been reported (77) that cinnamylcocaine is devoid of mydriatic and anaesthetic properties.

[5] For a time *d*-pseudoecgonine was incorrectly called methylecgonine (113).

Two more acyl derivatives of *l*-ecgonine methyl ester have been isolated from Java and Peruvian coca leaves (104). The mixture of these two, at first known as cocamine, is present to the extent of 0.6% in these leaves. Hydrolysis (HCl) of cocamine gave methanol, *l*-ecgonine, and a separable



LIX



LX

mixture of α- and β-truxillic acids. Cocamine is a mixture of the α- and β-truxillyl derivatives of *l*-ecgonine methyl ester. The separation of cocamine into pure α- and β-truxilline has not been achieved, but the pure alkaloids have been obtained by synthesis (106). β-Truxillyl-*l*-ecgonine, prepared by heating a benzene solution of β-truxillic anhydride with *l*-ecgonine, was esterified with methanol. The hydrolysis of these two alkaloids may be represented as follows:

$$\underset{\substack{\alpha\text{- or }\beta\text{-}\\ \text{Truxilline}}}{C_{38}H_{46}O_8N_2} + 4H_2O \longrightarrow \underset{\substack{\alpha\text{- or }\beta\text{-}\\ \text{Truxillic acid}}}{C_{18}H_{16}O_4} + 2CH_3OH + \underset{l\text{-Ecgonine}}{2C_9H_{15}O_3N}$$

The recovery of *l*-cocaine from crude extracts has been increased by hydrolysis of the truxillines and cinnamylcocaine in methanolic sulfuric acid and benzoylation of the resulting *l*-ecgonine methyl ester (125).

Methods similar to those described above have been applied to *d*-pseudoecgonine in the synthesis of *d*-pseudococaine (114). This isomer is formed to a limited extent in the isolation of *l*-cocaine (113).

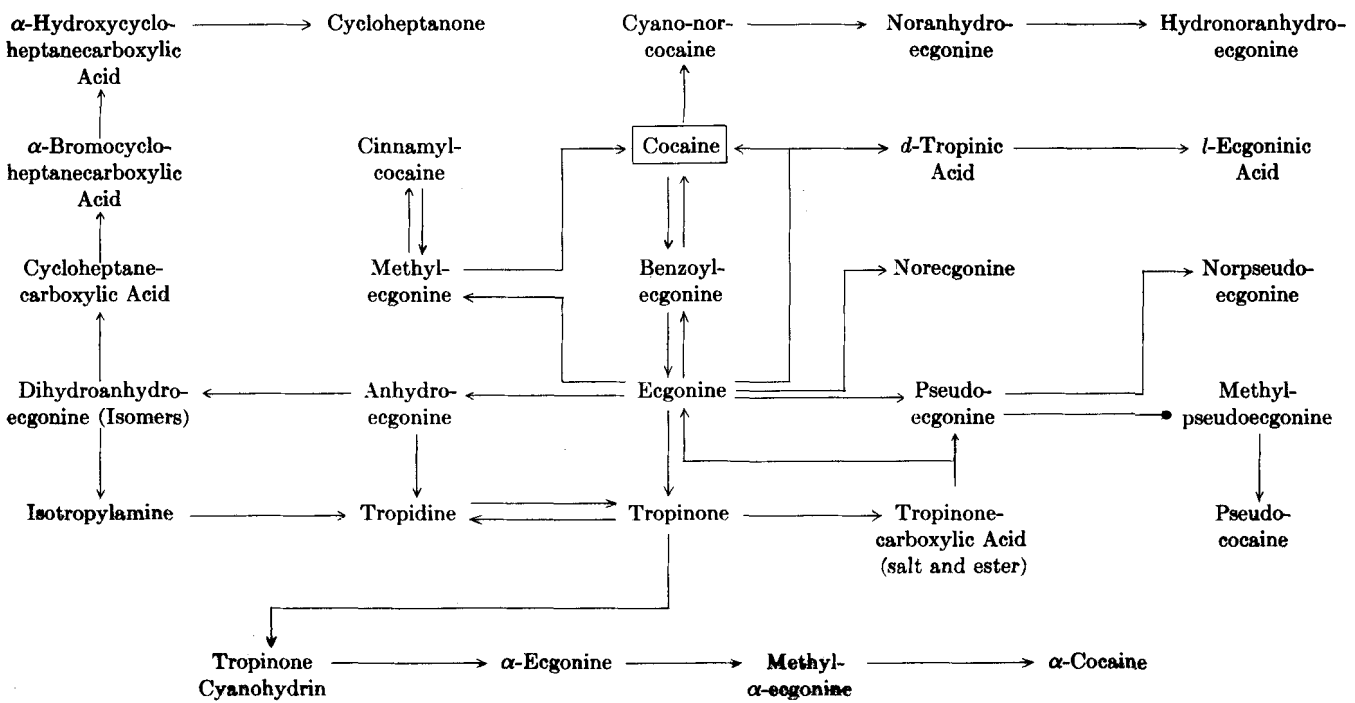
α-Cocaine, resulting from the methanolysis and benzoylation of α-ecgonine, is devoid of anaesthetic properties (134).

4. Anhydroecgonine

Anhydroecgonine (ecgonidine) ($C_9H_{13}O_2N$) (92) resulted from the dehydration of *l*-ecgonine (PCl_5 (91), $POCl_3$ (92)) or *d*-pseudoecgonine (HOAc + HCl (111)). The double bond of anhydroecgonine at various times has been assigned on rather speculative evidence (73, 145) to $\Delta^{2\text{-}3}$ or $\Delta^{3\text{-}4}$; however, the reduction (Paal-Skita catalyst (73), $PdCl_2$ (165a), Na + $C_5H_{11}OH$ (138)) of this unsaturated product to two dihydroanhydroecgonines (dihydroecgonidines) would seem to favor LIVA over LIVB. Reduction of the ester of either of these dihydroecgonidines with sodium and ethanol (165a) gave 2-methyloltropane (homotropine) (LX). The position of the hydroxyl of LX with respect to the nitrogen atom is the

CHART IV

TRANSFORMATION PRODUCTS OF COCAINE



same as in tropine, and, as might be expected, the tropyl ester is as strong a mydriatic agent as atropine.

The ethylenic bond of anhydroecgonine is very subject to attack by bromine (92, 117) and alkaline permanganate (146). The anhydroecgonine dibromide is very sensitive to alkali. With sodium carbonate even at 60° carbon dioxide and methylamine are lost and dihydrobenzaldehyde, identical with that from tropinone methiodide, is formed (117). Due to attack on the double bond by oxidizing agents noranhydroecgonine cannot be prepared by the alkaline permanganate oxidation of anhydroecgonine, but it has been prepared by a circuitous route from cocaine. Not only was the cyano group of cyanonorcocaine hydrolyzed by boiling hydrochloric acid, but simultaneously the ester groups were cleaved, and dehydration to noranhydroecgonine occurred (165a).

From ecgonine and its derivatives, by exhaustive methylation and reduction, three isomeric cycloheptatriene carboxylic acids, one cycloheptadienecarboxylic acid, three cycloheptenecarboxylic acids, and cycloheptanecarboxylic acid have been prepared (144).

The relationship of these transformation and degradation products to cocaine may be clearly seen from Chart IV.

V. *l*-Scopolamine or *l*-Hyoscine

The isolation of the levorotatory hyoscine from the mother liquors from the preparation of *l*-hyoscyamine from *Hyoscyamus muticus* L. was reported in 1881. From early analyses (20) the new base was assigned the formula $C_{17}H_{23}O_3N$ but this was subsequently revised to $C_{17}H_{21}O_4N$ (25, 52). In 1892 a second alkaloid, scopolamine (52), with the formula $C_{17}H_{21}O_4N$, was isolated from *Scopolia atropoides* Bercht and Presl. However, the conversion of hyoscine and scopolamine to the same hydrobromide (25) established that they were one and the same base.

Datura Metel, in which *l*-scopolamine is the chief alkaloid constituent, is used in the technical manufacture of this alkaloid (240). The finely powdered meal is moistened with 10% aqueous potassium hydroxide solution and is extracted with ether. The purified extract is converted to the hydrobromide and crystallized from a mixture of ethanol and acetone. The pure hydrobromide, upon conversion to the free base, gives a crystalline monohydrate from ether; the anhydrous base is a sirup.

The *l*-scopolamine molecule contains a hydroxyl group because a monoacetate (52, 232) and a monobenzoate (54) can be prepared. The basic nitrogen of this alkaloid must be tertiary since it is recovered unchanged from the action of sodium nitrite upon its hydrochloride and since it reacts with but one mole of methyl iodide in the formation of the

methiodide (54, 232). The basicity of *l*-scopolamine is much weaker than that of *l*-hyoscyamine, but if this is excepted there is a striking similarity in the chemical as well as the color reactions of these two bases. With aqueous silver oxide *l*-scopolamine is racemized to an inactive scopolamine (*i*-scopolamine, m.p. 56–56.5°) (54), while with alcoholic sodium hydroxide, atroscine (m.p. 38–40°) is formed from hyoscine (25, 59, 232). The characterization of these two inactive racemates as the mono- and dihydrates of the same base (owing to the different temperatures at which they were crystallized (59, 235)) and their reported interconversion (59, 232, 234, 235) removed the last difference between *l*-hyoscine and *l*-scopolamine. That these were hydrates of *dl*-scopolamine was demonstrated by the resolution of their *d*-α-bromo-π-camphosulfonates to *d*- and *l*-scopolamine (212, 214).

When *l*-scopolamine (*l*-hyoscine) is warmed with barium hydroxide (52, 56, 232), dilute alkalies (232), or acids (60, 212) it is hydrolyzed to tropic acid and a new base ($C_8H_{13}O_2N$), scopoline (oscine). Depending on the conditions of the experiment, the tropic acid recovered may be either the pure *l*-form or the partially racemized acid, or may even be dehydrated to atropic acid (52, 64, 232). The scopoline isolated from these experiments is invariably optically inactive (212). By analogy with *l*-hyoscyamine, *l*-scopolamine would appear to be a base (scopoline) in which the alcoholic

$$(1)\quad \underset{\text{Scopolamine}}{C_{17}H_{21}O_4N} + H_2O \longrightarrow \underset{\text{Scopoline}}{C_8H_{13}O_2N} + \underset{\text{Tropic acid}}{C_9H_{10}O_3}$$

$$(2)\quad C_9H_{10}O_3 \longrightarrow \underset{\text{Atropic acid}}{C_9H_8O_2} + H_2O$$

hydroxyl is esterified with a tropic acid residue and, hence, might be called *l*-tropylscopoleine. In agreement with expectation aposcopolamine (apohyoscine) (253) is the product of dehydration (H_2SO_4) of *l*-scopolamine. The same result may be attained by replacement of the hydroxyl group of

$$C_{17}H_{21}O_4N \xrightarrow{H_2SO_4} C_{17}H_{19}O_3N + H_2O$$

the tropic acid residue by chlorine (thionyl chloride), followed by elimination of hydrogen chloride (214). This unsaturated base is optically inactive and all attempts at resolution have failed. The catalytic reduction (platinum black) of this new center of unsaturation converted aposcopolamine to desoxyscopolamine (172). The amine oxide of *l*-scopolamine, like that of *l*-hyoscyamine, reacted vigorously with acetic anhydride with the formation of an *O,N*-diacetyl derivative of *l*-norscopolamine (182). The *O*-acetyl radical is cleaved by hydrochloric acid, whereas normal alcoholic potassium hydroxide causes a fission of the tropic ester linkage as well.

The analogy of *l*-scopolamine with *l*-hyoscyamine is not complete, failing in several instances:

(1) Tropylscopoleine prepared from tropic anhydride and scopoline, although not well characterized, does not appear to be identical with scopolamine (57).

(2) Two desoxytropylscopoleines (172) have been prepared (scopoline hydrobromide + desoxytropyl bromide) but the properties of neither one correspond with those of desoxyscopolamine.

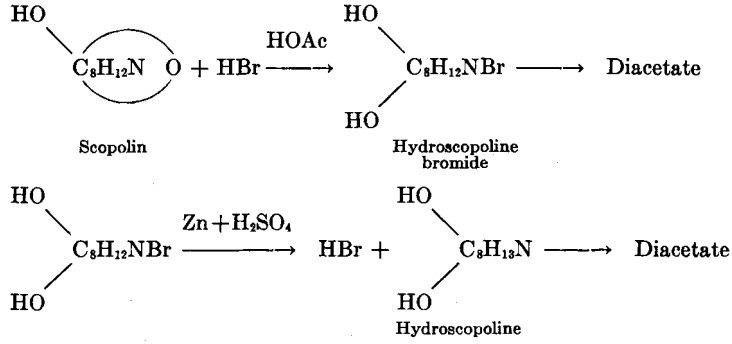
1. Scopoline (Oscine)

The structural features of the optically inactive scopoline from the hydrolysis of scopolamine are not as clearly defined as those of tropine. The hydrolysis of scopolamine and the isolation of scopoline was first reported in 1881. Early analyses indicated a formula isomeric with that of tropine ($C_8H_{15}ON$) (20), which was later revised to $C_8H_{15}O_2N$, and was finally corrected to $C_8H_{13}O_2N$ (25).

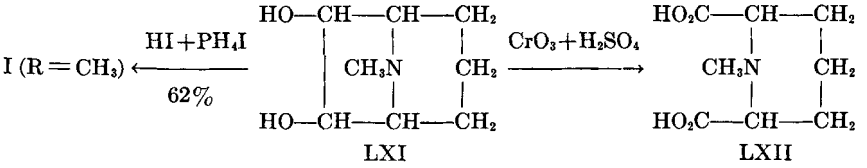
This hydramine is saturated towards bromine (64) and the tertiary amine (methiodide) liberates one mole of methyl iodide in a Herzig-Meyer determination. The grouping $\diagdown N\text{–}CH_3$ is present in both scopoline and scopolamine. One of the oxygen atoms of scopoline is present in a hydroxyl group which readily takes part in ester formation (monoacetate (172), monobenzoate (207)) or may be replaced by bromine (PBr_5) (70). However, scopoline was not oxidized to a ketone by chromic acid (64) under the conditions used for the preparation of tropinone, but, like barium permanganate (56), this reagent oxidized the $\diagdown N\text{–}CH_3$ group to carbon dioxide. Norscopoline (scopoligenine) is also obtained from *O,N*-diacetylnorscopolamine by a series of hydrolyses in acid and alkali (182). Norscopoline forms a crystalline nitrosamine (56), and its conversion to scopoline (CH_2O) (56, 162, 165) and scopoline methiodide (CH_3I) (56) is but confirmatory evidence for the $\diagdown N\text{–}CH_3$ of scopoline.

The nature of the second oxygen in scopoline is not as well defined. The substitution of bromine for hydrogen in scopoline suggested that the second oxygen of this base is a carbonyl oxygen; however, scopoline failed to form an oxime or a phenylhydrazone, nor did it condense with benzaldehyde (64). To remove any influence owing to its proximity to the carbonyl, the hydroxyl was replaced by bromine and the halogen in turn reductively eliminated. Desoxyscopoline, like scopoline, failed to react with carbonyl reagents (70). The passivity of scopoline to carbonyl reagents and its reaction with the halogen acids suggested the presence of an ether linkage in this base. The elements of hydrogen bromide (hydrogen iodide works equally well) add to scopoline in the formation of hydroscopoline

bromide. This was interpreted as the cleavage of a cyclic ether, because after the removal of the bromine atom with zinc and sulfuric acid (64, 162) or by catalytic reduction (71), the hydroscopoline, like hydroscopoline bromide, formed a diacetate. That no other alteration in the scopoline molecule had occurred during the cleavage of the ether was confirmed by the regeneration of scopoline from hydroscopoline bromide by dilute hydrochloric acid at 100° (64). The conversion of scopoline to hydroscopoline may be represented as follows:

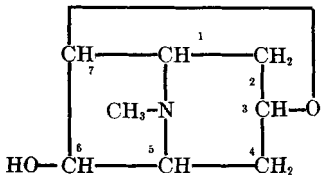


The bromine-free hydroscopoline (like dihydroxytropane) is readily oxidized by chromic acid to scopolic acid or 1-methylpiperidine-2,6-dicarboxylic acid (65, 68) which has since been synthesized (65, 161, 163). The oxidation of the dihydroxy compound, hydroscopoline, to a hydroxyl-free piperidine derivative would suggest (1) that there is a piperidine nucleus (also that pyridine is formed by the zinc dust distillation of norscopoline (64)) in hydroscopoline (and hence in scopoline) and (2) that the hydroxyls of hydroscopoline are not attached to the piperidine nucleus of this base. The close relationship of scopoline to tropine was first established by the reduction (hydriodic acid and phosphonium iodide at 200°) of hydroscopoline to tropane (167). Dihydroscopoline must be a dihydroxytropane with the hydroxyls, of necessity, located in the pyrrolidine nucleus to account for its oxidation to scopolic acid (LXI → LXII).

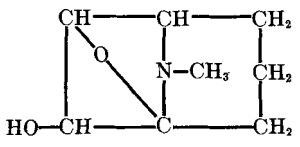


It appears that the hydroxyl of scopoline is attached to C_6 and that the other oxygen, at least in part, is attached to C_7. Positions C_3 (LXIIIA) and C_5 (LXIIIB) (based on results of exhaustive methylation) have been

considered for the other end of the ether bridge. Structures LXIIIA and LXIIIB imply that scopoline is an asymmetric molecule and should be



LXIIIA



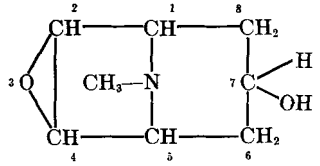
LXIIIB

resolvable — an assumption that was validated by the resolution of benzoyloscine through its *d*-bromocamphorsulfonate (207, 212), and later by the resolution of the base itself through its *d*-tartrate (212). Structures LXIIIA and LXIIIB both adequately account for the two hydroxyls of hydroscopoline bromide at C_6 and C_7; however, if the two hydroxyls are *cis* then the hydroscopoline bromide molecule derived from LXIIIA would no longer be asymmetric. The hydroscopoline bromide from *l*-scopoline was optically inactive. The isolation of an optically active hydroxyhydroscopoline (I, R = CH_3, R′ = R‴ = R^{IV} = OH) by rupture of the oxide bridge of *l*-scopoline with chlorosulfonic acid (71) can only be explained by this formula on the assumption that a Walden inversion occurs (the hydroxyls at C_6 and C_7 are *trans*). These observations are diametrically opposed to the previous conclusion that the basic residue in scopolamine is devoid of any center of asymmetry. Scopoline cannot be the primary product in the hydrolysis of scopolamine.

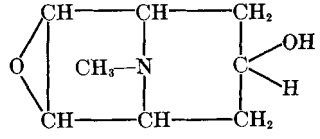
Failure to isolate a halogenated scopolic acid from the oxidation of hydroscopoline chloride has prompted some workers to conclude that the chlorine of hydroscopoline chloride, and hence the ether bridge of scopoline, cannot be attached to C_2, C_3, or C_4 (170). This, combined with exhaustive methylation studies, favored a C_5–C_7 ether bridge (LXIIIB).

2. Scopine and Pseudoscopine

The conclusion that scopoline is not the primary hydrolysis product of *l*-scopolamine proved to be well founded in that its hydrolysis by a



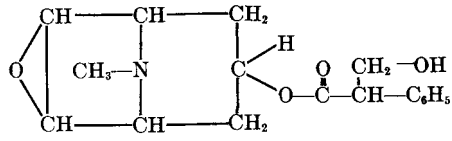
LXIV



LXV

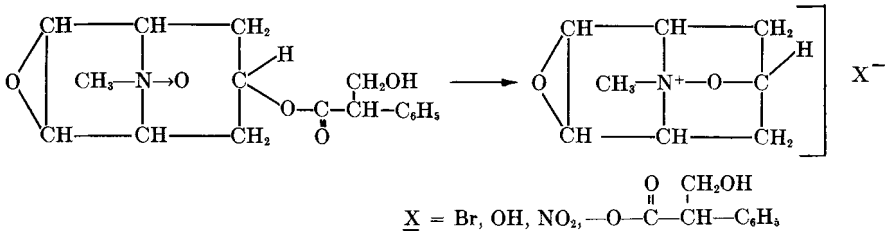
buffered solution (ammonia-ammonium chloride) of pancreatic lipase (174) led to *l*-tropic acid and the optically inactive base, scopine ($C_8H_{13}O_2N$)

(LXIV). Scopine is readily converted by either acid or base to scopoline (174). Hence *l*-scopolamine must be *l*-tropylscopeine (LXVI).



LXVI

Pseudoscopine (LXV), the analog of pseudotropine, is derived from *l*-scopolamine by a novel reaction. The quaternary salt, scopinium tropate, (LXVIII, X = $O-\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_2OH}{|}}{CH}-C_6H_5$), was formed in 20% yield as well as the amine oxide when *l*-scopolamine reacted with hydrogen peroxide (183, 190) and was isolated as the bromide, X = Br. Moist silver oxide liberated a



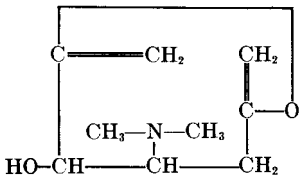
LXVII LXVIII

strong base which was soluble in water and insoluble in ether and which decomposed rapidly on heating. Pseudoscopine is formed by the reduction of scopinium bromide with either sodium amalgam or zinc and hydrochloric acid (183, 190). The ease of isomerization of scopine to scopoline has precluded any attempt to convert this base to pseudoscopine, but the stability of the pseudobase to boiling sodium amylate (183) would suggest that it is the stable isomer. Also, pseudoscopine may be converted to scopoline by sulfuric-acetic acid mixture, but only at a temperature of 150–160° (185). The conversion of pseudoscopine to norpseudoscopine ($KMnO_4$, or Ac_2O on the amine oxide) (185) proceeds quite normally, but *m*-hydroxybenzaldehyde is obtained by chromic acid oxidation (185). Finally, pseudoscopolamine resulted when acetyltropyl chloride reacted with pseudoscopine and the intermediate acetate was hydrolyzed with hydrochloric acid (185).

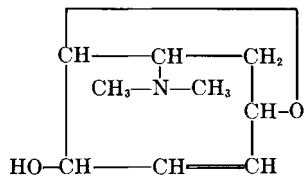
3. Exhaustive Methylation of Scopoline

The results of exhaustive methylation have not been as fruitful in the elucidation of the structure of scopoline as was the case for tropine.

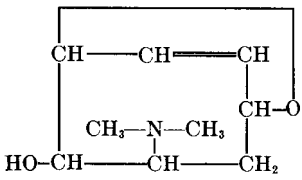
Attempts to get an insight into the position of the oxide bridge by degradation of scopoline to a nitrogen-free ring system failed due to a series of anomalous reactions. Rigorous control of the experimental conditions must be observed during the degradation of scopoline methohydroxide or rupture of the carbocyclic ring (with introduction of a second double bond[6]) will accompany the normal process (170). The pseudodesmethylscopoline (LXIX) absorbed two moles of hydrogen in the presence of colloidal plati-



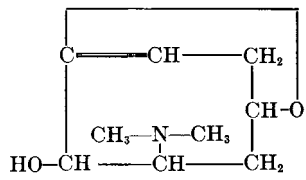
LXIX



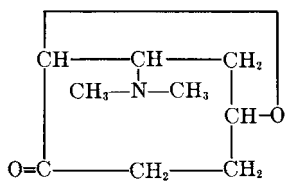
LXX



LXXI



LXXII

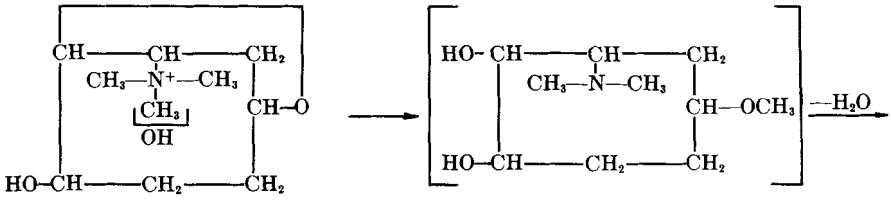


LXXIII

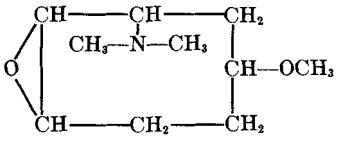
num to give a saturated base. From the controlled degradation of scopoline methohydroxide (172) α-, β- and γ-desmethylscopoline (LXX, LXXI, LXXII) and desmethylscopolinone (LXXIII) accounted for 90% of the material, while scopoline was regenerated to the extent of 10%.

The Hofmann degradation of dihydro-α-desmethylscopoline methohydroxide (LXXIV) provided only a limited amount of a nitrogen-free product. Loss of methyl alcohol from the methohydroxide accompanied by methanolysis of the ether bridge (LXXV) and dehydration of the glycol (LXXVI) were the predominant reactions.

[6] This was used for a time as evidence for a C_5–C_7 ether bridge in scopoline.



LXXIV LXXV



LXXVI

The relation of the various transformation products of scopolamine to each other is summarized schematically in Chart V.

VI. Dioscorine

Dioscorine, $C_{13}H_{19}O_2N$ (188, 248), has been isolated from the tubers ("gadoeng") of *Dioscorea hirsuta* Blume (241) and from the same organ ("nami") of *Dioscorea hispida* Dennst. which are indigenous to Batavia and the Tagalog provinces of the Philippines. Gadoeng and nami are used by the natives as a foodstuff after removal of the poisonous principle.

1. Isolation

The alkaloid or poisonous principle was isolated from the powdered and dried tubers by extraction with 96% ethanol that contained some acetic acid (40). The sirupy residue, after removal of the solvent, was agitated with aqueous sodium carbonate solution and the base extracted with chloroform. Crystallization of the base proved difficult but its purification as hydrobromide by fractional crystallization proved satisfactory. The alkaloid recovered represents 0.21% of the weight of the dried tubers (0.04% of the fresh tubers). It is a low melting solid and is sufficiently basic to liberate ammonia from its salts.

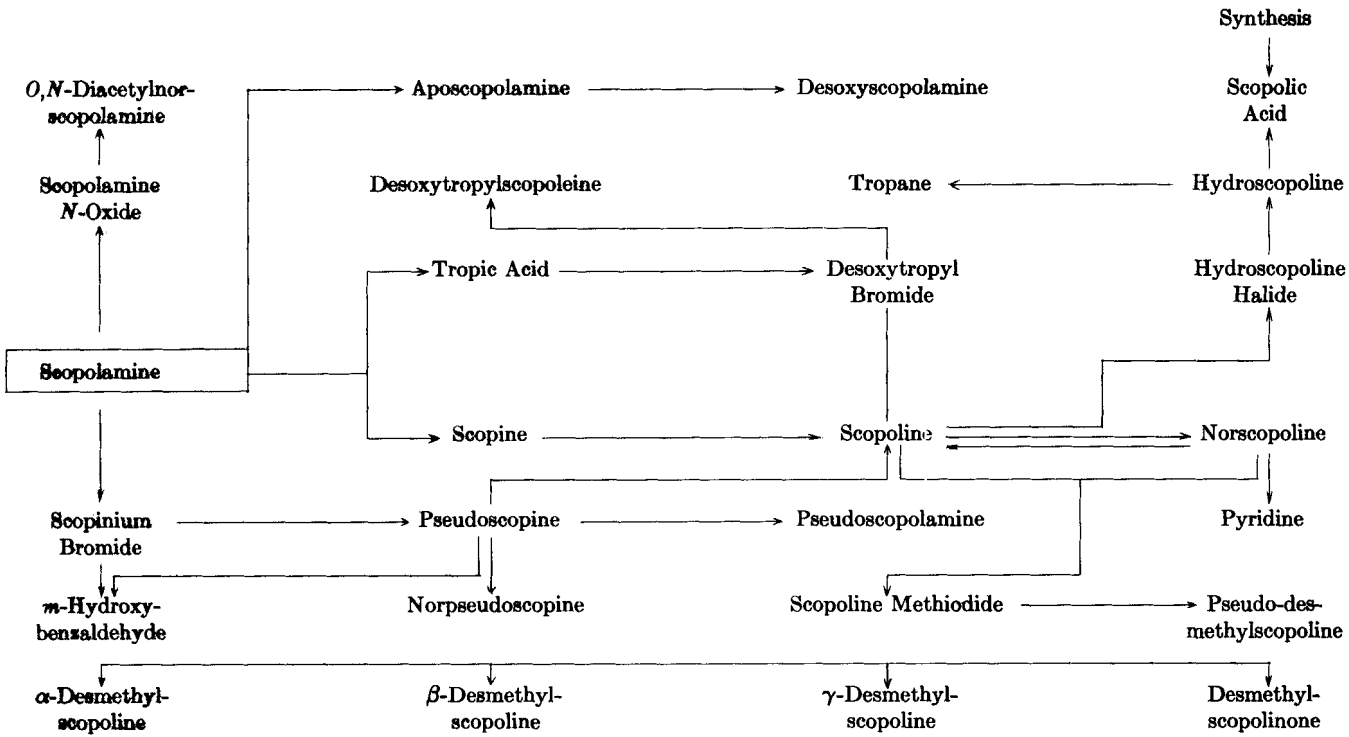
2. Lactone Ring Structure

Dioscorine, like tropine, shows a mydriatic activity when injected into monkeys. Other physiological properties are similar to, but weaker than, those of picrotoxin and in some instances they reflect those of the cardiac glycosides (vagal excitation, etc.).

Diagnostic reactions (40) that have been applied to dioscorine show the absence of methoxyl groups (Zeisel) and hydroxyl groups as well as

CHART V

TRANSFORMATION PRODUCTS OF SCOPOLAMINE



primary and secondary amines (failure to react with acetic anhydride). The tertiary $\diagdown\!\!\diagup N\text{–}CH_3$ grouping present in the alkaloid is a component of a ring system, only one mole of methyl iodide being required for methiodide formation while two Hofmann degradations were required to eliminate the nitrogen as trimethylamine (40). A lactone is also present for, although the base can be recovered by chloroform extraction directly after mixing with aqueous potassium hydroxide solution, it cannot be extracted after the mixture has stood for 24 hours or has been gently warmed for a short time. The original base is regenerated by gently warming the acidified (HCl) solution. Further evidence for a lactone in dioscorine may be drawn from the isolation of the lactone of *o*-hydroxyphenylacetic acid from its pyrolysis (200°) with potassium hydroxide.

Like tigloidine, dioscorine contains one double bond which instantly decolorizes potassium permanganate in acid solution. This double bond appears to be associated with the lactone ring for, like the cardiac aglycones, it gives a positive Legal test (alkaline sodium nitroprusside). The reduction by sodium amalgam of dioscorine ($C_{13}H_{19}O_2N$) to the dimeric hydrobidioscorine ($C_{13}H_{20}O_2N)_2$ also suggests the presence of an α,β-unsaturated lactone.

3. Exhaustive Methylation

The evidence so far has dealt solely with the nature of the lactone but has cast no light on the nature of the basic nucleus of this alkaloid. The experimental evidence necessary for complete elucidation of the structure of dioscorine is far from complete, yet the results of exhaustive methylation are sufficient to set up a working formula. Carbon dioxide as well as water is lost when dioscorine methohydroxide is distilled (dry) in vacuum with the formation of the triply unsaturated, oily base, methyldioscoridine (248). Methyldioscoridine no longer exhibits lactonic properties and molecular refraction measurements indicate that the three double bonds are

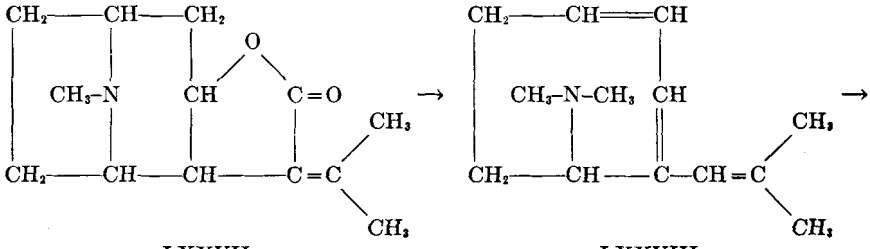
$$\underset{\substack{\text{Dioscorine}\\\text{methohydroxide}}}{[C_{13}H_{19}O_2N\text{—}CH_3]^+OH} \longrightarrow \underset{\substack{\text{Methyl-}\\\text{dioscoridine}}}{C_{13}H_{21}N} + CO_2 + H_2O$$

conjugated. A second exhaustive methylation removed the basic nitrogen as trimethylamine with the formation of a highly unsaturated and liquid C_{11}-hydrocarbon which rapidly polymerized to a white solid. Hydrogen bromide isomerized an acetic acid solution of this hydrocarbon to a methyl-

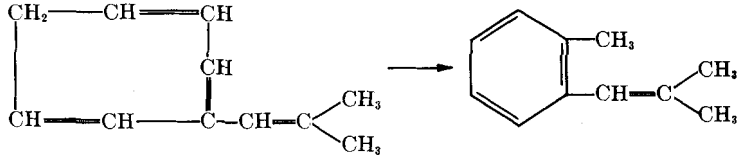
$$\underset{\substack{\text{Methyldioscoridine}\\\text{methohydroxide}}}{[C_{13}H_{21}N\text{—}CH_3]^+OH} \longrightarrow C_{11}H_{14} + (CH_3)_3N + H_2O$$

benzene with an ortho situated unsaturated C_4-side chain which is oxidized to *o*-toluic acid by dilute permanganate. This, combined with oxidation

experiments on dioscorine itself, suggests the presence of the grouping $CH_3 \diagdown C = CH-$ (XC) in the isomerized hydrocarbon. The methyl group $CH_3 \diagup$ is considered to result from a ring contraction of isobutenylcycloheptatriene during the isomerization with hydrogen bromide — a ring contraction which finds an analogy in some reactions of colchicine. Although no attempt has been made to determine which of the four possible isobutenylcycloheptatrienes is formed in this reaction, it is possible to set up a tentative formula (LXXVII) for dioscorine. The conversion of dioscorine to isobutenylcycloheptatriene through the intermediate methyldioscoridine (LXXVIII) finds expression in the reaction sequence LXXVII to LXXIX. As in the cardiac aglycones the physiological activity of dioscorine is intimately associated with the unsaturated lactone grouping because reduction of the double bond or hydrolysis of the lactone ring destroys the activity.



LXXVII LXXVIII



LXXIX XC

VII. Minor Alkaloids

A number of alkaloids occur in small amounts associated with *l*-hyoscyamine, *l*-scopolamine and *l*-cocaine which find no place in the previous narrative and, although some of them are not tropane derivatives, they will be briefly mentioned in alphabetical order.

(1) *Bellaradine* ($C_7H_{13}ON$) (225), an oily base isomeric with nortropine, is present to the extent of 0.008% along with *l*-hyoscyamine, *l*-scopolamine, and tropine in Bulgarian belladonna root. Its strong basic properties were employed in its separation from this mixture of alkaloids. It forms a crystalline and weakly *levo*rotatory hydrochloride which, like tropinone and

nortropinone hydrochlorides, liberates metallic gold from its chloride. The positive Runge test for the pyrolyzed (zinc dust) base combined with its reduction of gold chloride suggest that a ketone carbonyl is associated with a pyrrolidine nucleus. In anticipation of its close relationship to nortropine, 2-acetyl-1-methylpyrrolidine was synthesized (226) and shown to be different from bellaradine.

(2) *Convolvicine* ($C_{10}H_{16}N_2$) and *Convolvidine* ($C_{32}H_{42}O_8N_2$ or $C_{33}H_{44}O_8N_2$) occur in limited quantities in *Convolvulus pseudocantabrica* Schrenk associated with convolvine and convolamine (178).

Convolvidine is recovered from crude convolvine by fractional crystallization from petroleum ether. The base has a characteristically high melting point. Veratric acid has been identified as the acid resulting from the saponification (methanolic KOH) of convolvidine but the hydramine has not, as yet, been identified.

Convolvicine, as its hydrochloride, is recovered from the mother liquors from the isolation of convolvine and convolamine. When liberated from its salt it is an oily base which turns yellow on standing. By titration it appears to be a monoacidic base but it forms a dipicrate.

(3) *Cuscohygrine* ($C_{13}H_{24}ON_2$) and *hygrine* ($C_8H_{15}ON$) are minor alkaloids in various species of the Erythroxylaceae. Since these alkaloids have been characterized respectively as bis-2-(1-methylpyrrolidyl)-propanone and 2-(1-methylpyrrolidyl)-propanone they have been discussed in detail under the pyrrolidine alkaloids.

(4) *Bis-1,4-dimethylaminobutane* ($C_8H_{20}N_2$), an optically inactive liquid base, has been isolated from *Hyoscyamus muticus* (157) and occurs to the extent of 0.95% in the root of *Hyoscyamus reticulatus* L. (74). It is volatile in steam and is miscible in all proportions with water, alcohol and ether. It does not decolorize permanganate in acid solution. By the Hofmann degradation (moist Ag_2O) of the crystalline dimethiodide two moles of trimethylamine (characterized as the aurichloride) and one mole of butadiene (characterized as its tetrabromide) were formed.

The alkaloid has been synthesized from the dioxime of succinic dialdehyde. The steps involved in the synthesis were (a) reduction (Na + C_2H_5OH) of the dioxime to putrescine, (b) conversion of putrescine to the dimethochloride of the alkaloid, and (c) pyrrolysis of the dimethochloride.

Large doses of the hydrochloride of the alkaloid have proved to be nonpoisonous to dogs.

(5) *Mandragorine.* The first alkaloid to appear under this name was a resin isolated from *Mandragora officinarum* L. in 1889 (107) and was considered to be isomeric with atropine. A re-examination of the aurichloride of the so-called alkaloid demonstrated that it could be resolved into the aurichlorides of *l*-hyoscyamine, *l*-scopolamine, and a minute quantity

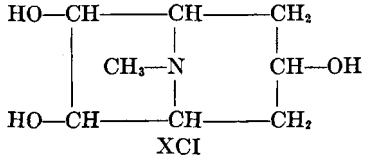
of the aurichloride of a third alkaloid thought to be $C_{15}H_{19}O_2N$ (150, 231). This C_{15}-alkaloid is mandragorine.

(6) *Meteloidine* ($C_{13}H_{21}O_4N$) (203), occurs to the extent of 0.07% along with *l*-scopolamine and atropine in *Datura meteloides*. This alkaloid is optically inactive and resisted all attempts at resolution (212). It is a tiglyl ester of an alkamine, teloidine, and its saponification ($Ba(OH)_2$) may be conveniently expressed as follows:

$$\underset{\text{Meteloidine}}{C_{13}H_{21}O_4N} + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Teloidine}}{C_8H_{15}O_3N} + \underset{\text{Tiglic acid}}{C_5H_8O_2}$$

The limited quantities of teloidine so far available have precluded an investigation of its structure. However, from the marked similarity of its chemical reactions with those of tropine and oscine and from the association of meteloidine with atropine and *l*-scopolamine in *Datura meteloides*, teloidine was considered to be one of the stereoisomers of the trihydroxytropane, XCI. This has been confirmed by synthesis. Teloidinone, the C_3-ketone of teloidine, has been synthesized (3) (*meso*tartaric aldehyde, methylamine, and acetonedicarboxylic acid) under physiological conditions. Teloidine and an isomer were formed in the reduction of this ketone.

Meteloidine shows no marked physiological activity.



XCI

(7) *l-Methylpyrrolidine*, *l-methylpyrroline*, and *pyridine* have been isolated in small amounts from the large-scale preparation of *l*-hyoscyamine (225).

(8) *Valeroidine* ($C_{13}H_{23}O_3N$) (222), has been isolated from the leaves, twigs, and berries of *Duboisia myoporoides* grown in various parts of Australia. It is usually found associated with tigloidine, poroidine, and isoporoidine from which it is separated as its insoluble hydrobromide. Tigloidine can be distinguished from valeroidine by its normal behavior with Mayer's reagent ($HgCl_2$ + KI).

The base is *levo*rotatory; its hydrobromide is *dextro*rotatory. The products of the alkaline hydrolysis ($Ba(OH)_2$) of this ester have been identified as isovaleric acid and the dihydroxytropane which has previously been isolated from a mixture of hydrolyzed bases from Java coca (242).

The free hydroxyl of valeroidine has been converted to the acetic and isovaleric esters but attempts to replace it by a chlorine atom ($SOCl_2$) resulted only in the formation of norvaleroidine (224). This unexpected

result appears to afford the first instance of the demethylation of the $>N-CH_3$ grouping by thionyl chloride. With methyl iodide this demethylated product reverted to the methiodide of valeroidine. Another anomalous reaction of this alkaloid is its resistance to oxidation by permanganate or chromic acid.

All attempts to locate the two hydroxyls of the dihydroxytropane have failed.

VIII. Table of Physical Constants

The alkaloids and their transformation products are listed in alphabetical order in Table 2, while the derivatives have been listed in the order (a) quaternary ammonium salts, (b) *N*-alkyl derivatives, and (c) *O*- and *N*-acyl derivatives. The physical data quoted have been taken from the first or at most the first two references cited, the remaining references having been arranged in numerical order. An asterisk indicates that the value for the melting point or boiling point has been corrected.

TABLE 2

THE PHYSICAL CONSTANTS OF THE TROPANE ALKALOIDS AND THEIR DERIVATIVES

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
Anhydroecgonine	235 (dec)	..	Crystals (CH_3OH – ether)	92, 38, 73, 98
Aurichloride	192	..	Small needles	73,91,92,111
Chloroplatinate	233–235	..	Reddish-yellow prisms (H_2O – HCl)	156, 92
Hydrobromide	223 (dec)	..	Crystals (C_2H_5OH)	228, 92
Hydrochloride	241	..	White needles (C_2H_5OH)	92, 156
Mercurichloride	165	..	..	73
Methiodide (monohydrate)	207–208	..	Long prisms (H_2O)	100
Perbromide	154–155 (dec)	..	Orange crystals (HOAc)	92
Periodide	185–186	..	Violet leaves (HOAc)	92, 195
Ethyl ester	130–132/11mm.	−51.55°	Oil, $d_4^{21} = 1.064$	156,29,73,92
Aurichloride	124	..	Citron-yellow crystals	156, 195
Chloroplatinate	217	..	Yellow prisms (H_2O)	156, 92
Hydrochloride	243–244	..	White needles (C_2H_5OH)	92, 73, 156

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methaurichloride	167	..	Sulfur-yellow crystals (H_2O)	122
Methiodide	177	..	Small leaves (C_2H_5OH)	122
Methochloroplatinate	218	..	Reddish-yellow crystals	122
Picrate	168	..	Yellow leaflets	156
Methyl ester	107/7 mm.	−47.2° (C_2H_5OH)	Hygroscopic sirup, $d_{24}^{24} = 1.0921$	195, 228
Aurichloride	152–153	..	Yellow microcrystals (acetone)	195
Hydrobromide	147	..	..	228
Methiodide	195–196	..	Yellow needles or prisms (C_2H_5OH)	100
Dibromide-hydrobromide	187–188 (dec)	..	Monoclinic prisms (C_2H_5OH – HOAc)	117
Perbromide	145 (dec)	..	Red prisms (HOAc)	117
Hydrochloride	173–174 (dec)	..	Monoclinic prisms (H_2O)	117, 92
Hydrochloride hydrate	169–170 (dec)	..	Tetragonal octahedra	117
Apoatropine (Atropamine)	62	..	Crystals (ether)	158,23,25,27, 51, 53, 54
Aurichloride	110–112	..	Fine yellow needles (H_2O)	27,22,23,25, 51, 53, 54
Chloroplatinate	212–214	..	Yellow glistening scales (H_2O)	51,23,25,27, 53, 158
Chromate	..	..	Golden-yellow leaflets (H_2O – HCl)	51
Hydriodide	..	..	Small white needles (H_2O)	51, 23
Hydrobromide	230–231	0°	Needles	51, 23, 53, 54
Hydrochloride	237–239	0° (H_2O)	White leaflets (H_2O)	158,23,25,27, 51, 53, 54
Mercurichloride	115 (sinter)	..	..	51, 23
Nitrate	..	..	Colorless leaflets	23
N-Oxide	127–128	..	Crystals(C_2H_5OH – acetone)	181
Hydrochloride	205	..	Crystals (C_2H_5OH)	181, 189
Salicylate	155	..	..	181, 189
Picrate	166–168	..	Yellow needles(H_2O)	51, 23, 53
Sulfate	..	..	Leaflets (C_2H_5OH)	23
Apohyoscine (see Aposcopolamine)				
Aposcopolamine (Apohyoscine)	*79–80	0° (C_2H_5OH)	Rhomboidal plates (pet. ether)	214, 253

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Aurichloride	178–179	..	Amorphous	54, 214
d-Camphor-*β*-sulfonate	*160.5–161.5	+9.76° (H_2O)	Leaflets (C_2H_5OH)	214
Hydrochloride	..	0° (H_2O)	Stout needles(ether)	214
d-Hydrogen tartrate	95–97	+8.59° (H_2O)	White needles (H_2O)	214
Methiodide	238 (dec)	..	Dense prisms (C_2H_5OH)	253
Nitrate	157 (dec)	..	Pearly leaflets	253, 214
Picrate	217–218	..	..	214, 253
Atropamine (see Apoatropine)				
Atropic acid	106.5	..	Rhombic plates (H_2O)	14, 12, 19, 20, 23, 45, 52, 54, 82, 83, 213
Atropine	116–117	0°	Long spears ($C_2H_5OH - H_2O$)	1, 8, 9, 20, 22, 25, 28, 45, 53, 91, 158, 187
Auribromide	*120	..	Chocolate colored prisms($H_2O - HCl$)	1, 197, 205
Aurichloride	137–139	..	Yellow crystals (H_2O)	1, 8, 20, 25, 25, 28, 42, 48, 50, 53, 96, 158, 205, 209, 243, 246
Chloroplatinate	207–208	..	Monoclinic crystals	23, 8, 53
Ethiodide	..	..	..	16
Hydrobromide	162	0°	Colorless needles (C_2H_5OH)	28
Hydrobromide gold salt	*144	..	Reddish-brown scales ($H_2O - HCl$)	197
Hydrochloride	165	..	Crystalline	28, 1, 8
Methaurichloride	..	..	Orange rhombic plates (H_2O)	16
Nitrate	..	..	Crystalline	8
Oxalate	196–197	..	Prisms (acetone-ether)	1, 25, 28, 209
N-Oxide	127–128	..	Hygroscopic powder (acetone-ether)	181, 189
Hydrochloride	192–193	..	White prisms (C_2H_5OH)	181, 189
Picrate	175–176	..	Rectangular plates	1, 53, 205, 209

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Sulfate	194	..	Needles	1, 8, 22, 158, 238
Acetyl-	..	..	Oil	158
Benzoyl-				
aurichloride	135	..	Leaflets ($C_2H_5OH - H_2O$)	54
chloroplatinate	215 (dec)	..	Red amorphous ppt.	54
Sulfuric ester	238–239	..	Colorless prisms (H_2O)	253
Atroscine (*i*-Scopolamine dihydrate)	*38–40	0° (C_2H_5OH)	Chisel-shaped prisms ($C_2H_5OH - H_2O$)	28, 59, 133, 212, 232
		B		
Belladonnine	*129	0°	Cubes (ethyl acetate)	78, 88
Aurichloride	120 (ca.)	..	Yellow powder	23, 27, 53, 78, 186
Chloroplatinate	..	..	Amorphous solid	78, 23, 27, 53, 88, 186
Hydrochloride	195–196	..	Spearlike crystals (C_2H_5OH – ether)	78, 23
Bellaradine	..	..	Oil	225
Aurichloride	189 (ca.)	..	..	225
Chloroplatinate	..	..	Oil	225
Hydrochloride	..	−0.04°	Hygroscopic needles (H_2O)	225
Mercurichloride	..	..	Oil	225
Methiodide	253	..	Clusters of crystals (CH_3OH)	225
Methopicrate	228 (dec)	..	Long orange needles (H_2O)	225
Picrate	224–225 (dec)	..	Small rods (H_2O)	225
8,9-Benz-$\Delta^{8,9}$-homogranatene-3-one	125	..	Six-sided plates ($C_2H_5OH - H_2O$)	220
Hydrobromide	235 (dec)	..	Oblique prisms (C_2H_5OH)	220
Picrate	204 (dec)	..	Yellow needles (ethoxy-ethyl acetate)	220
Bromoecgonine (lactone of-)	150 (froth)	..	Crystals (acetone)	117
Aurichloride	216	..	Long golden-yellow needles (H_2O)	117
Hydrochloride	203–204 (dec)	..	..	117
Trihydrate	197–198 (dec)	..	Octahedra (H_2O)	117

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
2-Bromopseudotropine				
Methiodide	238 (dec)	..	Plates or short prisms (H_2O)	32
Methobromide	237–238 (dec)	..	Four-sided plates (C_2H_5OH)	32, 148
2-Bromotropane				
Methiodide	262 (dec)	..	Prisms (C_2H_5OH)	31
Methobromide	296 (froth)	..	Prisms (C_2H_5OH)	31
	233 (dec)	..	Plates and needles (C_2H_5OH)	32
Methochloroplatinate	246–247 (dec)	..	Yellow-red crystals (H_2O)	31
3-Bromotropane	109–109.5/17.5 mm.	..	Oil, $d_4^{15} = 1.3682$	33
Aurichloride	157–158	..	Prisms (C_2H_5OH)	33
Chloroplatinate	210–211 (dec)	..	Bright red prisms (H_2O)	33
Hydrobromide	219–220 (dec)	..	Dense prisms (H_2O)	33
Methiodide	..	..	Dense prisms (H_2O)	33
6-Bromotropane				
Methobromide	>300	..	Prisms (C_2H_5OH)	31
Methochloroplatinate	250 (dec)	..	Reddish-yellow crystals (H_2O)	31
2-Bromotropine methiodide	233–234 (dec)	..	Prisms and needles (H_2O)	32
		C		
Chlorohydratropic acid	88–89	..	Glistening prisms (H_2O)	22, 84, 213
Chlorotropane (Bellatropine)	163–165/760 mm. (dec)	..	Colorless oil	186
Aurichloride	215	..	Golden-yellow flakes ($C_2H_5OH - H_2O$)	186, 27, 192a
Chloroplatinate	227–228	..	Yellow-orange needles ($C_2H_5OH - H_2O$)	186, 27, 192a
Hydrochloride	234	..	Colorless needles (H_2O)	192a, 27
Methiodide	305–306	..	..	186, 192a
N-Oxide	..	..	..	..
Hydrochloride	210	..	..	186, 192a
Picrate	174–175	..	..	186, 192a
Picrate	216–217	..	Long clear yellow needles	186, 192a

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
d-Chlorotropic acid	123–124	+12.6°(CH_3OH)	..	217
Morphine salt	..	..	Fine needles (CH_3OH)	217
dl-Chlorotropic acid	129–130	..	Crystals ($CHCl_3$)	217, 82
l-Chlorotropic acid	..	−12.4°(CH_3OH)	..	217
Cinnamylcocaine	121	−47°($CHCl_3$)	Rosettes, needles (pet. ether)	103, 77, 109
Aurichloride	156	..	Citron-yellow needles	103
Chloroplatinate	217	..	Fine needles	103
Chromate	..	..	Orange ppt.	103
Hydrochloride (*dihydrate*)	176	..	Shining flat needles (H_2O)	103
Mercurichloride	..	..	White ppt.	103
Picrate	..	..	Yellow resin	103
α-Cocaine	87–88	..	Four-sided prisms (pet. ether)	134
Aurichloride	222 (dec)	..	Golden leaves (CH_3OH)	134
Chloroplatinate	220 (dec)	..	Flesh-colored needles (H_2O)	134
Hydriodide (hydrate)	192 (dec)	..	Glistening needles (H_2O)	134
Hydrochloride	180 (dec)	..	Needles or prisms (amyl acetate)	134
Methiodide	220	..	Quadratic plates (CH_3OH)	134
Picrate	195	..	Golden-yellow prisms (CH_3OH)	134
Phosphomolybdate	..	..	Yellow flocculent ppt.	134
Tannate	..	..	White flocculent ppt.	134
d-Cocaine	98	+15.82° ($CHCl_3$)	Monoclinic prisms (ether)	38
l-Tartrate	112	+40.85° (H_2O)	..	38
dl-Cocaine	79–80	..	Rhombic prisms (pet. ether)	38
Hydrochloride	*187	..	Rhombic plates (C_2H_5OH)	38
Methiodide	*169	..	..	38
Nitrate	..	..	Oil	38
l-Cocaine	187–188/ 0.1 mm. 97–98	−16.15° ($CHCl_3$)	Prisms (C_2H_5OH)	10, 15, 38, 90, 101, 102

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Aurichloride	..	..	Bright yellow ppt.	15
Chloroplatinate	..	..	Rhombic leaflets (H_2O–HCl)	15
Hydrochloride	200–202	−71.95° (H_2O)	Prisms (C_2H_5OH)	15, 38
Hydrogen oxalate	..	..	Feathery crystals (C_2H_5OH)	15
Mercurichloride	..	..	Flocculent ppt.	15
Methiodide	164	..	Glistening leaflets (C_2H_5OH)	100
Methochloride	152.5	..	Fine needles (C_2H_5OH–ether)	100
Nitrate (hydrate)	58–63	..	Delinquescent crystals	15
Phosphomolybdate	..	..	Yellow flocculent ppt.	15
Picrate	..	..	Yellow powder	15
d-Tartrate (hydrate)	114–115	−41.2° (H_2O)	Prisms (H_2O)	38
Open Cocaine	74–75	..	Crystals (pet.ether)	76
Chloroplatinate	162	..	Orange prisms	76
Cocaethyline (see Methylcocaine)				
Convolamine	114–115	0° (C_2H_5OH)	Dense prisms (pet. ether)	176, 178
Aurichloride	201–202	..	Reddish-yellow needles(H_2O–HCl)	176
Chloroplatinate	216–217	..	Orange prismatic needles(H_2O–HCl)	176
Hydrochloride	237–239	..	White crystals (C_2H_5OH)	176
Methiodide	275–276	..	Needles (H_2O)	176, 178
Picrate	263–264 (dec)	..	Yellow glistening leaflets (H_2O)	176
Convolvicine	250–260/760 mm.	..	Oil	178
Picrate	202	..	Needles (H_2O)	178
Convolvidine	192–193	Active	Needles (C_2H_5OH)	178
Hydrolysis product	274–276	..	Microcrystals (CH_3OH)	178
Picrate	229–231	..	Yellow powder	178
Convolvine	115	0°	Crystals (pet. ether)	75, 178
Aurichloride	217 (dec)	..	Yellow glistening leaflets	75
Chloroplatinate	240–241 (dec)	..	Yellow solid	75
Hydrochloride	260–261	..	Crystalline powder (C_2H_5OH)	75
Methiodide	230–231	..	Needles (H_2O)	75

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Nitrate	212–213	..	Crystals (C_2H_5OH)	178
Oxalate	265–266	..	Glistening leaflets (C_2H_5OH)	75
Picrate	261–263	..	Yellow needles	75
N-β-Hydroxyethyl	128–129	..	..	227
Hydrochloride	235–237	..	..	227
Picrate	212–214	..	..	227
Benzoate	131–133	..	..	227
Benzoate hydrochloride	>250	..	..	227
Benzoate picrate	214–216	..	..	227
Cycloheptadiene	*120–121/760 mm.	..	Oil, $d_4^0 = 0.8809$	29, 140, 148
Dibromide	123/15 mm.	..	Viscous oil	148
Cycloheptadiene-carboxylic Acid	74–75	..	Long needles (H_2O)	138
Tetrabromide	196–197	..	Leaflets (HCO_2H)	138
Cycloheptanecarboxylic Acid	32	..	..	144
Amide	195	..	Flat needles (C_2H_5OH)	144
α-Bromo-	93–94	..	Glistening needles (HCO_2H)	144
Cycloheptatriene (Tropilidene)	*116/724 mm.	..	Oil, $d_4^0 = 0.9082$	29, 22, 121, 148, 194
Dibromide	126/15 mm.	..	Oil	148
Hydrobromide	74–75/8 mm.	..	Oil, $d_4^{14} = 1.4003$	29, 148
Dihydrobromide	125–126/15 mm.	..	Oil	29
β-Cycloheptatriene Carboxylic Acid	45–50	..	..	34
δ-Cycloheptatriene-Carboxylic Acid	163.5/760 mm. 32	..	..	29
Cycloheptene	114–115/760 mm.	..	Oil	30
3-Bromo-	85/12 mm.	..	Oil	29
Δ^1-Cycloheptene-Carboxylic Acid	49–51	..	Glistening plates (C_2H_5OH–H_2O)	29, 144
Amide	134–135	..	Silky glistening plates (C_2H_5OH–H_2O)	144
Δ^2-Cycloheptene-carboxylic Acid				
Amide	158–159	..	..	29 148
Acid chloride	88–90/13 mm.	..	Colorless oil	29
Ethyl ester-	100/17 mm.	..	Oil, $d_4^{15} = 0.9929$	29
Hydrazide	137–139	..	Prisms (ethyl acetate)	29

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		D		
Daturine (mixture Hyoscyamine and Atropine)				200
Desoxyscopolamine	69	..	Fine needles (ether)	172
Chloroplatinate	220	..	Wartlike structures (H_2O–acetone)	172
Hydrobromide	182–183	..	Quadratic crystals (C_2H_5OH–ether)	172
Methiodide	219 (dec)	..	Rosettes, leaflets (C_2H_5OH)	172
Picrate	209–210	..	Lancelike leaflets (H_2O–acetone)	172
α-Desoxytropyl-scopoleine	66–67	..	Dense rhombohedra (ether)	172
Chloroplatinate	155–157	..	Wartlike structures (H_2O–acetone)	172
Hydrobromide	205	..	Groups of dense needles (C_2H_5OH)	172
Methiodide	195	..	Rods notched at both ends (C_2H_5OH)	172
Picrate	172	..	Quadratic leaflets (H_2O–acetone)	172
β-Desoxytropyl-scopoleine	63–64	..	Prisms with sloping ends (pet. ether)	172
Aurichloride	..	..	Oil	172
Chloroplatinate	215 (dec)	..	..	172
Hydrobromide	176–177	..	Groups of leaflets (C_2H_5OH)	172
Methiodide	183	..	Fine needles (C_2H_5OH)	172
Picrate	132	..	Small cubes (H_2O)	172
Dibromodihydro-tigloidine	*196 (dec)	..	Stout prisms (C_2H_5OH–H_2O)	222
1,2-Dibromo-3-dimethylamino-cycloheptane Chloroplatinate	174–175	..	Fine needles (C_2H_5OH)	29
2,3-Dibromo-3-dimethylamino-cycloheptane Aurichloride	175–176 (dec)	..	Aggregates — feathery crystals (H_2O)	29
Dibromo-(des)-methyltropine Hydrobromide	178 (dec)	..	Plates (H_2O)	32

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
3,5-Dibromopyridine	110.5	..	Prisms (C_2H_5OH)	22
Dihydrotigloidine	..	..	Sirup	222
Aurichloride	*151	..	Orange-yellow plates	222
Hydrobromide	*186–187	..	Stout prisms	222
Methiodide	*209	..	Microcrystalline powder	222
Picrate	*134.5	..	Plates	222
Dihydrobenzaldehyde	120–122/124 mm. 70–72/14 mm.	..	Oil	117, 128, 129
Oxime (2 isomers)	α- β-43–44	..	Oil	117
Phenylhydrazone	127–128	..	Yellow crystals (C_2H_5OH)	117
Dihydrobenzoic Acid	94–95	..	Feathery crystals (H_2O)	117
Dihydropiperylenedicarboxylic Acid	91	..	Aggregates of prisms	143
Dihydro-α-desmethylscopoline	120–126/13 mm. 53	..	Glistening needles (pet. ether)	172
Methiodide	209–210	..	Crystals (C_2H_5OH)	172
Picrate	183	..	Crystals (C_2H_5OH)	172
Benzoyl-Hydrochloride	219	..	Crystals (C_2H_5OH)	172
Dihydro-β-desmethylscopoline	128–131/13 mm. 78	..	Fine needles (pet. ether)	172
Methiodide	249	..	Right-angled leaflets (C_2H_5OH)	172
Picrate	153	..	Cubes (C_2H_5OH)	172
Dihydro-γ-desmethylscopoline	120–123/13 mm.	..	Oil	172
Methiodide	171	..	Crystals (C_2H_5OH)	172
Picrate	194	..	Lance-like crystals (C_2H_5OH-H_2O)	172
Dihydro-α-desmethylscopoline chloride	115–118/13 mm. 45	..	Crystals (pet. ether)	172
Picrate	228 (dec)	..	..	172
Dihydro-β-desmethylscopoline chloride	122–125/13 mm. 38–39	..	Crystals (pet. ether)	172
Dihydro-α-desmethylscopoline methyl ether	110–115/14 mm.	..	Oil	172
Methiodide	174–175	..	Crystals (C_2H_5OH)	172
Nitrogen-free degradation product	70–71/13 mm.	..	Oil with fruity odor	172

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydro-β-desmethyl-scopoline methyl ether	110–120/13 mm.	..	Oil	172
Methiodide	225.5	..	Glistening leaflets (C_2H_5OH)	172
Nitrogen-free degradation product	80/15 mm.	..	Oil	172
Dihydroscopoline	165	..	Long crystals ($CHCl_3$)	162, 167
Dihydroxytropane	*212	−25.0° (C_2H_5OH) −16.0°(H_2O)	Colorless tabular crystals(C_2H_5OH–ether)	222, 242
Hydrochloride	..	+1.75°(H_2O)	..	242
Picrate	253 (dec)	..	..	242
Diacetyl-hydrobromide	*219–220	..	Prisms (C_2H_5OH–ether)	224
Dibenzoyl-hydrochloride	205	+41.8° (C_2H_5OH)	..	242
Nitrate	197	..	..	242
Diisovaleryl-hydrobromide	*176–177	..	Prismatic needles (C_2H_5OH–ether)	224
(bis)-1,4-Dimethyl-aminobutane	*169/760 mm.	0°	Colorless oil	157, 74
Aurichloride	206–207 (dec)	..	Crystalline powder (H_2O)	74
Chloroplatinate	234 (dec)	..	Dense prisms (H_2O)	157, 74
Dihydrochloride	273 (froth)	..	Prisms (H_2O)	157
Dipicrate	198–200	..	Glistening scales (C_2H_5OH)	74, 157
Dimethylaminocyclo-heptadiene	66/10 mm.	..	Oil, $d_4^{14} = 0.9113$	30
Dimethylaminocyclo-heptane	*190/760 mm.	..	Oil, $d_4^{14} = 0.8680$	30
Chloroplatinate	190–193 (dec)	..	Orange-red leaflets or plates (H_2O)	30, 148
Hydrochloride	..	..	Right-angled plates (C_2H_5OH–ether)	30
Methiodide	260 (dec)	..	Colorless prisms (H_2O)	30, 148
1-Dimethylamino-cycloheptanol-4	*251/760 mm.	..	Colorless oil	32, 148

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Δ^2-Dimethylamino-cycloheptene	*188/760 mm.	..	Oil with piercing odor	148
Aurichloride	94–95	..	Plates	148
Chloroplatinate	177–178 (dec)	..	Prisms	148
Methiodide	162–163	..	Diamond-shaped plates	148
Picrate	162–163	..	Needles	148
Aurichloride of HCl addition product	94–96	..	Yellow leaves(H_2O–HCl)	29
Dimethylcocaine	92	−18.02° (CH_3OH)	Columns	230
Hydrochloride	193 (dec)	..	..	230
Dioscorine	43.5	..	Greenish-yellow platelets	188, 248
Aurichloride (hydrate)	171	..	Citron-yellow needles	188, 248
Chloroplatinate	199–200 (froth) (211)	..	Orange-yellow platelets	188, 248
Hydrobromide	213–214	..	White crystals (C_2H_5OH)	248
Hydrochloride (dihydrate)	204	+4.66°	Needles or diamond-shaped plates (C_2H_5OH)	188, 248
Methaurichloride	188	..	Yellow leaflets(H_2O)	248
Methiodide	213	..	Crystals	248
Methochloroplatinate	188 (dec)	..	Yellowish-orange crystals (H_2O)	248
Oxalate	69.5–70.5	..	White prisms	248
Picrate	184	..	Yellow needles	188, 248
Duboisine (see Hyoscyamine)	..	..	..	20
		E		
Ecgonidine (see Anhydroecgonine)				
α-Ecgonine (hydrate)	305 (dec)	..	Silky leaflets (H_2O)	134
Aurichloride (monohydrate)	183–184 (dec)	..	Amber-yellow prisms (H_2O)	134
Chloroplatinate (tetrahydrate)	223–224 (dec)	..	Orange-yellow prisms	134
Methaurichloride	212 (dec)	..	Glistening leaflets (C_2H_5OH)	134
Benzoyl-	209 (dec)	..	Plates (H_2O)	134
Methyl ester	114	..	Colorless prisms (acetone)	134

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Aurichloride	95–96	..	Orange-yellow glistening leaflets (H_2O)	134
Chloroplatinate	204 (dec)	..	Reddish-yellow rhombic plates (H_2O)	134
Methaurichloride	120	..	Yellow glistening leaflets or needles (CH_3OH)	134
Methiodide	201–202	..	Glistening needles (CH_3OH)	134
Picrate	189–191	..	Orange-yellow leaflets (H_2O) Yellow cubes (C_2H_5OH)	134
dl-Ecgonine	212	..	..	38
Trihydrate	93–118	..	..	38
Aurichloride	205	..	Crossed needles (H_2O)	38
Hydrochloride	247 (dec)	..	Plates (C_2H_5OH)	38
Methyl ester Hydrochloride	*195	..	Crystals (CH_3OH)	38
l-Ecgonine	205	−45.4°	Monoclinic prisms (C_2H_5OH)	98, 15
Aurichloride	202	..	Yellow prisms	15
Chloroplatinate	226	..	Red needles (H_2O–C_2H_5OH)	10, 15
Hydrochloride	246	−57.1°	Rhombs (C_2H_5OH)	98, 104
Phosphomolybdate	..	..	Whitish-yellow ppt.	15
Amide	198	..	Prisms (C_2H_5OH) Needles ($CHCl_3$)	123
Aurichloride	140–142	..	..	123
Aurichloride hydrate	70–80	..	Hair-fine needles (H_2O)	123
Chloroplatinate	239 (dec)	..	Orange needles (H_2O)	123
Hydriodide (hydrate)	245	..	Groups of leaflets (C_2H_5OH)	123
Hydrobromide (hydrate)	260 (dec)	..	Prisms (C_2H_5OH)	123
Hydrochloride	275 (dec)	..	Matted needles (C_2H_5OH)	123
Methiodide	203	..	Groups of needles (C_2H_5OH)	123
Picrate (monohydrate)	150	..	Needles (C_2H_5OH–H_2O)	123

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Benzoyl-	195 (dec)	−63.3°	Long prismatic crystals	101
Benzyl ester	..	..	Oil	216a
Benzyl ester aurichloride	*111	..	Glistening plates (CH_3OH)	216a
Benzyl ester chloroplatinate	*211	..	Minute needles (H_2O)	216a
Benzyl ester hydrochloride	*171	−18.62°(H_2O)	Six-sided leaflets (acetone)	216a
Benzyl ester hydrogen sulfate	*206–208	..	Rectangular plates (C_2H_5OH)	216a
Benzyl ester nitrate	*163 (dec)	..	Fine needles (acetone)	216a
Benzyl ester picrate	*80	..	Needles (C_2H_5OH)	216a
p-Nitrobenzyl ester	..	..	Oil	216a
p-Nitrobenzyl ester aurichloride	*154	..	Prisms (CH_3OH)	216a
p-Nitrobenzyl ester chloroplatinate	*210	..	Elongated plates (H_2O)	216a
p-Nitrobenzyl ester hydrochloride	*178.5	+17.98°(H_2O)	Minute leaflets (H_2O)	216a
p-Nitrobenzyl ester hydrogen sulfate	*195	..	Needles (C_2H_5OH)	216a
p-Nitrobenzyl ester nitrate	*187	..	Fine silky needles	216a
p-Nitrobenzyl ester picrate	*84	..	Fine needles (C_2H_5OH)	216a
α-Phenylethyl ester	..	..	Oil	216a
α-Phenylethyl ester aurichloride	*170	..	Plates (C_2H_5OH)	216a
β-Phenylethyl ester	*100	..	Rosettes of needles (ether)	216a
β-Phenylethyl ester chloroplatinate	*216	..	Six-sided plates (CH_3OH)	216a
β-Phenylethyl ester hydrochloride	*196	−39.2°(H_2O)	Elongated prisms (acetone)	216a
β-Phenylethyl ester picrate	*66	..	Granular solid	216a

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Cinnamyl-	216 (dec)	..	Needles (C_2H_5OH–ether)	103, 101
Aurichloride	..	..	Egg-yellow ppt. (H_2O)	103
Chloroplatinate	..	..	Yellow ppt. (H_2O)	103
2-Hydroxy-3-methyl-benzoyl-				
Benzyl ester	..	..	Oil	216a
Benzyl ester picrate	*67	..	Solid	216a
2-Hydroxy-4-methyl-benzoyl-				
Benzyl ester	..	..	Oil	216a
Benzyl ester picrate	*70	..	Granular solid	216a
δ-Isatropyl-	202 (dec)	..	Colorless needles (C_2H_5OH)	106
Aurichloride	..	..	Yellow amorphous ppt.	106
Picrate	..	..	Yellow amorphous ppt.	106
Methyl ester	177/15 mm.	..	A neutral oil	125, 149
d-α-Bromo-camphor-π-sulfonate	243	+43.47°	Crystals (CH_3OH)	38
Hydrochloride (monohydrate)	212 (dec)	..	Prisms (C_2H_5OH)	102, 125
Methiodide	164	−18.2°(H_2O)	..	38
Isovaleryl-	..	..	Colorless oil	102
Phenylacetyl-	..	..	Oil	102
o-Phthalyl	..	..	Solid	102
Sulfuric ester	258–259	−85° (H_2O)	Needles (H_2O)	73
Aurichloride	155–157	..	Needles	73
Tropyl-				
Benzyl ester	..	..	Oil	216a
Benzyl ester aurichloride	*90	..	Small needles	216a
Benzyl ester picrate	*65	..	Granular solid	216a
Open Ecgonine	198–200	..	Needles (C_2H_5OH–ether)	76
Methyl ester	96	0°	Prisms (pet. ether)	76
r-Ecgonine (isomeric)	229 (froth)	..	..	38
Dihydrate	..	..	Prisms (H_2O–C_2H_5OH)	38
Hydrochloride	230–233	..	..	38

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
dl-Ecgoninic Acid	93–95	..	Needles (C_6H_6–ethyl acetate)	149,34a,119, 152, 193
Hydrochloride	80–133	..	Short prisms	34a
Methyl ester	165–170/19 mm.	..	Oil	34a
l-Ecgoninic Acid	117–118	−49.1° (H_2O)	Pointed prisms (ethyl acetate)	116, 149
Ethyl ester	..	−43.2° (H_2O)	Oil	119
Methyl ester	159/13 mm.	..	Oil	34a
l-Ecgoninenitrile	145.5	..	Glistening needles (ether)	123
Benzoyl-	105	..	Fernlike crystals	123
Aurichloride (monohydrate)	188	..	Yellow leaflets	123
Ethyltropine	..	..	..	14
Chloroplatinate	..	..	Yellow powder (C_2H_5OH–H_2O)	14
Ethiodide	..	..	Crystals (C_2H_5OH)	14
		H		
Homatropine	95.5–98.5	..	Colorless prisms (ether)	22, 239a
Aurichloride	..	..	Beautiful prisms (H_2O)	22
Ethobromide	209–210	..	Crystals (C_2H_5OH)	202
Hydrobromide	217–218 (dec)	..	Nodules (H_2O)	239a, 22,
Hydrochloride	224–225	..		239a
Methobromide	192–196	..	Crystals (C_2H_5OH)	202
Methonitrate	134–135	..	Crystals (C_2H_5OH)	202
Methosulfate	172–174	..	Crystals (C_2H_5OH)	202
N-Oxide	139–140	..	Prisms (acetone)	181
Hydrobromide	238	..	..	181, 189
N-Sulfonated ether	210	..	..	189
Picrate	..	..	Yellow leaflets (H_2O)	22
Sulfamic ether	210	..	..	181
Sulfate	..	..	Silky glistening needles (H_2O)	22, 239a
Acetyl-				
Hydrochloride	67	..	..	244
Picrate	229 (dec)	..	Yellow solid	244
Sulfuric ester	240	..	Rhombic plates (H_2O)	253
Homotropine (see 2-Methyloltropane)				
Hydratropic Acid	93.5–94	..	Needles (ligroin)	82
Hemihydrate	81	..	..	82

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrobidioscorine	266–267 (dec)	..	Leaflets (C_2H_5OH)	248
Hydroecgonidine	200	−3.0° (H_2O)	Needles (C_2H_5OH–ethyl acetate)	72, 138
Aurichloride (a)	210	..	Small dense needles	72, 138
Aurichloride (b)	230	..	Golden-yellow needles	72
Chloroplatinate (hydrates)	..	..	Red prisms (H_2O) or flesh-colored needles (C_2H_5OH)	138
Hydrochloride (a)	233	−2.77° (H_2O)	Leaflets	72
Hydrochloride (b)	233–234	−4.4° (H_2O)	Leaflets	72, 138
Amide	126–127	..	Six-sided plates (ethyl acetate)	145
Ethyl ester (two isomers) (a)	127–129/12 mm.	..	..	165a
Ethyl ester (two isomers) (b)	132–134/13 mm.	+6.7° (ether)	Colorless oil	72, 138
Aurichloride (a)	173–174	..	..	72, 165a
Aurichloride (b)	122–123	..	..	72
Hydrochloride (a)	..	0°	..	72
Hydrochloride (b)	..	+2.97°	..	72
Methaurichloride	168–169	..	Leaves and prisms (C_2H_5OH–H_2O)	138
Methiodide (a)	219	..	Long needles (C_2H_5OH)	165a
Methiodide (b)	156	..	Silky needles (C_2H_5OH)	138
Hydrazide-picrate	172	..	Needles (H_2O)	145
Hydroecgonidine Bromide				
Aurichloride	148–150	..	..	72
Hydrobromide	250	+41.5° (H_2O)	Prisms	72
Hydroscopolidine	..	..	..	64
Aurichloride	204–206	..	Yellow needles (H_2O)	64
Hydroscopoline	165	..	Crystals ($CHCl_3$)	162
Aurichloride	200–201	..	Needles (H_2O–HCl)	64, 162
Hydrobromide	260 (dec)	0°	Crystals (C_2H_5OH)	162
Picrate	232 (dec)	..	Needles (C_2H_5OH)	162
Diacetyl-	270–280 (dec)	..	Pyramids(C_2H_5OH)	162
Aurichloride	184–185	..	Yellow leaflets (C_2H_5OH–H_2O)	64
Dibenzoyl- Aurichloride	200–201	..	Crystals (C_2H_5OH)	64
Hydroscopoline Bromide				
Hydrobromide	210–211 (dec)	0°	Prisms (CH_3OH)	162, 64, 71

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Diacetyl-Aurichloride	187	..	Tabular crystals (C_2H_5OH)	64
Hydroscopoline Chloride Hydrochloride	289 (dec)	..	Needles (C_2H_5OH)	167
Hydroscopoline Iodide Hydriodide	196	..	Crystals (H_2O)	64
Hydrotropidine (see Tropane)				
Hydrotropilidine (see Cycloheptadiene)				
m-Hydroxybenzaldehyde	109	..	Crystals (pet. ether)	190, 183, 185
Semicarbazone	199	..	..	183
m-Hydroxybenzoic Acid	200	..	..	190, 183
α-Hydroxycycloheptanecarboxylic Acid	79	..	Six-sided plates (H_2O)	144
Hydroxyhydroscopoline Aurichloride	214	−14.0°	Leaflets	71
d-Hyoscyamine	106	+24.12°	Needles (C_2H_5OH–H_2O)	61, 53, 108
Auribromide	160	..	..	205
Aurichloride	165	..	Golden-yellow hexagonal plates	205, 108
d-Camphorsulfonate	135	+27.25° (H_2O)	Small needles	205
Picrate	163	..	Needles	205
l-Hyoscyamine	108–111	−22° (C_2H_5OH)	Silky needles (C_2H_5OH–H_2O)	206, 1, 9, 19, 20, 25, 50, 53, 60, 61, 96, 108, 205, 208, 209, 237, 243
Auribromide	160	..	Deep-red flattened needles	205, 197
Aurichloride	165	..	Golden-yellow hexagonal plates (H_2O–HCl)	205, 1, 19, 20, 25, 48, 50, 53, 63, 67,96,108, 199, 208, 209, 243, 246
d-Camphorsulfonate	159	−8.0° (H_2O)	Prismatic needles	205
Chloroplatinate	206	..	Orange prisms	25, 19, 20, 53, 96

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrobromide	149–150	..	..	208, 53
Hydrobromide-gold chloride salt	*164	..	Yellow scales (H_2O–HCl)	197
Hydrochloride (tetrahydrate)	..	..	Crystals (H_2O)	19
Mercurichloride	..	..	White ppt.	19
Oxalate	176	..	Long dense prisms	25, 1, 209
N-Oxide	..	−19°(H_2O) −15°(C_2H_5OH)	Hygroscopic powder	181, 189
Hydrochloride	198	−11.5°(H_2O)	Large prisms (C_2H_5OH)	181, 189
Picrate	165	..	Needles	205, 1, 53, 208, 209, 225, 246
Sulfate (dihydrate)	209–210	−28.6°(H_2O)	Radiating needles (H_2O)	25, 1, 19, 208, 243
Tannate	..	..	White flocculent ppt.	19
Benzoyl-				
Aurichloride	70 (ca.)	..	Amorphous	54
Chloroplatinate	164–170	..	Red amorphous ppt.	54
Hyoscine (see Scopolamine)				
		I		
2-Iodotropane-Methiodide	251–252 (dec)	..	Four-sided leaflets (H_2O)	31
3-Iodotropane				
Chloroplatinate	..	..	Red octahedra (H_2O)	22
Hydriodide	197 (dec)	..	Plates or prisms (H_2O)	33, 22
α-Isatropic Acid	239	..	..	23
β-Isatropic Acid	*205–206	..	Crystals (HOAc–H_2O)	78, 12
γ-Isatropic Acid	266	..	Small leaves(HOAc)	104
Isoporoidine (see *d*-α-methylbutyryl-nortropeine)	..	..	..	223
Isotropidine				
Aurichloride	255–257 (dec)	..	Small yellow plates or prisms (H_2O)	31
Chloroplatinate	234–235 (dec)	..	Reddish-yellow prisms (H_2O)	31
Methaurichloride	258 (dec)	..	Six-sided platelets (H_2O)	31

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide	293 (dec)	..	Four-sided plates (H_2O)	31
Methochloride	251–252(dec)	..	..	31
Methochloroplatinate	233–234 (dec)	..	..	31
Isotropylamine	206–207/760 mm. 8.5	..	..	145
Aurichloride	..	..	Canary-yellow needles (H_2O–HCl)	145
Chloroplatinate	261 (dec)	..	Orange prisms or plates	145
Hydrochloride	>300 (dec)	..	Six-sided plates	145
Isovaleric Acid	..	0° (CH_3OH)	Oil	222
p-Phenylphenacyl ester	*76	..	..	224, 222
	M			
Mandragorine (old)	mixture of hyoscyamine and scopolamine			150, 107
Mandragorine (new)				
Aurichloride	124–126	..	..	231
Metatropine	237–239/760 mm.	..	Oil	22
Meteloidine	*141–142	0°	Tabular needles (C_6H_6)	203
Aurichloride (hemihydrate)	149–150	..	Yellow needles (C_2H_5OH–H_2O)	203
d-α-Bromo-π-camphorsulfonate	*228.5–231.5	+47.42°(H_2O)	Clusters of prisms (C_2H_5OH)	212
Hydrobromide (dihydrate)	*250	0°	Chisel-shaped needles (H_2O)	203
Picrate	*177–180	..	Yellow hexagonal plates (C_2H_5OH)	203
l-Methylamino-Δ^4-*cycloheptenol*-3	103–104	..	..	32
Methylcocaine (see *d*-Pseudococaine)	..	..	..	112
Methylcocaine(Günther)	110–111	..	..	198
Methylcocaine (Ethyl-benzoylecgonine)	109	..	White prisms (C_2H_5OH)	95, 134
Aurichloride	188	..	Yellow leaflets (C_2H_5OH–H_2O)	134
Chloroplatinate	215 (dec)	..	Yellow rhombic leaves (H_2O)	90, 134
Methyldibromopyridine	108–109	..	Leaflets (ether)	22
Methylecgonine (see d-Pseudoecgonine)				

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
(des)-Methyldioscoridine	116–120/8 mm.	..	Colorless oil	248
(des)-Methylhydroecgonidine ethyl ester	156/16 mm.	..	Oil insoluble in H_2O	138
Aurichloride	..	..	Oil	138
Chloroplatinate	148	..	Orange-red leaflets (H_2O)	138
Mercurichloride	..	..	Well-formed prisms (H_2O)	138
Methaurichloride (hydrate)	153–154	..	Prisms	138
Methiodide	149–150	..	Dense plates (C_2H_5OH)	138
Picrate	..	..	Oil	138
O-Methyl-iso-α-dihydrodesmethylscopoline	116–120/13 mm.	..	Oil	172
Methiodide	240–241	..	Lance-like crystals (C_2H_5OH)	172
Picrate	185	..	Rhombic crystals (C_2H_5OH)	172
2-Methyloltropane (homotropine)	85	+24.50° (C_2H_5OH)	Needles (ligroin)	165a
Aurichloride	191	..	Fine crystals (H_2O)	165a
Hydrochloride	192	..	Crystals (ether–pet. ether)	165a
Methiodide	>300	..	..	165a
Picrate	208–209	..	Thin needles (C_2H_5OH)	165a
Benzoyl-	..	..	Colorless oil	165a
Aurichloride	161	..	Fine needles (H_2O)	165a
Chloroplatinate	201	..	Amorphous yellow solid	165a
Picrate	177	..	Citron-yellow needles (C_2H_5OH)	165a
Mandelyl-	..	..	Oil	165a
chloroplatinate	192	..	..	165a
Tropyl-	..	..	Oil	165a
chloroplatinate	192 (sinters)	..	..	165a
N-Methylpiperidine-α, α′-dicarboxylic Acid	225 (dec)	0°	..	65, 68, 69, 161, 162
Monohydrate	214–216 (dec)	..	Six-sided crystals (H_2O)	65, 68, 69, 161, 162
Aurichloride	..	..	Yellow plate-like crystals	65, 68, 69
Copper salt (pentahydrate)	..	..	Blue needles (H_2O)	68

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	224–225 (dec)	..	Polysided plates (H_2O)	65, 68, 161, 162
Dimethyl ester				
Methaurichloride	124–125	..	..	68
Methiodide	175–176	..	Crystals (H_2O)	68, 155
(des)-Methylpseudotropine	128–129/11 mm.	..	Colorless sirup	32
Aurichloride	..	..	Oily sirup	32
Benzoyl-				
Hydrochloride	166–167	..	Four-sided plates (C_2H_5OH)	32
1-Methylpseudotropine	138/15 mm. 71	..	Crystals (pet. ether)	221
Hydrobromide	286 (dec)	..	Rhombohedra (C_2H_5OH–ether)	221
Picrate	280 (dec)	..	Small yellow prisms (C_2H_5OH)	221
Benzoyl	210/15 mm.	..	Colorless oil	221
Picrate	163–164	..	Small yellow needles (C_2H_5OH)	221
N-Methylpyrrole-2,5-diacetic Acid	150 (dec)	..	Rhombic plates (H_2O)	36
Dimethyl ester	170–171	..	Long prisms (C_2H_5OH)	36
N-Methylpyrrolidine-2,5-Diacetic Acid				
Diethyl ester	162.5/9 mm.	..	Oil insoluble in H_2O	36
Methiodide	78	..	Small plates (C_2H_5OH)	36
Dimethyl ester	155.5/12 mm.	..	Colorless oil, soluble in H_2O	36
(des)-Methylscopoline	68–69	−48.75°	Pointed prisms (pet. ether)	172, 56, 64, 72, 170
Aurichloride	..	..	Crystalline	56
Chloroplatinate	..	..	Crystalline	56
Hydrobromide	250 (dec)	..	Prisms (HOAc)	170
Methiodide	248 (gas)	..	Needles (C_2H_5OH)	172, 170, 56
Methochloride	250	..	Crystals (C_2H_5OH–ether)	56
Picrate	152–153	..	Prisms (C_2H_5OH)	172, 170
Benzoyl-	120	..	Aggregates of needles (H_2O)	170
Hydrochloride (trihydrate)	214 (dec)	..	Long prisms (C_2H_5OH–ether)	170, 172

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Desmethyl-scopolinone	42	..	Pointed prisms (pet. ether)	172
Methiodide	233–234	..	Needles (C_2H_5OH)	172
Picrate	163	..	Rhombic platelets (C_2H_5OH)	172
Benzoyl-				
Hydrochloride	219	..	Prisms (pyridine)	172
Picrate	213–214	..	Crystals (C_2H_5OH)	172
(des)-Methyltropane (methylhydrotropidine)	*189–194/760 mm.	..	Oil	139
Chloroplatinate	192–193 (dec)	..	Orange-yellow plates	139
Methaurichloride	135 (gas)	..	Short prisms (C_2H_5OH–H_2O)	139
Methiodide	240 (dec)	..	Needles (C_2H_5OH)	139
Picrate	115	..	Yellow plates (H_2O)	139
Δ^2-(des)-Methyltropane	183–184/723 mm.	..	Oil, $d_4^{14} = 0.8842$	29, 30
Aurichloride	94–95	..	Yellow prisms(H_2O)	29, 30
Chloroplatinate	177–178	..	Prisms and spears (H_2O)	29, 30
Methaurichloride	143–144.5	..	Golden-yellow needles (C_2H_5OH)	29
Methiodide	162–163	..	Pyramids (acetone)	29, 30
Picrate	162–163	..	Fine needles (H_2O)	29
Δ^3-(des)-methyltropane	*188–189/760 mm.	..	Oil, $d_4^{14} = 0.8899$	148, 30
Aurichloride	77.5–78.5 (dec)	..	Golden-yellow crystals (H_2O)	30
Chloroplatinate	191–193 (dec)	..	Orange-red needles and prisms	30, 148
Methiodide	236–240 (dec)	..	Long needles (acetone)	30
Picrate	157–158	..	Yellow long needles (H_2O)	30, 148
Δ^4-(des)-Methyltropane	*189/760 mm.	..	Oil, $d_4^{14} = 0.8866$	148, 30
Chloroplatinate	178–179 (dec)	..	Six-sided plates	148, 30
Methiodide	226–227	..	Prisms	148, 30
Picrate	163–165	..	Needles	148, 30
α-(des)-Methyltropidine	66/10 mm.	..	Oil, $d_4^{14} = 0.9113$	148, 30, 121
Aurichloride	100 (ca)	..	Thin leaflets (H_2O)	30
Chloroplatinate	173–174 (gas)	..	Orange-yellow prisms (H_2O)	121, 30, 148
Methiodide	162 (dec)	..	Rosettes of fine needles	121

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
β-(des)-Methyltropidine	201/760 mm.	..	Oil	30
(des)-Methyltropine	247–248 (dec)/760 mm. 130–131/12 mm.	..	Colorless oil	32, 21, 22
Aurichloride	96	..	Prisms (H_2O–HCl)	32, 22
Chloroplatinate	161 (dec)	..	Orange-red prisms (H_2O)	32
Methiodide	..	..	Colorless needles (C_2H_5OH)	21
Methochloroplatinate	100–110 (dec)	..	Yellowish-green ppt.	21
Benzoylhydrochloride	171–172	..	Prisms and needles (C_2H_5OH–ether)	32
d-(des)-Methyltropinic Acid				
Dimethyl ester methiodide	121–122	..	Crystals (C_2H_5OH–ether)	127
r-(des)-Methyltropinic Acid				
Monomethyl ester methaurichloride	100 (ca)	..	Sulfur-yellow prisms (C_2H_5OH)	127
Dimethyl ester	280 (dec)/760 mm.	..	Oil	127
Aurichloride	..	..	Difficultly soluble oil	127
Chloroplatinate	147–148	..	Orange-red needles (C_2H_5OH–H_2O)	127
Methaurichloride	118	..	Golden-yellow prisms (C_2H_5OH–H_2O)	127
Methiodide (hemihydrate)	131–132	..	Nodules (C_2H_5OH–ether)	127
Picrate	77–78 (ca)	..	Amber-yellow spears (C_2H_5OH)	127
Dipropyl ester Methiodide	116–117	..	Prisms and needles (C_2H_5OH–ether)	127
1-Methyltropinone	124/27 mm.	..	Colorless oil	221
Picrate	201(dec)	..	Yellow needles (H_2O)	221
		N		
Noranhydroecgonine (Norecgonidine)	254–257	..	..	165a
Aurichloride	204	..	Yellow leaflets (H_2O)	165a
Chloroplatinate	251 (dec)	..	..	165a

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	257	..	..	165a
Ethyl ester	157/25 mm.	..	Colorless oil	165a
Aurichloride	135	..	Yellow leaves (H_2O)	165a
Hydrochloride	145	..	Long needles (ether–C_2H_5OH)	165a
Nitroso	..	..	Yellow oil	165a
Norapoatropine				
N-Acetyl	114	0°	..	182
Hydrochloride	140 (darkening)	..	..	182
Noratropine	113–114	0°	Crystals (acetone–ether)	209, 1
Monohydrate	73	..	..	209
Aurichloride	156–157	..	Dull yellow leaflets (C_2H_5OH–H_2O)	209, 1, 246
Hydrochloride	193	..	Silky filaments (C_2H_5OH–acetone)	209, 1
Oxalate	247–248	..	Crystals (H_2O)	209, 1
Picrate	227	..	Needles	209, 1
Sulfate	257	..	Long needles (H_2O)	209, 1
Norcocaine				
N-Cyano-	123–124	..	..	165a
Norecgonidine (see Noranhydroecgonine)				
l-Norecgonine	233	..	Prismatic crystals	100
Aurichloride (dihydrate)	211	..	Yellow needles (H_2O)	100
Benzoyl-	230 (dec)	..	Prisms (H_2O)	100
Aurichloride	228 (dec)	..	Yellow needles (H_2O)	100
Chloroplatinate (hydrate)	233	..	Reddish-yellow crystals (H_2O)	100
Hydrochloride (hydrate)	217	..	..	100
Ethyl ester				
Aurichloride	160.5	..	Yellow crystals (C_2H_5OH)	100
Methyl ester	..	..	Oil	100
Aurichloride	181–182	..	Long needles (H_2O)	100
Norhydroecgonidine				
Mercurichloride	..	..	Groups of needles	94
Ethyl ester	..	+5.88°	Oil, $d_4^{19} = 1.0856$	165a
Aurichloride	110	..	..	165a
Hydrochloride	149–150	..	..	165a

TABLE 2 (*Continued*)

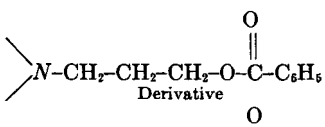
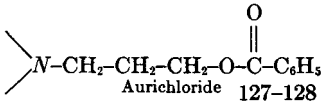
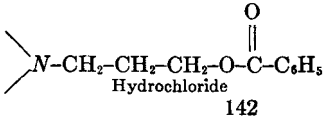
Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
 Derivative	..	..	Oil	165a
 Aurichloride	127–128	..	..	165a
 Hydrochloride	142	..	Needles (C_2H_5OH–ether)	165a
Norhyoscyamine (Solandrine)	140.5	−23°(C_2H_5OH)	Prisms or needles (acetone)	209, 1
Aurichloride	178–179	..	Golden scales (H_2O)	209, 1, 246
Chloroplatinate (trihydrate)	132–141	..	Reddish-yellow prisms (H_2O)	209
Hydrochloride	207	..	Rosettes of needles (C_2H_5OH–ether)	209, 1
Oxalate	245–246	..	Prisms (acetone–H_2O)	209, 1, 246
Picrate	220 (dec)	..	Yellow needles (H_2O)	246, 1, 209
Sulfate (trihydrate)	249	−33.8°(H_2O)	Silky needles (acetone–H_2O)	209, 1
N-Acetyl-	158	−15°(C_2H_5OH)	..	182
Diacetyl-	..	−30°(C_2H_5OH)	Oil	182
Norpseudoscopine	184	..	Prisms (ether–acetone)	185, 191
Aurichloride	224–225	..	Yellow needles (H_2O)	185, 191
Hydrochloride	262	..	White prisms (C_2H_5OH)	185, 191
Picrate	225	..	..	191, 185
d-Norpseudoecgonine	..	..	Needles (H_2O–C_2H_5OH)	124
Benzoyl-	..	..	Long needles (C_2H_5OH)	124
Ethyl ester	137	..	Needles (ethyl acetate)	124
Aurichloride	182	..	Needles (C_2H_5OH–H_2O)	124
Methiodide	178	..	Needles (C_2H_5OH)	124
N-Nitroso-	..	..	Dense yellow oil	124

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Benzoyl-	127	..	Needles (C_2H_5OH–ligroin)	124
Benzoyl-chloroplatinate	142	..	Yellow flakes (C_2H_5OH)	124
Methyl ester	160	..	Crystals (C_6H_6)	124
Norpseudotropine (Pseudotropigenine)	..	..	Fine needles	132
Aurichloride	212 (dec)	..	Orange-yellow leaflets (H_2O)	136, 132
Carbamate	140 (dec)	..	..	136, 132
Chloroplatinate	240 (dec)	..	Red leaflets (H_2O)	132
Hydrochloride	..	..	Plates (C_2H_5OH)	225
Picrate	187–188	..	Clusters of prisms (H_2O)	225
N-Acetyl	128	..	Prisms (acetone)	184
N-Benzoyl	166	..	Plates (C_6H_6 or H_2O)	132, 136
Norscopolamine				
N-Acetyl	..	−25°(C_2H_5OH)	..	182
Hydrochloride	205	..	..	182
Norscopoline	205	..	..	182
Aurichloride	242	..	..	182
Hydrochloride	282–284 (dec)	..	Broad needles (H_2O)	167, 182
N-Acetyl	..	..	Crystals (ether)	182
Nortropane (Norhydrotropidine)	161/760 mm.	..	Colorless crystals	94
Aurichloride	..	..	Yellow crystalline ppt.	94
Chloroplatinate	225 (chars)	..	Golden prisms (H_2O–HCl)	94
Hydrochloride	285 (dec)	..	Crystals (C_2H_5OH–acetone)	167, 94
Nitrosamine	116–117	..	Pale yellow crystals (ether)	94
Picrate	..	..	Yellow needles	94
Nortropanol (see Nortropine)	..	..	..	209
Nortropidine	160–163/760 mm.	..	Oil	227
Aurichloride	187	..	..	182
N-β-Hydroxyethyl-	140–141	..	..	227
p-Aminobenzoyl-	96–96.5	..	..	227
p-Aminobenzoyl-hydrochloride	206–207	..	..	227
p-Aminobenzoyl-picrate	150–151	..	..	227

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Benzoyl-	187–188	..	..	227
Butylaminobenzoyl-	66–68	..	..	227
Butylaminobenzoyl- hydrochloride	149–151	..	..	227
Butylaminobenzoyl- picrate	173–175	..	..	227
p-Nitrobenzoyl-	60–62	..	..	227
p-Nitrobenzoyl- hydrochloride	209–210	..	..	227
p-Nitrobenzoyl- picrate	225–226	..	..	227
Nortropine(Nortropanol or Tropigenine)	233/760 mm. 161	..	Colorless leaflets (toluene)	178, 21, 209
Aurichloride	217	..	Orange plates (C_2H_5OH)	21, 182, 209
Chloroplatinate	248–249	..	Orange plates (C_2H_5OH–H_2O)	21, 182
Hydrochloride	285	..	..	182, 178
Nitrate	186–187	..	Glistening leaflets (CH_3OH)	178
Picrate	170–171	..	Yellow crystalline powder (C_2H_5OH–H_2O)	178
N-Diethylaminoethyl-	59–61	..	..	227
Hydrochloride	200–201	..	..	227
Picrate	160–162	..	..	227
Benzoyl-	228–229 (dec)	..	..	227
N-Acetyl-	124	..	..	182
Hydrochloride	162	..	..	182
p-Aminobenzoyl-	201–202	..	Crystals (ethyl acetate)	227
Hydrochloride	222–224 (dec)	..	..	227
N-Benzoyl-Isovaleryl-(Poroidine)	125–126	..	Fine prisms (H_2O)	182, 131, 178,
Hydrobromide	*224–225	0° (H_2O)	Small plates (C_2H_5OH–ether)	223
Methiodide	*289 (dec)	..	Pearly laminae (C_2H_5OH–ether)	223
Oxalate	*301–302	..	Glistening laminae (H_2O)	223
Picrate	*172	..	Golden-yellow prisms (acetone–H_2O)	223
dl-α-Methylbutyryl- Hydrobromide	*201–202	..	Glistening plates (C_2H_5OH–ether)	223

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide	*295	..	Dull pearly laminae (C_2H_5OH–ether)	223
Oxalate	*296–297	..	Glistening laminae (H_2O)	223
Picrate	*188	..	Golden prismatic needles (acetone–H_2O)	223
p-Nitrobenzoyl-	223–224	..	Crystals (C_2H_5OH–acetone)	227
Nitroso	explodes	..	Colorless needles (C_2H_5OH–ether)	21
Tiglyl-				
Hydrobromide	*241–242	..	Dull laminae (C_2H_5OH–ether)	223
Methiodide	*285–286 (dec)	..	Opaque laminae (C_2H_5OH–ether)	223
Picrate	*207	..	Golden-yellow prismatic needles (acetone–H_2O)	223
Tropyl-	165	..	Crystals (H_2O)	209
Nortropinone	69–70	..	Thin needles (C_6H_6–ligroin)	131
Aurichloride	167–168 (dec)	..	Fine prisms (C_2H_5OH)	131, 132, 182
Carbamate	111 (dec)	..	..	131, 132
Chloroplatinate	200 (dec)	..	Orange-red prisms (H_2O)	131
Hydrochloride	201(dec)	..	Silky needles (C_2H_5OH)	131, 182
Picrate	159–160	..	Yellow prisms (C_2H_5OH)	131
N-Benzoyl-	..	..	Crystals	131
Oxime	175	..	Crystals (H_2O)	131
Nitroso-	127	..	Yellow needles(H_2O)	131
Oxime	182	..	Four-sided leaflets (H_2O)	131, 132
Phenylhydrazone	..	..	Oil	131
Open Nortropinone-carboxylic Acid				
Methyl ester	..	..	Oil	76
Hydrochloride	172–173 (dec)	..	Fine needles (C_2H_5OH)	76
N-Benzoyl-	126	..	Crystals (ligroin)	76
Norvaleroidine				
Hydrobromide	*270	..	Pearly laminae (C_2H_5OH–ether)	224
Nitroso-	..	..	Oily product	224

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		O		
Oscine (see Scopoline)				
		P		
Pimelic Acid	105–106	..	Glistening dense needles	143
Piperidine-α, α^1-Dicarboxylic Acid	158	..	..	65
Isomer	206–207	..	..	65
Piperylenedicarboxylic acid	169	..	Silky needles or prisms (H_2O)	127, 143
Tetrabromide	218 (dec)	..	Colorless prisms (HCO_2H)	127
Poroidine (see Isovaleryl-nortropeine)				
Pseudo-8, 9-Benz-$\Delta^{8,9}$-homogranatene-3-ol (monohydrate)	105–110	..	Short prisms (C_6H_6)	220
Benzoyl-	98	..	Rhombs (C_2H_5OH–H_2O)	220
Hydrobromide	257	..	Compact crystals (H_2O)	220
Hydrochloride	258 (dec)	..	Small crystals(H_2O)	220
d-Pseudocinnamyl-cocaine	68	..	Prisms	118
Aurichloride	164	..	Small orange needles (C_2H_5OH)	118
Chloroplatinate	208–210	..	Bright yellow needles (C_2H_5OH)	118
Hydrobromide	209	..	Small needles (H_2O)	118
Hydrochloride	186–188	+2.0°(C_2H_5OH)	White needles (H_2O)	118
Nitrate	197	..	Long needles (H_2O)	118
d-Pseudococaine	46–47	..	Prismatic crystals	112, 38, 113, 114
Aurichloride	148–149	..	Anhydrous needles (C_2H_5OH)	112, 114
Chloroplatinate	218 (dec)	..	Yellow needles (C_2H_5OH–H_2O)	114, 112
Hydriodide	..	..	Mother of pearl leaflets (H_2O)	114
Hydrobromide (hydrate)	..	..	Prismatic needles (H_2O)	114
Hydrochloride	205–210	+43° (H_2O)	Elongated leaflets (C_2H_5OH)	111, 112
Methiodide	*172	..	..	38

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Nitrate	..	..	Small crystals(H_2O)	112
Sulfate	..	..	Crystals (C_2H_5OH)	114
dl-Pseudococaine	81.5	..	Hexagonal plates (ligroin)	36, 34, 38, 151
Aurichloride (anhydrous)	164–165	..	Groups of prisms (ethyl acetate)	34
Hydrochloride	205–205.5 (dec)	..	Rhombic plates (C_2H_5OH)	34, 151
Methiodide	*213	..	..	38
Nitrate	172 (dec)	..	Plates or leaflets (H_2O)	34
d-Open Pseudococaine Hydrochloride	189–190	+50.8°(CH_3OH)	Needles (acetone)	76
dl-Open Pseudococaine	204 (dec)	..	Prisms (acetone)	76
α-Pseudo-desmethyl-scopoline (see Desmethyl scopoline)				
β-Pseudo-desmethyl-scopoline	135–140/15 mm.	−18.5°	Oil	170, 72
Methiodide	..	..	Oil	170
Picrate	205 (dec)	..	Stout cylinders (C_2H_5OH)	170
d-Pseudoecgonine	254 257	+21° (H_2O)	Plates (C_2H_5OH)	111, 112
Aurichloride	220 (dec)	..	Lemon-yellow needles (H_2O–HCl)	112, 124
Hydrochloride	236	+1.6°	Monoclinic prisms	112
Amide	173	..	Groups of needles (C_2H_5OH)	123
Methiodide (monohydrate)	220	..	Feathery crystals (C_2H_5OH)	123
Picrate	177	..	Fine needles (C_2H_5OH)	123
Amyl ester-aurichloride	152	..	Yellow prisms (C_2H_5OH)	114
Benzoyl-				
Hydrochloride	244–245	..	Needles or prisms (H_2O)	114, 113
Amyl ester hydrochloride	217	+1.7° (H_2O)	Needles (ethyl acetate)	114
Benzyl ester	..	..	Oil	216a
Benzyl ester-hydrochloride	*213 (dec)	..	Glistening platelets	216a
Benzyl ester-nitrate	*168	..	Square plates (C_2H_5OH–H_2O)	216a

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Benzyl ester-picrate	*80	..	Granular solid	216a
Ethyl ester	57	..	White prisms	114
Ethyl ester-hydrochloride	215	+40.0°	Leaflets (C_2H_5OH)	114
Isobutyl ester hydrochloride	201	+46°	Needles (C_2H_5OH–ethyl acetate)	114
β-Phenylethyl ester	*63	..	Square plates	216a
β-Phenylethyl ester hydrochloride	*197	..	Silky needles (acetone)	216a
Propyl ester hydrochloride	220	+46.1°	White prisms (C_2H_5OH)	114
Cinnamyl-				
Chloroplatinate	225 (dec)	..	Yellow needles(H_2O)	118
Hydrochloride	236 (dec)	..	Needles (H_2O)	118
Ethyl ester aurichloride	153	..	Citron-yellow crystals (C_2H_5OH–H_2O)	123, 114
Isobutyl ester aurichloride	130	..	Orange leaflets	114
Isovaleryl-	224 (dec)	..	Needles (CH_3OH–ether)	118
Chloroplatinate	216	..	Orange prisms(H_2O)	118
Hydrochloride	236 (dec)	..	Glistening needles (H_2O)	118
Methyl ester aurichloride	88	..	Yellow needles (C_2H_5OH–H_2O)	118
Methyl ester chloroplatinate	202	..	Citron-yellow needles (H_2O)	118
Methyl ester hydrochloride	192	+25.4°(C_2H_5OH)	Small leaflets (C_2H_5OH)	118
Methyl ester nitrate	163	..	Glistening leaflets (C_2H_5OH–ether)	118
Methyl ester	*116	+19.5° (H_2O)	Prismatic crystals (C_2H_5OH)	38, 111, 113
Aurichloride	172	..	Plates or leaflets	123
d-α-Bromocamphor-β-sulfonate	*201	+71.5° (H_2O)	Plates (ethyl acetate–C_2H_5OH)	38
Hydrochloride	..	+23.67°(H_2O)	..	38
Methiodide	209	..	Leaflets (CH_3OH)	38
o-Phthaloyl-	..	..	Yellow oil	118
Hydriodide	103	..	Yellow crystals (C_2H_5OH–ether)	118
Dimethyl ester hydriodide	226	..	Crystals (CH_3OH)	118

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Propyl ester aurichloride	132	..	Orange crystals (C_2H_5OH–H_2O)	114
dl-Pseudoecgonine	251 (dec)	..	Rhombic crystals (C_2H_5OH)	151, 34
Aurichloride	213 (dec)	..	Needles (H_2O)	34, 151
Hydrochloride (anhydrous)	193–194	..	..	34
Hydrate	149	..	Prisms (C_2H_5OH–H_2O)	34, 151
Methyl ester	*128	..	Prisms (ethyl acetate)	38, 34, 36, 151
Methiodide	*185	..	Needles (C_2H_5OH)	38,34,36,151
l-Pseudoecgonine				
Methyl ester	115	−14.74°(CH_3OH)	..	38
dl-Open pseudoecgonine (hydrate)	246–248 (dec)	..	Octahedra (H_2O–CH_3OH)	76
Hydrobromide	265–266	..	Needles (C_2H_5OH)	76
Methyl ester	135–137/11 mm.	..	Oil	76
Picrate	154–155	..	Crystals (C_2H_5OH)	76
l-Open Pseudoecgonine				
Methyl ester hydrochloride	221–222 (dec)	−66.6° (H_2O)	..	76
d-Pseudoecgoninenitrile				
Acetyl-	..	..	Oil	123
Hydriodide	243 (dec)	..	White needles (C_2H_5OH)	123
Benzoyl-	..	..	Oil	123
Chloroplatinate	..	..	Needles (C_2H_5OH)	123
Hydrobromide	210	..	Groups of needles	123
Picrate	227	..	Needles (C_2H_5OH)	123
Pseudohyoscyamine	133–134	−21.15° (C_2H_5OH)	Yellow needles ($CHCl_3$–ether)	53
Aurichloride	176	..	Yellow leaflets(H_2O)	53, 231
Chloroplatinate	150 (dec)	..	Feathery needles (H_2O)	53
Picrate	220	..	Yellow needles (C_2H_5OH)	53
Pseudoscopolamine	..	..	Oil	185
Pseudoscopine	126	0°	..	190, 183
Aurichloride	239–240	..	Yellow needles	183, 190
Chloroplatinate	223	..	..	190, 183
Hydrochloride	257–258	..	Needles	183, 190
Methiodide	249 (dec)	..	Crystals (CH_3OH)	183, 185, 190, 191

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
N-Oxide (hydrate)	177 (213)	..	Crystals (acetone)	183, 190
Hydrobromide	192	..	..	183, 190
Hydrochloride	185	..	..	183
Picrate	210	..	..	183
Phenylurethane	229	..	..	191
Aurichloride	210	..	..	191
Hydrochloride	244	..	..	191
Picrate	234	..	Yellow solid	190, 183
d-Tartrate	181	..	..	190
O-Acetyl-	..	..	Oil	183
Aurichloride	203	..	..	190, 183
Picrate	187	..	..	190, 183
O-Benzoyl-	142	..	..	191, 185
Aurichloride	220	..	..	191, 185
Hydrochloride	216	..	Crystals (acetone)	191, 185
Picrate	104	..	Needles (C_2H_5OH)	185, 191
Tropyl-	..	..	Vitreous mass	191
Pseudotropigenine (see Norpseudotropine)				
Pseudotropine	*108	0° (H_2O)	Needles (C_6H_6–ligroin)	222, 120, 130, 153, 184
Aurichloride	225 (dec)	..	Yellow plates and needles (H_2O)	130, 23, 120
d-Bromocamphorsulfonate	180	+60.5° (H_2O)	Fine needles (ethyl acetate)	205
d-Camphorsulfonate	224–226	+13.7° (H_2O)	Flat prisms (ethyl acetate)	205
Chloroplatinate (hydrate)	206–207 (dec)	..	Orange-red plates (H_2O)	130, 23
Hydrochloride	280–282 (dec)	..	Prisms (C_2H_5OH)	130, 120
N-Oxide	220	..	Needles (C_2H_5OH)	184
Hydrochloride	>286	..	White prisms	184
Picrate	287 (dec)	..	..	184
Picrate	258–259 (dec)	..	Pointed needles (H_2O)	147, 184
Acetyl-				
Hydrobromide	*205	..	Stout prisms	222
p-Aminobenzoyl-	163–165	..	..	227
Hydrochloride	>250	..	..	227
Benzoyl-	49	0° ($CHCl_3$)	..	120, 130
Aurichloride	208	..	Yellow needles(H_2O)	120, 130, 205
d-Bromocamphorsulfonate	190	+47.3°(H_2O)	Prisms (ethyl acetate–C_2H_5OH)	205
d-Camphorsulfonate	176–177	+11.1° (H_2O)	Prisms (ethyl acetate)	205
Chloroplatinate	120	..	Amorphous ppt.	120

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	283	..	Needles (C_2H_5OH)	205, 30, 120, 130
N-Oxide	152–153	..	Prisms (acetone)	184
Picrate	238–239	..	..	205
Butylaminobenzoyl-	109–111	..	..	227
Hydrochloride	>270	..	..	227
Cinnamyl-	87–88	..	..	120
p-Nitrobenzoyl-	126–127	..	..	227
Mandelyl-	..	..	Oil	254
Tropyl-	86	..	Colorless needles	254
Pseudotropine-*O*-carboxylic Acid	201–202 (dec)	..	Six-sided plates	151
Aurichloride	174–176 (dec)	..	..	151
Hydrochloride	239 (dec)	..	Plates (C_2H_5OH)	151
Open Pseudotropine (*meso*-)	105–107/11 mm.	..	Oil miscible with H_2O	76
Hydrobromide	265–266	..	..	76
Hydrochloride	267–268	..	Crystals (C_2H_5OH)	76
Benzoyl-	..	..	Oil	76
Hydrochloride	238	..	Crystals (C_2H_5OH)	76
Tropyl-	98	..	Crystals (pet.ether)	76
Nitrate	163–164	..	Crystals (C_2H_5OH)	76
Open Pseudotropine (racemic)	70	..	Crystals (pet.ether)	76
Hydrochloride	185	..	Crystals (C_2H_5OH)	76
Benzoyl-hydrochloride	165–168	..	Plates (acetone–ethyl acetate)	76
Pseudotropylamine	107/26 mm.	..	Oil (piperidine odor)	142
Aurichloride	223–224 (dec)	..	Canary-yellow needles (H_2O)	142
Chloroplatinate	257 (dec)	..	Orange-yellow leaflets (H_2O)	142
Dithiocarbamate	..	..	Prisms (H_2O)	142
Phenylthiourea	172	..	Prisms and needles (ethyl acetate)	142
Picrate	236–238 (dec)	..	Yellow spears (H_2O)	142
Pyridine-α, α^1-dicarboxylic Acid	236	..	..	65
Pyrrolediacetic Acid				
Diethyl ester	m.p. 74–75	..	Prisms (C_2H_5OH)	36
		S		
Scopine	76	0°	Needles (pet.ether)	174
Aurichloride	216 (dec)	..	Small prisms (H_2O)	174
Chloroplatinate (dihydrate)	219 (dec)	..	Domatic prisms (H_2O–HCl)	174

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	..	..	Small platelets (C_2H_5OH)	174
Picrate	231 (dec)	..	Prismatic angular leaflets	174
Scopinium				
Bromide	209–210	..	Crystals (C_2H_5OH)	183, 190
Chloride	187	..	Crystals (C_2H_5OH)	183
Nitrate	203	..	..	190
d-Scopolamine	..	..	Sirup	212
Aurichloride	*208–209 (dec)	..	Orange-yellow needles (H_2O–HCl)	212
d-α-Bromo-π-camphorsulfonate	*161.5–163.5	+60.3° (H_2O)	Glistening acicular crystals (C_2H_5OH–ethyl acetate)	212
Camphor-β-sulfonate (monohydrate)	*179–181	+29.25°(H_2O)	Leaflets or acicular crystals (ethyl acetate)	214
Hydrobromide	*197–198	+23.10° (H_2O)	..	212
Trihydrate	54.5–55	..	Rectantular tablets	212
Picrate	187–188	..	Matted needles	212
dl-Scopolamine	82–83	0° (H_2O)	Long prisms	28, 143
Monohydrate	56–56.5	0° (C_2H_5OH)	Needles or rhombohedra	58, 54, 59, 234
Dihydrate (see Atroscine)				
Auribromide	*213–214 (dec)	..	Chocolate-red leaflets (H_2O–HBr)	212, 197
Aurichloride	218–219 (dec)	..	Boat-shaped crystals (H_2O–HCl)	212, 28, 54, 58,143,197, 225, 232
Ethaurichloride	124	..	Yellow powder	232
Ethiodide	170	..	Octahedra (H_2O)	232
Ethochloride	..	..	Sirup	232
Hydriodide	192	..	White powder	232
Hydrobromide	*185–186	0° (H_2O)	..	212, 28, 54, 57, 232
Trihydrate	*55–58	..	Rhombic tablets (H_2O)	212, 232
Hydrochloride	..	..	Long needles (H_2O)	232
Methaurichloride	146	..	Yellow crystals (H_2O)	232
Methiodide	202	..	Prisms (H_2O)	232
Methobromide	207	..	Prisms (H_2O)	232
Methochloride	..	..	Glistening prisms (H_2O)	232

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Picrate	*177.5–178.5 (dec)	..	Rosettes of needles (H_2O)	212, 209
Acetyl-	..	..	Resinous sirup	232
Aurichloride	140	..	Yellow flocculent ppt.	232
Chloroplatinate	165	..	Yellow ppt. (H_2O)	232
l-Scopolamine (Hyoscine)	..	$-18°$ (C_2H_5OH) $-28°$ (H_2O)	Sirup	1, 20, 25
Monohydrate	59	..	..	52, 56
Auribromide	*191–192 (dec)	..	Rectangular chocolate-red leaflets (H_2O–HBr)	212, 197
Aurichloride	*208–209 (dec)	..	Needles serrated on edges (H_2O–HCl)	212, 20, 25, 26, 45, 48, 49, 52, 63, 67, 110, 225, 231, 232
d-α-Bromo-π-camphorsulfonate	*172.5–173.5	$+28.05°$ (H_2O)	Needles (ethyl acetate)	214
Labile form	150	$+25.5°$	..	214
Camphor-β-sulfonate	*190–191	$-7.6°$ (H_2O)	Large plates (ethyl acetate)	214
Chloroplatinate	..	..	Octahedra (H_2O)	20
Ethaurichloride	102	..	Crystalline powder	54, 232
Ethiodide	186	..	Colorless leaflets	54, 232
Ethochloroplatinate	..	..	Non crystalline	54
Hydriodide (hydrate)	197	..	White prisms (H_2O)	232, 26, 52
Hydrobromide (trihydrate)	193–194	$-22.75°$ (H_2O)	Rhombic tablets	25, 52, 53, 58, 63, 133, 212, 232, 253
Gold salt	215 (dec)	..	Red prisms (H_2O–HCl)	197
Hydrochloride	197	..	White powder (acetone)	232
Dihydrate	..	..	Prisms (H_2O)	52
Mercurichloride	..	..	Amorphous ppt.	20
Methiodide	215	..	Colorless prisms (C_2H_5OH)	54
Hemihydrate	208	$-13.8°$ (H_2O)	Crystals (H_2O)	232
Methaurichloride	145–146	..	Yellow leaflets (H_2O–HCl)	54, 232
Methobromide (monohydrate)	214	..	Crystals (H_2O)	232

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methochloride (hydrate)	180 (frothing)	..	Large prisms (H_2O)	232
Methochloroplatinate	..	..	Yellow amorphous solid	54, 232
N-Oxide	80	..	..	181
Hydriodide	102	..	..	181
Hydrobromide	*153	..	Prisms	181, 189
Perchlorate	167	..	..	181, 189
Picrate	*191–192	..	Primrose-yellow scales (H_2O)	212, 20, 54, 209, 214, 225
Sulfate	..	..	White crystals(H_2O)	52
Dihydrate	..	..	White needles(H_2O)	232
Acetyl-	100 (ca)	..	Amorphous	52
Aurichloride	148	..	Leaflets (H_2O)	232
Hydrobromide	..	−8.9°	White powder (C_2H_5OH)	232
Benzoyl-				
Aurichloride	161	..	Amorphous	54
Chloroplatinate	199–200	..	Amorphous	54
Sulfuric ester	244 (dec)	..	Needles (H_2O)	253
Scopolane (see Tropane)	167/760 mm.	..	Oil	167
Aurichloride	242–243 (dec)	..	Prisms (H_2O)	167
Chloroplatinate	229–230	..	Orange spearlike needles (H_2O)	167
Picrate	281 (dec)	..	Yellow pointed needles (C_2H_5OH)	167
Scopolic Acid (see *N*-Methylpiperidine-α, α^1-dicarboxylic acid)				
Scopoligenine	205–206	..	Prisms (C_2H_5OH–ether)	56
Aurichloride	235–236	..	..	56, 64
Chloroplatinate	..	..	Reddish-brown crystals	56
N-Nitroso-	174–175	..	..	56
d-Scopoline (*d*-Oscine)	*109.5–110.5	+54.8° (H_2O)	Radiating needles (pet. ether)	212, 71, 207
d-Bitartrate	*170–171	+27.3° (H_2O)	..	212
Monohydrate	55–56	..	Felted mass of needles (H_2O)	212
l-Bitartrate	174	..	..	71
Hydrochloride	273–274	+26.0°	Prisms (C_2H_5OH)	212
Methiodide	270	+31.7° (H_2O)	Needles (C_2H_5OH)	71
Picrate	*242–243.5	..	Rhombs or glistening needles (H_2O)	212
Benzoyl-				
Aurichloride	189–190	..	Yellow needles	207

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
d-α-Bromo-π-camphorsulfonate	247–248	+54.74° (H_2O)	Diamond-shaped crystals (C_2H_5OH)	212, 207
Hydrochloride	*287 (dec)	+11.79° (H_2O)	Rectangular leaflets	212, 207
Nitrate	200 (dec)	..	Irregular prisms (H_2O)	207
Picrate	211–212	..	Yellow needles	207
dl-Scopoline (*dl*-Oscine)	248/760 mm. 109–110	0°	Hygroscopic prismatic crystals (pet. ether)	20, 25, 52, 54, 56, 57, 58, 64, 87, 162, 167, 170, 174, 207, 212, 231, 232, 253
Aurichloride	225–226	..	Crystals (H_2O–HCl)	20, 26, 52, 56, 57, 64, 87, 167, 174
Hemihydrate	..	..	Prismatic orange platelets (H_2O)	64, 174
Monohydrate	..	..	Orange rhombic plates	52, 64
d-α-Bromo-β-camphorsulfonate	150–155	+61.4° (H_2O)	Needles (C_2H_5OH)	212
d-α-Bromo-π-camphorsulfonate	*237–238	+59.3° (H_2O)	Crystals (C_2H_5OH)	212
Chloroplatinate	228	..	Reddish-brown crystals	64, 20, 25, 235
Monohydrate	228–230	..	Dark orange-red crystals	52, 54, 174, 235
Hydrobromide	282	..	Tabular crystals (H_2O)	56, 167, 212
Hydrochloride (monohydrate)	..	..	Rectangular plates (H_2O)	56, 212
Mandelate	112	..	Leafy crystals (C_2H_5OH)	56
Mercurichloride	..	..	Groups of crystals (H_2O)	20
Methaurichloride	228 (246)	..	Orange four-sided leaflets (H_2O)	25, 56
Methiodide	>250	..	Rhombohedral crystals (CH_3OH)	25, 56, 87, 170
Methochloroplatinate	238	..	Reddish-yellow leaflets	56, 87
Methochloride	>250	..	..	56
N-Oxide	122 (gas)	..	Tabular crystals (H_2O)	64
Hydrobromide	180–190	..	Crystals (C_2H_5OH)	183

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	132–135 (gas)	..	Feathery needles (H_2O)	64
Perbromide	230 (dec)	..	Colorless leaflets (C_2H_5OH)	64
Picrate	237–238 (dec)	..	Flattened rhombs	212, 20, 174, 253
Sulfate	..	..	Crystalline powder (acetone)	56
Acetyl-				
Aurichloride	208–213	..	..	64
Hydrobromide	218–219	..	..	172
Benzoyl-	59	..	Needles	25
Aurichloride	184	..	Yellow needles (H_2O–HCl)	25, 207
d-Camphor-sulfonate	167–168	0°	Diamond-shaped crystals (C_2H_5OH–ethyl acetate)	207
Hydrochloride	266 (gas)	..	Colorless needles (C_2H_5OH)	207
Nitrate	195 (gas)	..	Colorless needles (H_2O)	207
Picrate	185	..	Flattened needles	207
Phenylglycollyl-				
Aurichloride	90 (ca)	..	Amorphous	57
Salicyl-	..	..	White needles (C_2H_5OH–H_2O)	57
Aurichloride	195 (froth)	..	Broad needles	57
Chloroplatinate (monohydrate)	212	..	Bright red needles	57
Dihydrate	205	..	Orange leaflets	57
Hydrobromide	..	..	..	57
Hydrochloride	..	..	Silky white needles (H_2O)	57
Sulfate	..	..	Fine white crystals	57
Tropyl-				
Aurichloride	190	..	Citron-yellow powder (H_2O)	57
Chloroplatinate	246–248 (dec)	..	Flesh-colored ppt.	57
Hydrobromide	..	..	Amorphous, soluble (C_2H_5OH)	57
l-Scopoline	*109.5–110.5	−52.4° (H_2O)	Long needles (pet. ether)	212, 71
d-Bitartrate	*176.5–177.5	+1.06° (H_2O)	Octahedra (H_2O)	71, 212
Hydrobromide	270	−6.6° (H_2O)	..	57
Hydrochloride	*281–282(dec)	−19.71°(H_2O)	Aggregates of prisms	212

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Picrate	*242.5–243.5 (dec)	..	Glistening needles or rhombs (H_2O)	212
Benzoyl-*d*-Bromocamphor-sulfonate	219–227	..	Not rigorously pure	207
Scopolyl Bromide				
Aurichloride	211 (froth)	..	Pale red cubes (H_2O–HCl)	70
Chloroplatinate	221–222	..	Brownish-red prisms and needles	70
Hydrobromide	226–227 (froth)	..	Dense prisms (H_2O)	70
Scopolyl Chloride	102–103/8 mm. 38	..	Long prisms (ether)	253
Chloroplatinate	229–230 (dec)	..	Prisms	253
Selenotropinone	142	..	Thin plates (pet. ether)	219
Dipiperonal-	240	..	Yellow leafy crystals	219
Solandrine (Norhyoscyamine)	..	..	Yellow viscous oil	245
Chloroplatinate	170 (dec)	..	Yellow cubes	245
Picrate	..	..	Radiating groups of prisms	245
Suberone	178.5–179.5/760 mm.	..	Oil	144
Dibenzal-	107–108	..	Prisms	144, 30
Semicarbazone	163–164	..	Plates (CH_3OH)	30, 144, 160
		T		
Teloidine	*168–169	..	..	203
B · H_2O	..	..	Chisel-shaped needles (H_2O–acetone)	203
Aurichloride (hemihydrate)	225 (dec)	..	Yellow hexagonal plates (H_2O)	203
Hydrobromide	295 (dec)	..	Hexagonal plates and needles (C_2H_5OH)	203
Hydrochloride	>300	..	Monoclinic prisms (C_2H_5OH)	203
Tetrabromotropinone	164	..	Yellow right-angled plates (ethyl acetate)	135
Tetrahydro-α-pseudo-desmethylscopoline	143–145/30 mm.	0°	Long white needles	170
Methiodides	(a) 209	..	Groups of crystals (C_2H_5OH)	170

TABLE 2 (*Continued*)

Compound		M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
	(b)	..	..	Oil	170
Picrates	(a)	182	..	Rhombic plates (C_2H_5OH)	170, 71
	(b)	128	..	Rhombs (C_2H_5OH)	170, 71
Tetrahydro-β-pseudo-desmethylscopoline		133–140/27 mm.	..	Oil	170, 71
Methiodide		..	..	..	170
Picrates	(a)	162	..	..	71
	(b)	118	..	..	71
Thiotropinone		126–127	..	Striated plates (ligroin)	219
Picrate		230	..	Yellow plates (acetone)	219
Dipiperonal-		241	..	Yellow leaflets (*i*-amyl alcohol)	219
Tiglic Acid		*64.5	..	Stout prisms (H_2O)	222, 203
Dibromide		*88	..	Long needles (pet. ether)	203, 222
Tigloidine		..	0°	Colorless sirup	222
Aurichloride		*213.5–214	..	Golden-yellow plates (acetone–H_2O)	222
Hydrobromide		*234–235	0° (H_2O)	Tabular crystals (H_2O)	222
Methiodide		*244–245	..	Square plates (C_2H_5OH–ether)	222
Picrate		*239	..	Rectangular plates (C_2H_5OH)	222
Tribromoacetoxy-Tropinone		148	..	Quadratic plates (C_2H_5OH)	141
Tribromopyridine		167–168 (dec)	..	Needles (HNO_3)	135
Trimethylamine					
Aurichloride		250	..	..	248
Chloroplatinate		..	..	Orange-red octahedra	121
Picrate		218	..	..	172
Tropacocaine (see Benzoylpseudotropeine)					
Tropane (see also Scopolane and Hydrotropidine)					
Base		167.5–168.5/760 mm.	..	Oil, $d_4^{15} = 0.9259$	85, 31, 139, 147, 159a
Aurichloride		234–235	..	Groups of yellow crystals (H_2O)	85, 31

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Chloroplatinate (hydrate)	220–221 (dec)	..	Orange-red needles (H_2O),dimorphous	85, 31, 147
Methaurichloride (hydrate)	296 (dec)	..	Golden needles (C_2H_5OH)	139, 31
Methiodide	>300	..	..	139, 31
Methiodide dihydrate	..	..	Cubic crystals(H_2O)	139
Picrate	280–281	..	Fine needles (H_2O)	85, 31
d-Tropic Acid	*129–130	+83.8°(acetone) +72.2° (C_2H_5OH) +81.6° (H_2O)	Glass clear prisms (ether)	61, 108, 212, 213
Quinine salt	*195.5–196.5	−104.3° (C_2H_5OH)	Groups of radiating needles (C_2H_5OH)	212, 61, 108, 213
dl-Tropic Acid	119	..	Fine prismatic needles (H_2O)	12, 17, 20, 82, 166, 168, 171, 192, 209, 213
Ethyl ester	..	..	..	166
Methyl ester	36.5–37.5 159–162/12 mm.	..	Colorless fine needles	168
l-Tropic Acid	*129–130	−81.2 (H_2O)°	Crystals (H_2O)	53, 61, 108, 212, 213
Morphine salt	..	−63° (C_2H_5OH)	Glassy crystals (C_2H_5OH)	213
Quinidine salt (monohydrate)	118–120	+149.1° (C_2H_5OH)	Stout transparent prisms (C_2H_5OH)	212
Quinine salt	*189–190	−140.7°	Glistening plates or needles (C_2H_5OH)	212, 61, 108
Tropidine	163/760 mm.	..	Oil, $d_4^0 = 0.9665$	22, 31, 115, 121, 130
Aurichloride	205 (dec)	..	Fine golden needles (H_2O)	22, 31
Chloroplatinate	225 (dec)	..	Orange needles (H_2O)	22, 31, 121, 130, 145
Ethiodide	..	..	Crystalline mass	22
Hydrobromide	..	..	Crystalline	22
Hydrochloride	..	..	Crystals (H_2O)	22
Methaurichloride	253 (dec)	..	..	31
Methiodide	>300	..	Cubic crystals(H_2O)	22,31,32,121
Methochloroplatinate	237 (dec)	..	..	31
Periodide	92–93	..	Prisms (C_2H_5OH)	22
Picrate	285 (dec)	..	Yellow needles(H_2O)	22, 31
Tropigenine (see Nortropine)				
Tropilene	186–188/759 mm.	..	Colorless oil, $d_4^0 = 1.0091$	22, 121

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Tropilene Amine	161–163/724 mm.	..	Oil	29
Aurichloride	190–191 (dec)	..	Golden-yellow leaflets (H_2O)	29
Chloroplatinate	227–229 (dec)	..	..	29
Phenylthiourea	124–125	..	..	29
Tropilidene (see Cycloheptatriene)				
Tropine	233/760 mm.	..	Colorless needles	176, 13, 20,
Base	63–64		(toluene-pet. ether)	21, 33, 45 147, 154
N-Atropate	..	..	Oil	12
Aurichloride	210–212 (dec)	..	Golden-yellow leaflets (C_2H_5OH)	12, 14, 45, 51, 147, 154, 176
d-Camphorsulfonate	236	+13.6 (H_2O)	Large tabular crystals (H_2O)	205
Chloroplatinate	197–198 (dec)	..	Orange-red monoclinic needles (H_2O)	235, 12, 13, 14, 19, 20 45, 51, 53, 147, 154, 176
Ethiodide	..	..	..	14, 16
Ethochloride	..	..	Fine needles	14, 16
Ethochloroplatinate	..	..	Orange-red monoclinic prisms	14, 16
Hydrochloride	..	..	Deliquescent solid	19
Mercurichloride	..	..	Sharp-angled glistening crystals (H_2O)	14
Methaurichloride	..	..	Fine yellow needles (H_2O)	21
Methiodide	>300	..	Colorless crystals (CH_3OH)	178, 21, 176
Methochloroplatinate	..	..	Orange-yellow prisms (H_2O)	22, 21
Methonitrate	>300	..	Transparent cubes (C_2H_5OH)	202
N-Oxide	238 (dec)	0°	Crystals (C_2H_5OH–CH_3–CO–CH_3)	181, 189
Hydrochloride	>280	..	..	181, 189
Picrate	290–295	..	Rhombs (H_2O)	225, 14, 78, 147, 176
Acetyl-Hydrobromide	*187–187.5	..	Prismatic needles (C_2H_5OH–C_2H_5–O–C_2H_5)	222

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methiodide	*279–280	..	Glistening needles	222
Picrate	*217	..	..	222
Acrylyl-				
Picrate	198	..	..	159
p-Aminobenzoyl-	149–150	..	..	227
Hydrochloride	>250	..	..	227
Dipicrate	173–175	..	..	227
Monopicrate	230	..	..	227
Acetylaminobenzoyl-	151–152	..	Crystals (ether–ethyl acetate)	227
Hydrochloride	>250	..	..	227
Atroglyceryl-	*124–125	..	Oblong plates(C_6H_6)	204
Aurichloride	*145–148	..	Golden prismatic needles(H_2O–HCl)	204
Hydrobromide	*144–145	..	Plates (C_2H_5OH)	204
Methobromide (dimorphous)	*218–219	..	Prismatic needles (C_2H_5OH)	204
	226–227	..	Laminar crystals (C_2H_5OH)	204
Picrate	*178–179	..	Yellow needles (C_2H_5OH)	204
Sulfate	*163–164	..	Matted needles (C_2H_5OH)	204
Atrolactyl- (Pseudo-atropine)	119	..	Brilliant needles	22
Aurichloride	112–114	..	Yellow needles(H_2O)	22
Chloroplatinate	..	..	Reddish-yellow crystals (H_2O)	22
Picrate	..	..	Fine yellow needles (H_2O)	22
Sulfate	..	..	..	22
Benzoyl- (dihydrate)	58	..	Silky glistening leaflets (H_2O)	22, 204
Aurichloride	*190–192	..	Yellow monoclinic plates (C_2H_5OH)	204, 22
d-Camphorsulfonate	240	+10.8° (H_2O)	Flat needles (C_2H_5OH)	22
Chloroplatinate	..	..	Yellow rhombs	22
Hydrochloride	*275	..	Prisms (C_2H_5OH)	204
Picrate	*252–255	..	Yellow pointed rhombic plates	22, 204, 205
β-Bromohydratropyl- hydrobromide	180	..	White crystals (H_2O)	158
Butylaminobenzoyl-	89–90	..	Crystals (ether)	227
Hydrochloride	>270	..	..	227

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
O-Carboxyphenyl-glyceryl(lactone)-	172–173	..	Rosettes acicular crystals(C_2H_5OH)	202
Aurichloride	215–216	..	Clusters of yellow needles (H_2O)	202
Chloroplatinate	193–194 (dec)	..	Groups of yellow needles(H_2O–HCl)	202
Hydriodide	204–205	..	Microscopic prisms (C_2H_5OH)	202
Hydrobromide (monohydrate)	212–213	..	Rosettes of fine acicular crystals (C_2H_5OH)	202
Hydrochloride	228–229	..	Rosettes acicular needles (H_2O)	202
Methobromide	257–258	..	Needles (C_2H_5OH)	202
Nitrate	174–175	..	Fine needles (C_2H_5OH)	202
Picrate	218–220	..	Short yellow needles (H_2O)	202
α-Chlorobutyryl-				
Aurichloride	125	..	..	159
Chloroplatinate	212	..	..	159
Picrate	209	..	..	159
β-Chlorobutyryl-				
Aurichloride	137	..	..	159
Chloroplatinate	210–212	..	Needles (C_2H_5OH)	159
Picrate	216	..	..	159
γ-Chlorobutyryl-				
Chloroplatinate	208	..	..	159
β-Chlorohydratropyl-	..	..	Oil	158
Chloroplatinate	60 (ca)	..	Orange-yellow solid	158
Hydrochloride	167–170	..	Crystalline powder (C_2H_5OH–ether)	158
Picrate	204	..	Crystalline	158
α-Chloropropionyl-				
Aurichloride	131	..	Yellow glistening scales	159
Picrate	211 (dec)	..	Transparent needles	159
β-Chloropropionyl-				
Aurichloride	135	..	..	159
Chloroplatinate	205	..	..	159
Picrate	222	..	..	159
Cinnamyl-	36–37	..	..	204
Monohydrate	45–46	..	Flat needles (pet. ether)	204, 22
Aurichloride	*174–175	..	Clusters of yellow plates (C_2H_5OH)	204, 22

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Chloroplatinate	..	..	Glistening plates (H_2O)	22
Hydrobromide (hydrate)	*254–255	..	Needles (ethyl acetate)	204
Hydrochloride (hydrate)	*272	..	White needles(H_2O)	204, 22
Methobromide	*288–291	..	Glistening leaflets (ethyl acetate)	204
Picrate	*244–245	..	Yellow needles (C_2H_5OH)	204
Sulfate (hydrate)	*227–229	..	Irregular plates (C_2H_5OH)	204
Crotonyl-				
Picrate	190 (dec)	..	Yellow platelets	159
α, β-Dibromopropionyl-				
Picrate	188	..	..	159
Fumaryl-	*165–166	..	Monoclinic scales (acetone)	204
Hydriodide (hydrate)	283–285	..	Clusters of plates (H_2O)	204
Hydrochloride (hydrate)	>*310	..	Plates (H_2O–acetone)	204
Glycollyl-	113–114	..	Laminar crystals (C_6H_6)	201
Aurichloride	186–187	..	Yellow acicular crystals	201
Chloroplatinate	225–226	..	Orange stout needles	201
Hydriodide (hydrate)	187–188	..	Acicular crystals (CH_3OH)	201
Hydrochloride	171–172	..	Deliquescent crystals	201
Nitrate	120–121	..	Laminar crystals (C_2H_5OH)	201
o-Hydroxybenzoyl-	*60–63	..	Silky leaflets (H_2O)	204, 22
Aurichloride	*222 (dec)	..	Golden needles (C_2H_5OH–H_2O)	204, 22
Chloroplatinate	..	..	Yellow prisms(H_2O)	22
Hydrochloride (hydrate)	*267	..	Prismatic needles (C_2H_5OH)	204
Hydrogen sulfate	*254	..	Prismatic needles (C_2H_5OH)	204
Picrate	..	..	Amorphous yellow solid	22
m-Hydroxybenzoyl-	*233–234	..	Rosettes of leaflets (C_2H_5OH–H_2O)	204, 22

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Chloroplatinate	..	..	Orange-yellow leaflets	22
Hydriodide	*248 (dec)	..	Stout needles (H_2O)	204
Hydrochloride	*304 (dec)	..	Prismatic needles (C_2H_5OH)	204, 22
Picrate	..	..	Rhombic plates (C_2H_5OH–H_2O)	22
Sulfate (tetrahydrate)	..	..	..	22
p-Hydroxybenzoyl-	*232–233 (dec)	..	Clusters of plates (C_2H_5OH)	204, 22
Aurichloride	*222 (dec)	..	Yellow plates (C_2H_5OH–H_2O)	204, 22
Chloroplatinate	..	..	Orange leaflets(H_2O)	22
Hydrochloride	*315 (dec)	..	Monoclinic plates (H_2O)	204
Nitrate	..	..	Prisms (HOAc)	22
Picrate	*235–237	..	Yellow monoclinic leaflets (C_2H_5OH)	204, 22
α-Hydroxy-β-phenylpropionyl-	*89–90	..	Rosettes needles (ether)	204
Aurichloride	*188–189	..	Yellow plates (C_2H_5OH)	204
Hydrobromide	*173–175	..	Chisel-shaped needles (acetone)	204
Methobromide	*213–215	..	Scales (C_2H_5OH)	204
Picrate	*159–160	..	Yellow needles (C_2H_5OH)	204
Sulfate	*192–193	..	Prismatic needles (acetone)	204
α-Hydroxy-β-2-pyridyl-propionyl-	..	..	Sirup	204
Diaurichloride (hydrate)	*223 (efferv)	..	Granular solid (C_2H_5OH)	204
Dihydrochloride	*208–210 (dec)	..	Prisms (C_2H_5OH)	204
Sulfate	*152–154	..	Prismatic needles (C_2H_5OH)	204
Isocoumarin-carboxyl-	179–180	..	Glistening leaflets (C_2H_5OH)	202
Aurichloride	254–256 (dec)	..	Yellow crystals (C_2H_5OH)	202
Chloroplatinate (monohydrate)	264–265 (dec)	..	Crystals (H_2O–HCl)	202
Hydriodide (monohydrate)	280–281	..	Glistening scales	202

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrobromide (hemihydrate)	252–253 (dec)	..	Matted needles (C_2H_5OH)	202
Hydrochloride	287–288 (dec)	..	Slender needles (C_2H_5OH)	202
Methobromide	..	..	Matted needles (C_2H_5OH)	202
Nitrate (hemihydrate)	228–229 (dec)	..	Glistening needles (C_2H_5OH)	202
Picrate	265 (dec)	..	Yellow needles (C_2H_5OH)	202
dl-α-Methylbutyryl-				
Hydrobromide	*210	..	Glistening laminae (C_2H_5OH–ether)	223
Methiodide	*288 (dec)	..	Rectangular plates (C_2H_5OH–ether)	223
Picrate	*225	..	Golden-yellow prisms (acetone–H_2O)	223
Methylparaconyl-				
Aurichloride	64–65	..	Silky leaflets (C_2H_5OH–HCl)	201
Chloroplatinate	233–234	..	Yellow powder (H_2O–HCl)	201
Hydriodide	177–178	..	Groups of crystals (C_2H_5OH)	201
Hydrobromide	196–197	..	Laminar crystals (C_2H_5OH)	201
Picrate	190–191	..	Yellow laminar crystals (C_2H_5OH)	201
p-Nitrobenzoyl-	135–136	..	..	227
Phenylacetyl-	..	..	Oil	22, 204
Aurichloride	*179	..	Yellow hexagonal plates (C_2H_5OH)	204, 22
Chloroplatinate	..	..	Orange-red cubes (H_2O–HCl)	22
Hydrobromide	..	..	Colorless crystals	22
Hydrochloride	198–200	..	..	227, 22
Picrate	*170–171	..	Yellow prisms (C_2H_5OH)	204, 244
Sulfate (hydrate)	*107–108	..	Glistening leaflets (acetone)	204
Formylphenylacetyl-	214 (dec)	..	..	244
Hydrochloride	204 (dec)	..	..	244
Oxime	134 (dec)	..	..	244
Oxime hydrochloride	165	..	..	244

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Phenylaminoacetyl-	..	..	Non-crystalline	204
Dihydrobromide	*199	..	Short needles (C_2H_5OH)	204
Dipicrate	*231 (dec)	..	Microscopic needles (C_2H_5OH)	204
Phenylcarbamo-	*171–172	..	..	204
Aurichloride	*188–189	..	Orange-red powder (H_2O)	204
Hydrochloride	*289–290	..	Rectangular plates (C_2H_5OH–H_2O)	204
Picrate	*223–224	..	Yellow plates (C_2H_5OH–H_2O)	204
Sulfate (hydrate)	*201	..	Prismatic needles (H_2O)	204
Phenylchloroacetyl-	..	..	Granular(pet.ether)	204
Aurichloride	*148–149	..	Golden grains (C_2H_5OH)	204
Hydrochloride	*205–206	..	Glistening needles (acetone)	204
Methobromide	*240–242 (dec)	..	Microcrystalline powder (C_2H_5OH)	204
Picrate	*203–204	..	Feathery needles (C_2H_5OH)	204
Phenylglycollyl- (see Homatropine)				
Phthalidecarboxyl-	79–80	..	Square laminar crystals (ethyl acetate)	201
Aurichloride	184–185	..	Golden-yellow leaflets (C_2H_5OH)	201
Chloroplatinate	234–235	..	Yellow powder	201
Hydrobromide	128–129	..	Glistening leaflets (C_2H_5OH)	201
Hydrochloride	242–244 (dec)	..	Laminar crystals (C_2H_5OH)	201
Nitrate (hydrate)	169–171	..	Square plates or needles (H_2O)	201
Phthaloyl-	70	..	Silky needles (H_2O)	22, 204
Aurichloride	*110–113	..	Diamond-shaped plates (C_2H_5OH–H_2O)	204
Chloroplatinate	..	..	Needles (H_2O)	22
Hydriodide (hydrate)	*205	..	Long needles (H_2O)	204
Sulfate	*160–165 (dec)	..	Short needles (C_2H_5OH–acetone)	204

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Protocatechyl-	253–254 (dec)	..	Acicular crystals (C_2H_5OH)	201
Chloroplatinate	228–229 (efferv)	..	Laminar crystals	201
Hydrochloride	>300	..	Small plates or needles (H_2O)	201
Picrate	260–262 (dec)	..	Yellow plates (C_2H_5OH)	201
Tartryl-	*223–224	..	Glistening prisms (C_2H_5OH)	204
Hydrochloride (hydrate)	*273 (dec)	..	Microscopic needles (C_2H_5OH)	204
Picrate	*287 (efferv)	..	Yellow grains (H_2O)	204
Sulfate (hydrate)	*287 (dec)	..	Long needles (H_2O)	204
Terebyl-	66–67	..	Diamond-shaped crystals (acetone)	201
Aurichloride (monohydrate)	85–86 (ca)	..	Crystals (H_2O–HCl)	201
Hydriodide	213–214	..	Laminar crystals (C_2H_5OH)	201
Hydrobromide	230–231	..	Laminar crystals (C_2H_5OH)	201
Hydrochloride	82	..	Leaflets (acetone)	201
Picrate	198–199	..	Yellow leaflets (C_2H_5OH–H_2O)	201
Tiglyl-				
Hydrobromide	*207	..	Rectangular laminae	222
Methiodide	*289–290	..	Colorless laminae	222
Picrate	*200	..	Golden-yellow plates	222
Vinylacetyl-				
Chloroplatinate	204	..	..	159
β-Tropine	60–61	..	Colorless needles	25
Chloroplatinate	187	..	Crystals (H_2O)	25
Tropine Isomer	225–230/760 mm. 53	..	Crystals (ether–pet. ether)	72
Aurichloride	..	..	..	72
Chloroplatinate	184	..	Yellow needles (C_2H_5OH–ether)	72
Hydriodide	185 (dec)	..	Granular powder	72
Hydrobromide	175	..	Crystals (C_2H_5OH–ether)	72
Hydrochloride	157–160	..	Plate-like crystals	72
Methiodide	238–240	..	Needles (C_2H_5OH–CH_3I)	72

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methochloride	..	..	Hygroscopic needles (C_2H_5OH)	72
Picrate	237 (dec)	..	Yellow crystals (C_2H_5OH)	72
Benzoyl-	139–140	..	Prisms (C_2H_5OH–ether)	72
d-Tropinic Acid	..	+15.1° (H_2O)	..	119
Dimethyl ester methaurichloride	114	..	Leaflets and needles (CH_3OH–H_2O)	127
Methiodide	176–177 (dec)	..	Leaflets and needles (CH_3OH)	127
Monomethyl ester methaurichloride	195 (dec)	..	Needles (C_2H_5OH)	127
dl-Tropinic Acid	248 (dec)	..	Colorless needles (C_2H_5OH–H_2O)	21, 126, 116
Chloroplatinate	..	..	Orange-yellow crystals	21
Hydrochloride	..	..	Rosettes of crystals (C_2H_5OH–ether)	21
Dimethyl ester	268–272/760 mm.	..	Colorless oil	127
Methaurichloride	116–117	..	Golden leaflets (C_2H_5OH)	127
Methiodide	171–172 (dec)	..	Thin prisms (H_2O)	127
Picrate	121	..	Orange-yellow four-sided prisms	127
Monomethyl ester methaurichloride	182 (dec)	..	Orange-yellow needles (H_2O)	127
Dipropyl ester	..	..	Oil	127
Methaurichloride	103	..	Sulfur-yellow needles (C_2H_5OH)	127
Tropinone	*224–225/760 mm. 42	..	Long flattened colorless needles (pet. ether)	130, 210, 36, 128, 129, 145
Aurichloride	160–170 (dec)	..	Yellow prismatic crystals (H_2O–HCl)	128
d-Camphorsulfonate	216 (dec)	..	Mosslike growths of fine needles (ethyl acetate)	205
Chloroplatinate	191–192 (dec)	..	Orange-red prisms (H_2O)	128, 145
Hydrochloride	188–189 (dec)	..	Rosettes of crystals (C_2H_5OH)	128
Methaurichloride	205–206 (dec)	..	Egg-yellow solid	128
Methiodide	263–265 (dec)	..	Cubes (H_2O)	128
Picrate	218–220 (dec)	..	Canary-yellow needles (H_2O)	210, 128, 205

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dibenzal-	152	..	Yellow prisms (C_2H_5OH)	140, 36, 141, 145, 146
Methiodide	264–265 (dec)	..	Silky needles (H_2O)	140
Phenylhydrazone	193	..	Yellow plates (C_2H_5OH)	140
Difural-	138	..	Canary-yellow prisms and needles (C_2H_5OH)	141
Hydrochloride	237–238 (dec)	..	Microscopic prisms (C_2H_5OH)	141
Methiodide	281 (dec)	..	Yellow leaflets(H_2O)	141
Diisonitroso-	197 (dec)	..	Bronze-yellow prisms (H_2O)	141
Hydrobromide	253 (dec)	..	Yellow cubes (H_2O)	141
Hydrochloride	260 (dec)	..	Yellow cubes or rhombohedra (H_2O)	141
Dibenzoyl	172 (dec)	..	Long needles (H_2O)	141
Oxime- (anhydride)	185–186 (dec)	..	Long silky needles	141
Oxime anhydride hydrochloride	220 (dec)	..	Four-sided plates (H_2O)	141
Oxime anhydride, benzoyl deriv.	150–152	..	Glistening needles (C_2H_5OH)	141
Dioxalyl-	176 (dec)	..	Prisms or rhombohedral plates (C_2H_5OH)	141
Dipiperonal-	214	..	Yellow needles (ethyl acetate)	210
Monooxalyl-	169.5 (dec)	..	Six-sided plates (C_2H_5OH)	141
Chloroplatinate	194–195	..	Four-sided leaflets	141
Hydrochloride	194 (dec)	..	Glistening prisms (C_2H_5OH)	141
Oxime	111–112	..	Fine prisms(ligroin)	128, 129, 130
Hydrochloride	242 (dec)	..	Prisms (C_2H_5OH)	128
Methaurichloride	182 (dec)	..	Yellow solid (H_2O)	128
Methiodide	236 (dec)	..	Long prisms (C_2H_5OH–H_2O)	128
Open tropinone (*meso*)	86/14 mm.	..	Yellow oil	76
Hydrobromide	174–175	..	Small prisms (isopropanol)	76
Hydriodide	169–170	..	Prisms (C_2H_5OH)	76
Methiodide	180 (dec)	..	Crystals (CH_3OH)	76
Perchlorate	166–168	..	Prisms (acetone)	76
Picrate	163–164 (dec)	..	Prisms (acetone)	76

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Oxime	92	..	Houselike crystals (pet. ether)	76
Hydrochloride	200 (froth)	..	Needles (C_2H_5OH)	76
Open tropinone(racemic)				
Oxime	93–94	..	..	76
Hydrochloride	215–217 (dec)	..	..	76
Tropinonecarboxylic Ester (ethyl)	107/0.5 mm.	..	Oil	38, 37
Hydrate	64–65	..	Crystals (H_2O)	179
Hydrochloride	*168	..	Prisms (C_2H_5OH–ether)	38
Methiodide	*190–192	..	Plates (CH_3OH)	38
Picrate	151	..	Yellow needles(H_2O)	179, 38
Tropinonecarboxylic Ester (methyl)	111	..	Crystals (CH_3OH)	38
Hydrate	96–98	..	Crystals from water	179
Hydrochloride	*180	..	Serrated prisms (CH_3OH–ether)	38
Picrate	163–164	..	Crystals (methyl-ethyl-ketone)	179
Benzoyl-	*75–76	..	Needles (C_6H_6–pet. ether)	38
Hydriodide	*210	..	..	38
Hydrochloride	*188	..	..	38
Nitrate	*171	..	..	38
d-Open tropinone-carboxylic Methyl Ester	127–128/16 mm.	..	Oil	76
Hydrochloride	93–95	+17.0° (H_2O)	Crystals (acetone)	76
Monohydrate	105–106	..	Crystals (acetone)	76
Methiodide	116–119 (dec)	..	Small needles (C_2H_5OH)	76
Oxime	153–155 (dec)	..	Crystals (C_2H_5OH)	76
Tropylamine	91–92/12 mm. 211/760 mm.	..	Oil even at −20° C.	142
Chloroplatinate	257 (dec)	..	Rhombohedral plates (H_2O)	142
Dithiocarbamate	194–195 (dec)	..	Aggregates of crystals (H_2O)	142
Picrate	235 (dec)	..	Four-sided leaflets (H_2O)	142
Thiourea	*144–146	..	Plates or prisms	142
α-Truxillic Acid (γ-Isatropic)	266–267 (274)	..	Needles (C_2H_5OH)	98, 236
Ethyl ester	146	..	Needles (C_2H_5OH)	98
Methyl ester	330/760 mm. 174	..	Needles (CH_3OH)	98

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
β-Truxillic Acid	206	..	Colorless leaflets (C_6H_6)	236, 98
Ethyl ester	264–270/760 mm.	..	Oil	98
Methyl ester	76	..	Prisms or needles	98
α-Truxilline	63 (sinter)	..	..	103a, 236
Hydrochloride	274	..	..	106
β-Truxilline	45–120 (dec)	−29.3°	Amorphous solid	106, 98
		V		
Valeroidine	85	−9.0°(C_2H_5OH) −4.0°(H_2O)	Laminar crystals	222
Aurichloride	..	..	Yellow oil	222
Hydrobromide	*170–172	+5.0°(H_2O) +2.5°(C_2H_5OH)	Small needles (C_2H_5OH–ether)	222
Methiodide	*205.5–206	..	Six-sided laminae (CH_3OH–ether)	222, 224
Oxalate	*202	..	Prismatic needles	222
Oxidation product	*136	−16.6°(C_2H_5OH)	Pearly laminae (acetone)	224
Hydrolysis product	*200 (ca)	..	Yellow tabular crystals (acetone-ether)	224
Picrate	*152–153	..	Needles (H_2O)	222
Acetyl-Hydrobromide	*197	..	Colorless needles (C_2H_5OH–ether)	224
Veratric Acid	182–184	..	Crystals (C_6H_6)	176, 178
		Z		
Z-(base) mixture poroidine and isoporoidine				223, 222

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Chapter VII

The Strychnos Alkaloids

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I. Isolation and Color Reactions

Strychnine and brucine, which occur in the seeds of *Strychnos nux-vomica*, L. and in the beans of *Strychnos ignatii*, Berg., are isolated (260) by mixing the powdered seeds with slaked lime and adding sufficient water to make a paste. The paste is dried and extracted with chloroform. The alkaloids are recovered from this chloroform solution by extraction with dilute sulfuric acid, followed by precipitation of the bases with ammonia. Extraction of the crude alkaloid mixture with 25% alcohol dissolves the brucine, while the residue contains most of the strychnine. The crude alkaloids are purified by crystallization from alcohol.

The mother liquors from the large-scale preparation of these alkaloids yield small amounts of α- and β-colubrine (189), pseudostrychnine (189) and vomicine (8). Struxine and strychnicine have been reported as constituents of the Ignatius bean; however, the homogeneity of these products is questionable (189).

A very dilute solution of strychnine and its derivatives, containing the lactam grouping, Na–CO, in 80% sulfuric acid gives a reddish-violet to bluish-purple color (Otto reaction) on the addition of a trace of potassium dichromate solution.

Strychnidine and a great majority of its derivatives develop a bright red color in weakly acid solutions on the addition of a little ferric chloride. Tetrahydrostrychnine, under similar conditions, develops a reddish-brown color.

Brucine gives the well-known intense orange-red coloration with traces of nitric acid. This color reaction is improved if the alkaloid is first dissolved in some acetic acid.

Brucidine, the brucine analog of strychnidine, gives a brownish-green coloration when a dilute mineral acid solution of the base is treated with ferric chloride.

II. Elucidation of the Structure of Strychnine and Brucine

1. Functional Groups

Strychnine ($C_{21}H_{22}O_2N_2$) (2, 37) is a monoacidic tertiary base (*tert*-basic N is termed N_b) which contains a cyclic amide (2, 244) (the N in $\overset{O}{\overset{\|}{N-C-}}$ is termed N_a). Hydrolysis of strychnine with alcoholic sodium hydroxide cleaves the lactam grouping with the formation of the amino acid, strychninic (strychnic) acid ($C_{20}H_{22}ON(N_aH)(CO_2H)$ (2, 47, 244). Strychninic acid, which forms a nitrosamine (2), is stable to cold mineral acid but on warming a molecule of water is lost, and the lactam of strychnine is reformed (2).

The basic nitrogen atom (N_b) of strychnine is tertiary for quaternary alkylstrychninium salts result from reaction with molar proportions of alkyl halides (18, 208). The alkylstrychnines (2, 4, 47, 208, 256) result from fission of the lactam grouping and betaine formation with the quaternary ammonium hydroxide grouping. The secondary amine (N_aH) of methylstrychnine ($C_{20}H_{22}O(N_b^+CH_3)(N_aH)(CO_2^-)$ may be further methylated with the formation of dimethylstrychnine ($C_{20}H_{22}O$) (N_aCH_3) ($N_b^+CH_3$) (CO_2^-) (2, 47), or if it is heated with mineral acid lactamization results in the formation of methylstrychninium salts (47).

Reduction of strychnine ($C_{21}H_{22}O_2N_2$) (dilute sulfuric acid solution) at a lead cathode (49, 198, 229) yields strychnidine ($C_{21}H_{24}ON_2$) and tetrahydrostrychnine ($C_{21}H_{26}O_2N_2$). (Similarly, brucine ($C_{23}H_{26}O_4N_2$) yields brucidine ($C_{23}H_{28}O_3N_2$) (51) and tetrahydrobrucine ($C_{23}H_{30}O_4N_2$) (51, 119, 130).) Strychnidine is no longer an amide, but a ditertiary diacidic base (dimethiodide (200)). Evidently the group $\overset{O}{\overset{\|}{-C-}}N_a$ has been reduced to $-CH_2-N_a$ (49, 51). Tafel demonstrated that other cyclic amides (succinimide, isopropylsuccinimide) under similar conditions underwent reduc-

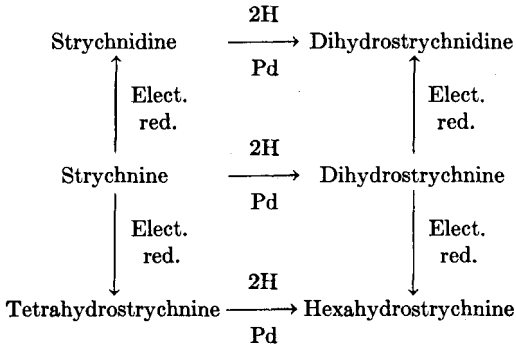
A solution of 150 g. of strychnine in 900 g. of sulfuric acid and 600 cc. of water is distributed equally between the cathode chambers of six cells (194) connected in series. A current of 5 amperes is passed through the solution for 16 hours and the temperature maintained at 12°. The solution is diluted with ice, filtered, and made alkaline with a large excess of concentrated sodium hydroxide solution. The granular precipitate, after washing and drying, is extracted with 800 cc. of boiling ethanol. The residue (54 g., m.p. 183–185°), after removal of the solvent, is fractionally crystallized from benzene and yields 36 g. of tetrahydrostrychnine (m.p. 202°) and then 17 g. of strychnidine melting at 244–245°.

The residue from the first extraction, when crystallized from alcohol, gives an additional 53 g. of strychnidine melting at 243–245°.

tion (50). In tetrahydrostrychnine the cyclic amide ring has been opened and the carboxyl reduced to a primary alcohol since mineral acid (3, 51), phosphorus pentoxide (3), or phosphorus oxychloride (197) dehydrate it to strychnidine. The preparation of tetrahydrostrychnine (although not well characterized) by the catalytic reduction (palladous chloride + gum arabic) of an acid solution of strychnine at three atmospheres pressure has also been reported (66, 132).

The oxidation ($KMnO_4$) of strychnine to *N*-oxalylanthranilic acid (114) suggests the direct attachment of a nitrogen atom to a benzene nucleus. This is the N_a atom because dimethylstrychnine exhibits the properties of an *N*-disubstituted aniline with a free *para*-position, where it couples with benzaldehyde (zinc chloride) to give a leuco base or with diazobenzenesulfonic acid to give a colored azo compound (2).

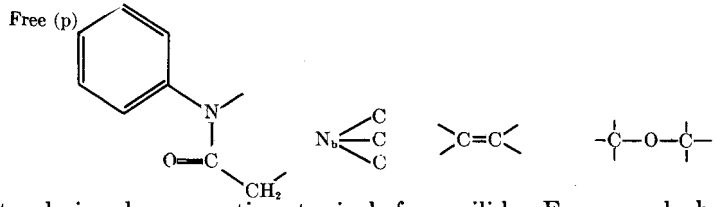
Strychnine and brucine contain one double bond since catalytic hydrogenation at room temperature and pressure yields dihydrostrychnine and dihydrobrucine respectively. Similarly dihydrostrychnidine-A (also dihydrobrucidine (222)) results from the absorption of two atoms of hydrogen by strychnidine (brucidine) or from the electrolytic reduction of dihydrostrychnine (198) (dihydrobrucine (203)). Similarly the absorption by tetrahydrostrychnine of two atoms of hydrogen (Pd) leads to hexahydrostrychnine (dihydrotetrahydrostrychnine) (198, 206). These conversions may be represented as follows:



The nature of the second oxygen of strychnine is most readily deduced from a study of dihydrostrychnidine-A. (The A is to distinguish it from the dihydrostrychnidines-B and -C, resulting from the phosphorus and hydriodic acid reduction of strychnidine (200), and from dihydrostrychnidine-D.) The passivity of the oxygen atom of dihydrostrychnidine-A to carbonyl reagents and phosphorus trichloride substantiates the conclusion that the oxygen of strychnidine-A is a component of a cyclic ether system because in the formation of dihydrostrychnidine-B strychnidine-A is cleaved without loss of carbon. Furthermore, the results of the catalytic

hydrogenation of strychnidine in the presence of a promoter (HCl) are in accord with this theory. Strychnidine, in the presence of a catalyst (132, 134), can be made to absorb one mole (reduction of the double bond), four moles (ethylene + benzene nucleus), or five moles (ethylene, benzene nucleus, and hydrogenolysis of the cyclic ether) of hydrogen with the formation of di-, octa-, and decahydrostrychnidines. The last forms a monoacetyl derivative which is characterized as its diperchlorate. Diperchlorate formation argues in favor of an *O*-acetate in preference to an *N*-acetyl derivative. The hydroxyl of decahydrostrychnidine results from hydrogenolysis of the original cyclic ether grouping of strychnidine.

Strychnine (200) (but not strychnidine), brucine (200) and their dihydro derivatives (19, 139) as well as a number of substitution products of strychnine (bromostrychnine (149) and chlorostrychnine (158)) condense with benzaldehyde in the presence of alcoholic sodium hydroxide or sodium ethylate to form the yellow benzalstrychnine (C_6H_5–CH = $C_{21}H_{20}O_2N_2$), etc. A colorless isomeric substance accompanying the yellow benzaldihydrobrucine has been shown to result from the condensation of benzaldehyde with isodihydrobrucine (148, 179). Benzalstrychnine has been reduced by sodium amalgam to benzylstrychnine (135, 149) and by catalytic hydrogenation to benzyldihydrostrychnine (135, 149). Strychnine (17) and brucine (17) also condense with amyl nitrite to form isonitroso derivatives. The isonitroso group of isonitrosostrychnine (20) and isonitrosobrucine (20) has been converted by standard methods to an amine, and thence to a hydroxyl group in the case of strychnine (but not brucine). The diagnosis of one of the oxygen atoms of strychnine as an ether and the absence of any α-picoline type of reactivity suggests that the active methylene must be alpha to the carbonyl of $-N_a-\overset{\overset{O}{\|}}{C}-$. Thus the following groups have been recognized in strychnine:

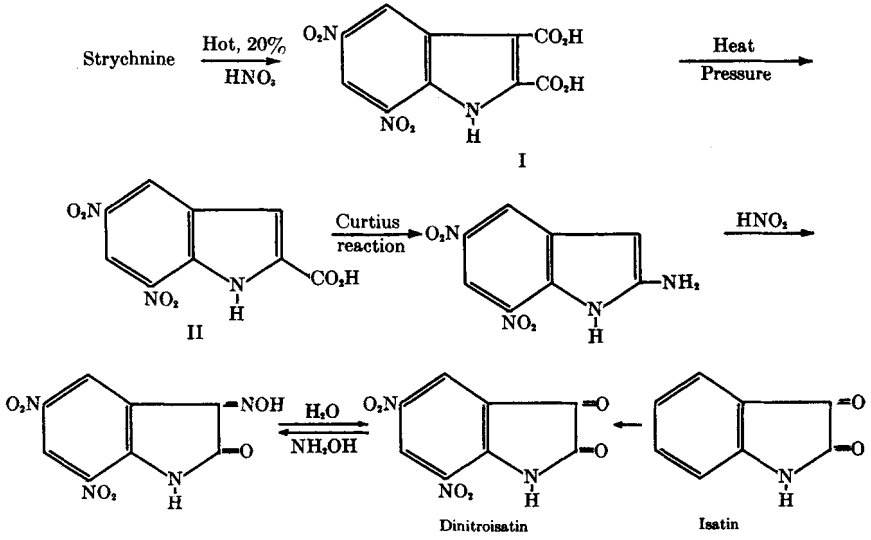


Strychnine shows reactions typical of an anilide. For example, bromine (40, 63, 81, 192, 243) and chlorine (158, 184) (under controlled conditions) substitute for a hydrogen in the free *para*-position of the benzene nucleus; however, halogenation will proceed further to give tri- and tetrahalogenated derivatives (158, 188). *p*-Nitrostrychnine (108, 243) and 3′,5′-dinitrostrychnine (37) have been prepared. Hydrolysis of dinitrostrychnine to

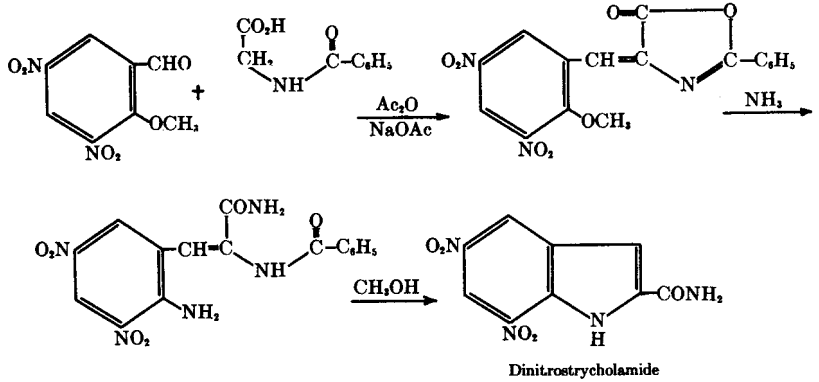
dinitrostrychninic acid followed by oxidation (HNO_3) to dinitrostrycholcarboxylic acid (I) (250) located the two nitro groups of dinitrostrychnine at carbons 3′ and 5′ (XV). Although the sulfonation of strychnine and brucine (59, 60, 68, 131, 135, 138) has been reported the evidence at hand indicates that the sulfonic acid residue does not enter the benzene nucleus (three sulfonic acids of brucine (138) and of strychnine (56, 59) have been reported) because oxidation of these brucinesulfonic acids yield the sulfonic acid derivatives (125, 131, 133) of dioxonucine dihydrate and of carboxyaponucine.

2. Nuclear Structure — Products of Alkaline Degradation

a. Indole Nucleus. Indole is one of the products of the alkaline pyrolysis of strychnine (38). However, indole derivatives are obtained from strychnine under more gentle conditions by oxidation with 20% nitric acid (3). By this reagent, strychnine is oxidized to a dicarboxylic acid, dinitrostrycholcarboxylic acid ($C_{10}H_5O_8N_3$) (diester (202)) as well as to variable amounts of picric acid and 3,5-dinitrobenzoic acid. The C_{10}-acid decarboxylates readily to the monocarboxylic acid (amide (213) and monomethyl ester (3, 201, 202)), dinitrostrychol ($C_9H_5O_6N_3$) (II) when heated with water under pressure (3). Dinitrostrychol, at first, was considered to be a dihydroxyquinoline derivative (201) but the degradation of this acid (Curtius method) to an amine followed by oxidation (nitrous acid) and hydrolysis of the resulting oxime to dinitroisatin necessitated a revision of the structure of dinitrostrychol to II (204, 210). This series of reactions finds expression in the following sequence:



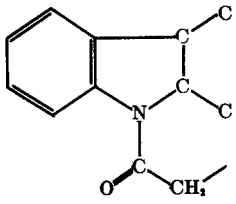
The structure of dinitrostrychol has been conclusively proven by synthesis of the corresponding amide (5,7-dinitroindole-2-carboxyamide) (213). There are a number of alternatives for the intermediates but the following is a possible method of representing this synthesis.



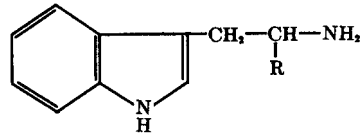
Dinitrostrycholamide

The most probable formula for dinitrostrycholcarboxylic acid is I, for alternative formulas with the carboxyl attached to the benzene nucleus are highly improbable in view of the simultaneous formation of picric acid and 3,5-dinitrobenzoic acid, and secondly because of the oxidation (alkaline permanganate) of strychnine to oxalylanthranilic acid (XI) (114). These other alternatives are definitely precluded by a consideration of the relation of strychnine to brucine and of the course of the degradation of the aromatic nucleus in derivatives of both these alkaloids.

The nuclear structure of strychnine may safely be expanded to III since the carbonyl of $\diagdown N_a\text{–}CO\text{–}$ cannot be in the α-position of the indole nucleus (dinitrostrychol formation).



III



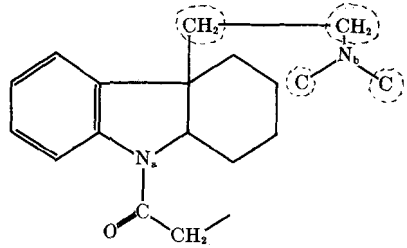
R = H, CO_2H

IV

b. Tryptamine. An alkaloid which is an indole derivative and contains two nitrogen atoms might be expected on biogenetic grounds to be related to tryptophane (IV, R = CO_2H). Experimental support for this conclusion was not forthcoming until 1936 when tryptamine (IV, R = H) was

isolated from the action of alcoholic potassium hydroxide upon strychnine (223, 249), strychninonic acid (249), and strychninolone (249). This base might be a product of rearrangement but it is more likely that the skeleton is present as such in the strychnine molecule.

c. Carbazole Nucleus. It has been known since 1888 that carbazole is a product of the vigorous decomposition of strychnine (245) and of methylstrychnine (196) which permits expansion of the working formula to V (258). The carbons attached to the tryptamine nitrogen of V are indicated in a circle to show that they may be part of a ring.



V

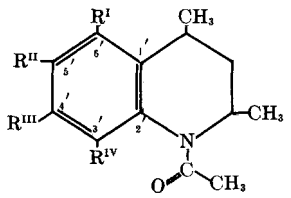
d. Other Products. Products, other than those already mentioned, resulting from the alkaline degradation of strychnine are β-picoline (45, 245), skatole (44, 245), β-collidine (223, 230), and a base $C_{10}H_{11}N$ (223), as yet unidentified. A similar reaction on brucine has yielded β-ethylpyridine, β-picoline, and five products (240) as yet not identified, as well as ammonia and methylamine.

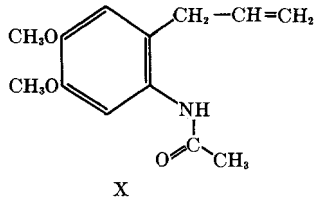
3. Relation of Brucine to Strychnine

Brucine ($C_{23}H_{26}O_4N_2$) (1) differs from strychnine ($C_{21}H_{22}O_2N_2$) by two methoxyl groups (Zeisel) which may be cleaved by heating brucine with concentrated hydrochloric acid (191) in a sealed tube. The degradations of brucine parallel those of strychnine and in many instances lead to the same degradation products. Both brucine and strychnine are oxidized (chromic and sulfuric acids) to a mixture of carboxyaponucine (Hanssen's C_{16}-acid) ($C_{16}H_{20}O_4N_2$) (8a, 9, 10, 41) and 2,3-dioxonucine dihydrate (Wieland's C_{17}-acid) ($C_{17}H_{22}O_6N_2$) (8a, 9, 10), while strychnidine (112) and brucidine (117) yield 2,3-dioxonucidine. This demonstrates that at least part of the nuclear structure is common to both alkaloids. More recently brucidine (132) has been reduced, in the presence of a promoter, (HCl), to octahydrostrychnidine ($C_{21}H_{32}ON_2$) (the two methoxyls of brucidine were eliminated by hydrogenolysis).

The action of nitric acid upon brucine under controlled conditions yields bruciquinone (159) while under more vigorous conditions cacotheline (the nitrate of nitrobruciquinone hydrate) ($C_{21}H_{21}O_7N_3 \cdot HNO_3$) results.

Quinone formation indicates that the two methoxyls of brucine are either *ortho* or *para* to each other. The methoxyl groups of brucine were tentatively assigned to C_4' and C_5' by applying the cacotheline reaction to the synthetic models VI–X. Only those models which had the methoxyls on carbons 4′ and 5′ (strychnine numbering) simulated the nitric acid reaction of brucine (195). The methoxyls of brucine were definitely assigned to



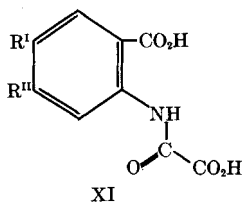


X

VI	$R' = R^{IV} = OCH_3$,	$R'' = R''' = H$
VII	$R' = R^{IV} = H$,	$R'' = R''' = OCH_3$
VIII	$R' = R'' = OCH_3$,	$R''' = R^{IV} = H$
IX	$R' = R'' = H$,	$R''' = R^{IV} = OCH_3$

these positions by oxidation of the alkaloid to *N*-oxalyl-4,5-dimethoxyanthranilic acid (XI, $R' = R'' = OCH_3$) (114).

The two minor alkaloids of *nux vomica*, α- and β-colubrine, have likewise been oxidized respectively to the 4-methoxy- (XI, $R' = H$, $R'' = OCH_3$) and the 5-methoxy- (XI, $R'' = H$, $R' = OCH_3$) derivatives of *N*-oxalylanthranilic acid (189). Although there is no experimental evidence as yet to substantiate the conclusion, it is considered (from analytical figures and similar origin) that these minor alkaloids and strychnine have a common nucleus.



$R^I = H, OCH_3$

$R^{II} = H, OCH_3$

XI

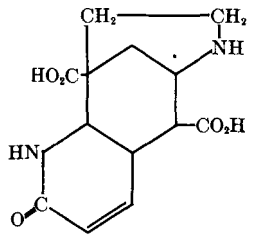
4. Products of Oxidative Degradation

The center of attack of the oxidizing agent upon the *Strychnos* alkaloids is dependent largely upon the reagent used. Chromic acid usually attacks the benzene nucleus (strychnidine → 2,3-dioxonucidine), while potassium permanganate in acetone solution usually attacks the double bond (strychnine → strychninonic acid). The isolation of *N*-oxalylanthranilic acid from the alkaline permanganate oxidation of strychnine indicates that the

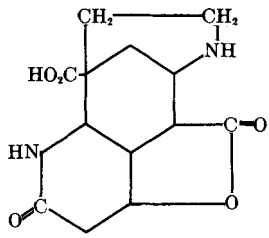
oxidative degradation by this reagent is far more extensive than when the solvent is acetone. Bromine in hydrobromic acid is considered to oxidize the double bond of carboxyaponucidine (113), 3-carboxymethylene-2-oxonucine hydrate (101, 104) and its N_b-alkyl derivative (161), 2,3-dioxonucidine (112, 123), 2,3-dioxonucine dihydrate (106, 111), and 3-hydroxy-2-oxonucidine (113) to keto aldehydes although only monocarbonyl derivatives (oxime and semicarbazone) have been prepared. Further oxidation of these keto aldehydes by mercuric oxide in many instances leads to the corresponding keto acid.

This method of attack on the structure of these alkaloids has not been too fruitful; in most cases the yields of the oxidation products are very low (55) so that, in many instances, little more than the characterization of these oxidation products has been reported.

a. Permanganate Oxidation of Brucine and Strychnine. The permanganate oxidation of strychnine and brucine in acetone solution has led to the elucidation of the structure of these alkaloids around N_b. Strychnine ($C_{21}H_{22}O_2N_2$) is oxidized, amongst other products, to strychninonic acid ($C_{21}H_{20}O_6N_2$) and a small amount of dihydrostrychninonic acid ($C_{21}H_{22}O_6N_2$) (55, 73) while brucine ($C_{23}H_{26}O_4N_2$) gives rise to the analogously constituted brucinonic acid ($C_{23}H_{24}O_8N_2$) and dihydrobrucinonic acid ($C_{23}H_{26}O_8N_2$) (55) as well as a number of other products (74, 126). Similarly a number of substitution products of strychnine (benzylstrychnine (135), bromostrychnine (63, 81), chlorostrychnine (158), and nitrostrychnine (108), as well as the dibenzoyl derivative of tetrahydrobrucine (130)) yield the respective strychninonic acids, XVI. (These substituted strychninonic acids are also available from halogenation (81) and nitration (64) of strychninonic acid.) Strychninonic acid and brucinonic acid differ from the parent bases by the addition of four oxygen atoms and the loss of two hydrogen atoms (55). While strychninonic acid and brucinonic acid are the final stages in the permanganate (acetone) oxidation, yet brucinonic acid has been further degraded to XII and XIII by chromic acid (126, 160). The changes are



XII

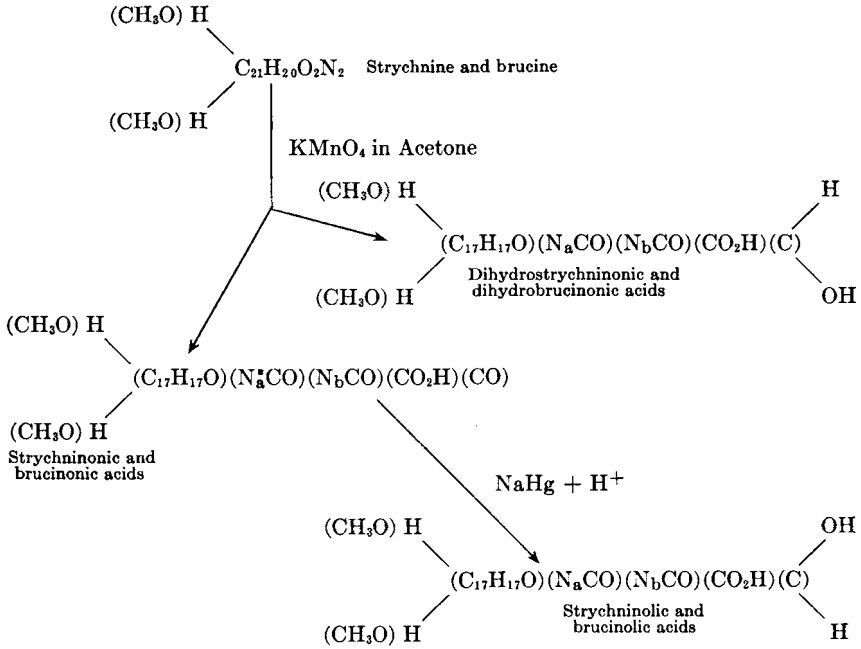


XIII

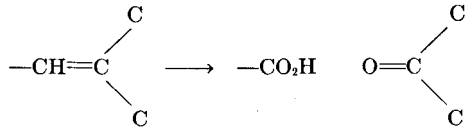
parallel in the two series so, from time to time, reference will be made first to one series and then to the other.

Strychninonic acid and brucinonic acid are monocarboxylic acids (ester formation (55, 58, 64, 96)) which contain two amide groups (N_a–CO, N_b–CO) (strychninonic acid and brucinonic acid are non-basic but on hydrolysis of one of the lactam groups diester formation occurs to give basic dimethyl esters (64, 96)) and a carbonyl group (oxime and semicarbazone (58)) but no double bond (58). The carboxyl group, the two amides, the carbonyl group and the original strychnine cyclic ether account for the six oxygens of these acids (128, 147).

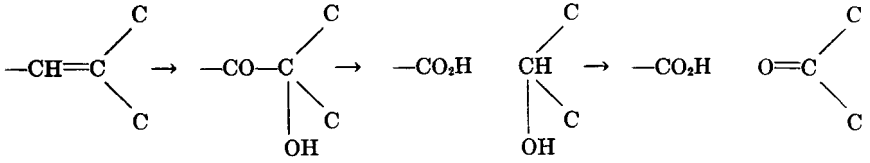
Brucinonic acid and dihydrobrucinonic acid are similarly constituted but the carbonyl group of the former is replaced by an alcoholic hydroxyl group (acetyl derivative (71) and oxidation to brucinonic acid (55)) in the latter. Contrary to expectation, brucinonic acid is not reduced (N_aHg in acid medium (57, 69, 122)) to dihydrobrucinonic acid but to the stereoisomeric brucinolic acid. These changes may be schematically represented as follows:



Since strychninonic acid does not contain an ethylenic double bond and is non-basic, oxidative cleavage of the double bond must have resulted



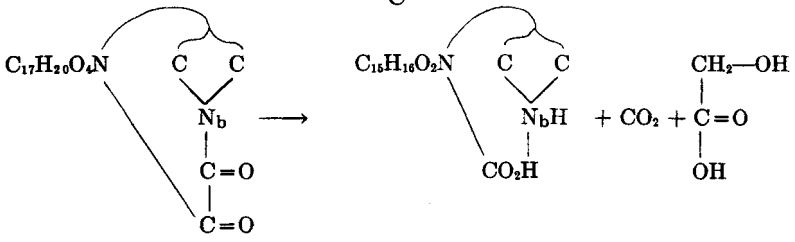
in ketone and carboxyl formation (251), accompanied by the conversion of $N_b–CH_2 \longrightarrow N_b–\overset{\overset{O}{\|}}{C}–$. The co-formation of dihydrostrychninonic acid indicates that the oxidative mechanism might be represented as follows:



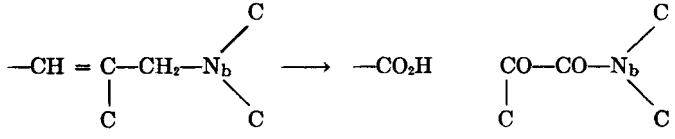
Strychninonic acid must be an α-ketoamide, the diagnostic barium hydroxide-hydrogen peroxide oxidation (147) giving carbon dioxide, glycolic acid (strychninolone type of cleavage), and the amino acid

$$C_{21}H_{20}O_6N_2 \xrightarrow{Ba(OH)_2 + H_2O_2} CO_2 + C_2H_4O_3 + C_{18}H_{18}O_4N_2$$

$C_{18}H_{18}O_4N_2$. The new C_{18} acid is no longer a ketone but now shows basic properties. The grouping $\overset{\overset{O}{\|}}{C}–\overset{\overset{O}{\|}}{C}–N_b\begin{matrix}\diagup C \\ \diagdown C\end{matrix}$ would account for this reaction.



The amide of the newly generated α-ketoamide cannot be N_a–CO since benzylstrychnine, under similar conditions, gives the benzyl analog of strychninonic acid (135). The oxidation of strychnine to strychninonic acid may be represented by the partial formulas:



From the fact that the C_{18}-amino acid shows no tendency to lactamize, the conclusion (if erroneous, p. 418) has been drawn that the ring broken by the barium hydroxide-hydrogen peroxide oxidation is a five-atom ring or a much larger ring, and almost certainly not a six-atom ring.

The electrolytic reduction of brucinonic acid at a lead cathode reduces N_a–CO → N_a–CH_2– and the ketone to an alcoholic hydroxyl; the resulting stereoisomeric brucidinolic acid and dihydrobrucidinonic acid show typical brucidine reactions (122).

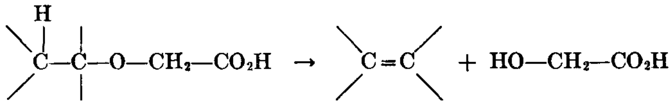
b. Strychninolones and Brucinolones. The reaction of strychninolic acid towards alkali is surprising. Strychninolic acid (but not strychninonic acid (236) when shaken for several minutes with 1.25 moles of 1 *N* alkali (77, 23) is cleaved with the formation of strychninolone-a ($C_{19}H_{18}O_3N_2$) and glycolic acid ($C_2H_4O_3$) (characterized as the zinc salt (57, 58)).

When 10 g. of strychninolic acid is shaken at room temperature, in a well-stoppered flask, with 1¼ mole equivalents of 1 *N* sodium hydroxide solution a precipitate of strychninolone-a settles out. The product is collected on a Büchner funnel, washed with water and dried. Crystallization of the crude product (6.8–7.2 g.) from alcohol yields pure strychninolone-a as prismatic crystals.

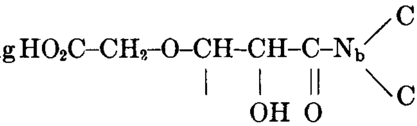
The above conditions must be adhered to rigorously or an isomerization (promoted equally well by alcoholic ammonia (80)) of strychninolone-a to strychninolone-b occurs which may even proceed further to strychninolone-c (80) (the analogs from brucinolic acid are brucinolone-a, brucinolone-b and cryptobrucinolone (84)). Brucinolic acid also forms brucinolone-b (30% yield) on treatment with methanolic hydrogen chloride (96). Alcoholic (CH_3OH, C_2H_5OH) potassium hydroxide upon strychninolone-a (91) and the brucinolones (84, 90) not only isomerizes them, in part, to strychninolone-c and cryptobrucinolone, but addition of the elements of a molecule of methanol or ethanol to the newly generated double bond of strychninolone-a and brucinolone-a results in the formation of methoxy-(ethoxy)-dihydrostrychninolone and methoxy-(ethoxy)-dihydrobrucinolone, respectively. Dihydrostrychninonic acid undergoes a similar cleavage in alkali but more drastic conditions are required for the formation of the isostrychninolones I and II (81). It should be noted that the stereoisomerism of strychninolic acid and dihydrostrychninonic acid persists in the derived strychninolones.

Such a hydrolysis is most unusual and a driving force for the elimination of glycolic acid from strychninolic acid must be found. The elements of strychninolone-a and glycolic acid make up exactly the composition of strychninolic acid. Strychninolone-a, like strychninolic acid, is non-basic (contains two N–CO groupings), is an alcohol (acetate formation (64, 80)), but is non-acidic (64) and contains one double bond (catalytic reduction to dihydrostrychninolone-a (142, 190)). The double bond may result (*a*) by dehydration of the secondary alcoholic hydroxyl of strychninolic acid, or (*b*) by cleavage of the original strychnine ether accompanied by the elimination of a hydrogen atom from an adjacent carbon atom. If the first premise is correct then the stereoisomerism of strychninolic acid and of

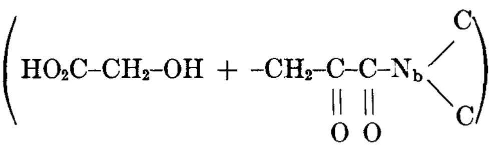
dihydrostrychninonic acid would be destroyed, and this is contrary to



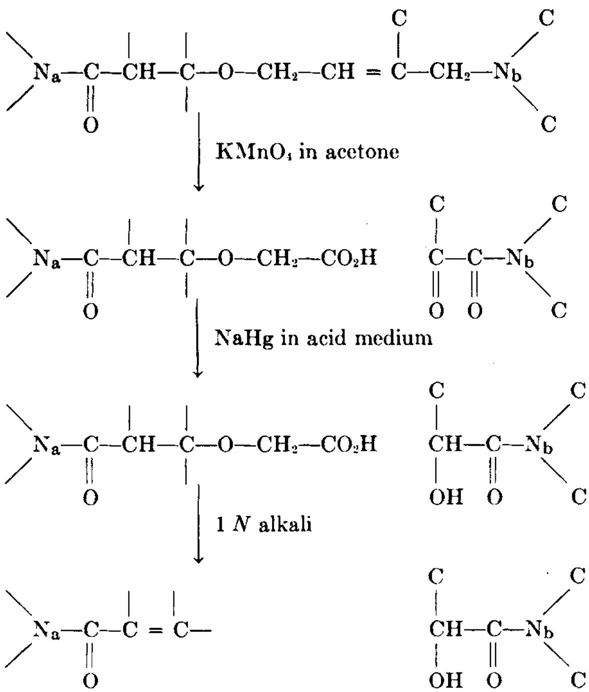
experimental evidence. The only reasonable driving force for the cleavage of the ether would be the location of the ether beta to a carbonyl (3-methoxycyclohexanone readily loses methanol). If the ether were beta to N_b–CO then the cleavage of the grouping



would not lead to a center of unsaturation but rather to an α-ketoamide



The conclusion is inescapable that the glycolic acid residue must be beta to N_a–CO (further support for this argument is found in the failure of brucidinolic acid to undergo a similar cleavage in alkali (122)) and permits the relation of N_a to N_b and implies



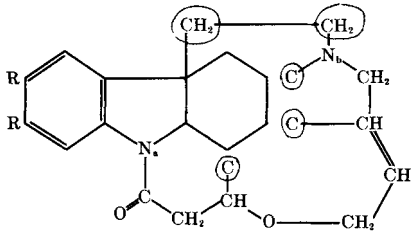
Strychnine

Strychninonic acid

Strychninolic acid

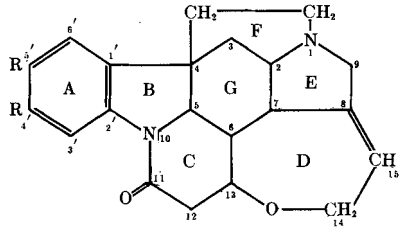
Strychninolone-a

that the following transformations occur in the conversion of strychnine to strychninolone-a. It is thus possible to extend the structure of strychnine and brucine to XIV in which the carbon atoms in the dotted circle may already be represented in some other part of the molecule. To conform with analytical results a working formula for these alkaloids may be constructed by elimination of three of these circled carbon atoms followed by attachment of the bonds, so broken, to the cyclohexane ring of the hexahydrocarbazole nucleus as in XV. Strychninonic acid and brucinonic acid, based on XV for strychnine and brucine, would be XVI, while strychninolone-a and brucinolone-a would be XVII (isostrychninolone and isobrucinolone in brackets).



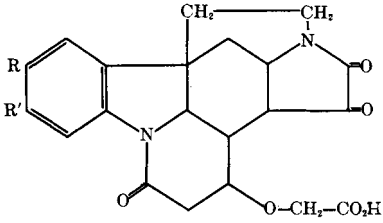
R = H, OCH_3

XIV



R = H, OCH_3

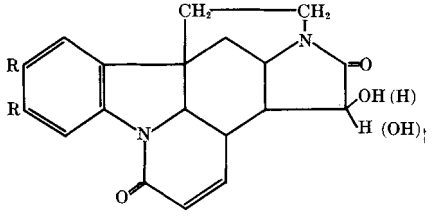
XV



R = H, Cl, Br, NO_2, OCH_3

R′ = H, OCH_3

XVI

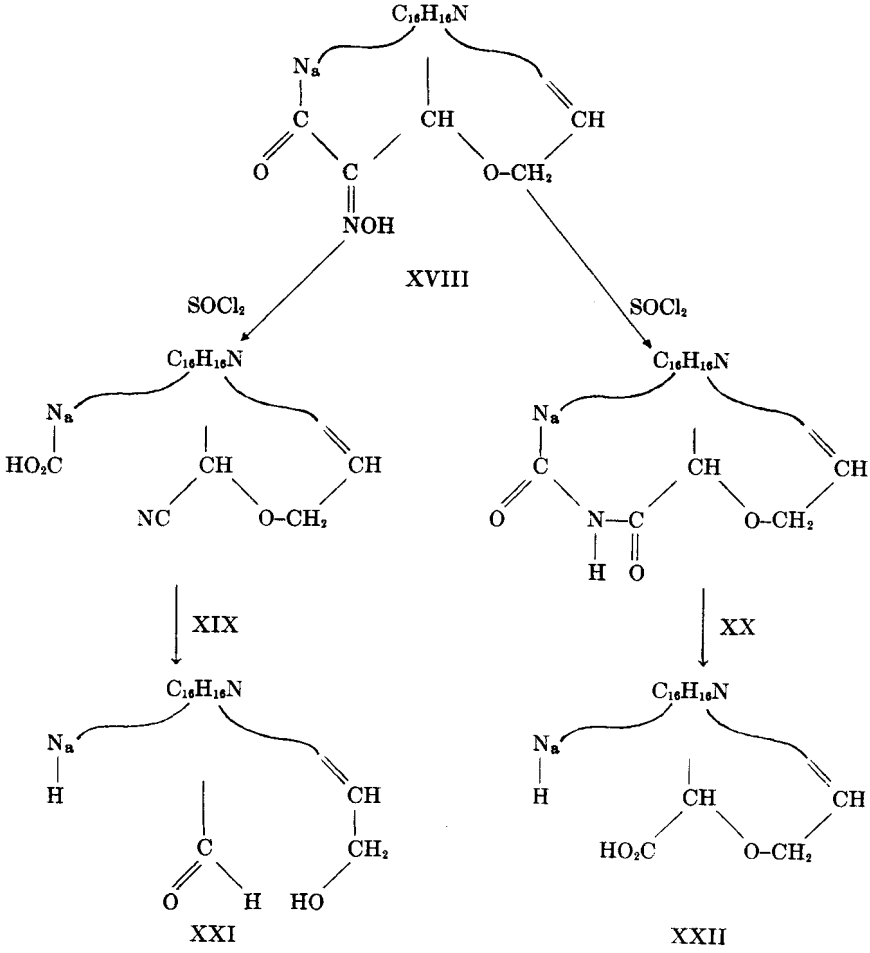


R = H, OCH_3

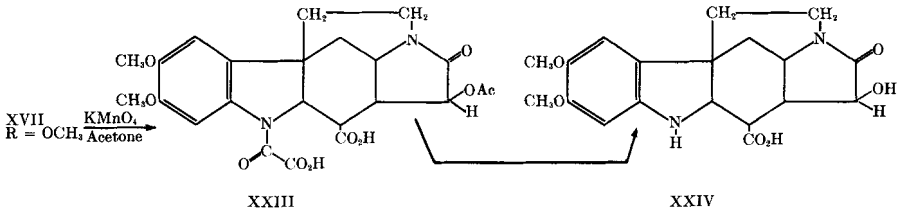
XVII

Confirmation of the position assigned to the ether oxygen of strychnine (and hence in strychninolic acid) is found in the results of the Beckmann rearrangement of 12-isonitrosostrychnine (12-oximinostrychnine) ($C_{21}H_{21}O_3N_3$) (XVIII). Thionyl chloride (also tosyl chloride) causes a rearrangement of 12-isonitrosostrychnine to an isomeric carbamic acid (XIX) and a substituted urea (XX) (20). Hydrolysis of XIX by barium hydroxide affords an aldehydic base (XXI), barium cyanide and barium carbonate, while alkaline hydrolysis of XX yields norstrychninic acid (XXII). This may be interpreted by partial formulas as follows:

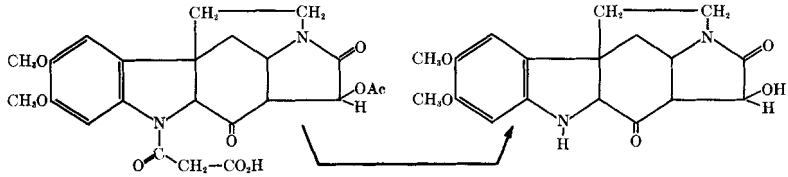
The isomerism of the strychninolones and brucinolones is dependent upon a shift of the double bond from the Δ^{12-13} position to the Δ^{6-12} posi-



tion. This has been established by oxidation of an acetone solution of the various acetylstrychninolones and acetylbrucinolones with potassium per-



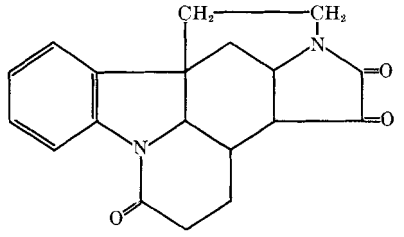
manganate (75). By way of illustration, acetylbrucinolone-a ($C_{23}H_{24}O_6N_2$) gives acetylbrucinolonic acid-a ($C_{23}H_{24}O_{10}N_2$) (XXIII) (75). Acid hydrolysis (HCl) of acetylbrucinolonic acid-a afforded acetic acid, oxalic acid, and the amino acid XXIV. A similar oxidation of acetylbrucinolone-b yields acetylbrucinolonic acid-b (XXV) (70). Hydrolysis of XXV gave acetic acid, malonic acid, and the keto base, curbine (XXVI). Hence the double bond of brucinolone-a must be at Δ^{12-13} while that of the b-isomer must be



XXV XXVI

at Δ^{6-13}. The positions of the double bond in the strychninolones-a and -b have been located in a similar manner (77, 78). As would be expected, strychninolone-a and -b and their acetyl derivatives are reduced to the same dihydro derivatives (142, 190c). The isomerism of the strychninolones-a and -c is considered to be a steric difference about C_6 (142). Some dihydrostrychninolone-c is also recovered from the reduction of strychninolone-b (190c).

Brucinone, the ketone of brucinolone-a, contrary to expectation is not readily available, if at all, from the alkaline cleavage of brucinonic acid (61, 100) or from its derivatives (oxime (95, 105), hydrazone (100), phenylhydrazone (102), and semicarbazone (102)). However, strychninone (236) and dihydrostrychninone (190, 232, 236) (XXVII) have been prepared by another method. The secondary hydroxyl of strychninolone-a and of dihydrostrychninolone-a (from the catalytic reduction of strychninolone-a) has been oxidized (CrO_3) to a ketonic group.

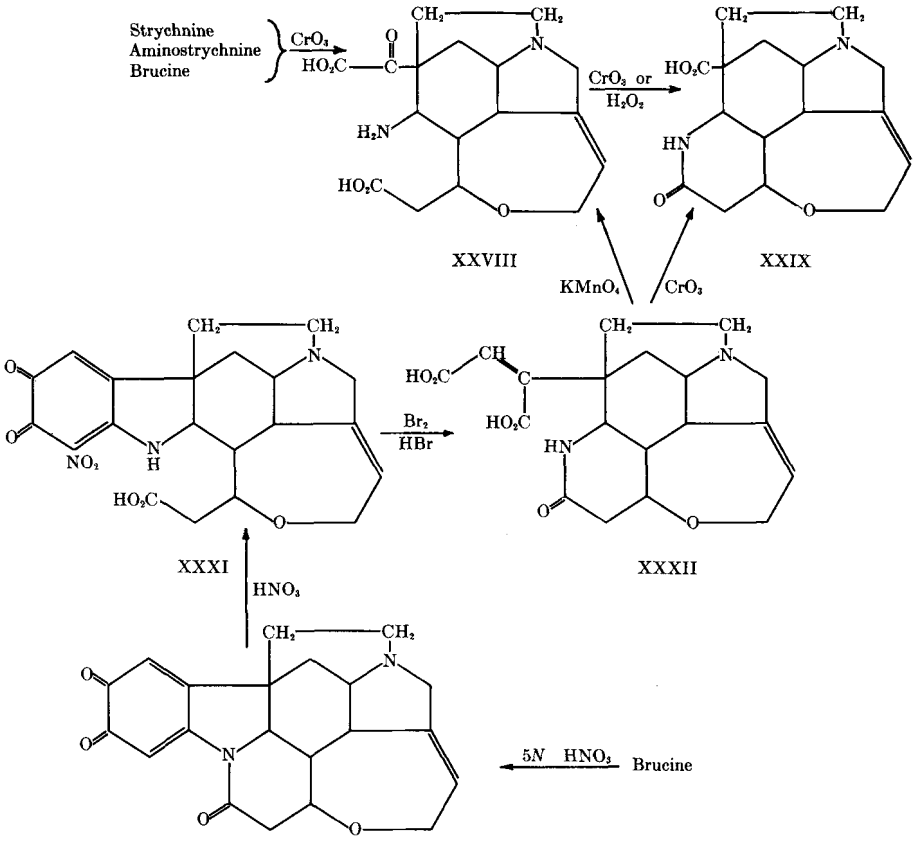


XXVII

c. Chromic and Nitric Acid Oxidations of Strychnine, Strychnidine, Brucine, and Brucidine. The benzene nucleus of these alkaloids is subject to attack by chromic acid. Strychnine (9), monoamino- and diamino-

strychnine (108) as well as brucine (8a) are oxidized by this reagent to 2,3-dioxonucine dihydrate ($C_{17}H_{22}O_6N_2$) (Wieland's C_{17}-acid) (XXVIII) and by a further oxidation with the same reagent (or H_2O_2) to carboxyaponucine ($C_{16}H_{20}O_4N_2$) (Hanssen's C_{16}-acid) (XXIX) (8a, 9, 39, 41). Similarly the sulfonic acids I, II, and IV of brucine have been oxidized to the corresponding sulfonic acids of Wieland's C_{17}-acid (125) and Hanssen's C_{16}-acid (125, 131, 133).

Wieland's C_{17}-acid has been derived from brucine by an alternate method. Brucine is oxidized by cold 5 *N* nitric acid to a quinone, bisdesmethylbrucine (bruciquinone) ($C_{21}H_{20}O_4N_2$) (XXX) (159), and by warm nitric acid to cacotheline (the nitrate of nitrobruciquinone hydrate)

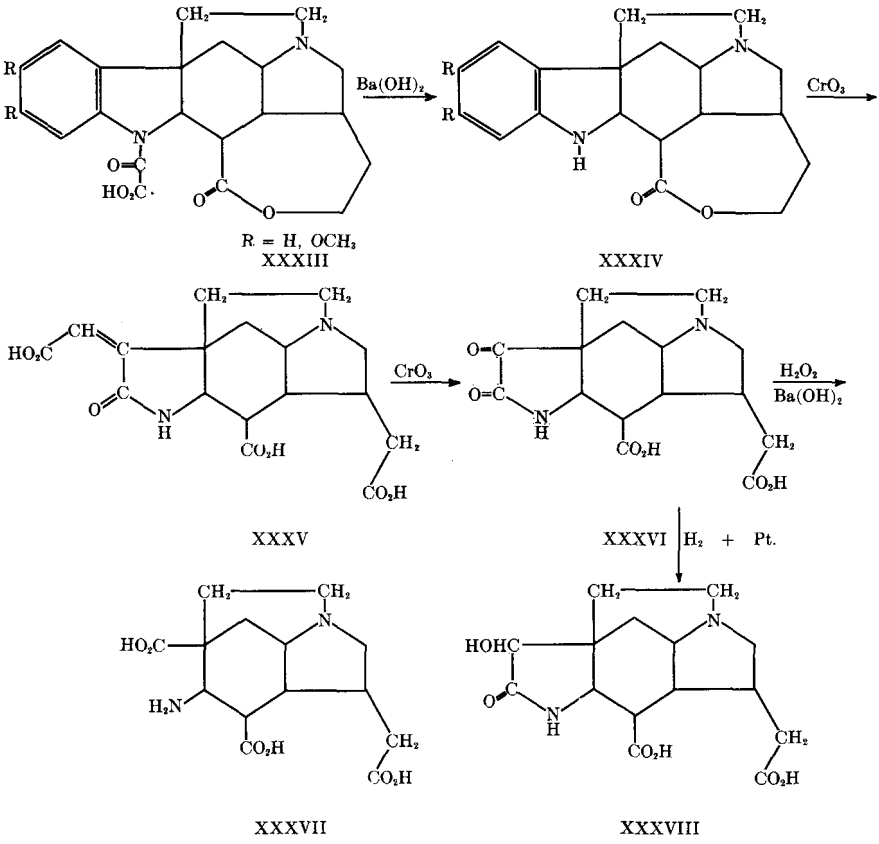


($C_{21}H_{21}O_7N_3 \cdot HNO_3$) (XXXI) (85). The quinonoid ring is partially degraded by bromine oxidation to 3-carboxymethylene-2-oxonucine hydrate (Hanssen's C_{19}-acid) ($C_{19}H_{22}O_6N_2$) (XXXII) (42a, 88). (Carbon dioxide

and bromopicrin are the other products (98).) This C_{19}-acid can be oxidized ($KMnO_4$) to Wieland's C_{17}-acid (106, 229). (See also cacotheline.)

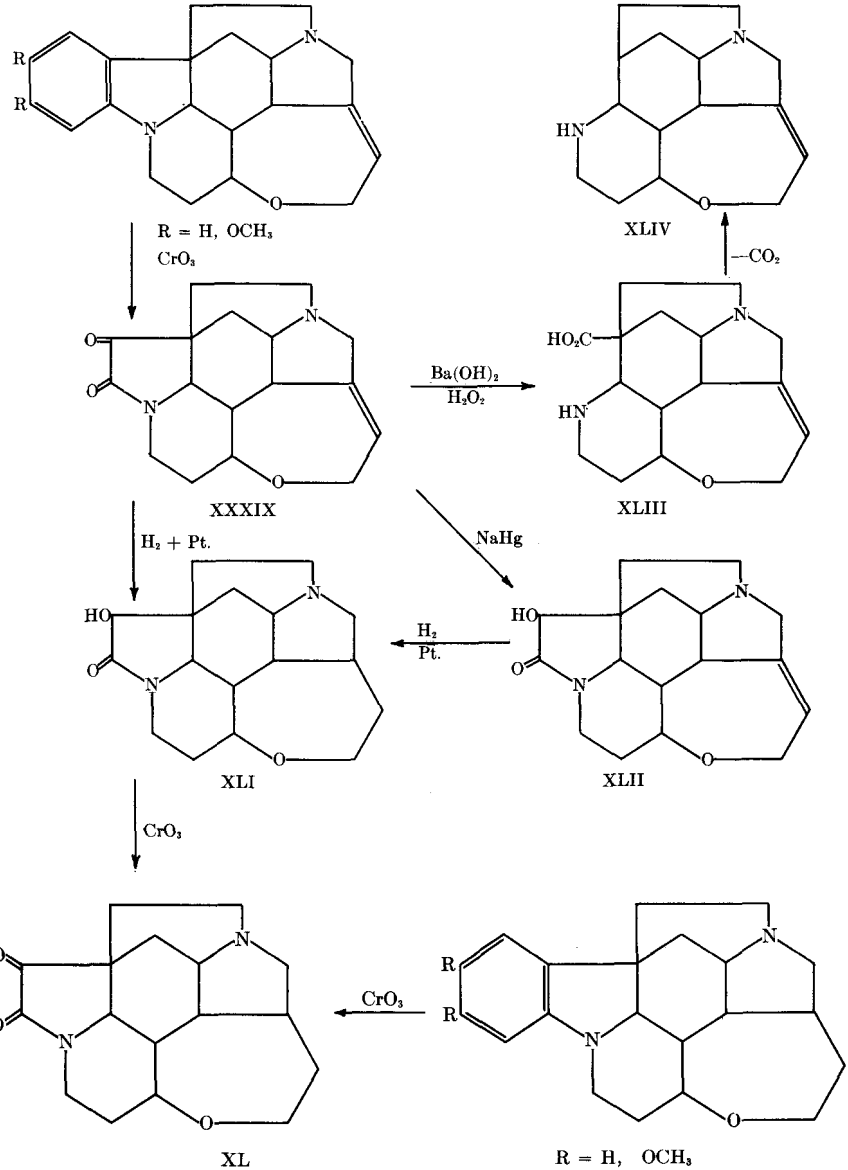
Both Hanssen's C_{19}-acid (9) and Wieland's C_{17}-acid (10, 112) have been degraded to carboxyaponucine.

d. The Oxidation of Benzaldihydrostrychnine and Benzaldihydrobrucine. The various oxidizing agents mentioned in this section have been used in the degradation of benzaldihydrostrychnine (19, 137, 139) and benzaldihydrobrucine (139, 151). Permanganate oxidation of an aqueous acetone solution of benzaldihydrobrucine gives a 50% yield of the amino acid, $C_{23}H_{26}O_7N_2$ (a moderate yield of a second product, $C_{30}H_{32}O_6N_2$, was also reported). This differs from the analogously constituted amino acid



$C_{21}H_{22}O_5N_2$ (XXXIII), from benzaldihydrostrychnine by two methoxyl groups. The *N*-oxalyl group of XXXIII is readily cleaved to XXXIV and oxalic acid by warm aqueous barium hydroxide solution. Chromic acid

attacks the benzene nucleus of the C_{23}-lactone (XXXIII, R = OCH_3) (accompanied by hydrolysis of the *N*-oxalyl group) leading, through the intermediate XXXV, to the α-ketoamide, XXXVI (semicarbazone and



dimethyl ester). (The same amino acid results from benzaldihydrostrychnine.) Catalytic reduction (Pt) reduces the ketone of XXXVI to the sec-

ondary alcohol, XXXVIII, while barium hydroxide-hydrogen peroxide reagent eliminates carbon dioxide from the α-ketoamide grouping.

e. 2,3-Dioxonucidine[1]. ($C_{17}H_{20}O_3N_2$) (XXXIX), the strychnidine analog of the anhydro form of Wieland's C_{17}-acid, is obtained by the chromic acid oxidation of strychnidine (112) or brucidine (117) (the yields are much superior from brucidine).

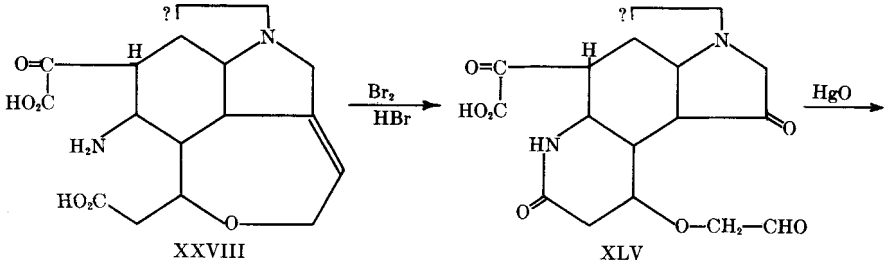
2,3-Dioxodihydronucidine (XL) results in an analogous manner from dihydrostrychnidine (229) and dihydrobrucidine (118). Sodium amalgam or zinc amalgam reduces the ketone group of 2,3-dioxonucidine (yielding 2-oxo-3-hydroxynucidine (XLII)) (113), while catalytic reduction (PtO_2) attacks both the double bond and the ketone groups to give 2-oxo-3-hydroxydihydronucidine (XLI) (118). The hydroxy base (XLI) may in turn be oxidized (CrO_3) to 2,3-dioxodihydronucidine (140). The α-ketoamide grouping of 2,3-dioxonucidine has been oxidized by the barium hydroxide-hydrogen peroxide reagent and the resulting carboxyaponucidine (XLIII) (113, 117) is the strychnidine analog of Hanssen's C_{16}-acid. Decarboxylation (dry distillation) of carboxyaponucidine leads in turn to aponucidine (XLIV) (117). It has been reported (113) that bromine in hydrobromic acid oxidizes the double bond of XLII to a keto aldehyde (229) (2-oxo-3-hydroxynucidinic aldehyde) which in turn is oxidized to 2-oxo-3-hydroxynucidinic acid by mercuric oxide.

Although Robinson's pyrrolidine formula (XV) for strychnine serves admirably as a working hypothesis for the interpretation of the various reactions, several pieces of experimental evidence appear to be incompatible with attachment of the carbon end of the ethanamine chain at C_4. At 100° bromine in hydrobromic acid attacks the ethenoid linkage of 2,3-dioxonucidine, but it has been reported (126) that bromine in water at 5° substitutes for one hydrogen atom. (It has been stated, without experimental confirmation, that the same holds true for 2,3-dioxodihydronucidine.) This has been interpreted by Leuchs as a bromination alpha to the ketone, which of necessity requires the location of a hydrogen at C_4 (strychnine numbering) in 2,3-dioxonucidine and its dihydro derivative. Such an argument precludes the attachment of the ethanamine chain to C_4 in strychnine.

The second piece of evidence against Robinson's strychnine formula arises from the bromine oxidation of Wieland's C_{17}-acid. If the double bond of Wieland's acid (XXVIII) is oxidized with bromine-hydrobromic acid reagent (106, 111), the keto aldehyde, XLV, is formd. It may be further oxidized by mercuric oxide to the corresponding acid (XLVI). Reduction of one of the ketonic groups of XLVI to an alcohol and dehydra-

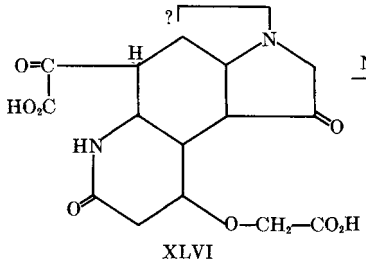
[1] The German prefix "oxo" is preferable to "keto" since one of the carbonyls is in an amide grouping. It is not a diketone but a ketoamide.

tion of XLVII to XLVIII requires that a hydrogen atom be attached to C_4 in strychnine (229). On these grounds Leuchs has located the side chain of strychnine at C_3 as in XLIX.

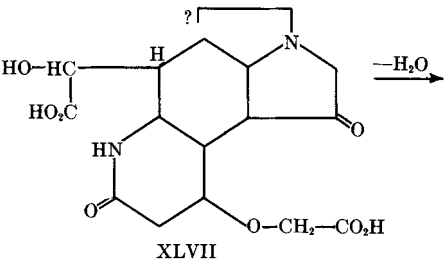


XXVIII

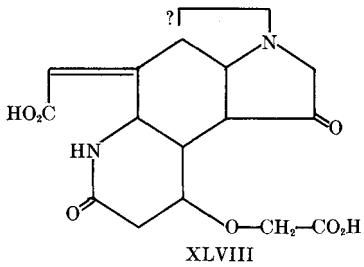
XLV



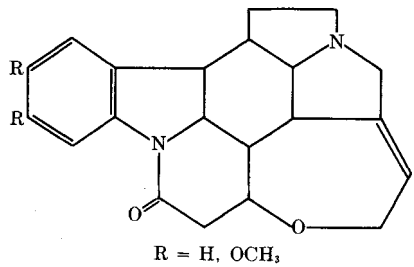
XLVI



XLVII



XLVIII



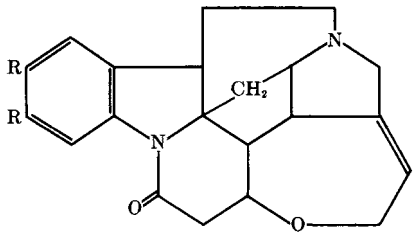
R = H, OCH_3

XLIX

However, Leuchs' formula (XLIX) fails on experimental grounds since it fails to account for the observed condensation of two moles of benzaldehyde with the ketone from the hydrolysis of the enol methyl ether of the des-base of methoxystrychnine.

In the event of the validity of Leuchs' objection to Robinson's strychnine formula, alternate positions for the location of the ethanamine side chain must be considered, namely, C_5 or C_6. The modified structure L has also been considered. The location of the carbonyl group in curbine at C_6 eliminates this position from consideration. Furthermore, the formation of carbazole from strychnine would be hard to accommodate on L without the assumption of an attendant rearrangement, while the C_5 and

C_6 attachment of the side chain would stultify the argument for a preformed tryptamine nucleus in strychnine.



R = H, OCH_3

L

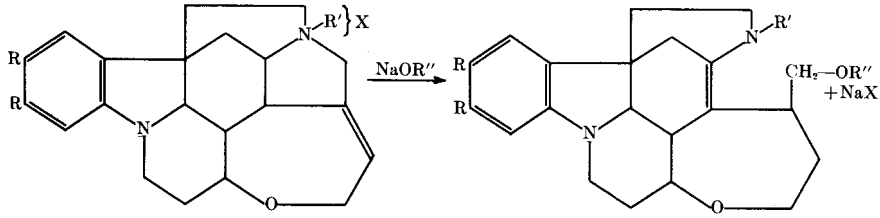
A re-examination of the Leuchs objections to Robinson's formula (XV) shows that they are not as serious as at first appeared (166). Firstly, a re-examination (229) of the bromination of 2,3-dioxonucidine and its dihydro derivative established the incorrectness of Leuchs' interpretation of this reaction. Analyses indicated that bromination did not occur under the described conditions although under somewhat modified conditions (40°) the addition of hypobromous acid to the ethylene group has been found to take place (163). Secondly, the evidence for the location of the double bond of XLVIII obtained by the dehydration of XLVII, as sketched, is far from conclusive. The reduction of XLVI to an alcohol and its dehydration to an unsaturated product might equally well have occurred in the nuclear portion of the molecule. Assuming that the reduction of the ketone to an alcohol has occurred at the position indicated, this may still be accommodated on Robinson's formula, for such substituted neopentyl alcohols are known to undergo rearrangement during dehydration, and until further experimental evidence is forthcoming to make the attachment of the ethanamine chain at C_4 untenable this formula will be used in the interpretation of the subsequent work.

5. Fission Around N_b

A variety of methods have been employed in the fission of rings E and F. Among the more successful approaches have been (a) alkoxylating fission, (b) reductive fission, (c) cyanogen bromide, and (d) fission by the Hofmann method.

a. Alkoxylating Fission. The cleavage of ring E accompanied by the addition of the elements of a molecule of an alcohol has been achieved by heating various N_b-alkylstrychninium (alkyl = methyl, ethyl, benzyl), N_b-alkylstrychnidinium, N_b-alkylbrucinium and N_b-alkylbrucidinium salts (chloride, iodide, and methosulfate (196, 197, 207, 208, 209)) with an alcoholic solution of a sodium alcoholate (methylate, ethylate, butylate).

For example, methoxymethyldihydroneostrychnidine (LII, R′ = R″ = CH_3) results from the rupture of $N_b - C_9$ and addition of the elements of methanol to methylstrychnidinium methosulfate (LI, R = H, R′ = CH_3, X = $CH_3SO_4^-$) when it is boiled with methanolic sodium methylate. The



R = H, OCH_3
R′ = CH_3, C_2H_5, C_6H_5—CH_2—
X = CH_3SO_4

LI

R″ = CH_3, C_2H_5, C_4H_9

LII

Twenty grams of strychnidine methosulfate is heated in an open flask on a steam bath with 120 cc. of 25% methanolic potassium hydroxide solution. After 30 minutes of heating the clear solution becomes turbid, and on cooling and diluting with 600 cc. of ice and water yields a caseous precipitate. This precipitate, after collecting on a Büchner funnel, is well washed with water and dried,; m.p. 115–119°. Pure methoxymethyldihydroneostrychnidine is obtained in large glistening prisms from methanol.

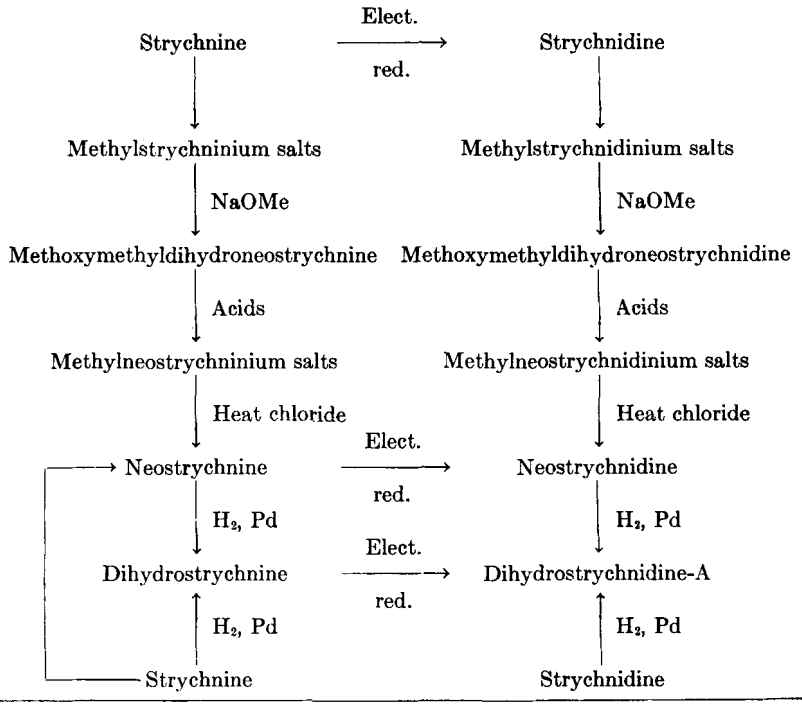
ethenoid linkage apparently is not involved directly in the fission process since methoxymethyldihydroneostrychnidine may be hydrogenated catalytically to a dihydromethoxymethyldihydroneostrychnidine (208, 225, 248, 253). However, the alkoxylating fission is more complex than a mere attack on the N_b—C_9 bond because it has been established beyond question that this process involves the migration of the double bond to some more favorable position (207). The alkoxyalkyldihydroneostrychnines, alkoxyalkyldihydroneostrychnidines as well as their brucine and brucidine analogs are very subject to cyclization or regeneration of the N_b—C_9 bond by heating with dilute mineral acids. However, contrary to expectation, methylstrychnidinium sulfate is not regenerated when methoxymethyldihydroneostrychnidine is heated with dilute sulfuric acid, but an isomeric substance, methylneostrychnidinium sulfate, is formed (196). The free

Methylneostrychnidinium iodide is formed when 20.0 g. of methoxymethyldihydroneostrychnidine is dissolved in 300 cc. of 10% sulfuric acid and heated to boiling under an air condenser. In a short time methyl alcohol can be detected at the open end of the condenser, and when, after 2 hours, all of it has boiled away, the reaction mixture no longer gives a turbidity when made ammoniacal. The pale brown solution is made just alkaline with ammonia, and a little sulfurous acid and 25.0 g. of sodium iodide are added. The clear solution is rapidly filtered and vigorously stirred. The methylneostrychnidinium-A iodide (there are two isomers) separates either as a heavy crystalline precipitate or as a gum which soon crystallizes. The iodide crystallizes in long needles from water containing a little sulfurous acid. The A-iodide darkens at 295° and decomposes to a black mass at 300°.

base, neostrychnidine, has been recovered by conversion of methylneostrychnidinium sulfate to the methiodide followed by pyrolysis of the derived methochloride (196). The isomerism of neostrychnidine and strychnidine may be ascribed to a shift of the double bond to the new neo-position since both strychnidine and neostrychnidine have been reduced catalytically or by electrolytic reduction to dihydrostrychnidine-A (207). Neostrychnine may be obtained in a like manner from methylstrychninium salts. However, the experimental difficulties attendant upon this conversion are a complicating factor. (Neostrychnine may be prepared in 50% yield by heating (260°) strychnine with selenium (238) or in 85% yield with Raney nickel (235).) The electrolytic reduction of neostrychnine to neostrychnidine (208) completes the cycle outlined in Chart I.

CHART I

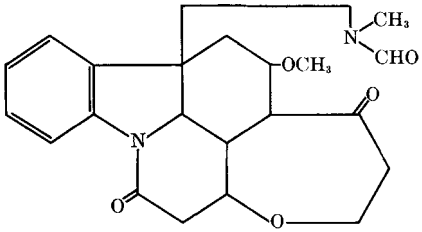
THE INTERRELATIONSHIP OF THE STRYCHNINE AND THE NEOSTRYCHNINE SERIES OF COMPOUNDS



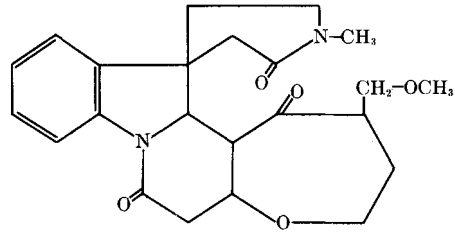
The fission process is dependent to a large extent upon the presence and position of the ethenoid linkage, for the process proceeds with greater facility in the case of methylstrychnidinium methosulfate than for its

dihydro derivative. A similar difficulty is found in the cyclization process for, although neostrychnidine is readily obtained from methoxymethyldihydroneostrychnidine, the cyclization of dihydromethoxymethyldihydroneostrychnidine was effected only with great difficulty (196, 208). The ease of fission of methylstrychnidinium salts and the generation of methylneostrychnidinium salts would be understandable (allyl amine and allyl methyl ether formation) if the neo position of the double bond were assigned to Δ^{7-8} (207). (It is understandable how this would exclude the consideration of the occurrence of methoxylating fission between N_b and the dimethylene chain.) While the location of the neo position of the double bond at Δ^{7-8} offers an attractive hypothesis for the ease of fission, and, at the same time, for the generation of the neo series of salts, the perbenzoic acid oxidation of methoxymethyldihydroneostrychnine to a ketoamide (oxime, *p*-nitrophenylhydrazone) tends to favor position Δ^{2-7} for the neo double bond (143). However attractive the former hypotheses may be (220), the neo series of bases have been characterized as vinylamines (the ethylene at Δ^{2-7} or Δ^{8-9}) (231).

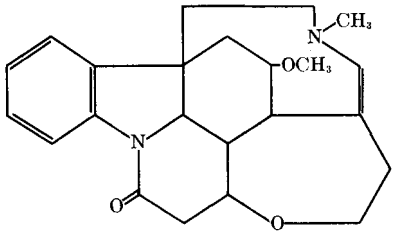
Two alternatives, LIII and LIV, must be considered for the ketoamide, methoxymethylchanodihydrostrychnone.[2] Formula LIII necessitates ring



LIII



LIV

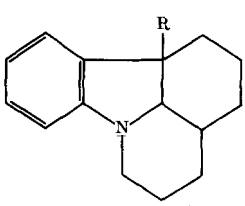


LV

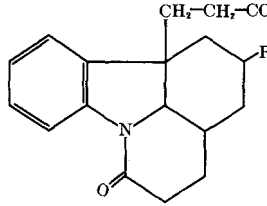
fission at N_b–C_2 with the neo position of the double bond at Δ^{8-9} (LV). However, the formamide structure LIII for methoxymethylchanodihydrostrychnone is negated on experimental grounds (143, 217).

[2] The prefix chano- (chasm) indicates the opening of a ring.

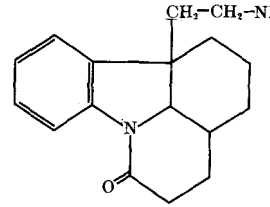
Reduction of the ketonic group (–CO– ⟶ –CH_2–) of LIV has been achieved by the Clemmensen method (217) and the N_a–CO–lactam of this methoxymethylchanodihydrostrychnane has been hydrolyzed (alcoholic barium hydroxide), although only with difficulty (217, 220). The methoxymethylchanodihydrostrychnanic acid lends itself admirably to the disproof of the Leuchs formula for strychnine (attachment of the ethanamine chain at C_3 (XLIX)). The Leuchs formula requires the location of hydrogen atoms at C_{10} and C_{11} of the hexahydrocarbazole nucleus of methoxymethylchanodihydrostrychnanic acid. Various hexahydrocarbazoles, LVI (224, 233), LVII (224, 234), LVIII (234), have been synthesized and of these hexahydrocarbazole (22C) and LVI (R = H) (224) are readily dehydrogenated (mercuric acetate, sulfur and quinoline, or catalytic dehydrogenation over palladium) to the corresponding tetrahydrocarbazole (formation of an indole nucleus). Similar conditions of dehydrogenation when applied to methoxymethylchanodihydrostrychnanic acid (220) resulted only in recovery of the starting material. These results favor the absence of a hydrogen atom at C_4 in strychnine, thus adding further support to Robinson's formula for the location of the ethanamine chain.



R = H, C_2H_5
LVI



R = H, CO_2H
LVII



LVIII

b. Reductive Fission. An alternate method for the fission of N_b–Cc is by reduction (sodium amalgam in weakly acid solution or catalytie reduction over palladized charcoal) of strychnidine methosulfate (Emde reduction) (214). It has been found that this fission is best achieved by adding sodium amalgam (3%) portionwise to a hot aqueous solution of strychnidine methosulfate (a similar reaction has been applied to strychnine methosulfate (211)) which is vigorously agitated by a rapid stream of carbon dioxide. During the reaction an oily base settled out which hardened to a gum. The gum proved to be a separable mixture of methyldihydroneostrychnidine[3] ($C_{22}H_{28}ON_2$; m.p. 142–143°) (LIX), methyltetrahydrostrychnidine ($C_{22}H_{30}ON_2$; m.p. 192–193°) (LX), and a third product

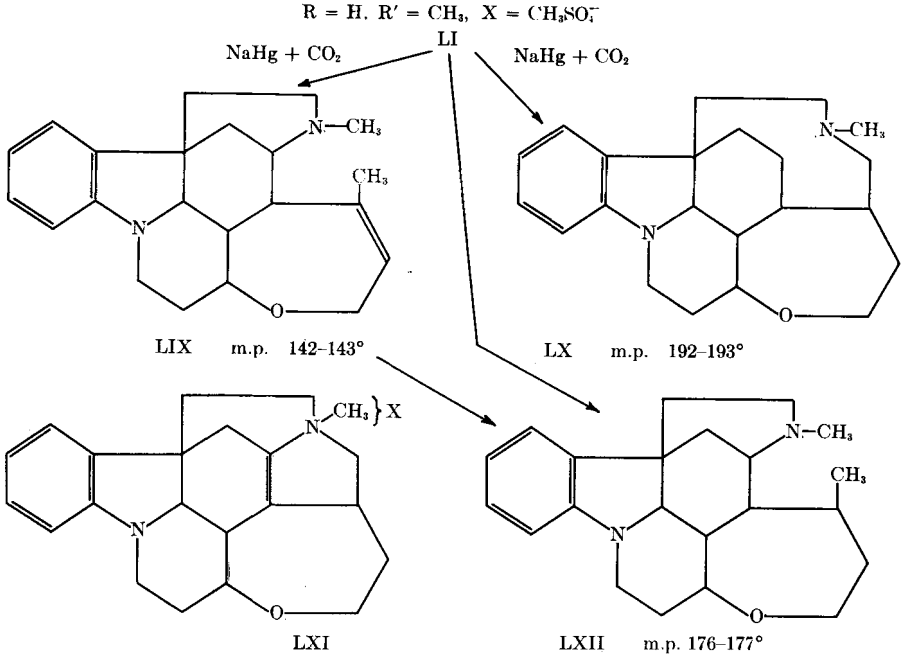
[3] Recent evidence (231) indicates that the double bond in this compound occupies the normal strychnine position but to conform with the terminology appearing in the literature the "neo" has been retained. This policy will be followed throughout the chapter and such deletions, where necessary, will be indicated by an asterisk.

of formula $C_{22}H_{30}O_2N_2$. From analytical values and the conversion of $C_{22}H_{30}O_2N_2$ by boiling phosphoryl chloride to LIX it is probable that it is a hydrate of methyldihydroneostrychnidine.*

Although the ethylenic linkage may have suffered an alteration of position during the reductive process, the absorption of one mole of hydrogen by catalytic reduction (palladized charcoal) indicated that the double bond was still present in methyldihydroneostrychnidine.* The resulting dihydromethyldihydroneostrychnidine* (m.p. 176–177°) is not identical but isomeric with the methyltetrahydrostrychnidine (m.p. 192–193°) from the Emde reduction. These two reductions were accomplished simultaneously when methylstrychnidinium chloride was reduced catalytically (two moles of hydrogen).

The Emde reduction in the strychnine series appears to be dependent to a large extent upon the presence and position of the ethylenic linkage for it is reported that dihydrostrychnidine-A methochloride is recovered unchanged from the action of sodium amalgam upon a boiling neutral solution of this dihydro base. The contrasting reduction (sodium amalgam and acetic acid) of neostrychnidine methochloride (LXI) to dihydrostrychnidine-methochloride (231) would suggest that the strychnine-allylamine system is a prime prerequisite for the promotion of this reductive fission. This assumption finds support in the results of the Kuhn-Roth oxidation of methyldihydroneostrychnidine* (LIX) and its dihydro derivative (LXII) (215). While some acetic acid was recovered from the oxidation (chromic acid) of dihydromethyldihydroneostrychnidine,* yet the nearly molar amount of acetic acid recovered from a similar oxidation of LIX suggests the presence of the grouping $\diagdown\!\!\diagup C = \overset{|}{C}\text{–}CH_3$ in methyldihydroneostrychnidine* (a similar oxidation of methyltetrahydrostrychnidine failed to give a detectable amount of acetic acid). The isolation of almost molar quantities of acetic acid from the oxidation of methyldihydroneostrychnidine* would suggest that reductive cleavage had occurred at N_b–C_9 in strychnidine methosulfate. Hence, dihydromethyldihydroneostrychnidine* must be one of the stereoisomers of LXII. A stereoisomeric relationship for methyltetrahydrostrychnidine (m.p. 192–193°) and dihydromethyldihydroneostrychnidine* has been considered but such an isomerism appears to be highly unlikely in the light of the isolation of a small amount of allodihydromethyldihydroneostrychnidine* from the catalytic reduction of LIX (226). Methyltetrahydrostrychnidine must be a structural isomer of LXII involving the reductive fission of strychnidine methosulfate at N_b–C_2. (From exhaustive methylation and Hofmann degradation it is known that the linkage between N_b and the dimethylene chain is the last to be broken.) The negative result from the Kuhn-Roth oxidation of methyltetrahydro-

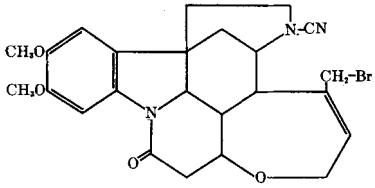
strychnidine is understandable through formula LX. Similar cleavages have been observed in the reduction of the quaternary salts of 2,3-dioxonucidine (140), 2-oxo-3-hydroxynucidine (140), *N*-acetylaponucidine (157), but not with those of Hanssen's C_{19}-acid (161) or 2,3-dioxodihydronucidine (140).



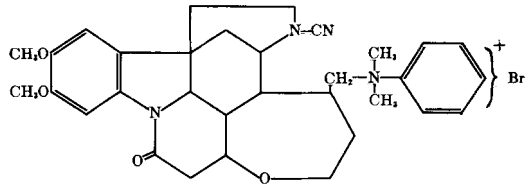
c. Fission by Cyanogen Bromide. A benzene or chloroform solution of cyanogen bromide reacts with strychnine (17), dihydrostrychnine (17), strychnidine (17), brucine (17, 127, 246), and dihydrobrucine (17). The quaternary salt from brucine is isomerized in boiling methanol to a brominated cyanamide ($C_{24}H_{26}O_4N_3Br$). (This is accompanied by a methoxylated cyanamide due to the metathetical reaction of the bromine with methanol.) Addition of the cyanogen bromide to the brucine ether is inadmissible on the grounds that the so-called brominated cyanamide may be oxidized ($KMnO_4$ in acetone) to the analog ($C_{24}H_{26}O_7N_3Br$) of strychninonic acid. Although the point of cleavage of ring E is somewhat speculative in nature, yet the observations of von Braun (94, 103) would indicate that rupture of the allylamine system (N_b–C_9) had occurred. Hence, the brominated cyanamide may be represented by LXIII although some reservation must be made with regard to the position of the double bond. (There is some evidence that the product from boiling methanol may be a mixture of isomers.)

Unlike methoxylating fission and reductive fission the cleavage of

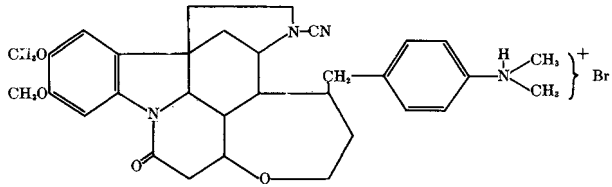
ring E by cyanogen bromide is not dependent upon the presence of the strychnine double bond because dihydrostrychnine and dihydrobrucine are cleaved just as readily as the unsaturated bases.



LXIII



LXIV



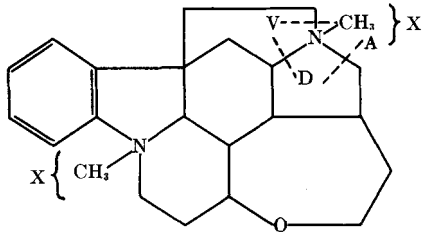
LXV

The halogen atom in the brominated cyanamides is very labile and readily undergoes metathetical reactions with methanol, pyridine, methylaniline, and dimethylaniline. For example, dimethylaniline and the dihydro derivative of LXIII probably yield LXIV which immediately isomerizes to LXV.

The bromine in the above cyanamides is resistant to reduction by zinc and acetic acid. However, LXIII reverts to brucine (with the formation of silver bromide and silver cyanide) when it is heated in benzene with silver benzoate.

d. Hofmann Degradation. The Hofmann degradation affords an alternative method of attack on the ring system around N_b of strychnine and brucine. Various conditions have been tried but the most suitable proved to be the action of hot sodium methylate upon the methohydrogencarbonate of the *Strychnos* bases (215). The cleavage of strychnine, brucine, strychnidine, and brucidine salts at N_b–C_9 by this method requires the location of a hydrogen atom at C_8 and, as might be expected, the desired cleavage was not realized. Two products were recovered from the attempted Hofmann degradation of the metho salts of these bases: (a) strychnine, brucine, strychnidine, and brucidine by the loss of methanol from the methohydroxide, a reaction which occurs in most Hofmann degradations to a greater or lesser extent, and (b) methoxymethyldihydroneostrychnine, etc. (which arose from the alkoxylating fission of these quaternary salts). For this reason attention has been directed to the degradation of dihydrostrychnidine and dihydrobrucidine. The degradation of dihydrostrychnidine methohydrogencarbonate (215) or preferably the dimethohydrogen-

carbonate (LXVI) (222) with hot sodium methylate has been effected with cleavage of an N_b–C bond (accompanied by formation of some methoxymethyldihydroneostrychnidine (methoxylating fission) and by the regeneration of some dihydrostrychnidine).



LXVI

Although theoretically three alternatives for the cleavage of an N–C bond must be considered, fission in certain directions appears favored. For convenience, these various fissions may be described as type A when cleavage occurs between N_b–C_9, type D when the N_b–C_2 bond is involved, and type V when the bond from N_b to the dimethylene chain is involved. Ring fission of type A is diagnosed by a positive Kuhn-Roth reaction. While the Kuhn-Roth oxidation is negative for products of type V fission, yet this type of cleavage is experimentally recognized by an increase in the side chain methyl content following catalytic reduction.

Fissions of types A and D appear to occur with greater facility; two isomeric des-bases ($C_{22}H_{28}ON_2$) are recovered from the Hofmann reaction upon dihydrostrychnidine-A methohydrogencarbonate. The des-base (termed des-base-A for convenience) which melted at 143–144° proved to be N_b-methyl-(chano)-dihydroneostrychnidine*, which in turn was reduced (Pd) to dihydromethyldihydroneostrychnidine* (m.p. 176°).

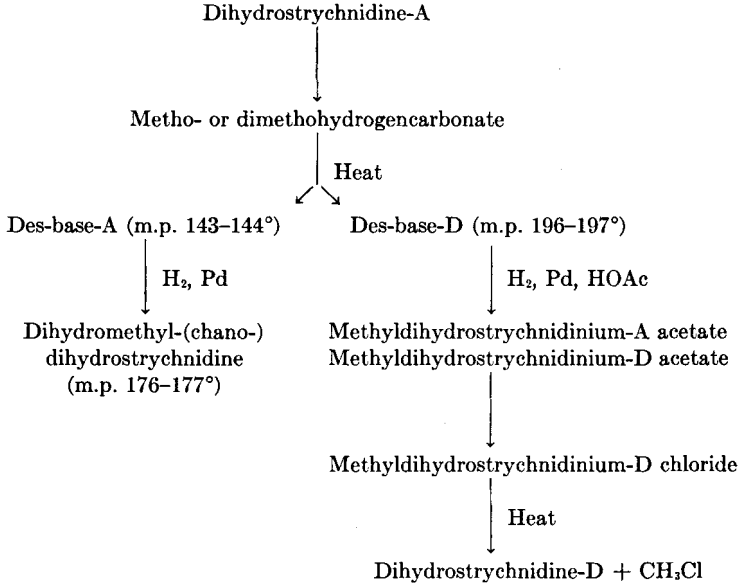
While the isolation of des-base-A as one of the products of the Hofmann reaction has added further support for the structure assigned to methyl-(chano)-dihydroneostrychnidine,* yet it is the isomeric des-base, anhydromethylstrychnidinium-D hydroxide (des-base-D, m.p. 196–197°) that has provided a whole series of new compounds by a novel reaction. Introduction of two hydrogen atoms into des-base-D by catalytic reduction (palla-

A solution of 9.0 g. of des-base-D in 130 cc. of 10% hydrochloric acid is shaken with hydrogen at 17–19° in the presence of palladium-charcoal catalyst. The uptake of hydrogen ceases when 355 cc. of hydrogen (theory 600 cc.) is absorbed. Further addition fails even at 90°. The hot solution is filtered, made ammoniacal, and concentrated under vacuum to one-third its volume. The concentrate, when treated with a solution of 10 g. of sodium iodide in 10 cc. of water, yields a colorless precipitate which is a mixture of methyldihydrostrychnidinium-D iodide and methyldihydrostrychnidinium-A iodide. Repeated fractional crystallization from water yields 8.7 g. of the former (m.p. 325–327°) and 3.2 g. of the latter (m.p. 345–350°).

dized charcoal in acetic acid) failed, but a mixture of methyldihydrostrychnidium-A acetate and a relatively larger amount of methyldihydrostrychnidinium-D acetate was formed (225). Dihydrostrychnidine-D (the designation D is due to the existence of dihydrostrychnidines-B and -C which are obtained when strychnidine is reduced by hydriodic acid and phosphorus (200)) has been isolated by conversion of the methoacetate to the methiodide and pyrolysis of the derived methochloride (AgCl on the methiodide). These reactions are summarized in Chart II.

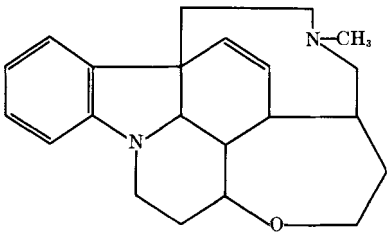
CHART II

CONVERSION OF DIHYDROSTRYCHNIDINE-A TO DIHYDROSTRYCHNIDINE-D

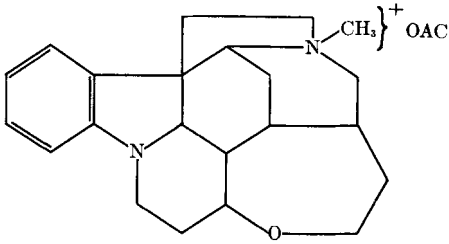


Failure to obtain a dihydro derivative of des-base-D precludes the use of the Kuhn-Roth oxidation (des-base-D does not give a positive Kuhn-Roth reaction) for the determination of the type of fission occurring in the formation of this base. However, color reactions and the ease of regeneration of methyldihydrostrychnidinium-A acetate would suggest that fission of type D (LXVII) has occurred. From the observation that no hydrogen was introduced into the molecule in the conversion of des-base-D into the saturated methyldihydrostrychnidinium-D acetate it is inescapable that a reductive cyclization of a novel type has occurred (a reverse Emde reaction). Whilst stereoisomerism in the case of the dihydrostrychnidines-A and -D may not be excluded, recovery of des-base-D, but no trace of des-

base-A, from the metho salts of dihydrostrychnidine-D implies a structural isomerism. Reductive cyclization of N_b to alternate ends of the double bond of LXVII in the formation of methyldihydrostrychnidinium-D acetate (LXVIII) and the isomeric-A salt would adequately account for



LXVII



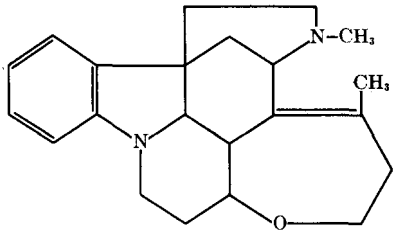
LXVIII

such a structural relationship. Furthermore, models indicate that the transformation of the ring system of LXVII into that of LXVIII is a very natural process and that LXVIII and the free base of LXVI, are strainless (231).

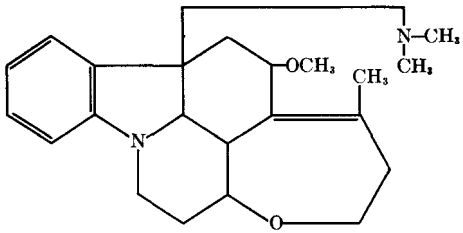
The second stage of the exhaustive methylation has been realized with both des-base-A (226) and des-base-D (227). When the dimetho salts of des-base-A were heated with sodium methylate some des-base-A was regenerated, and a difficultly separable mixture of N_b,N_b-dimethyldesneostrychnidine* (di-des-base-AD, $C_{23}H_{30}ON_2$, m.p.7 3°), N_b,N_b-dimethyldesbisneostrychnidine (di-des-base-AD, $C_{23}H_{30}ON_2$, m.p. 113°), and methoxy-N_b,N_b-dimethyldihydrochanodihydrobisneostrychnidine was formed. The two di-des-bases-AD are doubly unsaturated and are structural isomers for they are both reduced to the same tetrahydro derivative. Furthermore, the di-des-base-AD, m.p. 73°, is converted into the 113° isomer by heating the methochloride of the 73° isomer with sodium methylate (this reaction involves one type of a Hofmann degradation and the isomerization of one of the double bonds to a new position). The 113° isomer appears to be the stable modification, for the reverse isomerization under similar conditions has not been realized.

The conversion of des-base-A to methoxydimethyldihydrochanodihydrobisneostrychnidine presents certain analogies with the change, strychnidine methosulfate → methoxymethyldihydroneostrychnidine, and may be explained in a similar manner (methoxylating fission). Fission of ring F is accompanied by migration of the double bond, regeneration of this ring by dilute sulfuric acid yielding a base isomeric with des-base-A, which is reducible to the dihydro derivative of des-base-A. The ease of re-formation of ring F is more easily understood when the double bond is at Δ^{7-8} (allyl ether) (LXIX); hence methoxy-N_b,N_b-dimethylchanodihydrobisneostrychnidine* would be LXX. The Hofmann degradation of the metho salts of

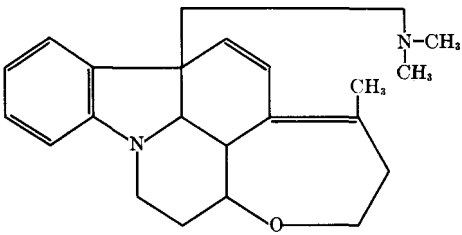
LXIX to the di-des-base-AD, m.p. 113°, would suggest that the double bonds of the latter base are located as in LXXI and that one double bond of di-des-base-AD, m.p. 73°, occupies the normal position (LXXII).



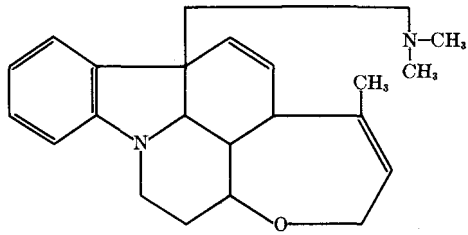
LXIX



LXX



LXXI



LXXII

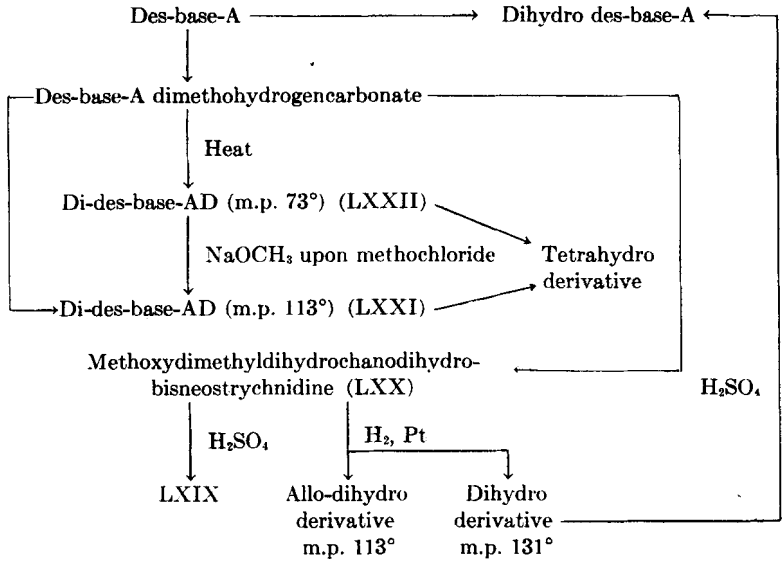
The catalytic reduction (H_2, Pt) of LXX yields a separable mixture of methoxy-N_b,N_b-dimethyldihydrochanotetrahydrostrychnidine (m.p. 131°; obtainable from dihydro des-base-A) and allomethoxy-N_b,N_b-dimethyldihydrochanotetrahydrostrychnidine (m.p. 113°). The isomer melting at 131° has been related to des-base-A. This was achieved by regeneration of ring F in this base through cyclization with dilute sulfuric acid when dihydro des-base-A was formed. The absence of isomers in the product of the Hofmann reaction on the metho salts of dihydro des-base-A, and result of migration of the double bond, indicates that the mobile double bond in di-des-base-AD, m.p. 73°, occupies the normal position. The relation of these products to each other is shown graphically in Chart III.

Although the regeneration of des-base-D is the main reaction when the methochloride or methocarbonate of des-base-D is heated with sodium methylate (215), it has been found that the true Hofmann elimination takes place when the dimethochloride is substituted for the above-mentioned salts. The products that have been identified from this reaction (227) are: (a) des-base-D, (b) di-des-base-AD (m.p. 73–74°), and (c) the isomeric N_b,N_b-dimethyldesstrychnidine-D (di-des-base-DV; $C_{23}H_{30}ON_2$; m.p. 156–157°). The di-des-base-DV contains an $-N\begin{matrix}CH_3\\CH_3\end{matrix}$ grouping and two double

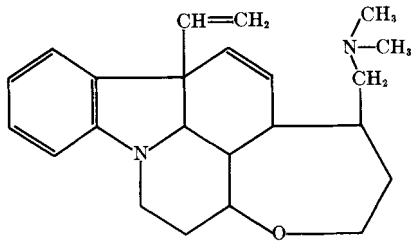
bonds (catalytic reduction). Negative Kuhn-Roth results for di-des-base-DV and the positive results for a side chain methyl grouping in the dihydro and tetrahydro di-des-base-DV confirm the view that di-des-base-DV (LXXIII) results from a cleavage of the N_b-dimethylene bond of des-base-D.

CHART III

PRODUCTS FROM THE HOFMANN DEGRADATION OF DES-BASE-A



The Hofmann elimination of trimethylamine from the dimethochloride of di-des-base-AD (m.p. 113°) and of di-des-base-DV (m.p. 156–157°)



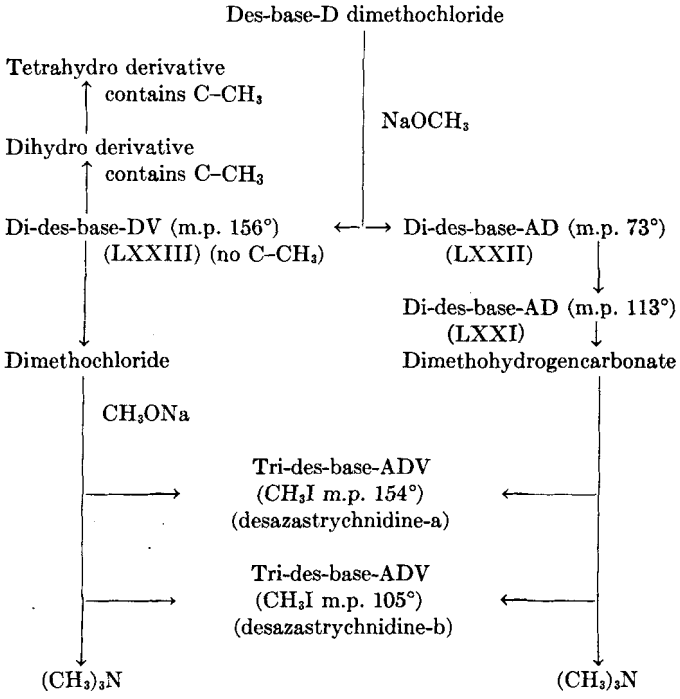
LXXIII

results in a separable mixture of desazastrychnidine-a (tri-des-base-ADV; $C_{21}H_{23}ON$; methiodide m.p. 154–155°) and desazastrychnidine-b (tri-des-base-ADV; methiodide m.p. 104–105°). This isomerism of the tri-des-bases

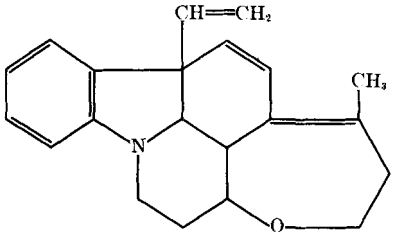
is probably due to a migration of the double bond (LXXIV → LXXV). The relationship of these products is illustrated in Chart IV.

CHART IV

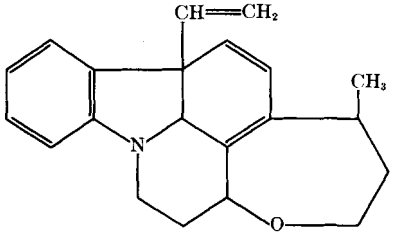
PRODUCTS FROM THE HOFMANN DEGRADATION OF DES-BASE-D



The intermediate steps in the conversion of dihydrobrucidine to desazabrucidine (197, 222, 228) with but few incidental variations are analogous



LXXIV



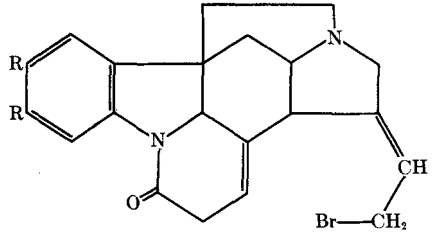
LXXV

with the formation of desazastrychnidine from dihydrostrychnidine-A. As yet no desazabrucidine-b has been isolated.

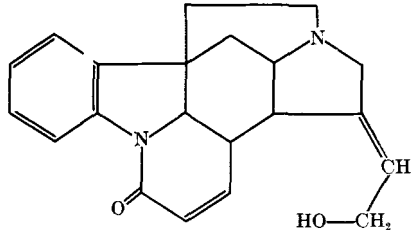
6. Isostrychnine ($C_{21}H_{22}O_2N_2$)

Strychnine (but not strychnidine (198)), dihydrostrychnine, and dihydrobrucine have been isomerized by such reagents as water at 180° (52), aqueous barium hydroxide (183), methanolic ammonia (89), alcoholic sodium alcoholates (146, 198), or hydrobromic acid-acetic acid mixture (33). The lactam grouping of isostrychnine, however, may be hydrolyzed (isostrychninic acid) by prolonged treatment of strychnine with some of these reagents (53, 177, 179). Moreover the conversion of dihydrostrychnine and dihydrobrucine (yielding three isomeric isodihydrobrucines (146)) to the corresponding isodihydro derivatives illustrates that the reaction is independent of the strychnine double bond. Isostrychnidine and its dihydro derivative result from the electrolytic reduction of isostrychnine and isodihydrostrychnine (198).

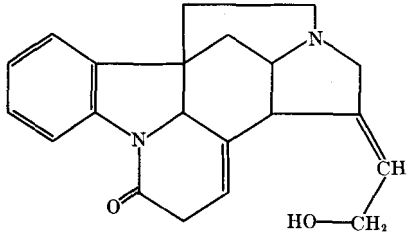
Although strychnine is isomerized, to a limited extent (10%), to isostrychnine by hydrobromic acid-acetic acid mixture, the main product is bromodesoxyisostrychnine (65%), $C_{21}H_{22}ON_2Br$ (LXXVI, R = H) (174), while 15% of a more soluble salt is recoverable from the filtrate. A similar reaction occurs with brucine but a simultaneous demethylation leads to bisapomethylbromodesoxyisobrucine (LXXVI, R = OH) (176). Hydrolysis of bromodesoxyisostrychnine by 1 *N* hydrobromic acid (174) or better



R = H, OH
LXXVI



LXXVII



LXXVIII

by .5 *N* sulfuric acid (176) yields isostrychnine-I, while the hydrolysis of the more soluble salt yields isostrychnine-II. The isomerism of the two isobases may be attributed to a difference in position of one of the two double bonds because the two isomers may be hydrogenated stepwise (176)

to the same tetrahydroisostrychnine (along with other stereo isomers). One double bond of isostrychnine-II must be alpha-beta to the lactam (LXXVII) for, unlike isobase-I (LXXVIII), it is reduced to *pyr*-dihydroisostrychnine II by sodium amalgam (176). Evidence for the hydroxyl of isostrychnine-I has been furnished by formation of an *O*-acetate which was characterized as its perchlorate (176, 179). Moreover the conversion of isostrychnine-II to the perchlorate of acetylisostrychnine-I by acetic anhydride and perchloric acid (176) is suggestive of the transformation that occurs when strychninolone-a is converted to acetylstrychninolone-b by acetic anhydride and hydrogen chloride (80).

Isostrychnine and isodihydrostrychnine (179) both give colorless condensation products with benzaldehyde. However, the product from isodihydrobrucine-II is identical with the isobenzal derivative of dihydrobrucine (148).

Isostrychninic acid, like strychninic acid, is an amino acid which gives a crystalline *N*-nitroso derivative and couples with various diazonium salts with the formation of colored azo compounds (177). Regeneration of isostrychnine results from dehydration of the acid with acetic anhydride or benzoyl chloride (241).

7. Pseudostrychnine and Pseudobrucine

Pseudostrychnine or hydroxystrychnine, $C_{21}H_{22}O_3N_2$, was discovered along with α- and β-colubrine in the mother liquors obtained from the large-scale isolation of strychnine (189). Pseudobrucine or hydroxybrucine has not as yet been isolated from a similar source but these two pseudo bases have been prepared from strychnine and brucine. While pseudostrychnine has been prepared by the ozonolysis of strychnine (258), both pseudo bases, along with the amine-oxide of the parent bases and strychnone ($C_{21}H_{20}O_3N_2$) (169) or bruzone ($C_{23}H_{24}O_5N_2$) (171) as the case may be, are available from the oxidation of strychnine (152, 169) or brucine (154) by gaseous oxygen in the presence of copper salts.

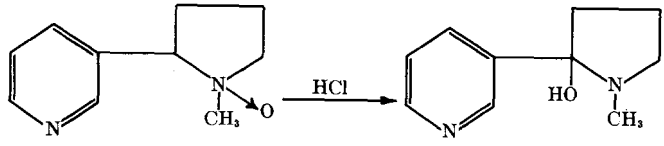
Twenty grams of strychnine in 60 cc. of chloroform is shaken with oxygen (renewed daily) in the presence of a solution of 10 g. of copper sulfate in 80 cc. of water and 160 cc. of 1 *N* ammonium hydroxide. On the seventh day the reaction mixture turns green and on the eleventh day a green sludge appears. The residue recovered from the chloroform layer is treated with sulfurous acid and ammonia and then taken up in chloroform. The residue from the second chloroform extract was crystallized from methanol when 9.6 g. of a solid melting at 160–165° is recovered. The undissolved resin from the crystallization, when dissolved in acid and decolorized, yields 0.7 g. of a solid (m.p. 215–245°) when precipitated with ammonia.

The combined fractions (10.3 g.) are dissolved in 35 cc. of hot 1 *N* hydrochloric acid, filtered, decolorized, and 4 g. of needles precipitated with 25 cc. of 1 *N* sodium acetate solution. Sodium bicarbonate (1 *N* solution) on the filtrate yields 3.7 g. (38.5%)

of a solid melting at 233° while ammonia precipitates a further 1.4 g. of the amine oxide of strychnine.

Solution of the base, melting at 233°, in 1 *N* hydrochloric acid and precipitation with hot ammonium hydroxide yields pseudostrychnine which melts at 265°.

It is conceivable that pseudostrychnine may result from the isomerization of the amine-oxide of strychnine by some catalyst in much the same manner as the amine-oxide of nicotine is isomerized to LXXIX by hydrochloric acid (48). The hydroxyl group of pseudostrychnine and pseudo-



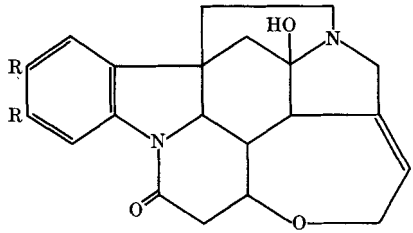
LXXIX

brucine is considered to be contiguous to N_b, for it exhibits the properties of a carbinolamine (e.g., berberine and cotarnine).

a. Strychnine Reactions. These pseudo-bases exhibit many of the properties and reactions characteristic of strychnine and brucine. Pseudostrychnine gives an Otto test (189) while with nitric acid, pseudobrucine gives first a red *o*-quinone (reduced to the hydroquinone by sulfurous acid) which in turn is nitrated to nitropseudobruciquinone hydrate (the pseudobrucine analog of cacotheline) (165). Halogenation (170, 180) and sulfonation (169) of pseudostrychnine is completely parallel to that of strychnine. The nuclear skeleton of strychnine and brucine has not suffered any alteration during the oxidation to the pseudo-bases since the parent bases are regenerated by reduction of the pseudo-bases with zinc and hydrochloric acid (152a, 154, 212). Catalytic reduction of pseudobrucine attacks first the double bond with the formation of pseudodihydrobrucine (identical with that from the oxidation of dihydrobrucine (154)), or it may proceed further with the formation of dihydrobrucine (165). Furthermore, pseudodihydrostrychnine (170) yields a mixture of a yellow benzal-derivative and a colorless isobenzal-derivative (of methyl ether) when condensed with benzaldehyde in the presence of sodium methylate (170). Benzylpseudodihydrostrychnine is available by the sodium amalgam reduction of benzalpseudodihydrostrychnine or the catalytic reduction of benzalpseudostrychnine. The cyclic ether of pseudodihydrostrychnine, like that in strychnine, is cleaved by sodium ethylate. The presence of the newly generated double bond was established by catalytic reduction (absorption of 6 atoms of hydrogen over PtO_2 yields dihydroisodihydrostrychnine) and that of the new hydroxyl group by acetate formation (170).

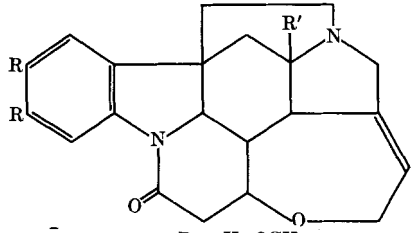
The passivity of pseudostrychnine to alkaline potassium ferricyanide

(212) and of pseudodihydrostrychnine to chromic acid and potassium permanganate (152a) has led to the conclusion that the hydroxyl group of the pseudo-bases and their dihydro derivatives occupies an angular position (LXXX) adjacent to N_b. However, the conversion of the amine-oxide of the weakly basic pseudobrucine to the neutral bruzone ($C_{23}H_{24}O_5N_2$) (181)



R = H, OCH_3

LXXX

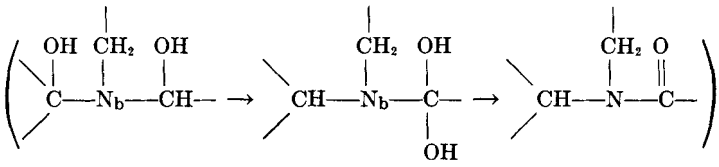


R = H, OCH_3

R′ = OCH_3, CN, $—CH_2NH_2$, $CH_2—CN$, $CH_2—CH_2—NH_2$, $CH_2—CO_2H$

LXXXI

would suggest that the carbinolamine grouping of pseudobrucine had been oxidized to an amide (hydrolysis by 12 *N* HCl to an amino acid). This evidence either refutes the previous hypothesis of an angular hydroxyl group in these bases or requires that a rearrangement or disproportionation

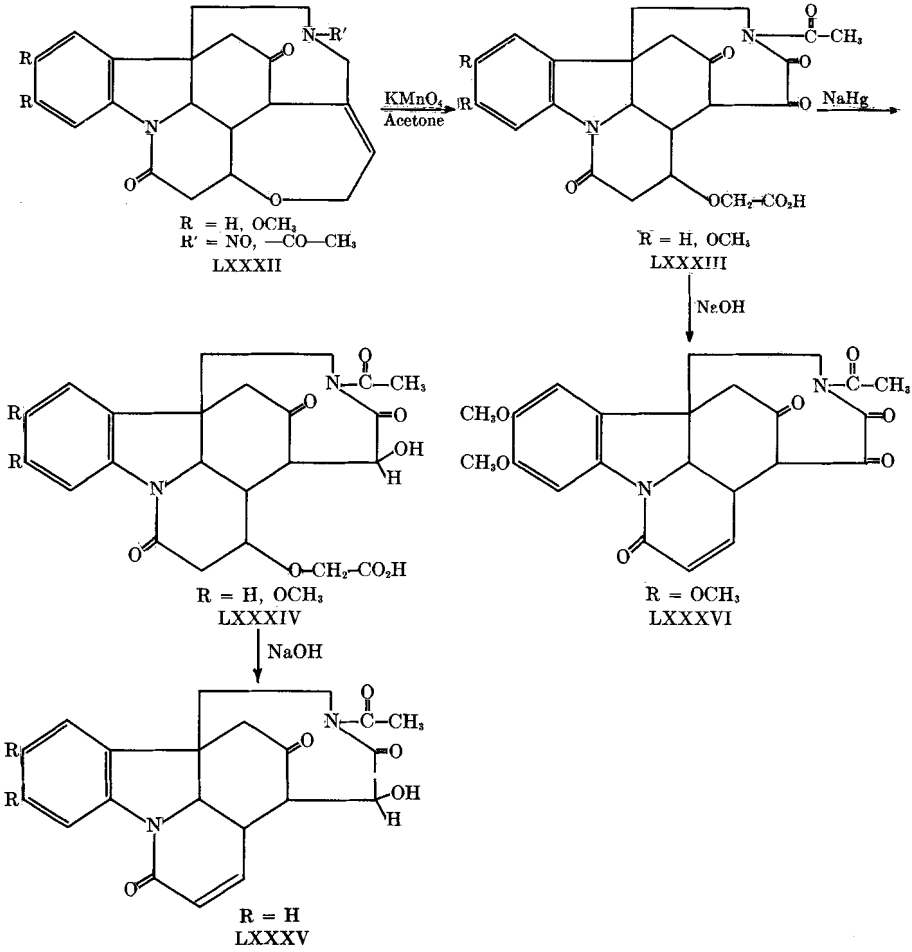


be involved in the conversion of pseudobrucine to bruzone. (Pseudostrychnine and pseudodihydrostrychnine have been converted in a similar manner to strychnone and dihydrostrychnone.) C_9 or one of the carbon atoms of the dimethylene chain comes into consideration as the center of the new amide grouping. The possibility of bruzone (the amide at C_9) being the first stage in the oxidation of brucine to brucinonic acid must be discounted since this acid does not result from bruzone under conditions obtaining in this oxidation.

The oxidation (without loss of the hydroxyl group) of pseudostrychnine to hydroxystrychninonic acid (190b) precludes the location of the hydroxyl of these pseudo-bases at C_9.

b. Carbinolamine Reactions. The hydroxyl group of pseudostrychnine, pseudobrucine, and their dihydro derivatives exhibits reactions diagnostic for a carbinolamine. The *O*-alkyl ethers (LXXXI, R′ = OCH_3) result from solution of these bases in alcohol (CH_3OH, C_2H_5OH), while the salts of the parent pseudo-bases are regenerated by solution of the ethers in

mineral acid. The nitrosamine of pseudostrychnine is doubtlessly derived from the keto-imino tautomeride (LXXXII, R′ = NO). The condensation of pseudostrychnine with hydrogen cyanide (180), cyanoacetic acid (180), and malonic acid (180) yields respectively, cyanostrychnine (LXXXI, R′ = CN), strychnineacetonitrile (LXXXI, R′ = $-CH_2-CN$) and strychnineacetic acid (LXXXI, R′ = $-CH_2-CO_2H$, in the last two reactions decarboxylation accompanies condensation). Hydrolysis of the cyanide of cyanostrychnine and strychnineacetonitrile to the respective acids failed. However, the absorption of six atoms of hydrogen (PtO_2) converted these



R = H, OCH_3
R′ = NO, —CO—CH_3
LXXXII

R = H, OCH_3
LXXXIII

R = H, OCH_3
LXXXIV

R = OCH_3
LXXXVI

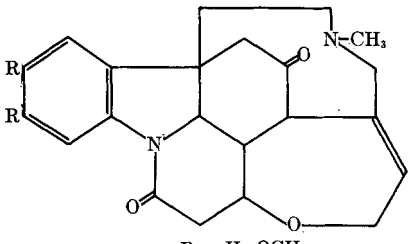
R = H
LXXXV

two nitriles to aminomethyldihydrostrychnine and aminoethyldihydrostrychnine respectively (180). Strychnineacetic acid absorbs one mole of hydrogen, and pyrolysis of the resulting dihydrostrychnineacetic acid yields

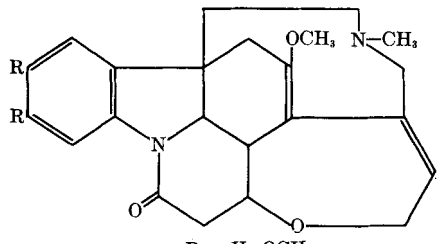
methyldihydrostrychnine (the dihydro derivative of LXXXI, R′ = CH_3).

The condensation of pseudostrychnine with acetic anhydride yields, besides a small amount of strychnineacetic acid, the neutral *N*-acetyl-*sec*-pseudostrychnine (LXXXII, R′ = CO–CH_3). The oxidation ($KMnO_4$-acetone) of *N*-acetyl-*sec*-pseudostrychnine to *N*-acetyl-*sec*-pseudostrychninonic acid (LXXXIII) followed by reduction of the ketone (NaHg) to *N*-acetyl-*sec*-pseudostrychninolic acid (LXXXIV) and cleavage of glycolic acid by alkali (yielding *N*-acetyl-*sec*-pseudostrychninolone (LXXXV)) finds a parallel in the strychnine series of bases. However, there is no analogy in the brucine series for the observed cleavage of *N*-acetyl-*sec*-pseudobrucinonic acid (LXXXIII, R = OCH_3) to glycolic acid and *N*-acetyl-*sec*-pseudobrucinone (LXXXVI) by .5 *N* sodium hydroxide solution (172).

c. Fission around N_b. Methyl iodide on pseudostrychnine methyl ether yields a separable mixture of the expected methiodide and the hydriodide of *N*-methylchanopseudostrychnine (LXXXVII) (152a). The normal methiodide in turn may be converted to LXXXVII by hydrolysis of the



R = H, OCH_3
LXXXVII



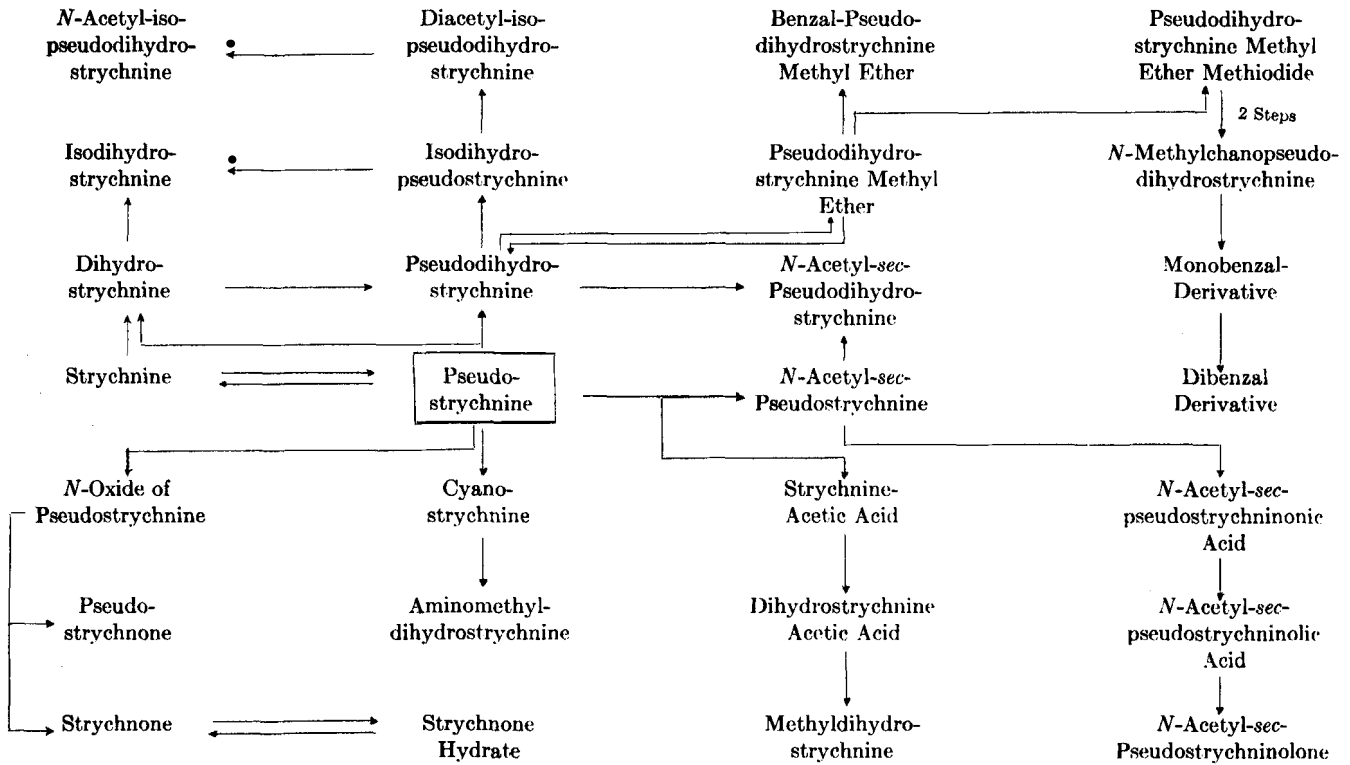
R = H, OCH_3
LXXXVIII

des-base (LXXXVIII) with dilute hydrochloric acid (212). (Robinson assumes that, during the process, the double bond has shifted to the Δ^{7-8} position in LXXXVII.) This ketone, as well as its dihydro derivative (catalytic reduction of LXXXVII over platinum black (218)), forms a monobenzylidene derivative while the former yields a dibenzylidene derivative under forcing conditions (hot concentrated alcoholic alkali (152a, 212, 218). This could not be explained by Leuchs' strychnine formula unless the double bond had isomerized to Δ^{7-8} position when condensation might be expected to occur at C_{15}.

A wandering of a methyl group from oxygen to nitrogen was observed when methyl iodide reacted with pseudobrucine methyl ether (164). The two products isolated were the hydriodide and methiodide of *N*-methylchanopseudobrucine (LXXXVII, R = OCH_3). Sodium ethylate on the methiodide induces a reversal of the migration of the methyl group (this time from nitrogen to oxygen) and the resulting tertiary base ($C_{25}H_{30}O_5N_2$)

CHART V

TRANSFORMATION PRODUCTS OF PSEUDOSTRYCHNINE AND DIHYDROPSEUDOSTRYCHNINE



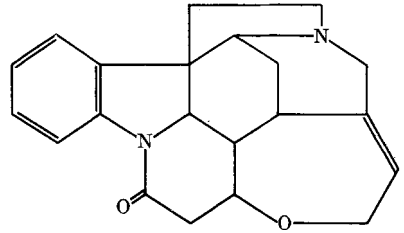
now contains a third methoxyl group and a newly generated double bond. Sodium amalgam effects a similar migration of the methyl group from nitrogen to oxygen but there is also a simultaneous reduction of the newly generated enol-ether double bond. Two moles of hydrogen (catalytic reduction or sodium amalgam) are absorbed by the methiodide of $C_{25}H_{30}O_5N_2$. The N_b–C_9 bond has been cleaved (Emde reduction) and the second mole of hydrogen has added 1,2 or 1,4 to the conjugated system of LXXXVIII (R = OCH_3).

The interrelationship of these various products may be seen from Chart V.

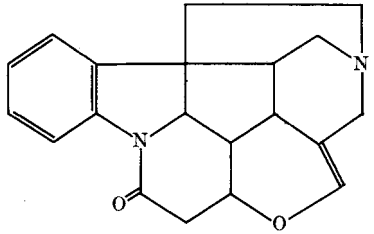
8. Piperidine Formulas for Strychnine

Recent work has cast doubt on the previous conclusions that ring E of strychnine is a five-membered ring. The α-ketoamide of dihydrostrychninone ($C_{19}H_{18}O_3N_2$) has been oxidized by barium hydroxide-hydrogen peroxide to carbon dioxide and an amino acid, cuninecarboxylic acid ($C_{18}H_{20}O_3N_2$) (232). The carboxyl of this β-amino acid (on formula XV for strychnine) should be lost by pyrolysis, but on the contrary lactamization occurred. This unexpected lactamization is explained most satisfactorily by the assumption of a piperidine nucleus for ring E (LXXXIX).

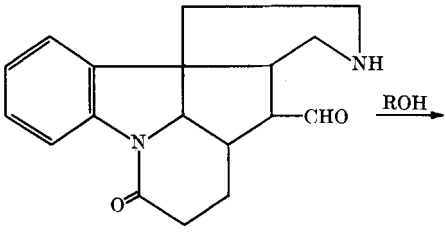
An alternate piperidine formula (XC) has been proposed on somewhat similar grounds (185, 190). Lead tetraacetate on dihydrostrychninone



LXXXIX

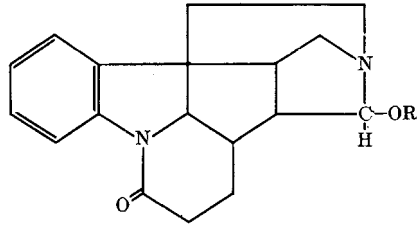


XC



XCI

ROH

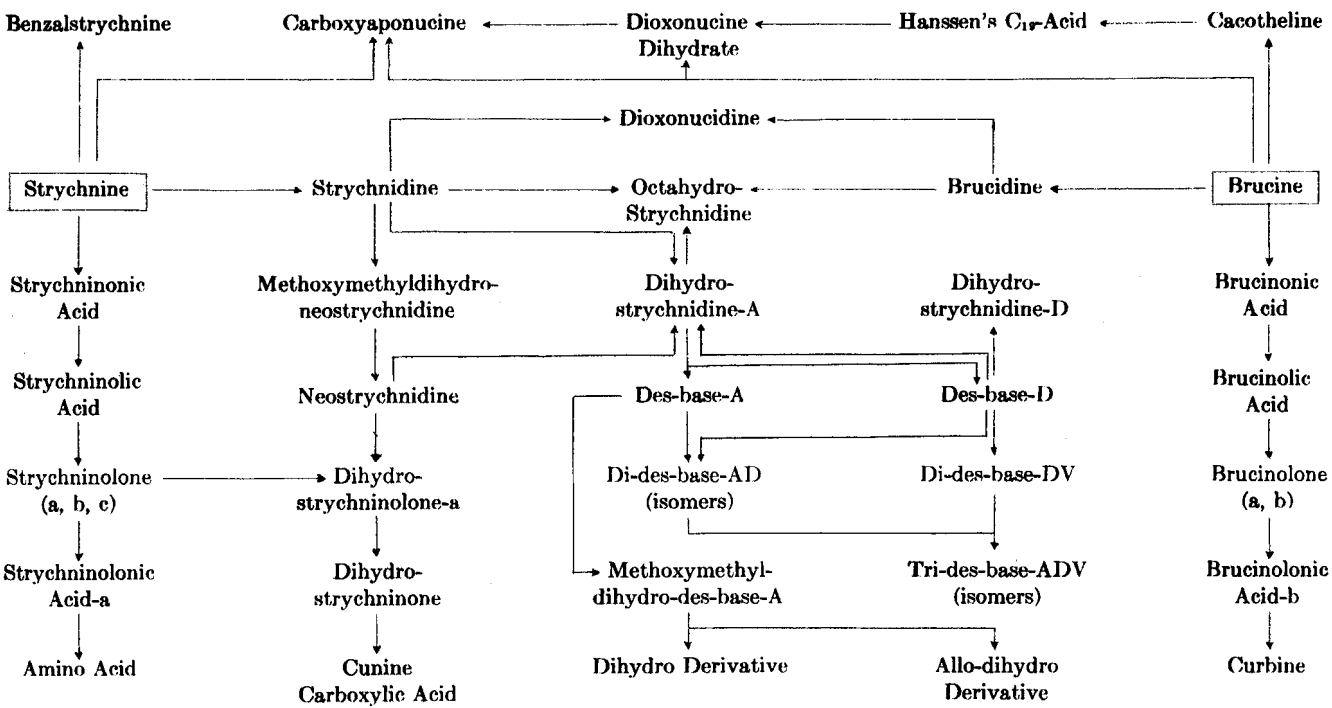


XCII

followed by heating in dry pyridine is reported to yield XCI. Recrystallization of XCI from methanol yields a methoxylated base considered to be XCII. Formula XC for strychnine stultifies the argument for a preformed

CHART VI

STRYCHNINE AND BRUCINE AND THEIR PRODUCTS OF TRANSFORMATION AND DEGRADATION



carbazole nucleus in these bases and fails to account adequately for the properties of pseudostrychnine.

Should structure LXXIX find acceptance, an examination of the previous work will disclose where revisions are necessary. Although dihydrostrychnidine-D may still be expressed by LXVIII (minus the methoacetate), yet the hypothesis of a structural isomerism if favored, and hence the structures LXVI and LXVIII, for dihydrostrychnidine-A and -D, must be interchanged. Secondly, the structure of the dibenzylidene derivative of LXXXVII must be altered to meet the demands of the new formula. Thirdly, the formation of a ketoamide in the perbenzoic acid oxidation of methoxymethyldihydroneostrychnine is not readily understandable if the double bond is in the neo position (this tends to favor Δ^{8-9} for the neo position of the double bond).

The relationship of the more important products of transformation and degradation of strychnine and brucine are graphically illustrated in Chart VI.

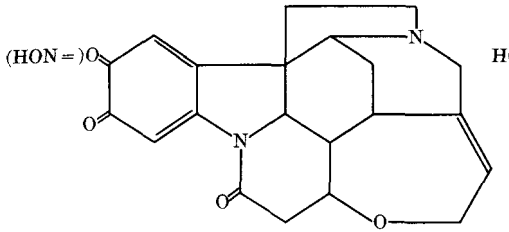
III. Cacotheline

1. Bis-desmethylbrucine and Bis-apomethylbrucine

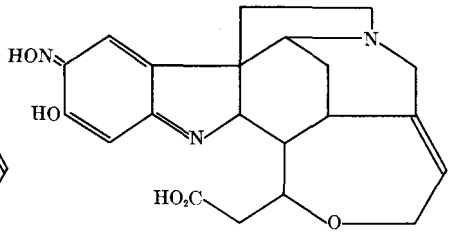
The dimethoxybenzene nucleus of brucine (159), its methosulfate (82), dihydrobrucine (159), the brucinesulfonic acids (60, 93), pseudobrucine and its dihydro derivative (162, 165), *N*-methyl-*sec*-pseudobrucine (168) as well as that of a number of transformation products of brucine (brucinonic acid (126), brucinolic acid (126), dihydrobrucinonic acid (126), bromodihydrodesoxybrucine (32), and dihydrodesoxybrucine (32)) is attacked by nitric acid (chromic acid in a few instances) at 0–5° with the formation of the respective *o*-quinones, which in turn may be reduced (SO_2) to the respective colorless hydroquinones (or isomerized by HCl to colored isomers). More vigorous conditions (temperature and concentration of the oxidant) effect a simultaneous nitration of the quinone nucleus and a hydrolysis of the lactam grouping.

Brucine is oxidized by 5 *N* nitric acid (or chromic acid (159)) at 0–5° to a rose-colored solution from which a red bruciquinone (bis-desmethylbrucine, ($C_{21}H_{20}O_4N_2$), XCIII) can be isolated as its perchlorate. It is a typical quinone because it is reduced by sulfurous acid to a hydroquinone, bis-apomethylbrucine (diacetate formation; brucine yields two moles of methyl chloride when heated with hydrochloric acid but bis-apomethylbrucine could not be isolated from the reaction mixture (191)). No other alterations occur in the brucine molecule during these transformations since methylation (dimethyl sulfate) converts bis-apomethylbrucine to the quaternary salt of brucine. The hydroquinone has been oxidized, with

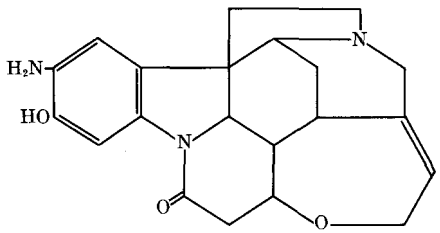
difficulty, to the quinone by chromic acid (65). The difficulty experienced in the oxidation of bis-apomethylbrucine to the quinone suggests that demethylation of the methoxyls of brucine is not the first step in the oxidation of this base to bis-desmethylbrucine (67, 87).



XCIII



XCIV



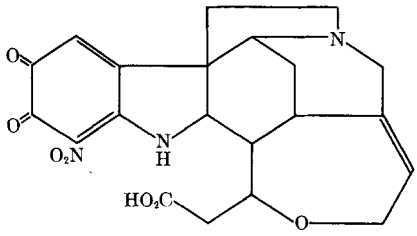
XCV

Bruciquinone forms a reddish-yellow monosemicarbazone and a yellowish-green monoxime (both isolated as perchlorates (159)), while at higher temperatures (80°) a reddish-violet hydrate of the monoxime is formed (probable structure XCIV). The formation of a monoxime, even with an excess of hydroxylamine, suggests that this derivative may exist as the tautomeric nitrosophenol. Reduction of either the monoxime or the monosemicarbazone by tin and hydrochloric acid yields aminohydroxystrychnine (XCV), while the dihydro derivative of XCV results from the uptake of six atoms of hydrogen over PtO_2 (159).

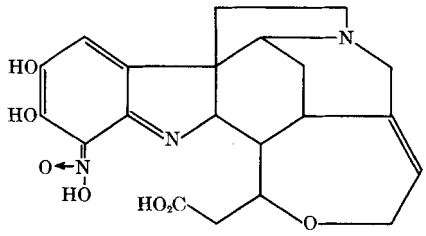
2. Cacotheline ($C_{21}H_{21}O_7N_3 \cdot HNO_3$) (4)

The oxidation of brucine, bis-apomethylbrucine, or bis-desmethylbrucine by concentrated nitric acid yields the nitrate of bis-desmethylnitrobrucine hydrate (XCVI; $C_{21}H_{21}O_7N_3 \cdot HNO_3$ (4, 62)) or cacotheline (ester formation established the cleavage of the lactam (85)). The methonitrate (methylcacotheline) and the dihydro derivative of XCVI result from the analogous oxidation of the quaternary salt of brucine (79, 83) and of dihydrobrucine (11). Reduction of cacotheline and methylcacotheline by sulfurous acid yields the hydroquinones (the analogous hydroquinone from brucinesulfonic acid-I is colorless (87)) which are isomerized by hydrochloric acid to deep violet-colored isomers. The analogous violet hydro-

quinone from brucinesulfonic acid-I yields a colorless triacetyl (two hydroxyls and the N_a-imine) and an N_a-acetyl derivative. The pale color of the N_a-acetyl derivative in contrast to the deep color of the hydroquinone itself would suggest that a tautomerism of the imine hydrogen is closely



XCVI



XCVII

associated with color formation. The tautomeric form, XCVII, has been suggested for the colored isomer (159). The quinone and nitro groups of cacotheline and methylcacotheline are reduced by tin and hydrochloric acid with formation of the respective aminohydroquinones. Cacotheline forms a readily hydrolyzable monoxime which is reduced by tin and hydrochloric acid to a diaminophenol (lactamization accompanies the reduction (85)).

The pseudobrucine analog of cacotheline reacts similarly towards sulfurous acid but there is a simultaneous elimination of the carbinolamine hydroxyl with reduction of the quinone and nitro groups by tin and hydrochloric acid. The resulting aminohydroquinone is identical with that from cacotheline (162).

3. 3-Carboxymethylene-2-oxonucine Hydrate ($C_{19}H_{22}O_6N_2$) (88)

The oxidative degradation of cacotheline with chromic acid has not led to any positive result (42a), but bromine-hydrobromic acid (chlorine-hydrochloric acid proved less satisfactory (98)) has provided a method for the stepwise degradation of cacotheline and dihydrocacotheline to a series of interesting compounds.

Three moles of bromine degrades a hydrobromic acid solution of cacotheline through the intermediate product, $C_{21}H_{23}O_8N_3Br_2$ (98, 112), to 3-carboxymethylene-2-oxonucine hydrate (Hanssen's C_{19}-acid; XCVIII). Bromopicrin and carbon dioxide as well as a small amount (5% at best (107)) of a very interesting by-product, $C_{17}H_{20}O_3N_2Br_2$, are the other products of this reaction.

A red amorphous precipitate settles out when a mixture of 9.6 g. of bromine in 20 cc. of hydrobromic acid (s.g. 1.46) is added to 10.16 g. of cacotheline in 200 cc. of water. The loosely corked flask is warmed on a steam bath and shaken from time to time and then finally heated for 15 minutes over a free flame when a clear yellow solution results. Yellow crystals (3.8 g.) settle out of the solution after cooling for many hours in an ice bath. The hydrobromide of Hanssen's C_{19}-acid is purified by dissolving

in dilute hydrobromic acid (Norit) from which the hydrobromide crystallizes in colorless prisms. The crystals are collected on a Büchner funnel, washed with acetone and ether, and dried in air.

Concentration of the mother liquors from the reaction mixture afford 0.65 g. of the hydrobromide of the base $C_{17}H_{20}O_3N_2Br_2$.

A dihydro derivative of Hanssen's C_{19}-acid results in an analogous manner from dihydrocacotheline (11). Although the mechanism for the degradation of cacotheline to the dicarboxylic acid $C_{19}H_{22}O_6N_2$ (XCVIII; dimethyl ester (88)) is somewhat obscure (88), the loss of two carbons and the absence of a nitro group in the acid make it appear that this part of the quinone nucleus is the focal point in the degradation. The C_{19}-acid absorbs two moles of hydrogen over PtO_2 (11), while the selective reduction of one of these double bonds by sodium amalgam yields a dihydro derivative (88) isomeric with that from dihydrocacotheline. These reduction reactions as well as the oxidation of the C_{19}-acid to 2,3-dioxonucine dihydrate (106, 229) (XCIX) and carboxyaponucine (9) support the above structure for Hanssen's C_{19}-acid. The ability of this acid as well as its dihydro derivative to form an anhydride makes it seem highly probable that this is a *cis* dicarboxylic acid (112).

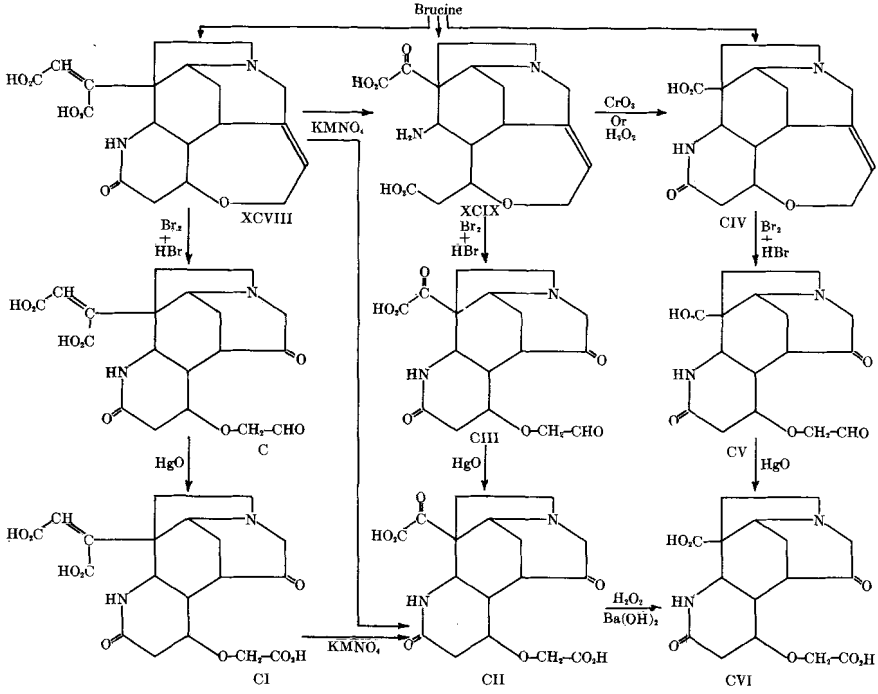
Hanssen's C_{19}-acid has also been related to 2,3-dioxonucine dihydrate (XCIX) and carboxyaponucine (CIV) through common degradation products. The keto dicarboxylic acid, $C_{17}H_{20}O_8N_2$ (CII), (oxalic acid being the other product) resulting from the permanganate oxidation of Hanssen's C_{19}-acid (106) has also been obtained in a stepwise fashion. The brucine double bond of Hanssen's acid was oxidized by bromine-hydrobromic acid and the resulting aldehydic acid, $C_{19}H_{22}O_8N_2$ (C) (101), oxidized with mercuric oxide to the tricarboxylic acid $C_{19}H_{22}O_9N_2$ (CI) (104). The remaining center of unsaturation was then oxidized by permanganate to oxalic acid and the keto acid CII ($C_{17}H_{20}O_8N_2$). An alternate route to the same acid is the gentle oxidation ($KMnO_4$) of Hanssen's C_{19}-acid to 2,3-dioxonucine dihydrate (XCIX) (106) followed by successive oxidations with bromine-hydrobromic acid and mercuric oxide (106). Furthermore, the acid CVI resulting from the $Ba(OH)_2$–H_2O_2 oxidation of CII has been derived from carboxyaponucine by a similar series of oxidations (CIV → CVI) (111).

The amorphous perbromide of carboxyaponucine, which is later transformed into needles, is formed when 2.04 g. of the acid is heated with 7.5 cc. of 4 *N* bromine in hydrobromic acid (5 atoms of bromine) at 100° for 30–45 minutes. The heating is stopped when the precipitate has completely dissolved and the color of the clear solution begins to darken. The reaction mixture is poured into water, decolorized, and evaporated to dryness in vacuum (0.6 g.). The pure dihydrobromide of CV (0.38 g.; 11.7%) crystallizes from dilute hydrobromic acid in six-sided leaflets.

The oxidation of CV to CVI is effected by heating a solution of 0.55 g. of the

dihydrobromide of CV in 50 cc. of water with 0.216 g. of yellow mercuric oxide for 30 minutes; the mercuric bromide is collected by filtration of the hot solution. This procedure was repeated five times with fresh mercuric oxide or until 0.38 g. (theory, 0.56 g.) of mercuric bromide had been collected. The pure hydrobromide of CVI (0.31 g.; 67.4%) is obtained as clear domatic prisms by evaporation of the metal-free filtrate to dryness and crystallization of the residue from dilute hydrobromic acid.

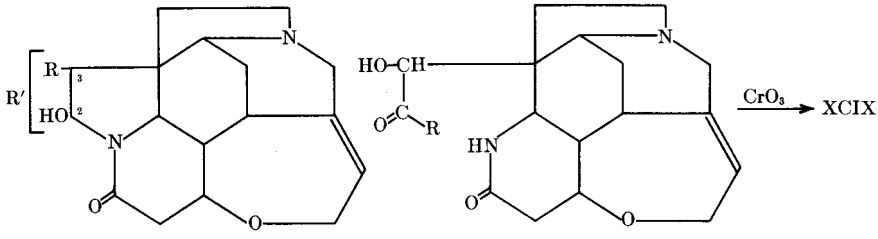
The catalytic reduction of the double bond of carboxyaponucine, in contrast to that of strychnine, yields a pair of isomeric dihydro derivatives (122).



4. Dibromohydroxynucine ($C_{17}H_{20}O_3N_2Br_2$) (88)

This base (methiodide formation (107)) which occurs as a by-product (5%) in the bromine-hydrobromic acid oxidation of cacotheline, being devoid of carboxyl groups (no ester formation (107)) and carbonyl groups (no oxime or semicarbazone (107)), is most readily purified by extraction of an ammoniacal solution of the base with chloroform followed by repeated crystallization of its hydrobromide salt (109). The loss of four carbon atoms in the formation of this base combined with the results of various transformations lead to the belief that it is a 2-hydroxy-3-bromonucine, CVII (R = R′ = Br), with a second and readily replaceable bromine at either C_2 or C_3.

The base $C_{17}H_{20}O_3N_2Br_2$ forms a monoacetate (109) while boiling water removes both halogen atoms. One or both of the halogens may be



R = H, Br; R′ = H, Br
CVII

R = OH, NH_2
CVIII

reductively eliminated, depending upon the reagent selected. Methanolic ammonium sulfite yields 2-hydroxy-3-bromonucine (CVII; R = Br, R′ = H), while sodium amalgam removes both halogen atoms (109). Nucine results, on the other hand, by elimination of the hydroxyl and the two bromine atoms by zinc amalgam (111). The catalytic hydrogenation (PtO_2) of dibromohydroxynucine effects the simultaneous elimination of a single halogen atom and the saturation of the brucine double bond, yielding a product identical with that from the catalytic reduction of 2-hydroxy-3-bromonucine (167).

Dibromohydroxynucine has been converted to 2,3-dioxonucine dihydrate (XCIX) by transformation (aqueous ammonia) of the dibromobase to the hydroxy amide CVIII (R = NH_2) (167) followed by hydrolysis of the amide to the hydroxy acid, $C_{17}H_{22}O_5N_2$ (CVIII, R = OH), and oxidation (CrO_3) of the hydroxyl to a ketone. The oxidation of the hydroxy acid to 2,3-dioxonucine dihydrate is accompanied by hydrolysis of the lactam. The neutral hydroxy acid, $C_{17}H_{22}O_5N_2$, has been obtained directly by hydrolysis of the dibromobase with aqueous barium hydroxide solution (109).

The brucine double bond of the acid $C_{17}H_{22}O_5N_2$ has been oxidized (3 Br_2 + HBr) to the aldehydic acid, $C_{17}H_{22}O_7N_2$, and this in turn converted to the dicarboxylic acid $C_{17}H_{22}O_8N_2$ by mercuric oxide (107).

IV. Vomicine

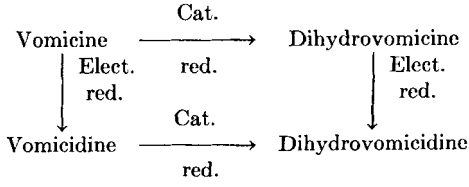
Vomicine ($C_{22}H_{24}O_4N_2$) (8), like strychnine, is a weak base (it will not form a methiodide directly (25, 29) as will dihydrovomicine (29)) but shows greater solubility in most solvents (especially acetone (8)) and hence is found in the mother liquors from the purification of strychnine. The common origin of these two alkaloids, as well as their similar properties and analogous reactions, makes it highly probable that vomicine has the strychnine nucleus and many of the characteristic groupings of the latter

base. In spite of this no direct relationship has yet been established by conversion of vomicine to strychnine or one of its degradation products. In the absence of such a relationship, and to avoid confusion, the pyrrolidine strychnine nucleus will be used to conform with that appearing in the literature.

1. Functional Groups of Vomicine

Vomicine is a monoacidic, tertiary base, with one double bond, dihydrovomicine (8) being readily obtained by catalytic reduction (PtO_2 in acetic acid). The ease with which one hydrogen atom is replaced by bromine would indicate that substitution has occurred in the benzene nucleus *para* to N_a (8). It is only on such a hypothesis that the failure of bromovomicine to form a substituted bivomicyl is understandable (12).

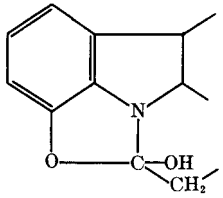
The presence of an N_a-lactam grouping in vomicine is manifest by much experimental evidence. Vomicine and dihydrovomicine are insoluble in cold alcoholic potassium hydroxide (13), but on warming, as in the case of strychnine, they are converted to soluble salts which have a characteristic sensitivity towards oxygen (8). However, by performing the hydrolysis in the absence of oxygen it is possible to isolate the readily oxidizable vomicinic and dihydrovomicinic acids. Vomicine is regenerated by lactamization of vomicinic acid by mineral acids (13) and, hence, esterification of this acid by the Fischer method has not been realized. A series of esters has been isolated when the sodium salt of vomicinic acid was treated consecutively with methyl iodide and diazomethane (13). From these reactions, N_a-methylvomicinic acid, O,N_a-dimethylvomicinic acid and their methyl esters have been isolated. Other reactions which parallel those of strychnine and brucine and which proceed under comparable conditions substantiate the assumption of a lactam grouping in vomicine. For example, vomicine has been converted to isovomicine (33, 34, 36a) and a crystalline isonitrosovomicine (22) (this has been converted in turn to aminovomicine and diazovomicine), while benzaldihydrovomicine has been prepared from dihydrovomicine (24). Furthermore, the lactam of vomicine (14, 25) is reduced at a lead cathode (more readily than strychnine) with the formation of the diacid, ditertiary base, vomicidine, $C_{22}H_{26}O_3N_2$ (the co-formation of tetrahydrovomicine was not observed). The catalytic reduction of vomicidine to dihydrovomicidine (21) and its preparation from dihydrovomicine completes the analogy with strychnine.



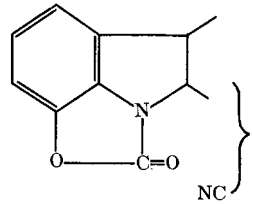
However, in contrast to strychnidine, vomicidine is phenolic (*O*-acetate (21) and *O*-benzoate (14)), it being soluble in alkali. While this sensitive aminophenol has been methylated with dimethyl sulfate, only an intractable black resin results from the action of diazomethane.

Vomicine, like strychnine and brucine, does not react with carbonyl reagents (8), while diagnostic reactions indicate the absence of methoxyl (Zeisel) and methylenedioxy (Späth) groupings. One of the oxygen atoms is considered to be present in a cyclic ether (8). Vomicine ($C_{22}H_{24}O_4N_2$) differs from strychnine ($C_{21}H_{22}O_2N_2$) by CH_2O_2. The nature of the remaining two oxygen atoms is still a puzzle, for the results of various reactions directed towards their characterization are contradictory and, to say the least, confusing. While the insolubility of vomicine in alcoholic potassium hydroxide and the negative ferric chloride test, as well as the absence of an active hydrogen (Zerewitinoff) (8), (other workers (18) report the presence of two active hydrogens when anisole is the solvent and one when pyridine is the solvent), militate against the presence of a phenolic group in this base, yet the formation of an *O*-acetate (34) and an *O*-benzoate (8) and the presence of a phenolic hydroxyl in vomicidine would suggest that a masked phenolic hydroxyl is indeed present. To account for these properties Wieland (13) concluded that there is an association of the phenol with the lactam as expressed in part formula CIX.

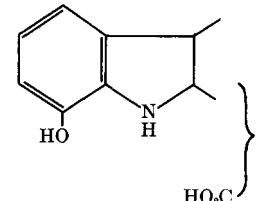
This part formula satisfactorily accounts for the products from the Beckmann rearrangement of isonitrosovomicine (22). The cyano-carbamic lactone, CX, resulting from the action of thionyl chloride upon isonitrosovomicine, is hydrolyzed to norvomicinic acid (CXI).



CIX



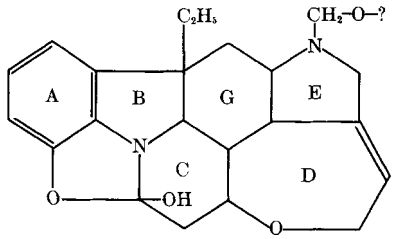
CX



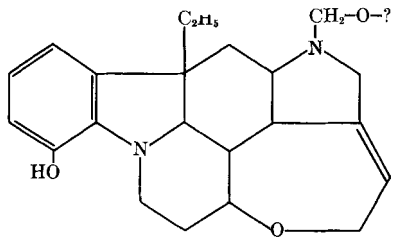
CXI

The weak basicity of vomicine has been ascribed to the grouping $-O-CH_2-N_b$. In the event of such a grouping in vomicine, the strychnine ethanamine chain must be replaced by an ethyl side chain which at various times has been located at C_3 and C_4 (CXII) to conform with the strychnine formula. In agreement with this formula vomicine is a tertiary amine (with no $N-CH_3$ grouping (Herzig Meyer) (8)) for, although the methiodide is not formed from the direct combination of the two reactants, it has been obtained by the action of sodium iodide upon an aqueous solution of vomi-

cine methosulfate (29). In contrast with vomicine, dihydrovomicine and vomicidine form methiodides by direct combination with methyl iodide.

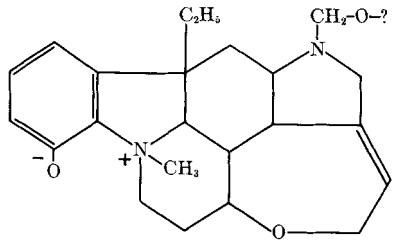


CXII[4]

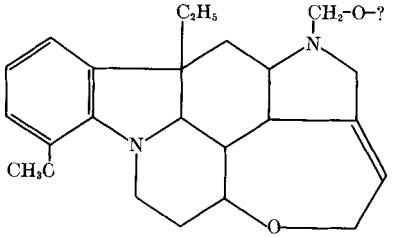


CXIII[4]

Both vomicidine (CXIII) and its dihydro derivative yield beautifully crystalline dimethiodides. An anomalous reaction was encountered when methylation of the phenol of these dimethiodides with diazomethane was attempted. Methyl iodide was evolved from vomicidine dimethiodide and the phenol betaine, CXIV, was formed (21). In agreement with the known properties of these phenol betaines, CXIV was converted to CXV when heated above its melting point (21) and into vomicidine N_a-methiodide when treated with hydriodic acid (21).



CXIV



CXV

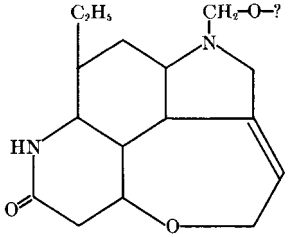
2. Products of Oxidation and Nitration

The point of attack by oxidizing agents, as with strychnine, is dependent to a large extent upon the type of oxidizing agent selected. Although in certain instances there are minor variations, in the main the results are analogous with those for strychnine. When the oxidative attack is centered on the benzene nucleus (chromic acid) the products of oxidation differ from those of the strychnine series by CH_2O (the grouping attached to N_b of vomicine).

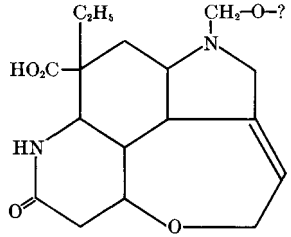
Three crystalline products have been recovered from the oxidation of vomicine ($C_{22}H_{24}O_4N_2$) with chromic acid (8, 15), (a) a base, $C_{16}H_{22}O_3N_2$, m.p. 304°, (b) an acid, $C_{17}H_{22}O_5N_2$, m.p. 264°, and (c) an acid, $C_{18}H_{24}O_7N_2$,

[4] Recent work supports a C_4 linkage for the ethyl side chain (see p. 432) with the oxygen attached to C_3 (35).

m.p. 266–268°. Base "a" is formed by the decarboxylation of "b" so that "a" is not considered to be a primary product of the oxidation of vomicine. The acid, $C_{17}H_{22}O_5N_2$, is the analog of carboxyaponucine (Hanssen's C_{16}-acid) and so would be CXVII while base, $C_{16}H_{22}O_3N_2$, would be CXVI. The marked ease of decarboxylation of CXVII (in contrast to Hanssen's C_{16}-acid) was for a time attributed to the attachment of the oxygen end of the oxido-methylene group (for convenience termed ether ring "b") to C_4. The carboxyl group is so readily lost that during the hydrogenation of

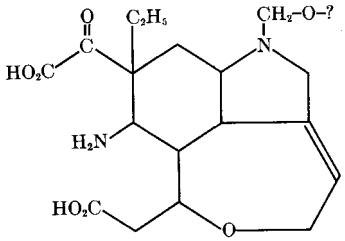


CXVI

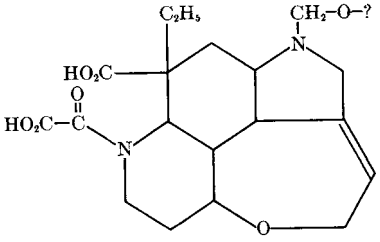


CXVII

CXVII to the dihydro derivative (obtainable also by the chromic acid oxidation of dihydrovomicine) a part of the material is simultaneously decarboxylated to the dihydro derivative of CXVI. The acid, $C_{18}H_{24}O_7N_2$, in analogy with dioxonucine dihydrate (Wieland's C_{17}-acid) exists in the hydrated form (lactam ring hydrolyzed). However, unlike Wieland's acid, CXVIII is not reduced by catalytic means and cannot be oxidized to CXVII.



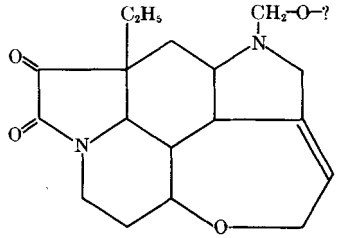
CXVIII



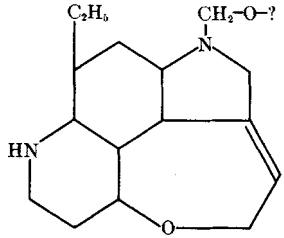
CXIX

Regardless of the surprising similarity of the products of oxidation of vomicine to those of the strychnine series this has contributed little to the elucidation of the structure of the hydropyrroquinoline as constituted in rings C, E and G. The chromic acid oxidation of vomicidine, on the other hand, does offer an approach to structures sufficiently simple to be within the scope of synthesis. The oxidation of vomicidine with this reagent is not as extensive (25, 31), as is the oxidation of strychnidine or brucidine to dioxonucidine. The oxidation product, CXIX, may, however, be converted to the analog of dioxonucidine by heating to 200° when CXX is

formed, accompanied by the interesting base, $C_{16}H_{24}O_2N_2$ (CXXI). The catalytic dehydrogenation (Pd at 200°) of CXXI affords the base, vomipyrine ($C_{15}H_{16}N_2$), (an intermediate, $C_{16}H_{18}ON_2$, has also been isolated (33)) as well as a base ($C_{13}H_{17}N$) considered to be CXXIII or CXXV. From the loss of one carbon and eight hydrogens it might be inferred that

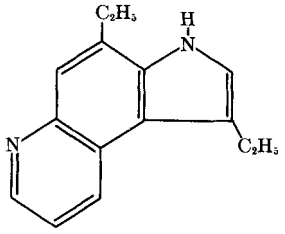


CXX

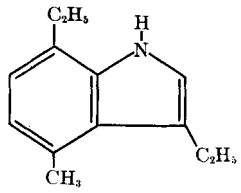


CXXI

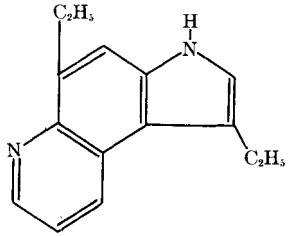
CXXI had been dehydrogenated to CXXII or CXXIV. The ultraviolet absorption spectrum of CXXII (27, 28) was almost identical with that of



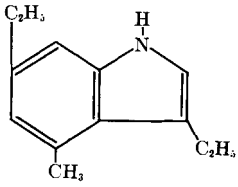
CXXII



CXXIII



CXXIV



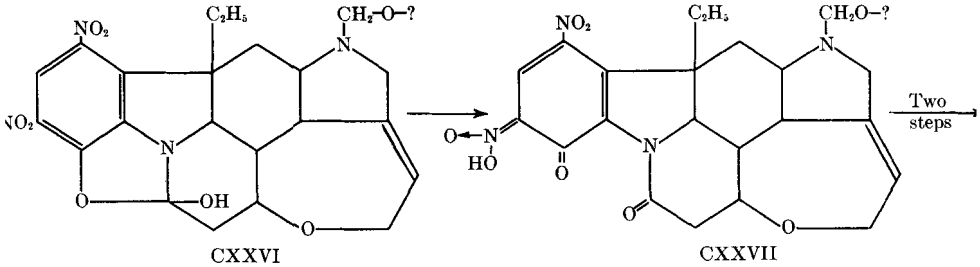
CXXV

vomipyrine, and that of CXXIV (28) was quite similar to it, yet the melting points clearly demonstrated that they are different compounds.[5]

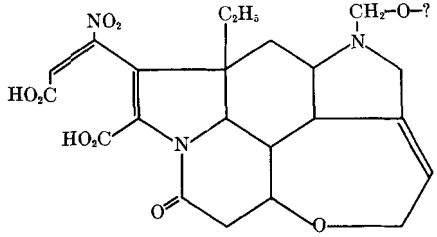
The action of nitric acid on vomicine is in no way as uniform as on brucine. With 20% nitric acid, mononitrovomicine can be isolated only under well-defined conditions (16), and then with widely varying yields.

[5] If the nuclear structure of vomicine may be represented in a manner similar to that shown in strychnine formula LXXXIX then it is understandable why CXXII and CXXIV should differ from vomipyrine.

The other product from the nitration contains three more oxygens than nitrovomicine and, in contrast to the latter, is non-basic. This acid, CXXVIII, could result from the action of nitric acid upon the unstable dinitrovomicine (CXXVI) by a mechanism analogous with that for the conversion of *o*-nitrocresol to isoprenedicarboxylic acid (6, 7). This conversion may be represented by the sequence CXXVI → CXXVIII.

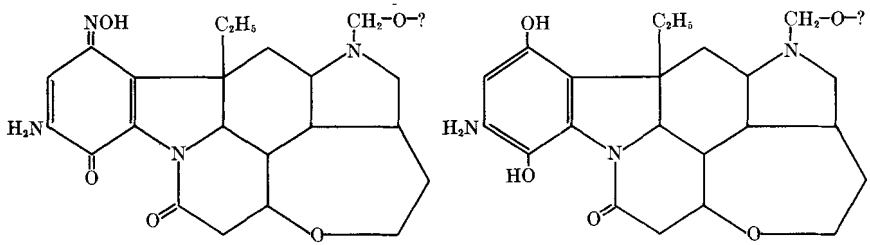


CXXVI CXXVII



CXXVIII

Nitration of dihydrovomicine proved more difficult (30% nitric acid), but a dinitro derivative has been characterized (16). Reduction of dinitrodihydrovomicine with tin and hydrochloric acid yields the aminohydroquinone, CXXX. This is quite understandable if the nitrosophenol (quinone monoxime), CXXIX, is assumed as the intermediate.

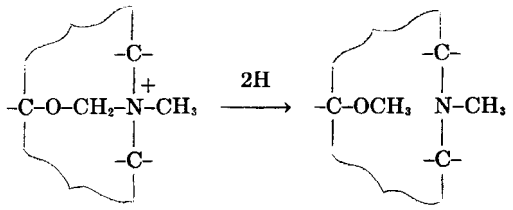


CXXIX CXXX

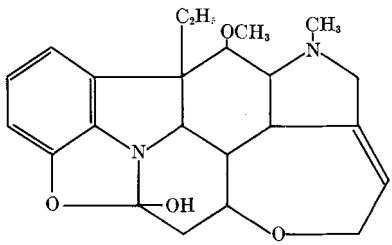
3. Fission around N_b

Vomicine methiodide is very similar to strychnine methiodide, with warm alkali converting the intermediate methohydroxide to the betaine, methylvomicine. The metho salts of vomicine are regenerated by mineral

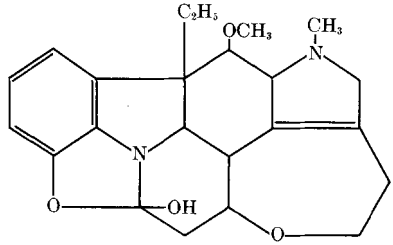
acids (29), and for this reason reduction of the quaternary salts of vomicine has been employed for the fission of ring E (29, 35). An acetic acid solution of vomicine methosulfate (but not dihydrovomicine methosulfate due to the absence of the allylamine system) is reduced by sodium amalgam to a separable mixture of isomeric tertiary bases, which for convenience may be termed *N*-methylvomicine-I and -II. *N*-Methylvomicine-I contains a methoxyl group (Zeisel) in addition to the expected methylimino grouping (Herzig-Meyer). The Emde reduction has apparently cleaved the oxidomethylene group at N_b as expressed in the following partial formulas:



A hydroxyl-containing compound (*O*-acetate (35) and *O*-benzoate (35)) which may be purified by distillation at 290° under high vacuum, results from the demethylation (HBr) of methylvomicine-I. From the formation of an *O*-acetate and the distillation of this hydroxy base without dehydration it may be inferred that it is not a tertiary hydroxyl, and hence precludes the attachment of the oxygen end of the oxidomethylene group to either C_4 or C_7. The location of the oxygen has been tentatively assigned to C_3, whence the ethyl side chain probably occupies position C_4 in agreement with Robinson's pyrrolidine formula for strychnine. Migration of the double bond to Δ^{7-8} (CXXXI → CXXXII) during the reduction may account for the observed isomerism.



CXXXI



CXXXII

A second Emde reduction on the quaternary salt of methylvomicine-I cleaved ring E, trimethylamine being liberated from the resulting product by a Hofmann degradation.

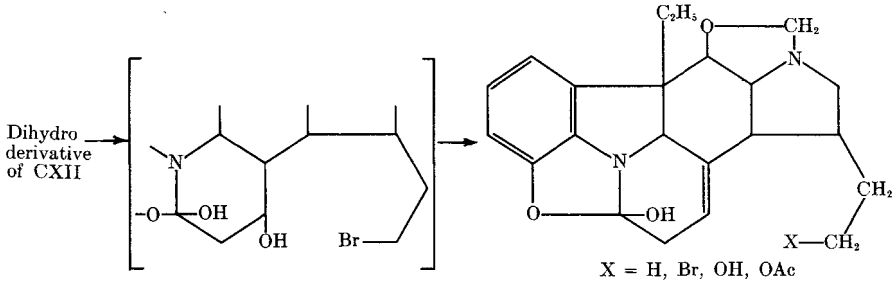
4. Desoxyvomicine and Isovomicine

The most complex aspect of this field is the chemistry of desoxyvomicine and its related products. The changes produced by the action of halogen acids on vomicine ($C_{22}H_{24}O_4N_2$) depend on the conditions and the acid used. Hydriodic acid in acetic acid causes the elimination of an oxygen atom with the formation of the yellow desoxyvomicine (a by-product, $C_{22}H_{25}O_3N_2I$ (8), was also formed), which is readily isomerized (alkali or heat (24, 36)) to the stable colorless desoxyvomicine ($C_{22}H_{24}O_3N_2$) (8, 36). The iodine-containing base has been reduced by zinc and acetic acid (8) to $C_{22}H_{26}O_3N_2$, a product isomeric with desoxydihydrovomicine (hydriodic acid upon dihydrovomicine (36)). When hydrobromic acid is substituted for hydriodic acid, a product containing bromine, $C_{22}H_{25}O_3N_2Br$, results from dihydrovomicine (32) (the analogous product, $C_{23}H_{26}O_3N_2Br_2$, results from vomicine methobromide but not from vomicine (32)). Vomicine, under similar conditions, yields isovomicine, $C_{22}H_{24}O_4N_2$.

The modified lactam grouping is still present in desoxyvomicine and desoxydihydrovomicine; a monobenzylidene derivative is readily formed (piperidine as condensing agent (36)), and desoxyvomicine and desoxydihydrovomicine have been reduced at a lead cathode to the phenolic bases, desoxyvomicidine ($C_{22}H_{26}O_2N_2$) (22, 24) (a small amount of an isomeric desoxydihydrovomicine (22)) and desoxydihydrovomicidine (31) (an isomerization may have occurred, however, in the pretreatment of desoxyvomicine with sodium hydroxide and boiling pyridine (24)). Desoxyvomicine cannot be hydrogenated directly (but this has been achieved indirectly by addition of hydrogen bromide and reductive elimination of the halogen (36)) to desoxydihydrovomicine, since three moles of hydrogen (PtO_2) are absorbed with the formation of $C_{22}H_{28}O_2N_2$, which may be further hydrogenated to $C_{22}H_{30}O_2N_2$ (8, 24). The benzene nucleus has not been involved in this reduction; the two reduction products have been electrolytically reduced to the phenolic bases, $C_{22}H_{30}ON_2$ and $C_{22}H_{32}ON_2$ (24), respectively, and the monobromo derivative of $C_{22}H_{28}O_2N_2$ has been prepared. Hence, formation of desoxyvomicine must involve the cleavage of either the original strychnine-ether structure (termed ether ring "a") or the oxide structure tentatively located at N_b–C_3 (ether ring "b") with the simultaneous introduction of a second ethylenic bond (24).

The nature of the mechanism leading to the formation of desoxyvomicine is still obscure. The presence of two imino-methyl groups and the absence of a methoxyl in the product from the Emde degradation of desoxyvomicine methiodide (29) was considered, for a time, as evidence that ether ring "b" was cleaved in the formation of these desoxy bases. However, the marked similarity of this conversion with that for strychnine has led to the assumption of a cleavage of ether ring "a," an interpretation

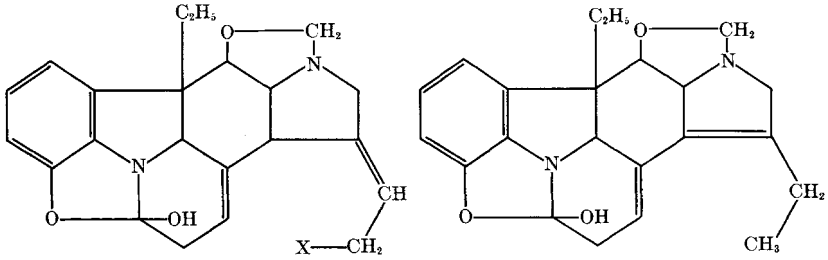
herein presented. The analogy of vomicine and dihydrovomicine with strychnine and dihydrostrychnine towards halogen acids seems to be complete, for, while vomicine and strychnine are isomerized by these reagents, dihydrovomicine and dihydrostrychnine are converted to halogenated desoxy bases (32, 36a). This may be considered to result from fission of ether ring "a" followed by the introduction of a double bond at Δ^{6-13}, CXXXIII, X = Br (the ease of formation of a benzylidene derivative has been used as an argument for the location of the double bond at the position assigned (36, 36a)). The presence of the double bond in bromodesoxydihydrovomicine is demonstrated by replacement of the bromine by an acetoxyl group (sodium acetate) and the absorption of one



CXXXIII

mole of hydrogen (PtO_2) by the derived dihydroisovomicine (CXXXIII X = OH) (36a). Reductive elimination of the bromine (Zn + HOAc (32)) of bromodesoxydihydrovomicine yields desoxydihydrovomicine(CXXXIII, X = H).

An analogous process must occur in the formation of isovomicine, for, although the intermediate bromodesoxyvomicine has not been isolated (the bromine-containing intermediate has been isolated in the case of vomicine

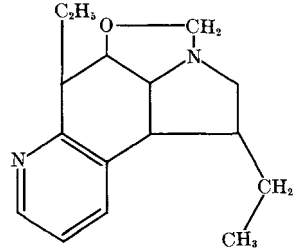


CXXXIV CXXXV

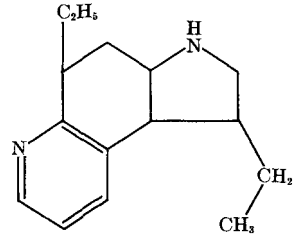
methobromide (32)), its formation is manifest by conversion of the crude reaction product, prior to hydrolysis, to acetylisovomicine (sodium acetate (36a)). The ease of hydrolysis of the allyl bromide system in bromodesoxyvomicine would account for the formation of isovomicine (CXXXIV,

X = OH) by the above reagent, while reduction of the iodine of the intermediate iododesoxyvomicine by hydriodic acid would accommodate the formation of desoxyvomicine (CXXXIV, X = H) by the latter reagent. The isolation of acetaldehyde (36) (80% yield) from the ozonolysis of the colorless form of desoxyvomicine has been used as an argument in favor of CXXXIV (X = H) for this base, while it is considered that the double bond may be at Δ^{7-8} (CXXXV) in the yellow isomer (36) although this hardly explains the color of this compound.

The oxidation of desoxyvomicine by chromic acid failed to produce any crystalline products. However, the oxidation of desoxyvomicidine (30) and desoxydihydrovomicidine (31) proved to be more fruitful. An oxygen poorer base, $C_{16}H_{20}ON_2$, has been isolated as its crystalline dihydrochloride from the chromic acid oxidation of desoxyvomicidine and $C_{16}H_{22}ON_2$ from desoxydihydrovomicidine. However, in analogy with the oxidation of dihydrovomicidine, a base, $C_{16}H_{26}ON_2$, is to be expected from the oxidation of desoxyvomicidine. The loss of four hydrogen atoms during the oxidation would suggest that dehydrogenation of the piperidine nucleus (30) to CXXXVI has occurred. The bases, $C_{16}H_{20}ON_2$ and $C_{16}H_{22}ON_2$, have been catalytically reduced to $C_{16}H_{24}N_2$. Dehydrogenation of $C_{16}H_{22}ON_2$ eliminated the oxygen complex attached to N_b with the formation of $C_{15}H_{20}N_2$ (CXXXVII).



CXXXVI



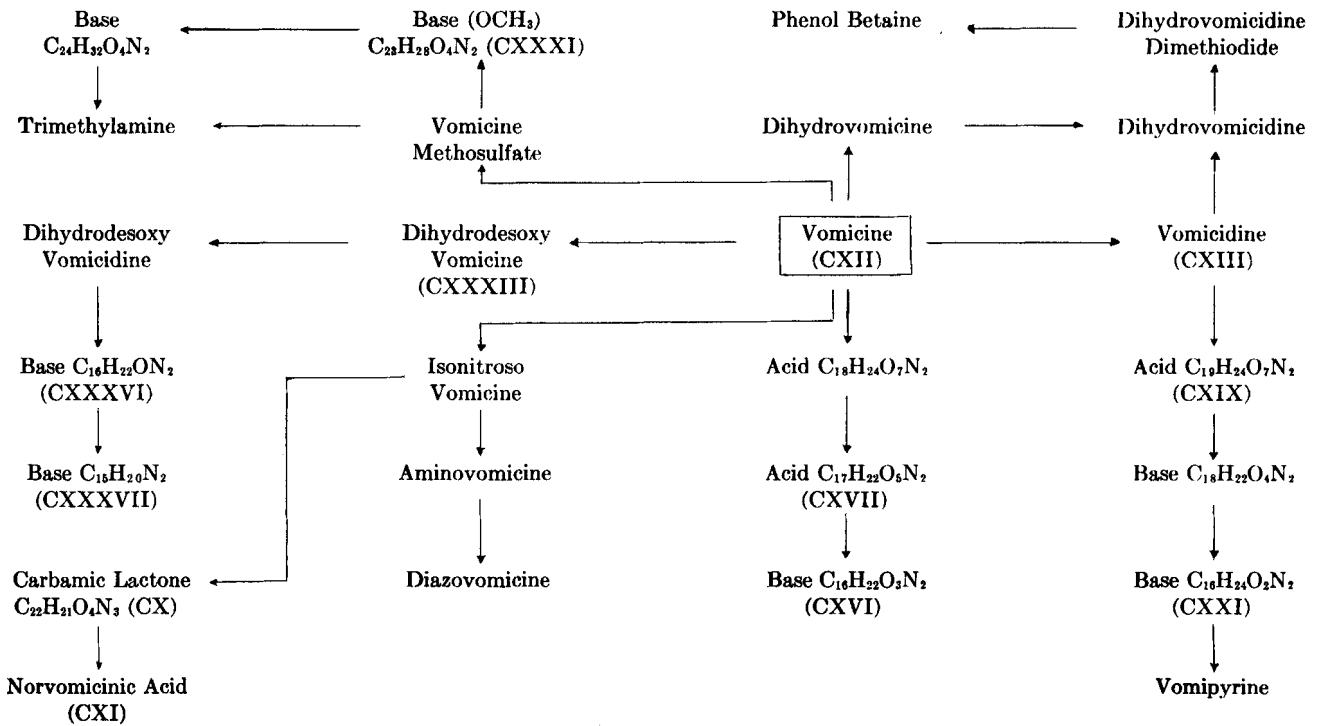
CXXXVII

The above structure for the colorless desoxyvomicine fails to offer a satisfactory explanation for the formation of a methiodide by this base, while vomicine fails to react with methyl iodide under similar conditions. Reduction of an acetic acid solution of desoxyvomicine methiodide by sodium amalgam yields the base $C_{23}H_{30}O_3N_2$ with two imino-methyl groups (29) (desoxydihydrovomicine and methane result from a similar reduction of desoxydihydrovomicine methiodide (32)). Base $C_{23}H_{30}O_3N_2$ reacts smoothly with methyl iodide, while thermolysis of the derived methohydroxide yields trimethylamine. It would seem difficult to find an adequate explanation for the formation of trimethylamine on the present formula for desoxyvomicine.

The relationship of these products of transformation and degradation of vomicine are graphically indicated in Chart VII.

CHART VII

RELATIONSHIP OF PRODUCTS OF TRANSFORMATION AND DEGRADATION OF VOMICINE



V. Tables of Physical Constants

The table of physical constants for *strychnine* and its products of transformation and degradation, arranged in alphabetical order, is followed in sequence by those for *brucine*, *vomicine*, and the *colubrines*. Products of oxidation, reduction, and isomerization of the main products, lacking a trivial name, are listed first in order of their decreasing number of carbon atoms. These are followed in order by quaternary salts and then *O*- and *N*-acyl derivatives. An asterisk, preceding a melting point, signifies that the value as recorded is corrected, while a melting point anteceded by a bracketted "V" or dec indicates respectively that the melting point was determined in vacuum (or in the absence of air) or that decomposition occurred at the melting point. The physical constants quoted in the tables will be found in the first two references cited, the remaining references appearing in numerical order.

TABLE 1

STRYCHNINE AND ITS DERIVATIVES

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
N-Acetyl-*sec*-pseudodihydrostrychnine	269 (V)	. .	Needles (CH_3OH)	172, 170
N-Acetyl-*sec*-pseudostrychnine	. .	. .	Plates ($CHCl_3$)	172
N-Acetyl-*sec*-pseudostrychninolic Acid	. .	. .	Resin	172
N-Acetyl-*sec*-pseudostrychninone	280 (dec)	. .	Needles (H_2O)	172
N-Acetyl-*sec*-pseudostrychninonic Acid	225–230 (dec)	+321°/d (HOAc)	Prisms (acetone–H_2O)	172
Semicarbazone	205–220 (dec)	. .	Needles (HOAc–H_2O)	172
Amide	230–234 (dec)	. .	Prisms (H_2O)	172
Methyl ester	230 (V)	. .	Needles (CH_3OH)	172
Allo-methoxy-N_b,N_b-dimethyldihydrochanotetrahydrostrychnidine	113–114	. .	Plates (pet. ether)	226
Allo-N_b-methyldesdihydrostrychnidine				
Dimethiodide	274–275	. .	Yellow prisms(H_2O)	227
Dimethochloride	. .	. .	Needles (H_2O)	227

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Allo-N_b-methyldihydrochanodihydrostrychnidine	117–118	..	Plates (CH_3OH)	226
Aminoethylstrychnine	230 (V)	..	Needles	180
Aminohydroxydihydrostrychnine	308 (dec)	..	Needles and prisms	159
Hydrochloride	>300	..	Colorless prisms	159
Hydroperchlorate	..	..	Wedge-shaped crystals	159
Monoacetyl	298 (dec)	..	Crystalline powder	159
Aminohydroxystrychnine				
Diacetyl-hydroperchlorate	..	..	Plates (H_2O)	159
Monoacetyl-hydroperchlorate	..	..	Prisms (H_2O)	159
Aminoisostrychninic Acid	240–245	..	Crystals	177
Aminomethyldihydrostrychnine	254–256	..	Plates (C_6H_6)	180
N-Acetyl-	269–271	..	Needles (ethyl acetate)	180
Aminostrychnidine	>330 (dec)	..	Crystals ($CHCl_3$–ligroin)	198
Aminostrychnine	275–278 280/5mm.	..	Cubes (C_2H_5OH)	243, 108, 244
Acetyl-	205	..	Plates (C_2H_5OH)	244
Hydrochloride	..	..	Colorless plates	244
12-Aminostrychnine	83–86	..	Yellow needles(H_2O)	20
Dihydrochloride	>250 (dec)	..	Needles (C_2H_5OH–ether)	20
Aminostrychnine-sulfonic Acid-I	270	−244.8°(NaOH)	Needles or prisms	63
Aminostrychnine-sulfonic acid-II	..	..	Colorless prisms	131
Anhydrodecahydrostrychnidine-I				
Zinc chloride double salt	..	−10.6°	Plates (HCl–H_2O)	141
Anhydromethylstrychnidinium-D hydroxide	196–197	..	Needles (CH_3OH)	215, 225
Dimethiodide	214–216	..	Plates (H_2O)	227
Dimethochloride	292–294	..	Needles (C_2H_5OH–CH_3OH)	227
Methiodide	289–290	..	Needles (CH_3OH)	215
Methochloride	308–310	..	Crystalline powder (H_2O)	215

TABLE 1 (*Coniinued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Anhydrotetrahydrostrychnine	174 (dec)	..	..	182a
Hydroperchlorate	240–245 (dec)	..	Prisms (H_2O)	182a
Aponucidine	123–124 (V)	−84°/d (H_2O)	Plates (ether)	117
Dipicrate	195–198	..	Plates (C_2H_5OH)	117, 118
Hydroperchlorate	..	..	Needles	117
N-Acetyl-				
Hydroperchlorate	262 (dec)	−64° (H_2O)	Prisms (H_2O)	157, 117
Methoperchlorate	240–245	−46 °(H_2O)	Columns (H_2O)	157
N-Benzoyl-				
Hydroperchlorate	230–240 (dec)	−49.2° (H_2O)	Leaflets (C_2H_5OH)	157
Methoperchlorate	247 (dec)	−13° (H_2O)	Prisms (C_2H_5OH)	157
Aponucine dihydroperchlorate	..	+218.7°/d	Crystals	117
Apostrychnine	242–244	..	Crystals (acetone)	36
		B		
Benzylchlorodihydrostrychnine	217 (V)	−64.7°/d ($CHCl_3$)	Prisms (ether)	158
Benzyldihydrostrychnine	185–187	−13.4°/d (C_2H_5OH)	Prisms (ether)	135, 149
Methiodide	310 (dec)	..	Plates (acetone)	135
Benzylpseudodihydrostrychnine	208–220 (V)	..	Prisms (CH_3OH)	170
Benzylpseudostrychnine	145 (froth)	..	Needles (acetone)	170
C-Benzylstrychnine	102–105 (froth)	−76°/d (C_2H_5OH)	Leaflets (C_2H_5OH)	135, 149
Methiodide	305 (dec)	..	Prisms (acetone)	135
Benzylstrychnine (betaine)	270	..	Needles (H_2O)	208, 5
C-Benzylstrychnine-sulfonic Acid-I	..	−159° (NaOH)	Powder	135
C-Benzylstrychnine-sulfonic Acid-II	..	−123° (NaOH)	Prisms	135
C-Benzylstrychnine-sulfonic Acid-III	205	..	Amorphous	135
C-Benzylstrychninolic Acid	220–223	..	Needles (HOAc)	135
C-Benzylstrychninolone	..	..	Powder	135
C-Benzylstrychninonic Acid	208–210	−19° (NaOH)	Prisms (HOAc)	135
Bromodesoxydihydrostrychnine	280	..	Needles (C_2H_5OH–H_2O)	32

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bromodesoxyiso-strychnine	290–300 (dec)	..	Powder	174
Hydrobromide	..	..	Crystals($HBr-H_2O$)	176
Bromodihydrostrych-nine	202–204	−37.6° ($CHCl_3$)	Prisms (acetone)	149
Hydrobromide	239–245	..	Prisms (H_2O)	149
Isobenzal-	234–235	−676°/d($CHCl_3$)	Prisms (acetone)	149
Bromodihydrostrych-nineacetic Acid	290 (V)	..	Needles (H_2O)	173
Bromodihydrostrych-ninonic Acid	310 (dec)	−19.7° (NaOH)	Leaflets	81
3-Bromo-2-hydroxydi-hydronucine	252 (V)	..	Needles (C_2H_5OH)	167
Hydrobromide	..	+43.3°/d	Plates (H_2O)	167
Methiodide	265 (dec)	..	Prisms (H_2O)	167
Methobromide	>300	..	Prisms ($HBr-H_2O$)	167
Methoperchlorate	..	..	Dense crystals(H_2O)	167
Bromoisostrychnino-lone-1	273	−24.2° (HOAc)	Needles (C_2H_6OH)	81
Bromo-*N*-methyl-*sec*-pseudo-strychnine	..	..	Needles	169
Bromopseudodihydro-strychnine	240–244 (V. dec)	−61°/d($CHCl_3$)	Leaflets	170
Methyl ether	205–207 (V)	..	Needles (CH_3OH)	170
Bromopseudostrychnine	225	−130°/d($CHCl_3$)	Prisms (acetone)	180
Hydrochloride	210–220 (dec)	..	Leaflets (*HCl*)	180
Picrate	235 (dec)	..	Prisms (acetone)	180
Methyl ether	195–197	..	Plates (CH_3OH)	180
Bromostrychnine	221–222	..	Rhombic plates (acetone)	63, 40, 81, 192, 243
Hydrobromide	240–243(froth)	..	Prisms (H_2O)	81
Hydrochloride	..	..	Needles	192, 40
Methiodide	..	..	Crystals (CH_3OH)	192, 40
Nitrate	..	..	Silky needles	40
Sulfate	..	..	Rosettes of needles	40
Benzal-	239–241	−533°/d($CHCl_3$)	Prisms (C_2H_5OH)	149
Bromostrychnine-sulfonic Acid-I	..	−237° (NaOH)	Domatic prisms	63
Bromostrychninolic Acid	265–270(froth)	..	Prisms (HOAc)	81
Bromostrychninolone-a	254–256	−63.2° (HOAc)	Plates (C_2H_5OH)	81
Bromostrychninolone-b	233–235	−72.8° (HOAc)	Needles (C_6H_6)	81
Bromostrychninonic Acid	*274–276	−54.8° (NaOH)	Needles (H_2O)	63, 81
Ethyl ester	*247	..	Domatic prisms	81
Methyl ester	230–231	..	Needles (acetone)	81

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		C		
Carboxyaponucidine	>290	−165°/d (H_2O)	Domatic prisms (H_2O)	117
Diperchlorate	140	..	Prisms	117
Hydroperchlorate	..	−59.7°/d (H_2O)	Plates (H_2O)	113
Methiodide	255–260 (dec)	−56.1°/d(H_2O)	Rods (CH_3OH)	117
N-Acetyl-	300 (dec)	−197.1°/d(H_2O)	Prisms (acetone–H_2O)	117
Carboxyaponucidinic Acid				
Hydrobromide	..	−3.6°/d(H_2O)	Plates (H_2O)	113
Hydroperchlorate	..	..	Prisms	113
Carboxyaponucidinic Aldehyde				
Dihydrobromide	..	+11.1°/d(H_2O)	Prisms	113
Oxime	..	−8.5°/d(H_2O)	Prisms (HBr–H_2O)	113
Semicarbazone	..	−16°/d(H_2O)	Plates (HBr–H_2O)	113
Hydroperchlorate	..	..	Prisms	113
Carboxyaponucine	312–314 (dec)	−118° (H_2O)	Octahedra or cubes	9, 8a, 10, 39, 41, 112
Dihydrobromide	290–295 (dec)	..	Leaflets (HBr)	111
Hydrobromide	210–215	+100.8°/d(H_2O)	Plates (H_2O)	111
Semicarbazone	>240	..	Prisms (HBr–H_2O)	111
Hydroperchlorate	..	−94° (H_2O)	Rt. ∟'d prisms (H_2O)	112
Methyl betaine	250–252 (dec)	−94° (H_2O)	Leaflets (CH_3OH)	10, 125
Methiodide	288–290 (dec)	..	Prisms (CH_3OH)	10
Carboxyaponucine-sulfonic Acid-I	..	−185°/d	Prisms (H_2O)	125
Methoperchlorate	..	+42.8°/d	Rt. ∟'d leaflets	125
Carboxyaponucine-sulfonic Acid-II	..	−192° (H_2O)	Prisms (H_2O)	131
Carboxyaponucine-sulfonic Acid-IV	..	−193.2° (H_2O)	Plates	133
Chano-N_b-methyldihydrostrychnine	145	..	..	254
Chlorodesoxyisostrychnine Hydrochloride	..	..	Prisms (HCl–H_2O)	176
Chlorodihydrostrychnine	208–210	−32.5°/d ($CHCl_3$)	Needles (CH_3OH–H_2O)	158
Hydrobromide	..	..	Silky prisms (H_2O)	158
Benzal-	275 (V)	−228°/d($CHCl_3$)	Yellow polyhedra (C_2H_5OH)	158
Isobenzal-	217	−716°/d($CHCl_3$)	Columns (acetone)	158
Hydrochloride	..	..	Fine needles	158

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Chlorodihydrostrychninonic Acid	305 (dec)	..	Short prisms	158
Chloropseudodihydrostrychnine	280–282 (V. dec)	−59.7°/d ($CHCl_3$)	Plates (acetone)	170
Methyl ether	212–215 (V)	+51°/d($CHCl_3$)	Columns	170
Chloropseudostrychnine	240	−133°/d($CHCl_3$)	Prisms (acetone–H_2O)	158
Methyl ether	168–169 (V)	−120°/d($CHCl_3$)	Prisms (CH_3OH)	158
Chlorostrychnine	235 (V)	−104.6° (C_2H_5OH)	Plates (acetone)	158, 184
Hydroperchlorate	..	..	Prisms or leaflets (H_2O)	158
Benzal-	252	−589°/d($CHCl_3$)	Yellow prisms (C_2H_5OH)	158
Chlorostrychninesulfonic Acid-I	..	−240° (NaOH)	Domatic prisms	63
Chlorostrychninonic Acid	270 (dec)	..	Plates (HOAc–H_2O)	158
Cuninealdehyde	..	..	..	190
Ethyl derivative	194–195	+28° ($CHCl_3$)	Crystals (ethyl acetate-ligroin)	190
Methyl derivative	214	+34° ($CHCl_3$)	Crystals (ethyl acetate-ligroin)	190
Methiodide	206 (V)	..	Crystals (ethyl acetate)	190
Cuninecarboxylic Acid	265–270	−22° (HOAc)	Prisms (H_2O)	232
Lactam	296–297	−220° (HOAc)	Plates (CH_3OH)	232
Methyl ester	167–168	−25° (HOAc)	Needles (CH_3OH)	232
Cyanodihydrostrychnine	283–286 (V)	..	Dense prisms (CH_3OH)	173
Cyanostrychnine	278–280	..	Rhombohedra (acetone)	180
Hydroperchlorate	..	−141.5°/d ($CHCl_3$)	Prisms	180
Benzal-	295–298 (V)	−450°/d($CHCl_3$)	Yellow prisms (HOAc)	180
Isobenzal-	201–203	−570°/d($CHCl_3$)	Needles (C_2H_5OH)	180
Cyanostrychninonic Acid	230	..	Crystals (H_2O)	180
		D		
Decahydrostrychnidine-I	264–265 (V)	−62.5°/d ($CHCl_3$)	Lancets	134, 141
Dihydroperchlorate	285–290 (dec)	+27.6°	..	134
Zinc chloride double salt	..	+23.6°/d(H_2O)	Plates	141
O-Acetyl-	..	..	..	134
Hydroperchlorate	..	+63.4°	..	134, 141

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Decahydrostrychnidine-II	269–271 V)	+22.6°/($CHCl_3$)	Needles (C_2H_5OH)	134
Dihydroperchlorate	..	+21.5°	Six-sided prisms	134
Desazastrychnidine-a	..	..	Oil	226
Methiodide	154–155	..	Crystals (acetone)	227, 226
Desazastrychnidine-b	109–110	..	Colorless plates	227
Methiodide	105–106	..	Yellow needles(H_2O)	227, 226
Des-base-A (see N_b-Methyl(chano)dihydroneostrychnidine				
Des-base-D (see Anhydromethylstrychnidinium-D Hydroxide				
Desoxyethylstrychnine Ethobromide	235 (dec)	..	Plates and rods (C_2H_5OH)	18
Desoxyisostrychnine	195–197	..	Needles (C_2H_5OH–H_2O)	174
Desoxymethyldihydrostrychnine Methiodide	241 (dec)	+741°(C_2H_5OH-H_2O)	Polyhedra	18
Desoxymethylstrychnine Methiodide	245–246 (dec)	+137.3° (H_2O)	Needles (C_2H_5OH)	18
Desoxystrychnine	197–198	..	..	36
Diaminostrychnine	>300	..	Needles (H_2O)	108, 250
Diaminostrychol-carboxylic Acid	..	..	Prisms	3
Hydrochloride	..	..	Prisms (HCl)	3
12-Diazostrychnine	107–108 (dec)	..	Crystals (C_2H_5OH–H_2O)	20
Hydrochloride	170 (dec)	..	Prismatic needles (H_2O)	20
Dibromohexahydrostrychnine	210	−92.2°/d ($CHCl_3$)	Prisms (C_2H_5OH–H_2O)	121
Methiodide	262 (dec)	..	Prisms (CH_3OH)	121
O-Acetyl-	184–186	..	Needles (C_2H_5OH)	121
Methiodide	258–259 (dec)	..	Leaflets (H_2O)	121
Dibromostrychnine	230 (dec)	..	..	40, 192
Dibromotetrahydrostrychnine	264–266	−174.9°/d ($CHCl_3$)	Prisms (acetone–$CHCl_3$)	121, 115
Hydrobromide	..	..	Lancets (H_2O)	121, 115
Hydrochloride	..	−23.2°/d(H_2O)	..	115
Methiodide	285 (V)	..	Prisms and needles	121
O-Acetyl-	260–261	−163.2°/d ($CHCl_3$)	Leaflets (acetone)	121
Methiodide	280 (dec)	..	Needles (H_2O)	121
Dichlorostrychnine-sulfonic Acid-I	..	−155.9°(NaOH)	Plates	63
Di-des-base-AD (see N_b,N_b-Dimethyldesneostrychnidine and N_b,N_b-Dimethyldesbisneostrychnidine)				
Di-des-base-DV (see N_b,N_b-Dimethyldesstrychnidine-D)				

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydroallostrychnyl Chloride	..	..	..	129
Hydrochloride	..	+59°/d(H_2O)	Needles (HCl)	129
Picrate	259–263	..	Leaflets (acetone)	129
Dihydroaponucidine				
Dipicrate	187–189	..	Plates (acetone)	118
N-Acetyl-				
Hydroperchlorate	260 (dec)	+42.2° (H_2O)	Plates (H_2O)	157
Methoperchlorate	215–220	..	Prisms (H_2O)	157
Dihydrobromodesoxy-isostrychnine	280	..	Prisms (CH_3OH)	174
Dihydrocarboxyaponucidine	289–291 (froth)	−32.1°	Prisms (acetone–H_2O)	118
Hydroperchlorate	..	..	Needles (H_2O)	118
Dihydrocarboxyaponucine-I	292–294 (dec)	−7.8° (H_2O)	Rods (C_2H_5OH–H_2O)	10, 122
Hydroperchlorate	..	−11.5	Plates (H_2O)	122
Dihydrocarboxyaponucine-II	..	−21.6	Polyhedra (H_2O)	122
Dihydrochano-N_b-2-oxo-3-hydroxy-hydronucidine-I	199–201 (V)	+63.6°/d (C_2H_5OH)	Leaflets (C_2H_5OH)	140
Hydroperchlorate	..	+45.5°	Prisms and plates	140
Dihydrochano-N_b-2-oxo-3-hydroxy-hydronucidine-II	170–175	+36°/d (C_2H_5OH)	Prisms (C_6H_6)	140
Hydroperchlorate	–	+33°	Crystals	140
Dihydrodesoxyiso-strychnine	170–180 (V)	..	Prisms and plates	174
Hydroperchlorate	214–216	..	Leaflets	174
Dihydrodesoxystrych-nine	180	..	Plates (ether)	32
Dihydro-N_b,N_b-dimeth-yldesstrychnidine-D	126–127	..	Plates (CH_3OH)	227
Methiodide	244–246	..	Needles (CH_3OH)	227
Dihydro-2-hydroxy-nucine	190 (dec)	..	Prisms (CH_3OH)	167
Dihydroisodihydro-strychnine	228	−23.7° (HOAc)	..	148
Hydroperchlorate	139–142	..	Prismatic needles	149, 158
Methiodide	310 (froth)	−5° (HOAc)	Prisms (CH_3OH)	148
O-Acetyl-				
Hydroperchlorate	105	−2.6° (HOAc)	Prisms	148
Dihydroisostrychni-dine (a)	191–192	..	Needles (C_6H_6)	198

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydroisostrychnidine (b)	151–153	..	Needles (pet. ether)	198
Dihydroisostrychnine-I	249–251	+8.1° ($CHCl_3$)	Needles (C_6H_6–pet. ether)	198, 176
Methiodide	320 (dec)	..	Rods(C_2H_5OH–H_2O)	198
O-Acetyl-	202–204	..	Needles (pet. ether)	198
(Pyr)-Dihydroisostrychnine-II	213–215 (V)	−53° (C_2H_5OH)	Tetrahedra (acetone)	176
Dihydromethoxymethyldihydroneostrychnine	174	..	Prisms (CH_3OH)	208
Dihydromethoxymethylhexahydrostrychnine	116–118	..	..	253
Methiodide	249–250	..	..	253
Methochloride	210–212	..	..	253
Dihydro-N_a-methylaponucidine				
Dimethoperchlorate	280–282 (dec)	..	Needles (H_2O)	157
Hydriodidemethiodide	312–317 (dec)	..	Prisms (C_2H_5OH)	157
Dihydro-N_b-methylchanodihydrostrychnidine	177–178	..	Crystals (CH_3OH)	226, 215, 254
Dihydro-N_b-methylchanodihydrostrychnine	201	..	..	254
Dihydronucine Hydroperchlorate	..	..	Needles (H_2O)	167
Dihydrostrychnidine-A	215–216	..	Prisms (CH_3OH)	207, 196, 198, 215, 225, 229
Dimethiodide	285–290 (dec)	..	Plates (H_2O)	198
Ethiodide	345–350	..	Colorless needles	215
Methiodide	345–350	..	Prisms (H_2O)	225, 196, 198, 215
Methochloride	345 (efferv)	..	Needles (H_2O)	196, 198, 231
Methosulfate	250 (dec)	..	Needles (C_2H_5OH–pet. ether)	198
Dihydrostrychnidine-B	151	..	Colorless prisms	200
Benzylochloride	..	..	Plates (CH_3OH–ether)	200
Dimethiodide-A	238–242 (dec)	..	Prisms (H_2O)	200
Dimethiodide-B	260–265	..	Needles (CH_3OH)	200
Dimethobromide-A	345 (efferv)	..	Needles (CH_3OH)	200

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydriodide	235–240 (efferv)	..	Needles (CH_3OH)	200
Hydrochloride	123 (dec)	..	Needles (H_2O)	200
Methiodide-a	340–345 (dec)	..	Prisms (H_2O)	200
Methiodide-b	>250	..	Needles (CH_3OH)	200
Methobromide-b	340–345	..	Plates (H_2O)	200
Methochloride-a	335–340	..	Crystals	200
Methosulfate-a	..	..	..	200
Dihydrostrychnidine-C	132–134	..	Needles (CH_3OH)	200
Dimethiodide	265–270	..	Needles (H_2O)	200
Dihydrostrychnidine-D	199–201	..	Brown plates (C_6H_6)	225, 215
Methiodide	325–327 (efferv)	..	..	225, 215
Methoacetate	307–308	..	Needles (H_2O)	215
Methochloride	330–332	..	Needles (H_2O)	225, 215
Dihydrostrychnidine-E	254–255	..	Crystals (CH_3OH)	215
Dihydrostrychnine-A	220–222	..	Needles (CH_3OH–H_2O)	198, 19, 66, 119, 149, 182a, 208, 230, 255
Methiodide	>300	+30.3°(CH_3OH)	Rods(C_2H_5OH–H_2O)	198, 18
Methochloride	250	..	..	254
Methosulfate	322 (dec)	..	Rods (C_2H_5OH)	198
Benzal-	255	..	Yellow crystals ($CHCl_3$)	19
$C_{28}H_{28}O_5N_2$	280	..	Prisms	19
$C_{21}H_{22}O_5N_2$	..	+93.7°/d (NaOH)	Prisms	137
$C_{21}H_{22}O_5N_2 \cdot HClO_4$	..	..	Plates and leaflets	137
$C_{21}H_{21}O_5N_2Br$	237–239 (dec)	+63.8° (NaOH)	Prisms	137
Picrate	230	..	Yellow needles (C_2H_5OH)	19
Isobenzal-	187–189	−325.1/d (C_2H_5OH)	Plates (acetone)	136, 144, 148
Dihydrostrychnine-B	196	..	Prisms (acetone)	200
Hydriodide	350–355 (dec)	..	Crystals (CH_3OH)	200
Methiodide	365 (dec)	..	Yellow prisms (CH_3OH)	200
Methobromide	375 (dec)	..	Needles (CH_3OH)	200
Methochloride	370–375 (efferv)	..	Needles (CH_3OH)	200
Benzal-	270–275	..	Yellow crystals (CH_3OH)	200
Dihydrostrychnine-acetic Acid	300–303 (V)	+43° (H_2O)	Needles (H_2O)	173
Hydroperchlorate	285	..	Leaflets	180

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methyl ester	227–228° (V)	..	Prisms (ether-pet. ether)	173
Methiodide	..	..	Clear crystals	173
Dihydrostrychnine-acetonitrile	300–305	−15.4°/d ($CHCl_3$)	Prisms (CH_3OH)	180
Isobenzal	227–229	−507°/d($CHCl_3$)	Needles (C_2H_5OH)	180
Dihydrostrychninic Acid	285	..	Crystals	200
N-Acetyl	245–248	..	Prisms (H_2O)	119
Dihydrostrychninolone-a	268–270°	−12.2° (HOAc)	Prisms (CH_3OH)	142, 190, 232
Acetyl-	256–258	−57.2° (HOAc)	Prisms (CH_3OH)	142
Dihydrostrychninolone-a Hydrate				
Hydroperchlorate	180	+46.6° (H_2O)	Needles	142
Dihydrostrychninolone-b (is a mixture)	205–208	−62.1°	Prisms (CH_3OH)	190c, 142
Acetyl-	233–235	−35° (HOAc)	Polyhedra (CH_3OH)	142
Dihydrostrychninolone-c	227–229	−88° (HOAc)	Rt. ∟'d prisms	142, 190c
Acetyl-	265	−124	Prisms (CH_3OH)	142
Dihydrostrychninone	264 318	−29.8° (HOAc) −49° ($CHCl_3$)	Prisms (C_2H_5OH)	190, 232, 236
Oxime	278 (dec)	..	Crystals (C_2H_5OH)	190
Dihydrostrychninonic Acid	*315 (dec)	+4.3° (NaOH)	Rt. ∟'d plates	55, 73, 232
Dihydrostrychnone	165–175 (V)	−365°/d ($CHCl_3$)	Needles (C_6H_6)	169, 181
Dihydroxyacetyl-strychninolone-b	232	..	Prisms (C_2H_5OH)	77
N_b,N_b-Dimethyldesbis-neostrychnidine	113–114	..	Plates (acetone)	226
Dimethiodide	273–275	..	Plates (H_2O)	226
Dimethochloride	242–244	..	Yellow needles(H_2O)	226
Methiodide	310–312	..	Prisms (H_2O)	226
Methochloride (monohydrate)	235–237	..	..	226
Methosulfate	227–229	..	Tablets (C_6H_6)	226
N_b,N_b-Dimethyldesdi-hydrobisneo-strychnidine	..	..	Amorphous	226
Methiodide	177–178	..	Plates (CH_3OH)	226
Methochloride	..	..	Amorphous	226
N_b,N_b-Dimethyldesdi-hydrostrychnidine-D	..	..	Amorphous	226
Methiodide	299–301	..	Needles (CH_3OH)	226
Methochloride	225–227	..	Plates (H_2O)	226

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
N_b,N_b-Dimethyldesneostrychnidine				
Methiodide	263–267	..	Needles (H_2O)	226
Methochloride	271–273	..	Needles (CH_3OH)	226
N_b,N_b-Dimethyldesstrychnidine-D	156–157	..	Colorless plates	227
Dimethiodide	219–221	..	Needles (H_2O)	227
Dimethochloride	212–213	..	Needles (H_2O)	227
Methiodide	244–246	..	..	227
Dimethylstrychnine	..	..	Prisms (H_2O)	47, 2
Methiodide	..	..	Needles (H_2O)	47
Dinitroisostrychnic Acid	>325	..	..	241
Ethyl ester	195	..	Prisms (C_6H_6)	242
Hydrochloride	247 (dec)	..	Plates($CHCl_3$–ether)	242
Picrate	261 (dec)	..	Yellow needles (CH_3OH)	242
Sulfate	250 (dec)	..	Prisms (C_2H_5OH–H_2O)	242
Hydrazide	>280	..	Crystals	242
Methyl ester	225	..	Prisms (C_6H_6)	242
Hydrochloride	225–235	..	Prisms ($CHCl_3$–ether)	242
Methiodide	276–280 (dec)	..	Needles ($CHCl_3$)	242
Picrate	259 (dec)	..	Yellow powder (CH_3OH)	242
Sulfate	>280–290	..	Needles (H_2O)	242
Propyl ester	118–122	..	Needles ($CHCl_3$–propanol)	242
Hydrochloride	225	..	Needles (C_2H_5OH)	242
Picrate	241–244 (dec)	..	Yellow powder	242
Sulfate	247–248 (dec)	..	Needles (H_2O)	242
Dinitrostrychnine	226	..	Orange leaflets (C_2H_5OH)	37
Dinitrostrychnine Hydrate	..	..	Yellow needles	3
Nitrate	Explodes	..	Golden prisms(H_2O)	3, 108
Methyl ester hydrochloride	215–230	..	Golden platelets	108
Dinitrostrychninic Acid	..	..	..	250
Ethyl ester	226 (dec)	..	..	250
Methyl ester	210–211 (dec)	..	Crystals (C_6H_6)	250
Hydriodide	245–246 (dec)	..	..	250
Hydrochloride	245–247 (dec)	..	..	250
Methiodide	240–242	..	..	250
Picrate	275 (dec)	..	..	250

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Propyl ester	246–247 (dec)	..	..	250
Hydrochloride	230 (dec)	..	..	250
Picrate	254 (dec)	..	..	250
Sulfate	210	..	..	250
Dinitrostrychol	284 (dec)	..	Yellow needles (HOAc)	3, 201
Amide	263	..	Crystals (C_2H_5OH)	213
Methyl ester	195–196	..	Needles (C_6H_6)	202, 3, 201
Urethane	199–200	..	Yellow needles (HOAc)	202
Dinitrostrychol-carboxylic Acid	300	..	Needles (H_2O)	3, 250
Diethyl ester	111–112	..	Needles (C_2H_5OH)	202
2,3-Dioxodihydronucidine	252–252.5	+184	Yellow prisms (C_2H_5OH)	118, 229
Hydroperchlorate	—	+136°	Rt. ∟'d prisms	118
Semicarbazone	252–254	..	Leaflets (CH_3OH)	118
Hydroperchlorate	..	+135.4°/d(H_2O)	..	229
Methoperchlorate	..	+138.1°	Prisms (H_2O)	140
Perbromide	..	..	Leaflets (H_2O)	163
2,3-Dioxodihydronucine Hydrate	224–227 (dec)	..	Leaflets (H_2O)	10
Hydroperchlorate	..	−12.5° (H_2O)	Plates	150
Semicarbazone hydroperchlorate	..	..	Plates	150
2,3-Dioxodihydronucine-sulfonic Acid-1 Hydrate	..	−74°	Prisms	131
2,3-Dioxonucidine	271–272 (V)	+55.6°/d(H_2O)	Prisms (H_2O)	112, 117 118, 229
$C_{17}H_{20}O_5N_2 \cdot HClO_4$	..	..	..	112
Bromohydrin	190–320	+99.8°/d (C_2H_5OH)	Prisms (C_2H_5OH)	163
$C_{17}H_{20}O_4N_2$ ($Ba(OH)_2$)	232	−29.3°/d (C_2H_5OH)	Prisms (C_2H_5OH)	163
Methiodide	..	..	Rt. ∟'d plates (H_2O)	163
Hydroperchlorate	..	+95°	Prisms (H_2O)	229, 112
Methoperchlorate	..	+113°	..	140
Methosulfate	>300	+117° (H_2O)	Leaflets (H_2O)	140
Semicarbazone	303 (dec)	..	Plates (CH_3OH)	112
Hydroperchlorate	..	..	Trapezoidal plates	112
2,3-Dioxonucidine Hydrate				
Methiodide	>320	..	Prisms (H_2O)	112

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methonitrate	..	..	Domatic prisms (H_2O)	112
Methoperchlorate	..	..	Rt. ∟'d plates	112
2,3-Dioxonucidinic Acid Hydrate	260 (dec)	+166°	Prisms (H_2O)	123
2,3-Dioxonucidinic Aldehyde Hydrate	..	..	..	123
Hydrobromide	..	+150.8°	Plates (HBr–H_2O)	123
Dioxime-hydroperchlorate	..	..	Prisms (H_2O)	123
2,3-Dioxonucine	..	..	..	116
Hydroperchlorate	..	+53.3°	Rhombs (CH_3OH)	116
2,3-Dioxonucine Dihydrate	>345	+49.2° (H_2O)	Hexagonal crystals (H_2O)	8a, 9, 108, 109, 111
$C_{17}H_{20}O_8N_2$	..	..	Crystals (H_2O)	111
$C_{17}H_{20}O_7N_2 \cdot HBr$	280–310	..	Polyhedra (HBr)	111
Disemicarbazone	>305	..	Leaflets (HBr–H_2O)	111
Chloroplatinate	..	..	Yellow leaflets (HCl–H_2O)	8a
Hydriodide	..	..	..	8a
Hydrobromide	High	..	Rods (H_2O)	8a
Hydrochloride	>320	..	Rods (H_2O)	8a
Hydroperchlorate	..	..	Rt. ∟'d plates	112
Semicarbazone	>300	..	Prisms (H_2O)	10
Amide hydrochloride	>315	..	Rt. ∟'d prisms (H_2O)	112
Dimethyl ester	130	..	Plates (H_2O)	112
Dihydrochloride	205–210	..	Rods (C_2H_5OH–ether)	10
Monohydrochloride	225	..	Prisms (CH_3OH–HCl)	112
2,3-Dioxonucine Monohydrate				
Oxime hydrochloride	115 (froth)	..	Prisms (HCl–H_2O)	112
Semicarbazone hydrobromide	..	..	Rt. ∟'d plates (HBr)	111
2,3-Dioxonucinesulfonic Acid-1 Hydrate	..	−82.3°/d(H_2O)	Leaflets (H_2O)	125
Methoperchlorate	..	−79.6°	Plates (H_2O)	125
Semicarbazone	..	−192°/d(H_2O)	Tetrahedra (H_2O)	131
2,3-Dioxonucinic Acid Hydrate	..	..	..	113
2,3-Dioxotetrahydronucine Hydrate	245–247 (V)	..	Yellow prisms (C_6H_6)	115
Hydroperchlorate	..	+73.8°	Plates (H_2O)	115

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dodecahydrostrychnine-I	248–250 (V)	−6.3°/d (C_2H_5OH)	Prisms (acetone)	141
Dodecahydrostrychnine-II	153 (V)	−14.3°/d (C_2H_5OH)	Needles	141
		E		
Epoxyisostrychnine	250	..	Leaflets	179
Hydroperchlorate	193–195	..	Prisms (H_2O)	179
N-Oxide	208–209	..	Prisms (acetone)	179
Ethoxydihydrostrychninolone-a	100	−52° (HOAc)	..	91
Ethoxydihydrostrychnone	296–308 (V. dec)	−403°/d ($CHCl_3$)	Prisms (C_2H_5OH)	181
Ethoxymethyldihydroneostrychnine	158–159	..	Needles (CH_3OH–NH_3)	208
Ethylstrychnine	260 (dec)	..	Needles (H_2O)	5
		H		
Hanssen's C_{16}-Acid (see Carboxyaponucine)				
Hanssen's C_{19}-Acid (see 3-Carboxymethylene-2-oxonucine Hydrate)				
Hexahydrostrychnine	198–199	..	Tablets (C_6H_6)	206, 198, 208
$C_{21}H_{22}O_4N_2$	281–282 (dec)	+10.7° (HCl)	Prisms (H_2O)	206
Methiodide	280–287 (dec)	..	..	206
Methochloride	320 (dec)	..	..	206
Picrate	..	..	Crystals (H_2O)	206
Hexahydrostrychninonic Acid				
Diacetyl-	140 (gas)	..	Needles (ethyl acetate)	76
Hydroxyanhydromethylstrychnidinium-D Hydroxide	162	..	Needles (CH_3OH)	215
Hydroxyaponucidine	216–218	−123°/d(H_2O)	Rt. ∟'d prisms (acetone)	118
N-Oxalyl	..	+35°	..	118
12-Hydroxydihydrostrychnine	282–284 (froth)	..	Needles (C_6H_6)	20
$C_{21}H_{24}O_5N_2$(oxidation)	296 (dec)	..	Colorless prisms	20, 26
Hydroxymethoxymethyldihydroneostrychnidine	305–306	..	..	207
Hydroxymethylneostrychnine Hydriodide	238–240	..	Needles (CH_3OH)	207

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydroxymethyltetrahydrostrychnidine Hydrate	158–159	..	Yellow needles (ethyl acetate)	215
O-Acetyl-	254–255	..	Needles (ethyl acetate)	215
12-Hydroxystrychnine	204–205	..	Prisms (H_2O)	20
Hydroxystrychninolic Acid	257–259 (dec)	..	Needles from water	190b
Methyl ether	219–221	+64° (CH_3OH)	Prisms (CH_3OH)	190b
Methyl ester	199–201	+44° ($CHCl_3$)	Plates ($CHCl_3$–CH_3OH)	190b
Hydroxystrychninonic Acid	274–276 (dec)	−39° (NaOH)	Crystals (H_2O)	190b
Methyl ether	237–239	..	..	190b
Methyl ester	215–217	−1° ($CHCl_3$)	Needles ($CHCl_3$–CH_3OH)	190b
		I		
Isobenzyldihydrostrychnine	95–100	−150°/d (C_2H_5OH)	Needles (CH_3OH)	149
Methiodide	290	..	Needles	149
Isobromodihydrostrychnine-I	219	−54.3°/d ($CHCl_3$)	Prisms (acetone)	149
Hydrobromide	285–290	..	Rhombic plates	149
Hydroperchlorate	..	..	Polyhedra	149
Isobromodihydrostrychnine-II	254–269	−247°/d($CHCl_3$)	Powder (acetone)	149
Isochlorodihydrostrychnine-I	198 & 222	−40.7°/d ($CHCl_3$)	Polyhedra (acetone)	158
Hydrochloride	..	..	Dense plates (H_2O)	158
Isochlorodihydrostrychnine-II	320	−101°/d (C_2H_5OH)	Prisms (C_6H_6–CH_3OH)	158
Isodihydrocarboxyaponucine				
Hydroperchlorate	..	−46.2° (H_2O)	Prisms (H_2O)	150
Acetyl-	..	−33.5° (H_2O)	Prisms (H_2O)	150
Isodihydrostrychnine-I	246–250	+21.5° (C_2H_5OH)	Crystals (acetone)	149, 146, 170,182a
Hydroperchlorate	258–260 (dec)	+37° (H_2O)	Leaflets (H_2O)	146
Methiodide	318 (dec)	..	Rods (CH_3OH)	146
O-Acetyl-	202	+33.5° (HOAc)	Plates	148, 146
Hydroperchlorate	260 (dec)	..	Prisms	146
Isodihydrostrychnine-II	298–300	−270°/d($CHCl_3$)	Needles (acetone)	149
Isopseudodihydrostrychnine				
Diacetyl-	248–250 (V. dec)	..	Needles (CH_3OH)	170

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Isopseudostrychnine	315	..	..	182a
Methyl ether	310–315	..	..	182a
Isostrychnidine	163–168 (dec)	..	Brown needles(H_2O)	198
Methosulfate	200–205 (dec)	..	Prisms (C_2H_5OH–pet. ether)	198
Isostrychnine-I	226–227 (V)	+32°	Prisms (CH_3OH–H_2O)	176, 32, 53, 89, 174, 183, 241
Hydrochloride	314 (dec)	..	Crystals	53
Methiodide	223 (froth)	..	Leaflets (C_2H_5OH–H_2O)	89
N-Oxide Perchlorate	149–150	..	Long needles (H_2O)	179
Picrate	>245 (dec)	..	Red crystals	53
O-Acetyl-	195–196 / 133–134	..	Needles (pet. ether)	198, 241
Hydrochloride	225–226	..	Powder	241
Hydroperchlorate	260	..	Needles (H_2O)	176
Picrate	184 (dec)	..	..	241
Isostrychnine-II	218–219 (V)	−258°(C_2H_5OH)	Prisms (acetone)	176
O-Acetyl-hydroperchlorate	288 (froth)	..	Prisms and needles	176
Isostrychninic Acid	247–248	..	Needles (H_2O)	177, 2, 53, 179, 198, 241
Hydrochloride	190–195	..	Needles (C_2H_5OH–ether)	241
Methiodide	..	..	Crystals (H_2O)	2
N-Nitroso-	243	..	..	177
Picrate	187–189 (dec)	..	Yellow prisms (CH_3OH)	241
Acetyl-	180–185	..	Prisms (H_2O)	179
Azo-compounds	..	..	..	177
Isostrychninolone-I	246–247	+46.4° (HOAc)	Pyramids (CH_3OH)	81
Isostrychninolone-II	>310	−126° (HOAc)	Needles (CH_3OH)	81
		M		
Methoxybenzyldihydro-neostrychnidine	270/1 mm.	..	Noncrystalline	207
Methoxybenzyltetra-hydrostrychnidine	106–107	..	Rhombs (C_2H_5OH)	207
Methoxybenzyltetra-hydrostrychnidine-B	126–127	..	Needles (CH_3OH)	200
Methoxydihydrostrych-ninolone				
Acetyl-	237–239	−109° (HOAc)	Crystals	91

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methoxydihydrostrychnone	300–306 (V. dec)	−418°/d($CHCl_3$)	Prisms (CH_3OH)	181
Methoxy-N_b,N_b-dimethyldihydrochanodihydrobisneostrychnidine	129–130	..	..	226
Methoxy-N_b,N_b-dimethyldihydrochanotetrahydrostrychnidine	131–132	..	Plates (CH_3OH)	226
Methoxyethyldihydroneostrychnidine	102–103	..	Plates	207
Methiodide	258–260	..	Crystals (CH_3OH)	207
Methoxyethyltetrahydrostrychnidine	175–176	..	Prisms (C_6H_6)	207
Methoxymethylchanodihydrostrychnane	160–161	..	Crystals (C_6H_6–pet. ether)	217, 220
Methoxymethylchanodihydrostrychnanic Acid	205–206	..	Needles (C_2H_5OH–H_2O)	220
Methoxymethylchanodihydrostrychnone	198–199	..	Needles (acetone–ether)	216, 217
Benzal-	248–256	..	Yellow powder (C_2H_5OH)	216
p-Nitrophenylhydrazone	265.5–266 (dec)	..	Yellow prisms (acetone)	216, 231
Oxime	260–261 (dec)	..	Prisms (C_2H_5OH)	216
Methoxymethyldihydroneostrychnidine	125–126	..	Crystals (CH_3OH)	196, 207
Dimethiodide	297 (dec)	..	Needles (CH_3OH)	196
Dimethochloride	255–257 (dec)	..	Prisms (H_2O)	196
Dimethosulfate	..	..	Nodules (C_6H_6)	196
Methoxymethyldihydroneostrychnine	143–144	..	Silky needles (C_2H_5OH)	216, 208
Methoxymethyltetrahydrostrychnidine-A	220–222 235/1 mm.	..	Prisms (xylene)	196, 208, 215,225, 231,248, 253
Dimethiodide-A	315–320 (dec)	..	Needles (H_2O)	196
Dimethiodide-B	..	..	Prisms (CH_3OH)	196
Hydriodide	235 (dec)	..	Prisms (H_2O)	196
Methiodide-a	227	..	Prisms (C_2H_5OH)	196
Methiodide-b	325 (dec)	..	Powder (CH_3OH)	196
Methochloride-a	..	..	Waxy crystals	196

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methoxymethyltetrahydrostrychnidine-B	179–180	..	Glistening needles (CH_3OH)	200
Dimethiodide	210	..	Nodules (CH_3OH)	200
Hydriodide	325 (dec)	..	Yellow crystals	200
Methiodide	235–238	..	Prisms (CH_3OH)	200
Methochloride	170	..	..	200
Methoxystrychninolone-a	253–259 (dec)	−109° ($CHCl_3$)	Prisms ($CHCl_3$–CH_3OH)	190b
N_a-Methylaponucidine Dimethoperchlorate	>300	..	Prisms (H_2O)	157
N_b-Methyl(chano)dihydroneostrychnidine	143–144	..	Prismatic needles (CH_3OH)	215, 226
Dimethiodide	..	..	Crystals	226
Methiodide	208–210	..	Needles (C_6H_6)	226, 215
Methochloride	..	..	Amorphous	215
N-Methylchanopseudostrychnine (see *N*-Methyl-*sec*-pseudostrychnine)				
N_b-Methyldihydrochanodihydrostrychnidine	177–178	..	Crystals (CH_3OH)	226
Methyldihydrostrychnidine-A	178–180	..	Needles (acetone)	198
Methyldihydrostrychnine	274–276	..	..	254
Methyldihydrostrychnine	219–221	..	Quadratic leaflets	180
Hydroperchlorate	282 (dec)	..	Crystals (H_2O)	180
Methyldihydrostrychnine (Isomer)	225–227	..	..	180
Methylneodihydrostrychnidinium Iodide (see Dihydrostrychnidine-A Methiodide)				196
N-Methylneostrychnine	227–229	..	..	238
Methylpseudodihydrostrychnidine (see Dihydrostrychnidine-A)				196
N-Methyl-*sec*-pseudodihydrostrychnine	296–297	..	Prisms (C_2H_5OH)	218
Benzylidene-	264–266	..	Yellow needles (C_2H_5OH)	218
N-Methyl-*sec*-pseudostrychnine	273	..	Prisms (CH_3OH)	155, 212
Hydroperchlorate	295 (dec)	..	Plates (H_2O)	212
Methiodide	216	..	..	155
Methoperchlorate	285–293 (dec)	..	Needles or prisms (H_2O)	155
Dibenzal	284–285 (dec)	..	Yellow prisms ($C_5H_{11}OH$)	212
N-Methyl-*sec*-pseudostrychninesulfonic Acid	..	−128° (NaOH)	..	169
	..	−32° (NaOH)	..	169

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methylstrychnine (Betaine)	318–320	..	Colorless powder	196, 2, 47, 256
Methiodide	280 (dec)	..	Leaflets (C_2H_5OH)	47
Sulfobenzeneazo-	..	..	Red solid	198
Methylstrychnine	..	..	..	180
Hydroperchlorate	285 (dec)	..	Lancets (H_2O)	180
Methylstrychninic Acid Methiodide	..	..	Needles (H_2O)	2
Methyltetrahydro-strychnine	..	..	Gum	211
		N		
Neostrychnidine-A	204–205	..	Crystals (CH_3OH)	208, 207
Benzyloiodide	238–240 (dec)	..	Needles (CH_3OH)	207
Benzylochloride	230–232	..	Prisms (H_2O)	207
Dimethiodide	295	..	..	252
Dimethochloride	..	..	..	252
Ethiodide	285–286	..	Crystals (CH_3OH)	207
Ethochloride	285–286 (dec)	..	Prisms (CH_3OH)	207
Methiodide	312	..	..	207
Methochloride	275–280	..	Crystals (H_2O)	196, 207
Neostrychnidine-B Methiodide	277 (dec)	..	Crystals (H_2O)	196
Neostrychnine	228–229	..	Plates (C_2H_5OH)	208, 235, 238
$C_{21}H_{22}O_4N_2$	234–235	..	..	238
Methiodide	325	..	Long needles (H_2O)	208
Methochloride	289–290	..	Plates (CH_3OH)	208
Nitrostrychnine	240	..	Yellow leaflets (C_2H_5OH–H_2O)	108, 243
Hydroperchlorate	..	..	Six-sided leaflets	108
Picrate	..	..	Thin prisms	108
Nitrostrychninesulfonic Acid-I	300	−364° (NaOH)	Yellow prisms	63
N-Oxide	..	−240°	Yellow needles	63
Nitrostrychninesulfonic Acid-II	..	−28.9°	Yellow prisms	131
Nitrostrychninonic Acid	264–266 (dec)	..	Leaflets (HOAc)	64, 108
Norstrychninic Acid	295–296 (dec)	..	Prisms (H_2O)	20
		O		
Octahydromethoxy-methyldihydro-neostrychnidine	119–120	..	Tetrahedra (C_2H_5OH)	134
Dihydroperchlorate	..	..	Prisms (H_2O)	134

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Octahydrostrychnidine-I	109–110	+5.4°/d (C_2H_5OH)	Polyhedra (acetone)	141
Dihydroperchlorate	..	+16.7°	Quadratic plates	132
Dimethiodide	..	+11.5° (H_2O)	Prisms (H_2O)	134
Octahydrostrychnidine-II	110–112	+2° (C_2H_5OH)	Prisms (acetone)	141
2-Oxo-3-bromodihydronucidine	292 (dec)	..	Leaflets (C_2H_5OH)	118
2-Oxo-bromonucine Hydrate				
Hydroperchlorate	..	..	Prisms (H_2O)	116
2-Oxo-3-[carboxymethylene]-dihydronucidine-I	258–260 (dec)	+176°	Needles (acetone–H_2O)	120
Hydroperchlorate	..	+141.1°	Needles (H_2O)	120
2-Oxo-3-[carboxymethylene]-dihydronucidine-II	..	+64.1°	Rt. ∟'d prisms (H_2O)	120
Hydroperchlorate	..	..	..	120
2-Oxodihydronucidine-3-acetic Acid	315	+104.4°	..	120
Hydroperchlorate	..	+74.9°	..	120
2-Oxo-2¹,3-dihydroxynucidine	271–273 (dec)	−33.6° (H_2O)	Prisms (acetone)	119
2-Oxo-3-hydroxydihydronucidine	257–259 (V)	+67.7° (H_2O)	Octahedra (C_2H_5OH)	118, 119
Hydrochloride	..	+68.4°	..	118
Hydroperchlorate	..	+61.7°	Prisms (H_2O)	118
Methiodide	..	..	Prisms (CH_3OH)	140
Methoperchlorate	..	+59.2°	Plates (H_2O)	140
Acetyl-	..	..	..	118
2-Oxo-3-hydroxydihydrohydroxynucidine				
Hydroperchlorate	..	+57.6° (H_2O)	Plates (CH_3OH–H_2O)	163
2-Oxo-3-hydroxydihydronucine Hydrate	224–225	+5.9°	Plates (H_2O)	118
Hydroperchlorate	..	..	Domatic plates(H_2O)	118
2-Oxo-3-hydroxynucidine	257–260 (V)	−21.3° (H_2O)	Plates (acetone)	119, 140, 113
Hydroperchlorate	..	+33°	Prisms (H_2O)	113
Methiodide	>290°	..	Plates (CH_3OH)	113, 140
Methoperchlorate	..	+44° (H_2O)	Prisms (H_2O)	140
Acetyl-	180	..	Plates (acetone)	113

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
2-Oxo-3-hydroxy-nucidinic Acid	>300	+119.7°	Plates (H_2O)	113
Hydroperchlorate	..	..	Dense prisms	113
2-Oxo-3-hydroxynucidinic Aldehyde	158–160	..	Prisms (acetone)	113
Hydrobromide	..	+106° (H_2O)	Domatic prisms	113
Hydroperchlorate	..	..	Six-sided plates	113
Oxime-hydrobromide	..	..	Prisms (HBr–H_2O)	113
Semicarbazone-hydroperchlorate	..	..	Prisms ($HClO_4$–CH_3OH)	113
2-Oxo-3-hydroxynucine Hydrate	..	+4.5° (H_2O)	Prisms	116
Hydrobromide	..	..	Octahedra (HBr–H_2O)	116
Hydroperchlorate	..	..	Rt. ∟'d leaflets	116
Acetyl-hydrobromide	..	+27.8° (H_2O)	Leaflets	116
2-Oxo-3-hydroxynucine-sulfonic Acid-I Hydrate	..	−106°/d (H_2O)	Plates (H_2O)	131
2-Oxo-Δ^3-nuceinic Acid Hydrate	270 (froth)	..	Prisms (H_2O)	113
2-Oxonucidine-3-acetic Acid	..	+48.8°	Leaflets (H_2O)	120
$C_{19}H_{24}O_7N_2$(oxidation)	248–250	+46.1°	Needles (H_2O)	122
		P		
Pseudodihydrostrychnine	240–243 (V)	+38.7°/d ($CHCl_3$)	Polyhedra (acetone)	170, 152a
Benzal-	209–215	−108°/d($CHCl_3$)	Yellow leaflets (CH_3OH)	170
Isobenzal-	160–170	−531°	Colorless crystals	170
Methyl ether	209 (V)	+75.7°/d ($CHCl_3$)	Needles (CH_3OH)	170, 152a
N-Nitroso-	228 (dec)	+443°/d($CHCl_3$)	Prisms (acetone)	152a
Pseudodihydrostrychnine (Isomer)	332–334 (V. dec)	.	Quadratic plates	170
Methyl ether	345 (dec)	+116°/d($CHCl_3$)	Plates (CH_3OH)	170
Pseudodihydrostrychnone	330 (dec)	+116°/d(HOAc)	Polyhedra (HOAc)	169
Pseudostrychnine	262–268 (dec)	−44.2°(C_2H_5OH)	White powder	189, 152, 169
Ferrichloride	234–235 (dec)	..	Orange-red plates (HOAc)	212

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrochloride	..	+3.9° (H_2O)	Octahedra (H_2O)	189, 152a
Hydroperchlorate	260–300 (dec)	..	Colorless prisms (H_2O)	152a, 212
Nitrate	..	+7.6° (C_2H_5OH)	..	189
N-Nitroso	292–294	−139.3°($CHCl_3$)	..	189
Ethyl ether	224–225	−42.5°(C_2H_5OH)	..	189
Benzal-	208–209	..	Rt. ∟'d prisms (C_2H_5OH)	152a
Methyl ether	198–200	−49.9°(CH_3OH)	Needles (CH_3OH)	189, 152, 258
Methiodide	215–216 (dec)	..	Woolly needles (CH_3OH)	152a, 212
$C_{23}H_{26}O_3N_2$	188–190 (V)	+241°/d($CHCl_3$)	Prisms (CH_3OH)	152a
$C_{22}H_{26}O_3N_2$	293	..	Prisms (CH_3OH)	152a
Benzal derivative ($C_{22}H_{26}O_3N_2$)	255–261	..	Yellow prisms (CH_3OH)	152a
$C_{22}H_{24}O_3N_2$	272–273 (dec)	−16°/d($CHCl_3$)	Prisms (CH_3OH)	152a
Hydriodide ($C_{22}H_{24}O_3N_2$)	224–244 (dec)	..	Needles (CH_3OH)	152a
Hydroperchlorate ($C_{22}H_{24}O_3N_2$)	285 (dec)	..	Plates	152a
Benzal-	198–200	..	Needles (CH_3OH)	155
Benzal-methiodide	267 (dec)	..	Prisms (CH_3OH–H_2O)	155
Isobenzal-	153	..	Needles or prisms (CH_3OH)	155
Pseudostrychnine-sulfonic Acid	280–305 (dec)	−150°/d(NaOH)	..	169
Pseudostrychnone	315–317 (V. dec)	+33.3°/d ($CHCl_3$)	Needles ($CHCl_3$)	169
		S		
Strychnidine	246–248 290–295/14 mm.	−8.28° ($CHCl_3$)	Needles (C_2H_5OH)	113, 3, 51 196, 229
$C_{21}H_{22}O_4N_2$ (oxidation)	>320	..	Needles (H_2O)	113
Benzylochloride-A	330–335	..	Plates (CH_3OH–ether)	200, 207
Benzylochloride-B	300–302 (dec)	..	Powder (H_2O)	207
Cyanogen bromide adduct	145–150 (dec)	−57°/d(C_6H_6)	Prisms (CH_3OH)	123
Dihydrochloride	..	..	Needles (H_2O)	3
Dimethiodide	..	..	Needles (H_2O)	200
Dimethochloride	..	..	..	200
Di-*N*-Oxide	..	..	Colorless crystals	132

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Ethiodide	335	..	..	207
Ethochloride	300–302	..	..	207
Hydrochloride	..	−13.5°	Needles (HCl)	3, 115
Hydroperchlorate	..	−10.1° (H_2O)	Prisms (H_2O)	115
Methiodide	325 (dec)	..	Needles (H_2O)	196, 3
Methobromide	>300	..	Needles (H_2O)	196
Methochloride	310–370	..	Needles (H_2O)	196, 200
Methosulfate	..	..	Crystals (CH_3OH)	196, 200
Sulfobenzeneazo-	..	..	Powder	198
Strychnine	286–288	−104°(C_2H_5OH)	Rhombs (C_2H_5OH)	189,37,40, 41, 42, 119,149, 152a, 180,212, 244
$C_{21}H_{26}O_2N_2$(reduction)	252	..	Prisms (C_2H_5OH)	230
$C_{21}H_{22}O_5N_2$(oxidation)	252–255	..	Crystals (C_2H_5OH)	73
$C_{19}H_{18}O_4N_2$(oxidation)	332 (V)	..	Prisms (H_2O)	232, 73
$C_{19}H_{20}O_4N_2$	244–245	+18.5° (HOAc)	Needles (H_2O)	232
Benzylochloride	303–305	..	Needles (H_2O)	208
Methiodide	320	0°	Cubes (H_2O)	196, 18
Methobromide	320 (efferv)	..	Needles (H_2O)	196
Methosulfate	282 (dec)	..	Needles (CH_3OH)	196, 211
N-Oxide	209–212	..	Prisms	178, 52
Benzal-	235–237	..	Leaflets ($C_5H_{11}OH$)	200
Isobenzal-	160–170	..	..	179
Isonitroso-	>300 (dec)	..	Prisms ($CHCl_3$–C_2H_5OH)	17
$C_{21}H_{23}O_4N_3$ (Beckmann)	275–276 (dec)	..	Cubic crystals	20
$C_{21}H_{23}O_4N_3 \cdot HCl$	270–272 (dec)	..	Colorless needles	20
$C_{21}H_{21}O_3N_3$ (Beckmann)	260–263 (dec)	..	Pyramids	20
$C_{21}H_{21}O_3N_3 \cdot HCl$	>300 (dec)	..	Needles (C_2H_5OH)	20
$C_{20}H_{21}ON_3$	258–259	..	Needles (CH_3OH)	20
$C_{19}H_{22}O_2N_2$	217	..	Crystals (acetone)	20
$C_{19}H_{22}O_2N_2 \cdot HCl$	310 (dec)	..	Plates (C_2H_5OH–acetone)	20
$C_{19}H_{22}O_2N_2 \cdot CH_3I$	>300	..	Needles (CH_3OH)	20
Oxime of $C_{19}H_{22}O_2N_2$	245 (dec)	..	Needles (CH_3OH)	20
Strychnineacetic Acid	270–272 (gas)	−54° (H_2O)	Needles (H_2O)	180
Hydroperchlorate	290–300 (dec)	..	Prismatic needles	180
Benzal-hydroperchlorate	260–300 (dec)	..	..	180
Strychnineacetonitrile	246 (V)	..	Prisms (C_2H_5OH)	180

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydroperchlorate	..	−137.5°/d ($CHCl_3$)	Rhombohedra	180
Benzal-	180	−531°/d($CHCl_3$)	Yellow needles (acetone)	180
Strychninesulfonic Acid-I	170	−230° (NaOH)	..	169, 42, 46, 59, 125
N-Oxide	..	−101.8°(NaOH)	Colorless needles	63
Benzal-	..	−250°/d(NaOH)	Yellow needles (acetone–H_2O)	131
Strychninesulfonic Acid-II	370 (dec)	−441° (NaOH)	Prisms (H_2O)	135, 56, 59
Strychninesulfonic Acid-III	*276 (dec)	+163° (NaOH)	Needles (C_2H_5OH)	59
$C_{21}H_{24}O_7N_2S$ (oxidation)	..	..	Needles	133
Benzal-	..	..	Yellow amorphous ppt.	135
Strychninesulfonic Acid-IV Hydrate	275 (dec)	+18.3° (NaOH)	Prisms (H_2O)	72
Strychninic Acid	..	..	Needles (H_2O)	47, 2, 178, 244
Methiodide	..	..	Needles (H_2O)	2
N-Nitrosamine	..	..	Yellow crystals	2
N-Oxide	232–234 (dec)	..	..	178
N-Acetyl-	305 (gas)	+130.6°/d	Prisms	119, 115
Methiodide	247–249 (dec)	..	Needles (H_2O)	119
Ethyl ester	..	..	Leaflets (C_2H_5OH)	119
Ethyl ester hydroperchlorate	..	..	Rhombohedra(H_2O)	119
Strychninolic Acid	238	..	Prisms (H_2O)	58, 77, 190, 232
$C_{19}H_{20}O_4N_2$ (cleavage)	280–290 (dec)	..	Prisms (H_2O)	77
Acetyl-	*281 (dec)	..	Needles (H_2O–HOAc)	58
Strychninolone-a	*236	−112° (HOAc)	Leaflets (H_2O)	58, 77, 80, 190, 232
Acetyl-	126–128 (froth)	..	Crystals (CH_3OH)	64
Strychninolone-b	228–230	−37.3° (HOAc)	Needles (H_2O)	77,80,190c
Acetyl-	241–243	−168° (HOAc)	..	77, 80
Strychninolone-a Hydrate-I	240 (froth)	−7° (HCl)	Prisms	142
Hydrochloride	305–310 (dec)	..	Prisms (H_2O)	64
Methyl ester hydrochloride	305–310 (dec)	..	Prisms (H_2O)	142
Strychninolone-a Hydrate-II	239–240	..	Needles (H_2O)	64

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Strychninolone-b Hydrate-I	239–240 (gas)	..	Needles	80
Strychninolone-b Hydrate-II				
Hydroperchlorate	245 (gas)	+24° (H_2O)	Prismatic needles	142
Methyl ester hydroperchlorate	255 (dec)	+26.7° (H_2O)	Rt. ∟'d prisms (H_2O)	142
Strychninolone-c	251–252	−176.1°(HOAc)	Prisms (CH_3OH)	80, 190c
Acetyl-	256–257	−231.3°(HOAc)	Prisms (C_2H_5OH)	91
Strychninolonic(a) Acid $C_{17}H_{18}O_4N_2$				
Hydrochloride	278 (dec)	..	Rt. ∟'d plates(H_2O)	78
Sulfate	..	..	Leaflets	78
Amide	280 (dec)	..	Prisms	78
Methyl ester-hydrobromide	278	..	Green prisms	78
Strychninolonic(b) Acid				
Acetyl-	..	..	Green sirup	77
Strychninolonic(c) Acid				
Acetyl-	280–282 (gas)	..	Colorless prisms	91
Strychninone	*246–247	−127.3°(HOAc)	Plates (CH_3OH)	232, 236
Strychninonic Acid	*265–267 (dec)	−43.3° (NaOH)	Prisms (H_2O)	55, 93, 190, 232
$C_{18}H_{18}O_4N_2 \cdot HClO_4$	240–243 (dec)	−17.4°	Prisms (H_2O)	147
$C_{18}H_{18}O_4N_2 \cdot CH_3ClO_4$	262 (dec)	..	Prisms	147
Oxime	268–271 (dec)	+119° (NaOH)	Rt. ∟'d prisms (H_2O)	58
Semicarbazone	*256–257	..	Needles (H_2O)	58
Anilide	255 (dec)	..	Prisms (HOAc–H_2O)	64
Ethyl ester	*209–210	..	Prisms (C_2H_5OH)	58
Methyl ester	247–249	−166.6°(NaOH)	Crystals (CH_3OH)	64, 232
Strychninonic Acid Dihydrate	235–240	..	Needles (HOAc)	64
Strychninonic Acid Hydrate	270–275 (dec)	+39.6° (NaOH)	Needles (HOAc)	64
Dimethyl ester chloroplatinate	..	..	..	64
Methyl ester	184–186	..	Prisms (CH_3OH)	64
Strychnone	268 (V. dec)	−669° ($CHCl_3$)	Needles (HOAc–H_2O)	169, 181
Strychnone (Robinson)				
p-Nitrophenylhydrazone	269–271 (dec)	..	Yellow prisms (acetone)	231

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		T		
Tetrachlorostrychnine	>250	..	Prisms (C_2H_5OH)	188
Tetrahydroallostrychnyl Chloride	233–236 (dec)	..	Plates (acetone)	129
Tetrahydrocarboxyaponucinesulfonic Acid-I	..	−26° (H_2O)	Domatic plates (H_2O)	131
Tetrahydrocarboxyaponucinesulfonic Acid-II	..	−62.6°	Prisms (H_2O)	131
Tetrahydrocarboxyaponucinesulfonic Acid-IV	..	−56.8° (H_2O)	Prisms (H_2O)	133
Tetrahydrodesoxyisostrychnine	174–176 (V)	..	Needles	174
Hydroperchlorate	150–151	..	Plates (HOAc)	174
Tetrahydrodesoxymethylstrychnine Methiodide	287 (dec)	−69° (H_2O)	Polyhedra(C_2H_5OH)	18
Tetrahydrodimethyldesbisneostrychnidine Methiodide	263–264	..	Crystals (H_2O)	227
Tetrahydrodimethyldesstrychnidine-D Methiodide	278–280	..	Needles (CH_3OH)	227
Tetrahydroisostrychnine-I	208–211	..	Needles (acetone)	176
Tetrahydroisostrychnine-II	228–230 (V)	−36.3°	Plates (acetone)	176
Tetrahydroneostrychnine	167–168	..	Crystals	208
Tetrahydrostrychnine	202 (V)	..	Silky needles(H_2O)	115, 3, 66, 113, 196
$C_{21}H_{22}O_4N_2$	>320	..	Brown needles(H_2O)	115
Hydrochloride	..	−24°	..	115
Ethyl ester	178–180	..	Needles (C_2H_5OH)	119
Benzylochloride	202–204	..	Yellow needles (CH_3OH)	207
Hydrochloride	..	−86.6°	Needles (HCl–H_2O)	115, 3
Hydroperchlorate	..	−74.9°	Prisms (H_2O)	115
Methiodide	312–314	..	Needles (H_2O)	207, 3
Methochloride	270–272	..	Needles (CH_3OH)	207
Methosulfate	266–268 (dec)	..	Crystals (CH_3OH)	207
N-Nitrosohydrochloride	..	..	Yellow crystals (H_2O)	3
N-Acetyl-	197–199	..	Prisms (C_6H_6)	115, 76

TABLE 1 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
O-Acetyl-	166–168	−78.6°/d(HCl)	Prisms (C_2H_5OH)	121
N-Benzoyl-	235	..	Needles ($CHCl_3$–ether)	17
Diacetyl-	142–143	+96°	Prisms (H_2O)	76, 115
Hydrochloride	..	+112.2°	..	115
Methiodide	165–168	..	Prisms (acetone)	121
Dibenzoyl-	..	..	..	17
Tetrahydrostrychnine (Isomer)	255–257	+45° (C_2H_5OH)	Prisms (C_2H_5OH)	182a
Trichlorostrychnine	206–208	−477°/d($CHCl_3$)	Needles (C_2H_5OH)	158
Hydrobromide	..	..	Fine needles	158
Hydrochloride	280 (dec)	..	Needles (C_2H_5OH)	158
Trinitrostrychol	215–218 (gas)	..	Leaflets (H_2O)	3, 201
		W		
Wieland's C_{17}-Acid (see 2,3-Dioxonucine Dihydrate)				

TABLE 2

BRUCINE AND ITS DERIVATIVES

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
N-Acetyl-*sec*-pseudobrucine	..	..	..	172
N-Acetyl-*sec*-pseudobrucinolic Acid	235–237	..	Rt. ⌊ 'd plates (C_2H_5OH)	172
N-Acetyl-*sec*-pseudobrucinonic Acid	235–238	+281°/d(HOAc)	Leaflets (CH_3OH)	172
Amide	205 (dec)	..	Fine needles	172
Methyl ester	..	..	Resin	172
Semicarbazone	215 (froth)	..	Needles (H_2O)	172
N-Acetyl-*sec*-pseudobrucinone	229–231 (V)	..	Needles (H_2O)	172
N-Acetyl-*sec*-pseudodihydrobrucine (Hydrate)	100 (froth, V)	..	Leaflets (H_2O)	173
Methiodide	218 (froth)	..	Prisms (CH_3OH)	173
Picrate	231–235 (dec)	..	Orange crystals	173
Allo-N_b-methyl-desdihydrobrucidine-A				
Dimethiodide	245–246 (dec)	..	Needles (CH_3OH)	222
Dimethochloride	202–204 (dec)	..	Leaflets (CH_3OH)	222

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Amino-bisapomethyl-brucine				
Dihydrochloride	..	..	Plates (HCl)	85
Hydroperchlorate	..	..	Rods (dilute $HClO_4$)	162
Amino-bisapomethyl-brucinesulfonic Acid	..	..	Six-sided plates (H_2O–C_2H_5OH)	87
12-Aminobrucine	169	..	Needles (C_2H_5OH–ether)	23
Dihydrochloride	230 (dec)	..	Needles (CH_3OH)	23
Zinc chloride double salt	>300 (dec)	..	Needles (HCl–H_2O)	20
12-Aminodihydrobrucine	224	..	Prisms (ethyl acetate)	23
Dihydrochloride	>196	..	Crystals (C_2H_5OH)	23
Dibenzoyl-	225	..	Pointed needles (ethyl acetate)	23
Hydrochloride	197 (dec)	..	Crystals (C_2H_5OH)	23
Aminomethyldihydro-brucine	160–162	+39.3°/d($CHCl_3$)	Needles	182, 175
Dihydroperchlorate	300 (dec)	..	Needles ($HClO_4$–H_2O)	182, 175
Monohydroperchlorate	275–278	..	Prisms	182
		B		
C-Benzylbrucine	255–258	..	Needles (acetone)	135
N-Benzylbrucine	195–196	..	Needles (H_2O)	209
C-Benzylbrucinesulfonic Acid-I	..	−146.3°(NaOH)	Long prisms	135
C-Benzylbrucinesulfonic Acid-II	..	−112°(NaOH)	Plates	135
C-Benzylbrucinesulfonic Acid-IV	..	−115°	Plates and prisms	138
C-Benzylbrucinonic Acid	210–212 (dec)	..	Amorphous powder	144
C-Benzyldihydrobrucine	..	..	Amorphous	135
Methiodide	..	..	Amorphous	135
C-Benzyl-*N*-methyl-*sec*-pseudobrucine	195–197 (V)	..	Plates (CH_3OH)	171
C-Benzyl-*N*-methyl-*sec*-pseudodihydro-brucine	..	..	Amorphous	171
Hydrobromide	215–225	..	Needles (HBr)	171
Hydrochloride	215–225	..	Needles (HCl)	171
C-Benzylpseudodi-hydrobrucine				
Hydrochloride	220	..	Leaflets (HCl–H_2O)	171

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bisapomethyl-bromo-desoxy-dihydroiso-brucine				
Hydrobromide	268 (dec)	..	Leaflets (HOAc–H_2O)	176
Bisapomethyl-bromo-desoxy-isobrucine				
Hydrobromide	..	..	Leaflets (HOAc–HBr)	176
Bisapomethylbrucine	>305	..	Prisms (C_2H_5OH)	65
Hydrobromide	..	..	Silky needles (H_2O)	67
Hydrochloride	>300	..	..	65
Methiodide	280 (dec)	..	Needles (CH_3OH)	67
Methochloride	..	+6.54° (H_2O)	Pyramids (H_2O)	82
Nitrate	..	..	Leaflets (H_2O)	67
Sulfate	..	..	Silky needles (C_2H_5OH)	65
Diacetyl-	232–233 (V)	..	Needles (ligroin)	67
Bisapomethylbrucine Hydrate				
Methohydrogensulfate	..	..	Prisms	82
Bisapomethylbrucine-sulfonic Acid-I	..	..	..	60
Bisapomethylbrucinolic Acid	267 (dec)	..	Crystals (C_2H_5OH)	126
Triacetyl-	259	..	Leaflets (H_2O)	126
Bisapomethylbrucinolone				
Triacetyl-	260–261	..	Crystals (HOAc–H_2O)	69
Bisapomethylbrucinonic Acid	..	..	Prisms (H_2O)	126
Ethyl ester	285 (dec)	..	Prisms (C_2H_5OH)	126
Bisapomethyl-desoxy-isobrucine				
Triacetyl-hydroper-chlorate	236–237	..	Prisms (H_2O)	176
Bisapomethyldihydro-brucine	>320	..	Crystalline powder (H_2O)	203
Diacetyl-hydroper-chlorate	..	..	Rt. ∟'d leaflets (H_2O)	159
Bisapomethyldihydro-brucinonic Acid	..	..	Needles	126
Bisapomethyldihydro-isobrucine				
Triacetyl-hydroper-chlorate	218–220 (V)	..	Fine needles (H_2O)	176

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bisapomethyl-isobrucine	..	..	Amorphous	176
Hydrobromide	..	..	Prisms ($HBr-H_2O$)	176
Triacetyl-hydroperchlorate	142–143	..	Needles (H_2O)	176
Bisapomethyl-pseudobrucine	..	..	Prisms and columns	165
Hydroperchlorate	..	..	Needles ($HClO_4-H_2O$)	162
Bisapomethyltetrahydroisobrucine				
Triacetyl-hydroperchlorate	160–162 (froth)	..	Needles (H_2O)	176
Bisdesmethylbromodihydrodesoxybrucine	..	..	Amorphous	32
Hydrobromide	268 (dec)	..	Yellow leaflets(H_2O)	32
Bisdesmethylbrucine	..	..	Red needles	65, 159
Hydroperchlorate	..	..	Tetrahedra	159
Oxime-hydroperchlorate	..	..	Green rhombic crystals	159
Oxime hydrate-hydroperchlorate	..	..	Reddish-violet crystals	159
Semicarbazone-hydroperchlorate	..	..	Reddish-yellow needles (H_2O)	159
Bisdesmethylbrucine-sulfonic Acid-I	..	..	..	60
Bisdesmethylbrucinolic Acid	230–235 (dec)	..	Crystals (H_2O)	126
Semicarbazone	185–190 (dec)	..	Yellow needles(H_2O)	126
Bisdesmethylbrucinolone	300	..	Red prisms (H_2O)	61
Bisdesmethylbrucinonic Acid	..	..	Reddish-yellow prisms	126
Semicarbazone	>300	..	Yellow needles	126
Bisdesmethyldihydrobrucine	255 (dec)	..	Red octahedra	159
Hydroperchlorate	..	..	Four-sided plates	159
Oxime-hydrochloride	..	..	Reddish-yellow prisms	159
Semicarbazone-Hydrochloride	..	..	Orange needles	159
	..	..	Reddish-brown crystals	159
Bisdesmethyldihydrobrucinonic Acid	..	..	Orange needles	126
Bisdesmethyldihydrodesoxybrucine	..	..	Unstable	32
Hydrobromide	>295	..	Prisms (H_2O)	32

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bisdesmethylethoxydihydrobrucinolone	..	..	Amorphous	90
Semicarbazone	240	..	Orange needles(H_2O)	90
Bisdesmethylisobrucinolone	300	..	Long prisms	97
Bisdesmethylkryptobrucinolone	250 (dec)	..	Needles (HOAc)	84
Bisdesmethylpseudobrucine	..	..	..	162
Hydroperchlorate	..	..	Crystals	162
Bromocyanodihydro(neo)brucine	218–220	+53°(C_6H_6)	Needles (C_2H_5OH–H_2O)	17, 127
Acid $C_{24}H_{26}O_7N_3Br$ (oxidation)	..	+86°/d(HOAc)	Needles (CH_3OH–H_2O)	127
Bromocyanotetrahydrobrucine	240–242 (dec)	+58.2°/d ($CHCl_3$)	Rt. ⌊ 'd plates (acetone)	17, 18, 127
Pyridinium salt	280 (dec)	+39.2°/d(H_2O)	Yellow prisms (acetone)	127
Brucidine	203–203.5	..	Needles (CH_3OH)	197, 51
$C_{19}H_{22}O_4N_2$(oxidation)	286–288	+132.8°/d(H_2O)	Octahedra (H_2O)	117
Benzylochloride	305–307 (dec)	..	Crystals (H_2O)	209
Dihydriodide	255 (dec)	..	Gray needles (CH_3OH)	197
Dihydrochloride	310 (dec)	..	Needles (CH_3OH)	197
Hydroperchlorate	..	+3.4°/d	Needles (H_2O)	119
Methiodide	322 (dec)	..	Needles (CH_3OH)	197
Methohydroxide	268 (dec)	..	Needles (H_2O)	197
Methosulfate	291 (dec)	..	Needles (CH_3OH)	197
Brucidinolic Acid	270 (dec)	+42.2°/d (NaOH)	Prisms (C_2H_5OH)	122
Brucidone	..	..	Gum	197
Semicarbazone	226 (gas)	..	Needles (C_2H_5OH)	197
Brucine	178	−89°/d(C_6H_6)	Needles (acetone–H_2O)	127, 154
$C_{23}H_{26}O_7N_2$(oxidation)	240	+5.66° (HOAc)	Needles (H_2O)	74, 126
Acetyl-	290 (dec)	..	Prisms (CH_3OH)	126
$C_{23}H_{24}O_7N_2$(oxidation)	336 (dec)	+87.4° (HCl)	Plates (H_2O)	74
$C_{23}H_{24}O_7N_2$(oxidation)	..	0°	Crystals	126
Semicarbazone	228	..	Crystals (CH_3OH)	126
$C_{23}H_{24}O_7N_2$(oxidation)	265–282 (dec)	−28°/d(HOAc)	Prisms (H_2O)	126
$C_{21}H_{24}O_6N_2$(oxidation)	289–292	+30.7°/d (HOAc)	Rhombic plates (HOAc–H_2O)	126
$C_{21}H_{22}O_6N_2$(oxidation)	292	+72.8° (HOAc)	Prisms (H_2O)	74, 126
Benzylochloride	275–280 (dec)	..	Prisms	209
Cyanogen bromide adduct	170–171	..	Crystals (C_2H_5OH–H_2O)	18, 123

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Cyanogen bromide adduct dimer	209–211	−25.0°/d (HOAc)	Prisms (C_2H_5OH)	123, 246
Cyanogen bromide-	(see also Bromocyanodihydro(neo)brucine)			
Dimethosulfate	268 (dec)	..	Needles	67
Methiodide	295 (dec)	0°(CH_3OH–H_2O)	Needles (H_2O)	18, 197
Methohydrogen-carbonate	202–203 (dec)	..	Yellow plates (C_2H_5OH)	197
Methosulfate	278 (dec)	..	Needles (CH_3OH)	197
Benzal-	..	..	Poorly crystalline	200
Hydrochloride	..	..	Yellow needles (C_2H_5OH)	200
Isonitroso-	..	..	Yellow needles ($CHCl_3$)	17
$C_{23}H_{27}O_6N_3$ (carbamic acid)	206–207 (dec)	..	Needles	26
$C_{23}H_{27}O_6N_3$ (urea)	251 (dec)	+31.2° (NaOH)	Plates	26
$C_{23}H_{25}O_5N_3$ (cyclic urea)	228 (dec)	..	Needles (CH_3OH)	26
$C_{23}H_{25}O_5N_3 \cdot HCl$ (cyclic urea)	..	+30.1°(H_2O)	Crystals	26
$C_{23}H_{24}O_4N_3Cl$ (cyclic chlorimine)	247 (dec)	..	Needles (C_2H_5OH–H_2O)	26
$C_{22}H_{25}O_4N_2$	258 (dec)	..	Crystals	26
$C_{21}H_{26}O_6N_2$	163	..	Yellow prisms (CH_3OH)	26
Brucineacetic Acid	245–247 (V)	−64° (H_2O)	Prisms (H_2O)	175
Hydroperchlorate	240–250 (V)	..	Fine needles	175
Benzal-hydroperchlorate	305	..	Yellow needles (HOAc)	175
Methyl ester-hydroperchlorate	191–194 (V)	..	Rt. ⌊ 'd prisms (CH_3OH)	175
Brucineacetonitrile	255 (V)	−84.4°/d ($CHCl_3$)	Long needles	182
Hydroperchlorate	242–244	..	Prisms	182
Benzal-	285	..	Yellow crystals	182
Brucinesulfonic Acid-I	>300	−241.3°(NaOH)	Needles (H_2O)	60, 131
Benzal-	..	−232° (NaOH)	..	135
Brucinesulfonic Acid-II	260 (dec)	+29.2° (NaOH)	Plates (H_2O)	60, 138
Benzal-	..	−386.5°(NaOH)	Prisms (C_2H_5OH–H_2O)	135
Brucinesulfonic Acid-III	245 (dec)	+156.9°(NaOH)	Prisms (H_2O)	60
Brucinesulfonic Acid-IV	..	−122.2°(NaOH)	Prisms	68
Benzal-	..	−389°	Rt. ⌊ 'd prisms	138
Brucinic Acid	245 (dec)	..	Crystalline powder	4
Methiodide	218 (dec)	..	Needles (H_2O)	4

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
N-Nitrosamine hydrochloride	236	..	Yellow needles(H_2O)	4
Brucinolic Acid	*250–251 (dec)	−22° (NaOH)	Plates (H_2O)	57, 69, 122
$C_{21}H_{24}O_6N_2$ (cleavage product)	290 (dec)	..	Leaflets (H_2O)	61
Acetyl-	295 (dec)	..	Rt. ⌊'d plates (H_2O–HOAc)	57
Ethyl ester	121–123	..	Rt. ⌊'d leaflets (CH_3OH)	96
Methyl ester	205–207	..	Plates (CH_3OH)	96
Brucinolic Acid Hydrate				
Dimethyl ester methiodide	140–144 (froth)	..	Leaflets (H_2O)	96
Brucinolone-a	289	−32.12°(HOAc)	Needles (H_2O)	57, 69, 75
Acetyl-	253–254	..	Prisms (C_2H_5OH)	69, 75
Hydrochloride	320 (dec)	..	..	75
Brucinolone Hydrate-I	267–268	..	..	61
Phenylisocyanate derivative	192 (froth)	..	..	69
Ethyl ester hydrochloride	181	..	Octahedra(C_2H_5OH)	69
Methyl ester hydrochloride	189–190	..	Octahedra(CH_3OH)	69
Brucinolone Hydrate-II	240 (gas)	..	Rhombohedral crystals (H_2O)	69
Hydrochloride	255	..	Prisms (H_2O)	69
Brucinolone-b	269–274	−36.8° (HOAc)	..	96, 190c
Acetyl-	280–290	−291° (HOAc)	Needles (C_2H_5OH)	84
Benzoyl-	235–236	−148° (HOAc)	Prisms (C_2H_5OH)	97
Diethylphosphate	232–235	..	Leaflets (C_2H_5OH)	97
Brucinolone-b Hydrate				
Hydrochloride	..	..	..	145
Hydroperchlorate	230 (dec)	+15.6° (H_2O)	..	145
Methyl ester hydroperchlorate	157–158	+21.2° (H_2O)	Prisms	145
Brucinolonic-a Acid				
Acetyl-	..	..	Yellow sirup	70
$C_{19}H_{22}O_6N_2 \cdot HCl$	235–236 (gas)	..	Prisms (H_2O)	75
Barium salt	..	..	Fine needles(H_2O)	70
Brucinolonic-b Acid				
Acetyl-	275	..	Prisms (H_2O)	69
$C_{22}H_{24}O_7N_2$	281 (dec)	..	Crystals (C_2H_5OH)	69
Brucinonic Acid	*266 (gas)	−48.5° (NaOH)	Prisms (C_2H_5OH)	55
$C_{20}H_{23}O_6N_2Cl$ (H_2O_2–oxidation)	220–225 (dec)	..	Rt. ⌊'d leaflets (H_2O)	128

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
$C_{20}H_{23}O_6N_2Cl$ (lactone)	>220	..	Needles (H_2O)	128
$C_{20}H_{22}O_6N_2$	250 (dec)	..	Prisms and needles (H_2O)	128
Hydrochloride	..	..	Leaflets (H_2O)	128
$C_{20}H_{22}O_6N_2$ (amino acid)	254–255 (dec)	−24.4°/d (H_2O)	Yellow octahedra (C_2H_5OH)	124
Hydrochloride	..	−33.3°/d	Rhombs (HCl–H_2O)	124
Hydroperchlorate	..	−25.4°/d	Octahedra	124, 128
$C_{20}H_{24}O_5N_2$	305 (dec)	..	Crystals (H_2O)	128
Hydroperchlorate	..	..	Octahedra (H_2O)	128
$C_{19}H_{24}O_3N_2 \cdot HClO_4$	..	..	Leaflets (H_2O)	128
$C_{19}H_{20}O_3N_2 \cdot HClO_4$	..	..	Rhombs (H_2O)	128
$C_{13}H_{18}O_5N_2$(amino acid)	..	−115.3°/d(HCl)	Needles	160
$C_{13}H_{16}O_5N_2$ (amino acid)	>305	−210.5°/d(HCl)	Needles (H_2O)	126
$C_{13}H_{16}O_5N_2$ (lactone)	..	−24°/d(HCl)	..	160
Anilide	239–240	..	Prisms(HOAc–H_2O)	61
Hydrazone-I	203 (froth)	..	Crystals (H_2O)	100
Hydrazone-II	236 (froth)	−121° (HOAc)	Needles (C_2H_5OH)	102
Oxime	*293 (dec)	+128° (NaOH)	Prisms (CH_3OH)	57
Phenylhydrazone	225–228	..	Needles (C_2H_5OH)	102
Semicarbazone	*250–251 (gas)	+252° (NaOH)	Prisms (C_2H_5OH)	57
Ethyl ester	132	..	Prisms (C_2H_5OH)	55
Hydrazone	180	..	Rt.⌊'d prisms(H_2O)	100
Oxime	280 (dec)	..	Prisms (C_2H_5OH)	96
Phenylhydrazone	186–188	..	Needles (C_2H_5OH)	102
Semicarbazone	192–196 (froth)	+231° (HOAc)	Domatic prisms (H_2O)	102
Hydrazide				
Hydrazone	210	..	Needles and prisms (C_2H_5OH)	100
Oxime	265 (dec)	..	Prisms (H_2O)	96
Phenylhydrazone	195–204	..	Fine needles (C_2H_5OH)	102
Semicarbazone	250–260	+339° (HOAc)	Needles (H_2O)	102
Methyl ester	221–224	..	Prisms (CH_3OH)	96
Oxime	265 (dec)	+81.7° (HOAc)	Leaflets (CH_3OH)	96, 122
Oxime hydroperchlorate	..	..	Octahedra (H_2O)	122
Brucinone (see Dehydrobrucinolone)				
Brucinonic Acid Hydrate	245	..	Needles (HOAc)	61
Dimethyl ester-oxime	144–146	..	Prisms (H_2O)	96
Hydrochloride	193 (gas)	..	Rt. ⌊'d leaflets	96
Methiodide	185–187	..	Leaflets (acetone)	96

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bruciquinone (see Bisdesmethylbrucine)				
Bruzone	175–185	−595°/d($CHCl_3$)	Prisms (CH_3OH)	181, 171
Hydrate	195–200	−441°/d($CHCl_3$)	Octahedra	181
		C		
Cacotheline (see Nitrate of Nitrobisdesmethylbrucine Hydrate)				
3-Carboxymethylene-2-oxonucine Hydrate	−(dec)	−37°	Prisms or needles (H_2O)	88, 11, 42a
$C_{19}H_{24}O_8N_2$(acid)	..	..	..	104
Hydrobromide	..	..	Leaflets (HBr–H_2O)	104
Nitrate	..	..	Rt. ⌊ 'd leaflets (HNO_3–H_2O)	104
$C_{19}H_{22}O_9N_2$ (acid)	..	..	Prisms (CH_3OH)	104
Hydrobromide trihydrate	..	..	Domatic prisms	104
$C_{19}H_{22}O_8N_2$ (Acid) Br_2 Oxidation	..	..	..	104
Hydrobromide	..	..	..	101
Monoxime	..	..	Prisms (H_2O)	104, 101
Monosemicarbazone	..	..	Plates (H_2O)	104
Monosemicarbazone hydrochloride	..	..	Dense plates	104
Dimethyl ester	225–227 (dec)	..	Needles or prisms (CH_3OH)	104
Dimethyl ester nitrate	..	..	Plates	104
$C_{17}H_{18}O_8N_2$ (acid)	>300	..	Tetrahedra (H_2O)	104
Hydrochloride	250–290	..	Rt. ⌊ 'd prisms (acetone–HCl)	104
Dimethyl ester hydrochloride	..	..	Dense rt. ⌊ 'd prisms	104
Hydrobromide	..	..	Prisms (HBr–H_2O)	88, 101
Hydrochloride	..	..	Prisms (CH_3OH)	88
Hydroperchlorate	..	−19.0°/d(H_2O)	Prisms	116
Methiodide	..	..	Yellow needles(H_2O)	88
Methobromide	..	−6.75° (H_2O)	Crystals (CH_3OH)	92
Bromohydrin	..	..	Prisms	161
$C_{19}H_{21}O_6N_2Br \cdot CH_3ClO_4$	..	..	Glistening prisms	161
Methoperchlorate	..	..	Pointed tetrahedra (H_2O)	161
Methylbetaine	..	−5.6° (H_2O)	Prisms (CH_3OH)	88
Nitrate	..	−30.0° (H_2O)	Rt. ⌊ 'd plates	88, 101
N-Oxide	..	..	Needles (HBr)	101
Monoamide-hydrobromide	..	..	Leaflets (HBr)	112

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Anhydride	..	..	Prisms (HOAc)	112
Hydroperchlorate	..	..	Needles and prisms	112
Dimethyl ester	153–155 (froth)	..	Prisms (H_2O)	88
Hydrochloride	..	..	Dense prisms (CH_3OH)	88
Methiodide	..	..	Dense prisms (H_2O)	88
Methoperchlorate	..	..	..	42a
Monomethyl ester	..	..	Resin	88
Hydrochloride	..	..	Fine needles (CH_3OH)	88
Hydroperchlorate	..	..	Leaflets (H_2O)	112
Methiodide	..	..	Prisms (CH_3OH–H_2O)	88
3-Carboxymethylene-2-oxonucine-sulfonic Acid-II	..	−90.5°/d (NaOH)	Needles or prisms	131
12-Chlorobrucine	..	..	Needles (CH_3OH)	23
Methiodide	219 (dec)	..	Yellow needles (acetone)	23
12-Chlorodihydrobrucine	274 (dec)	..	Needles (ethyl acetate–$CHCl_3$)	23
Cryptobrucinolone	190–192	−151° (HOAc)	Yellow leaflets (CH_3OH)	84, 190c
Acetyl-	272–274	−199.5°(HOAc)	Prisms (C_2H_5OH)	84
$C_{23}H_{24}O_{10}N_2$ (oxidation)	280	..	Octahedra (HOAc)	84
Cryptobrucinolone Hydrate Hydrochloride	..	..	Prisms (C_2H_5OH)	84
Cyanobrucine	228–232 (V)	..	Prisms(HOAc–H_2O)	175
Hydrochloride	..	..	Needles	175
Hydroperchlorate	..	..	Plates	175
Benzal-	268 (dec)	−380.5°/d ($CHCl_3$)	Yellow needles (acetone)	182
Cyanobrucinonic Acid	275–280 (dec)	..	Prismatic needles (H_2O)	175
Cyanodihydrobrucine	176–178 (V)	..	Long prisms (C_2H_5OH)	173
Hydrochloride	..	..	Prismatic needles	173
Hydroperchlorate	..	..	Six-sided leaflets	173
Benzal-	269	−90.7°/d ($CHCl_3$)	Yellow needles (CH_3OH)	182
Isobenzal-	..	−511.5°/d ($CHCl_3$)	..	182
Hydroperchlorate	240–242	..	Needles (HOAc–H_2O)	182

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Curbine	322	..	..	70
Hydrochloride	270 (dec)	..	Needles (H_2O)	70, 97
N-Acetyl-oxime	185–187	..	Rt. ∟'d prisms (H_2O)	97
		D		
Dehydrobrucinolone Oxime	295–300 (dec)	..	Prisms and lancets	105
Acetate	240	..	Prisms (C_2H_5OH)	105
Dehydrobrucinolone Oxime (Isomer)	254–258 (dec)	..	Green plates (CH_3OH)	105
Desazabrucidine	133–134	..	Yellow plates (ligroin–ethyl acetate)	228
Desoxymethylbrucine Methiodide	263 (dec)	+173° (H_2O)	Needles (C_2H_5OH–$CHCl_3$)	18
12-Diazobrucine	189 (dec)	..	Yellow needles (C_2H_5OH–H_2O)	23, 20
Dihydrobrucidine-A	172–173	..	Prisms (acetone)	209, 203, 222
Dihydriodide	235–240 (dec)	..	Diamond-shaped plates (H_2O)	203, 197
Dimethiodide	286–288 (dec)	..	Plates (CH_3OH)	221
Dimethosulfate	270	..	Rods (acetone–CH_3OH)	203
Methiodide	298 (dec)	..	Plates (CH_3OH)	221, 222
Methosulfate	287–288 (dec)	..	Silky needles	221
Dihydrobrucidine-C				
Methiodide	304–306 (dec)	..	Plates (CH_3OH)	222
Methochloride	233–235	..	Powder	222
Dihydrobrucidine-D	197–199	..	Needles (CH_3OH)	225
Methiodide	317–318 (dec)	..	Plates (H_2O)	222
Methochloride	304–306 (dec)	..	Red powder	222
Dihydrobrucidinonic Acid	300 (dec)	+64.9°/d (NaOH)	Leaflets	122
Acetyl-	275 (dec)	..	Rt. ∟'d prisms ($CHCl_3$–ether)	122
Dihydrobrucine	179–181	+7.6°	Prisms (ethyl acetate)	203, 17, 66, 209, 255
Cyanogen bromide adduct (see Bromocyanotetrahydrobrucine)				
Hydriodide	260–262	..	Rods (H_2O)	203
Hydrobromide	220	+29.4°/d(H_2O)	Prisms (H_2O)	127
Hydroperchlorate	..	..	Rhombic leaflets	165
Methiodide	290–295 (dec)	+29.4°(CH_3OH)	Double pyramids (H_2O)	146, 18, 11, 203

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methobromide	..	+31.6°/d(H_2O)	Tabular crystals (H_2O)	127
Methochloride	..	..	..	255
Methosulfate	242–244	..	Hexagonal tablets (H_2O)	203
Benzal-	243–244	−140.7°/d ($CHCl_3$)	Yellow leaflets (acetone)	139
$C_{30}H_{32}O_6N_2$ (oxidation)	246–247	..	Leaflets ($CHCl_3$–acetone)	139
Acetyl deriv. of $C_{30}H_{32}O_6N_2$	226–228	..	Needles ($CHCl_3$–acetone)	139
$C_{28}H_{28}O_4N_2$ (oxidation)	306 (dec)	..	Plates ($CHCl_3$–acetone)	139, 136
$C_{23}H_{26}O_7N_2$ (oxidation)	245–246 (dec)	+81.9°/d (NaOH)	Pointed needles	139
$C_{15}H_{20}O_6N_2$ (red. of $C_{15}H_{18}O_6N_2$)	305 (froth)	−54.4°	Prisms (H_2O)	151
Acetyl deriv. of $C_{15}H_{20}O_6N_2$ as hydroperchlorate	150–160 (froth)	−19.8°/d(H_2O)	Polyhedra	139, 151
Monoethyl ester of $C_{15}H_{20}O_6N_2$ as hydrochloride	..	−18.2° (H_2O)	Needles (C_2H_5OH)	151
$C_{15}H_{18}O_6N_2$ (oxidation)	>310	−16°	Plates (H_2O)	151
Hydroperchlorate of $C_{15}H_{18}O_6N_2$	..	+9.9°/d(H_2O)	Plates	139
Dimethyl ester of $C_{15}H_{18}O_6N_2$ as hydrochloride	98–100	..	Lancets (CH_3OH)	151
Monoethyl ester of $C_{15}H_{18}O_6N_2$ as hydrochloride	240–250	+21.8° (H_2O)	Rhombic leaflets	151
Hydroperchlorate	..	..	Leaflets (C_2H_5OH–H_2O)	139
Zinc chloride double salt	..	..	Yellow prisms (H_2O–HCl)	139
Isobenzal-methiodide	262–264 (dec)	−310° (HOAc)	Plates (H_2O)	144
Acetyl-	221–223 (V)	−288.5°(HOAc)	Needles (CH_3OH)	144
Dihydrobrucine(Isomer)	218	−20.1°($CHCl_3$)	Needles (H_2O)	17
Methiodide	230 (dec)	..	Prisms (H_2O)	17
Dihydrobrucineacetic Acid	282–284 (V)	..	Leaflets (H_2O)	173, 175
Hydroperchlorate	260–280 (dec)	..	Prisms	173
Benzal-(hydrate)	245–255 (froth)	..	Citron-yellow prisms	173

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Dihydrobrucineacetonitrile	314–315 (dec)	+19.4°/d ($CHCl_3$)	Prisms ($CHCl_3$–CH_3OH)	182
Hydroperchlorate	255	..	Needles (HOAc)	182
Benzal-	291 (dec)	−256°/d($CHCl_3$)	Needles ($CHCl_3$–CH_3OH)	182
Dihydrobrucinesulfonic Acid-II	..	+146.5°/d (NaOH)	Needles (H_2O)	131
Dihydrobrucinesulfonic Acid-III	..	+88.5°/d (NaOH)	Prisms (H_2O)	133
Dihydrobrucinic Acid				
Nitrosamine of iso-nitrosoderivative	170 (dec)	..	Crystals	17
Dihydrobrucinolone-b (is a mixture)	285	−9° (HOAc)	Prisms (HOAc–ether)	190c, 145
Acetyl-	253	−34.5° (HOAc)	Prisms (C_2H_5OH)	145
Dihydrobrucinolone-b Hydrate	250	−11.9° (HOAc)	Needles (H_2O)	145
Dihydrobrucinonic Acid	*315 (dec)	−14.8° (NaOH)	Prisms (C_2H_5OH)	55
Acetyl-	235–238	..	Prisms (H_2O)	71
Azide	..	..	..	99
$C_{21}H_{24}O_6N_2$	>300	+89.4° (HOAc)	Prisms (H_2O)	99
Acetyl deriv. of $C_{21}H_{24}O_6N_2$	210–212	+94.8° (HOAc)	Leaflets (C_2H_5OH)	99
Ethyl ester	227–229	..	Six-sided prisms (C_2H_5OH)	96
Hydrazide	205 (froth)	..	Plates (H_2O)	99
Methyl ester	223–224	..	Short prisms (CH_3OH)	96
Dihydrobrucinonic Acid Hydrate				
Dimethyl ester hydrochloride	175–176	..	Rt. ∟'d prisms (CH_3OH)	96
Dimethyl ester methiodide	165 (gas)	..	Prisms (H_2O)	96
Dihydrobruzone	175–185 (V)	−253°/d($CHCl_3$)	Crystals	181
Dihydrocarboxymethylene-2-oxonucine Hydrate-I	..	..	Plates (H_2O)	104, 88
$C_{19}H_{26}O_9N_2$(oxidation)	..	..	..	110
Oxime of anhydride	..	..	Plates (H_2O)	110
Semicarbazone of anhydride	..	..	..	110
Hydrobromide of semicarbazone	..	..	Prisms (HBr–H_2O)	110
$C_{19}H_{24}O_9N_2$(oxidation)	..	..	Leaflets (H_2O)	110

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydrobromide	..	..	Prisms ($HBr-H_2O$)	104
Hydrochloride	..	..	Quadratic leaflets (H_2O)	88
Methiodide	..	..	Prisms (HI)	104
Methobromide	..	+17.3°/d(H_2O)	Prisms (H_2O)	161, 104
Bromohydrin	..	..	Colorless needles	161
Methoperchlorate	..	..	Domatic prisms	161
Anhydride	250 (dec)	..	Crystals (CH_3OH)	112
Dimethyl ester	143–147 (froth)	..	Prisms (acetone)	88
Hydrochloride	..	..	Plates (CH_3OH)	88
Nitrate	..	..	Prisms (HNO_3-H_2O)	88
Methiodide	..	..	Prisms or plates (CH_3OH)	88
Monomethyl ester	..	..	Crystals	112
Dihydrocarboxymethylene-2-oxonucine Hydrate-II	..	−2.9° (H_2O)	Prisms (H_2O)	11
Hydrobromide	..	..	Prisms ($HBr-H_2O$)	11
Dihydrocryptobrucinolone	180	−78.5° (HOAc)	Prisms ($C_2H_5OH-H_2O$)	145, 190c
Acetyl-	235	−113° (HOAc)	Prisms (ethyl acetate)	145
Dihydrodihydroxy methoxymethyldihydroneobrucidine	227–229	+99.6°/d(H_2O)	Dense prisms	134
Oxime	268–271 (froth)	..	Rt. ∟'d plates	134
Semicarbazone	272–276 (dec)	..	Plates (C_2H_5OH)	134
Dihydroisobrucinolone	260	−24° (HOAc)	Prisms (C_2H_5OH)	145
Acetyl-	185	−58.5° (HOAc)	Prisms (H_2O)	145
Dihydroisobrucinolone Hydrate	255–260	−21.6° (HOAc)	Prisms (HOAc)	145
Dihydronorbrucinic Acid	286–287	..	Prisms (CH_3OH-H_2O)	26
Dihydroxydihydrobrucinolone-b				
Diacetyl-	280 (dec)	−149.2°(HOAc)	Plates ($HOAc-H_2O$)	97
Dihydroxydihydroacetylisobrucinolone	245	..	Needles (H_2O)	97
Dihydroxymethoxymethyldihydroneobrucidine	228–230	+228.3°/d(H_2O)	Plates (CH_3OH)	134
p-Dimethylaminophenyl-cyanotetrahydrobrucine	168–170	+41.7°/d ($CHCl_3$)	Prisms (C_2H_5OH)	127

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
N_b,N_b-Dimethyldesbrucidine	155–156	..	Needles (CH_3OH)	222
Dimethiodide	251–253	..	Plates (H_2O)	228
Dimethochloride	214–218	..	Needles (H_2O)	228
		E		
Ethoxydihydrobrucinolone	132 (gas)	−44.2° (HOAc)	Prisms (CH_3OH)	84
Acetyl-	219–220	−78.2° (HOAc)	Prisms (C_2H_5OH)	84
		H		
Hanssen's C_{19}-acid (see 3-Carboxymethylene-2-oxonucine Hydrate				
Hexahydrobrucine	131–133	..	Crystals (C_6H_6–ligroin)	203
Hydroperchlorate	..	−69.3°/d	Prisms (acetone)	130
Diacetyl-	135	+66.5°/d(H_2O)	Crystals (ether)	130
Methiodide	176–180	+64.6°/d(H_2O)	Prisms (CH_3OH)	130
Dibenzoyl-	135	+62°/d (C_2H_5OH)	Needles (ligroin)	130
Methiodide	175–190	..	Prisms (C_2H_5OH)	130
N-Monoacetyl-	185–186	+70°/d(H_2O)	Leaflets (acetone)	130
Methiodide	200	+78.4°/d(H_2O)	Needles (CH_3OH)	130
N-Monobenzoyl-	135	+83°/d (C_2H_5OH)	Prisms (H_2O)	130
Methiodide	300 (dec)	..	..	130
Hexahydro-N_b-methylchanodihydrobrucine	143–144	..	..	255
Methiodide	218–222	..	..	255
Diacetyl-	108–110	..	..	255
Hydroxybrucine (see Pseudobrucine)				
12-Hydroxybrucine	178	..	Colorless needles	23
Hydrochloride	>300 (dec)	..	Yellow leaflets (CH_3OH)	23
12-Hydroxydihydrobrucine	233 (dec)	..	Leaflets ($CHCl_3$)	23
Hydroxydihydrobrucinolone-I				
Acetyl-	253–254	−22.3°(HOAc)	Prisms (C_2H_5OH)	84
Hydroxydihydrobrucinolone-III	219–221	−49.5°(HOAc)	Leaflets (H_2O)	84
Hydroxymethyltetrahydrobrucidine	169–171	..	Yellow needles (ligroin)	222
Acetyl-	258–260 (dec)	..	Leaflets (ligroin)	222

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		I		
Isobenzaldihydrobrucine	..	..	..	148
Methiodide	a) 195	..	..	148
	b) 264	..	..	148
Isobrucinolone	..	+34° (HOAc)	Prisms (HOAc)	71, 69, 97
Acetyl-	312–315	+22° (HOAc)	Large leaflets	97, 71
Benzoyl-	250	+99° (HOAc)	Needles (C_2H_5OH)	97
Isobrucinolone Hydrate	310–315 (dec)	..	Prisms (H_2O)	71
Hydroperchlorate	195–200	+4° (H_2O)	Needles	145
Isodihydrobrucine-I	225–235	−165°(C_2H_5OH)	Needles (H_2O)	146
Hydroperchlorate	..	−231° (H_2O)	Prisms (H_2O)	146
Methiodide	>300	+43.9° (H_2O)	Needles (CH_3OH)	146
Sulfate	>290	..	Prisms and plates (H_2O)	146
O-Acetyl-	..	−172°	..	148
Hydrobromide	..	−167°	Four-sided prisms	148
Hydroperchlorate	240–260 (dec)	..	Small plates	146
Methiodide	295–305	−43.9° (HOAc–H_2O)	Crystals	148
Isodihydrobrucine-II	218	−11.6°($CHCl_3$)	Octahedra (CH_3OH)	146
Hydroperchlorate	215–230	+24° (H_2O)	Lancets (H_2O)	146
Methiodide	208–218	+17.2° (HOAc–H_2O)	Needles (H_2O)	146
O-Acetyl-hydroperchlorate	138–143	+12° (H_2O)	Prisms (H_2O)	146
Isodihydrobrucine-III	..	..	..	148
Hydrobromide	>330	+17.5°	Tetrahedra (HBr–H_2O)	148
		M		
Methoxybenzyldihydroneobrucidine	159–160	..	Prisms (C_2H_5OH)	209
Methiodide	249–250	..	..	209
Methoxybenzyltetrahydrobrucidine	107–108	..	Prisms (CH_3OH)	209
Methoxybrucine (see Pseudobrucine Methyl Ether)				
12-Methoxybrucine	192	..	Yellow crystals (acetone)	23
Methiodide	236 (dec)	..	Crystals (CH_3OH)	23
Methoxycyanodihydro(neo)brucine	98–100	−67.8° (HOAc)	Prisms (CH_3OH)	127
12-Methoxydihydrobrucine	237	..	Needles (ethyl acetate)	23

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Methoxydihydro-brucinolone	82–84	−50.3° (HOAc)	Prisms (CH_3OH)	90
Acetyl-	270	−91.5° (HOAc)	Prisms (C_2H_5OH)	90
Methoxydihydrobruzone	190 (V)	−313°/d($CHCl_3$)	Prisms (CH_3OH)	181
Methoxymethyldihydroneobrucidine	115 267/1.5 mm.	..	Needles (C_2H_5OH)	197
Dihydriodide	217–218 (dec)	..	Leaflets (H_2O)	197
Dimethiodide-A	215–230	..	Leaflets (CH_3OH)	197
Dimethiodide-B	290 (dec)	..	Columns (H_2O)	197
Dimethochloride-B	..	..	Colorless glass	197
Methiodide-A	190	..	Prisms (H_2O)	197
Methiodide-B	291	..	Prisms (H_2O)	197
Methochloride-A	..	..	..	197
Methochloride-B	164 (dec)	..	Prisms (acetone)	197
Methosulfate-A	231–232 (dec)	..	Plates (C_2H_5OH)	197
Methoxymethyldihydroneobrucine	204–205	..	Needles (CH_3OH)	209
Methoxymethyltetrahydrobrucidine	133–135 235/2 mm.	−7.6°/d (C_2H_5OH)	Needles (hexane)	197, 134
Dihydriodide	212	..	Needles (H_2O)	197
Dihydrochloride	150	..	Plates (acetone–C_2H_5OH)	197
Dimethiodide-A	166–167	..	Leaflets (C_2H_5OH)	197
Dimethiodide-B	287 (dec)	..	Needles (H_2O)	197
Dimethochloride-A	..	..	Glass	197
Dimethochloride-B	214 (dec)	..	Plates (C_2H_5OH)	197
Dimethohydrogen-carbonate-A	103–104	..	Crystals	197
Dimethohydrogen-carbonate-B	109	..	Prisms (C_2H_5OH–ethers)	197
Methiodide-A	166–167	..	Leaflet (C_2H_5OH)	197, 222
Methiodide-B	298 (dec)	..	Prisms (H_2O)	197
Methochloride-A	..	..	Glass	197
Methochloride-B	..	..	Glass	197
p-Methylaminophenyl-cyanotetrahydrobrucine	178–180	+40.8°/d ($CHCl_3$)	Prisms (C_2H_5OH)	127
N-Methylbrucinolic Acid Hydrate	..	..	Amorphous	122
Dimethyl ester hydriodide	140–144	..	Leaflets (acetone)	122
N-Methylbrucinonic Acid Hydrate	207–211 (dec)	..	..	122
Oxime	150–190	..	Leaflets (H_2O)	122
Dimethyl ester	151	..	Rhombic crystals (C_2H_5OH)	122

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Hydroperchlorate	..	..	Leaflets (C_2H_5OH)	122
Oxime	110–119	..	Pointed needles (H_2O)	122
N_b-Methyl-des-dihydro-brucidine-A	221–222	..	Plates (C_2H_5OH)	222
Dimethiodide	284–286 (dec)	..	Plates (H_2O)	222
Dimethochloride	296–298 (dec)	..	Prismatic needles (CH_3OH)	222
N_b-Methy -des-dihydro-brucidine-B	133–134	..	Yellow plates	222
Methiodide	242–244	..	Plates (CH_3OH)	222
Methochloride	245–248	..	Reddish powder	222
N_b-Methyl(chano)-dihydroneobrucine	147–148	..	Crystals	255
Methiodide	263–265	..	..	255
Methochloride	214–216	..	Crystals	255
Picrate	147–150	..	Crystals	255
Methylbrucine (Betaine)	300 (dec)	..	Needles (acetone–H_2O)	197, 4, 67
N-Acetyl-	157–158	..	Plates (ethyl acetate)	67
Methylbrucine Perchlorate	260–300 (dec)	..	Needles	175
Methyldihydrobrucine				
Hydroperchlorate	240–280 (dec)	..	Columns and prisms	182
Methylpseudohydrobrucidine (see Dihydrobrucidine-A)				
N-Methyl-*sec*-pseudo-brucine	228–230	..	Prisms (C_2H_5OH)	164
Hydriodide	222–224	..	Plates (CH_3OH)	164
Hydroperchlorate	210–215	..	Prisms or lancets	164, 171
Methiodide	220–222	..	Plates or prisms (H_2O)	164, 171
$C_{26}H_{38}O_5N_2$ (reduction)	..	..	Resin	164
$C_{26}H_{38}O_5N_2 \cdot HClO_4$	165	..	Prisms (H_2O)	164
$C_{26}H_{36}O_5N_2$	175 (V)	..	Prisms (C_2H_5OH)	164
$C_{26}H_{36}O_5N_2 \cdot CH_3I$	275–278 (dec)	..	Prisms (H_2O)	164
$C_{25}H_{32}O_5N_2$ (reduction)	184–185 (V)	..	Polyhedra (acetone)	164
$C_{25}H_{32}O_5N_2 \cdot CH_3I$	203–204 (V)	..	Plates (H_2O)	164
$C_{25}H_{32}O_5N_2 \cdot CH_3ClO_4$	285 (dec)	..	Polyhedra	164
$C_{25}H_{30}O_5N_2$	225 (V)	..	Prisms (CH_3OH)	164
$C_{25}H_{30}O_5N_2 \cdot CH_3I$	245–247 (dec)	..	Prisms (CH_3OH)	164
$C_{23}H_{28}O_3N_2$ (reduction)	170–172 (V)	..	Crystals	156

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
$C_{23}H_{28}O_3N_2 \cdot HBr$	215 (dec)	..	Polyhedra	156
$C_{23}H_{28}O_3N_2 \cdot HClO_4$	239–243 (dec)	..	Prisms or plates	156
Methoperchlorate	280 (dec)	..	Needles or leaflets (H_2O)	164
Benzal-	234–236 (V)	..	Yellow prisms (C_2H_5OH)	171
N-Methyl-*sec*-pseudo-brucinesulfonic Acid	..	−120.3°/d (NaOH)	Prisms (H_2O)	171
Isomer	..	+41°/d	Plates (H_2O)	171
N-Methyl-*sec*-pseudo-dihydrobrucine	235–237 (V)	..	Polyhedra(C_2H_5OH)	164
Hydroperchlorate	215	..	Leaflets or plates	164
Methiodide	252–254 (dec)	..	Prisms (H_2O)	164, 171
		N		
Neobrucidine	198–199	..	Plates (C_2H_5OH)	209, 197
Benzyloiodide	260–261 (dec)	..	Needles (H_2O)	209
Benzyl-methyl diiodide	246–248 (dec)	..	Needles (H_2O)	221
Benzyl-methyl dichloride	156–158	..	Gray prisms (H_2O)	221
Dihydriodide	259 (dec)	..	Leaflets (H_2O)	197
Dimethiodide	298 (dec)	..	Crystals (H_2O)	221
Methiodide	297–298	..	Plates (CH_3OH)	197
Methochloride	188	..	Needles (C_2H_5OH)	197
Neobrucine	225–226	..	Silky needles (CH_3OH)	209, 235
Methiodide	302–306 (dec)	..	Crystalline powder (CH_3OH)	209, 235
Methochloride	255–260 (dec)	..	Needles (H_2O)	209
Nitro-bisapomethyl-brucinesulfonic Acid-I	..	..	Violet rt. L'd prisms	87
Diethyl ester	..	..	Violet prisms (C_2H_5OH)	87
Triacetyl-	..	..	Yellow rhombic leaflets	87
Nitro-bisapomethyl-brucinesulfonic Acid-II Hydrate	..	..	Violet prisms	93
Nitro-bisapomethyl-brucinesulfonic Acid-III Hydrate	..	..	Dark violet prisms	93
Nitro-bisapomethyl-brucinesulfonic Acid-IV Hydrate	..	..	Dark violet prisms (CH_3OH)	93
Nitro-bisapomethyl-brucinolone	..	..	Yellow octahedra (H_2O)	71

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Nitro-bisapomethyl-dehydrobrucinolone	..	..	Crystals (HNO_3)	69
Nitro-bisapomethyl-dihydroiso-brucinolone	340 (dec)	..	Orange-yellow needles	71
Nitro-bisapomethyl-ethoxydihydrobru-cinolone Hydrate	185	..	Violet powder	90
Triacetyl-	175–180	..	Orange prisms(H_2O)	90
Nitro-bisapomethyl-isobrucinolone	320 (dec)	..	Long leaflets	71
Nitro-bisapomethyl-pseudobrucine Hydroperchlorate	..	..	Violet cubic crystals (H_2O–$HClO_4$)	165
Nitro-bisdesmethyl-brucine Hydrate	..	..	Yellowish leaflets	4
Methonitrate	280 (dec)	..	Orange plates	67, 82
$C_{17}H_{21}O_3N_2Br$	..	..	Pointed prisms (HBr–H_2O)	107
$C_{17}H_{20}O_3N_2Br_2$	..	−4.3° (HBr)	Prisms or needles	92
Nitrate	..	..	Orange crystalline powder	4, 67, 85
$C_{21}H_{23}O_8N_3Br_2$	..	..	Yellow needles	98
$C_{21}H_{23}O_8N_3Cl_2$	..	..	Leaflets (H_2O)	98
$C_{20}H_{23}O_6N_3$	..	..	..	98
$C_{20}H_{23}O_6N_3 \cdot HBr$	..	..	Yellow leaflets (HBr–H_2O)	98
$C_{20}H_{23}O_6N_3 \cdot CH_3Br$	..	..	Spears (C_2H_5OH)	98
$C_{17}H_{23}O_4N_3$	..	..	Prisms or needles (HBr)	107
$C_{17}H_{22}O_8N_2$	>300	..	Tetrahedra (H_2O)	107
$C_{17}H_{22}O_7N_2 \cdot HBr$	..	..	Needles (HBr–H_2O)	107
$C_{17}H_{22}O_5N_2$	234	+6.06°/d(H_2O)	..	109
$C_{17}H_{22}O_5N_2 \cdot HBr$	..	..	Needles (HBr–H_2O)	107
$C_{17}H_{22}O_5N_2 \cdot CH_3I$	>220	..	Prisms (CH_3OH)	107
$C_{17}H_{22}O_3N_2$	220	..	Prisms (CH_3OH)	109
$C_{17}H_{22}O_2N_2$	168–170	..	Plates (C_6H_6)	111
$C_{17}H_{21}O_3N_2Br$	232–234 (dec)	..	Plates (CH_3OH)	109
$C_{17}H_{21}O_3N_2Br \cdot HBr$	..	..	Prisms (HBr–H_2O)	109
$C_{17}H_{20}O_3N_2Br_2$	>300 (dec)	..	Plates (CH_3OH)	107, 88
$C_{17}H_{20}O_3N_2Br_2 \cdot HBr$	..	..	Plates or needles (H_2O)	88
$C_{17}H_{20}O_3N_2Br_2 \cdot HCl$	..	..	Plates (HCl–H_2O)	107
$C_{17}H_{20}O_3N_2Br_2 \cdot CH_3I$	245 (dec)	..	Rt. ⌊'d plates(H_2O)	107

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Acetyl deriv. of $C_{17}H_{20}O_3N_2Br_2$	210 (dec)	..	Plates (acetone)	109
Oxime hydrochloride	..	..	Yellow needles(H_2O)	85
Phenylhydrazone hydrochloride	..	..	Yellow plates(HCl–H_2O)	85
Semicarbazone nitrate	..	..	Needles (HNO_3)	85
Ethyl ester hydrochloride	..	..	Needles (C_2H_5OH)	85
Methyl ester hydrochloride	..	..	Crystals (CH_3OH)	85
Oxime	..	..	Yellow prisms	85
Nitro-bisdesmethyl-brucinesulfonic Acid-I Hydrate	..	..	Prisms	87
$C_{20}H_{23}O_9N_3S$	..	..	Yellow crystals	98
Monoxime	..	..	Yellow needles	87
Monosemicarbazone	..	..	Yellow leaflets	87
Nitro-bisdesmethyl-brucinesulfonic Acid-II Hydrate	..	..	Orange-red prisms	93
Nitro-bisdesmethyl-brucinesulfonic Acid-III Hydrate	..	..	Plates (H_2O)	93
Nitro-bisdesmethyl-brucinesulfonic Acid-IV Hydrate	..	..	Prisms (H_2O)	93
Nitro-bisdesmethyl-cryptobrucinolone	..	..	Orange needles	84
Nitro-bisdesmethyl-ethoxydihydro-brucinolone Hydrate	..	..	Yellow leaflets (HN_3–H_2O)	90
Nitro-bisdesmethyl-dihydrobrucine Hydrate	..	..	Yellowish-red crystals	11, 159
Nitro-bisdesmethyl-pseudobrucine Hydrate Perchlorate	..	..	Polyhedra ($HClO_4$–H_2O)	162, 165
Oxime	..	..	Yellow-green plates	162
Semicarbazone	..	..	Plates (H_2O)	162, 165
Nitromethoxymethyl-dihydro-neo-brucidine	276–278 (dec)	..	Prisms (C_2H_5OH)	134
Norbrucinic Acid	292–293 (dec)	..	Needles (CH_3OH–H_2O)	26
Amide	156–158	..	Needles (H_2O)	26
Ethyl ester	231	..	Crystals	26

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		P		
Pseudobrucine	267–268	..	Prismatic needles	154, 171
Hydroperchlorate	220–240 (dec)	+4.4°/d (CH_3OH)	Prisms or needles	154
N-Nitroso-	248 (dec)	..	Needles (CH_3OH)	154
Benzal-	165 (dec)	..	Polyhedra	154
Methyl ether	226	..	..	171, 154, 164
Hydriodide	222	..	Six-sided leaflets	164
Methiodide	219	..	Needles (CH_3OH)	164, 171
Pseudodihydrobrucine	258–260 (dec)	+29°/d($CHCl_3$)	Polyhedra	154, 165
N-Nitroso	160–190 (dec)	..	Prisms (C_2H_5OH)	154
Isobenzal-hydroperchlorate	236–238 (dec)	..	Needles (HOAc–H_2O)	182
Methyl ether	118 (froth)	+85°/d($CHCl_3$)	Prisms (CH_3OH)	154
		T		
Tetrahydrobrucine	200–201 (dec)	..	Needles (CH_3OH)	51, 197
$C_{19}H_{26}O_5N_2$ (reduction $C_{19}H_{22}O_5N_2$)	315	+69.7°/d	Leaflets (acetone–H_2O)	119
$C_{19}H_{22}O_5N_2$(oxidation)	300–305 (dec)	+63.8°/d(H_2O)	Plates (H_2O)	119
$C_{19}H_{22}O_5N_2 \cdot HClO_4$	..	+38.7°/d	Leaflets or prisms	119
$C_{17}H_{20}O_4N_2$(oxidation)	245–247	..	..	119
$C_{17}H_{20}O_4N_2 \cdot CH_3I$	291–293 (dec)	..	Rhombic plates	119
Dihydriodide	225 (dec)	..	Plates (C_2H_5OH)	197
Dihydrochloride	305 (dec)	..	Needles (CH_3OH)	197, 51
Dihydroperchlorate	..	−49.7°/d	Prisms or needles (H_2O)	119, 130
Methiodide	290 (dec)	..	Needles (CH_3OH)	197
Monohydrochloride	..	..	Leaflets (C_2H_5OH)	51
Monohydroperchlorate	..	−67.5°/d	Prisms	130
N-Nitroso-	213–214 (dec)	..	Yellow needles (C_2H_5OH–H_2O)	197
Hydrochloride	288 (dec)	..	Buff needles (C_2H_5OH)	197
Diacetyl-	125–127	..	Prisms (ether)	119
Hydrochloride	..	+95.4°/d	..	119
Hydroperchlorate	..	+85°/d	Plates (H_2O)	119
Methiodide	285–290	..	Needles (CH_3OH)	119
Dibenzoyl-benzoate	166–168	+63.7°/d (C_2H_5OH)	Crystals (acetone)	130
N-Monoacetyl-	130–135	..	Rt. ∟'d plates(H_2O)	119
Hydrochloride	..	+95.3°/d	..	119
Hydroperchlorate	..	+87.2°/d	Needles (H_2O)	119
Methiodide	305 (dec)	..	Prisms (CH_3OH)	119

TABLE 2 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
O-Monoacetyl-	219–221	..	Prisms (acetone)	130
Methiodide	240–242	..	Prisms (CH_3OH)	130
N-Monobenzoyl-	266–268 (dec)	+71.5°(C_2H_5OH)	Prisms (acetone)	130
Tetrahydrobrucine-sulfonic Acid	..	+77.3°/d(H_2O)	Needles	133
O,N-Dibenzoyltetrahydrobrucinonic Acid	170	..	Crystalline powder	130
Tetrahydro-3-carboxymethylene-2-oxonucine Hydrate	..	+17.7°(H_2O)	Prisms (H_2O)	11, 161
Tetrahydrodesoxymethylbrucine Methiodide	262–264 (dec)	−31.5° (H_2O–C_2H_5OH)	Rods (C_2H_5OH)	18
Tetrahydro-N_b-N_b-dimethyldesbrucidine	135–136	..	Silky needles (CH_3OH)	228
Methiodide	282–284	..	Leaflets (CH_3OH)	228

TABLE 3

VOMICINE AND ITS DERIVATIVES

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		A		
Aminohydroxydihydrovomicine Dihydrochloride	>300	..	Needles (acetone–H_2O)	16
Aminovomicine-$ZnCl_2$-salt	..	..	Needles (HCl)	22
		B		
Bivomicidyl	..	..	Yellow hexagonal leaflets	21
Bivomicyl	>320 (dec)	..	Rhombohedra (pyridine)	12
Hydrochloride	..	..	Crystals	12
Bromodesoxyvomicine	266 (dec)	..	Yellow prisms(pyridine–C_2H_5OH)	18
Bromodihydrodesoxyvomicine	243 (dec)	..	Silky needles (C_2H_5OH)	32, 36
Hydrobromide	258 (dec)	..	Crystals (H_2O)	32
Methobromide	272 (dec)	..	Prisms (H_2O)	32
Bromodihydrovomicine	280	..	Crystals (pyridine–C_2H_5OH)	8

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Bromoisodesoxyvomicine Methobromide	>300	..	Needles (acetone)	32
Bromotetrahydrodesoxyvomicine	250 (dec)	..	Needles ($CHCl_3$)	36a
Bromovomicine	306	..	Crystals (pyridine–C_2H_5OH)	8
Bromovomicinic Acid	306	..	Needles (pyridine)	8
		C		
Chlorodihydrodesoxyvomicine	214	..	Long needles (CH_3OH)	36a
		D		
Desoxydihydrovomicidine-II	269 (dec)	..	Needles (ether)	36, 22, 31
$C_{16}H_{22}ON_2$(oxidation)	88	..	Needles (sublimation)	31
$C_{16}H_{22}ON_2 \cdot 2HCl$	255	..	Prisms (C_2H_5OH–acetone)	31
Methiodide	204 (dec)	..	Needles (C_2H_5OH)	31
Desoxydihydrovomicine-I	207–210	+243° ($CHCl_3$)	Needles (C_2H_5OH)	36, 8, 32
Hydrobromide	>290	..	Crystals (H_2O)	32
Methiodide	272 (dec)	..	Needles (CH_3OH–ether)	32
Methobromide	276 (dec)	..	Prisms (C_2H_5OH–H_2O)	32
Benzal-	222	..	Yellow leaflets (acetone)	36
Desoxydihydrovomicine-II	168	+345° ($CHCl_3$)	Rods (ether)	36
Hydrochloride	235 (dec)	..	Crystals (C_2H_5OH)	36
Desoxydihydrovomicine (Isomer)	194	+173° ($CHCl_3$)	Lancets (C_2H_5OH)	30
Desoxyvomicidine	227	..	Prisms (C_2H_5OH)	24, 22
$C_{16}H_{20}ON_2$ (oxidation)	70 170–180/ <1 mm.	+341° ($CHCl_3$)	..	30
$C_{16}H_{20}ON_2 \cdot 2HCl \cdot H_2O$	256 (dec)	..	Crystals (C_2H_5OH–ether)	30
Methiodide	175	..	Silky needles (H_2O)	30
Benzoyl-	190	..	Prisms (C_2H_5OH)	24
Desoxyvomicine-I (yellow)	198	+242° ($CHCl_3$)	Yellow crystals ($CHCl_3$–C_2H_5OH)	30, 8, 24, 36
Desoxyvomicine-II (colorless)	207	+209° ($CHCl_3$)	Colorless crystals ($CHCl_3$–C_2H_5OH)	30, 24, 34

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
$C_{22}H_{30}O_2N_2$ (red.)	211	−98.2° ($CHCl_3$)	Prisms (CH_3OH)	22, 8, 24, 36a
$C_{22}H_{30}ON_2$(elect.red.)	217	..	Needles (C_2H_5OH)	24
$C_{22}H_{29}O_2N_2Br$	159	..	Leaflets (C_2H_5OH–H_2O)	8
$C_{22}H_{28}O_3N_2$	220	..	Rhombic prisms (CH_3OH)	22
$C_{22}H_{28}O_2N_2$	185	+61.0° ($CHCl_3$)	Needles (CH_3OH)	22, 8
$C_{22}H_{28}O_2N_2 \cdot CH_3I$	236 (dec)	..	Prisms (C_2H_5OH)	8
Methiodide	270 (dec)	..	Prisms (H_2O)	30
Benzal-	198–199	..	Yellow needles (acetone–CH_3OH)	36
Monoacetyl	220	..	Needles (C_2H_5OH)	34
Desoxyvomicinic Acid Dihydrate	205	..	Needles (C_2H_5OH–H_2O)	18
Diazovomicine	..	..	Yellow prisms acetone–H_2O)	22
Dihydrodimethylvomicine-II	165	..	Rhombic crystals (CH_3OH)	35
Dihydroisovomicine	225	+235° ($CHCl_3$)	Prisms	36a
Benzal-	245	..	Yellow prisms (C_2H_5OH)	36a
Acetyl-	210	..	Silky needles (C_2H_5OH)	36a
Ethyl ether	151	..	Needles (C_2H_5OH)	36a
Methyl ether	183	+229°	Crystals (CH_3OH)	36a
Dihydroneodesoxyvomicine	321	..	Needles (pyridine)	34
Dihydrovomicidine	296–298 (dec)	..	Yellow prisms (C_2H_5OH–H_2O)	21
$C_{16}H_{20}O_4N_2$(oxidation)	264	..	Prisms (C_2H_5OH–H_2O)	31
$C_{16}H_{20}O_4N_2 \cdot HCl$	>300	..	Needles (acetone–H_2O)	31
Methyl ester	286 (dec)	..	Crystals (acetone–H_2O)	31
Dimethiodide	230 (dec)	..	Needles (C_2H_5OH–H_2O)	21
Dimethochloride	..	..	Colorless crystals	21
Hydrogen sulfate	..	+37.6° (H_2O)	Rhombic crystals (C_2H_5OH–H_2O)	21
Phenol betaine	>300	..	Prisms (acetone)	21
Dihydrovomicine	296	..	Needles (C_2H_5OH–H_2O)	8, 29
$C_{22}H_{24}O_{10}N_4$ (nitration)	>300 (dec)	..	Red plates (HNO_3–H_2O)	16

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
$C_{19}H_{29}O_5N_3 \cdot 2HCl$	..	..	Needles (H_2O)	16
$C_{19}H_{25}O_3N_3 \cdot HBr$	..	..	Yellow crystals (HBr)	16
$C_{18}H_{26}O_7N_2$(oxidation)	315 (dec)	+15.9° (H_2O)	Crystals	15
$C_{17}H_{24}O_5N_2$(oxidation)	264–265 (dec)	−21°	..	15
Methyl ester	178–179	..	Prisms (C_2H_5OH–ether)	18
$C_{16}H_{24}O_3N_2$	274	+34.4°	..	15
Methyl betaine	260	..	Needles (CH_3OH–H_2O)	29
Methiodide	261	..	Prisms (H_2O)	29
Benzal-	285 (dec)	..	Prisms ($CHCl_3$–C_2H_5OH)	24
$C_{29}H_{30}O_6N_2$ (oxidation)	274	..	Rhombic prisms (C_2H_5OH)	24
Benzoyl-hydrochloride	185 (dec)	..	Leaflets (C_2H_5OH)	13
Dihydrovomicinic Acid	291	..	Rods (C_2H_5OH–H_2O)	18, 8
O,N-Dimethyldihydrovomicinic Acid				
Methyl ester	183–185	..	Prisms (C_2H_5OH–H_2O)	13
Dimethylvomicidine-I	236	..	Rt. ∟'d plates (C_2H_5OH)	35
Dimethylvomicidine-II	236	..	Needles (H_2O)	35
Dimethylvomicine-I	114	..	Crystals (C_2H_5OH)	29
Hydroperchlorate	250 (dec)	..	Prisms (CH_3OH–H_2O)	35, 29
Methiodide	261	..	Needles (H_2O)	29
Dimethylvomicine-II	184	..	Rt. ∟'d crystals (CH_3OH)	35
Methiodide	290 (dec)	..	Leaflets (H_2O)	35
N,O-Dimethylvomicinic Acid	242–244	+48.4°	Needles (H_2O)	13
Betaine	195–198	+14.2°(C_2H_5OH)	Needles (H_2O)	13
Hydriodide	185–200	+49.1°	Leaflets (H_2O)	13
Methyl ester	214–216	+61.7°(C_2H_5OH)	Prisms (ether)	13
Methiodide	210 (dec)	..	Plates (C_2H_5OH–H_2O)	13
Dinitrodihydrovomicine	..	..	Needles (C_2H_5OH)	16
$C_{15}H_{18}O_7N_2 \cdot HBr$	..	..	Crystals (HBr–H_2O)	16
Nitrate	..	..	Pointed prisms (HNO_3–H_2O)	16

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		H		
Hexahydrodesoxyvomicine	177	−94.4° ($CHCl_3$)	Plates (CH_3CH)	30
Hydroxyvomipyrine	>300	..	Silky needles	36a
		I		
Iododihydrodesoxyvomicine-I	220–242 (dec)	..	Needles (C_2H_5OH)	36, 8, 24
Hydriodide	..	..	Prisms (H_2O)	24
Iododihydrodesoxyvomicine-II	214 (froth)	..	Crystals (HOAc–H_2O)	36
Isodesoxydihydrovomicidine				
$C_{16}H_{20}O_3N_2 \cdot 2HCl$	295 (dec)	..	Prisms (H_2O–C_2H_5OH)	31
Dihydrochloride	215 (dec)	..	Needles (C_2H_5OH–ether)	31
Isodesoxyvomicine Methobromide	206	..	Prisms (CH_3OH)	32
Isodihydrovomicine	185	..	Crystals (CH_3OH)	32
Isovomicidine	290 (dec)	..	Tetrahedra (C_2H_5OH)	34
$C_{22}H_{32}O_2N_2$(reduction)	245	..	Crystals (C_2H_5OH)	36a
Isovomicine	256	+260.3°($CHCl_3$)	Yellow needles (acetone)	32, 36a
$C_{22}H_{30}O_2N_2$(reduction)	210	..	Crystals (C_2H_5OH)	34
$C_{22}H_{25}O_3N_2I$	223 (dec)	..	Crystals (C_2H_5OH)	34
Benzal-	225	..	Yellow needles (C_2H_5OH–H_2O)	36a
Acetyl-	193	+216.5°($CHCl_3$)	Plates (C_2H_5OH)	36a, 34
Diacetyl-	173	..	..	34
Isovomicinic Acid	239	..	Needles	34
		M		
N-Methylbisdehydrovomicinic Acid	290 (dec)	..	Needles (C_2H_5OH–H_2O)	13
Dimethyl ester dihydrochloride	>320	..	Needles (HCl–H_2O)	13
Methyldesoxyvomicine	221	+99.6° ($CHCl_3$)	Needles (C_2H_5OH)	29
Methiodide	248 (dec)	..	Needles (CH_3OH)	29
Methylvomicidine-I	230 (dec)	..	Leaflets (ether–acetone)	35
Methylvomicine	232.5	+156.5°	Prisms ($CHCl_3$–C_2H_5OH)	35, 29

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Demethylated ($OCH_3 \rightarrow OH$)	272	..	Prisms (C_2H_5OH)	35, 29
Methiodide	215	..	Needles (H_2O)	35
Benzal-	208–210	..	Yellow plates	35
Benzoyl-	244	..	Leaflets (ethyl acetate	35
Hydrochloride	308 (dec)	..	Leaflets (H_2O)	29
Hydroperchlorate	>300	..	Colorless needles	29
Methiodide	244–245 (dec)	..	Yellow prisms(H_2O)	29
Methylvomicine-II	240	+126°	Leaflets (C_2H_5OH)	35
Methiodide	206 (dec)	..	Leaflets (H_2O)	35
N-Methylvomicinic Acid	255 (dec)	+207°(C_2H_5OH)	Needles (C_2H_5OH–H_2O)	13, 8
Hydrochloride	>320	..	Needles (HCl–H_2O)	8
Methyl ester	262–266 (dec)	+38.6°(C_2H_5OH)	Prisms (C_2H_5OH)	13
O-Methylnorvomicinic Methyl Ester	194	..	Needles (CH_3OH)	22
		N		
Neodesoxyvomicine	312 (dec)	..	Prisms (C_2H_5OH)	34
Nitrovomicine	253 (dec)	..	Plates (C_2H_5OH)	16
Nitrate	>200	..	Leaflets	16
Norvomicinic Acid	>350	..	Leaflets(HOAc–H_2O)	22
		T		
Tetrahydrodesoxy-vomicidine-C	241 (dec)	..	Needles (ether)	36a
Tetrahydrodesoxy-vomicine-A	246–247	+210° ($CHCl_3$)	Needles (C_2H_5OH)	36, 36a
Methiodide	222 (dec)	..	Needles (CH_3OH)	36
Benzal-	247	..	Feathery crystals (C_2H_5OH)	36
Tetrahydrodesoxy-vomicine-B	185–186	+270° ($CHCl_3$)	Needles (C_2H_5OH)	36
Tetrahydrodesoxy-vomicine	215	+73° ($CHCl_3$)	Prisms (C_2H_5OH)	30
Tetrahydroisovomicine	257	..	Crystals (acetone)	36a
Acetyl-	194	..	Silky needles (C_2H_5OH)	36a
Methyl ether	198	+170° ($CHCl_3$)	Crystals (CH_3OH)	36a
Tetrahydromethyl-desoxyvomicine-I	214	..	Polyhedra(C_2H_5OH)	29
Tetrahydromethyl-desoxyvomicine-II	150	..	Woolly needles	29
Tetrahydromethyl-vomicine-II	142–144	..	Prisms (C_2H_5OH)	35
Tetrahydrovomipyrine Hydrochloride	220–221	..	Crystals (C_2H_5OH–ether)	25, 36a

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
		V		
Vomicidine	283–284	..	Plates (C_2H_5OH–H_2O)	14, 21, 25
$C_{19}H_{24}O_8N_2$(oxidation)	242	..	Polyhedra (H_2O)	21
$C_{19}H_{24}O_7N_2$(oxidation)	219–220	..	Crystals (H_2O)	25
Dimethyl ester	235–236 (dec)	..	Prisms (CH_3OH–ether)	25
Monomethyl ester-I	255 (dec)	..	Crystals (H_2O)	25
Monomethyl ester-II	276 (dec)	..	Crystals (H_2O–CH_3OH)	25
$C_{18}H_{30}O_3N_2$	197	..	Crystals (H_2O)	25
Methiodide	262	..	Crystals	25
$C_{18}H_{24}O_5N_2$	214 (froth)	..	Crystals (H_2O)	25
Methyl ester	157	..	Feathery crystals (CH_3OH–ether)	25
$C_{18}H_{24}O_3N_2$	186	..	Crystals(pet.ether)	25
$C_{18}H_{22}O_4N_2$(oxidation)	280–286 (dec)	..	Long needles (sublimation)	25
Dinitrophenyl-hydrazone	>330	..	..	25
Hydrazone	251 (froth)	..	Crystals (H_2O)	25
$C_{16}H_{26}O_2N_2$	167	..	Crystals (acetone–pet. ether)	25
$C_{16}H_{28}ON_2$ (HI.–reduction)	269 (dec)	..	Crystals (CH_3OH–ether)	33
$C_{16}H_{28}ON_2 \cdot HCl$	284 (dec)	+28° (H_2O)	..	33
$C_{16}H_{24}O_2N_2$	146	..	Crystals (ether)	25
$C_{16}H_{28}ON_2$ (cat. hydrogenation)	300 (dec)	+31° (C_2H_5OH)	Crystals (C_2H_5OH–ether)	33
$C_{16}H_{18}ON_2$ (dehydrogenation)	157	..	Crystals (acetone)	33
$C_{14}H_{20}O_4N_2$ (oxidation)	245 (dec)	..	Rods (CH_3OH–H_2O)	33
$C_{13}H_{17}N$ (dehydrogenation)	150–160/2 mm.	..	Yellow oil	25
Hydrochloride	278 (dec)	..	Crystals (C_2H_5OH)	25
Methiodide	259 (dec)	..	Crystals (CH_3OH–acetone)	25
N-Acetyl-Dimethiodide	223–225 (dec) >250	.. ..	Crystals (ether) Prisms (C_2H_5OH)	25 21
Methiodide	>300	..	Prisms (H_2O)	29
N_a-Methiodide-N_b-hydriodide	..	..	Crystals	21
Methoperchlorate	280 (dec)	..	Colorless needles	29

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Acetyl-	229–230 (dec)	..	Brown prisms (C_2H_5OH–H_2O)	21
Benzoyl-	208–209	..	Yellow needles (CH_3OH)	14
Methyl ether	296 (dec)	..	Plates ($CHCl_3$–C_2H_5OH)	21
N_a-methiodide	295 (dec)	..	Needles (C_2H_5OH–acetone)	21
N_b-methiodide	>300	..	Prisms (C_2H_5OH–H_2O)	21
Phenol betaine	246	..	Rhombohedra (C_2H_5OH–acetone)	21
Vomicine	282	+80.4° (C_2H_5OH)	Prisms (acetone)	8, 34
$C_{22}H_{25}O_3N_2Cl$ ($HCl + ZnCl_2$)	245 (dec)	..	Yellow crystals (pyridine–H_2O)	34
$C_{22}H_{23}O_9N_3$(nitration)	..	..	Crystals	16
$C_{18}H_{24}O_7N_2$(oxidation)	266–269	−80.6° (H_2O)	Crystals	15
$C_{17}H_{24}O_5N_2$	264 (dec)	..	Polyhedra (H_2O)	15
$C_{17}H_{22}O_7N_2$(oxidation)	262 (dec)	..	Needles (H_2O)	8
$C_{17}H_{22}O_5N_2$(oxidation)	307–310 (dec)	−90.6° (H_2O)	..	15, 8
Methyl ester	261–262 (dec)	..	Rods (C_2H_5OH–ether)	18
$C_{16}H_{26}O_2N_2$	201	..	Plates (H_2O)	15
Methiodide	295 (froth)	..	Rods (H_2O)	15
Benzoyl-	158	..	Needles (C_2H_5OH)	15
$C_{16}H_{22}O_3N_2$(oxidation)	302–310 (dec)	−86.2° (H_2O)	Crystals (CH_3OH)	15
$C_{16}H_{20}O_3N_2$(oxidation)	304 (dec)	..	Rhombs (H_2O)	8
$C_{15}H_{20}O_4N_2$	264–266	−51.3° ($CHCl_3$)	Prisms (C_2H_5OH–ether)	30
Hydrochloride	245 (dec)	..	Rods (H_2O)	8
Methiodide	220	..	Prisms (H_2O)	29, 8
Methobromide	221	..	Needles (C_2H_5OH)	29
Methochloride	265 (dec)	..	Prisms (H_2O)	29
Methoperchlorate	>315 (dec)	..	Long rods	29
Methosulfate	272 (dec)	..	Needles (H_2O)	29
Methyl betaine	224	..	Leaflets (CH_3OH–H_2O)	29
Benzal-	280 (dec)	..	Yellow leaflets (C_2H_5OH–$CHCl_3$)	13
Isonitroso-	..	..	Yellow prisms ($CHCl_3$–C_2H_5OH)	22
$C_{22}H_{21}O_4N_3$ (carbamic lactone)	218	..	Prisms (C_2H_5OH)	22
Acetyl-	204–205	..	Needles (C_2H_5OH)	34
Benzoyl-	182	..	Needles (C_2H_5OH)	8

TABLE 3 (*Continued*)

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
Vomicinic Acid	282	..	Needles (C_2H_5OH)	8
N-Nitroso-	190 (dec)	..	Yellow prisms (H_2O)	13
Vomipyrine	105–106	..	Crystals (pet. ether)	25, 33, 36a
Hydrochloride	..	..	Yellow crystals (C_2H_5OH–ether)	25

TABLE 4

α- AND β-COLUBRINE AND THEIR DERIVATIVES

Compound	M.p. or b.p. °C.	$[\alpha]_D$	Crystal form	References
α-Colubridine	..	..	..	233
β-Colubridine	..	..	..	233
α-Colubrine	184	−76.5° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	189
Hydrochloride	..	−3.1° (C_2H_5OH)	Leaflets (H_2O)	189
Sulfate	..	..	Leaflets (H_2O)	189
β-Colubrine	222	−107.7° (C_2H_5OH)	Crystals (C_2H_5OH–H_2O)	189
Hydrochloride	..	−32.7° (H_2O)	Leaflets	189
Sulfate	..	..	Prisms	189

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Author Index*

*Numbers in parentheses are reference numbers and are included to assist in locating references where the author's name is not mentioned in the text. Numbers in italics refer to the page of the article on which the reference is listed.

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Subject Index*

* Botanical names are printed in italics. Prefixes such as *nor-*, *iso-*, *proto-*, *apo-*, are set in italics and disregarded for indexing purposes.

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