Manske & Holmes, The Alkaloids, Volume III (1953)

CHAPTER 22

β-Phenethylamines

L. RETI

I. Introduction

After the determination of the structure of the adrenaline molecule (Friedmann, 1904) and the discovery of tyramine in putrified meat and ergot (1) much interest was aroused in compounds of similar chemical constitution. Shortly afterwards, Barger and Dale (2) examined pharmacologically a large series of amines, structurally related to adrenaline and tyramine.

The basic skeleton of the adrenaline molecule is that of a β-phenethylamine. In 1910, when Barger and coworkers made their first studies, only three naturally occurring compounds of this type were

known: adrenaline, tyramine, and hordenine. Since then several other β-phenethylamines have been identified as constituents of plants of widely separated botanical families. It is a remarkable coincidence that the majority of the newly-found natural phenethylamines had already been studied by Barger and Dale (phenethylamine, *N*-methylphenethylamine, *N*-methyltyramine, candicine, oxytyramine, coryneine, halostachine, noradrenaline).

Interest in natural and synthetic phenethylamines mounted when Späth in 1919 (3) recognized the β-phenethylamine skeleton in mescaline, the hallucinatory principle of the "peyote." Peyote has been recently discussed in newspapers and current magazines in connection with the campaign against narcotics. An interesting statement has been made by La Barre *et al.* (174) against the inclusion of peyote in the list of narcotics. It is partially transcribed as follows:

"In connection with the campaign against narcotics, there has been some propaganda to declare illegal the peyote used by many Indian tribes. The authors, professional anthropologists, protest against this campaign. Peyote is not a narcotic. It does not excite, stupefy, or produce muscular incoordination; there is no hangover; and the habitual user does not develop any increased tolerance or dependence. As for the immorality that is supposed to accompany its use, the charge is also completely invalid. Actually Peyotism is a religion, incorporated under the name of "The Native American Church of the United States." Its modern form, developed about 1870, is Christianity adapted to traditional Indian beliefs and practices . . . is a legitimate religious organization deserving of the same right to religious freedom as other Churches; also that peyote is used sacramentally in a manner corresponding to the bread and wine of white Christians."

There is little doubt that other β-phenethylamines will be found to be primary plant constituents and their structures can even be predicted based on the regularity with which the substituents appear to occur in the already known natural compounds. A "missing link" has been recently discovered by Kirkwood and Marion (4) in certain strains of barley. The newly found *N*-methyltyramine completes the series which begins with tyramine and terminates in the quaternary cactus alkaloid candicine.

It would appear as though the natural phenethylamines were connected with some general biochemical mechanism, which is not even limited to plants alone. Even adrenaline, this typical animal hormone may be expected to occur in plants: its chemical skeleton is already represented in halostachine (side chain) and in oxytyramine and coryneine (3:4 position of the hydroxyls). The occurrence of adrenaline (5%) in the skin secretion of a number of tropical and subtropical toads may be mentioned (5).

II. Biosynthesis

There is a general agreement that the natural phenethylamines are biogenetically linked to the naturally occurring aromatic amino acids, such as phenylalanine, tyrosine, *N*-methyltyrosine and 3:4 dihydroxyphenylalanine (dopa). This derivation involves only very simple and biologically plausible reactions, such as decarboxylation, oxidation, and *O*- and *N*-methylation.

The biological formation of simple and more complex natural amines is thoroughly discussed in Guggenheim's fundamental treatise (6).

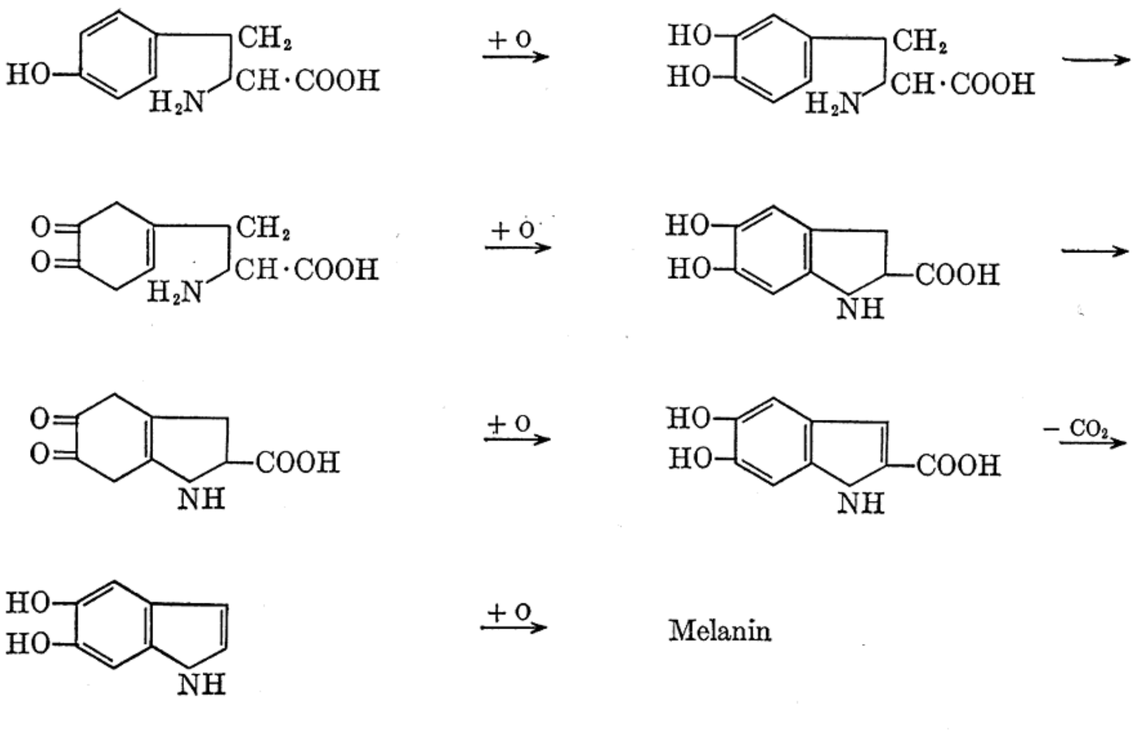
Naturally occurring β-phenethylamines may have been formed by biological decarboxylation of the protein amino acids, phenylalanine, and tyrosine. For the di- and trihydroxy derivatives the corresponding substituted phenylalanines should be considered, although 3:4-dihydroxyphenylalanine (dopa) does not seem to occur in proteins while the trihydroxy derivative has yet to be found in nature. However, it is not necessary to suppose that alkaloids are formed directly from the amino acids of proteins. Several workers, especially Guggenheim, suggest the possibility that both amino acids and alkaloids originate from common parent substances.

The biological oxidation of phenylalanine to tyrosine and its conversion to 3:4-dihydroxy derivatives is an established fact. The direct conversion of phenylalanine to tyrosine in the animal body has been demonstrated by Moss and Schoenheimer (7), by feeding phenylalanine with deuterium in the benzene ring. According to Bernheim and Bernheim (8), this conversion can be regarded as a step in normal intermediary metabolism and is probably dependent upon a specific enzyme system.

The oxidation of tyrosine, tyramine, or *N*-methyltyramine by tyrosinase has been the subject of extended studies. The reaction sequence follows the route outlined by Raper (9, 10) and Duliére and Raper (11) as shown in the formula on page 316.

The biological conversion of phenylalanine into adrenaline in mammalian tissues (involving oxidation, decarboxylation, and methylation) is strongly supported by the work of Gurin and Delluva (12). *d,l*-Phenylalanine, labelled with ^{14}C in the carboxyl group and α-carbon, was converted to adrenaline in which the ^{14}C was located in the terminal carbon of the side chain. Similar results were obtained with tritium-labeled phenylalanine. The results suggest that this biological conversion not only involves decarboxylation of phenylalanine (or one of its derivatives) but that the aminoethyl side chain formed remains attached to the benzene nucleus during the biological synthesis.

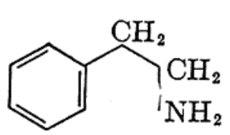
It may be assumed that the biosynthesis of β-phenethylamines in plant tissues follows a similar pattern. The general occurrence of decarboxylases, tyrosinases as well as melanization phenomena gives strong support to this hypothesis, although reliable experimental evidence, such as has been obtained in the case of animal metabolism, is not yet available.



It is interesting that the tertiary and quaternary tyramine derivatives found in the cacti, such as hordenine and candicine, although they take up appreciable amounts of oxygen, do not form pigments when oxidized by tyrosinase [Duliére and Raper (11)]. However, tyrosine or some other derivative must be present in all cacti since the darkening of cut stems, preceded by a red phase, is characteristic for the whole family. Roca (13) found tyrosine, tyrosinase, and unidentified alkaloidal substances in the Mexican cactus, *Pachycereus marginatus* Britton and Rose. Tyrosinase has been observed also in *Trichocereus candicans* Britton and Rose, which contains the alkaloids candicine and hordenine.

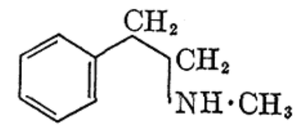
III. Chemistry of the β-Phenethylamines Found in Plants

1. β-Phenethylamine, $C_8H_{11}N$



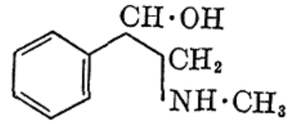
Phenethylamine, isolated in many instances from the putrefactive decomposition products of proteins (cf. Guggenheim (6)), occurs also as a primary plant constituent. The base found by Leprince (14) in mistletoe (*Viscum album* L.) was probably phenethylamine. White (15) isolated the compound from many species of acacia. It is a colorless strongly basic oil, $D^{24°} = 0.9580$; b.p. 198° (760 mm); slightly soluble in water, readily soluble in alcohol and ether. The hydrochloride has m.p. 217°; oxalate, m.p. 218°; the platinichloride crystallizes in golden leaflets from alcohol containing hydrochloric acid; insoluble in water, m.p. 253–254°; aurichloride, m.p. 98–100°; picrate, m.p. 171–174°.

2. *N*-Methyl-β-phenethylamine, $C_9H_{13}N$



N-Methyl-β-phenethylamine occurs together with dipterine (*N*-methyltryptamine) and leptocladine (3:4-dimethyl-3:4:5:6-tetrahydro-4-carboline), in the Chenopodiaceae *Arthrophytum leptocladum* Popov (16, 17). The colorless oil has b.p. 72–75° (4 mm.); hydrochloride, m.p. 161–162°, picrate 141–142° (from alcohol); picrolonate, m.p. 217–218° (from alcohol); platinichloride, m.p. 220–221°; methiodide of the methyl compound, m.p. 227–228°.

3. Halostachine (Phenethanolmethylamine), $C_9H_{13}ON$



Halostachine was discovered by Yu. I. Syrneva (18) in the Chenopodiaceae *Halostachys caspica* C. A. Mey. The erroneously assigned molecular structure, $C_6H_5{\cdot}CH(NH{\cdot}CH_3)CH_2OH$, was later corrected by G. P. Menshikov and M. N. Rubinstein (19) to $C_6H_5{\cdot}CH(OH)CH_2NH{\cdot}CH_3$.

The plant contains, according to the mentioned authors, an optically inactive amino acid, $C_5H_{11}O_2N$, and the base halostachine, $C_9H_{13}ON$. The free base melts at 43–45° and has $[\alpha]_D$ – 47.03°; the hydrochloride, m.p. 113–114, has $[\alpha]_D$ – 52.21°; *N*-methylhalostachine has b.p. 125–127° (20 mm.), $[\alpha]_D$ – 65°, it yields a methiodide, m.p. 230–231° (from alcohol).

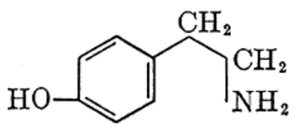
Halostachine is oxidized to benzoic acid by permanganate. It reacts with thionylchloride giving $C_6H_{12}NCl{\cdot}HCl$, m.p. 168–169° (from alcohol); *N*-methylhalostachine yields with thionylchloride $C_{10}H_{14}NCl{\cdot}HCl$, m.p. 202–203°. This compound is reduced by sodium amalgam to the base $C_{10}H_{15}N$ (identical with *N*-dimethyl-β-phenethylamine), b.p.

203–205° (picrate, from alcohol, m.p. 133–134°). Halostachine has thus the structure $C_6H_5 \cdot CH(OH)CH_2NH \cdot CH_3$.

The racemic compound has been prepared synthetically and examined by Barger and Dale (2) and later by Hyde, Browning, and Adams (20).

G. P. Menshikov and G. M. Borodina (21) synthesized both optical isomers of methylaminophenethanol and showed the identity of the *l*-form with natural halostachine. The compound, $C_6H_5 \cdot CO \cdot CH_2N \cdot CH_3(CH_2 \cdot C_6H_5)$ was reduced with hydrogen and palladium chloride, and after treatment with sodium hydroxide solution, inactive $C_6H_5CH(OH)CH_2NH \cdot CH_3$ was obtained. The racemate, m.p. 75–76° (from ether-petrol ether) was resolved with *d*- and *l*-tartaric acid to the optical antipodes. The *d*-tartrate of the *l*-base had m.p. 112–115° and $[\alpha]_D$ − 18.73°; the *l*-tartrate of the *d*-base also melted at 112–115°; $[\alpha]_D$ + 18.62°. The free bases were recovered by treatment of the tartrates with 20% sodium hydroxide and isolated as hydrochlorides; m.p. of both hydrochlorides, 113–114°; *l*-form $[\alpha]_D$ − 52.46°; *d*-form $[\alpha]_D$ + 52.78°. Mixed melting points of the derivatives of natural halostachine with the *l*-derivatives of the synthetic base showed their identity.

4. Tyramine (*p*-Hydroxy-β-phenethylamine), $C_8H_{11}ON$



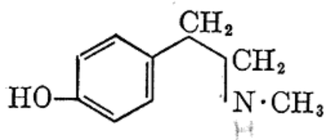
Tyramine, as a degradation product of tyrosine, appears in several metabolic and fermentation processes involving proteins. Observations of this nature are surveyed in Guggenheim's book (6). However, tyramine occurs also as an unquestionable primary constituent in plants and animals. Barger (1, 22), found small quantities of tyramine in ergot, where it is accompanied by a considerable number of other bases (see also Freudweiler (23); Funck and Finck (24). It occurs together with tyrosine in the salivary or venom glands of cephalopods (Henze (25, 26; Bottazzi (27)). Crawford and Watanabe (28, 29) found the base in several species of American mistletoes (*Phoradendron flavescens* Nutt., *Ph. villosum* Nutt., *Ph. californicum* Nutt.). The European mistletoe, *Viscum album* L., also contains tyramine, according to Ostemberg (30). Ullmann (31) found tyramine in the thistle, *Silybum marianum* Gaertn. According to Schmalfuss and Heider (32) the common broom, *Cytisus scoparius* Link. (*Sarothamnus scoparius* Koch.), contains tyramine and 3:4-dihydroxyphenethylamine.

Tyramine crystallizes from alcohol in white, hexagonal leaflets, m.p. 161°; b.p. 175–178° (8 mm.); one part is soluble at 15° in 95 parts of water and in 10 parts of hot alcohol. It is slightly soluble in amyl alcohol and much less so in ether or chloroform. The salts crystallize well: the hydrochloride, from conc. hydrochloric acid, is very soluble in water, m.p. 268–269°; picrate, m.p. 206°; dibenzoate, m.p. 174°; oxalate, m.p. 203–204°. The dicarbomethoxy derivative melts at 100.5°.

Tyramine, like other *p*-hydroxy compounds, gives a positive Millon reaction.

Barger (22) synthesized the base by reduction of *p*-hydroxyphenylacetonitrile with sodium. Barger and Walpole (33) later described two other syntheses. The *p*-hydroxy group was introduced into phenylethylamine by nitration, reduction, diazotization etc., or anisaldehyde was converted to *p*-methoxyphenylpropionamide, from which, by Hofmann degradation and demethylation, tyramine was obtained. Rosenmund (34) condensed anisaldehyde with nitromethane, and obtained tyramine by reduction followed by demethylation. Further syntheses of tyramine have been described by Kondo and Shinozaki (35), Slotta and Altner (36), Koessler and Hanke (37), Kindler and Peschke (38) and Buck (39, 40). A well known method of preparation is the thermal decarboxylation of tyrosine. Waser (41) obtained a 96% yield by heating the amino acid suspended in a high boiling solvent (fluorene).

5. *N*-Methyltyramine (β-*p*-Hydroxyphenethylmethylamine)

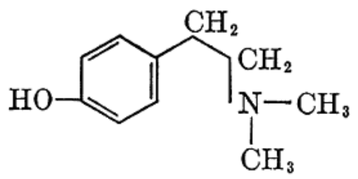


N-Methyltyramine was recently discovered by Kirkwood and Marion (4) in certain strains of barley. All attempts to isolate hordenine from these strains, which were regarded as spontaneous mutants, failed and it is presumed that they produce only *N*-methyltyramine. The base has long been known as a product of the thermal or putrefactive decarboxylation of the natural *N*-methyltyrosine, having been described at various times as surinamine, angeline, andirine, geoffroyine, and rhatanine (42–47).

The free base is only slightly soluble in water. It crystallizes well from alcohol in prisms, from benzol in leaflets, from anisole in stubby needles, m.p. 130–131°; hydrochloride, m.p. 148.5°; platinichloride, m.p. 205–206°; picrate, m.p. 149°; picrolonate, m.p. 234–235°; *N*-acetyl-*N*-methyltyramine, from *N*-methyltyramine and acetic anhydride, m.p. 143°; *O*-methylether hydrochloride, m.p. 181–182°, picrate, m.p. 112° (47a). A synthesis of *N*-methyltyramine was described by Walpole (43).

Corti (48) prepared the base by heating *N*-methyltyrosine, suspended in fluorene, at 250°. Kirkwood and Marion (4) condensed *O*-methyltyramine with benzaldehyde and treated the derived benzal derivative with dimethyl sulfate. After decomposition of the quaternary compound and hydrolysis of the *O*-methyl-*N*-methyltyramine with hydrobromic acid *N*-methyltyramine was obtained.

6. Hordenine (Anhaline, β-*p*-hydroxyphenethyldimethylamine), $C_{10}H_{15}ON$



This compound was found first in the cactacea *Anhalonium fissuratum* Engelm. (*Mammillaria fissurata* Engelm.) by Heffter (49) in 1894 and named anhaline. In 1906 Leger (50–58) isolated from barley malt germs a base that he called hordenine—a discovery made by Gaebel (59) almost simultaneously. Subsequently, it was shown by Späth (3) that anhaline is identical with hordenine. Hordenine occurs also in the seedlings of other cereals: barley, *Hordeum sativum* Pers. (*H. vulgare* L.) contains 0.17%, *Panicum miliaceum* L. 0.24% and *Sorghum vulgare* Pers. (*Andropogon sorghum* Brot.) 0.07 (Hashitani, 60, 61). Reti (62) found hordenine and candicine, the corresponding quaternary ammonium-base, in the cacti *Trichocereus candicans* and *Trichocereus lamprochlorus* Britton and Rose (63). The former may be considered the richest natural source of hordenine (0.5–5%); *Anhalonium fissuratum* contains only 0.014% hordenine (Heffter, 49). Torquati (64), Reilhes (65) and Raoul (66–75) have studied the formation of hordenine during the germination of barley. Unsprouted seeds contain no hordenine; the alkaloid content reaches a peak (0.45%) 4 days after germination and disappears again about a month later. Raoul (67, 69, 72, 73) attempted to demonstrate that hordenine is formed in the barley by decarboxylation of tyrosine and methylation of the resulting tyramine by formaldehyde.

Methods of estimation have been described by Janot and Faudemay (76), Hashitani (61), Arnolt (77), Raoul (71), Gonnard (78) and Pedinelli (79).

In the absence of other *p*-hydroxy compounds the color reaction with Millon's reagent can be used quite satisfactorily for qualitative and quantitative estimations.

Hordenine may be obtained, starting from sprouted barley, as follows:

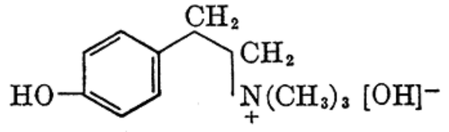
Dry seedlings are extracted with 95% ethyl alcohol and the extract concentrated to dryness. The residue is taken up in dilute sulfuric acid and the filtered solution extracted with ether. The aqueous layer is made alkaline with sodium carbonate and extracted with ether. The ether extract is dried over sodium sulfate and allowed to evaporate until hordenine crystallizes. The base may be purified by destillation under reduced pressure or by recrystallization from alcohol or ether.

Hordenine crystallizes well in colorless prisms, m.p. 117–118°; b.p. 173–174° (11 mm.); it sublimes at 140–150°; is readily soluble in water, alcohol, ether, and chloroform. It is strongly alkaline and liberates ammonia from its salts; hydrochloride, m.p. 176.5–177.5°; sulfate, m.p. 209–211°; picrate, m.p. 139–140°; picrolonate, m.p. 219–220°; methiodide, m.p. 233–234° (Kirkwood and Marion, 4); acetylhordenine hydriodide, m.p. 176–177°; reineckate, m.p. 176–178° (78); benzoylhordenine, m.p. 47–48°.

Léger (56) showed that *O*-methyl-hordenine methiodide yields *p*-vinylanisole and trimethylamine on treatment with alkali and *O*-acetylhordenine is oxidized by permanganate to *p*-acetoxybenzoic acid. Hordenine is therefore β-*p*-hydroxyphenethyldimethylamine, a structure confirmed by several syntheses.

Barger (80) starting from phenethyl alcohol, obtained phenethyl chloride, which, when heated with dimethylamine, yielded dimethylphenethylamine. By nitration, reduction, diazotization, etc. a base identical with natural hordenine was obtained. Rosenmund (81) condensed *p*-methoxybenzaldehyde with nitromethane and reduced the alkoxy nitrostyrene to *p*-methoxyphenethylamine. With methyliodide a mixture of bases was formed from which, after demethylation with boiling hydroiodic acid, hordenine was obtained in low yield. Voswinckel (82) treated *p*-methoxyphenacyl chloride with dimethylamine, then demethylated and reduced to hordenine. Ehrlich and Pistschimuka (83) started from tyrosol, $p\text{-}OH\cdot C_6H_4\cdot CH_2CH_2OH$, converted it to the chloride, which, with dimethylamine gave hordenine. Further synthesis have been elaborated by Späth and Sobel (84) and by Kindler (38). Raoul (67, 69) obtained hordenine in 50% yield, by methylating tyramine with formaldehyde and formic acid.

7. Candicine (β-*p*-hydroxyphenethyltrimethylammonium hydroxide), $C_{11}H_{19}O_2N$



The quaternary ammonium base candicine was found by Reti (62) in the Argentine cactus *Trichocereus candicans*, in *T. lamprochlorus*

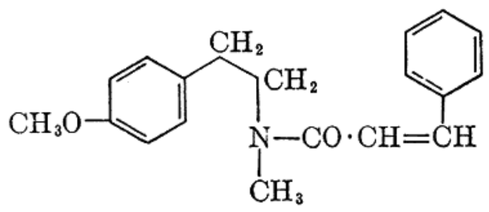
0.3 – 0.5% (Reti and Arnolt, 63), and in *T. spachianus* Riccob. (85). *T. candicans* may contain as much as 5% candicine, together with variable amounts of hordenine.

Candicine, like other quaternary compounds, cannot be extracted from alkaline solution with immiscible solvents. It was isolated by precipitating the purified plant extract with concentrated Mayer's reagent and then decomposing the precipitated mercuriiodide with hydrogen sulfide, the base being recovered in the form of its slightly soluble iodide.

It forms well-crystallized salts (Castrillón, 86). The iodide (hordenine methiodide) has m.p 234°; chloride, very hygroscopic, m.p. 285° (dec); platinichloride, m.p. 208–209°; aurichloride, m.p. 127–128; picrate, m.p. 162–163°; picrolonate, m.p. 218–219°; mercuriiodide, m.p. 190–191°.

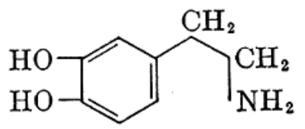
Candicine gives a red color reaction with Millon's reagent. The free base, obtained by heating a solution of the iodide with silver hydroxide, can be crystallized. Upon heating with alkali, it yields trimethylamine. *O*-Methylcandicine, under the same conditions is transformed into trimethylamine and *p*-vinylanisole. Anisic acid is obtained if *O*-methylcandicine is oxidized with permanganate.

8. *O*-Methyltyramine-*N*-methylcinnamide [*N*-(2-*p*-anisylethyl)-*N*-methylcinnamide], $C_{19}H_{21}O_2N$



La Forge and Barthel (87) isolated this compound, which melts at 76°, from the bark of the southern prickly ash, *Zanthoxylum americanum* Mill (*Z. Clava-Herculis* Lam.), where it occurs together with berberine and asarinin. It has been obtained synthetically by the same authors, by reacting *O,N*-dimethyltyramine with cinnamoyl chloride.

9. 3-Hydroxytyramine (β-3:4-dihydroxyphenethylamine), $C_8H_{11}O_2N$



Schmalfuss and Heider (32) identified the blood pressure-raising substances contained in the pod of the common broom, *Cytisus scoparius*, as tyramine and hydroxytyramine. Both may be considered as melanin

precursors. The amines were isolated with the aid of their carbomethoxy derivatives. The roots of *Hermidium alipes* S. Wats. (Nyctaginaceae) also contain hydroxytyramine, according to Buelow and Gisvold (88).

It gives the Millon test, reduces cold ammoniacal silver nitrate solution and shows characteristic color reactions with ferric chloride followed by alkalies. The following salts are known: hydrochloride, needles, very soluble in water, m.p. 241°; hydrobromide, m.p. 212°; tricarbomethoxy derivative, m.p. 92–93°; tribenzoyl derivative, m.p. 141°; picrate, m.p. 189°; styphnate, m.p. 206°.

The base can be obtained by heating 3:4-dihydroxyphenylalanine above its melting point. A synthesis starting from tyramine was described by Waser and Sommer (89): it was first nitrated to 3-nitrotyramine, reduced, and the diazo compound decomposed to 3-hydroxytyramine.

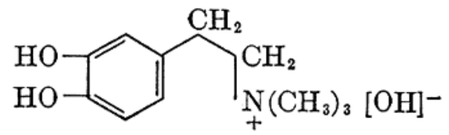
According to Holz and Credner (90) tyramine, in aqueous solution, when irradiated with ultraviolet light in the presence of air, is partly converted into 3-hydroxytyramine. The same substance results when oxygen is bubbled through a solution of tyramine and ascorbic acid. In both cases hydrogen peroxide seems to be an intermediate product.

Werle and Raub (91) observed that the seedlings of *Cytisus scoparius* are able to decarboxylate 3:4-dihydroxyphenylalanine to 3-hydroxytyramine, and Vinet (92) showed that kidney tissue, *in vitro*, can effect the same decarboxylation. Adrenal medulla converts the latter to adrenaline by methylation and oxidation, but cannot form adrenaline from dihydroxyphenylalanine or tyramine.

Some simple isoquinoline alkaloids (carnegine, salsoline, corypalline, hydrohydrastinine) may be considered as bio-products of the interaction of hydroxytyramine and acetaldehyde or formaldehyde, followed by methylation. Actually, Schöpf and Bayerle (93) obtained a surprisingly high yield of norcarnegine by carrying out this condensation under mild ("physiological") conditions, that is, at pH 5 and 25°.

The hydroxytyramine nucleus is chiefly involved in melanin formation (8, 9, 10, 11).

10. Coryneine (3-hydroxycandicine, β-3:4-dihydroxyphenethyltrimethylammonium hydroxide), $C_{11}H_{19}O_3N$



This quaternary base was isolated by Reti, Arnolt, and Ludueña (94) from *Stetsonia coryne* (Salm-Dyck) Britton and Rose, one of the

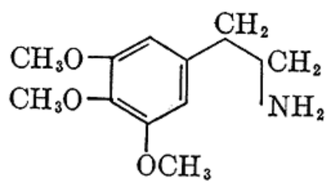
most striking tree-like cacti, which often forms the dominant feature of the landscape on the high plains of northern Argentina.

The base was extracted following the method used for isolating candicine. Special precautions had to be taken to avoid degradation of this sensitive catechol compound. The dry plant contains approximately 1% of this alkaloid.

Coryneine forms a crystalline chloride, $C_{11}H_{18}O_2NCl$, m.p. 201°. Three *N*-methyl groups are present in the molecule but *O*-methyl is absent. By *O*-methylation and subsequent permanganate, oxidation veratric acid is formed. Coryneine salts give the characteristic color reactions of catechol derivatives (ferric chloride and alkalies).

Barger and Ewins (95) prepared synthetic β-3:4 dihydroxyphenethyltrimethylammonium chloride and Barger and Dale (2) studied its pharmacological action. The two cactus alkaloids, coryneine and candicine, are interesting examples of substances found in nature long after they had been synthesized in the laboratory.

11. Mescaline (β-3:4:5-trimethoxyphenethylamine), $C_{11}H_{17}O_3N$



Mescaline, the active hallucinatory principle of the "mescal buttons" or "pellote," was isolated by Heffter (96) in 1896. Pellote (*Anhalonium lewinii* Hennings) contains up to 6% mescaline. Reti (97, 98) observed the presence of mescaline in the Argentine cactus *Trichocereus terscheckii*, Britton and Rose, which contains 0.2% trichocereine (dimethylmescaline) and 0.05% mescaline. Herrero-Ducloux (99) has assumed that one of the bases extracted from *Echinocactus gibbosus* D.C., (*Gymnocalycium gibbosum* Pfeiff.) was mescaline.

Microchemical reactions of mescaline have been described by Rosenthaler (100), Herrero-Ducloux (101), and Bolland (102).

The free base is a colorless strongly alkaline oil or crystals having m.p. 35–36° (Kindler and Peschke, 103), b.p. 180° (12 mm.). It is soluble in water, alcohol, and chloroform, but only slightly so in ether. It readily absorbs carbon dioxide from the air forming the solid carbonate. The sulfate $(C_{11}H_{17}O_3N)_2 \cdot H_2SO_4 \cdot 2H_2O$ is particularly suited for isolation since it is insoluble in alcohol, only slightly soluble in cold water but very soluble in hot water; it forms brilliant prisms, m.p. 183–186°. The hydrochloride forms colorless crystals, m.p. 184°; picrate, m.p. 222°; the aurichloride crystallizes with 1 H_2O, orange needles, m.p. 140–141°; platinichloride, straw-yellow needles, m.p. 187–188°; benzoyl derivative, m.p. 123°; *m*-nitrobenzoyl derivative, m.p. 161–162°; dimethylmescaline methiodide, m.p. 226–228°.

Heffter (104, 105, 106) determined the empirical formula of mescaline and found that upon oxidation the base yields trimethylgallic acid. Unfortunately, mescaline behaves in methylimino determinations as though it contained an *N*-methyl group. Heffter (107) synthesized 3:4:5-trimethoxybenzylmethylamine and found that it was not identical but isomeric with mescaline.

The irregularity mentioned was confirmed by Späth (3) who, guided by biogenetical considerations, arrived at the correct structure, in spite of the confusing analytical evidence. In Späth's mescaline synthesis 3:4:5-trimethoxybenzoyl chloride was reduced by the Rosenmund method (108) to the corresponding aldehyde, wihich when condensed with nitromethane yielded ω-nitro-3:4:5-trimethoxystyrene. This was reduced with zinc dust and acetic acid to the corresponding oxime and the latter was further reduced, by sodium amalgam, to β-3:4:5-trimethoxyphenethylamine, i.e., mescaline. Subsequently a number of improved syntheses have been reported.

Slotta and Heller (109, 110) prepared their starting material, viz., trimethoxyphenylpropionic acid by condensation of the substituted benzaldehyde with malonic acid and reduction of the resulting cinnamic acid. Mescaline was then obtained by Hofmann degradation of the trimethoxyphenlypropionamide. Kindler and Peschke (103) synthesized very pure, crystallized mescaline by condensation of 3:4:5-trimethoxybenzaldehyde with potassium cyanide, acetylation, and catalytic reduction to the amine. Slotta and Szyska (111, 112) improved Späth's first synthesis, obtaining mescaline directly by the electrolytic reduction of ω-nitrotrimethoxystyrene. Hahn and Wassmuth (113, 114) started from elemicine and first prepared trimethoxyphenylacetaldehyde by ozonization. The oxime was then reduced to mescaline. Kindler (115) and Kindler and Peschke (38, 103) improved the catalytic reduction of ω-nitrostyrenes to the corresponding phenethylamines. Hahn and Rumpf (116) described the preparation of mescaline by reduction of ω-nitrotrimethoxystyrene with Adam's catalyst. A review has been published by Jensch (117).

Several isomers of mescaline as well as mescaline-like compounds have been synthesized by Jansen (118–120); Slotta and Heller (110); Slotta and Szyska (111, 112); Slotta and Müller (121); Grace (122); Iwamoto and Hartung (123), and Hey (124). None of these compounds cause the euphoric state produced by mescaline.

a. Synthesis of Mescaline According to Kindler and Peschke (103)

i. 3:4:5-Trimethoxyacetylmandelonitrile. Twenty grams 3:4:5-trimethoxybenzaldehyde, prepared according to Slotta and Heller (110), is mixed with 40 cc. of saturated sodium bisulfite solution. The separated bisulfite compound in a slurry with water is treated with a solution of 9.5 g. of potassium cyanide in 20 cc. water. The resulting nitrile is filtered, washed first with bisulfite solution then with water, and finally dried on a porous plate.

The mandelonitrile is acetylated by boiling for 1 hour with 100 cc. of acetic anhydride. The excess anhydride is distilled, the residue is dissolved in ether, and the solution washed successively with sodium carbonate solution, with bisulfite solution, and with water. The residue from the dried ether solution distils at 163–165° (0.1 mm.); yield, 82% based on the 3:4:5-trimethoxybenzaldehyde.

ii. Mescaline. Twenty-two grams of 3:4:5-trimethoxyacetylmandelonitrile is dissolved in 200 cc. glacial acetic acid and the solution dropped into a suspension of 3 g. palladium black in 75 cc. acetic acid and 5 cc. concentrated sulfuric acid (for apparatus see *Arch. Pharm.* **1931,** 74). The introduction is made with agitation, at 18°, and under a hydrogen pressure of 2 atm. In 2½ hours, 95% of the calculated amount of hydrogen is absorbed. An amount of potassium carbonate equivalent to the sulfuric acid is added, the acetic acid is eliminated *in vacuo*, and the residue dissolved in water. The aqueous solution is washed twice with ether, treated with excess potassium hydroxide, and the separated mescaline taken up in ether. The residue from the ether extract distils at 173° (10 mm.) and solidifies to white crystals, m.p. 35–36°.

b. Synthesis of Mescaline, According to Slotta and Syszka (111)

i. 3:4:5-Trimethoxybenzoyl Chloride. Five hundred grams of 3:4:5-trimethoxybenzoic acid (cf. Gilman-Blatt, "Organic Syntheses," John Wiley & Sons, New York 1941, Collective Volume I, 537) is added to 285 cc. of thionyl chloride freshly distilled over linseed oil and the mixture is heated for 2 hours on a water bath. The still-hot mixture is then distilled under reduced pressure from a Claisen-flask, avoiding rubber stoppers. There is obtained 510 g. (93% of theory) of trimethoxybenzoyl chloride boiling at 185° (18 mm.).

ii. 3:4:5-Trimethoxybenzaldehyde. To a solution of 200 g. of 3:4:5-trimethoxybenzoyl chloride in 1000 cc. of xylene freshly distilled over sodium, there is added 60 g. of a 5% palladium-barium sulfate catalyst. The mixture is heated in an oil bath maintained at 150° and a vigorous stream of hydrogen is introduced into the boiling solution. The hydrogen should be washed with aqueous permanganate and then dried with sulfuric acid. After 60–80 hours the reaction is complete. The solution is filtered and the aldehyde conveniently isolated as its bisulfite compound. Yield 120 g. (70.6% of theory), m.p. 74°.

iii. 3:4:5-Trimethoxy-ω-nitrostyrene. A solution of 40 cc. of nitromethane and 100 g. of trimethoxybenzaldehyde in 200 cc. alcohol is cooled to 0° and while it is stirred mechanically there is introduced a solution of 45 g. pure potassium hydroxide in 45 cc. water and 90 cc. methanol at the rate of about one drop per second, care being taken that the temperature does not rise. Fifteen minutes after the addition is completed the solution is poured into 500 cc. concentrated hydrochloric acid mixed with sufficient ice to assure its presence throughout the slow addition and to maintain a temperature of −10°. The precipitated nitrostyrene is separated by filtration and washing and may be purified by recrystallizing from 700 cc. alcohol. The pale

yellow plates which melt at 120–121° are obtained in a yield of approximately 78% of theory.

iv. Mescaline. (A) APPARATUS (Fig. 1). A cell of porous porcelain (PC) (external dimensions: 75 × 160) with a glazed rim is placed in a glass jar of 500 cc. capacity

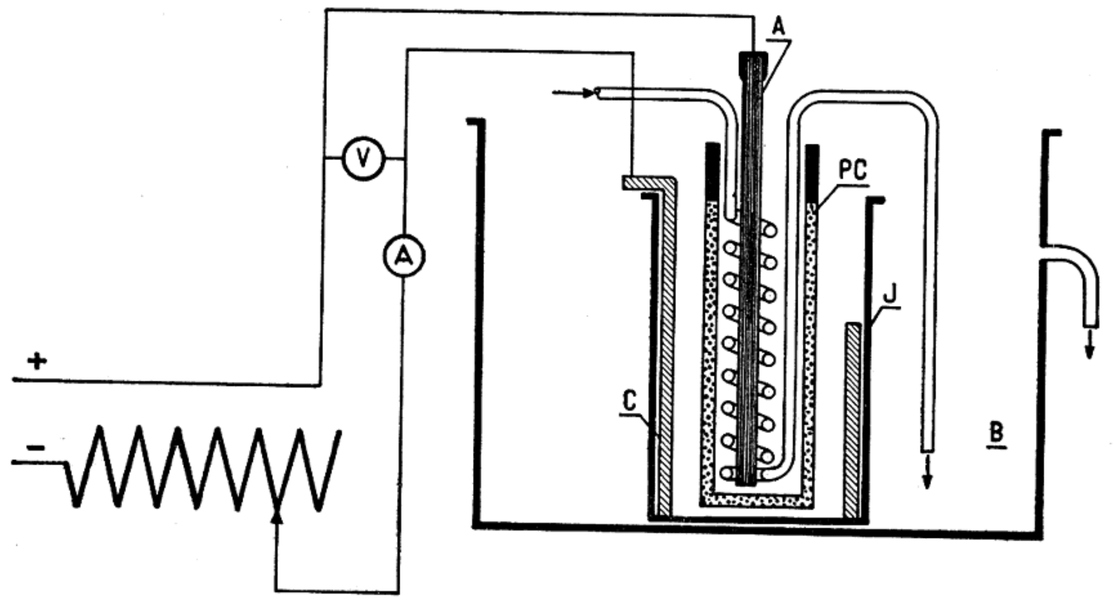


FIG. 1

(J), surrounded by a cooling bath (B). The anode (A) is a lead or carbon rod, surrounded by a glass coil; the cooling water flows through the coil and discharges into the cooling bath. The cathode (C) is a sheet of lead (220 × 90 × 2 mm.), which previous to each experiment is electrolytically coated with lead peroxide, in a bath of dilute sulfuric acid.

(B) REDUCTION. The cathode liquor consists of a solution of 30 g. 3:4:5-trimethoxy-ω-nitrostyrene in 100 cc. glacial acetic acid and 100 cc. alcohol, to which 50 cc. conc. hydrochloric acid has been added. The anodic compartment is filled, to the same level occupied by the catholyte, with a solution of 25 cc. conc. sulfuric acid in 175 cc. water.

The reduction requires 12 hours, using a current of 5–6 amperes; the cathode current density should be about 3 amperes per square centimeter. The temperature is regulated by the flow of the cooling water and the catholyte should be kept at 20° for the first six hours; the temperature is then allowed to rise until it reaches 40° at the end of the reduction.

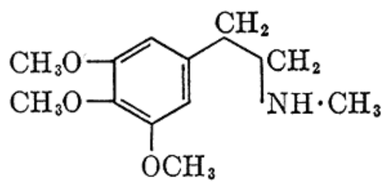
When the reduction is complete, the catholyte is filtered, evaporated in vacuum and the residue taken up in 300 cc. water. Unreduced nitrostyrene is extracted successively with ethyl acetate and with ether. The crude mescaline hydrochloride solution in a separatory funnel is then treated with a cold concentrated solution of 100 g. of sodium hydroxide and the liberated base exhaustively extracted with ether. The somewhat concentrated and dried (potassium carbonate) solution is treated with a stream of dry hydrogen chloride and the separated hydrochloride twice recrystallized from absolute alcohol. The pure mescaline hydrochloride thus obtained in 77% yield forms white leaflets melting at 184°.

An improved synthesis of mescaline has been described by Benington and Morin (175). 3,4,5-Trimethoxy-β-nitrostyrene (176) was reduced

with lithium aluminum hydride, using a method described by Ramirez and Burger (177). The yield was of 86%.

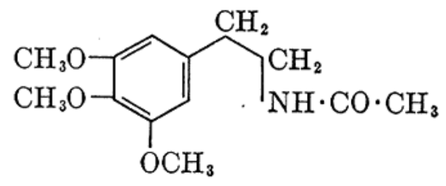
A new synthesis of mescaline has been recently elaborated by Tsao (178). The synthesis is outlined as follows: gallic acid → 3,4,5-trimethoxybenzoic acid → methyl ester of the 3,4,5-trimethoxybenzoic acid → 3,4,5-trimethoxybenzyl alcohol → 3,4,5-trimethoxybenzyl chloride → 3,4,5-trimethoxyphenylacetonitrile → mescaline. The reduction of the methyl ester and of the nitrile has been achieved using lithium aluminum hydride.

12. *N*-Methylmescaline, $C_{12}H_{19}O_3N$



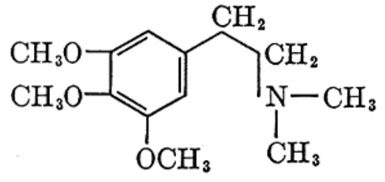
N-Methylmescaline was isolated by Späth and Bruck (125) from the mother liquors from the crystallization of the nonphenolic bases of "mescal-buttons." The identity of this base was established by comparison with synthetic *N*-methylmescaline which was obtained by the condensation of mescaline with benzaldehyde, followed by methylation of the benzal derivative with methyliodide, and hydrolysis of the quaternary base; picrate, m.p. 177.5–178°; trinitro-*m*-cresolate, m.p. 189.5–190.5; *p*-nitrobenzoyl derivative, m.p. 142–143°.

13. *N*-Acetylmescaline, $C_{13}H_{19}O_3N$



Späth and Bruck (126) detected *N*-acetylmescaline in "mescal buttons"; m.p. 93–94°. It is identical with *N*-acetylmescaline prepared by heating mescaline with acetic acid at 170–175°.

14. Trichocereine (*N*,*N*-dimethylmescaline), $C_{13}H_{21}O_3N$



Trichocereine, together with mescaline, was found by Reti (97) in the Argentine giant cactus *Trichocereus terscheckii*. A further study and

the synthesis of the alkaloid was achieved by Reti and Castrillón (98). The dried plant contains 0.25 to 1.2% alkaloids. The ratio of trichocereine to mescaline was found to be 5:1, but in some lots, with high alkaloidal content, no mescaline could be detected. This is the first case where mescaline, the active principle of the "mescal buttons" (*Anhalonium lewinii*), has been found in a second species.

Trichocereine can be separated from mescaline by extraction with ether, in which the latter is only slightly soluble.

Trichocereine is a colorless basic oil; it distils *in vacuo* without decomposition and is soluble in water, alcohol, ether, and chloroform. The salts crystallize well; hydrochloride (from alcohol), m.p. 205°; picrate (from acetone), yellow needles, m.p. 171–172°; picrolonate (from alcohol-acetone), yellow prisms, m.p. 166°. If the melted salt is heated again, it melts at 175°. The platinichloride crystallizes from water and melts at 184–185°; aurichloride, m.p. 136–139 (with decomp.); methiodide, m.p. 226–228°; picrate of the quaternary *N*-methyl trichocereine (from water), m.p. 165°.

Trichocereine contains three methoxyl and two *N*-methyl groups. Upon oxidation with permanganate trimethylgallic acid is obtained. Trichocereine methiodide is identical with the methiodide obtained by exhaustive methylation of mescaline and trichocereine is therefore *N*-dimethylmescaline.

The alkaloid has been synthesized by reacting β-3:4:5-trimethoxyphenethylchloride with dimethylamine.

IV. Pharmacology of the β-Phenethylamines

1. Sympathomimetic Amines

The elucidation of the structure of adrenaline was the stimulus that started Barger and Dale on their classical studies, published in 1910 (2). They examined the adrenaline-like effect of a large number of compounds, and they found, on the whole, that approximation to adrenaline in the chemical structure is linked with an increase and a sharper specificity of the action. Barger and Dale introduced the term "sympathomimetic," which means that the effects produced resemble those obtained by stimulation of the so-called sympathetic system of nerves. The study of the sympathomimetic amines represents one of the earliest and most successful attempts to correlate pharmacological action with chemical structure. The sympathomimetic action includes rise of arterial blood pressure, stimulation of the heart muscle, constriction of the arterioles and either stimulation or inhibition of smooth muscle. Some of the drugs also stimulate the central nervous system.

The literature on sympathomimetic compounds is extensive and only some of the several excellent surveys such as Guggenheim's book (6), Beyer (127) and the 1945 Symposium in Industrial and Engineering Chemistry (128) can be mentioned.

According to Barger and Dale, the relative effects of some β-phenethylamines on blood pressure in decerebrated cats (isoamylamine = 1) are:

β-Phenethylamine	2–3
β-Phenethylmethylamine	2–3
Phenethanolmethylamine (racemic halostachine)	2–3
Tyramine	10
N-Methyltyramine	10
Hydroxytyramine	20
N-Methylhydroxytyramine (Epinine)	100
Noradrenaline	1000
l-Adrenaline	1077

The sympathomimetic action of natural and synthetic hydroxytyramine has been studied by Raymond-Hamet (129).

2. Halostachine

The pharmacological action of the natural alkaloid is similar to that of ephedrine (18). The racemic synthetic compound had already been examined by Barger and Dale. Hyde, Browning, and Adams prepared a series of homologues of *d,l*-ephedrine, in which the alkyl group on the β-carbon was replaced by H, ethyl, and *n*-propyl. The only homologue that gave a dependable increase in blood pressure was the α-phenyl-β-methylaminoethanol, i.e., racemic halostachine (20).

3. Hordenine

The pharmacological action of anhaline (hordenine) was first described by Heffter (49). In frogs it causes paralysis of the central nervous system without previous excitation. Camus (130–133) reported that the compound is slightly antiseptic; it also has an inhibitory effect on some soluble ferments. In mammals it shows relatively low toxicity. Small doses have no effect on the circulation of the blood; larger ones raise the blood pressure and accelerate the pulse; in very large doses hordenine causes death by arrest of respiration.

Rietschel (134, 135) found that the pressor effect is not of central origin and that hordenine stimulates the heart muscle. Although much less active than adrenaline, it is analogous in its action, resembling ephedrine rather than adrenaline. According to Raymond-Hamet (136–138) and Ludueña (139), hordenine displays a nicotine-like action.

In large doses it decreases or reverses the hypertensive effect of adrenaline (Raymond-Hamet, 140).

4. Candicine

This alkaloid was first examined by Barger and Dale (2), and its pharmacological properties were thoroughly studied by Lewis and Ludueña (141, 142) as well as by Ludueña (139, 143–147).

Candicine displays a nicotine-like action on the visceral nervous system, first stimulating and then blocking the ganglionic synapse. It has no muscarine-like effect. In the dog, intravenous injection provokes hypertension owing to vasoconstriction due to stimulation of vasoconstrictor nerves and secretion of adrenaline from the adrenal gland. The adrenaline secretory effect is not modified significantly by yohimbine, cocaine, or atropine. Sparteine and tetrapropylammonium iodide completely counteract this effect. Large doses (6 mg./kg.) of candicine have a curare-like action in the dog; this effect has also been observed in the toad, *Bufo arenarum*. The LD50 is 5 mg. per 100 g. for the rat, death occurring owing to respiratory paralysis.

5. Coryneine

Coryneine had already been examined by Barger and Dale (1); further data were given by Reti, Arnolt, and Ludueña (94). The action is very similar to, but more intense than that of candicine.

6. Mescaline

The sliced and dried heads of the cactus, *Anhalonium lewinii* (*Lophophora williamsii*) have long been used as an intoxicant by the natives of Mexico and the southwestern part of the United States. Interest in the cactus alkaloids arose when the remarkable use by the Indian tribes and the strange pharmacological properties of this little plant became known.

The chroniclers of the Spanish conquest of Mexico are the first who mention this drug and describe its use and properties. Bernardino de Sahagun, a Franciscan monk and missionary, writes as follows in his "Historia General de las Cosas de Nueva Espana" (the manuscript, dated 1560, was only printed in 1829): "There is another plant like earth nopal, called peyote; it is white, grows in the Northern parts, and produces in those who eat or drink it terrible or ludicrous visions; the inebriation lasts for two or three days and then disappears. The Chichimecas eat it commonly, it gives them strength and incites them to battle, alleviates fear, and they feel neither hunger nor thirst, and they say it protects them from every kind of danger."

This first reference to peyote summarizes in a remarkable manner all our knowledge on the nature of this astonishing drug. Sahagun also points out accurately the botanical nature of the plant which is a "tuna de la tierra," i.e., a cactus. The word "tuna," of Mexican origin, is used in Spanish America to indicate cacti only. The use of the "satanic plant" called peyote is mentioned by Cárdenas, Francisco Hernández, and several other chroniclers of the Spanish conquest. The use and cult of the peyote remained alive among the Indian tribes of the area mentioned in spite of church and state prohibitions. Merchants in Indian territories call it mescal or mescal buttons, the Mexicans on the Río Grande, pellote, peyote or peyotl. Petrullo reported (148) that in 1918 a numerous sect, restricted to Indians, was founded in Oklahoma. It was called the "Peyote-Church" and joined in a strange synthesis of old Mexican, Christian, and local religious rites.

Further details and bibliography on the uses and religious cult of the peyote will be found in Lewin (149–152), Mooney (153), Diguet (154), Lumholtz (155), Newberne and Burke (156), and especially in the books by Rouhier (157) and Beringer (158).

Up to 1886 nothing was known of the nature and character of the "mescal buttons." At that time Louis Lewin, travelling in America, came to know the plant and obtained specimens that he examined. Hennings recognized it as a new species of *Anhalonium* and named the plant *Anhalonium lewinii*. Lewin's examination showed that the drug contained alkaloids, and a crystallized base, anhalonine, was isolated. However, anhalonine is not responsible for the sensory excitation caused by peyote. Lewin's discovery raised considerable interest in the pharmacological effect of the drug and in the chemical compounds that account for it. This interest was extended to the whole family of the Cactaceae, which, until then, had been considered as being free of alkaloids.

The most striking physiological effect of the pellote is the production of *visual color hallucination*. According to Heffter (105), among the pellote alkaloids only mescaline is responsible for these symptoms although Lewin (150) attributes a certain hallucinatory power to anhalonidine. Taking into account the high percentage of isoquinoline bases in pellote and their strong toxicity, the effects of intoxication by pellote are evidently not identical with those produced by the administration of pure mescaline. Nevertheless, in both cases, the visual hallucinations, described by different observers are of a similar nature.

Pellote inebriation has been described by numerous authors such as Prentiss and Morgan (159, 160), Heffter (105), Weir (161), Havelock (162), Rouhier (157), Hobschette (163), and others. The action of pure mescaline salts was reported by Dixon (164), Buchanan (165), Foerster

(166), Beringer (158), Marinesco (167), etc. In Beringer's book (158) numerous cases are reported and a full bibliography is given.

Marinesco (168) has also published an interesting study in which the impressions of two artists during mescaline intoxication are described, and six colored plates, painted during the effect of the drug, are reproduced.

Color visions were provoked by doses of 0.36–0.44 g. of mescaline sulfate distributed in several subcutaneous injections. The state of intoxication and the visions lasted for 5 to 10 hours. The effects varied widely in different individuals. The most characteristic symptom is that of wonderful visual color hallucinations. Clear consciousness is generally preserved and the subject is fully aware of his condition. Sensory illusions and transposition of sensorial excitation are the interesting factors in this inebriation. Ordinary objects appear to be marvelous. Sounds and music are "seen" in color. In comparison, the impressions of everyday life seem pale and inert. Color symphonies and new, unknown colors of unimaginable beauty and brilliancy are perceived. Euphoria is not always present. Hallucinations of hearing, taste, or other senses were reported more rarely. Bradycardia, nausea, a feeling of oppression in the chest, faintness, and headache may also occur.

The interest in these remarkable properties of mescaline has led to the synthesis of numerous similar compounds (p. 325). However, the slightest structural changes destroy the typical effects of mescaline. Until now no natural or synthetic compound with the pharmacological properties of mescaline has been found.

In the frog, mescaline causes narcotic effects (dose, 15 to 30 mg.). In rats the lethal dose is 20 mg./100 g. (Ludueña). Rabbits are extraordinarily resistant to mescaline (Slotta and Müller, 121); injection of even 0.1–0.25 g. of the hydrochloride per kilo body weight causes no visible symptoms. Dogs and particularly cats are more sensitive. A dog after having received a dose of 0.2 g. of mescaline hydrochloride showed the following strange behavior: the dog started to whine and bark, not at the observer but towards the opposite side of the cage; when called, it turned and wagged its tail.

Raymond-Hamet (169, 170) found that small doses of mescaline do not have any effect on the blood pressure of dogs while larger ones (20 mg./kg.) caused hypotension. Mescaline is antagonistic to the pressor action of adrenaline and the subsequent vagal effect. Slotta and Müller (121) observed that 40 to 50% of the mescaline fed to rabbits is excreted in form of trimethoxyphenylacetic acid; the latter is not found in human urine after the administration of mescaline. According to Richter (171) mescaline is excreted by humans unchanged, at least to a high extent (recovery, 58%). Bernheim and Bernheim (172) studied the mecha-

nism of mescaline oxidation in the rabbit. Grace (122) observed that intravenously injected mescaline produces respiratory depression and fall in blood pressure in anesthesized cats and dogs. It stimulates the contractions of the intestine and uterus *in situ* but not that of the isolated organs.

7. Trichocereine

Trichocereine was first examined by Ludueña (173). The lethal dose in the rat is approximately 22 mg. of hydrochloride per 100 g. weight. In this animal trichocereine causes excitation, tremor convulsions, paralysis of the extremities, and respiratory paralysis. In dogs large doses provoke a fall in blood pressure. Ingestion of 0.55 g. had no apparent effect in a self experiment of Ludueña, particularly no effect of a sensory nature.

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