THE ALKALOIDS

Edited by
ARNOLD BROSSI

VOLUME 26

THE ALKALOIDS

Chemistry and Pharmacology

Volume 26

This Page Intentionally Left Blank

THE ALKALOIDS

Chemistry and Pharmacology

Edited by
Arnold Brossi
National Institutes of Health
Bethesda, Maryland

VOLUME 26

1985

ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers

Orlando • San Diego • New York • Austin
London • Montreal • Sydney • Tokyo • Toronto

ACADEMIC PRESS, INC.
Orlando, Florida 32887

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
24–28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 50-5522

ISBN: 0-12-469526-4

PRINTED IN THE UNITED STATES OF AMERICA

85 86 87 88 9 8 7 6 5 4 3 2 1

CONTENTS

Chapter 4. Benzophenanthridine Alkaloids

V. ŠIMÁNEK

Chapter 5. Lycopodium Alkaloids

D. B. MACLEAN

Chapter 6. Peptide Alkaloids

ULRICH SCHMIDT, ALBRECHT LIEBERKNECHT, AND ERNST HASLINGER

Chapter 7. Pyrrolizidine Alkaloids

JERZY T. WRÓBEL

This Page Intentionally Left Blank

CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

JOHN A. FINDLAY (89), Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick, Canada E3B 6E2

ERNST HASLINGER (299), Institute for Organic Chemistry, University of Vienna, A 1090 Vienna, Austria

HENRI-PHILIPPE HUSSON (1), Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France

ALBRECHT LIEBERKNECHT (299), Institute for Organic Chemistry, Biochemistry and Isotope Research, University of Stuttgart, 7000 Stuttgart 80, West Germany

D. B. MACLEAN (241), Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1

ULRICH SCHMIDT (299), Institute for Organic Chemistry, Biochemistry and Isotope Research, University of Stuttgart, 7000 Stuttgart 80, West Germany

V. ŠIMÁNEK (185), Institute of Chemistry, Palacký University,775 15 Olomouc, Czechoslavakia

GEORGE M. STRUNZ (89), Maritimes Forest Research Centre, Canadian Forestry Service, Fredericton, New Brunswick, Canada E3B 5P7

JERZY T. WRÓBEL (53, 327), Department of Chemistry, University of Warsaw, Warsaw 02-093, Poland

This Page Intentionally Left Blank

PREFACE

The chapter "Simple Indole Alkaloids Including β-Carbolines and Carbazoles" updates chemistry of naturally occurring indoles and tricyclic analogs containing an indole moiety, earlier discussed in Vols. 8, 10, and 13. The review on "Sulfur-Containing Alkaloids" does not include Nuphar alkaloids, which were discussed in Vols. 9 and 16 and which will be covered separately in a future volume. The chapter "Pyridine and Piperidine Alkaloids," long overdue, updates occurrence, chemistry, and pharmacology of natural heterocyclic bases, reviewed in Vol. 11 under "Pyridine Alkaloids." "Benzophenanthridine Alkaloids," mentioned in Vol. 17 under "Papaveraceae Alkaloids II," are presented in this volume as a separate group of alkaloids; the antitumor activity of representative congeners was also assessed in Vol. 25, "Antitumor Alkaloids." "Lycopodium Alkaloids," representing a large group of classical alkaloids, were discussed in Vols. 5, 7, 10, and 14, and are here again brought to the latest state of the art. "Peptide Alkaloids," reviewed in Vol. 15, now also include linear representatives from marine sponges. Although "Pyrrolizidine Alkaloids," discussed in Vols. 6 and 12 under the heading "Senecio Alkaloids," are well-known and notorious toxins to livestock, some representative *N*-oxides mentioned in Vol. 25, "Antitumor Alkaloids," seem to have antitumor properties; this important group of alkaloids is therefore updated.

Arnold Brossi

This Page Intentionally Left Blank

— CHAPTER 1 —

SIMPLE INDOLE ALKALOIDS INCLUDING β-CARBOLINES AND CARBAZOLES

HENRI-PHILIPPE HUSSON

Institut de Chimie des Substances Naturelles
Centre National de la Recherche Scientifique
Gif-sur-Yvette, France

I. Introduction

This chapter will deal with the origins and chemistry of "Simple Indole Alkaloids," i.e., those alkaloids that are either derived by functionalization of the indole nucleus itself or are formed from tryptophan (or tryptamine) but do not contain an isoprenoid precursor.

This review will thus be limited to simple alkylindoles and to certain tricyclic compounds containing an indole ring such as the carbazole and the simple β-

THE ALKALOIDS, VOL. 26

carboline alkaloids. A review on the carbazole alkaloids appeared in Volume 13 of this series (*1*) and another was published more recently (*2*). The β-carbolines have also been previously reviewed, the literature being covered up to 1978 (*3*). The biologically important mammalian β-carbolines are included in Volume 21 of this series (*4*). This report is therefore a complement to previous studies on these two latter classes of alkaloids. Alkaloids from marine organisms are not included and are covered in Volume 24 of *The Alkaloids*.

II. Occurrence

Apart from the Rutaceae, which appears to be the only family of higher plants known to biosynthesize the carbazole nucleus, the other indole alkaloids described here have a widespread taxonomic distribution. There are two principal reasons for this: (1) the alkaloids as defined in this study display considerable structural diversity and (2) they are formed from simple ubiquitous precursors that do not undergo further condensation with elaborated precursors as, e.g., monoterpenoid indole alkaloids. Except for carbazoles, their occurrence is thus of limited taxonomic interest.

The nontryptamine alkaloids are found in microorganisms, mushrooms, or plants, whereas nonisoprenoid tryptamine alkaloids are mainly produced in plants belonging to more than 20 botanical families. The most representative are the Cruciferae, Elaeagnaceae, Gramineae, Leguminosae, and Passifloraceae.

The alkaloids are listed in Tables I through V with species of botanical or microorganism origin and references. For β-carbolines already reviewed (*3*), only the new alkaloids or natural sources discovered since 1979 are presented.

III. Nontryptamine Alkaloids

A. Simple Alkylindoles

Very few simple alkylindoles have been reported. The three indole alcohols (**1,2,** and **3**) (Scheme 1) were extracted from *Balansia epichloë* Weese (*8*) and were shown to be responsible for the toxicity observed in cattle grazing on grasses infected with this microorganism (Clavicipitaceous). Confirmation of the structures of **2** and **3** was achieved by synthesis from indole and glyceraldehyde.

Isoprenylindoles were found in different species of the family Annonaceae, which usually contain more complicated alkaloids of the benzyl–isoquinoline–aporphine series.

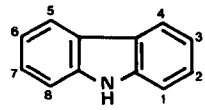
The monosubstituted isoprenylindoles (**4–6**) and the 3,6-bis(γ,γ-dimethylallyl) alkaloid **7** (Scheme 1) are the first naturally occurring indoles of this type (*9–11*), although similar derivatives of other heterocycles are often found in plants.

Synthesis of **4** has recently been achieved (*23*). A Wittig reaction of 6-for-

TABLE I
OCCURRENCE OF SIMPLE INDOLE ALKALOIDS

Compound	Number	Source	Reference
Indole derivatives			
Indole			
3-Formyl		*Murraya exotica*, barley malt, tomato	*5,6*
3-Acetic acid		Barley malt, tomato	*6*
3-Acetic acid myoinositol ester		*Oriza sativa, Zea mays*	*7*
3-(1′,2′,3′-Trihydroxypropyl)	**2**	*Balansia epichloë* Weese	*8*
3-(2′,3′,4′-Trihydroxybutyl)	**1**	*B. epichloë*	*8*
3,3-(2′,3′-Dihydroxypropyl) Diindole	**3**	*B. epichloë*	*8*
6-(3′-Methylbuta-1′,3′-dienyl)	**4**	*Monodora tenuifolia* Benth.	*9*
6-(γ,γ-Dimethylallyl)	**5**	*Riccardia sinuata* (Hook) Trev.	*10*
7-(γ,γ-Dimethylallyl)	**6**	*R. sinuata*	*10*
3,6-Bis(γ,γ-dimethylallyl)	**7**	*Uvaria elliotiana* Engl. et Diels	*11*
Di-β-indolylmethyleneindolenine		*Saccharomyces cerevisiae*	*12*
(−)-Indolmycin	**8**	*Streptomyces griseus* *S. hygroscopicus*	*13,14*
Neosidomycin	**13**	*S. hygroscopicus*	*15*
Chuangxinmycin	**15**	*Actinoplanes tsinanensis*	*16*
Oxindole derivatives			
3-(3′-Methyl-2′-butenyliden)-2-indolinone	**30**	*Cimifuga dahurica* Maxim	*17,18*
Isatine derivatives			
4-(5′-Phenylpentyl)-6,7-dimethoxy (melosatin A)	**33**	*Melochia tomentosa* L.	*19,20*
4-(5′-Phenylpentyl) (melosatin B)	**34**	*M. tomentosa*	*19,20*
4-(5′-Phenylpentyl)-7-methoxy (melosatin C)	**35**	*M. tomentosa*	*19,20*
Gramine derivatives			
3-Aminomethylindole		Barley malt	*6*
3-Methylaminomethylindole		Barley malt	*6*
3-Dimethylaminomethylindole (gramine)		Barley malt	*6*
1,5-Dimethoxygramine	**47b**	*Gymnacranthera paniculata* A. D.C.	*21*
Gramodendrine	**48**	*Lupinus arbustus* ssp. *calcaratus*	*22*

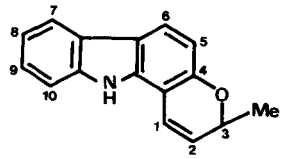
TABLE II
OCCURRENCE OF TRICYCLIC CARBAZOLE ALKALOIDS



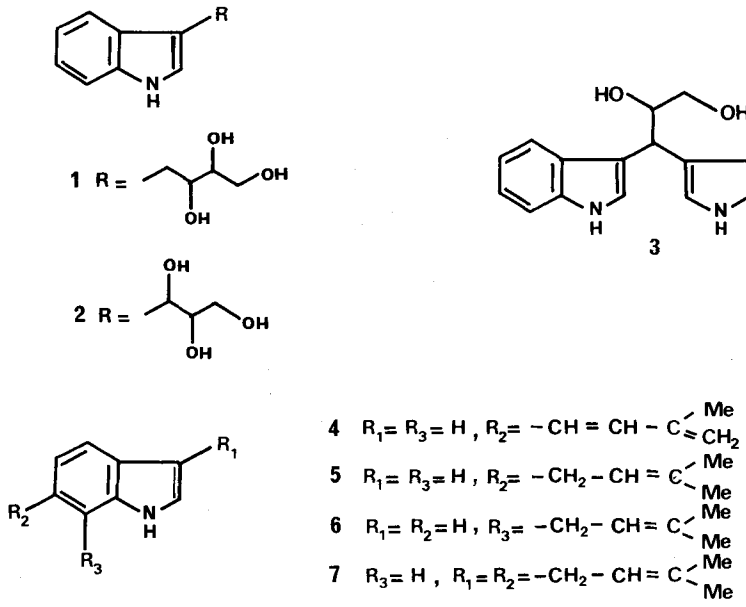
Compound	Number	Source	Reference
1,2-Dimethyl-3,4-dimethoxy (carbazomycin A)	**50**	*Streptomyces* sp.	*37*
1,2-Dimethyl-3-methoxy-4-hydroxy (carbazomycin B)	**51**	*Streptomyces* sp.	*37*
1-Methoxy-3-formyl (murrayanine)		*Murraya koeniggi* Spreng. *Clausena heptaphylla* Wt. et Arn.	*40* *41,42*
1-Methoxy-3-carboxylic acid (mukoeic acid)		*M. koenigii*	*43*
1-Methoxy-3-methoxycarbonyl (mukonine)		*M. koenigii*	*44*
1-Methoxy-2-isopentenyl-3-formyl (indizoline)	**54**	*Clausena indica* Oliv.	*45*
1-Isopentenyl-2-hydroxy-3-formyl (heptaphylline)	**55**	*C. heptaphylla* *C. excavata* Burm. f.	*46,47*
1-Isopentenyl-2-hydroxy-3-formyl-6-methoxy (6-methoxyheptaphylline)	**69**	*C. indica*	*45,48,49*
1-Isopentenyl-2,8-dihydroxy-3-formyl (8-hydroxyheptaphylline = heptazoline)		*C. heptaphylla*	*50,61*
1-Geranyl-2-hydroxy-3-methyl (mahanimbinol)	**56**	*M. koenigii*	*51*
2-Hydroxy-3-methoxycarbonyl (mukonidine)		*M. koenigii*	*52*
2,6-Dimethoxy-3-methyl (glycozolidine)	**73**	*Glycosmis pentaphylla* (Retz.) D.C.	*53*
2-Hydroxy-3-formyl-6-methoxy (lansine)	**57**	*Clausena lansium* (Lour.) Skeels	*48,49*
2-Hydroxy-3-formyl-7-isopentenyl (clausanitin)	**58**	*Clausena anisata* Willd.	*54*
2-Methoxy-3-formyl-8-isopentenyl (atanisatin)	**59**	*C. anisata*	*54*
3-Methyl		*C. heptaphylla* *C. indica*	*41,42* *45*
3-Methyl-6-hydroxy (glycozolinine)	**72**	*G. pentaphylla*	*55*
3-Methyl-6-methoxy (glycozoline)	**71**	*G. pentaphylla*	*56,57*

TABLE III

OCCURRENCE OF TETRACYCLIC CARBAZOLE ALKALOIDS (PYRANOCARBAZOLES)



Compound	Number	Source	Reference
3,5-Dimethyl (girinimbine)		*Murraya koenigii*	*58,70*
		Clausena heptaphylla	*58,59,60*
3-Methyl-5-formyl (murrayacine)		*M. koenigii*	*59,60*
3,5-Dimethyl-8-hydroxy (koenine)		*M. koenigii*	*61*
3,5-Dimethyl-8-methoxy (koenimbine)		*M. koenigii*	*62,64*
3,5-Dimethyl-8-methoxy-9-hydroxy (koenigine)		*M. koenigii*	*63,64*
3,5-Dimethyl-8-9-dimethoxy (koenimbidine = koenigicine = koenidine)	**83**	*M. koenigii*	*64*
3,8-Dimethyl-5-methoxy (heptazolidine)		*C. heptaphylla*	*65*
3,5-Dimethyl-10-methoxy (mupamine)	**74**	*C. anisata*	*66*
3-Isohexenyl-5-formyl (murrayacinine)	**75**	*M. koenigii*	*67*
3-Isohexenyl-5-methyl (mahanimbine)	**76**	*M. koenigii*	*62,64*
		M. exotica L. (syn. *M. paniculata* L. Jack.)	*78*
3-Isohexenyl-8-methyl (isomahanimbine = mahanimbicine)		*M. koenigii*	*64*
3-Isohexenyl-5-methyl-9-hydroxy (mahanine)		*M. koenigii*	*63*
3-(4′-Hydroxy-4′-methylpentyl)-5-methyl (mahanimbinine)		*M. koenigii*	*68*
3-(3′-Hydroxy-4′-methyl-4′-penten) (mahanimboline)	**77**	*M. koenigii*	*69*



SCHEME 1

mylindole and 2-methylallylphosphorane yielded a mixture of *Z* and *E* isomers (**4**).

B. (−)-INDOLMYCIN

The antibiotic indolmycin (**8**, $C_{14}H_{15}N_3O_2$, mp 213°C) is elaborated by strains of *Strepotomyces griseus* (formerly classified *S. albus*) and *S. hygroscopicus* (*13,14*). The structure and the relative configuration of this molecule were deter-

TABLE IV
OCCURRENCE OF PENTA- AND HEXACYCLIC CARBAZOLE ALKALOIDS

Compound	Number	Source	Reference
Murrayazolidine (= currayanine = cyclomahanimbine)	**84**	*Murraya koenigii*	*75,76* *84*
Bicyclomahanimbine	**85**	Artefact (?) from *M. koenigii*	*75*
Bicyclomahanimbicine	**86**	*M. koenigii*	*65,77*
Exozoline	**91**	*M. exotica* L.	*78,79*
Murrayazoline (= curryangine = mahanimbidine)	**87**	*M. koenigii*	*78,80*
Isomurrayazoline	**88**	*M. koenigii*	*81*

TABLE V
OCCURRENCE OF NONISOPRENOID TRYPTAMINE ALKALOIDS

Compound	Number	Source	Reference
(−)-Tryptophan derivatives			
N(*b*)-Trimethyl (L-hypaphorine)	**92**	*Erythrina hypaphorus*	*89*
		Pterocarpus officinalis	*89*
N(*b*)-Acetyl		*Claviceps purpurea*	*90*
Methyl ester			
N(*b*)-Methyl		*Aotus subglauca*	*91*
		Gastrolobium callistachys	*141*
N(*b*)-Dimethyl		*Abrus precatorius*	*92*
N(*b*)-Trimethyl		*A. precatorius*	*92*
Indoleacetamide		Chinese cabbage	*93*
1-Methoxyindoleacetonitrile		Chinese cabbage	*93*
4-Methoxyindoleacetonitrile		Chinese cabbage	*93*
Tryptamine derivatives			
Tryptamine		*Desmodium tilaefolium*	*94*
		Prosopis nigra (Gris.) Hieron	*95*
		Tachigalia paniculata	*96*
N(*b*)-Methyl		*T. paniculata*	*96*
		Acacia simplicifolia	*97*
		Nectandra megapotamica (Sprg.)	*98*
N(*b*)-Methyl-*N*(*b*)-formyl		*A. simplicifolia*	*97*
N(*b*)-Dimethyl		*A. simplicifolia*	*97*
		Desmodium candatum D.C.	*99*
		Desmodium gyrans	*100*
N(*b*)-Dimethyl-*N*(*b*) oxide		*D. gyrans*	*100*
N(*b*)-Dimethyl-1-methoxy (lespedamine)	**93**	*Lespedeza bicolor* var. japonica	*101*
N(*b*)-Acetyl		*P. nigra*	*95*
N(*b*)-Benzoyl		*Myrtopsis myrtoidea*	*102*
N(*b*)-*p*-Coumaryl	**109**	*Zea mays*	*103*
		Cinnamosma madagascariensis	*104*
N(*b*)-Ferulyl	**110**	*C. madagascariensis*	*104*
N(*b*)-Aminoethylthiazole carboxamide	**111**	*Thermoactinomyces* strain TM-64	*105*
4-hydroxytryptamine			
N(*b*)-Methyl-*O*-phosphate (baeocystin)		*Psylocybe semilanceata*	*108*
N(*b*)-Dimethyl (psilocin)		*Psylocybe* sp.	*106*
O-dihydrogen phosphate		*P. argentipes*	*106*
(psilocybin)		*Gymnopilus* sp.	*107,111*
		Psathyrella candolleana	*107*
		Agrocybe farinacea	*107*
		P. semilanceata	*108*

(*continued*)

TABLE V (*Continued*)

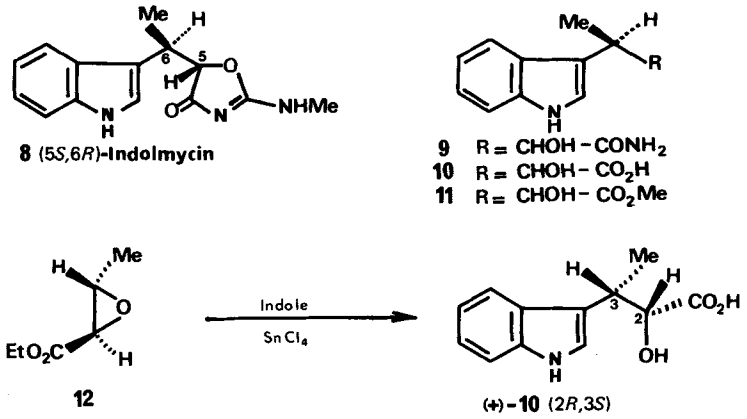
Compound	Number	Source	Reference
5-Hydroxytryptamine		Barley malt, tomato	*6*
		Peganum harmala	*109*
N(*b*)-Methyl		Barley malt	*6*
N(*b*)-Dimethyl (bufotenine)	**118**	*D. gyrans*	*100*
		D. candatum	*99*
Bufotenine *N*-oxide		*D. candatum*	*99*
O-Methylbufotenine		*Dutaillyea oreophila*	*110*
		D. drupacea	*110*
6-Hydroxytryptamine		*P. harmala*	*109*
		Shepherdia sp.	*112*
Glucosinolates			
3-Indolylmethyl (glucobrassicin)	**121**	*Isatis tinctoria* L.	*113*
		Brassica olearacea L.	*118*
1-Methoxy-3-indolylmethyl (neoglucobrassicin)	**122**	*I. tinctoria*	*114*
		B. olearacea	*118*
1-Sulfo-3-indolylmethyl	**123**	*I. tinctoria*	*115*
4-Hydroxy-3-indolylmethyl	**124**	*B. olearacea*	*116*
		B. napus	*116*
4-Methoxy-3-indolylmethyl	**125**	Brussels sprouts	*117*
β-Oxotryptamine			
34 N	**127**	*Streptomyces ramulosus*	*119*
34 M	**126**	*S. ramulosus*	*119*
Indolyloxazole			
Pimprinine	**129**	*Streptomyces pimprina*	*120*
		Streptoverticillium olivoreticuli	*121*
Pimprinethine	**130**	*S. olivoreticuli*	*121*
		Streptomyces cinnamomeus	*122*
Pimprinaphine	**131**	*S. olivoreticuli*	*121*
Oxo-2-tryptamine			
3-[2-(*trans*-Cinnamoylamino) ethyl]-3-hydroxyindolin-2-one	**138**	*Cinnamomum triplinervis*	*123*
Donaxarine	**140**	*Arundo donax*	*124*
Donaxaridine	**141**	*A. donax*	*124*
β-Carbolines			
1-Acetyl		*Picrasma quassioides* Bennet	*133*
1-Acetyl-3-methoxycarbonyl	**147**	*Vestia lycioides*	*142*
1-Acetyl-4-methoxy		*Ailanthus altissima* Swingle	*134*
1-Carbomethoxy		*A. altissima*	*135*
1-Carbamoyl		*A. altissima*	*135*
1-Propionic acid		*A. altissima*	*135*
1-Ethyl-4-methoxy (crenatine)	**170**	*Picrasma crenata* Vell.	*136*
1-Ethyl-4,8-dimethoxy		*P. quassioides*	*133*
1-(2′-Hydroxyethyl)-4-methoxy	**148**	*A. altissima*	*134*
1-(2′-methoxyethyl)-4,8-dimethyoxy	**149**	*P. quassioides*	*133*
1-(1′,2′-Dihydroxyethyl)-4-methoxy	**150**	*A. altissima*	*134*

TABLE V (*Continued*)

Compound	Number	Source	Reference
1-(1′-Hydroxy-2′-methoxyethyl)-4-methoxy 3,4-Dihydro-β-carbolines	**151**	*A. altissima*	*135*
N(*a*)-Acetyl (AV_1) 1,2,3,4-Tetrahydro-β-carbolines	**152**	*Adhatoda vasica* Nees	*137*
1-Oxo-*N*(*b*)-methyl (strychnocarpine)	**153**	*Strychnos elaeocarpa* Gilg. ex Leeuwenberg	*138*
		S. floribunda	*139*
1-Oxo-5-methoxy	**154**	*Alstonia venenata*	*140*
(+)-*N*(*b*)-Methyl-3-carboxylate	**155**	*G. callistachys*	*141*

mined by chemical correlation and synthesis (*24,25*). The UV spectrum of **8** indicated the presence of a tryptophan-like moiety. This was confirmed by alkaline hydrolysis, which afforded the amide (**9**) and the two diastereomeric hydroxy acids, (−)-α-indolmycenic and β-indolmycenic acids (**10**) (epimeric at the carbinol carbon) (Scheme 2). Indeed, indolmycin (**8**) epimerizes in alkaline medium to (+)-indolmycin. Acid hydrolysis of **8** was reported to give methylamine and an oxazolidinedione derived from hydrolysis of the methylimino group. Finally, partial synthesis of **8** was achieved on treatment of α-indolmycinic acid methyl ester (**11**) with *N,N′*-dimethylguanidine.

The absolute configuration of **8** was independently determined by two groups. A chemical correlation between indolmycenic acid and (*R*)-(−)-indole-isopro-



SCHEME 2

pionic acid led to the absolute configuration (*R*) at C-3; since the relative configurations of the indolmycenic acids had already been settled by both NMR studies and stereoselective synthesis (*26*), the absolute configuration of natural α-indolmycenic acid is (2*S*,3*R*) (*27,28*).

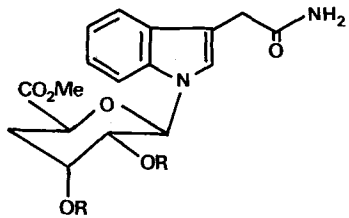
The synthesis of the enantiomer of α-indolmycenic acid (*29*) from available (−)-*trans*-2,3-epoxybutyric acid ethyl ester (**12**) and indole was achieved by the same route followed for the preparation of the racemic acid (*24*). This synthetic (+) acid **10** (Scheme 2) was chemically identical with the hydrolysis product of **8** and it has the (2*R*,3*S*) configuration. The (2*S*,3*R*) configuration in the natural (−) enantiomer was thus confirmed. Indolmycin (**8**) therefore has the (5*S*,6*R*) configuration.

The biosynthesis of indolmycin has been carefully studied (*28*) (see Section V).

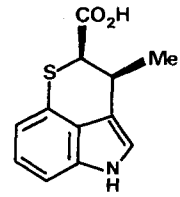
C. Neosidomycin

Neosidomycin [**13**, $C_{17}H_{20}N_2O_6 \cdot \frac{1}{2}H_2O$, $M^{+\cdot}$ 432, mp 93–103°C, $[\alpha]_D^{26}$ + 51° (MeOH)] was isolated from the fermentation of *Streptomyces hygroscopicus* (*15*). This antibiotic was only weakly active against gram-negative bacteria. Its structure is interesting because it is the only natural product having an indole *N*(*a*)-glycoside linkage. After column chromatography (silica gel, Sephadex LH 20) of a butanol extract of the culture filtrate, a colorless amorphous compound (**13**) (Scheme 3) was obtained whose UV spectrum (λ_{max} 270, 279, 298 nm) indicated the presence of an indole chromophore. The IR spectrum possessed absorptions for two carbonyl functions (1745 and 1670 cm^{-1}).

Acetylation of **13** with acetic anhydride–pyridine yielded a di-*O*-acetyl derivative (**14**) whose ^{1}H-NMR spectrum displayed signals for the *O*-acetyl groups (δ2.11, s, 3H and 1.67, s, 3H) and a methoxycarbonyl function (δ3.86, s, 3H). On hydrolysis with 1 *N* HCl, **13** afforded indole-3-acetic acid and ammonium chloride. These chemical and spectral data suggested that neosidomycin is composed of an indole-3-acetamide moiety and a deoxysugar moiety. The latter



13 R = H Neosidomycin
14 R = Ac



15 Chuangxinmycin

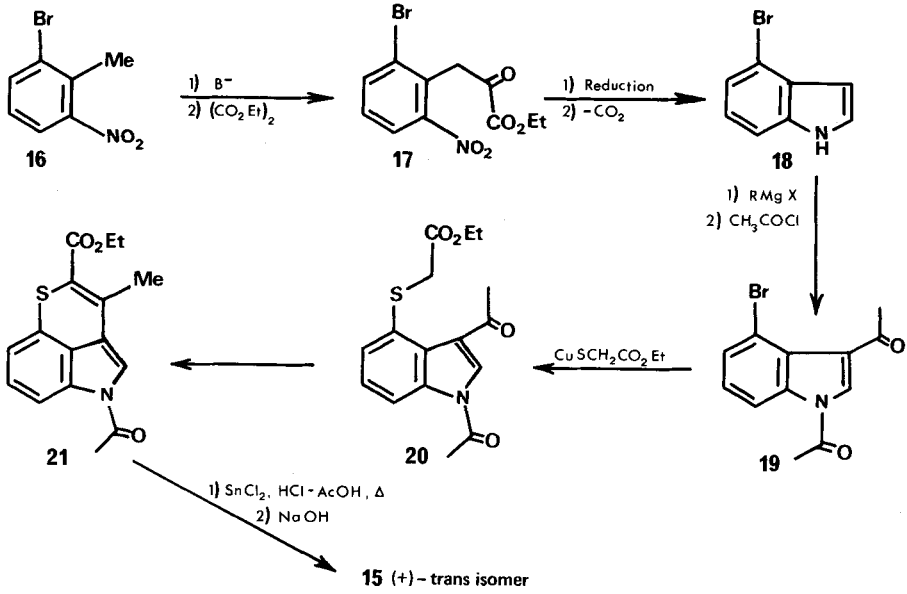
Scheme 3

component was proved to be identical with methyl-4-deoxy-D(or L)-ribohexapyranuronate as the result of a complete interpretation of its ^{1}H-NMR spectra. The position of the glycosidic linkage and its β configuration were deduced from IR, ^{1}H-, and ^{13}C-NMR data. The observation of a shielded resonance for the methyl group of one of the acetyls (δ1.67, see above) was in agreement with the proposed structure wherein the C-2 acetyl group is influenced by the anisotropic effect produced by the indole ring.

The absolute configuration of the deoxysugar moiety remains to be determined.

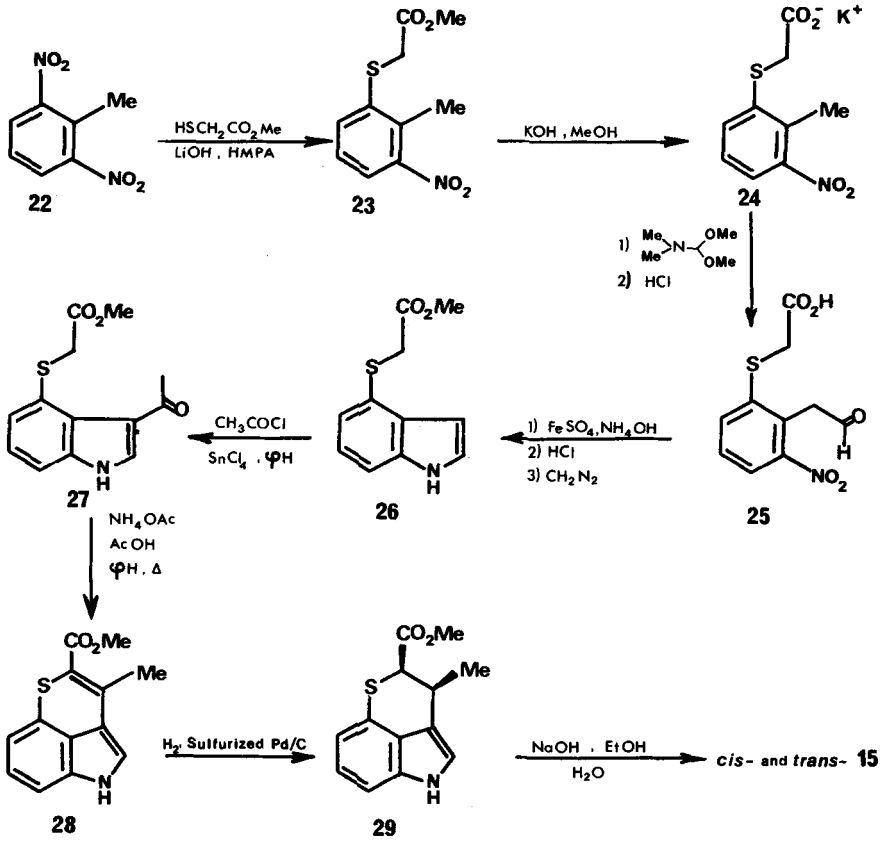
D. CHUANGXINMYCIN

Chuangxinmycin (**15**, $C_{12}H_{11}NO_2S$, $M^{+\cdot}$ 233, mp 145°C) is produced by *Actinoplanes tsinanenis*, obtained from a soil sample collected in the People's Republic of China and was studied by the Chuangxinmycin Research Group in Peking (*16*). This new type of antibiotic exhibits antimicrobial activity against a number of gram-positive and gram-negative bacteria. The interest in this alkaloid stemmed mainly from its unique structural features (Scheme 3), whose absolute configurations were not established, and from its very promising biological activities. The first synthesis of chuangxinmycin was achieved by the Chinese group (*30*). The key step of their approach (Scheme 4) was an intramolecular Knoevenagel condensation of the ethyl (3-acetyl-4-indolylthio)acetate (**20**). A



SCHEME 4

Reissert indole synthesis led to 4-bromoindole (**18**) from *o*-nitrotoluene (→ **16** → **17** → **18**). The indole Grignard of **18** reacted with acetyl chloride to give the diacetyl derivative (**19**), which was treated with the cuprous salt of ethyl thioglycolate in a mixture of quinoline and pyridine at 180°C. 1-Acetyldehydrochuangxinmycin (**21**) was obtained without isolation of the intermediate **20.** Racemic chuangxinmycin was finally obtained, accompanied by its trans isomer, on reduction with stannous chloride in acidic medium, followed by hydrolysis with sodium hydroxyde. The second synthesis (*31,32*) employed the same type of compound, namely, **27** as crucial intermediate (Scheme 5). The displacement of a nitro group in 2,6-dinitrotoluene by methyl thioglycolate in the presence of lithium hydroxyde in HMPA proved to be an efficient method to prepare **23.** The elaboration of the indole ring of **26** was based on the Leimgruber modification of the Reissert indole synthesis. The introduction of the acetyl chain was achieved



SCHEME 5

by reaction of **26** with acetyl chloride catalyzed by stannic chloride. Cyclization of **27** in refluxing benzene in the presence of ammonium acetate monohydrate and acetic acid led to the high-yield formation of **28.** Stereospecific hydrogenation of **28** (poisoned catalyst, sulfurized palladium on charcoal) furnished chuangxinmycin methyl ester (**29**). A cis relationship between the two vicinal hydrogens was rationally expected from this hydrogenation and was confirmed by observation of their small coupling constant (4 Hz) in the ^{1}H-NMR spectrum. Thus the relative configuration of chuangxinmycin (**15**) is well established. Unfortunately, hydrolysis of the methyl ester of **29** to the natural acid led to partial epimerization. However pure *cis*-chuangxinmycin (**15**) was easily obtained by crystallization.

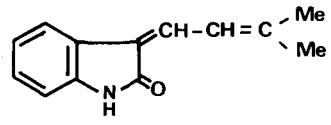
These two syntheses were based on similar strategies. The main difference is the order in which substitution of the C-3 and C-4 positions of the indole nucleus is achieved. In the former synthesis, the sulfur chain is introduced after indole ring formation and acetyl substitution. In the latter approach, the sulfur substitution takes place before the indole synthesis. The advantage of the stereospecific hydrogenation of **28** in the second synthesis was lost during the hydrogenolysis step wherein some epimerization occurred.

E. Oxindoles and Isatin Derivatives

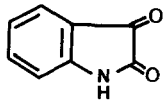
Two yellow pigments (**30** and **31**) (Scheme 6) were isolated (*17,18*) from the rhizomes of *Cimicifuga dahurica* Maxim. (Ranunculaceae). Compound **30** ($C_{13}H_{13}NO$, $M^{+\cdot}$ 199, yellow needles, mp 200–203°C) exhibited an IR spectrum suggesting the presence of an NH and lactam carbonyl groups as well as an aromatic ring. Its ^{1}H-NMR spectrum showed signals that were attributed to a 3-methyl-2-butenylidene chain. Ozonolysis of compound **30** yielded a red crystalline product whose melting point and spectral data were identical with those of isatin (**32**). Hydrogenation of **30** in the presence of PtO_2 afforded a product having a characteristic 3-methyloxindole chromophore [λ_{max} [nm (log ϵ)] = 209 (4.39), 250 (3.96), 279 (3.2)]. The ^{1}H-NMR spectrum of the hydrogenated product revealed a 3-methylbutyl side chain. Thus the structure of alkaloid **30** was determined to be 3-(3′-methyl-2′-butenyliden)-2-indolinone.

The second pigment (**31,** mp 213–214°C) proved to be a geometrical isomer of **30** since interconversion of the two compounds was readily achieved on heating with dilute alkali in ethanol. Confirmation of structures **30** and **31** was made by a partial synthesis from isatin (**32**) via a Wittig reaction. Finally, the *E* geometric configuration of **30** was determined by X-ray diffraction analysis (*18*).

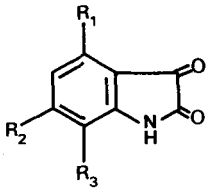
The novel alkaloids melosatin A (**33,** $C_{21}H_{23}NO_4$, $M^{+\cdot}$ 353, yellow needles, mp 119–121°C), melosatin B (**34,** $C_{19}H_{19}NO_2$, $M^{+\cdot}$ 293, amorphous) and melosatin C (**35,** $C_{20}H_{21}NO_3$, $M^{+\cdot}$ 323, red needles, mp 124–125°C) were isolated from the tumourigenic plant *Melochia tomentosa* L. (Sterculiaceae)



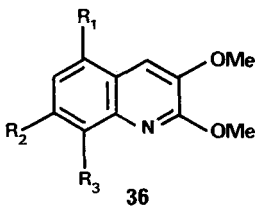
30 E isomer
31 Z isomer



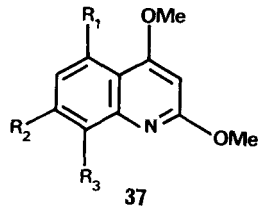
32



33 $R_1=(CH_2)_5\varphi$, $R_2=R_3=OMe$ **Melosatin A**
34 $R_1=(CH_2)_5\varphi$, $R_2=R_3=H$ **Melosatin B**
35 $R_1=(CH_2)_5\varphi$, $R_2=H$ $R_3=OMe$ **Melosatin C**



36



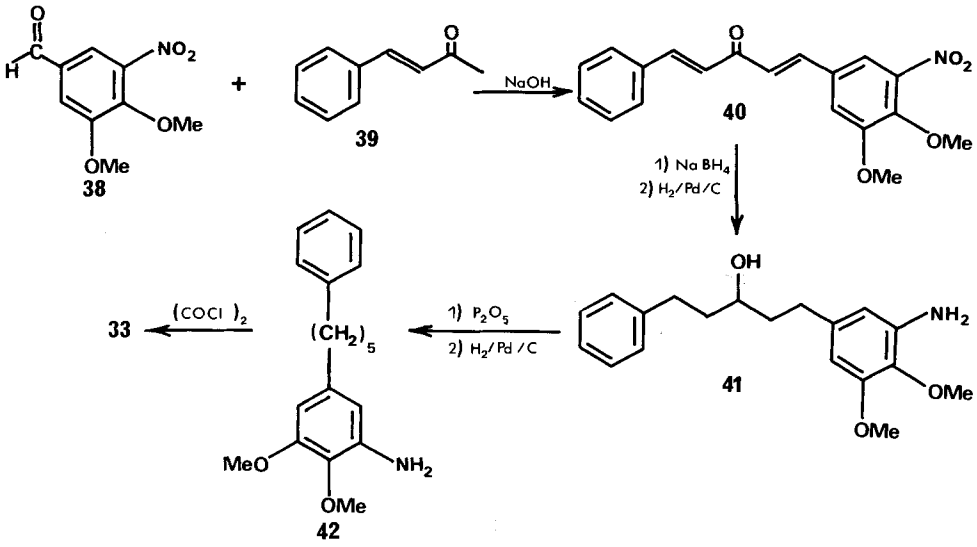
37

SCHEME 6

(*19,20*). The presence of the isatin-1,2-dicarbonyl functionality in melosatin A (**33**) was demonstrated by formation of an *O*-phenylenediamine adduct.

Furthermore, a ring expansion to quinolines **36** and **37** was observed on treatment of **33** with diazomethane (Scheme 6). This reaction was also consistent with an isatin nucleus. Examination of the ^{1}H-NMR spectrum of **34** permitted the elucidation of its basic structure. In particular, the resonances of the three vicinal protons on the isatin ring were characteristic of a C-4 alkylated isatin. However, it was impossible to assign the position of the two methoxyls of melosatin A (**33**): two isomeric substitution patterns, C-5 and C-6 or C-6 and C-7, were in accord with the ^{1}H-NMR data. Definite proof for the structure of melosatin A was obtained by its synthesis from 5-nitrovanillin (*20*) (Scheme 7). Methylation of 5-nitrovanillin with diazomethane gave the methyl ether **38,** which was condensed with benzalacetone (**39**). The resulting dibenzalacetone (**40**) was reduced to the anilino alcohol **41.** Dehydration of the alcohol function of **41,** followed by catalytic hydrogenation, yielded **42,** which was cyclized with oxalyl chloride, giving melosatin A (**33**).

Melosatin C (**35**), a closely related alkaloid, exhibited spectral data very similar to those of melosatin A and B when allowance was made for the presence of only one aromatic methoxy group. The position of this methoxy substituent



SCHEME 7

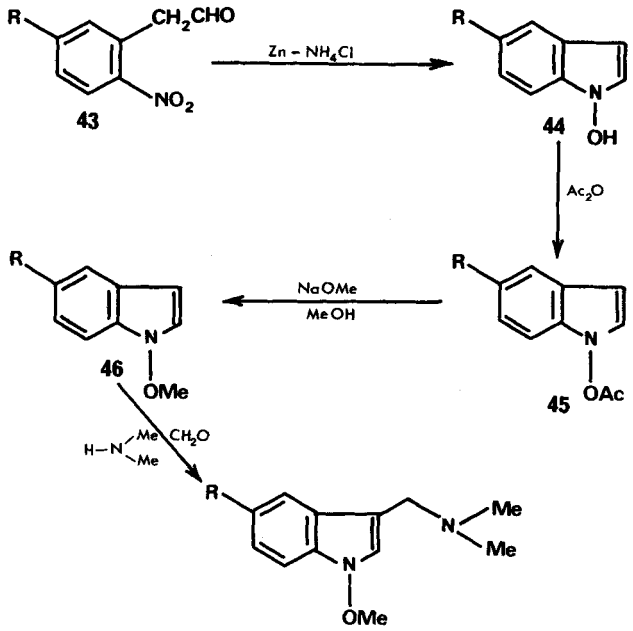
became clear only after detailed comparison of the ^{1}H-NMR spectrum of **35** with that of 4-methyl-7-methoxyisatin synthesized for this purpose. Ultraviolet and mass spectra of this series of new alkaloids as well as synthetic models have been studied in detail. It appears that these alkaloids are the first examples of naturally occurring substituted isatins.

F. GRAMINE DERIVATIVES

The simple alkaloids 3-aminomethylindole and its *N*(*b*)-methyl and *N*(*b*)-dimethyl (gramine) derivatives occur naturally in barley malt (*6*). 1,5-Dimethoxygramine (**47b**) (Scheme 8), the major alkaloid of *Gymnacranthera paniculata* (Myristicaceae) (*21*) is a member of a small group of unusual *N*(*a*)-methoxyindole alkaloids also found in the tryptamine series (see below).

The structure of **47b** was elucidated from its spectroscopic data, particularly the ^{1}H-NMR and the mass spectra. A definitive proof was provided by the hydrogenolysis of **47b** (H_2, Pd–C, ethanol) to 5-methoxygramine.

The first synthesis of 1-methoxyindoles and the corresponding gramines was reported 10 years ago (*33,34*). Partial reduction of 2-nitrophenylacetaldehyde (**43**) (Scheme 8) with Zn–NH_4 Cl (*35*) afforded 1-hydroxyindole (**44**) (in equilibrium with the tautomeric nitrone) isolated as its 1-acetoxy derivative (**45**). Treatment of **45** in methanol with sodium methoxide yielded 1-methoxyindole (**46**, R = H). 1,5-Dimethoxyindole was prepared according to the same scheme, starting from the corresponding aldehyde (**43**, R = OMe). Classical Mannich-



SCHEME 8

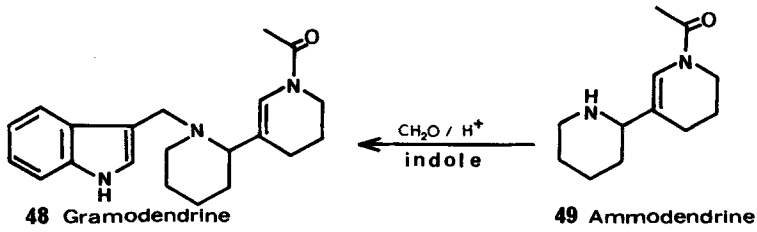
type reaction of indole (formaldehyde and dimethylamine) led to the gramines **47a** and **47b.**

Extraction of *Lupinus arbustus* (Leguminosae) (*22*) in connection with central nervous system activity studies resulted in the isolation of gramodendrine (**48**) (Scheme 9).

The mass spectrum and gas chromatography retention time of **48** were identical with those for ammodendrine [**49,** 1-acetyl-1,2,3,4-tetrahydro-5-(2′-piperidinyl)pyridine], a natural product also isolated from the genus *Lupinus* (*36*). However the NMR and IR spectra of these two alkaloids are different. These observations suggested a facile thermal decomposition of **48** to ammodendrine (**49**). Indeed, electron-impact and chemical-ionization mass spectrometry revealed a molecular weight of 337 instead of 208 as previously measured.

The presence of an indole ring in the structure of **48** was deduced from the ^{1}H-NMR spectrum (5 H between δ7.0 and 7.7 and ^{1}H exchangeable with D_2O at δ8.3). The other signals were in agreement with the presence of an ammodendrine moiety.

The molecular weight of **48** and spectral data suggested that a methylene bridge linked the two identified moieties. This latter hypothesis led to final proof



48 Gramodendrine **49** Ammodendrine

SCHEME 9

of the structure **48** by partial synthesis from ammodendrine (**49**) and indole via a Mannich-type reaction with formaldehyde (Scheme 9).

G. CARBAZOLES

The first carbazole alkaloid murrayanine was isolated from extracts of *Murraya koenigii* (Rutaceae) in 1965 by Chakraborty *et al.* (*40*). This Indian plant and related genus of the same family have since been extensively studied by Indian workers. The first review on this class of alkaloids was published in Volume 13 of this series (*1*); a second detailed study on this subject appeared in 1977 (*2*).

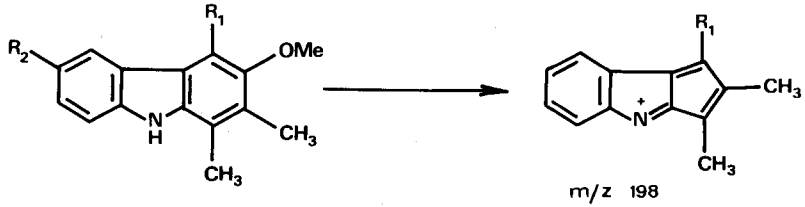
The structures of some of the previously reported alkaloids along with those recently isolated will be discussed.

Over the last 10 years a number of carbazole alkaloids have been found in marine sources (not discussed in this chapter) and microorganisms.

1. Carbazomycins A and B

Carbazomycin A (**50**, $C_{16}H_{17}NO_2$, $M^{+\cdot}$ 255, mp 51.0–52.5°C) and carbazomycin B (**51**, $C_{15}H_{15}NO_2$, $M^{+\cdot}$ 241, mp 137.5–138°C) (Scheme 10) were isolated as pale yellow substances from an unidentified Streptomyces (*37*). These alkaloids are the first known antibiotics derived from the carbazole ring system. Carbazomycin B (**51**) exhibited a more important antibiotic activity than did carbazomycin A, inhibiting the growth of phytopathogenic fungi and showing weak antibacterial properties.

The UV spectra of **50** and **51** displayed a characteristic carbazole chromophore, and inspection of the aromatic region of the ^{1}H-NMR spectrum of **51** revealed complex signals for four coupled protons and the absence of uncoupled signals (*38,39*). These observations suggested a peculiar 1,2,3,4-tetra-substituted structure. Methylation of **51** with diazomethane afforded **50**, demonstrating that carbazomycin A was the monomethyl ether of carbazomycin B. Reduction of *O*-tosylcarbazomycin B over Raney nickel led to deoxycarbazomycin B (**52**) whose UV spectrum was closely related to that of 3-methoxycarbazole and 3-meth-



50 Carbazomycin A $R_1 = OMe$, $R_2 = H$
51 Carbazomycin B $R_1 = OH$, $R_2 = H$
52 Deoxycarbazomycin $R_1 = R_2 = H$
53 O,6-diacetylcarbazomycin B $R_1 = OAc$, $R_2 = Ac$

SCHEME 10

oxy-2-methylcarbazole: λ_{max} [nm (ϵ)] = 219 (29,300), 236 (29,900), 253 (17,600), 264 (13,200), 303 (16,700), 336 (3700), and 352 (3500).

A singlet for one aromatic proton appeared at δ7.45 in the ^{1}H-NMR spectrum of **52.** An NOE of 20% was observed for this proton on irradiation of the methoxy singlet at δ3.98, demonstrating the close proximity of these two centers.

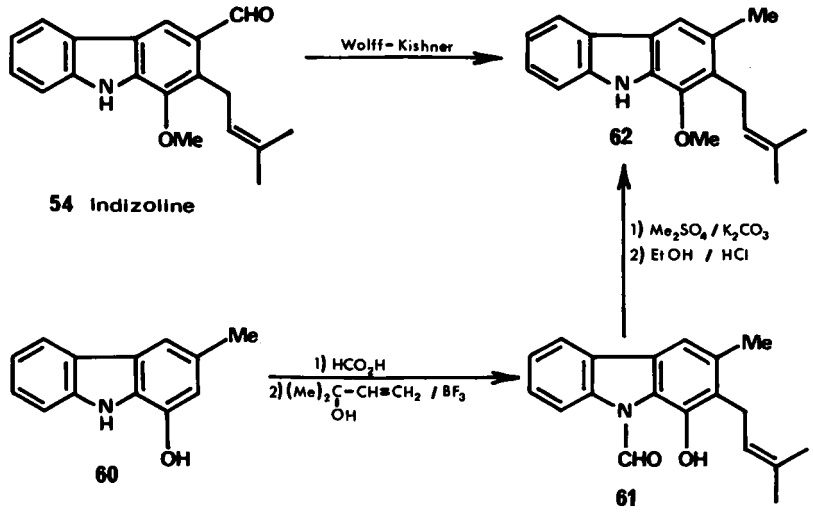
Acetylation of **51** with acetic anhydride in the presence of $ZnCl_2$ gave *O*,6-diacetylcarbazomycin B (**53**) for which an NOE ($\simeq$ 15%) between the NH proton and one of the two aromatic methyl groups was observed. The presence of a characteristic fragment at *m/z* 198 $(M - CH_3CO)^+$ in the mass spectrum of **51** indicated that the methoxy group was located at C-3 (Scheme 10). A detailed analysis of the ^{13}C-NMR spectrum of **51** showed that the four substituents were present on the same side of the molecule.

From the above results, the tentative structure **51,** containing an unprecedented substitution pattern has been assigned to carbazomycin B. Conclusive proof of the structure of carbazomycin B was provided by an X-ray analysis.

Carbazomycins A and B are unique among carbazole alkaloids in having substituents at C-1, C-2, C-3, and C-4. This structural feature at four adjacent carbon atoms is interesting from the biosynthetic point of view. Biogenetic studies have been announced (*38,39*) but not yet published.

2. Indizoline

Indizoline (**54,** $C_{19}H_{19}NO_2$, $M^+ \cdot$ 293, mp 171°C) was isolated from the roots of *Clausena indica* Oliv. (Rutaceae) (*45*). Its UV spectrum (λ_{max} 237, 247, 275, 294, and 330 nm) is similar to that for 3-formylcarbazoles with the exception of a hyperchromic shift of the maximum at λ275 nm. The ^{1}H-NMR spectrum showed the presence of a γ,γ-dimethylallyl moiety (2d, δ1.7, and 1.85, J = 1 Hz: $2CH_3$; δ3.9: benzylic CH_2; δ5.25 vinylic H) a methoxy group (s, δ3.29), and an



SCHEME 11

aldehydic group (s, δ10.3). Wolff–Kishner reduction of **54** with hydrazine hydrate afforded **62** whose UV spectrum was characteristic of a 1-methoxy-3-alkylcarbazole. The singlet resonance (δ8.4) of C-4 H of **54** thus indicated a location of the γ,γ-dimethylallyl group at C-2.

Confirmation of structure **54** and particularly the position of the isopentenyl group was achieved by an independent synthesis of its reduction product (**62**). Treatment of 1-hydroxy-3-methylcarbazole (**60**) with formic acid led to an N-protected derivative (Scheme 11), which was subsequently treated with 2-methyl-3-buten-2-ol in the presence of BF_3 etherate in dioxane to give **61** and the 2,4-dialkyl derivative. Cyclization of **61** to a dimethylchromene derivative of type **64** (see below, Scheme 12) proved its structure. Finally, methylation of **61** with dimethyl sulfate, followed by acidic N-deprotection, yielded **62.**

3. Heptaphylline and Derivatives

Heptaphylline (**55,** $C_{18}H_{17}NO_2$, $M^+ \cdot$ 279, mp 170–171°C) was isolated from the roots of *Clausena heptaphylla* Wt. et Arn. (*46,47,70*). The UV spectrum (λ_{max} 234, 278, 298, and 346 nm) indicated a 3-formylcarbazole chromophore. The presence of a formyl group was confirmed by examination of its IR spectrum (1640 cm^{-1}, chelated aldehyde).

The ^{1}H-NMR spectrum exhibited signals that were assigned to a γ,γ-dimethylallyl (isopentenyl) group: two Me signals (d, δ1.66 and 1.83, J = 1 Hz), a benzilic CH_2 (d, δ3.6, J = 6 Hz) and a vinyl proton (t, δ5.35, J = 6 Hz).

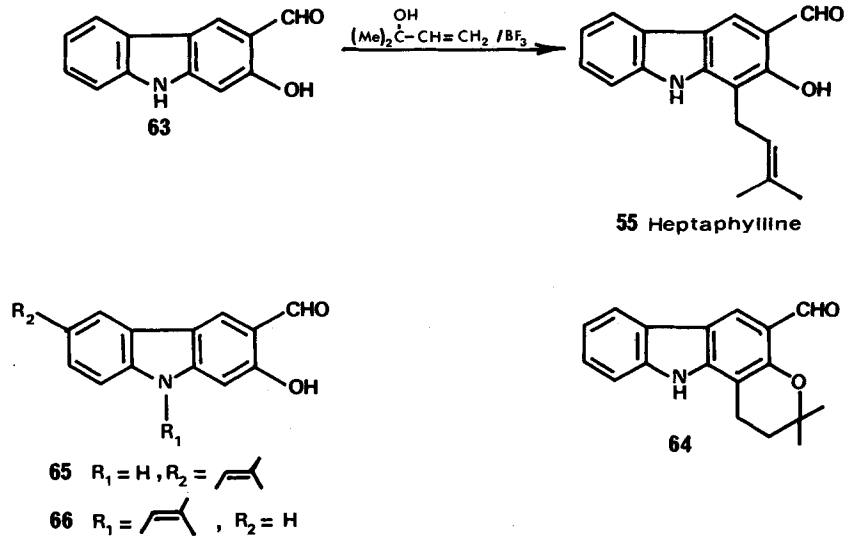
Heptaphylline monomethyl ether was obtained on treatment of **55** with Me_2SO_4 in boiling acetone in the presence of anhydrous K_2CO_3.

A crucial bit of information was provided by the observation that heptaphylline cyclized to **64** when polyphosphoric or formic acid was used at reflux. Final evidence for structure **55** was obtained by synthesis of heptaphylline (*70*) from 2-hydroxy-3-formylcarbazole according to the usual method of isopentenylation (Scheme 12; see also Scheme 11). However, since the nitrogen was not protected, heptaphylline (**55**) was obtained in poor yield along with two isomeric products (**65** and **66**).

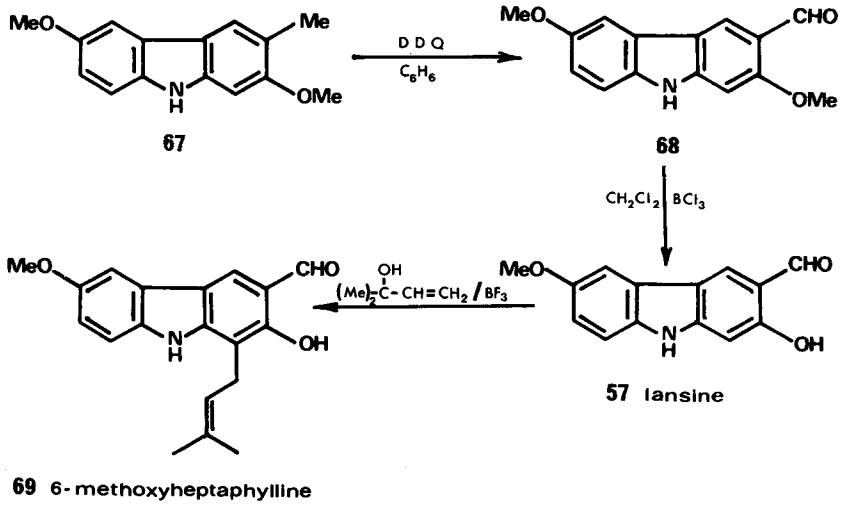
6-Methoxyheptaphylline (**69**, $C_{19}H_{19}NO_3$, $M^{+\cdot}$ 309; mp 173–174°C) is a component of *Clausena indica* (*45*). Its synthesis (*48*) as well as that of lansine (**57**) was achieved starting from 2,6-dimethoxy-3-methylcarbazole (**67**) (Scheme 13). DDQ oxidation of **67** gave 2,6-dimethoxy-3-formylcarbazole (**68**), which was selectively demethylated with BCl_3, giving lansine (**57**) in 80% yield. Isopentenylation of **57**, as described above, afforded 6-methoxyheptaphylline (**69**).

The same reaction scheme was recently used for the synthesis (*50*) of 8-hydroxyheptaphylline (heptazoline) ($C_{18}H_{17}NO_3$, $M^{+\cdot}$ 295, mp 212–214°C), isolated from *C. heptaphylla* (*61*). In this instance 2,8-dimethoxy-3-methylcarbazole was obtained by boiling 3′,4-dimethoxy-3-methyl-6-nitrobiphenyl with triethyl phosphite.

Two other alkaloids clausanitin (**58**) and atanisatin (**59**) were isolated from the roots and the stem respectively of *Clausena anisata* (*54*).

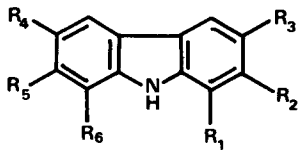


SCHEME 12



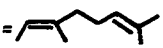
SCHEME 13

Clausanitin (**58**, $C_{18}H_{17}NO_2$, $M^{+\cdot}$ 279, mp 154–156°C) exhibited spectral data in agreement with a 3-formylcarbazole system wherein the formyl substituent is chelated to a hydroxy group at either the C-2 or C-4 position.



54 Indizoline R_1 = OMe, R_2 =  , R_3 = CHO, R_4 = R_5 = R_6 = H

55 Heptaphylline R_1 =  , R_2 = OH, R_3 = CHO, R_4 = R_5 = R_6 = H

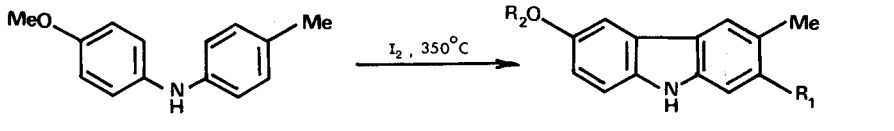
56 Mahanimbinol R_1 =  , R_2 = OH, R_3 = Me, R_4 = R_5 = R_6 = H

57 Lansine R_1 = R_5 = R_6 = H, R_2 = OH, R_3 = CHO, R_4 = OMe

58 Clausanitin R_1 = R_4 = R_6 = H, R_2 = OH, R_3 = CHO, R_5 = 

59 Atanisatin R_1 = R_4 = R_5 = H, R_2 = OMe, R_3 = CHO, R_6 = 

The C-2 position for the hydroxy group was inferred from biogenetic considerations [see heptaphylline (**55**)] and NMR studies. Since the spectral data and mp of Clausanitin (**58**) were different from those for atanisatin (**59**) (unpublished results) and the synthetic C-6 prenylated isomer (**65**) (Scheme 12) it was deduced



70

71 glycozoline $R_1 = H$, $R_2 = Me$
72 glycozolinine $R_1 = R_2 = H$
73 glycozolidine $R_1 = OMe$, $R_2 = Me$

SCHEME 14

that the γ,γ-dimethylallyl group was present at the C-7 position. Information from the literature is presently insufficient to verify the structures of clausinatin and atanisatin, although they are without doubt closely related to heptaphylline (**55**).

4. Mahanimbinol

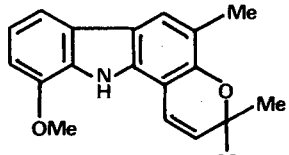
Mahanimbinol (**56**, $C_{23}H_{27}NO$, $M^{+\cdot}$ 333, amorphous) was isolated from *Murraya koenigii* (*51*). This alkaloid has been assigned the structure **56** by examination of its NMR spectrum, which suggested the presence of a geranyl group attached at the C-1 position. The presence of base peak at *m/z* 210 (loss of C_9H_{15}) in the mass spectrum was also in agreement with a C_{10} chain in mahanimbinol.

Mahanimbinol can be considered to be the precursor of the penta- or hexacyclic carbazoles isolated from the same plant family.

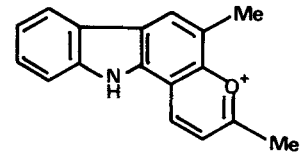
3-Methylcarbazole has been regarded as the key intermediate for the biogenesis of carbazole alkaloids (*2*); however, it was only recently isolated from natural sources (*C. heptaphylla*) (*41,42,45*).

Glycozolinine (**72**, $C_{13}H_{11}NO$, $M^{+\cdot}$ 197, mp 231–232°C), extracted from *Glycosmis pentaphylla* (*55*) was proved to be the *O*-demethyl derivative of glycozoline (**71**, $C_{14}H_{13}NO$, $M^{+\cdot}$ 211, mp 181–182°C), previously isolated from the same plant source (*56,57*). Advantage was taken of phenylamine cyclization to carbazole under thermal condition (350°C, traces of I_2) for the synthesis (*71,72*) of glycozoline (**71**) and glycozolidine (**73**) (Scheme 14).

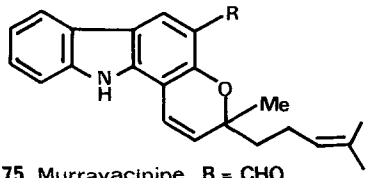
The first two syntheses of **71** were achieved earlier by photolysis of **70** (*73*) and by a Fischer indole synthesis (*74*).



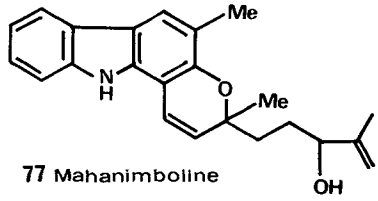
74 Mupamine



78



75 Murrayacinine R = CHO
76 Mahanimbine R = Me



77 Mahanimboline

5. Tetracyclic Carbazole Alkaloids

Mahanimboline (**77**, $C_{23}H_{25}NO_2$, $M^+ \cdot$ 347, mp 170–172°C) was found in the root bark of *M. koenigii* (*69*). The IR spectrum of **77** suggested the presence of a hydroxy function (3440 cm^{-1}) and a secondary amine (3300 cm^{-1}). The UV spectrum was characteristic of a pyranocarbazole like mahanimbine (**76**) (*62,64*). Zinc dust distillation of **77** led to the formation of 3-methylcarbazole, proving a part of the structure of mahanimboline. The mass spectrum of **77** exhibited, in addition to the molecular ion peak at *m/z* 347, fragments at *m/z* 329 (M − 18) and at *m/z* 248 (base peak) attributable to the carbazolopyrilium ion (**78**). Thus **77** is a 3-methylpyranocarbazole bearing a C_6 side chain like mahanimbine (**76**) including an additional hydroxy function.

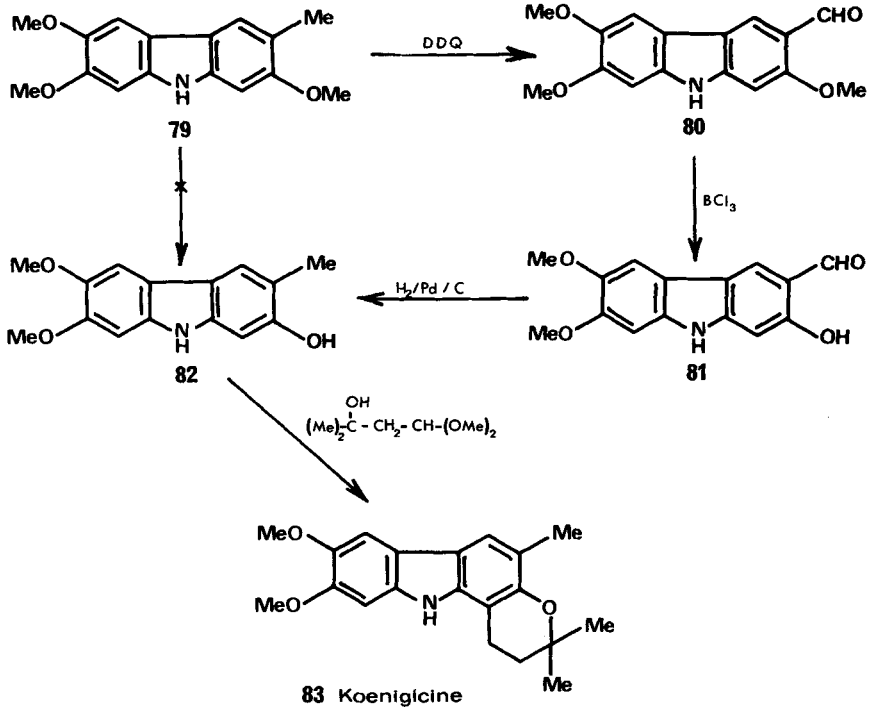
The aromatic region of the ^{1}H-NMR spectrum of **77** was identical with that of **76.** The substitution pattern of the side chain was deduced from comparison of the ^{1}H-NMR spectrum of **77** with that of its *O*-acetyl derivative.

Recently a partial synthesis of murrayacinine (**75**) has been achieved (*67*) by DDQ oxydation of mahanimbine (**76**) and the structure of mupamine (**74**) from *Clausena anisata* (*66*) disclosed.

The structure of koenigicine (**83**) has been confirmed by synthesis (*82*) according to a variation of the classical scheme (*83*). Ullmann condensation of 5-iodo-2-methoxytoluene with 2-bromo-4,5-dimethoxynitrobenzene afforded the required biphenyl derivative, which was cyclized with triethyl phosphite to 3-methyl-2,6,7-trimethoxycarbazole (**79**) (Scheme 15). Selective demethylation of **79** to **82** failed. The synthetic strategy was subsequently changed. DDQ oxidation of **79** was performed prior to selective demethylation of **80** to **81.** Finally, hydrogenolysis of the formyl group of **81** over Pd–C led to the desired phenol **82.** Condensation of **82** with 3-hydroxyisovaleraldehyde dimethylacetal in pyridine afforded the natural koenigicine (**83**).

6. Penta- and Hexacyclic Alkaloids

The penta- and hexacyclic alkaloids of this series have been studied independently by several Indian workers with the result that different names have been given to the same alkaloid extracted from the same plant, *M. koenigii.* The co-occurrence of some of these compounds was later established by direct com-



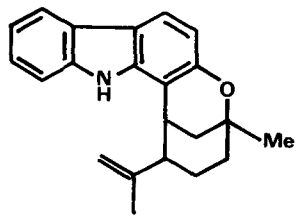
SCHEME 15

parisons. For this and related reasons, the literature over the last 15 years was carefully examined in order to eliminate confusion or mistakes that could arise because of the revision of structures, e.g., **85** and **86** (*86*). Murrayazolidine [**84,** $C_{23}H_{25}NO$, mp 143°C, $[\alpha]_D^{20}$ +20° ($CHCl_3$)], the first naturally occuring pentacyclic carbazole alkaloid, was also isolated from the stem bark of *M. koenigii* (*76*). This compound appeared to be identical in all respects to cyclomahanimbine (*75*) and currayanine (*84*); however, the latter are optically inactive. A synthesis of **84** from murrayazoline (**87**) confirmed its structure. Acid-catalyzed hydration of murrayazoline (**87**) led to murrayazolinine (**89**) (*80*). Subsequent dehydration with phosphoric oxide gave a mixture of products containing **84.** The reverse transformation of murrayazolinine (**89**) to murrayazoline (**87**) was possible (*87*). Murrayazolidine (**84**) was also formed by cyclization of mahanimbine (**76**) at 200°C (*88*).

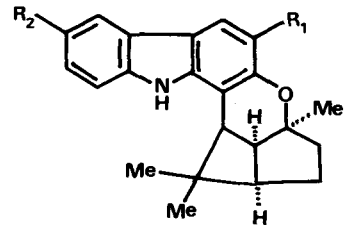
The structure of murrayazoline (curryangine, mahanimbidine) ($C_{23}H_{25}NO$, $M^{+\cdot}$ 331, mp 260–262°C), was postulated to be **87** on the basis of chemical and spectral data. The structure was finally settled after X-ray crystals studies (*80*).

Recently a new carbazole alkaloid, isomurrayazoline [**88,** $C_{23}H_{25}NO$, $M^{+\cdot}$ 331, mp 269–270°C, $[\alpha]_D$ −7.33° ($CHCl_3$)], was found on further examination

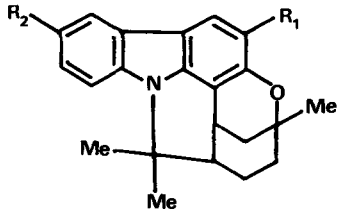
of the stem bark of *M. koenigii* (*81*). The ^{1}H-NMR spectrum of **88** exhibited peaks for five aromatic protons very similar to those of isomahanimbine (*64*), whereas the nonaromatic region closely resembled the spectrum for **87.** Treatment of **88** with 80% aqueous acetic acid, as used previously for **87** (*76*), afforded a hydroxy compound (**90**) whose physical properties were nearly identical with those of murrayazolinine (**89**). These observations led to the assignment of structure **88** for isomurrayazoline.



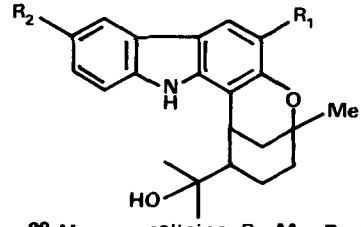
84 Murrayazolidine (α_D +20°)
(=cyclomahanimbine = currayanine : α_D 0°)



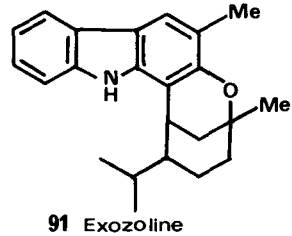
85 Bicyclomahanimbine R_1 = Me, R_2 = H
86 Bicyclomahanimbicine R_1 = H, R_2 = Me



87 Murrayazoline R_1 = Me, R_2 = H
(=curryangine = mahanimbidine)
88 Isomurrayazoline R_1 = H, R_2 = Me



89 Murrayazolinine R_1 = Me, R_2 = H
90 Isomurrayazolinine R_1 = H, R_2 = Me



91 Exozoline

The leaves of another species of *Murrya, M. exotica* (*79*) contain a new carbazole alkaloid, exozoline ($C_{23}H_{27}NO$, $M^{+\cdot}$ 333, mp 180–182°C). The

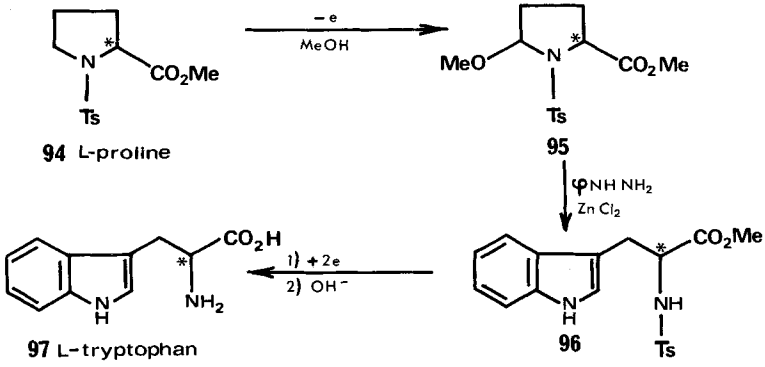
structure of exozoline (**91**) was elucidated from its spectroscopic data, particularly the ^{1}H-NMR and mass spectra. A confirmation of its structure was provided by the comparison of **91** with dihydromurrayazolidine (dihydrocyclomahanimbine), obtained by hydrogenation of **84.**

IV. Nonisoprenoid Tryptamine Alkaloids

A. Tryptophan and Tryptamine Derivatives

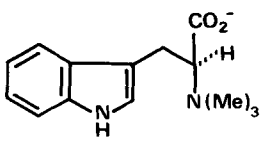
1. Tryptophan

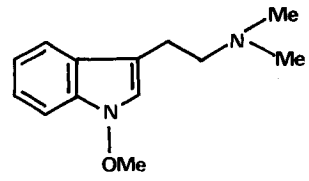
A general method for the synthesis of β-substituted indoles and, in particular, L-tryptophan has recently been reported (*125,126*) (Scheme 16). The anodic oxidation of the L-proline derivative **94** led to the α-methoxylated amide **95,** which is an equivalent of an amino aldehyde. A Fischer indole synthesis was performed on **95,** in the presence of $ZnCl_2$, to give **96.** The conversion of **96** to optically pure L-tryptophan (**97**) was achieved by electrochemical elimination of the tosyl group, followed by ester hydrolysis.



SCHEME 16

Hypaphorine (**92**) mp 255°C, $[\alpha]_D^{22}$ +102°) was first isolated from seeds of *Erythrina hypaphorus* and was later found to be the major constituent of the



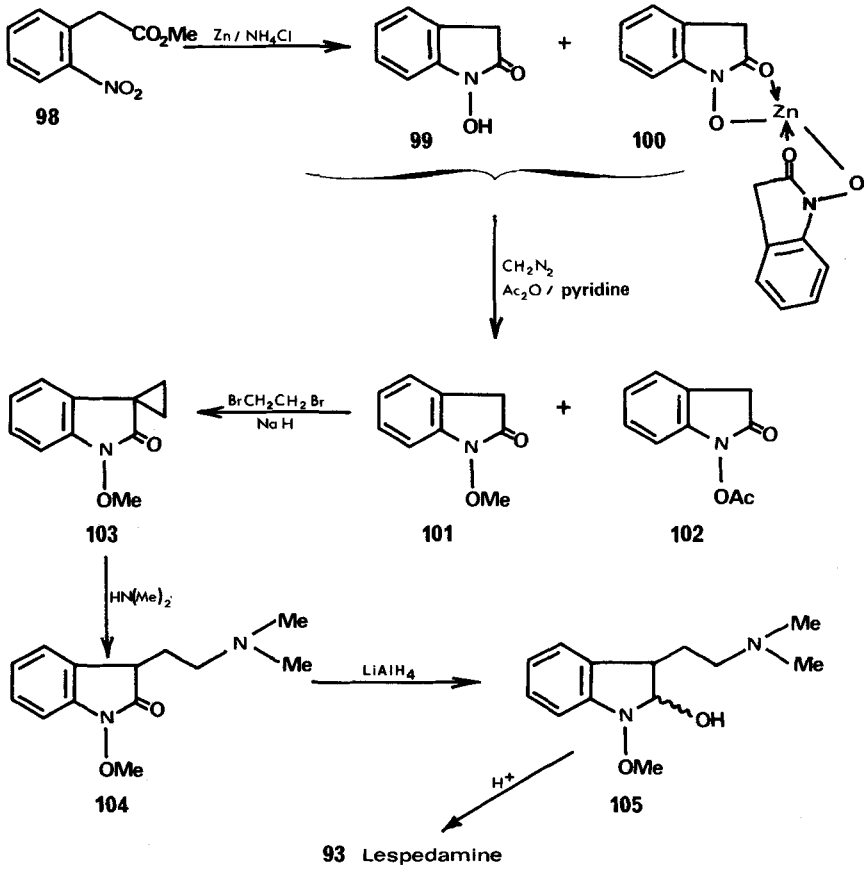


seeds of *Pterocarpus officinalis* (*89*). This quaternary salt derived from tryptophan was shown to be an effective mammalian feeding deterrent for a seed-eating rodent (*Liomys salvini*).

2. Lespedamine

Lespedamine (**93**, $C_{13}H_{18}N_2O$, hydrochloride mp 163–164°C) was isolated from *Lespedeza bicolor* var. *japonica* (*101*). Interest in the synthesis of 1-hydroxy- and 1-methoxyindole derivatives has been stimulated by the isolation of several alkaloids of this type (*21,93,114,118*). Lespedamine (**93**) was synthesized by two routes. The first of these employed a method published earlier for 1-methoxyindoles (*33,34*) (Scheme 8); however, in this case the yield was low.

The second synthesis (*127*) was achieved by a strategy that also provided for



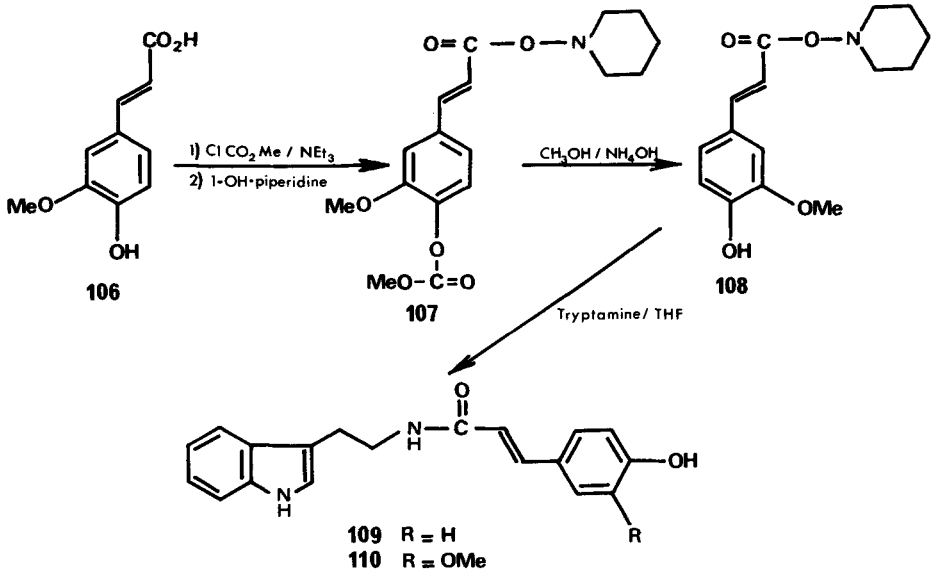
SCHEME 17

the preparation of 1-acetoxy-2-oxindole (**102**). Reduction of the nitro ester **98** (Scheme 17) with zinc and ammonium chloride led to the formation of a mixture of **99** and the complex (**100**). Treatment of the reaction mixture with CH_2N_2 and pyridine containing acetic anhydride afforded 1-methoxyoxindole (**101**) and its 1-acetoxy analog (**102**) in excellent yields.

The latter gave back **99** on hydrolysis with sodium carbonate. Reaction of the enolate derived from **101** with ethylene dibromide led to the cyclopropyl derivative **103.** Subsequent opening of the cyclopropane ring with dimethylamine afforded the expected oxindole (**104**) in 54% yield. Reduction of **104** to **105** with $LiAlH_4$, followed by treatment with hydrochloric acid led to lespedamine (**93**). The total synthesis of **93** was thus achieved in five steps (overall yield 24%).

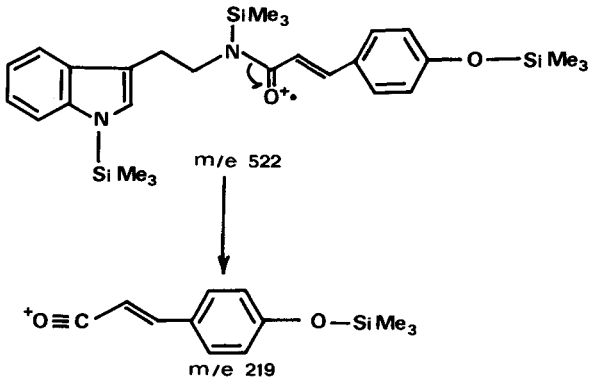
3. *N(b)*-(*p*-Coumaryl)tryptamine and *N(b)*-Feruloyltryptamine

The two phenolamides *N(b)*-(p-coumaryl)tryptamine (**109**) and *N(b)*-feruloyltryptamine (**110**) (Scheme 18) were extracted in trace amounts from ground kernels of *Zea mays* L. (*103*). Gas chromatographic–mass spectroscopic analysis of their TMS derivatives indicated a molecular ion at *m/e* 522 and a major fragment at *m/z* 219 for **109.** This suggested that the acyl moiety of **109** could be derived from hydroxycinnamic acid. Identification of this acid was made by



SCHEME 18

treatment of **109** by trifluoroacetic acid, followed by GLC–MS analysis of the TMS ethers of the hydrolysis products. TMS–tryptamine and TMS–*p*-coumaric acid were thus characterized. The same methodology applied to **110** led to the conclusion that it was *N*(*b*)-ferulyltryptamine.

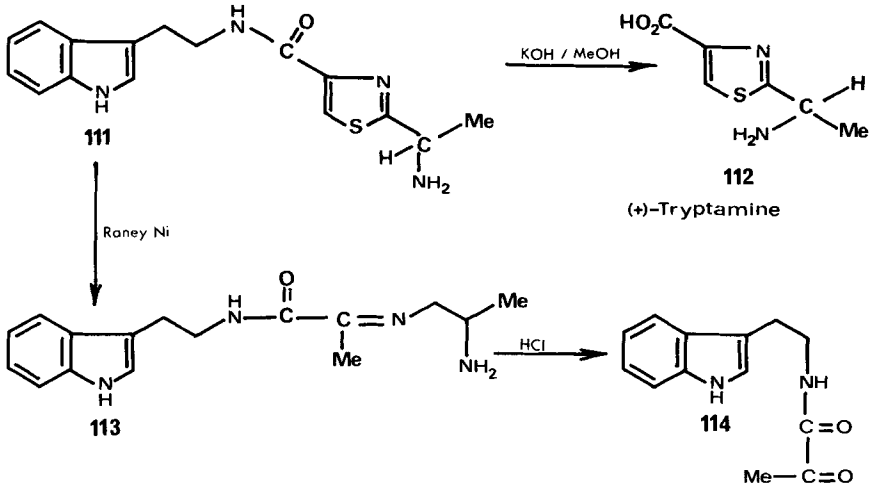


Considerable effort has been directed over the past several years toward the synthesis of phenolcarboxamides because of the role that some of these compounds play in biochemical processes and as a result of their occurrence as secondary metabolites in living organisms. The occurrence of compounds such as **109** or **110** in μg/kg quantities has attracted much interest toward their synthesis.

The problems that are presented in the synthesis of polyamine derivatives are the selective acylation of the primary amino groups and the usual protection–deprotection of the phenol hydroxy groups of these sensitive molecules. An efficient synthesis of phenolcarboxamides, taking advantage of the reactivity of hydroxy-1-piperidine esters, has been recently described (*128*). This method was particularly useful for the synthesis of **110** (Scheme 18). The reaction of ferulic acid (**106**) with $ClCO_2CH_3$ in the presence of $(C_2H_5)_3N$ in CH_2Cl_2 at 0°C gave an intermediate phenol methylcarbonate mixed anhydride. This product reacted with 1-hydroxypiperidine, affording **107.** The phenol function was subsequently liberated by treatment of **107** with NH_4OH–CH_3OH to give **108** (yield 90% from **106**). A THF solution of tryptamine was refluxed under nitrogen in the presence of active ester **108** (1 equiv) for 18 hr to give *N*(*b*)-ferulyltryptamine (**110**) in excellent yield.

4. *N*(*b*)-Aminomethylthiazolecarboxamide

N(*b*)-Aminomethylthiazolecarboxamide [**111,** $C_{16}H_{18}ON_4S$, $M^{+\cdot}$ 314, mp 120–122°C, $[\alpha]_D^{20}$ −6° (MeOH)] was produced by *Thermoactinomyces* sp. strain TM-64 (*105*).



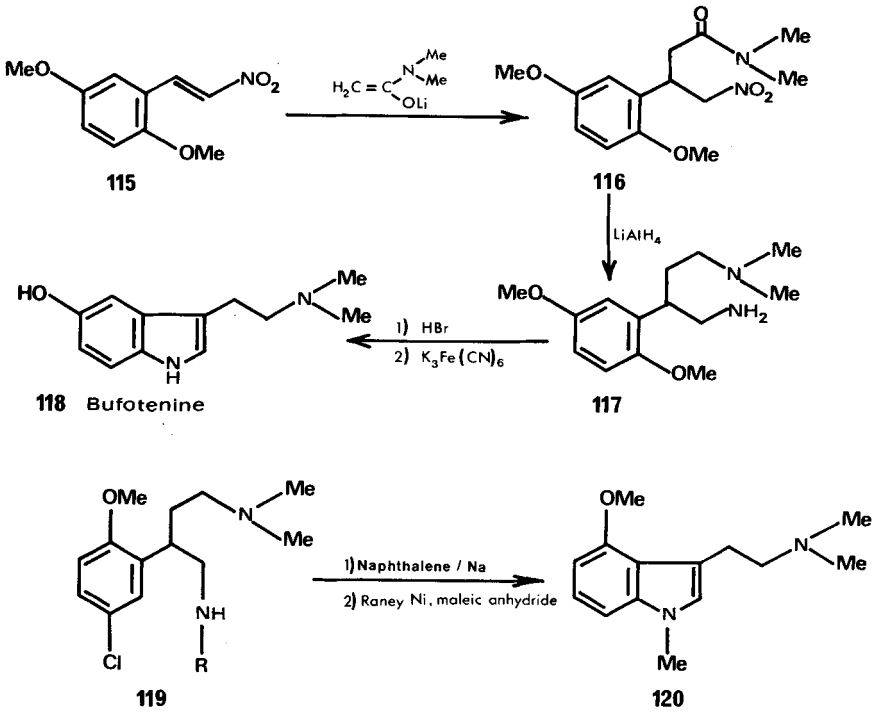
SCHEME 19

The UV spectrum of this compound displayed an indole chromophore and its IR spectrum an amide carbonyl band at 1630 cm^{-1}. Hydrolysis of **111** with KOH–MeOH afforded tryptamine and a carboxylic acid (**112**) (Scheme 19), which was shown to be a 2,4-substituted thiazole on the basis of its UV and NMR spectra. Desulfurization of the thiazole moiety with Raney nickel gave **113,** which was hydrolyzed to the keto amide **114.** From these results the structure of **111** was established as *N*(*b*)-3′-β-indolylethyl-2-α-aminoethylthiazole-4-carboxamide.

From the circular dichroism of the *N*-salicylidene derivative of **111** the *S* configuration was tentatively assigned to the asymmetric carbon on the α-aminoethyl group.

5. Hydroxytryptamines

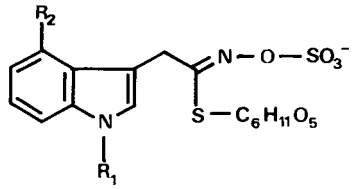
An efficient synthesis (*129*) of bufotenine (**118**) has been achieved starting from the Michael addition product of the lithium enolate of dimethylacetamide and nitrostyrene (**115**) (Scheme 20). Reduction of the adduct (**116**) with $LiAlH_4$ afforded the diamine (**117**), which was subsequently transformed to bufotenine (**118**). This approach to the preparation of amines of type **117** permitted also the synthesis of the chloro intermediate **119,** which was previously converted to *O,N*-dimethylpsylocin (**120**) via an aryne cyclization (*130*).



SCHEME 20

B. GLUCOSINOLATES

The three indole glucosinolates glucobrassicin (**121**), neoglucobrassicin (**122**), and **123** were proved to be natural constituents of plants of the family Cruciferae and not to be produced by microbial contaminants (*115*). Two new indole

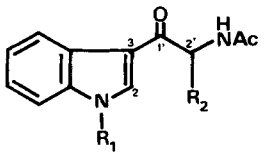


121 Glucobrassicin $R_1 = R_2 = H$
122 Neoglucobrassicin $R_1 = OMe$, $R_2 = H$
123 $R_1 = SO_3^-$, $R_2 = H$
124 $R_1 = H$, $R_2 = OH$
125 $R_1 = H$, $R_2 = OMe$

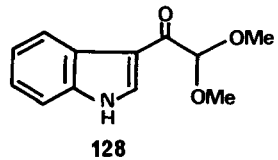
glucosinolates recently isolated from *Brassica oleracea* and *Isatis tinctoria* (*116,117*) were tentatively assigned the structures **124** and **125.** Degradation of indole glucosinolates by myrosinase led to the formation of the parent indolacetonitrile. Note that the substituted acetonitrile corresponding to the abovementioned glucosinolates have been found in the Chinese cabbage (*93*), belonging also to the family Cruciferae. Concerning **123** it is noteworthy that it was the first indole 1-sulfonate identified from plants sources.

C. β-Oxotryptamines

Two compounds referred to as 34-M [$C_{12}H_{12}N_2O_3$, $M^{+\cdot}$ 232, mp 146–147°C, $[\alpha]_D^{20}$ −92° (MeOH)] and 34-N [$C_{12}H_{12}N_2O_2$, $M^{+\cdot}$ 216, mp 203–204°C, $[\alpha]_D^{20}$ 0°] were isolated from *Streptomyces ramulosus* (*105*). The compound 34-N was identified as the previously synthesized *N*(*b*)-acetyl-β-oxotryptamine (**127**) (*131,132*).



126 34-M R_1=H, R_2=OH
127 34-N R_1= R_2= H



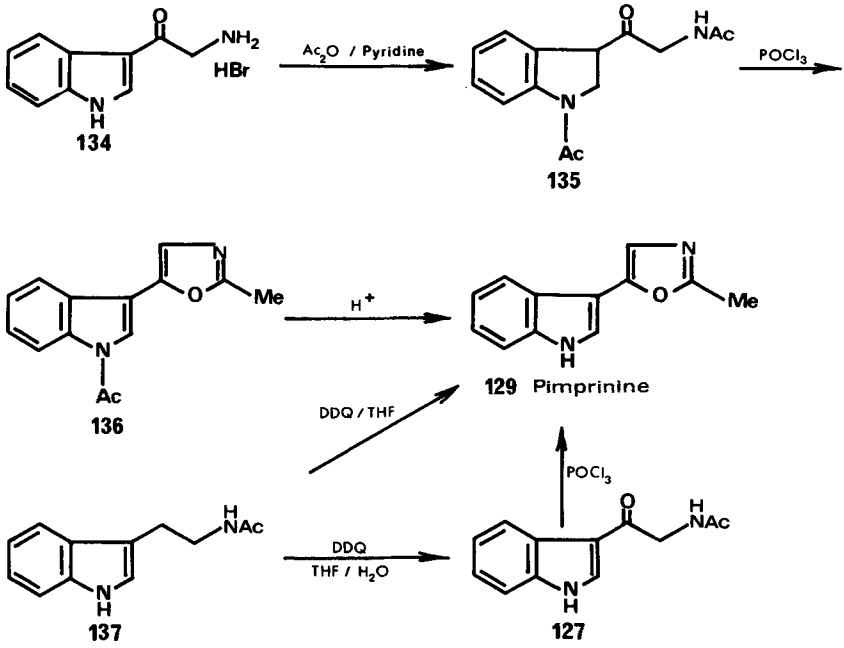
128

The MS of 34-M (**126**) showed an ion at *m/z* 173, corresponding to 3-indoleglyoxal and a fragment at *m/z* 59 (CH_3CONH_2) resulting from a McLafferty rearrangement involving an acetyl carbonyl and a proximal hydroxy group. Furthermore, treatment of 34-M with methanolic HCl led to the dimethyl acetal of 3-indoleglyoxal (**128**), which exhibited characteristic fragments in its MS at *m/z* 144 and *m/z* 75 for a $CH(OMe)_2$ moiety. These physical and chemical properties led to the proposal of structure **126** for 34-M. Conclusive proof of the structure was provided by a detailed analysis of ^{1}H- and ^{13}C-NMR spectra.

D. Indolyloxazoles

Pimprinine (**129,** $C_{12}H_{10}N_2O_2$, $M^{+\cdot}$ 198, mp 204–205°C) was isolated from *Streptomyces pimprina* (*120*). From a combination of ^{1}H-NMR spectral data (CH_3, s, δ2.4 and 6 aromatic-type protons δ6.80–7.25) and an alkali-fusion experiment, which yielded indole, indole-3-acetic acid, acetic acid, and ammonia, structure **129** was proposed for pimprinine. This structure was subsequently confirmed by synthesis from 3-aminoacetylindole (**134**).

Cyclization of the diacetyl derivative of **134** in refluxing $POCl_3$ afforded



SCHEME 21

indolyl-2-methyloxazole (**136**) from which pimprinine was obtained after hydrolysis (Scheme 21).

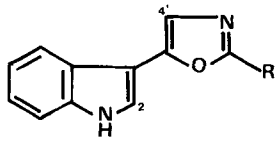
Two very similar alkaloids, pimprinethine (**130**, $C_{13}H_{12}N_2O$, $M^{+\cdot}$ 212, mp 163–165°C), and pimprinaphine (**131**, $C_{18}H_{14}N_2O$, $M^{+\cdot}$ 274, mp 200–201°C), were isolated later together with pimprinine from *Streptoverticillum olivoreticuli* (*121*) and synthesized by the same method.

Another route for the synthesis of oxazolylindole alkaloids of this type is based on DDQ oxidation of tryptamine or tryptophan derivatives.

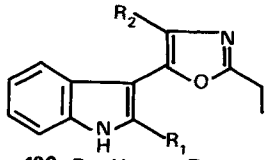
Treatment of *N*-acetyltryptamine (**137**) with DDQ in refluxing THF led in a one-pot reaction to pimprinine in poor yield (10%) (Scheme 21). However, when the reaction was carried out in the presence of water (90% aqueous THF) at room temperature, *N*(*b*)-acetyl-β-oxotryptamine (**127**) was isolated in high yield. As published earlier (see above, *120*), $POCl_3$ dehydrative cyclization of **127** gave pimprinine.

Bromination of pimprinethine (**130**) with bromine in chloroform in the presence of iron or with 2,4,4,6-tetrabromocyclohexa-2,5-dione afforded the mono (**132**) and the dibromo (**133**) derivatives (*122*).

An X-ray analysis of **130** indicated that the (*S*)- cis configuration of the coplanar ring system is favored (*122*).



129 Pimprinine R = Me
130 Pimprinethine R = Et
131 Pimprinaphine R = $CH_2\varphi$



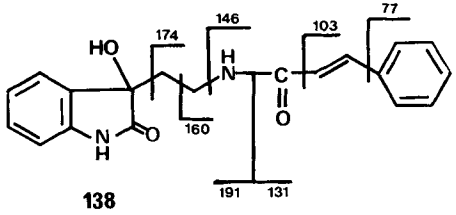
132 R_1 = H , R_2 = Br
133 R_1 = R_2 = Br

It is interesting to note that **127** is a metabolite produced by *Streptomyces ramulosus* (see above), indicating that this microorganism produces enzymes that are able to oxidize tryptamine.

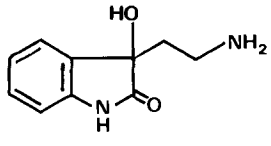
However, pimprinine was not observed in the extract of this strain. In the same way β-oxotryptamine was not detected in extracts from *Streptomyces pimprina*, although it is a likely biogenetic intermediate of pimprinine.

E. Oxo-2-tryptamines

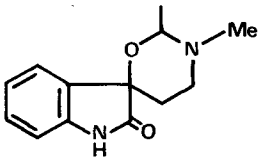
Compound **138**, $C_{19}H_{18}N_2O_3$, M^+ · 322, mp 162–164°C, optically inactive) has been isolated from the leaves of *Cinnamomum triplinervis* (*123*).



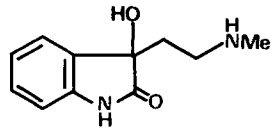
138



139



140 Donaxarine



141 Donaxaridine

Acid hydrolysis of **138** afforded the 3-hydroxyindolin-2-one (**139**) and *trans*-cinnamic acid. The IR spectrum of **138** indicated that these two moieties are linked by an amide bond (1685 cm^{-1}). The mass spectrum of **138** exhibited fragments characteristic of the 3-[2-(*trans*-cinnamoylamino)ethyl]-3-hydroxyindolin-2-one structure.

Donaxaridine (**141**) extracted from *Arundo donax* (*124*) is the N(b)-methylated derivative of **139** and gave isatin (**32**) (Scheme 3) on oxidation with $KMnO_4$. The

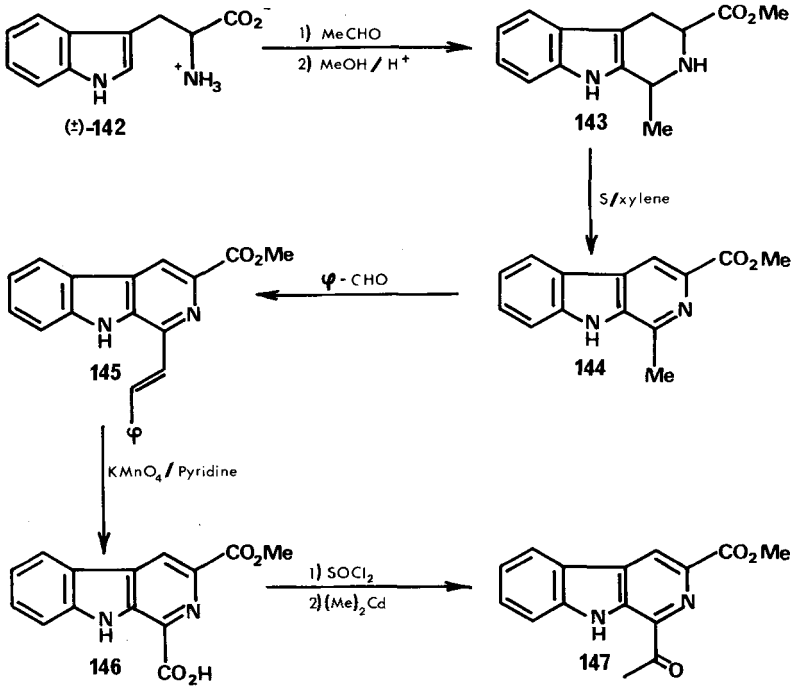
second alkaloid of *A. donax*, donaxarine (**140**), was obtained on cyclocondensation of **141** with acetaldehyde.

F. β-Carbolines

1. Occurrence and Structure

An exhaustive review on this class of alkaloids covering reports to April 1979 is available (*3*). Recent publications in this field deal with isolation of some new alkaloids; however most of the works are devoted to synthesis, ^{13}C-NMR, and biogenetic studies. Simple β-carbolines have recently been shown to be present also in mammalian urine, which has stimulated extensive investigation of their pharmacological activity.

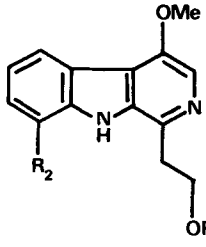
1-Acetyl-3-methoxycarbonyl-β-carboline (**147**, $C_{15}H_{12}N_2O_3$, $M^{+\cdot}$ 268, mp 230–232°C) was found in *Vestia lycioides* (Solanaceae) (*142*). Pictet–Spengler condensation of (±)-tryptophan (**142**) with acetaldehyde in the presence of sulfuric acid yielded the 1,2,3,4-tetrahydro-β-carboline **143** (Scheme 22). Dehydrogenation to β-carboline **144** was achieved in boiling xylene in the presence



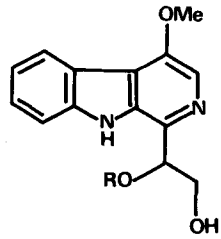
SCHEME 22

of sulfur. The 1-styryl-β-carboline **145,** obtained by condensation of **144** with benzaldehyde, was oxidized to the carboxylic acid (**146**) with $KMnO_4$ in pyridine. Finally, the acid chloride derived from **146** was converted to 1-acetyl-3-methoxycarbonyl-β-carboline on treatment with dimethylcadmium.

The only two plants of the family Simaroubaceae of Japanese origin, *Picrasma quassioides* (*133*) and *Ailanthus altissima* (*134,135*) have been examined for alkaloid content. Apart from a number of known β-carboline alkaloids, four new bases (**148–151**) have been characterized.



148 $R_1 = R_2 = H$
149 $R_1 = Me$, $R_2 = OMe$



150 R = H
151 R = Me

The UV spectrum of compound **148** ($C_{14}H_{14}N_2O_2$, $M^{+\cdot}$ 242, mp 253–254°C) displayed a characteristic methoxy-β-carboline chromophore [λ_{max}^{EtOH} [nm (log ε)] = 232 (4.17), 241 (4.24), 278 (4.53), 336 (4.11), 348 (4.17)]. Examination of its ^{1}H-NMR spectrum showed the presence of a methoxy group (δ3.97, s) and two methylene protons (δ3.35 and 3.66, 2 t) attributed to a hydroxyethyl group in agreement with the ^{13}C-NMR data (δ28.84 and 63.01).

The presence of the methoxy group and the hydroxyethyl chain was also supported by fragments at *m/z* 224 (M − H_2O), 211 (M − OMe), and 197 (M − CH_2CH_2OH) in the mass spectrum.

Acetylation of **148** yielded a mono-*O*-acetyl derivative whose ^{1}H-NMR spectrum exhibited a downfield shift for the 2-H triplet at δ3.66, confirming the presence of a hydroxyethyl chain.

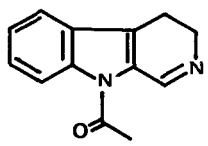
The absence of substitution on ring A of the β-carboline ring, as deduced from the ^{1}H-NMR spectrum, finally fixed the position of the hydroxyethyl group at C-1.

Compound **149** ($C_{16}H_{18}N_2O_3$, $M^{+\cdot}$ 286, mp 201–202°C) showed fragments at *m/z* 255 (M − OMe) and 227 (M − $CH_2CH_2OCH_3$) suggesting the presence of methoxy and methoxyethyl groups. This was confirmed by observation of three methoxy singlets (at δ3.8, 3.96, and 4.06) in the ^{1}H-NMR spectrum. By comparison of this spectrum with those of related β-carbolines (e.g., **148**) previously isolated, it was concluded that the second methoxy group was located at C-8.

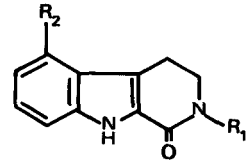
Compound **150** ($C_{14}H_{14}N_2O_3$, $M^{+\cdot}$ 258, mp 189–190°C) possessed UV and IR spectra very similar to those of **148** but gave a di-*O*-acetyl derivative by acetylation with acetic anhydride and pyridine. The ^{1}H-NMR spectrum showed a system characteristic of a 1-(1′-2′-dihydroxyethyl) chain found in pyridindolol (**162**) (*143*) (see Scheme 23). Compound **150** was therefore identified as 1-(1′,2′-dihydroxyethyl)-4-methoxy-β-carboline. The configuration at C-2′ is unknown.

Compound **151** ($C_{15}H_{16}N_2O_3$, $M^{+\cdot}$ 272, mp 223°C) gave a monoacetate derivative on acetylation. Identification as the 2′-methoxy derivative of **150** was easily achieved by comparison of MS and ^{1}H-NMR data with those for related alkaloids in this series.

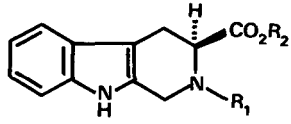
A novel norharmalan alkaloid called AV_1 [**152,** $C_{13}H_{12}N_2O$, $M^{+\cdot}$ 212, mp 165–166°C, $[\alpha]_D^{33}$ − 54.2° (MeOH)] was extracted from *Adhatoda vasica* (Acanthaceae) (*137*). Alkaline hydrolysis of AV_1 afforded norharmalan, and $NaBH_4$ reduction gave tetrahydronorharman. The *N*(*a*)-acetyl-3,4-dihydro-β-carboline structure (**152**) for this new alkaloid was also supported by its ^{1}H- and ^{13}C-NMR spectra.



152 AV_1



153 Strychnocarpine
R_1 = Me , R_2 = H
154 R_1 = H , R_2 = OMe



155 $R_1 = R_2$ = Me
156 R_1 = H , R_2 = Me

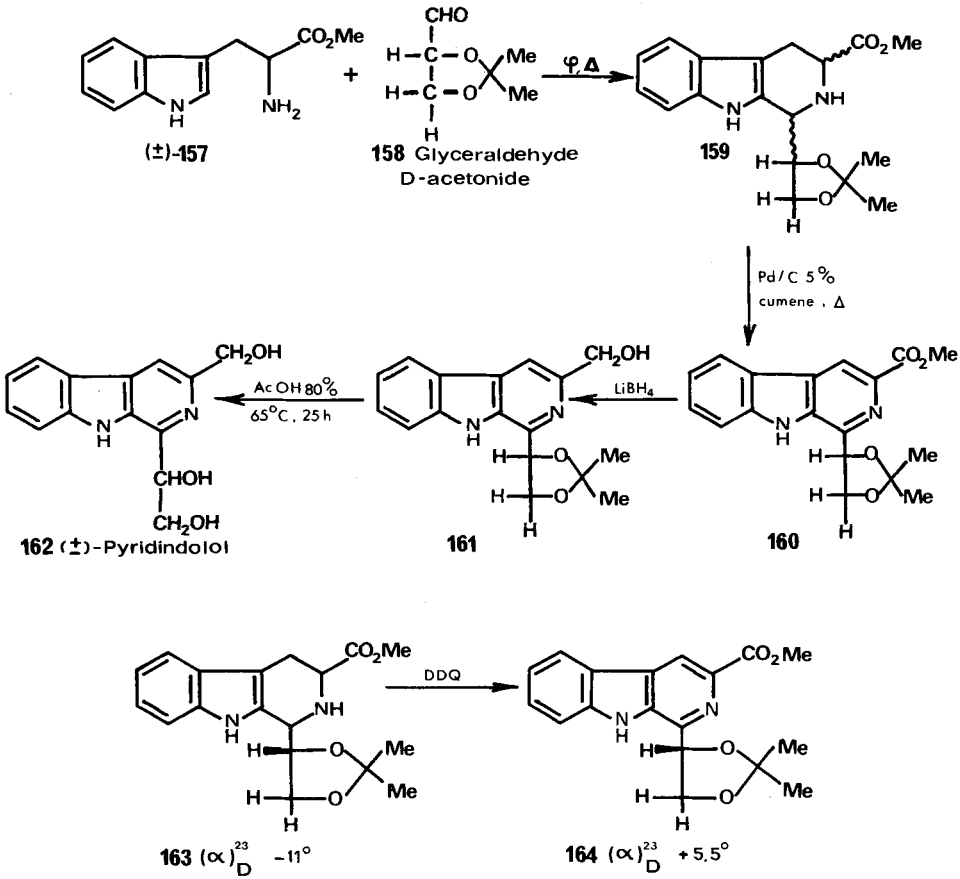
Strychnocarpine (**153,** $C_{12}H_{12}N_2O$, $M^{+\cdot}$ 200), a constituent of *Strychnos elaeocarpa* (Loganiaceae) (*138*) and of *S. floribunda* (*139*), is 1-oxo-*N*(*b*)-methyl-1,2,3,4-tetrahydro-β-carboline.

1-Oxo-5-methoxytetrahydro-β-carboline (**154,** $C_{12}H_{12}N_2O_2$, $M^{+\cdot}$ 216, mp 182–184°C) is a new base extracted from *Alstonia venenata* (Apocynaceae) (*140*). The UV spectrum [λ_{max}^{EtOH} [nm (log ε)] = 238 (3.91), 258 (2.57), 295 (3.61)] and the IR spectrum (1660 cm^{-1}) were in agreement with a 1-oxotetrahydro-β-carboline ring system. The position of the methoxy group on the

aromatic ring was inferred from ^{13}C-NMR spectra comparison of a series of methoxy alkaloids.

Alkaloid **155** [$C_{14}H_{16}N_2O_2$, mp 196–197°C, $[\alpha]_D$ +18° (EtOH)] was found in *Gastrolobium callistachys* (Leguminosae) together with (*S*)-(+)-*N*(*b*)-dimethyltryptophan methyl ester (*141*). Both of these alkaloids have quite similar ^{1}H-NMR spectra; however, the C-2 proton of indole was absent, and only one *N*-CH_3 group was observed.

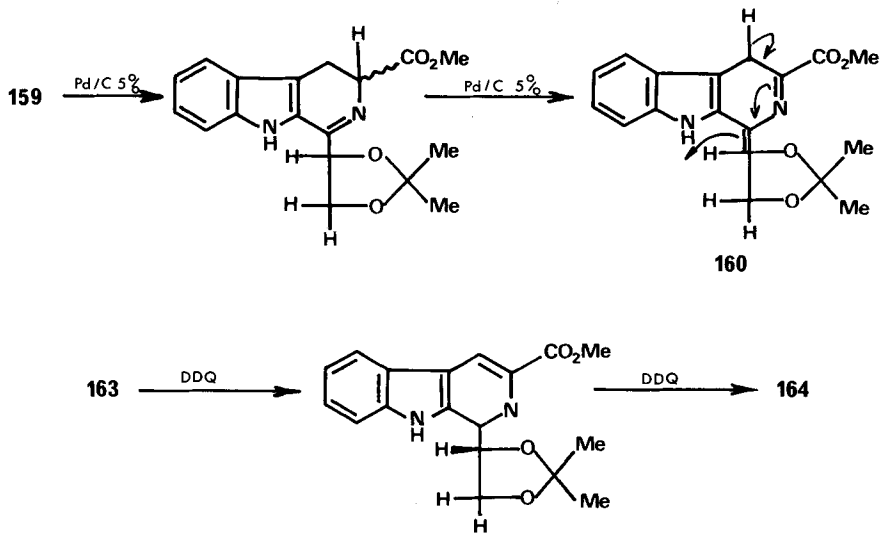
Synthesis of **155** from (*S*)-(+)-tryptophan confirmed its structure. Pictet–Spengler condensation of (+)-tryptophan methyl ester with formaldehyde gave **156,** which was then methylated (formaldehyde, H_2, Raney nickel) to yield the natural product **155.**



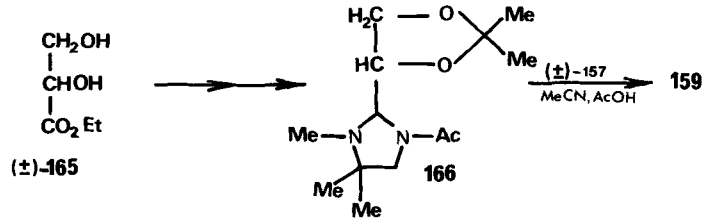
SCHEME 23

2. Chemistry and Synthesis

The current interest in the pharmacology of β-carbolines and their hydro derivatives has resulted in many structural studies and synthetic endeavours. The Pictet–Spengler condensation, the most widely used reaction, is generally carried out in a protic solvent, which most likely resembles the *in vivo* conditions. However, it has been claimed that the Pictet–Spengler reaction works better in aprotic solvents (*144,145*). Thus the synthesis of tetrahydro-β-carbolines, heretofore difficult to obtain, e.g., pyridindolol (**162**), produced by *Streptomyces alboverticillatus* (*143*), has been achieved in good yield. Reaction of (±)-tryptophan methyl ester (**157**) (Scheme 23) with the optically active glyceraldehyde acetonide (**158**) in refluxing benzene afforded the diastereomers (**159**) (yield 90%). Aromatization of **159** in refluxing cumene in the presence of Pd–C (5%) led to the racemic β-carboline **160.** The ester of **160** was reduced to the primary alcohol **161** with $LiBH_4$ in refluxing methanol. Finally, acid treatment of **161** afforded racemic pyrindolol (**162**). An enamine–iminium equilibrium has been proposed to explain racemization of the chiral center of the acetonide during the aromatization step. In order to prevent this inconvenience and to test this postulated mechanism, DDQ oxidation of enriched diastereomer **163** was tried. Indeed, Pd–C aromatization is thought to involve prior formation of a 1,2-dehydro-β-carboline (allowing the enamine–iminium equilibrium), whereas DDQ has been reported (*146*) to attack the C-4 position (Scheme 24). The β-carboline (**164**) formed under these conditions was optically active.



SCHEME 24



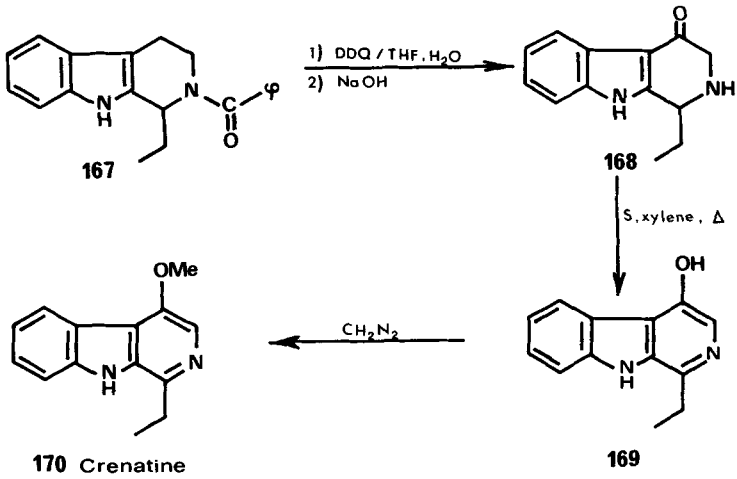
SCHEME 25

Despite the good results described for the synthesis of tetrahydro-β-carbolines in the absence of acid catalysis, it appeared that the above-mentioned experimental conditions had to be reexamined (*147*). Only the Schiff base, and no β-carboline, was formed in the absence of acids in repetition of the original work (*144,145*). It was thus observed that the reaction is inevitably acid catalyzed, and it was concluded that the cyclization occurred because of acid impurities.

A formal synthesis of racemic pyridindolol (**162**) was achieved by preparation of **159** (Scheme 25) via the application of folic acid models in carbon-fragment transfer reactions (*148*).

The folic acid model (**166**), prepared from (±)-glyceric acid in six steps is able to transfer its substituted methylene moiety to (±)-tryptophan (**157**) to give **159** as a diastereomeric mixture.

DDQ oxidation (*149*) of tetrahydro-β-carbolines has also been employed for the synthesis of the alkaloid crenatine (**170**). Advantage was taken of the above-mentioned oxidation of β-carboline at the C-4 position of **167**, leading to 4-



SCHEME 26

oxotetrahydro-β-carboline (**168**), which was aromatized to the phenol (**169**) precursor of crenatine (**170**) (Scheme 26).

Selenium dioxide oxidation of 1-ethyl-3-carbomethoxytetrahydro-β-carboline was used to synthesize **147** (*150,151*) in a short two-step process [compare with the more complex former synthesis (Scheme 22)].

It has been shown that β-carboline alkaloids (harmane, harmine, and harmaline) dimerized on UV irradiation. Two series of compounds were obtained: N(a)–N′(a) and N(a)–C′3 dimers (*152*).

^{13}C-NMR spectra of dihydro- (*153*) and tetrahydro-β-carbolines (*154*) have been discussed and, especially in the latter case, the configurations of 1,3-disubstituted compounds have been assigned.

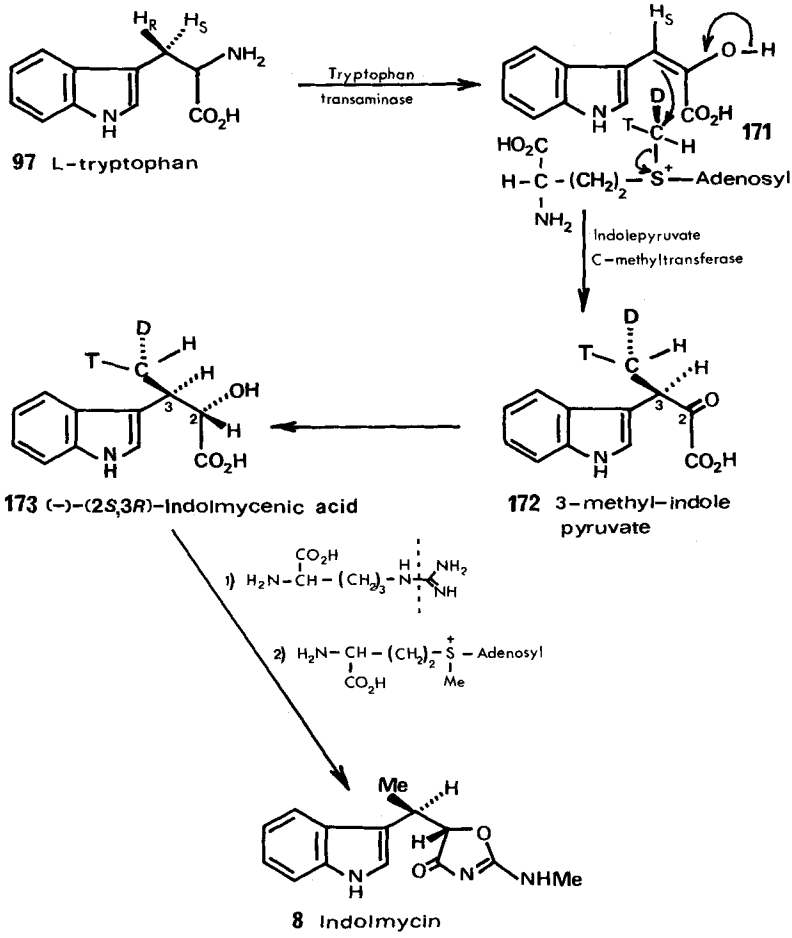
V. Biosynthesis

Although considerable work has been devoted to the biosynthesis of indole alkaloids and in particular to monoterpenoid indole alkaloids, much less interest has been directed toward the simple alkaloids included in this chapter.

A. Indolmycin

The interesting feature in the structure of indolmycin (**8**) is the presence of a methyl substituent at C-3 of the tryptophan side chain. Such an arrangement was also found in 3-methyltryptophan (*155*) and in 3-methylphenylalanine (*156*), which are constituents of peptide antibiotics produced by different *Streptomyces* strains. A similarity in the biosynthesis of these compounds was postulated, and it was shown that indoleisopropionic acid, also found in *Streptomyces* cultures, was biosynthesized from tryptophan and methionine (*157*). The same authors have established that indolmycin (**8**) is also derived from tryptophan and the methyl group of methionine. The amidino group of arginine is believed to be the precursor of the two nitrogen atoms of the oxazolinone part; this stage, however, has not yet been fully elucidated (*158*). The first two stages of the biosynthetic pathway (Scheme 27) have been studied, using cell-free extracts of *Streptomyces griseus* and more recently with purified enzymes (*159*).

The first enzyme, tryptophan transaminase, catalyzes the α-ketoglutarate and pyridoxal phosphate-dependent transamination of L-tryptophan (**97**). The second enzyme, indolepyruvate *C*-methyl transferase, belongs to a biologically important group of enzymes involved in many biosynthetic processes (e.g., nucleic acids, vitamin K). Using **171**, stereospecifically tritiated at C-3, it was demonstrated that the enzyme transfers a methyl group of (*S*)-adenosylmethionine to the C-3 position of indolepyruvic acid (**171**) with retention of configuration (*160*).

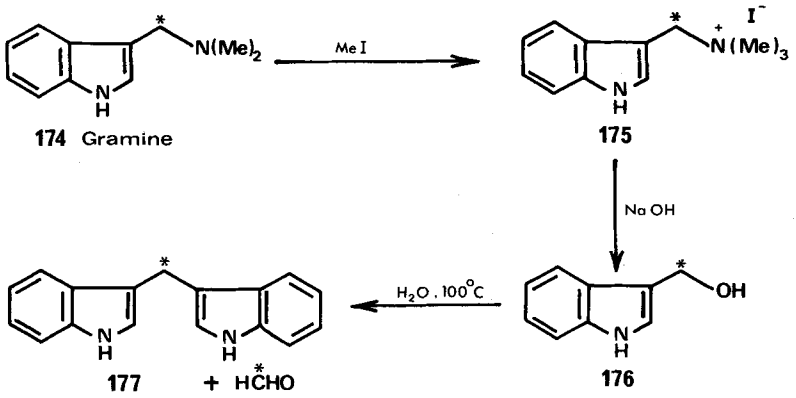


SCHEME 27

By incubation of chirally labeled methionine (methyl-*R* and methyl-*S*) in cultures of *S. griseus*, it has been shown that the C-methylation of indole-3-pyruvate (**171**) proceeded with inversion of configuration at the methyl group (*161*). An S_N2-like transition state is believed to occur during methyl transferase reactions by nucleophilic attack on the methyl group of (*S*)-adenosylmethionine (*162*).

B. GRAMINE

Gramine (**174**) is formed from tryptophan with loss of the carboxy group and C-2 (*163*). Investigations into its biosynthesis have been carried out with ger-



SCHEME 28

minating barley (gramineae) (*163,164*) and with *Lupinus hartwegii* (Leguminosae) (*165*). In the latter case, the administration of L-tryptophan-*3*-^{14}C resulted in the formation of gramine (**174**), which was shown to be labeled at C-3 (Scheme 28). Indole-3-aldehyde was also found as a metabolite of gramine in *L. hartwegii*.

C. CARBAZOLE ALKALOIDS

Little is known concerning the biosynthesis of the carbazole alkaloids, an important group that displays widely varied structural features.

Several working hypotheses have been proposed for the origin of the carbazole tricyclic system. Possible precursors include anthranilic acid, mevalonic acid, and tryptophan (*1,2*).

Feeding experiments with ^{14}C-2 and ^{3}H-2 mevalonolactone in *M. koenigii* led to incorporation of radioactivity in koenimbine, koenigicine, and mahanimbine (Table III); however, the position of the radiolabel was not determined (*1*).

A second experiment, using methyl-^{14}C-L-methionine, afforded koenigicine whose activity was located only in the two methoxy groups, demonstrating that the 3-methyl substituent comes from another carbon precursor.

It has been postulated that 3-methylcarbazole, found in the genus *Clausena* (*41,42,45*) could be the key intermediate for the biogenesis of carbazole alkaloids (*1*).

Further oxidation of the aromatic *C*-methyl group would lead to the formyl or carboxylic acid groups. The addition of a mevalonate at the C-1 position α to the phenol group at C-2 provides a route to the C_{18} carbazole alkaloid group. The incorporation of a monoterpene unit, e.g., in alkaloids **75–77** would give C_{23} alkaloids whose cyclization affords, for example, murrayazolidine (**84**).

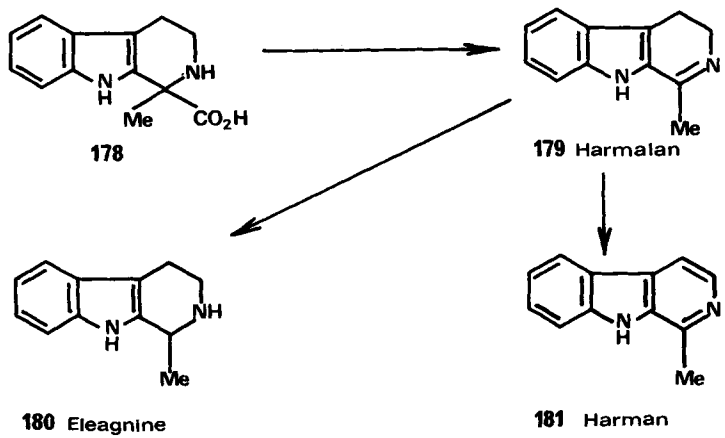
D. Tryptophan and Tryptamine

The formation of tryptamine from tryptophan has been demonstrated in cucumber seedlings (*166*). Although tryptophan decarboxylase might be expected in plants producing complex indole alkaloids, it has not been isolated from any of these plants. *Phalaris tuberosa* (Gramineae) producing *N*(*b*)-dimethyltryptamine and its 5-methoxy derivative appeared as the suitable material for these studies.

From this plant a pyridoxal phosphate-dependent tryptophan decarboxylase has been purified and its properties tested (*167*). Feeding and trapping experiments, using labeled compounds, were performed in this plant (*168*) in order to study the biosynthesis and turnover of the alkaloids. Several routes could be operating in the biosynthesis of 5-methoxy-*N*(*b*)-dimethyltryptamine, and conclusions concerning the relative importance of these pathways were not established.

E. β-Carbolines

The β-carboline alkaloids eleagnine (**180**) and harman (**181**) have been shown to be biosynthesized from (±)-tryptophan-*3'*-^{14}C in *Eleagnus angustifolia* (*169*) and *Passiflora edulis* (*170*) respectively. The two remaining carbon atoms come from pyruvic acid, which by condensation with tryptamine gave 1-methyl-1,2,3,4 tetrahydro-β-carboline-1-carboxylic acid (**178**) (Scheme 29). The key intermediate **178,** tritium labeled in the benzene ring and ^{14}C labeled on the methyl group, was found to be a significantly better precursor for eleagnine (**180**) and harman (**181**) (*171,172*). However, *N*(*b*)-acetyltryptamine was also reported to be a specific precursor for harman via **179** in *P. edulis* and to be found in the



Scheme 29

same plant (*170*). In contrast, *N*(*b*)-acetyltryptamine is not a constituent of *E. angustifolia* and is not incorporated in eleagnine (**180**) (*173*). In repeated experiments (*172*) *N*(*b*)-acetyltryptamine was found to be a very poor precursor for harman (**181**).

Harmalan (**179**) is the decarboxylation product of the amino acid (**178**) and was incorporated in both eleagnine (**180**) and harman (**181**) (*170,173*). In conclusion, the biosynthesis of the β-carboline alkaloids closely parallels that of isoquinoline alkaloids.

VI. Biological Activities

Some simple indole alkaloids produced by microorganisms have been reported to have antibiotic activities. Indolmycin (**8**) was moderately active against gram-positive and gram-negative bacteria (*174*) and was effective against sepsis caused by polyresistant *Staphylococci*. Neosidomycin (**13**) showed weak antibacterial activity against gram-negative bacteria only. Chuangxinmycin (**15**) was shown to be effective in treatment of infection caused by *Echerichia coli* in preliminary clinical results (*16*). Carbazomycin B inhibited the growth of some kinds of phytopathogenic fungi (*37*). The β-carboline pyrindolol (**162**) displayed at 100 μg/ml neither antibacterial or antifungal activity and has low toxicity in mice (*175*). It is a β-galactosidase inhibitor under both neutral and acidic conditions. None of these compounds is active enough to be used as a drug in therapeutics.

Pimprinine (**129**) was reported as having antiepileptic and monoamine oxidase inhibitory activities (*176*). *N*(*b*)-aminomethylthiazole carboxamide (**111**), extracted from a thermophilic actinomycete, has local anesthesic action.

The hydroxytryptamines (Table V) are usually classified as hallucinogens (*177*). The prototypes of these substances are 4-hydroxytryptamine (psilocin) and its dihydrogen phosphate derivative (psilocybin). 5-Hydroxy-1,2,3,4-tetrahydro-β-carbolines, hybrid molecules between two naturally occuring groups of hallucinogens, the 4-hydroxytryptamines and the 6- and 7-hydroxy-β-carbolines, have been synthesized (*178*).

The 5-hydroxy isomer of psilocin, bufotenin (**118**) is a much less potent hallucinogenic agent. Comparison of solution conformational preferences of these two compound, using 360-MHz proton NMR, suggested a weak intramolecular hydrogen bond for psilocin that could explain its lower basicity. As a consequence, the observed difference of octanol–water partition coefficients between psilocin and bufotenin accounts for the biological activity (*179*).

β-Carboline alkaloids were first known for their hypotensive activity, but recent interest has been generated by the isolation of the ethyl ester of β-carboline-3-carboxylic acid from urine (*4*). It has been proposed that β-carbolines could be an endogenous ligand of a benzodiazepin receptor (*180,181*). In

connection with interaction of harman and related alkaloids with neurotransmitters (*182*), the crystal structure of 3-carboxylic acid 1,2,3,4-tetrahydroharman has been made (*183*). Moreover, ionization and UV–visible spectral properties of these alkaloids were studied. The comparative pharmacology was discussed and related to their partition coefficients and pK_a values (*184*).

It has been reported that β-carbolines were able to potentiate mutagenicity of benzo[*a*]pyrene, but that they are not themselves mutagenic (*185*). This effect is induced by intercalation in DNA (*186*).

Acknowledgments

The author especially wishes to thank Dr. D. S. Grierson for his kind help in the preparation of the English version of this chapter.

References

1. R. S. Kapil, *Alkaloids* **13,** 273 (1971).
2. D. P. Chakraborty, *Fortschr. Chem. Org. Naturst.* **34,** 299 (1977).
3. J. R. F. Allen and B. R. Holmstedt, *Phytochemistry* **19,** 1573 (1980).
4. M. A. Collins, *Alkaloids (N.Y.)* **21,** 329 (1983).
5. B. K. Chowdhury and D. P. Chakraborty, *Phytochemistry* **10,** 481 (1971).
6. E. A. Schneider, R. A. Gibson, and F. Wightman, *J. Exp. Bot.* **23,** 152 (1972).
7. P. J. Hall, *Phytochemistry* **19,** 2121 (1980).
8. J. K. Porter, C. W.Bacon, J. D. Robbins, D. S. Himmelsbach, and H. C. Higman, *J. Agric. Food Chem.* **25,** 88 (1977).
9. M. N. Nwaji, S. O. Onyirinka, and D. A. H. Taylor, *J. Chem. Soc., Chem. Commun.,* 327 (1972).
10. V. Benesova, Z. Samek, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.* **34,** 1807 (1969).
11. H. Achenbach and B. Raffelsberger, *Tetrahedron Lett.,* 2571 (1979).
12. H. Budzikiewicz, H. Eckau, and M. Ehrenberg, *Tetrahedron Lett.,* 3807 (1972).
13. J. B. Routien, *J. Bacteriol.* **91,** 1663 (1966).
14. Y. Kawaguchi *et al.* (Bristol Banyu), Jpn. Patent 10,247 (1964).
15. R. Furuta, S. Naruto, A. Tamura, and K. Yokogawa, *Tetrahedron Lett.,* 1701 (1979).
16. H. T. Liang, H.-D. Hsu, C.-P. Chang, H.-E. Ku, and W.-S. Wang, *Hua Hsueh Hsueh Pao* **34,** 129 (1976); *Chem. Abstr.* **87,** 165948 (1977).
17. K. Hata, K. Baba, and M. Kozawa, *Chem. Pharm. Bull.* **26,** 2279 (1978).
18. K. Baba, M. Kozawa, K. Hata, T. Ishida, and M. Inoue, *Chem. Pharm. Bull.* **29,** 2182 (1981).
19. G. J. Kapadia, Y. N. Shukla, B. K. Chowdhury, S. P. Basak, H. M. Fales, and E. A. Sokoloski, *J. Chem. Soc., Chem. Commun.,* 535 (1977).
20. G. J. Kapadia, Y. N. Shukla, S. P. Basak, E. A. Sokoloski, and H. M. Fales, *Tetrahedron* **36,** 2441 (1980).
21. S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.* **20,** 1737 (1967).
22. W. J. Keller and G. M. Hatfield, *Phytochemistry* **21,** 1415 (1982).
23. S. O. Onyiriuka and M. N. Nwaji, *J. Chem. Res. Synop.,* 21 (1983).

24. M. Schach von Witteneau and H. Els, *J. Am. Chem. Soc.* **83,** 4678 (1961).
25. M. Schach von Witteneau and H. Els, *J. Am. Chem. Soc.* **85,** 3425 (1963).
26. M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron* **24,** 6131 (1968).
27. U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *Tetrahedron Lett.*, 2255 (1970).
28. U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Am. Chem. Soc.* **93,** 3028 (1971).
29. T. H. Chan and R. K. Hill, *J. Org. Chem.* **35,** 3519 (1970).
30. C.-P. Chang, H.-D. Hsu, L.-C. Huang, Y.-C. Lin, H.-S. Li, C.-L. Yu, and C.-L. Chao, *Acta Chim. Sin.* **34,** 133 (1976); *Chem. Abstr.* **88,** 62309 (1978).
31. A. P. Kozikowski and M. N. Greco, *J. Am. Chem. Soc.* **102,** 1165 (1980).
32. A. P. Kozikowski, M. N. Greco, and J. P. Springer, *J. Am. Chem. Soc.* **104,** 7622 (1982).
33. R. M. Acheson, D. M. Littlewood, and H. E. Rosenberg, *J. Chem. Soc., Chem. Commun.*, 671 (1974).
34. R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans.*, 1117 (1978).
35. M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. Chim. Fr.*, 1296 (1967).
36. R. F. Raffauf, "A Handbook of Alkaloids and Alkaloid-Containing Plants." Wiley (Interscience), New York, 1970.
37. K. Sakano, K. Ishimaru, and S. Nakamura, *J. Antibiot.* **33,** 683 (1980).
38. K. Sakano and S. Nakamura, *J. Antibiot.* **33,** 961 (1980).
39. M. Kaneda, K. Sakano, and S. Nakamura, *Heterocycles* **15,** 993 (1981).
40. D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron* **21,** 681 (1965).
41. P. Bhattacharyya and D. P. Chakraborty, *Phytochemistry* **12,** 1831 (1973).
42. S. Roy, P. Bhattacharyya, and D. P. Chakraborty, *Phytochemistry* **13,** 1017 (1974).
43. B. K. Chowdhury and D. P. Chakraborty, *Chem. Ind. (London),* 549 (1969).
44. D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya, and A. K. Biswas, *Phytochemistry* **17,** 834 (1978).
45. B. S. Joshi and D. H. Gawad, *Indian J. Chem.* **12,** 437 (1974).
46. B. S. Joshi, V. N. Kamat, A. K. Saksena, and T. R. Govindachari, *Tetrahedron Lett.*, 4019 (1967).
47. T. S. Wu and H. Furuka, *J. Nat. Prod.* **45,** 718 (1982).
48. R. B. Sharma and R. S. Kapil, *Chem. Ind. (London),* 58 (1980).
49. D. Prakash, K. Raj, R. S. Kapil, and S. P. Popli, *Indian J. Chem. Sect. B* **19,** 1075 (1980).
50. R. B. Sharma and R. S. Kapil, *Chem. Ind. (London),* 268 (1982).
51. A. V. Rama Rao, K. S. Bhide, and R. B. Mujumdar, *Chem. Ind. (London),* 697 (1980).
52. D. P. Chakraborty, S. Roy, and R. Guha, *J. Indian Chem. Soc.* **55,** 1114 (1978).
53. D. P. Chakraborty and B. P. Das, *Sci. Cult.* **32,** 181 (1966).
54. D. O. Okorie, *Phytochemistry* **14,** 2720 (1975).
55. S. Mukherjee, M. Mukherjee, and S. N. Ganguly, *Phytochemistry* **22,** 1064 (1983).
56. D. P. Chakraborty, *Tetrahedron Lett.*, 661 (1966).
57. D. P. Chakraborty, *Phytochemistry* **8,** 769 (1969).
58. D. P. Chakraborty, *J. Indian Chem. Soc.* **46,** 177 (1969).
59. D. P. Chakraborty and K. C. Das, *J. Chem. Soc., Chem. Commun.*, 967 (1968).
60. D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *J. Org. Chem.* **36,** 725 (1971).
61. D. P. Chakraborty, K. C. Das, and A. Islam, *J. Indian Chem. Soc.* **47,** 1197 (1970).
62. N. S. Narasimhan, M. V. Paradkar, and V. P. Chitguppi, *Tetrahedron Lett.*, 5501 (1968).
63. N. S. Narasimhan, M. V. Paradakar, and S. L. Kelkar, *Indian J. Chem.* **8,** 473 (1970).
64. N. S. Narasimhan, N. V. Paradakar, V. P. Chitguppi, and S. L. Kelkar, *Indian J. Chem.* **13,** 993 (1975).

65. D. P. Chakraborty, P. Bhattacharyya, A. Islam, and S. Roy, *Chem. Ind. (London)*, 303 (1974).
66. I. Mester, K. Szendrei, and J. Reisch, *Planta Med.* **32,** 81 (1977).
67. S. Roy and D. P. Chakraborty, *J. Indian Chem. Soc.* **57,** 759 (1980).
68. S. P. Kureel, R. S. Kapil, and S. P. Popli, *Experientia* **26,** 1055 (1970).
69. S. Roy, S. Gosh, and D. P. Chakraborty, *Chem. Ind. (London)*, 669 (1979).
70. B. S. Joshi, V. N. Kamat, D. H. Gawad, and T. R. Govindachari, *Phytochemistry* **11,** 2065 (1972).
71. P. Bhattacharyya, A. R. Mitra, and D. P. Chakraborty, *J. Indian Chem. Soc.* **53,** 321 (1976).
72. A. Islam, P. Bhattacharyya, and D. P. Chakraborty, *J. Chem. Soc., Chem. Commun.*, 537 (1972).
73. W. Carruthers, *J. Chem. Soc., Chem. Commun.*, 272 (1966).
74. D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *Phytochemistry* **8,** 773 (1969).
75. S. P. Kureel, R. S. Kapil, and S. P. Popli, *Tetrahedron Lett.*, 3857 (1969).
76. D. P. Chakraborty, P. Bhattacharyya, and A. R. Mitra, *Chem. Ind. (London)*, 260 (1974).
77. S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. Ind. (London)*, 958 (1970).
78. P. Bhattacharyya, S. Roy, A. Biswas, L. Bhattacharyya, and D. P. Chakraborty, *J. Indian Chem. Soc.* **55,** 308 (1978).
79. S. N. Ganguly and A. Sarkar, *Phytochemistry* **17,** 1816 (1978).
80. J. Bordner, D. P. Chakraborty, B. K. Chowdhury, S. N. Ganguly, K. C. Das, and B. Weinstein, *Experientia* **28,** 1406 (1972), and references cited therein.
81. L. Bhattacharyya, S. K. Roy, and D. P. Chakraborty, *Phytochemistry* **21,** 2432 (1982).
82. R. B. Sharma, R. Seth-Verma, and R. S. Kapil, *Experientia* **36,** 815 (1980).
83. S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. Ind. (London)*, 1262 (1970).
84. N. L. Dutta, C. Quascin, and M. S. Wadia, *Indian J. Chem.* **7,** 1168 (1969).
85. D. P. Chakraborty, A. Islam, S. P. Basak, and R. Das, *Chem. Ind. (London)*, 593 (1970).
86. W. M. Bandaranayeke, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Perkin Trans.* **1,** 998 (1974).
87. D. P. Chakraborty, S. N. Ganguly, P. N. Maji, and A. R. Mitra, *Chem. Ind. (London)*, 322 (1973).
88. N. S. Narasimhan and S. L. Kelkar, *Indian J. Chem. Sect. B* **14,** 430 (1976).
89. D. H. Janzen, D. G. Lynn, L. E. Fellows, and W. Hallwachs, *Phytochemistry* **21,** 1035 (1982).
90. H. J. L. Liang and J. A. Anderson, *Phytochemistry* **17,** 597 (1978).
91. S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.* **24,** 439 (1971).
92. S. Ghosal and S. K. Dutta, *Phytochemistry* **10,** 195 (1971).
93. M. Nomoto and S. Tamura, *Agric. Biol. Chem.* **34,** 1590 (1970).
94. S. Ghosal and S. Srivastava, *Phytochemistry* **12,** 193 (1973).
95. G. A. Moro, M. N. Graziano, and J. D. Coussio, *Phytochemistry* **14,** 827 (1975).
96. K. S. Svoboda, S. J. Smolenski, and A. D. Kinghorn, *J. Nat. Prod.* **42,** 307 (1979).
97. C. Poupat, A. Ahond, and T. Sévenet, *Phytochemistry* **15,** 2019 (1976).
98. D. dos Santos Filho and B. Gilbert, *Phytochemistry* **14,** 821 (1975).
99. A. Ueno, Y. Ikeya, S. Fukushima, T. Noro, K. Morinaga, and H. Kuwano, *Chem. Pharm. Bull.* **26,** 2411 (1978).
100. S. Ghosal, V. K. Mazumder, and R. Mehta, *Phytochemistry* **11,** 1863 (1972).
101. H. Morimoto and H. Oshio, *Annalen* **682,** 212 (1965).
102. M. S. Hifnawy, J. Vaquette, T. Sévenet, J. L. Pousset, and A. Cavé, *Phytochemistry* **16,** 1035 (1977).
103. A. Ehmann, *Phytochemistry* **13,** 1979 (1974).
104. V. Vecchietti, G. Ferrari, F. Orsini, and F. Pellizzoni, *Phytochemistry* **18,** 1847 (1979).

105. Y. Konda, Y. Suzuki, S. Omura, and M. Onda, *Chem. Pharm. Bull.* **24,** 92 (1976).
106. A. Hofmann and F. Troxler, *Experientia* **15,** 101 (1959).
107. Y. Koike, K. Wada, G. Kusano, S. Nozoe, and K. Yokoyama, *J. Nat. Prod.* **44,** 362 (1981).
108. A. L. Christiansen and K. E. Rasmussen, *J. Chromatogr.* **244,** 357 (1982).
109. E. McKenzie, L. Nettleship, and M. Slaytor, *Phytochemistry* **14,** 273 (1975).
110. G. Baudoin, F. Tillequin, M. Koch, J-L. Pousset, and T. Sévenet, *J. Nat. Prod.* **44,** 546 (1981).
111. G. M. Hatfield, L. J. Valdes, and A. H. Smith, *Lloydia* **41,** 140 (1978).
112. W. A. Ayer and L. M. Browne, *Can. J. Chem.* **48,** 1980 (1970).
113. R. Gmelin and A. I. Virtanen, *Ann. Acad. Sci. Fenn., Ser. A2,* 107 (1961).
114. R. Gmelin and A. I. Virtanen, *Acta Chem. Scand.* **16,** 1378 (1962).
115. M. C. Elliott and B. B. Stowe, *Phytochemistry* **9,** 1629 (1970).
116. R. J. W. Truscott, D. G. Burke, and I. R. Minchinton, *Biochem. Biophys. Res. Commun.* **107,** 1258 (1982).
117. R. J. W. Truscott, I. R. Minchinton, D. G. Burke, and J. P. Sany, *Biochem. Biophys. Res. Commun.* **107,** 1368 (1982).
118. J. K. Goetz and H. Schraudolf, *Phytochemistry* **22,** 905 (1983).
119. Y. Chen, A. Zeeck, Z. Chen, and H. Zähner, *J. Antibiot.* **36,** 913 (1983).
120. D. S. Bhate, R. K. Hulyalkar, and S. K. Menon, *Experientia* **16,** 56 (1960).
121. Y. Koyama, K. Yokose, and L. J. Dolby, *Agric. Biol. Chem.* **45,** 1285 (1981).
122. M. Noltemeyer, G. M. Sheldrick, H. U. Hoppe, and A. Zeeck, *J. Antibiot.* **35,** 549 (1982).
123. H. Ripperger, M. Diaz, and K. Schreiber, *Phytochemistry* **20,** 1453 (1981).
124. K. A. Ubaidullaev, R. Shakirov, and S. Y. Yunusov, *Khim. Prir. Soedin.,* 553 (1976); *Chem. Abstr.* **86,** 121586 (1977).
125. T. Shono, Y. Matsumara, and T. Kanazawa, *Tetrahedron Lett.* **24,** 1259 (1983) (for syntheses of racemic tryptophans see Ref. *126*).
126. U. Hengartner, A. D. Batcho, J. F. Blount, W. Leimgruber, M. E. Larscheid, and J. W. Scott, *J. Org. Chem.* **44,** 3748 (1979).
127. M. Somei, H. Sato, and C. Kaneko, *Heterocycles* **20,** 1797 (1983).
128. A. Husson, R. Besselièvre, and H.-P. Husson, *Tetrahedron Lett.* **24,** 1031 (1983).
129. D. Seebach, V. Ehrig, H. F. Leitz, and R. Henning, *Chem. Ber.* **108,** 1946 (1975).
130. M. Julia and H. Gaston-Breton, *Bull. Soc. Chim. Fr.,* 1335 (1966).
131. T. Yoshioka, K. Mohri, Y. Oikawa, and O. Yonemitsu, *J. Chem. Res. Synop.,* 194 (1981).
132. Y. Oikawa, T. Yoshioka, K. Mohri, and O. Yonemitsu, *Heterocycles* **12,** 1457 (1979).
133. T. Ohmoto and K. Koike, *Chem. Pharm. Bull.* **30,** 1204 (1982).
134. T. Ohmoto, K. Koike, and Y. Sakamoto, *Chem. Pharm. Bull.* **29,** 390 (1981).
135. T. Ohmoto and K. Koike, *Chem. Pharm. Bull.* **32,** 170 (1984).
136. E. Sanchez and J. Comin, *Phytochemistry* **10,** 2155 (1971).
137. M. P. Jain, S. K. Koul, K. L. Dhar, and C. K. Atal, *Phytochemistry* **19,** 1880 (1980).
138. W. Rolfsen, A. M. Breski, M. Andersson, and J. Strömbom, *Acta Pharm. Suec.* **17,** 333 (1980).
139. R. Verpoorte, F. T. Joosse, H. Groenink, and A. B. Swendsen, *Planta Med.* **42,** 32 (1981).
140. J. Banerji, A. Chatterjee, D. J. Roy, and J. N. Shoolery, *Phytochemistry* **21,** 2765 (1982).
141. J. R. Cannon and J. R. Williams, *Aust. J. Chem.* **35,** 1497 (1982).
142. I. Razmilic, M. Castillo, and J. T. Lopez, *J. Heterocycl. Chem.* **17,** 595 (1980).
143. M. Kumagai, H. Naganawa, T. Aoyagi, and H. Umezawa, *J. Antibiot.* **28,** 876 (1975).
144. D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.* **44,** 535 (1979).
145. F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.* **46,** 164 (1981).
146. Y. Oikawa and O. Yonemitsu, *J. Org. Chem.* **42,** 1213 (1977).

147. R. Grigg, H. Q. N. Gunaratne, and E. McNaghten, *J. Chem. Soc., Perkin Trans.* **1,** 185 (1983).
148. H. Bieraügel, R. Plemp, and U. K. Pandit, *Heterocycles* **14,** 947 (1980).
149. M. Cain, R. Mantei, and J. M. Cook, *J. Org. Chem.* **47,** 4933 (1982).
150. O. Campos, M. DiPierro, M. Cain, R. Mantei, A. Gawish, and J. M. Cook, *Heterocycles* **14,** 975 (1980).
151. M. Cain, O. Campos, and J. M. Cook, *J. Am. Chem. Soc.* **105,** 907 (1983).
152. R. E. Balsells and A. R. Frasca, *Tetrahedron* **39,** 33 (1983).
153. C. A. Coune, L. J. G. Angenot, and J. Denoel, *Phytochemistry* **19,** 2009 (1980).
154. F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.* **102,** 6976 (1980).
155. J. C. Sheehan, D. Mania, S. Nakamura, J. K. Stock, and K. Maeda, *J. Am. Chem. Soc.* **90,** 462 (1968).
156. S. Nakamura, T. Yajima, Y. C. Lin, and H. Umezawa, *J. Antibiot.* **20,** 1 (1967).
157. U. Hornemann, M. K. Speedie, K. M. Kelley, L. H. Hurley, and H. G. Floss, *Arch. Biochem. Biophys.* **131,** 430 (1969).
158. U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Am. Chem. Soc.* **93,** 3028 (1971).
159. M. K. Speedie, U. Hornemann, and H. G. Floss, *J. Biol. Chem.* **250,** 7819 (1975).
160. L. Zee, U. Hornemann, and H. G. Floss, *Biochem. Physiol. Pflanz.* **168,** 19 (1975).
161. L. Mascaro, R. Hörhammer, S. Eisenstein, L. K. Sellers, K. Mascaro, and H. G. Floss, *J. Am. Chem. Soc.* **99,** 273 (1977).
162. M. F. Hegazi, R. T. Borchardt, and R. L. Showen, *J. Am. Chem. Soc.* **98,** 3048 (1976).
163. D. O'Donovan and E. Leete, *J. Am. Chem. Soc.* **85,** 461 (1963).
164. D. Gross, H. Lehmann, and H. R. Schütte, *Tetrahedron Lett.*, 4047 (1971).
165. E. Leete, *Phytochemistry* **14,** 471 (1975).
166. J. E. Sherwin, *Plant Cell. Physiol.* **11,** 865 (1970).
167. C. Baxter and M. Slaytor, *Phytochemistry* **11,** 2763 (1972).
168. C. Baxter and M. Slaytor, *Phytochemistry* **11,** 2767 (1972).
169. D. G. O'Donovan and M. F. Kennealy, *J. Chem. Soc., Sect. C,* 1109 (1967).
170. M. Slaytor and I. J. McFarlane, *Phytochemistry* **7,** 605 (1968).
171. R. B. Herbert and J. Mann, *J. Chem. Soc., Chem. Commun.*, 841 (1980).
172. R. B. Herbert and J. Mann, *J. Chem. Soc., Perkin Trans. 1,* 1523 (1982).
173. I. J. McFarlane and M. Slaytor, *Phytochemistry* **11,** 229 (1972).
174. M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron* **24,** 6131 (1968).
175. T. Aoyagi, M. Kumagai, T. Hazato, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.* **28,** 555 (1975).
176. M. J. Narasimhan and V. G. Ganla, *Hind. Antibiot. Bull.* **9,** 138 (1967).
177. R. W. Brinblecombe and R. M. Pinder *in* "Hallucinogenic Agents" p. 106. Wright Scientechnica, Bristol, England, 1975.
178. D. B. Reske and N. J. Ferguson, *J. Heterocycl. Chem.* **19,** 845 (1982).
179. G. P. Migliaccio, T. L. N. Shieh, S. R. Byrn, B. A. Hathaway, and D. E. Nichols, *J. Med. Chem.* **24,** 206 (1981).
180. C. Braestrup, M. Nielson, and C. Olsen, *Proc. Natl. Acad. Sci. U.S.A.* **77,** 2288 (1980).
181. P. Skolnick and S. M. Paul, *Annu. Rep. Med. Chem.* **16,** 21 (1981).
182. W. E. Müller, K. J. Fehske, H. O. Borke, U. Wollert, C. Nanzand, and H. Rommelspacher, *Pharmacol. Biochem. Behav.* **14,** 693 (1981).
183. P. W. Codding, *Can. J. Chem.* **61,** 529 (1983).

184. K. T. Douglas, R. K. Sharma, J. F. Walmsley, and R. C. Hider, *Mol. Pharmacol.* **23,** 614 (1983).
185. J. Pezzuto, P. Lau, Y. Luh, P. Moore, G. Wogan, and S. Hecht, *Proc. Natl. Acad. Sci. U.S.A.* **77,** 1427 (1980).
186. R. Leavitt, C. Legraverent, D. Nevert, and O. Pelkonen, *Biochem. Biophys. Res. Commun.* **79,** 1167 (1977).

This Page Intentionally Left Blank

— CHAPTER 2 —

SULFUR-CONTAINING ALKALOIDS

JERZY T. WRÓBEL

Department of Chemistry
University of Warsaw
Warsaw, Poland

THE ALKALOIDS, VOL. 26

I. Introduction

Sulfur-containing alkaloids constitute a group of natural products that has never been reviewed in *The Alkaloids*, although the first example of such a compound was recognized as early as 1944 in the group of Erythrina alkaloids (*1*). Some of the sulfur-containing alkaloids were reported in the review by S. F. Aripova and S. Yu. Yunusov in 1978 (*2*), and the sulfur-containing Nuphar alkaloids were described in this series (*3,4*).

The actually known sulfur-containing alkaloids could be listed in more than 30 different groups, representing more than 60 individual alkaloids.

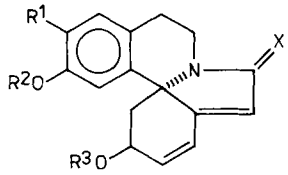
A great variety of structures with different chromophores were recognized together with different numbers of sulfur atoms (one to four), which could be placed either in the side chain or in the ring. The increasing interest in this group of alkaloids is connected with new structures and chemical properties as well as with pharmacological activity. A historical view of the discovery of sulfur-containing alkaloids is given in Table I.

The sulfur-containing alkaloids may be classified in many ways. In this chapter the guide for the classification will be the number of sulfur atoms and their presence in the side chain or in the ring.

II. Alkaloids with One Sulfur Atom in the Side Chain

A. Erysothiovine and Erysothiopine

Erysothiovine (**1**) and erysothiopine (**2**) were isolated (*1*) in 1944 from *Erythrina* seeds, and their structures proposed on the basis of chemical degradation:



1 Erysothiovine $R^1 = OCH_3$, $R^2 = HO_2CCH_2SO_2$, $R^3 = CH_3$, $X = 2H$

2 Erysothiopine $R^1 = HO_2CCH_2SO_2$, $R^2 = H$, $R^3 = CH_3$, $X = 2H$

Compounds **1** and **2** were isolated from *Erythrina glauca* Willd, from *Erythrina pallida* Britton and Rose, and *Erythrina poeppigiana* (Walp.) O. F. Cook. They produced curare-like paralysis in frogs and were more active when compared with bases obtained from natural sources or with their hydrolysis products erysovine and erysopine, which do not contain sulfur.

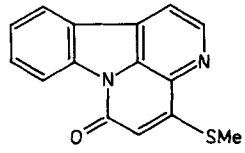
TABLE I
SULFUR-CONTAINING ALKALOIDS: HISTORICAL VIEW OF ISOLATION AND STRUCTURE ELUCIDATION

Year	Alkaloid and source	Reference
1944	Erysothiovine (from *Erythrina glauca* Willd.)	*1*
1952	PA-2 (from *Pentaceras australis* Hook)	*5*
1958	Gliotoxine (from *Gliocladium fimbriatum*)	*39–41*
1961	Zapotidine (from *Casimiroa edulis* Llave et Lex)	*6*
1964	Nuphar (from *Nuphar luteum*)	*3,4*
1965	Glucobrassicin (from Capparidaceae)	*18*
1966	Brugine (from *Bruguiera sexangula*)	*32–34*
1966	Planchonelline (from *Planchonella thyrsoidea* C. T. White)	*9,10*
1966	Sporidesmins (from *Pithomyces chartarum*)	*95*
1967	Cassipourine (from *Cassipourea gerrardii*, Rhisophoraceae)	*35,36*
1968	Aranotin [from *Arachniotus aurens* (Eidam) Schroeter]	*76*
1970	Chaetocin (from *Chaetonium minutum*)	*85*
1972	Sporidesmin (from *Pithomyces chartarum*)	*59,60*
1973	Japindine (from *Chonemorpha macrophylla*)	*14*
1973	Verticillin A, B, and C (from *Verticillium* species)	*84*
1973	Hyalodendrin (from *Hyalodendron* species)	*79–81*
1974	Amanitin (from *Amanita phalloides*)	*92*
1975	Resedinine (from *Brassica*, Cruciferae)	*11–13*
1976	Alkaloid from *Thermoactinomyces* (TM-64)	*22*
1977	Sirodesmin (from *Sirodesmium diversum*)	*74*
1977	Diptocarpidine (from *Dipthychocarpus strictus*)	*15–17*
1978	Chetomin (from *Chaetomium cochliodes*)	*87*
1980	Xylostosidine (from *Lonicera xylosteum* L.)	*27*
1980	Ulicyclamid (from *Lissoclinum patella*)	*91*
1980	Chuangxinmycin (from *Actinoplanes tsinanensis*)	*19*
1980	Latrumculine A and B (from *Latrunculia magnifica*)	*29,30*
1980	Ferrithiocin (from *Streptomyces antibioticus*)	*25*
1980	Myxothiasol (from *Myxococcus fulvus*)	*26*
1982	Gliovirine (from *Gliocladium vireus*)	*57,58*
1978	Amatoxines (from *Amanita phalloides*)	*93,95*
1978	Phalloine (from *Amanita phalloides*)	*92*
1978	Norphalloine (from *Amanita phalloides*)	*92,94*

B. 4-METHYLTHIOCANTHIN-6-ONE

Nelson and Price isolated 4-methylthiocanthin-6-one (**3**), an indole alkaloid, from an Australian plant in the family Rutaceae, *Pentaceras australis* Hook F. (*5*).

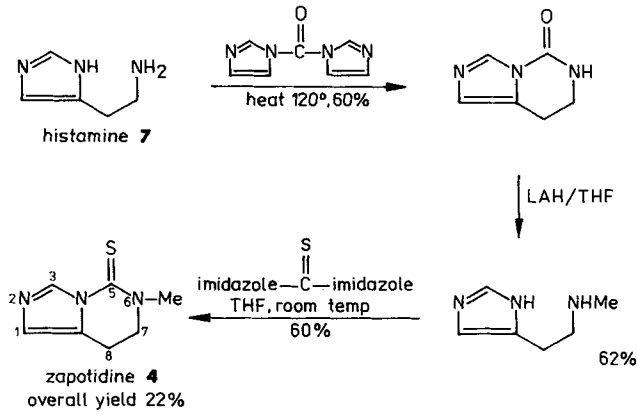
The structure was proved by alkaline hydrolysis, Raney nickel reduction, and preparation of the alkaloid from the corresponding hydroxyl derivative, first by reaction with PCl_5, then with $KSCH_3$.



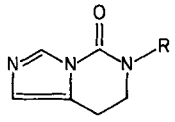
3

C. ZAPOTIDINE

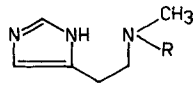
The seeds of the Mexican tree *Casimiroa edulis* Llave et Lex were found to contain zapotidine (**4**) (*6*), which might be one of the constituents responsible for hypnotic, sedative, and hypotensive activity. It has no effect on the autonomic nervous system and no action against bacteria. Zapotidine was found to be toxic in mice.



The structure of **4** was suggested (*7*) on the basis of the results of Ag_2O oxidation, $LiAlH_4$ reduction, and alkaline hydrolysis, which resulted in products **5** and **6a,b** respectively. Mechoulam and Hirshfeld (*8*) carried out a total synthesis of **4** from histamine in three steps shown in the scheme. The overall yield was 22%.



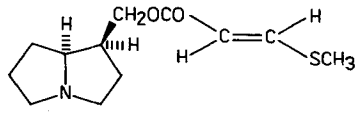
5 R = CH_3



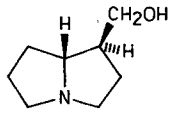
6a R = CH_3
6b R = H

D. Planchonelline

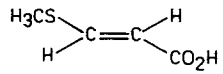
Planchonelline (**8**, $C_{12}H_{19}O_2NS$) was found (*9,10*) to be a major alkaloid of the leaves of *Planchonella thyrsoidea* C. T. White and *Planchonella auteridifera* (White and Francis) H. J. Lam. The structure of **8** was established as an ester of *trans*-β-thioacrylic acid (**9**) and the necine base laburnine (**10**), based on hydrolysis of **8** and identification of the resulting base **10** and acid **9**, which are known compounds.



8



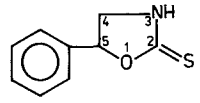
10



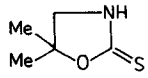
9

E. Resedinine and Related Alkaloids

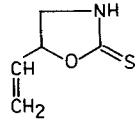
Resedinine (**11**, C_9H_9NOS) and two other compounds (**12** and **13**) represent alkaloids with structures of the oxazolidinethione type. They were isolated from the plants of the genus *Brassica* (family Cruciferae) (*11–13*). The structure of residinine was suggested by the spectroscopic data and comparison of their properties with those of resedine (**12**).



11



12

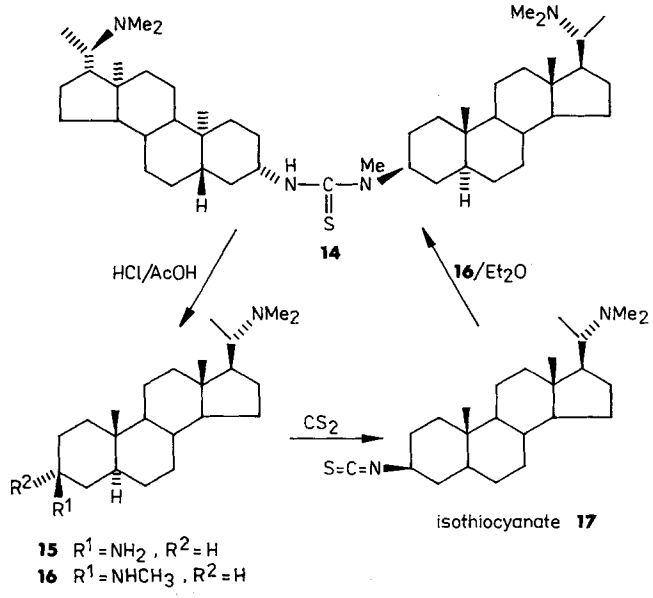


13

F. Japindine

Japindine (**14**, $C_{48}H_{84}N_4S$) is a thiourea derivative with a chonemorphine skeleton. It was isolated from *Chonemorpha macrophylla* G. Don (C. Fragrans

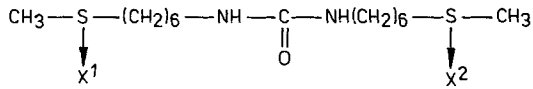
Moon Alston) (*14*). The structure was established on the basis of results obtained by hydrolysis in acetic acid, which resulted in both acetylated chonemorphine (**15**) and *N*-methylchonemorphine (**16**). Further support for structure **14** was obtained from spectroscopic data (^{1}H NMR) and partial synthesis from chonemorphine and carbon disulfide, which first produced **17** and which in turn reacted with *N*-methylchonemorphine to yield **14.**



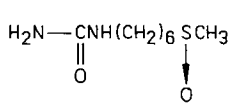
15 $R^1 = NH_2$, $R^2 = H$
16 $R^1 = NHCH_3$, $R^2 = H$

G. Diptocarpidine and Related Alkaloids

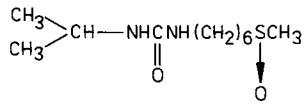
Diptocarpidine (**18**) and related alkaloids are derivatives of urea and were isolated from the species *Diphychocarpus strictus* (family Cruciferae) (*15–17*). Diptocarpidine (**18a**) and its monodeoxy derivative diptocarpiline (**18b**), diptocarpaine (**19**), and diptocarpamine (**20**) are the compounds whose structures have been established. The desulfurization with Raney nickel was used in the structure elucidation.



18a $X^1 = X^2 = O$
18b $X^1 = O$; $X^2 =$:



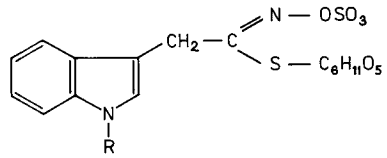
19



20

H. GLUCOBRASSICIN

H. Schrandorf (*18*) has isolated a group of indoleglucosinolates from plants of families Capparidaceae, Resedaceae, and Tovariaceae, in which two alkaloids, glucobrassicin (**21**) and neoglucobrassicin (**22**), were found.



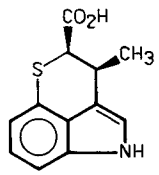
21 R = H glucobrassicin
22 R = OCH_3 neoglucobrassicin

III. Alkaloids with One Sulfur Atom in the Ring

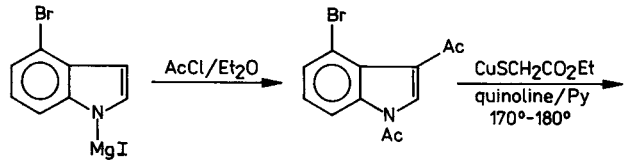
A. CHUANGXINMYCIN

Chuangxinmycin (**23**, $C_{12}H_{11}NO_2S$) of undetermined absolute configuration was isolated from *Actinoplanes tsinanensis* by Chinese researchers (*19*) who suggested the structure of the alkaloid on the basis of spectroscopic data [NMR, IR, UV, and mass spectrometry (MS)], Chuangxinmycin was found active *in vitro* against a number of gram-negative and gram-positive bacteria. In mice, activity against *Escherichia coli* and *Shigella dysenteriae* was demonstrated (*20*). This structure was confirmed by the synthesis of racemic **23** (*20*). The synthesis was completed in three steps starting with indole derivative **24.**

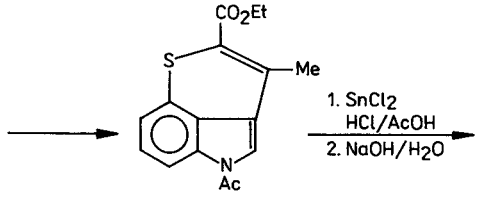
By a different route, (±)-**23** was synthesized by Kozikowski and Greco (*21*) from dinitrotoluene (**25**).

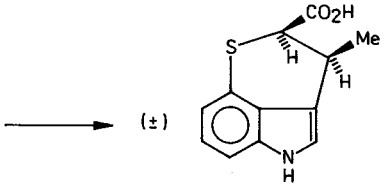


23

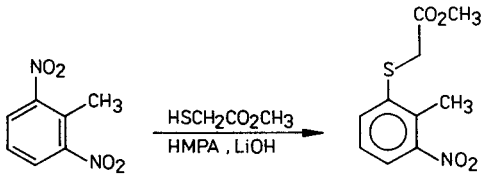

Br
AcCl/Et2O
Br
Ac
N
Ac
CuSCH2CO2Et
quinoline/Py
170°-180°
N
MgI

24

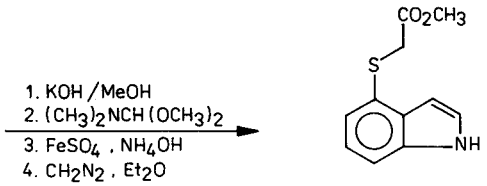

CO2Et
S
Me
1. SnCl2
HCl/AcOH
2. NaOH/H2O
N
Ac

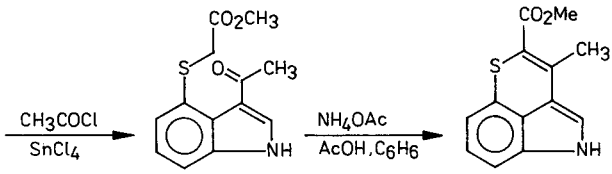

CO2H
S
Me
H
H
(±)
N
H

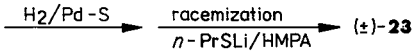
23

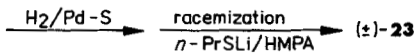

NO2
CH3
HSCH2CO2CH3
HMPA , LiOH
CO2CH3
S
CH3
NO2
NO2

25


CO2CH3
S
1. KOH / MeOH
2. (CH3)2NCH(OCH3)2
3. FeSO4 , NH4OH
4. CH2N2 , Et2O
NH

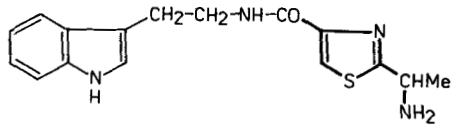

CO2CH3
S
O
CH3
CH3COCl
SnCl4
NH
NH4OAc
AcOH,C6H6
CO2Me
CH3
S
NH


H2/Pd-S
racemization
n-PrSLi/HMPA
(±)-23



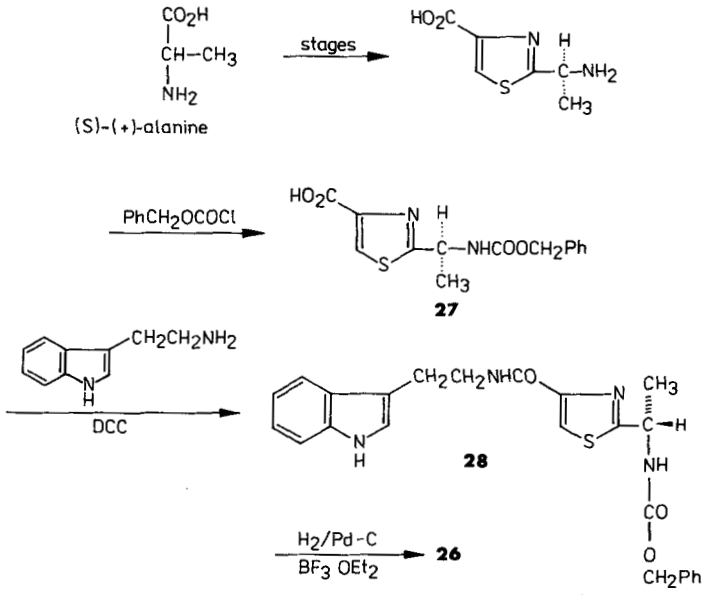
B. ALKALOID TM-64

Alkaloid TM-64, containing sulfur in the thiazole ring, is an amide with an indole skeleton (**26**, $C_{16}H_{18}ON_4S$). It was isolated first by a Japanese group from a thermophilic actinomycete, *Thermoactinomyces* strain TM-64 (*22*). ^{1}H-NMR and ^{13}C-NMR spectra together with other spectral data and hydrolysis (basic and acidic) furnished sufficient evidence to confirm the structure **26** for TM-64 (*23*).



26

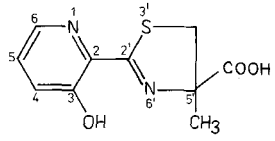
Stereospecific total synthesis of **26** was completed by Onda and Konda (*24*). Starting with (*S*)-(+)-alanine, they prepared optically active thiazole-4-carboxylic acid derivative **27**, which was combined with tryptamine, resulting in **28**, possessing the skeleton of the alkaloid. Compound **28** was transformed to **26** in one step. The synthesis is shown in the scheme.



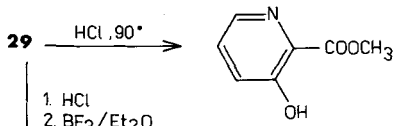
Compound **26** was found to possess a local anesthetic action and a weak deteriorated reflex action of cornea when dropped into an eye of a guinea pig.

C. Ferrithiocin

Ferrithiocin (**29,** $C_{10}H_{10}N_2O_3S$) is another example of a thiazole derivative. It was isolated from *Streptomyces antibioticus* strain Tü 1998 (*25*). Ferrithiocin on acidic hydrolysis (HCl) results in **30,** and on hydrolysis (HCl) followed by esterification (CH_2N_2) in the presence of BF_3–Et_2O it affords **31.**

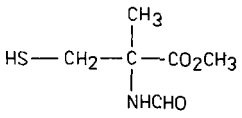


29



1. HCl
2. BF_3/Et_2O
CH_2N_2

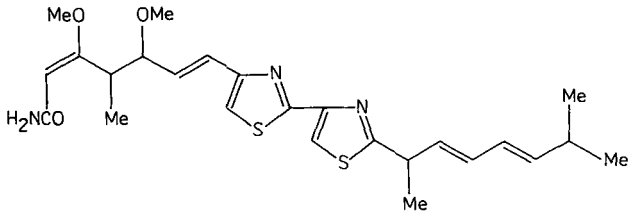
30



31

D. Myxothiazol

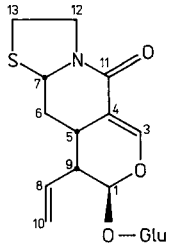
Myxothiazol (**32,** $C_{25}H_{33}N_3O_3S_2$) was isolated from *Myxococcus fulvus* (Myxobacteriales) (*26*). It is active against many fungi. The structure of **32** was established by spectroscopic methods (^{1}H- and ^{13}C-NMR and MS).



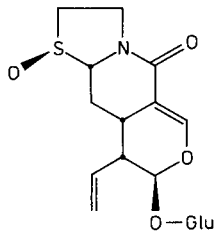
32

E. Xylostosidine and Its *S*-Oxides

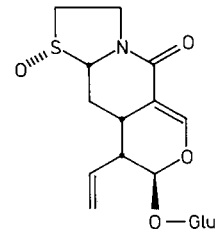
Xylostosidine (**33**) is a monoterpene glycoside with sulfur in a thiazole ring. It was isolated from the species *Lonicera xylosteum* L. (Carprifoliaceae) (*27*). There were no earlier reports on the occurrence of any alkaloids in the family Carprifoliaceae. The structure of **33** ($C_{18}H_{25}O_8NS$) was suggested on the basis of spectroscopic data (UV, IR, MS, and ^1H and ^{13}C NMR) supported by 360-MHz ^1H NMR, which confirmed the configuration at C-1, C-5, and C-9 by comparing it with **35** of known configuration.



33

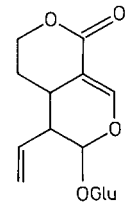


34a



34b

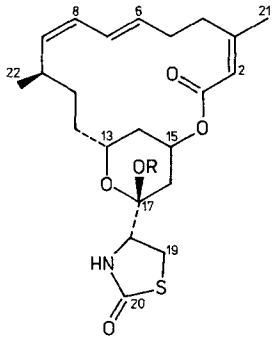
Two isomeric sulfoxides of **33** were isolated from the same species (*28*). Loxylostosidine A (**34a**) and loxylostosidine B (**34b**) differ only by their configuration at the sulfur atom.



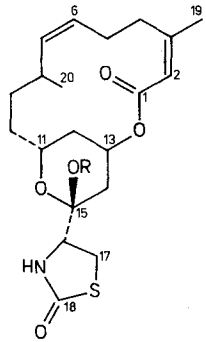
35

F. Latrunculin A and B

From the Red Sea sponge *Latrunculia magnifica,* three new toxins were isolated (*29,30*). Latrunculin A and B (**36a** and **37,** respectively) are macrolides with sulfur in a 2-thiazolidinone moiety. Latrunculin A ($C_{22}H_{31}NO_5S$) was shown to have structure **36a** by 270-MHz ^1H-NMR, 22.63-MHz ^{13}C-NMR, and MS. The relative configuration of **36b** was finally confirmed by X-ray diffraction analysis. The support for the structural fragment of the molecule came from ozonolysis, which resulted in levulinaldehyde. Latrunculin B ($C_{20}H_{29}NO_5S$) is a 14-macrolide with no diene moiety. Latrunculin C was suggested to be a ster-



36a R = H
36b R = CH_3



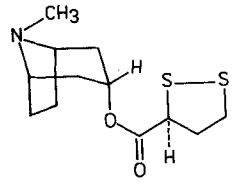
37

eoisomer of **36a.** Sigmosceptvillin, isolated from Red Sea sponge *Sigmosceptrella magnifica* Keller by another group of chemists, appeared to be identical with latrunculin B (*31*). Latrunculins cause poisoning of fish.

IV. Alkaloids with More than One Sulfur Atom

A. Brugine

Bark from the stem of *Bruguiera sexangula* (Lour.) Poir. (Rhizophoraceae), a tropical mangrove, was shown to contain alkaloids, and the major base was brugine (**38**). Hydrolysis of compound **38** ($C_{12}H_{19}NO_2S_2$), produces tropine and 1,2-dithiolane-3-carboxylic acid. Desulfurization yielded tropine *n*-butyrate. This result, supported by UV, ^1H NMR, and MS, furnished the structure of the alkaloid (*32–34*). Brugine was also found in the related Australian species *Bruguiera exaristata* Ding Hou. Brugine is toxic.

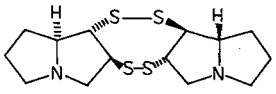


38

B. Cassipourine and Related Alkaloids

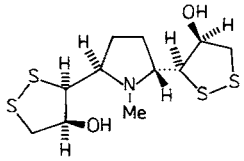
The alkaloids from *Cassipourea gummiflua,* which are active against *Salmonella* spp. and a number of *Shigella* strains, were isolated and studied by Warren

et al. (*35,36*). Gaffner and Admiraal conducted X-ray diffraction analyses on cassipourine (**39**) and gerrardine (**40**) the major alkaloids of this group (*37*). Cassipourine together with gerrardine, gerrardamine (**41**), and gerrardoline (**42**) represent the group of alkaloids from *Cassipourea gummiflua* (Rhisophoraceae).



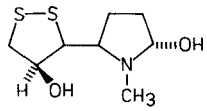
$C_{14}H_{22}N_2S_4$

39



$C_{11}H_{19}NO_2S_4$

40



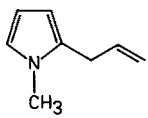
$C_8H_{15}NOS_2$

41

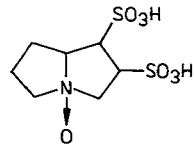
$C_8H_{15}NO_2S_2$

42

Cassipourine is remarkably resistant to Zn–HCl, sodium amalgam, sodium in liquid ammonia, and lithium aluminum hydride, as well as to catalytic hydrogenation. Desulfurization over Raney nickel results in pyrrolizidine, and distillation with zinc dust affords 5,6,7,8-tetradehydropyrrolizidine. Hofmann degradation of cassipourine dimethiodide results in 2-allyl-1-methylpyrrole (**43**). Hydrogen peroxide converted **39** to its di-*N*-oxide. Oxidation with concentrated nitric acid gave pyrrolizidinedisulfonic acid *N*-oxide (**44**). All of these chemical transformations are in agreement with the structure suggested for cassipourine. The mass spectrum of **39** shows fragments at *m/e* 346 (M^+), 205, 174, 141, and 108.

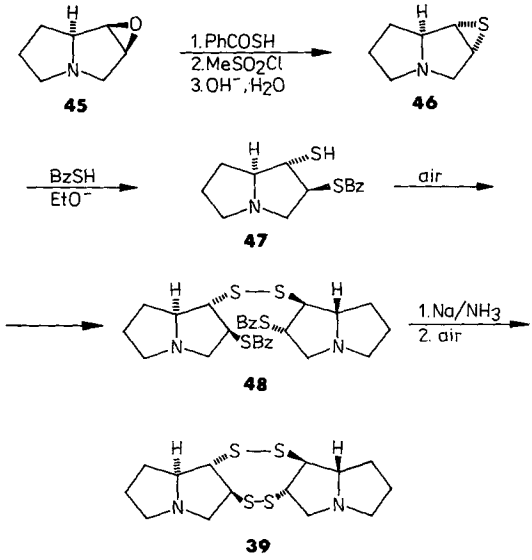


43



44

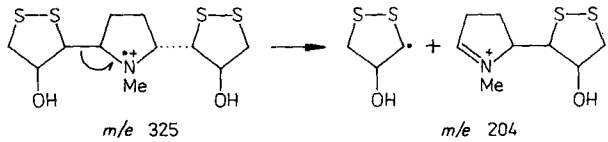
Stereospecific total synthesis of cassipourine was carried out by Wróbel and Gliński (*38*). β-Epoxypyrrolizidine (**45**) was prepared from 1,2-didehydropyrrolizidine and transformed in three steps to α-epithiopyrrolizidine (**46**). Compound **46** reacted stereospecifically with $PhCH_2SH$, resulting in pyrrolizidinedithiol derivative **47;** the latter, when oxidized in air, gave three stereoisomers from which racemate **48** was isolated by chromatography, and after debenzylation in $Na–NH_3(l)$ was oxidized in air to racemic cassipourine (**39**).



Reaction of gerrardine (**40,** $C_{11}H_{19}NO_2S_4$) with Raney nickel produces decane-2,9-diol (**49**). Desulfurization with Raney nickel in methanol gave **50.** Two dithiolanyl groups are trans to one another (determined by X-ray). Compound **40** does not show the molecular ion at *m/e* 325 but does show peaks at *m/e* 204, 205, and 206.

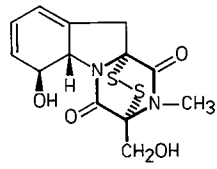
Me CH(OH)CH_2 CHR$(CH_2)_4$ CH(OH)Me

49 R = H
50 R = NMe_2



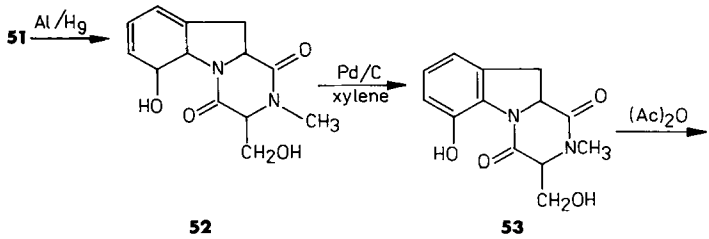
C. GLIOTOXIN

Gliotoxin (**51**, $C_{13}H_{14}N_2O_4S_2$) was isolated from the imperfect fungi *Gliocladium fimbriatum*, *Aspergillus fumigatus*, and *Penicillium* spp. (*39–41*). Compound **51** has antiviral activity and limited use as an agricultural fungicide.

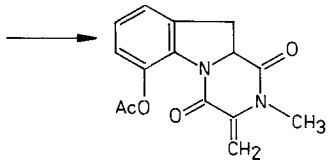


51

Dethiogliotoxin was used to examine the structure of gliotoxin (*42*), but the final structure was given by R. B. Woodward and co-workers in 1958 (*43*). This was based on the following transformations:



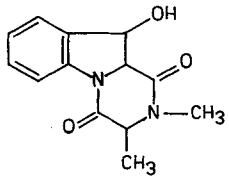
52 **53**



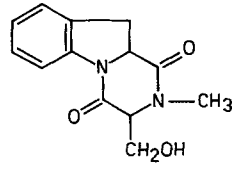
54

Dethiogliotoxin (**52**) was obtained from gliotoxin and transformed to dehydrodethiogliotoxin (**53**), which was converted by acetic anhydride to compound **54.**

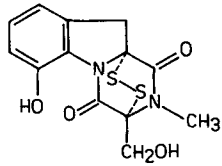
The compounds obtained in this way were compared chemically and spectroscopically with synthetic 10-hydroxypirazinoindole (**55**), known anhydrodethiogliotoxin (**56**), and dimeric products obtained from dipeptides or 2,5-piperazinediones containing a serine unit.



55

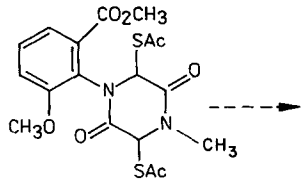


56

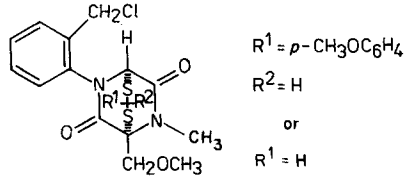


57

The crystal structure and absolute configuration of **51** was given by Beecham (*44*). The total synthesis of gliotoxin was preceded by the total synthesis of dehydrogliotoxin (**57**), which included following main steps (*45*):

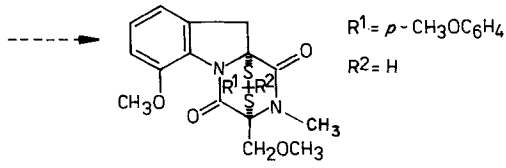


58



59

$R^1 = p\text{-}CH_3OC_6H_4$
$R^2 = H$
or
$R^1 = H$
$R^2 = p\text{-}CH_3OC_6H_4$



60

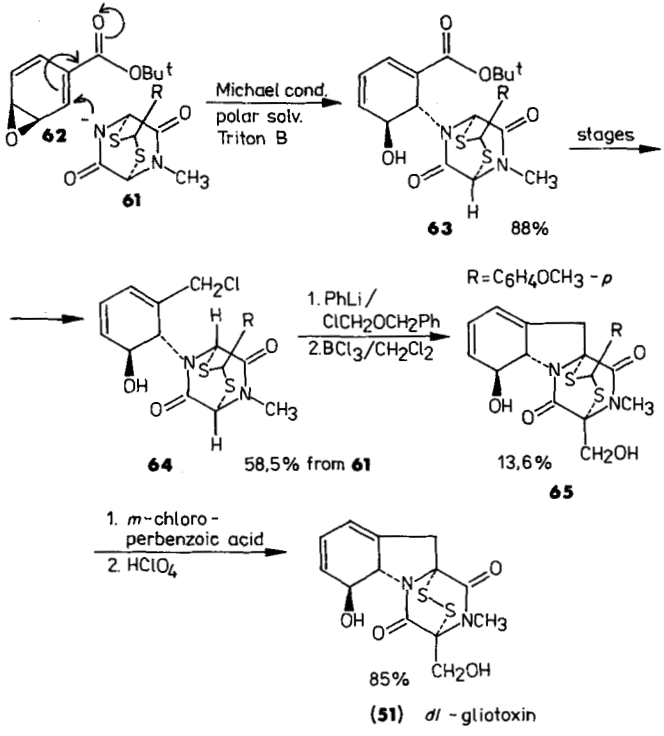
$R^1 = p\text{-}CH_3OC_6H_4$
$R^2 = H$

1. $MCPBA/CH_2Cl_2$
2. BCl_3/CH_2Cl_2

→ *dl* - **57**

Dehydrogliotoxin is a natural product found in cultures of *Penicillium terlikowskii*.

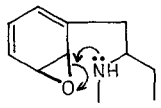
The total synthesis of gliotoxin was published in 1976 by Fukuyama and Kishi (*46*) and was based on a novel solvent–dependent Michael reaction. Two synthons, thioacetal (**61**) and carbobutoxybenzene oxide (**62**), were used for the synthesis:



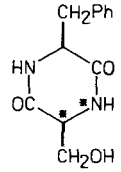
62 **61** **63** 88% **64** 58,5% from **61** 13,6% **65** 85% **(51)** *dl*-gliotoxin

Adduct **63** was converted in 11 steps to **51** in 8.5% overall yield.

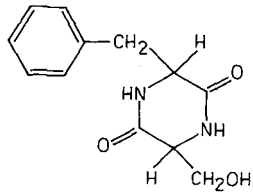
Biosynthesis of gliotoxin was the subject of interest of many research groups (*47–56*). Although not all the aspects of biosynthesis of **51** have as yet been solved, several observations can be made regarding this field. Phenylalanine is incorporated into gliotoxin with a very high efficiency (*47–52*). Since the incorporation of *dl*-phenylalanine-*3-t* occurs without any loss or migration of tritium, arene oxide of type **66** can be considered as an intermediate (*51,52*). Incorporation of phenylalanine into gliotoxin takes place with loss of the pro-*R* and retention of the pro-*S* proton from the β-methylene group (*53,54*). The doubly labeled diketopiperazine (**67**) is incorporated very efficiently without alteration



66



67

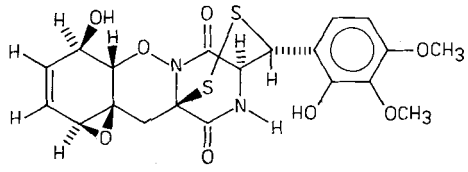


68

of the labeling ratio (*55*); dipeptides of type **68** (cyclo-l-Phe-l-Ser) are not free intermediates in the biosynthesis of gliotoxin (*56*).

D. Gliovirine

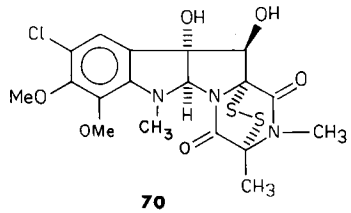
Gliovirine (**69**) has been isolated from *Gliocladium virens* (*57*), a common soil mycoparasite. Gliovirine is toxic to *P. ultimum* but is inactive against other fungi that attack cotton seedlings. The structure was determined (*58*) by X-ray crystallographic analysis and correlated with NMR and mass spectra. The mass spectrum of compound **69** ($C_{20}H_{20}N_2O_8S_2$) showed the molecular ion at *m/e* 480 and the main ions at *m/e* 448, 416, 415, and 388.



69

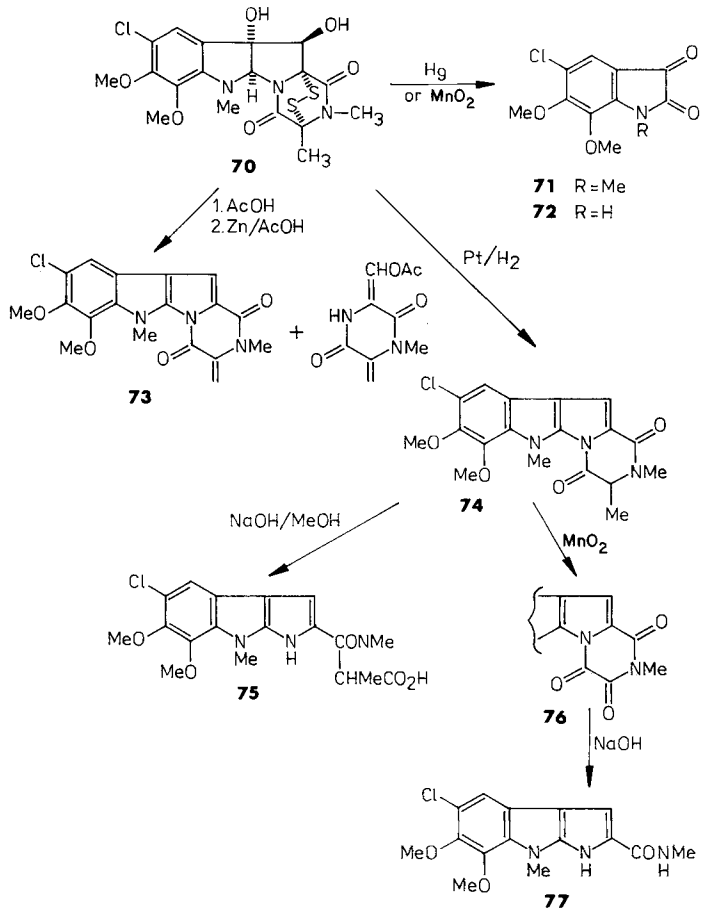
E. Sporidesmins

Sporidesmin A (**70**, $C_{18}H_{20}ClN_3O_6S_2$) was isolated from the metabolites of the mold Pithomyces chartarum (*59,60*). It causes facial eczema in sheep. Extensive studies on the chemistry of **70** together with X-ray crystallographic studies

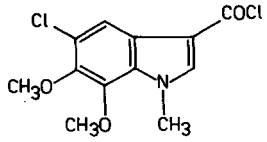


70

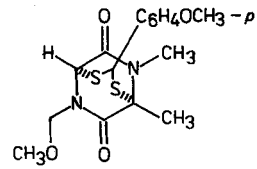
(*61,62*) resulted finally in determination of the structure of Sporidesmin A (*62*). Some of the chemistry of **70** is shown below.



In 1973 (*63*) Kishi *et al.* reported the total synthesis of Sporidesmin A. This synthesis was based on two synthons: indole **78** and thioacetal **79.** From these

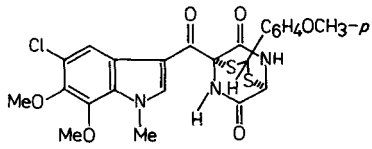


78

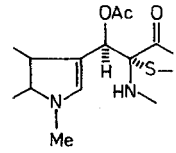


79

synthons, in the presence of BuLi, followed by HCl treatment and NaOH work-up, ketone **80** was obtained.

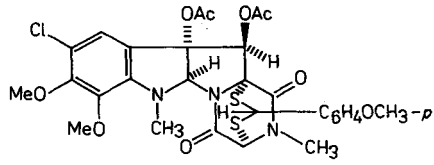


80



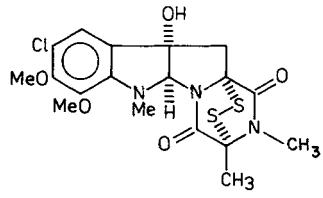
81

Compound **80,** upon stereospecific reduction, resulted in an alcohol of which its acetate, **81,** was cyclized with iodosobenzene diacetate in CH_3CN in the presence of $(CH_3)_2S$ to afford **82.** Compound **82,** which was independently prepared from Sporidesmin A, was converted to **70** in three steps.



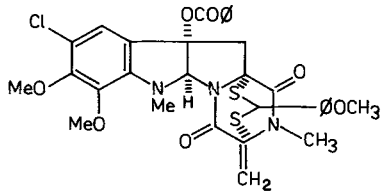
82

Sporidesmin B is also produced by *Pithomyces chartarum* and has been found to be deoxysporidesmin A (*59*). On the basis of NMR spectra, supported later by ORD and CD measurements, structure **83** was suggested for sporidesmin B



83

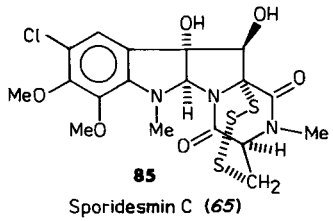
($C_{18}H_{20}ClN_3O_5S_2$). The total synthesis of sporidesmin B (*64*) was completed from acetate **81,** used before in the synthesis of sporidesmin A. Compound **81** was reduced to the methylene derivative by $NaBH_3CN$ and then cyclized by benzoyl peroxide to result in **84.** Hydrolysis of **84** and *m*-chloroperbenzoic acid oxidation, followed by treatment with BF_3/Et_2O, afforded *dl*-sporidesmin B.



84

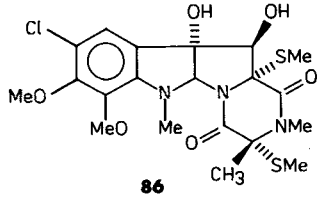
Besides sporidesmin A and B, seven other sporidesmins were isolated, and their structures were established. Sporidesmins C, D, E, F, G, H, and J were isolated from *Pithomyces chartarum,* and their structures were suggested by converting them in simple ways, mostly by reduction to sporidesmin A or B and by X-ray analysis (*65–72*).

In the field of biosynthetic studies on sporidesmins, it has been shown that side-chain hydroxylation in **70** takes place with retention of configuration at the site of attack (*73*).



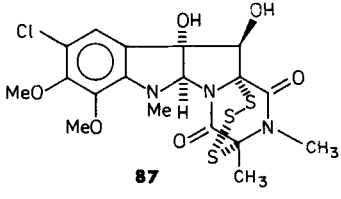
85

Sporidesmin C (*65*)
$C_{18}H_{20}ClN_3O_6S_3$



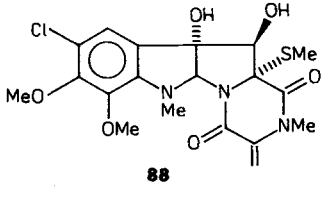
86

Sporidesmin D (*66*)
$C_{20}H_{26}ClN_3O_6S_2$



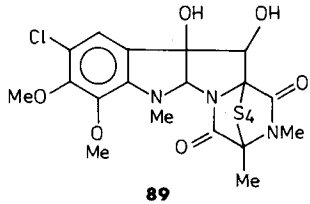
87

Sporidesmin E (*67*)
$C_{18}H_{20}ClN_3O_6S_3$



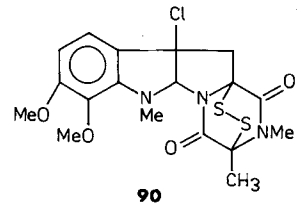
88

Sporidesmin F (*66*)
$C_{19}H_{22}ClN_3O_6S$



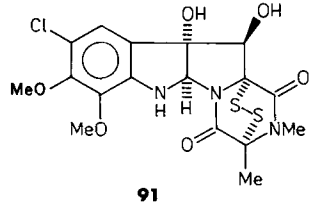
89

Sporidesmin G (*68–71*)
$C_{18}H_{20}ClN_3O_6S_4$



90

Sporidesmin H (*72*)
$C_{18}H_{20}ClN_3O_4S_2$

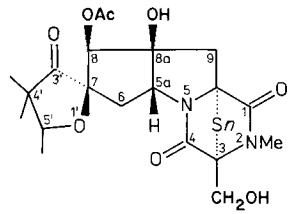


91

Sporidesmin J (*72*)
$C_{17}H_{18}ClN_3O_6S_2$

F. Sirodesmins

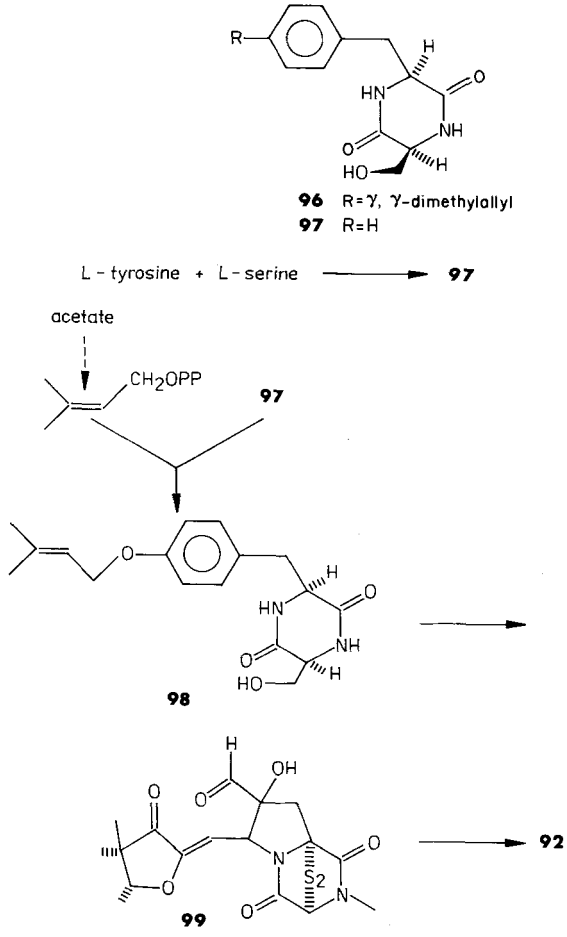
Sirodesmins A, B, C, and G (**92, 93, 94,** and **95,** respectively) are produced by *Sirodesmium diversum* and differ from each other by the number of sulfur atoms (*74*). They display an antiviral activity. Compound **95** is epimeric to **92** at C-7. The structure of **92** was determined by X-ray analysis of its diacetate. Absolute configurations of **92, 93,** and **94** are the same as that of gliotoxin (**51**).



92 A $n=2$
93 B $n=4$
94 C $n=3$
95 G $n=2$

All sirodesmins in their mass spectrum give the ion m/e ($M - S_n$) at 422. Biosynthesis of sirodesmin has been investigated in the fungus *Phoma lingam*

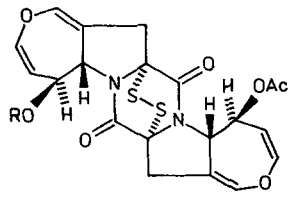
Tode, using various labeled precursors (*75*). Incorporation of labeled acetates, serine, tyrosine, phomamide (**96**), and cyclotyrosylserine (**97**) suggested the following scheme for the biosynthesis of **92.**



G. Aranotin and Related Alkaloids

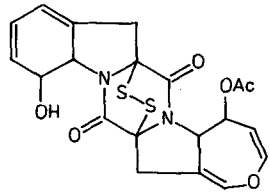
Aranotin (**100,** $C_{20}H_{18}N_2O_7S_2$) was isolated from the fungus *Arachniotus aurens* (Eidam) Schroeter and possesses antiviral activity (*76*). Acetylaranotin (**101**) was isolated from the same species. Apoaranotin (**102,** $C_{20}H_{18}O_6N_2S_2$) is another metabolite from *Arachniotus aurens* (Eidam) Schroeter (*77*).

The structure of aranotin was established from the mass spectrum, which gives the molecular ion at *m/e* 382, from the similarity of its UV spectrum to that of



100 R = H

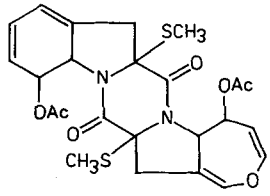
101 R = Ac



102

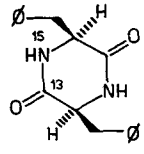
gliotoxin (**51**), and from the identity of one-half of the molecule with that of acetylaranotin (**101**).

The alkaloid named "BDAA" (*77*) appeared to be the compound corresponding to M = 518 (MS), its empirical formula being $C_{24}H_{26}N_2O_7S_2$ and its molecular structure **103.**

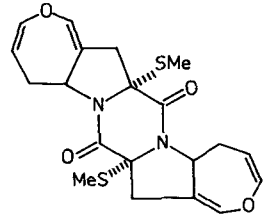


103

It was shown (*78*) that cyclo-(L-phenylalanyl-L-phenylalanyl) (**104**) was incorporated intact in Aspergillus terrens into **105,** which is a derivative of acetylaranotin (**101**).



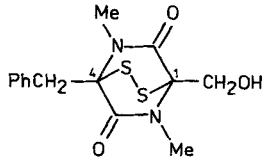
104



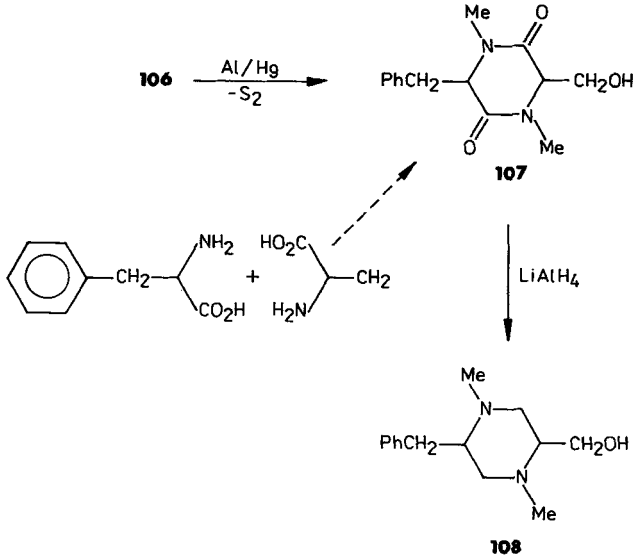
105

H. HYALODENDRIN

Fungitoxic hyalodendrin (**106**) of unknown absolute configuration, produced by a *Hyalodendron* species (imperfect fungus), is used to treat Dutch elm disease (*79–81*). Its structure was suggested as a result of some degradation and synthetic results along with spectral evidence. Conversion of **106** to **107** and piperazine derivative **108,** together with synthesis of **107** and spectral data, give support for structure **106** of hyalodendrin.

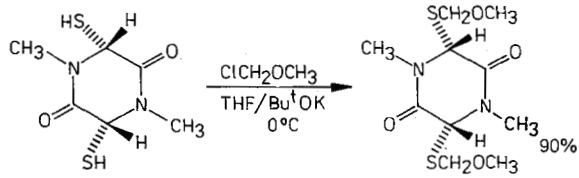


106

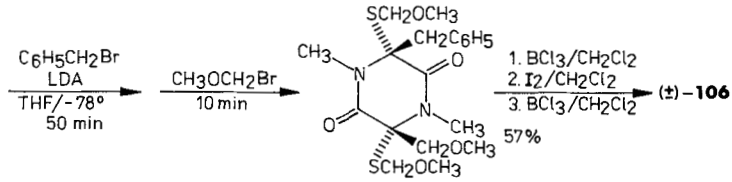


108

Two groups of researchers used the same general method for the synthesis of **106** (*82,83*). A derivative of piperazinedione (**109**) was the starting compound. Compound **109** was converted to the di-*S*-alkyl derivative **110,** and the latter was alkylated stepwise, first with benzyl bromide, then with bromomethyl methyl ether, resulting in **111.** Compound **111** was transformed to (±)-hyalodendrin (**106**) in three steps.



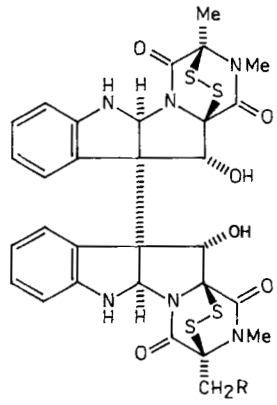
109 **110**



111

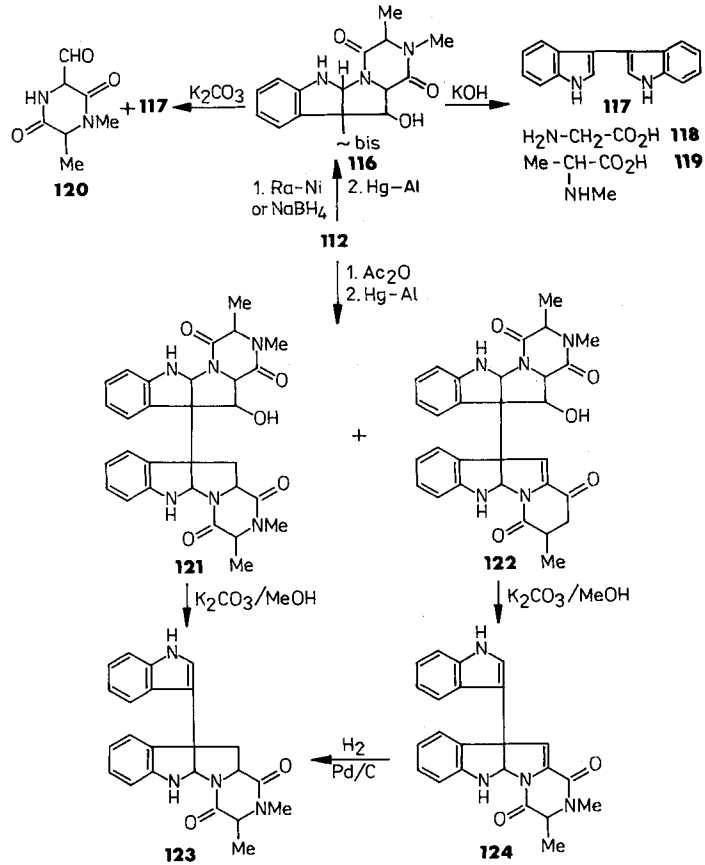
J. VERTICILLINS

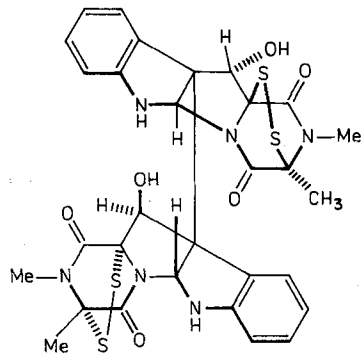
From *Verticillium* sp. (strain TM-759) three alkaloids, verticillin A (**112**, $C_{30}H_{28}N_6O_6S_4$), verticillin B (**113**, $C_{30}H_{28}N_6O_7S_4$), and verticillin C (**114**, $C_{30}H_{26}N_6O_7S_5$), have been isolated (*84*). In these three compounds anti-



112 A R = H
113 B R = OH

microbial activity has been found against gram-positive bacteria and mycobacteria. They are not active against gram-negative bacteria and fungi. The structure elucidation of this complex structure of verticillin A was based on spectral data and the following chemical transformation:


CHO
HN
NMe
Me
120
+117
K2CO3
~ bis
116
1. Ra-Ni
or NaBH4
2. Hg-Al
112
KOH
117
H2N-CH2-CO2H 118
Me-CH-CO2H 119
NHMe
1. Ac2O
2. Hg-Al
121
122
K2CO3/MeOH
K2CO3/MeOH
H2
Pd/C
123
124

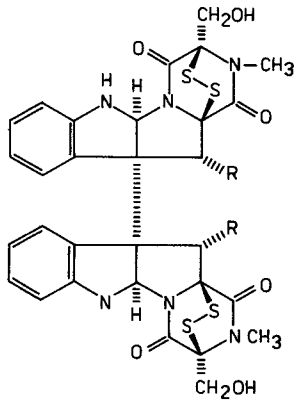


115

The same reactions were applied to verticillin B, thus proving structure **113** of this alkaloid. The conformation of **112** was concluded to be **115** according to some correlations with gliotoxin (**51**), sporidesmin (**70**), aranotin (**100**), and chaetocin (**125**).

K. CHAETOCIN

Chaetocin (**125**, $C_{30}H_{28}N_6O_6S_4$) is a metabolite of the fungus *Chaetomium minutum* and has antibacterial and cytostatic activity. Spectral data and X-ray analysis indicated structure **125** for chaetocin (*85*). Dihydroxychaetocin (**126**) was isolated from fungus *Verticillium tenerum* (*86*).

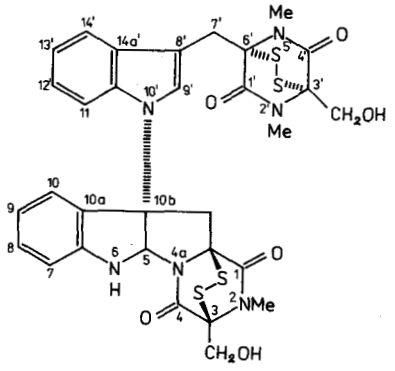


125 R = H
126 R = OH

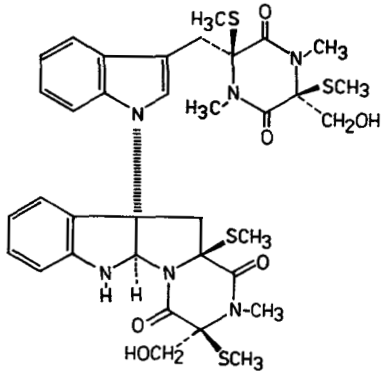
L. CHETOMIN

Chetomin (**127**, $C_{31}H_{30}N_6O_6S_4$) is a toxic metabolite of *Chaetomium* and *Chaetomium globosum* (*87*). The analysis of ^{15}N- and ^{13}C-NMR spectra and some simple chemical transformations established the structure for chetomin (**127**) together with its absolute configuration (*88,89*).

Dethiotetra(methylthio)chetomin has been isolated from *Chaetomium globosum* Kinze ex Fr. (*90*). It showed antimicrobial activity, and its structure (**128**) was determined on the basis of chemical correlation with the structure of chetomin and X-ray analysis.



127



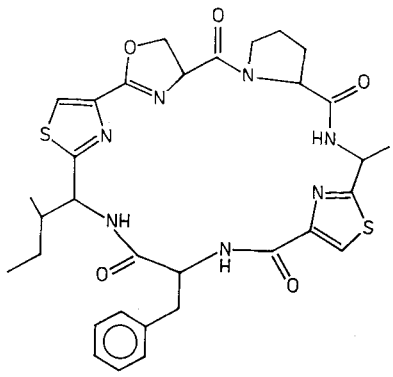
128

V. Sulfur-Containing Alkaloids of Peptide Structure

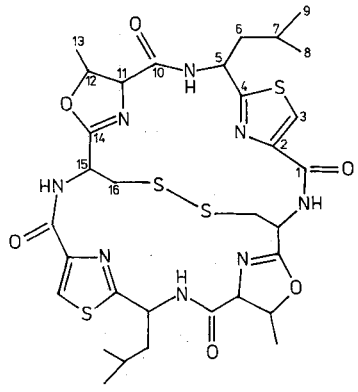
A. Ulicyclamide

Ulicyclamide (**129**, $C_{33}H_{39}N_7O_5S_2$) and ulithiacyclamide (**130**, $C_{32}H_{42}N_8O_6S_4$) were isolated from the marine plant *Lissoclinum patella* (*91*). The hydrolysis (HCl) of **129**, followed by PhCOCl treatment, resulted in compound **131**. Hydrolysis with 5% H_2SO_4–MeOH, followed by acylation, resulted in an acyclic ester in which the amino acid sequence was established by high-resolution MS.

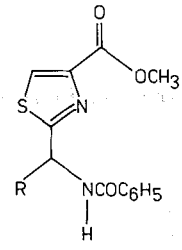
These results together with ^{13}C-NMR spectroscopy furnished the arguments for structures **129** and **130** of two alkaloidal peptides, respectively.



129



130

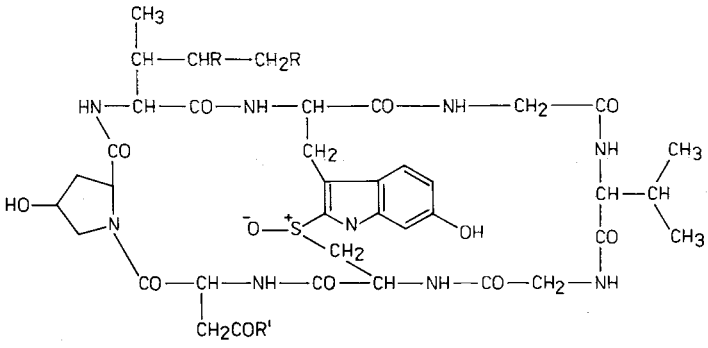


131

B. Amanitin and Related Compounds (Amatoxins)

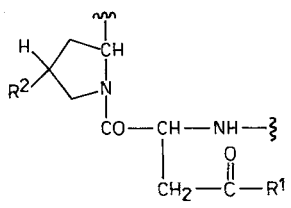
Amanitin is the highly toxic constituent of the mushroom Green Deathcap Toadstool, *Amanita phalloides* (*92*). Its extreme toxicity to humans arises from its ability to kill hepatocytes and secretory cells of the kidney.

Most of the contribution to the structure elucidation of amatoxins has been achieved in Wieland's laboratory. Structures **132** and **133** represent α- and β-amanitin, respectively. The absolute configurations of the amanitins has been established by X-ray analysis, which has shown the 2-amino-3-methyl-4,5-dihydroxyvaleric acid, obtained from both **132** and **133,** to be (2*S*,3*R*,4*R*) (*93*).



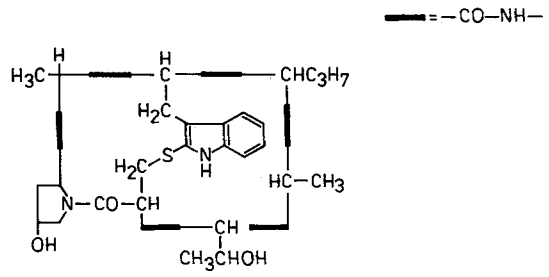
α - amanitine R = OH , $R^1 = NH_2$ **132**
β - amanitine R = R^1 = OH **133**
Amanullinic acid R = H , R^1 = OH **134**

It was observed (*94*) that the toxicity of the amatoxins depends on the configurations of the sulfoxides. All (*R*)-sulfoxides are toxic, whereas the (*S*)-sulfoxides are nontoxic. The derivatives of β-amanitin, amanullin (**135**), amanulic acid (**134**), and proamanulin (**136**), were found to be nontoxic.



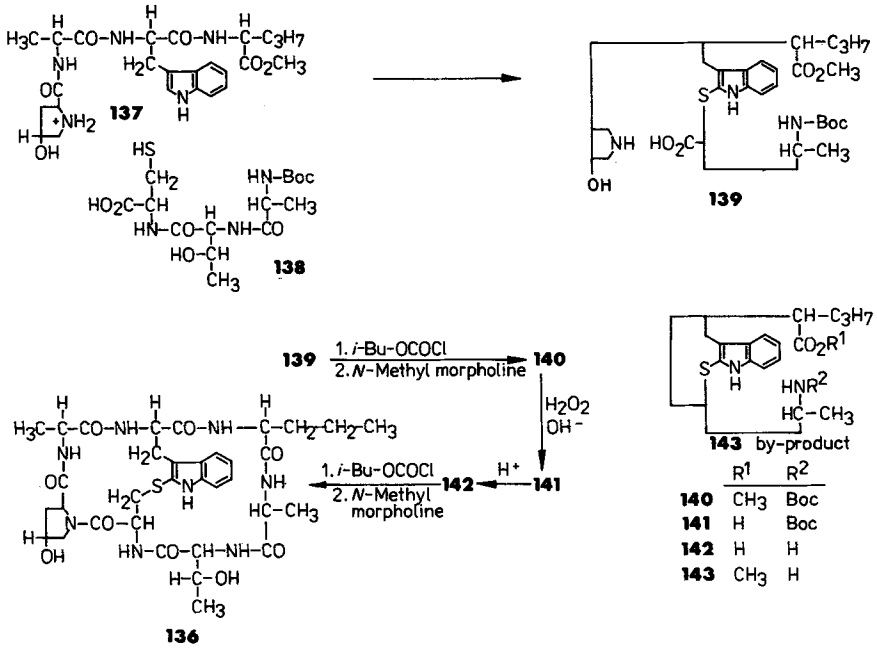
	R^1	R^2
134	NH_2	OH
133	OH	OH
135	NH_2	H

Conformation of the molecule of β-amanitin was shown by X-ray diffraction analysis (*95*). The eight peptide groups are in the transoid conformation, and four hydrogen bonds are present in the structure.



136

Norphalloine (**136**), representing the phallotoxin group of toxic peptides, was synthesized (*92*). The scheme shows the main steps of the synthesis.



References

1. K. Folkers, F. Koniuszy, and J. Shavel, *J. Am. Chem. Soc.* **66,** 1083 (1944).
2. S. F. Aripova, and S. Y. Yunusov, *Khim. Prir. Soedin.* **14**(1), 26 (1978).
3. J. T. Wróbel, *Alkaloids (N.Y.)* **9,** 450 (1967).
4. J. T. Wróbel, *Alkaloids (N.Y.)* **16,** 181 (1977).
5. E. R. Nelson and J. R. Price, *Aust. J. Sci. Res. Ser. A* **5,** 768 (1952).

6. F. A. Kincl, J. Romo, G. Rozenkranz, and F. Soudheimer, *J. Chem. Soc.*, 4163 (1956).
7. R. Mechoulam, F. Soudheimer, A. Melera, and F. A. Kincl, *J. Chem. Soc.*, 2022 (1961).
8. R. Mechoulam and A. Hirschfeld, *Tetrahedron*, 239 (1967).
9. N. K. Hart and J. A. Lamberton, *Aust. J. Chem.* **19,** 1259 (1966).
10. N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.* **21,** 1393 (1968).
11. R. M. Altamura and L. Long, *J. Biol. Chem.* **234,** 1847 (1959).
12. M. M. Tadzhibaev, K. P. Lutfullin, V. M. Malikov, and S. Y. Yunusov, *Khim. Prir. Soedin.* **12,** 270, 271 (1976).
13. E. B. Astwood, M. A. Greer, and M. G. Etlinger, *J. Biol. Chem.* **181,** 121 (1949).
14. J. Banerji, A. Chatterjee, Y. Itoh, and T. Kikuchi, *Indian J. Chem.* **11,** 1056 (1973).
15. S. F. Aripova, S. T. Akramov, and S. Y. Yunusov, *Khim. Prir. Soedin.* **11,** 762 (1975).
16. S. F. Aripova, O. Abdilalimov, V. M. Malikov, and S. Y. Yunusov, *Khim. Prir. Soedin.* **12,** 556 (1976).
17. S. F. Aripova, O. Abdilalimov, V. M. Malikov, and S. Y. Yunusov, *Khim. Prir. Soedin.* **12,** 674 (1976).
18. H. Schrandorf, *Experientia* **21,** 520 (1965).
19. H.-T. Liang, H.-D. Hsu, Ch.-P. Chang, H.-E. Ku, and W.-S. Wang, *Hua Hsueh Hsueh Pao* **34**(2), 129 (1976); *Chem. Abstr.* **87,** 165948 (1977); *Sci. Sin. (Engl. Ed.)* **20,** 106 (1977).
20. C.-P. Chang, H.-D. Hsu, L.-C. Huang, Y.-C. Lin, H.-S. Li, C.-L. Yu, and C.-L. Chao, *Acta Chim. Sin.* **34,** 133 (1976); *Chem. Abstr.* **88,** 62309 (1978).
21. A. P. Kozikowski and M. N. Greco, *J. Am. Chem. Soc.* **102,** 1165 (1980); A. P. Kozikowski, M. N. Greco, and J. P. Springer, *J. Am. Chem. Soc.* **104**(26), 7622 (1982).
22. S. Omura, Y. Suzuki, C. Kitao, Y. Takahashi, and Y. Konda, *J. Antibiot.* **8,** 609 (1975).
23. Y. Konda, Y. Suzuki, S. Omura, and M. Onda, *Chem. Pharm. Bull.* **24**(1), 92 (1976).
24. M. Onda and Y. Konda, *Chem. Pharm. Bull.* **26**(7), 2167 (1978).
25. H. U. Naegeli and H. Zahner, *Helv. Chim. Acta* **63,** 1400 (1980).
26. K. Gerth, H. Irschik, H. Reichenbach, and W. Trowitzsch, *J. Antibiot.* **33**(12), 1479 (1980).
27. R. K. Chaudhuri, O. Sticker, and T. Winkler, *Helv. Chim. Acta* **63**(4), 1045 (1980).
28. R. K. Chaudhuri, O. Sticker, and T. Winkler, *Tetrahedron Lett.*, 559 (1981).
29. Y. Kashman, A. Groweiss, and U. Shmueli, *Tetrahedron Lett.*, 3629 (1980).
30. I. Neeman, L. Fishelson, and Y. Kashman, *Mar. Biol.* **30,** 293 (1975).
31. S. Sarel, S. Halevy, and N. Kolodny, Poster at the Second International Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Budapest, Hungary, 1983.
32. J. W. Loder and G. B. Russel, *Tetrahedron Lett.*, 6327 (1966).
33. J. W. Loder and G. B. Russel, *Aust. J. Chem.* **22,** 1271 (1969).
34. A. F. Beecham, J. W. Loder, and G. B. Russel, *Tetrahedron Lett.*, 1785 (1968).
35. W. G. Wright and F. L. Warren, *J. Chem. Soc.*, 283, 284 (1967).
36. R. G. Cooks, F. L. Warren, and D. H. Williams, *J. Chem. Soc.*, 286 (1967).
37. G. Gaffner and L. J. Admiraal, *Acta Crystallogr., Sect. B* **25,** 2114 (1969).
38. J. T. Wróbel and J. A. Gliński, *Can. J. Chem.* **59**(7), 1101 (1981).
39. J. R. Johnson, W. F. Bruce, and J. D. Dutcher, *J. Am. Chem. Soc.* **65,** 2005 (1943).
40. G. A. Glister and T. J. Williams, *Nature (London)*, 651 (1944).
41. J. R. Johnson, W. C. McCrone, Jr., and W. F. Bruce, *J. Am. Chem. Soc.* **66,** 50 (1944).
42. J. R. Johnson and J. B. Buchanan, *J. Am. Chem. Soc.* **75,** 2103 (1953).
43. M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Am. Chem. Soc.* **80,** 1001 (1958).
44. A. A. Beecham, J. Fridrichsons, and A. M. Mathieson, *Tetrahedron Lett.*, 3131 (1966).
45. Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.* **95,** 6492 (1973).
46. T. Fukuyama and Y. Kishi, *J. Am. Chem. Soc.* **98,** 6723 (1976).
47. R. J. Suhadolnik and R. G. Chenoweth, *J. Am. Chem. Soc.* **80,** 4391 (1958).

48. J. A. Winstead and R. J. Suhadolnik, *J. Am. Chem. Soc.* **82,** 1644 (1960).
49. A. K. Bose, K. G. Das, P. T. Funke, I. Kugachevsky, O. P. Sukla, K. S. Khanchandani, and R. J. Suhadolnik, *J. Am. Chem. Soc.* **90,** 1038 (1968).
50. A. K. Bose, K. S. Khanchandani, R. Tavares, and P. T. Funke, *J. Am. Chem. Soc.* **90,** 3593 (1968).
51. J. D. BU'Lock and A. P. Ryles, *J. Chem. Soc., Chem. Commun.*, 1404 (1970).
52. N. Johns and G. W. Kirby, *J. Chem. Soc., Chem. Commun.*, 163 (1971).
53. J. D. BU'Lock, A. P. Ryles, N. Johns, and G. W. Kirby, *J. Chem. Soc., Chem. Commun.*, 100 (1972).
54. N. Johns, G. W. Kirby, J. D. BU'Lock, and A. P. Ryles, *J. Chem. Soc., Perkin Trans. 1*, 383 (1975).
55. J. D. BU'Lock and C. Leigh, *J. Chem. Soc., Chem. Commun.*, 628 (1975).
56. J. C. MacDonald and G. P. Slater, *Can. J. Biochem.* **53,** 475 (1975).
57. C. R. Howell and R. D. Stipanovic, *Can. J. Microbiol.* **29,** 321 (1983).
58. R. D. Stipanovic and C. R. Howell, *J. Antibiot.*, 1326 (1982).
59. R. Hodges, J. W. Ronaldson, A. Taylor, and E. P. White, *Chem. Ind. (London)*, 42 (1963).
60. J. W. Ronaldson, A. Taylor, E. P. White, and R. J. Abraham, *J. Chem. Soc.*, 3172 (1963).
61. H. Herrmann, R. Rodges, and A. Taylor, *J. Chem. Soc.*, 4315 (1964).
62. J. Fridrichsons and A. M. Mathieson, *Tetrahedron Lett.*, 1265 (1962).
63. Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Am. Chem. Soc.* **95,** 6493 (1973).
64. S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Lett.*, 1549 (1974).
65. N. K. Hart and J. A. Lamberton, *Aust. J. Chem.* **19,** 1059 (1966).
66. W. D. Jamieson, R. Rahman, and A. Taylor, *J. Chem. Soc.*, 1564 (1969).
67. R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc. C*, 1665 (1969).
68. M. Przybylska and E. M. Gopalakrishna, *Acta Crystallogr., Sect. B* **30,** 597 (1974).
69. M. Przybylska, E. M. Gopalakrishna, A. Taylor, and S. Safe, *J. Chem. Soc., Chem. Commun.*, 554 (1973).
70. E. F. R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 470 (1972).
71. E. Francis, R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc., Perkin Trans.* **1,** 470 (1972).
72. R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1476 (1978).
73. G. W. Kirby and M. J. Varley, *J. Chem. Soc., Chem. Commun.*, 833 (1974).
74. P. J. Curtis, D. Greatbanks, B. Hesp, A. F. Cameron, and A. A. Freer, *J. Chem. Soc., Perkin Trans. 1*, 180 (1977).
75. J. P. Ferezon, A. Q-Thierry, C. Servy, E. Zissmann, and M. Barbier, *J. Chem. Soc., Perkin Trans. 1*, 1739 (1980).
76. R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Am. Chem. Soc.*, **90,** 2980 (1968).
77. N. Neuss, R. Nagarajan, B. B. Molov, and L. L. Huckstep, *Tetrahedron Lett.*, 4467 (1968).
78. M. I. P. Boente, G. W. Kirby, and D. J. Robins, *J. Chem. Soc., Chem. Commun.*, 619 (1981).
79. G. M. Strunz, M. Kakushima, M. A. Stillwell, and Ch. J. Heissner, *J. Chem. Soc., Perkin Trans. 1*, 2600 (1973).
80. M. A. Stillwell, L. P. Magasi, and G. M. Strunz, *Can. J. Microbiol.* **20,** 759 (1974).
81. G. M. Strunz, M. Kakushima, and M. A. Stillwell, *Can. J. Chem.* **52,** 295 (1974).
82. T. Fukuyama, S. Nakatsuka, and Y. Kishi, *Tetrahedron Lett.*, 3393 (1976).
83. G. M. Strunz and M. Kakushima, *Experientia* **30,** 719 (1974).
84. M. Minato, M. Matsumoto, and T. Katayama, *J. Chem. Soc.*, 1819 (1973).
85. D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta* **53,** 1061 (1970).
86. D. Hauser, H. R. Loosli, and P. Niklaus, *Helv. Chim. Acta* **55,** 2182 (1972).
87. S. Save and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 472 (1972).

88. D. Brewer, A. G. McInnes, D. G. Smith, A. Taylor, J. A. Walter, H. R. Loosli, and Z. L. Kis, *J. Chem. Soc., Perkin Trans. 1,* 1248 (1978).
89. A. G. McInnes, A. Taylor, and J. A. Walter, *J. Am. Chem. Soc.* **98,** 674 (1976).
90. T. Kikuchi, S. Kadota, K. Nakamura, A. Nishi, T. Taga, T. Kaji, K. Osaki, and K. Tubaki, *Chem. Pharm. Bull.* **30,** 3846 (1982).
91. C. Ireland and P. J. Scheuer, *J. Am. Chem. Soc.* **102,** 5688 (1980).
92. F. Fahrenholz, H. Faulstich, and T. Wieland, *Liebigs Ann. Chem.* **743,** 83 (1971), and preceding papers.
93. A. Gieren, P. Narayanan, W. Hoppe, M. Hassan, K. Michl, T. Wieland, H. O. Smith, G. Jung, and E. Breitmaier, *Liebigs Ann. Chem.* **746,** 1561 (1974).
94. A. Buku, R. Altmann, and T. Wieland, *Liebigs Ann. Chem.* **746,** 1580 (1974).
95. E. C. Kostanek, W. N. Lipscomb, R. R. Yocum, and W. E. Thiessen, *Biochemistry,* 3790 (1978).

This Page Intentionally Left Blank

— CHAPTER 3 —

PYRIDINE AND PIPERIDINE ALKALOIDS

GEORGE M. STRUNZ

Maritimes Forest Research Centre
Canadian Forestry Service
Fredericton, New Brunswick, Canada

AND

JOHN A. FINDLAY

Department of Chemistry
University of New Brunswick
Fredericton, New Brunswick, Canada

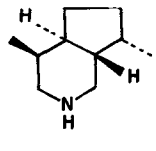
I. Introduction

Although the term "alkaloid" has a useful and secure place in the vocabulary of all chemists, a number of authors in recent years have drawn attention to the somewhat arbitrary criteria according to which a nitrogenous natural product is, or is not, considered to be an alkaloid (*1*), and some new rational and general definitions of the term have been proposed (*2,3*).

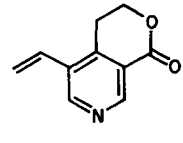
THE ALKALOIDS, VOL. 26

In this context it must be admitted that the designation of pyridine and piperidine alkaloids as a group introduces yet another level of arbitrariness. These compounds do not stem from a common biosynthetic precursor, they are not unique to a single taxonomic family (or indeed kingdom!), and even the structural characteristics that might seem to define the group are open to interpretation. However, the historical recognition of these alkaloids as a class, and the practice of reviewing them as such (*4–6*) are sufficient reasons to continue these traditions, and this chapter represents a survey of the relevant literature since the last review in this series (*4*).

Other authors have considered the group to include "alkaloids which have piperidine or pyridine rings as the distinguishing skeletal features" (*7*). Thus compounds such as the monoterpene alkaloid β-skytanthine (**1**) were included. In order to confine this chapter to manageable proportions, we have chosen to limit the class, in general, to alkaloids containing a piperidine-type nitrogen heterocycle (at any oxidation level) that is not fused to a carbocyclic system; thus compounds such as **1** are not reviewed exhaustively here. Alkaloids in which the nitrogen-containing ring is fused to a second heterocycle, such as gentianine (**2**) have in some cases been included, except where such fusion generates another readily identifiable heterocyclic moiety, such as the quinolizidine system.



1



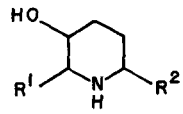
2

The conjugated piperidine amide alkaloids from *Piper* spp., the piperidine metacyclophane alkaloids from Lythraceae, the nuphar alkaloids, the solanum steriod alkaloids, and the sesquiterpene nicotinic acid esters from Celastraceae have recently been reviewed elsewhere in this series and have, for the most part, been omitted from this chapter.

The alkaloids are grouped in sections, largely on the basis of their structural characteristics, although biogenetic or taxonomic considerations have also been taken into account in some instances.

II. 2,6-Disubstituted Piperidin-3-ols

A series of piperidin-3-ols (**3**), most bearing C_1 and n-C_{12} side chains at positions 2 and 6, respectively, have been isolated from *Cassia* and *Prosopis* species, tropical Leguminosae. These alkaloids differ in the stereochemistry and oxygenation patterns of their side chains (Table I).



3

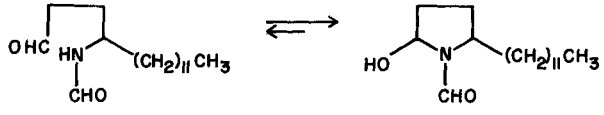
The previous review in this series (*4*) included reports of the structures of cassine and carnavoline from *Cassia* spp. and prosopine and prosopinine from *Prosopis africana*. Full details of the structure elucidation of the latter two alkaloids, as well as prosophylline, prosafrine, and prosafrinine, also from foliage of *P. africana*, and isoprosopinines A and B from roots and bark of the same plant, have since been published (*13*) (Table I).

Structures were determined on the basis of spectroscopic and chemical evidence. Alkaloids with a C-2 hydroxymethyl group could readily be distinguished from those possessing a methyl group at C-2 by mass spectrometry: the former show an abundant ion at *m/e* 130 resulting from cleavage of the C-6 side chain, while the corresponding ion for the latter has *m/e* 114.

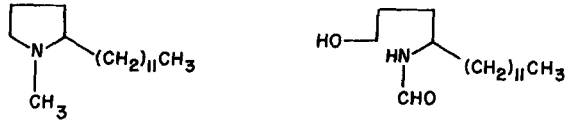
Alkaloids with identical functionality at C-2 and C-3 and the same stereochemistry at C-2, C-3, and C-6 could be simply correlated by removal of the oxygen functionality in the C-6 side chain.

Thus prosopine, prosopinine, and the two isoprosopinines were found to belong to the same stereochemical series, while prosophylline was shown to possess different stereochemistry. The nature and position of oxygen functionality in the C-6 side chain of the various alkaloids or their derivatives was ascertained spectroscopically or by oxidative degradation to the appropriate *n*-alkanoic acid.

Periodate oxidation of deoxoprosopinine and deoxoprosophylline was structurally diagnostic, resulting in cleavage to give a tautomeric mixture of **4** and **5**, in which the latter was predominant. The mixture afforded **6** on LAH reduction, but gave **7** on treatment with KBH_4.



4 5



6 7

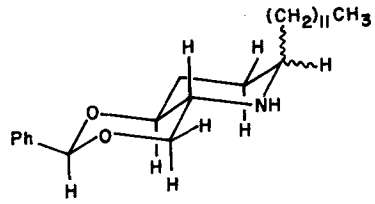
TABLE I

2,6-DISUBSTITUTED PIPERIDIN-3-OLS FROM *CASSIA* AND *PROSOPIS* SPP.

Source	Name	C-3-OH configuration	C-2 substituent	C-6 substituent	Reference
Cassia excelsa	Cassine	α	α-CH_3	α-$(CH_2)_{10}COCH_3$	*8*
C. spectabilis	Iso-6-cassine	α	α-CH_3	β-$(CH_2)_{10}COCH_3$	*9*
Prosopis spp.	*N*-Methylcassine	α	α-CH_3	α-$(CH_2)_{10}COCH_3$	*10*
C. spectabilis	Carnavaline	α	α-CH_3	α-$(CH_2)_{10}CHOHCH_3$	*11*
C. spectabilis	Iso-6-carnavaline	α	α-CH_3	β-$(CH_2)_{10}CHOHCH_3$	*12*
Prosopis africana	Prosopine	β	α-CH_2OH	β-$(CH_2)_{10}CHOHCH_3$	*13*
P. africana	Prosopinine	β	α-CH_2OH	β-$(CH_2)_9COCH_2CH_3$	*13*
P. africana	Isoprosopinine A	β	α-CH_2OH	β-$(CH_2)_6CO(CH_2)_4CH_3$	*13*
P. africana	Isoprosopinine B	β	α-CH_2OH	β-$(CH_2)_7CO(CH_2)_3CH_3$	*13*
P. africana	(±)-Prosophylline	β	α-CH_2OH	α-$(CH_2)_9COCH_2CH_3$	*13*
P. africana	Prosafrine	α	α-CH_3	α-$(CH_2)_9CHOHCH_2CH_3$	*13*
P. africana	Prosafrinine	α	α-CH_3	α-$(CH_2)_9COCH_2CH_3$	*13*
C. carnaval	Prosopinone	?	CH_2OH	$(CH_2)_{10}COCH_3$	*14*
P. juliflora	Julifloridine	?	CH_3	$(CH_2)_{11}CH_2OH$	*15*
P. spicigera	Spicigerine	α	α-CH_3	α-$(CH_2)_{11}COOH$	*16*
C. spectabilis	Spectaline	β	β-CH_3	β-$(CH_2)_{12}COCH_3$	*9*
C. spectabilis	Spectalinine	β	β-CH_3	β-$(CH_2)_{12}CHOHCH_3$	*12*
C. carnaval	Alkaloid D	?	CH_3	$(CH_2)_3CHOH(CH_2)_{10}CHOHCH_3$	*14*

Prosafrine (which could be oxidized to prosafrinine) was converted to a deoxo derivative, which, after N-methylation was correlated with *N*-methyldeoxocassine of known (2*R*,3*R*,6*S*) configuration.

The relative stereochemistry of prosopinine and its stereochemical relatives, and the (racemic) C-6 epimer prosophylline, could be deduced by analysis of the NMR spectra of the *O*,*O*′-benzylidine derivatives **8**, obtained from reaction of the deoxo products with benzaldehyde.



8

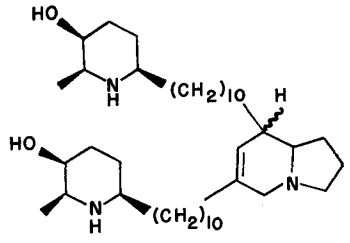
The absolute configuration of prosopine at C-3 was determined by Horeau's method: the alkaloid possesses (2*R*,3*S*,6*R*) stereochemistry. The side-chain hydroxy group in prosopine has the (*S*) configuration.

An investigation of the basic constituents of *Cassia spectabilis* led to the isolation of four new 2,6-disubstituted piperidin-3-ols, two possessing *n*-C_{12} and two with *n*-C_{14} side chains (*9,12*). The leaves of this species afford spectaline and iso-6-cassine, while the seeds also yield spectalinine and iso-6-carnavaline as well as traces of cassine (Table I). Evidence derived from spectroscopic analysis, reinforced by comparison of the data with those for known related alkaloids, provided the basis for structure elucidation of these compounds.

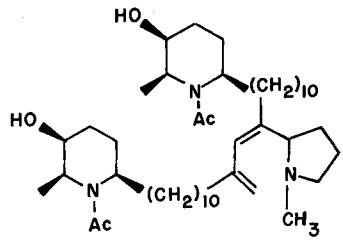
The predominant ion at *m/e* 114 in the mass spectra of these bases results from the expected cleavage of the C-6 side chain adjacent to nitrogen: cleavages around the oxygen functionality in the side chain were also structurally diagnostic. The relative stereochemistry of spectaline was deduced from infrared data indicating intramolecular hydrogen bonding of the hydroxylic proton with the piperidine nitrogen. This behavior is characteristic of the all-cis alkaloids such as cassine, which assume a conformation in which the hydroxy group is axial. NMR evidence supported the assigned configuration. Infrared- and NMR-based arguments were also advanced for the configuration of iso-6-cassine (Table I) and confirmed by X-ray crystallography. The method of Horeau was used to establish the absolute configurations of spectaline (2*S*,3*S*,6*R*) and iso-6-cassine (2*R*,3*R*,6*R*). That spectalinine and iso-6-carnavaline are the diols corresponding to spectaline and iso-6-cassine, respectively, was established by spectroscopy and chemical correlation. The configurations of the side-chain alcohols were not determined.

Three new alkaloids, designated juliflorine, julifloricine, and julifloridine, were isolated from foliage of *Prosopis juliflora* (*15*). The structure of the minor base, julifloridine, was proposed on the basis of spectroscopic evidence (Table I).

In a subsequent examination of this species from a different region (*17*) four alkaloids were isolated, but julifloridine was not detected. Analysis of chemical and spectroscopic evidence led to the relative configuration and structure **9** for one of the new bases, designated juliprosopine. The formation of an *N,N',O,O'*-tetraacetate, followed by selective hydrolysis of the ester groups, established that the alkaloid possesses two secondary hydroxy groups, as well as two secondary and one tertiary amino group. The presence of a single olefinic double bond was indicated by the NMR spectrum and by hydrogenation. The mass spectrum of juliprosopine displays the familiar base peak at *m/e* 114 resulting from cleavage of the chain at C-6 (and C-6') adjacent to nitrogen. The magnitude of the coupling between the hydrogens on C-2 and C-3 of the hydrogen-bonded piperidin-3-ol ring systems suggests the relative configuration depicted (signals for the corresponding protons on each ring are coincident). Hofmann degradation of the hydroxide derived from the *N,N'*-diacetate-*N''*-methiodide provided the key to the central hexahydroindolizine system. The product (**10**) afforded, on hydrogenation, both the expected tetrahydro derivative and a hexahydro product, the latter arising from prior cleavage of the pyrrolidine ring through hydrogenolysis of the allylic C—N bond. The Hofmann base (**10**) was also degraded to the expected fragments by ozonolysis.



9



10

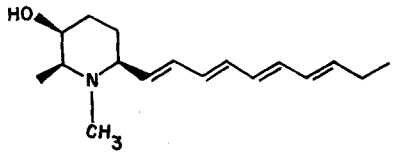
Detailed analyses of the spectra, including ^{13}C NMR, of the alkaloid and some of its derivatives are reported (*17*).

It is postulated that the biosynthetic precursors of juliprosopine are two molecules of a 3-hydroxy-2-methylpiperidine bearing a suitably functionalized C_{12} side chain at C-6, and dihydropyrrole.

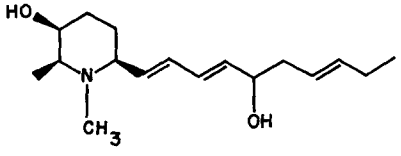
Assuming the appropriate absolute configuration, a derivative (such as a thioester) of spicigerine (Table I) (*16*) could condense with dihydropyrrole (from

ornithine) to give a keto lactam, reducible to julifloridine. Spicigerine is found in *P. spicigera* (*16*).

Foliage of *Bathiorhamnus cryptophorus* (H. Perrier) R. Capuron (Rhamnaceae) affords the alkaloids cryptophorine and cryptophorinine (*18*). On the basis of chemical and spectroscopic data, cryptophorine was assigned the structure and relative configuration **11.**



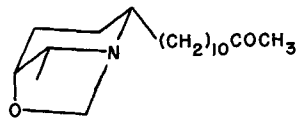
11



12

That the extended chromophore of **11** is present in the side chain was demonstrated by the fact that both cryptophorine and its octahydro derivative show a strong ion in their mass spectra at *m/e* 128, resulting from cleavage of the side chain adjacent to nitrogen at C-6. NMR spectroscopy of the alkaloid itself, and the 3-hydroxypyridine resulting from its catalytic dehydrogenation, were central to the structure elucidation. The all-cis configuration of the piperidine part of cryptophorine followed from analysis of the NMR signals for the C-2 and C-3 hydrogens and from the intramolecular hydrogen bonding manifested in the infrared spectrum (see above). The minor alkaloid cryptophorinine could be assigned structure **12** by virtue of its NMR and mass spectrometric characteristics.

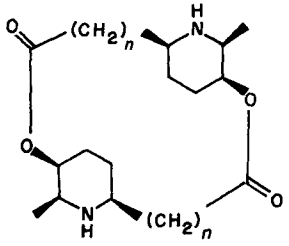
For reasons obvious from the foregoing discussion, mass spectrometry has played a prominent role in the structure elucidation of all of these 2,6-disubstituted piperidin-3-ols. The mass spectra of cassine (Table I), bicyclocassine (**13**) (formed by treatment of cassine with formaldehyde) and other derivatives, in fact, show anomalous fragmentation patterns, in that the expected McLafferty rearrangement is not observed (*19*). While the fragmentation is dominated by the familiar and diagnostic cleavage of the chain adjacent to nitrogen,the strongest ion of *m/e* greater than 114 is *m/e* 240, arising from the loss of CH_2COCH_3 from the molecular ion. Because the charge is localized at the nitrogen atom, it seems that McLafferty rearrangements are insignificant, and "fragmentations which involve the carbonyl group are directed by the stability of the radical expelled" (*19*).



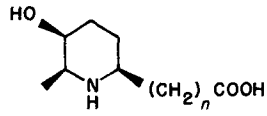
13

The application of chemical ionization mass spectrometry to a variety of alkaloids has been investigated, including the pyridine–piperidine bases nicotine and cassine (*20*). Spectra were measured, using methane as reactant gas, and invariably showed abundant quasi-molecular ions $(M + 1)^+$. Since the spectra are often simpler and less likely to reflect skeletal rearrangement than those obtained using conventional electron impact, fragmentation patterns observed in the two modes can provide useful structural information of a complementary nature (*20*).

Azimine (**14**) (*21*) and carpaine (**15**) (*22*) are macrocyclic dimeric bislactones elaborated, respectively, by *Azima tetracantha* L. and *Carica papaya* L. [Carpaine occurs in the leaves of various *C. papaya* varieties in concentrations ranging from 0.01 to 0.2% of dry weight (*23*).] They are hydrolyzed to azimic (**16**) and carpamic (**17**) acids, which are presumably their biosynthetic progenitors. In a short historical review of the chemistry and pharmacology of carpaine, it has been suggested that the interesting pharmacological properties reported for the alkaloid in earlier publications warrant further investigations, using modern techniques and purified carpaine (*24*).



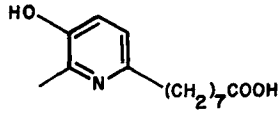
14 $n = 5$
15 $n = 7$



16 $n = 5$
17 $n = 7$

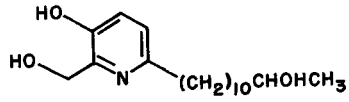
While most of the recent chemical interest in these bislactone alkaloids has focused on synthesis, isolation of two new dehydrocarpaines as major alkaloids of *C. papaya* leaves has been reported (*25*). These alkaloids, possessing Δ^1 and $\Delta^{1,1'}$ unsaturations, may be intermediates in the biosynthesis of carpaine [cf. γ-coniceine in coniine biosynthesis (*25*)].

Dehydrogenation of carpaine affords carpyrinic acid (**18**), an important derivative in the structure elucidation of the alkaloid. Several syntheses of carpyrinic



18

acid were accomplished during the 1950s: one of these earlier routes, involving rearrangement of a 2-acetylfuran derivative with ammonia, has been modified to give carpyrinic acid (**18**) in an improved overall yield of 9% (*26*). Synthesis of dehydroprosopine (**19**) from 3-hydroxypyridine (5.3% overall yield) is described in the same paper (*26*), which also reviews earlier synthetic approaches to related compounds.



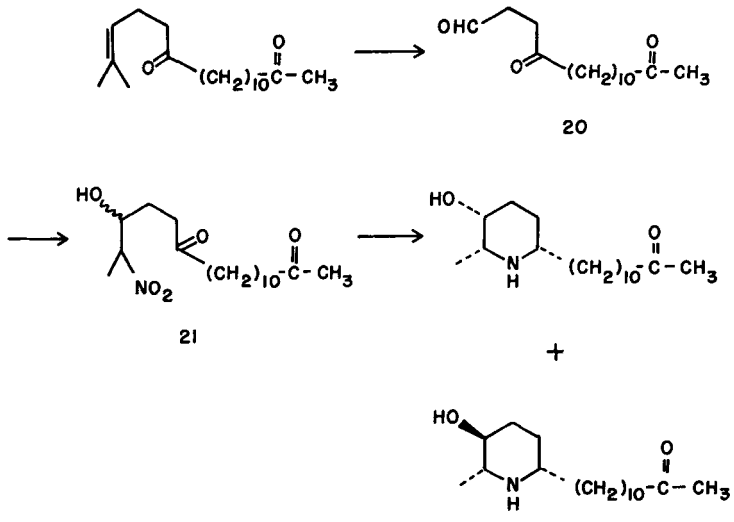
19

Intuitively, it might be predicted that the all-cis carpamic acid (**17**) should be accessible by hydrogenation of carpyrinic acid (**18**), but this transformation does not appear to have been accomplished (*27*).

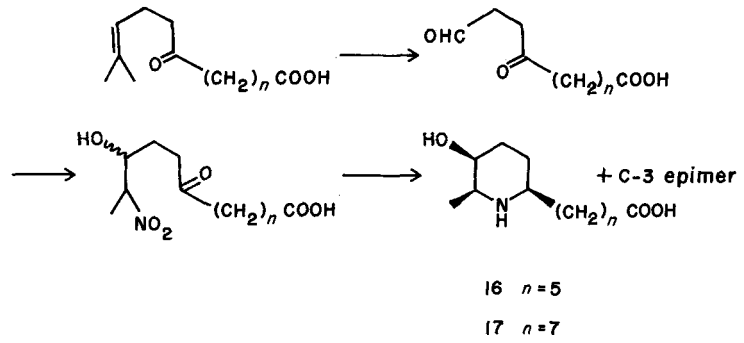
Brown and co-workers have developed a versatile synthetic route to 2-methyl-6-substituted piperidin-3-ol alkaloids (*28*). The first syntheses of racemic cassine (Table I), and azimic (**16**) and carpamic (**17**) acids were accomplished using this approach.

The key steps in the synthesis of cassine (*29*) are depicted in Scheme 1.

Base-catalyzed condensation of nitroethane with hexadecanal-4,15-dione (prepared in some seven steps from undecylenic alcohol) afforded the nitro alcohol **21** quantitatively as a mixture of erythro and threo isomers. Catalytic hydrogena-



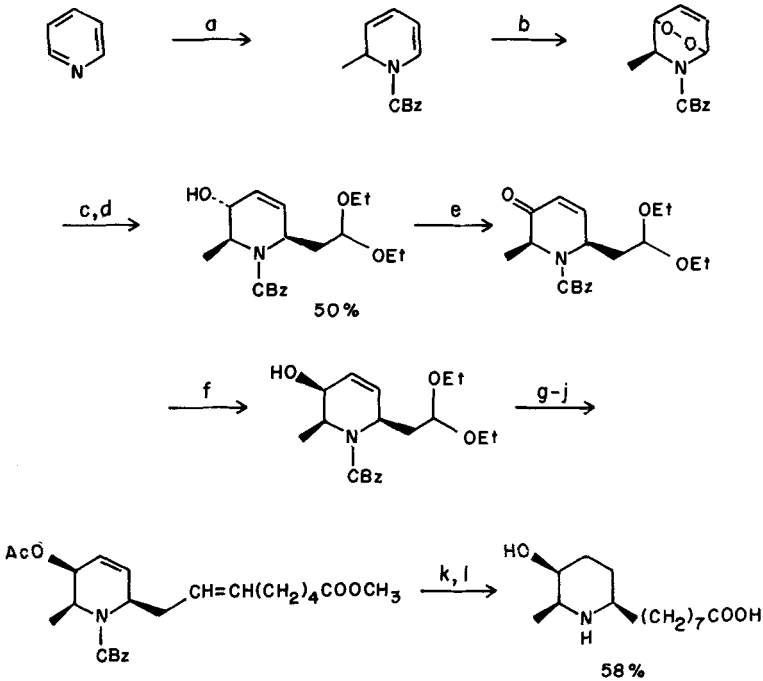
SCHEME 1



SCHEME 2

tion of the mixture **21** with palladium on charcoal in ethanol at 95°C and at 3 atmospheres pressure yielded a mixture of racemic cassine (Table I) and iso-3-cassine (90%), separable by fractional crystallization and sublimation or by preparative thin-layer chromatography.

It may be noted that while cassine was originally isolated as a levorotatory



SCHEME 3. (a) CH_3MgBr, $ClCOOCH_2Ph$, (b) $O_2/h\nu$/sensitizer, (c) ethyl vinyl ether–$SnCl_2$, (d) EtOH, (e) Collins reagent, (f) $NaBH_4$, (g) H^+, (h) $Ph_3P{=}CH(CH_2)_4COOLi$, (i) CH_2N_2, (j) Ac_2O/py, (k) $Ba(OH)_2$, (l) H_2–cat.

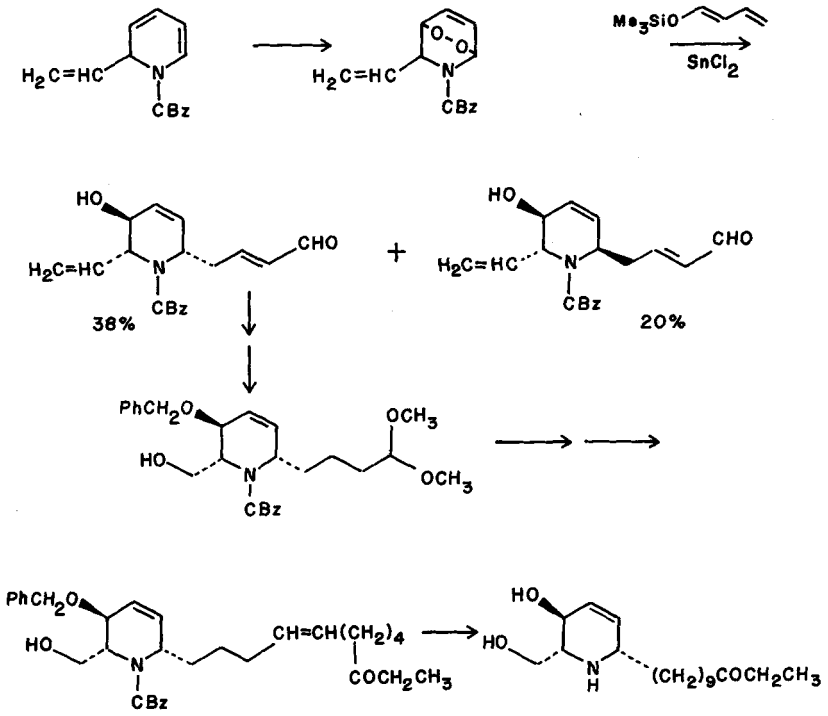
alkaloid with the configuration depicted (Table I), it has also been obtained from natural sources in racemic form (*30*).

The synthesis of cassine constitutes, in addition, a formal synthesis of the alkaloid carnavaline, which is accessible from the former by sodium borohydride reduction (*31*). Application of the nitroalkane–keto aldehyde condensation–reductive cyclization approach to the synthesis of racemic carpamic (**17**(*27,32*) and azimic (**16**) (*33*) acids is depicted in Scheme 2.

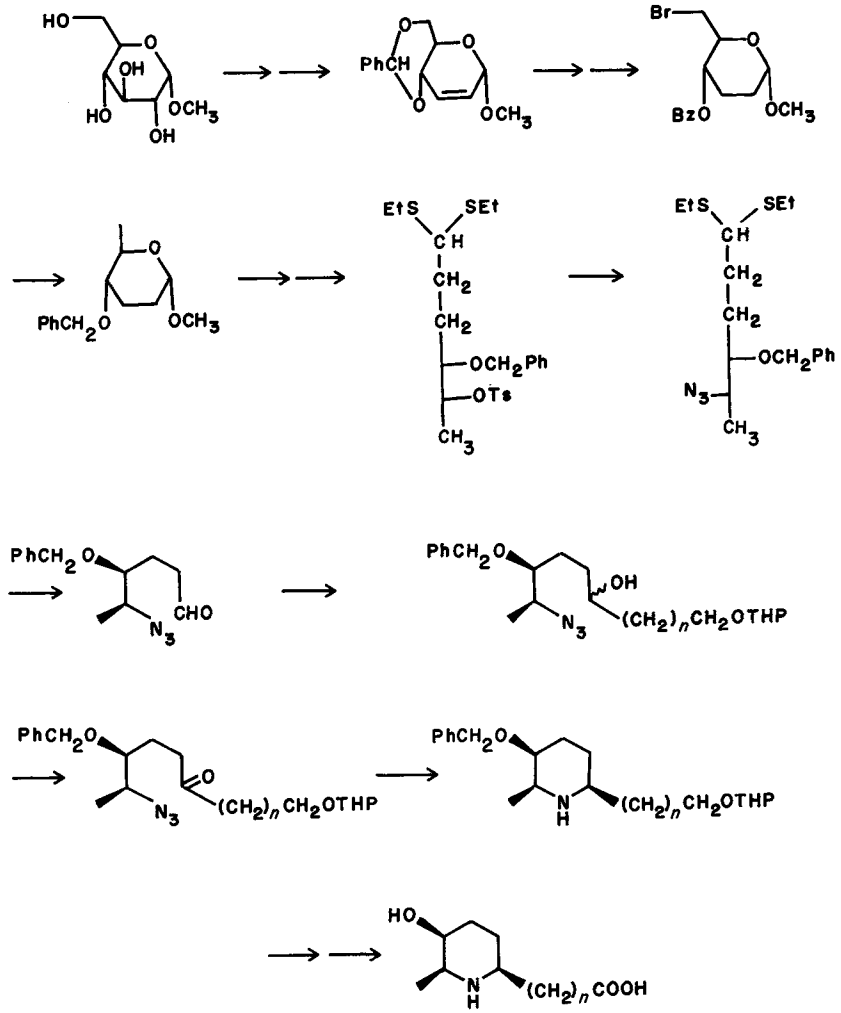
In each instance the desired product was accompanied by its C-3 epimer, e.g., the cyclization produced azimic acid (**16**) and its C-3 epimer from the appropriate precursor in yields of 45 and 35%, respectively.

Natsume and Ogawa have developed an alternative elegant and versatile strategy for the synthesis of 2,6-disubstituted piperidin-3-ols. This approach is based on the tin(II) chloride–catalyzed condensation of vinyl ethers with endoperoxides derived by photooxidation of 1,2-dihydropyridines.

The methodology has been exploited in the synthesis of carpamic (**17**) (*34,35*), pseudocarpamic (2-epicarpamic) (*36*), and azimic (**16**) (*35*) acids, as well as prosafrinine (Table I) (*36*), prosophylline (Table I) (*37*), and sedacryptine (see below) (*92*). The approach is exemplified by the synthesis of carpamic acid (**17**) and prosophylline, depicted in Schemes 3 and 4, respectively.



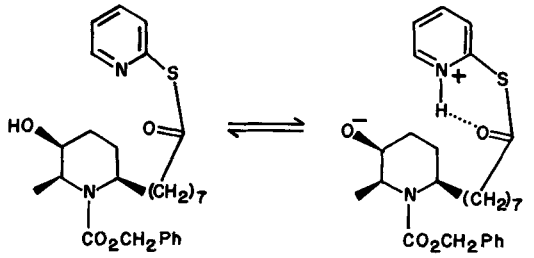
SCHEME 4



SCHEME 5

Hanessian has developed stereospecific syntheses of (+)-azimic and (+)-carpamic acids from D-glucose ("chiral template") (*38*). The key features are depicted in Scheme 5.

Syntheses of carpamic acid are, in effect, formal syntheses of carpaine, since bislactonization of the former to the latter has been accomplished (*39,40*). The "double activation" macrocyclization process developed recently by Corey (*40*) effects the cyclization reasonably efficiently. Thus *N*-benzyloxycarbonylcar-

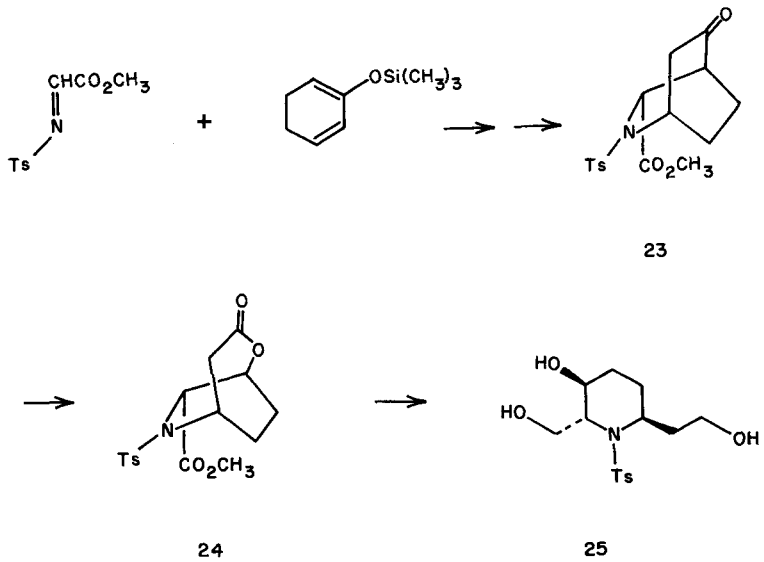


22

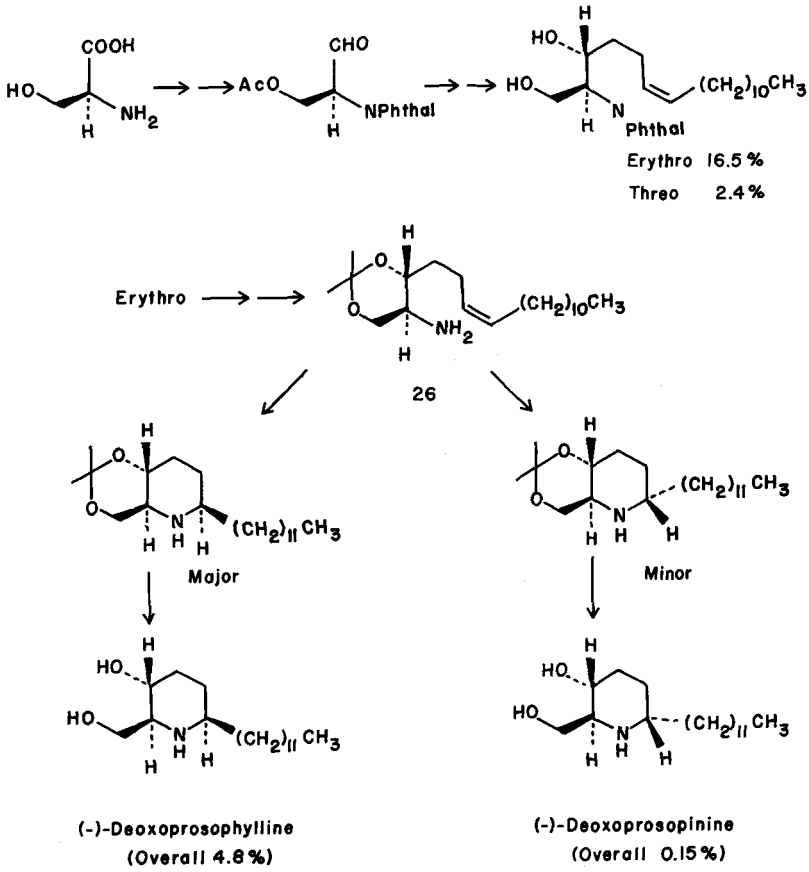
pamic acid was cyclized via its 2-pyridinethiol ester **22** at high dilution to the bisbenzyloxycarbonyl derivative of carpaine in >50% yield.

The protecting group was removed quantitatively by catalytic hydrogenation under acidic conditions. It appears likely that azimic acid could be dimerized to azimine using the same methodology.

Holmes and his colleagues recently brought to fruition an interesting and efficient approach to certain *Prosopis* alkaloids, centered on the key intermediate **24,** which embodies the correct configuration at each of the three chiral centers on the ring (*41*). This intermediate is prepared by Baeyer–Villiger oxidation of the 2-azabicyclo[2.2.2]octan-5-one (**23**) (Scheme 6). Reduction of **24** to the triol **25** and further elaboration led smoothly to (±)-isoprosopinine B and (±)-desoxoprosopinine (*41*).



SCHEME 6

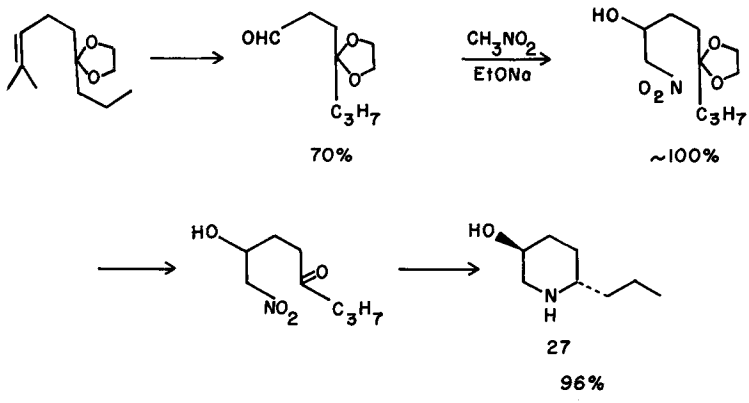


SCHEME 7

The deoxy products derived from natural (+)-prosopinine and (±)-prosophylline have been prepared as the (−)-enantiomers by a chiral and stereoselective route starting from L-serine (*42*). The crucial cyclization reaction in this approach is accomplished by intramolecular aminomercuration of the olefin **26** (Scheme 7). [A similar strategem has also been employed successfully for the synthesis of (±)-solenopsin A (see below).]

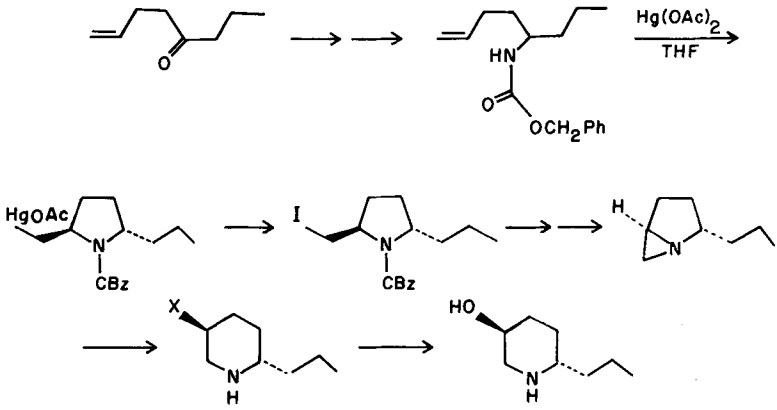
III. Other Piperidin-3-ols

Pseudoconhydrine (**27**) one of the minor alkaloidal constituents of poison hemlock, *Conium maculatum* L. (Umbelliferae), has been synthesized in racemic form via Brown's nitro ketone reductive cyclization approach (*43*) as depicted in Scheme 8.



SCHEME 8

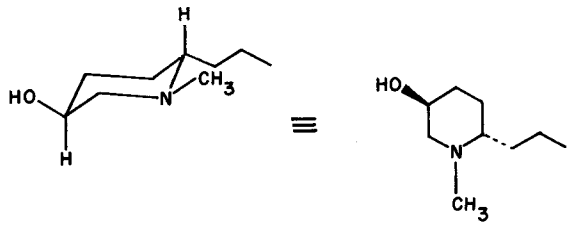
In a very recent publication, Harding (*44*) reported the synthesis of pseudoconhydrine by a sequence involving intramolecular amidomercuration of an olefin. Ring expansion of a pyrrolidine intermediate via an aziridine is another important feature of this approach (Scheme 9).



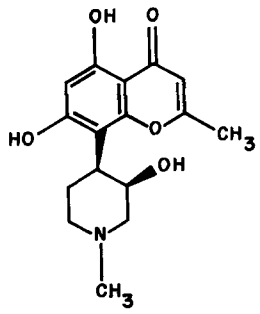
SCHEME 9

Under a variety of conditions, acid-catalyzed ring opening of the aziridine was observed to give the pyrrolidine as the major kinetic product. The piperidine is, however, the thermodynamically favored product, and by suitable selection of reaction conditions it was possible to obtain a good yield of the piperidine product, readily convertible to pseudoconhydrine.

N-Methylpseudoconhydrine (**28**), a new natural product, has been isolated as a major alkaloid from *Conium maculatum* growing at high altitude in South Africa (*45*). Its structure was determined by spectrometric methods, among which NMR was prominent.



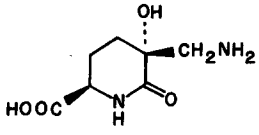
28



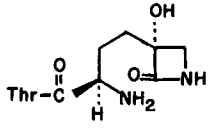
29

The major alkaloid from the foliage and stems of *Amoora rohituka* (Meliaceae) is rohitukine, whose structure (**29**) has been determined by X-ray crystallography (*46*). Rohitukine appears to be the first known example of a chromone alkaloid.

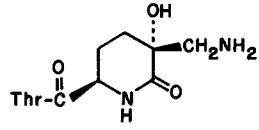
Tabtoxin-δ-lactam (**30**) is a 2-piperidonamino acid produced by various pseudomonad species, and is also a product of hydrolysis of tabtoxin (**31**), the chlorosis-inducing exotoxin produced by *Pseudomonas tabaci* and other phytopathogenic *Pseudomonas* spp. (*47*). Tabtoxin readily undergoes isomerization to the more stable nontoxic δ-lactam isotabtoxin (**32**), which can also be hydrolyzed to **30** (*47*).



30

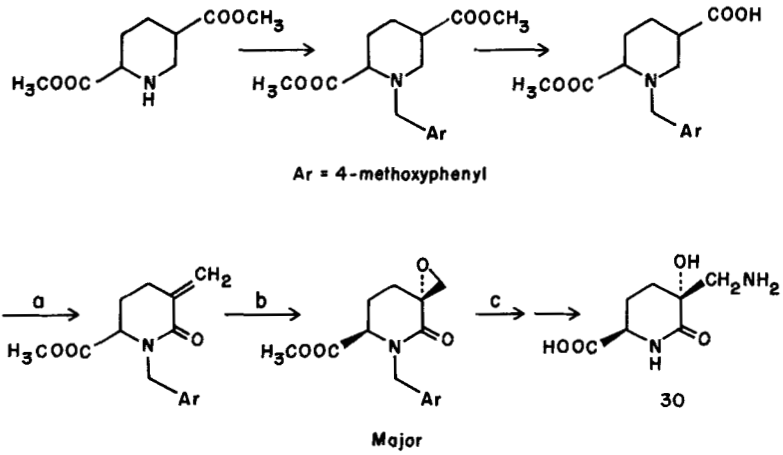


31



32

The synthesis of racemic tabtoxin δ-lactam has been reported by Rapoport (*48*), exploiting the α-methylene lactam rearrangement, which he had previously

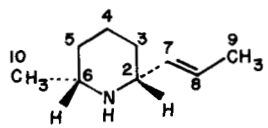


SCHEME 10. (a) Ac_2O, (b) MCPBA, (c) NH_4OH.

used effectively in the synthesis of camptothecin (*49*). The route is outlined in Scheme 10.

IV. Pinus Alkaloids

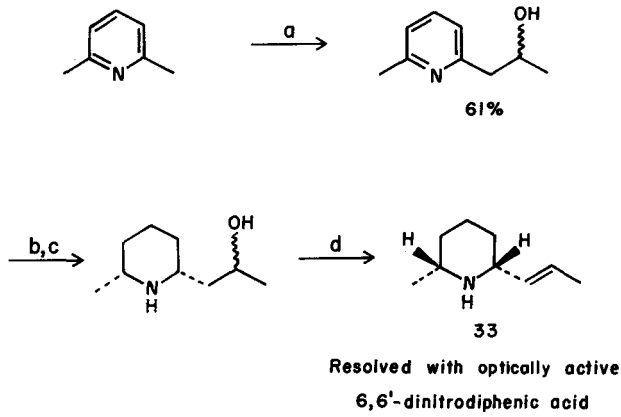
Alkaloids are not major metabolites of *Pinus* species; indeed, reports of their isolation from this genus have been rare. A base that has been obtained from various species of *Pinus* is (−)-pinidine (**33**) (*4*).



33

The first synthesis of (−)-pinidine (Scheme 11) was accomplished by Leete (*50*), who has also investigated the biosynthesis of the alkaloid (*50,51*). The synthesis [as well as syntheses of other alkaloids via 2,6-dialkylpiperideines (see above)] depends on the fact that catalytic reduction of 2,6-dialkylpyridines and piperideines affords mainly the *cis*-dialkylpiperidines, with the substituents in the equatorial conformation.

Following his earlier observation (*51*) that administration of acetate-*1*-^{14}C to *Pinus jeffreyi* plants yields pinidine labeled on alternate carbons, C-6, C-4, C-2,



SCHEME 11. (a) BuLi, CH_3CHO, (b) HCl gas, (c) H_2PtO_2, (d) $KHSO_4$, Δ.

and C-8, Leete has directed his attention to the identification of more advanced biosynthetic intermediates. In principle, the alkaloid might be formed from polyacetate-derived intermediates such as 3,7-dioxodecanoic acid, 5,9-dioxodecanoic acid, or their decarboxylation product 2,6-nonadione.

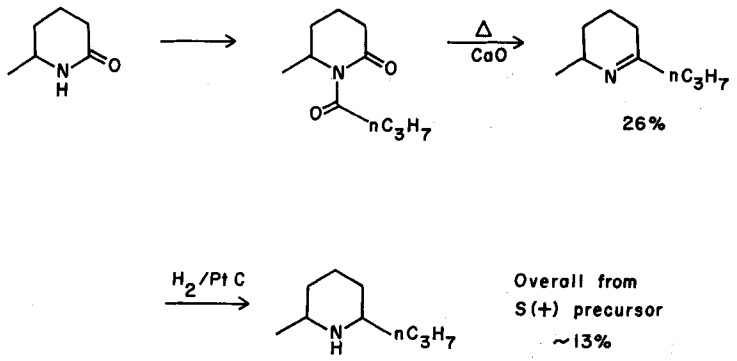
Feeding experiments, using labeled material, indicated that neither 5,9-deoxodecanoic acid nor 2,6-nonadione is significantly incorporated into pinidine in *P. jeffreyi*. Labeled decanoic acid was also not incorporated (*51*). By feeding experiments with unlabeled acetate ("starter") and labeled malonate, it was shown that C-6 and C-10 of pinidine are derived from acetate starter. The order in which the biosynthetic steps occur is unknown, and it is possible that the absence of appropriate unsaturation at C-3–C-4 in 5,9-dioxodecanoic acid was responsible for its failure to be incorporated.

Dihydropinidine has been a vehicle for the testing of several different synthetic methods.

Starting from (*S*)-(+)-6-methyl-2-piperidone, Hill has synthesized (−)-dihydropinidine, using the Mundy *N*-acyllactam rearrangement (*52*) (Scheme 12).

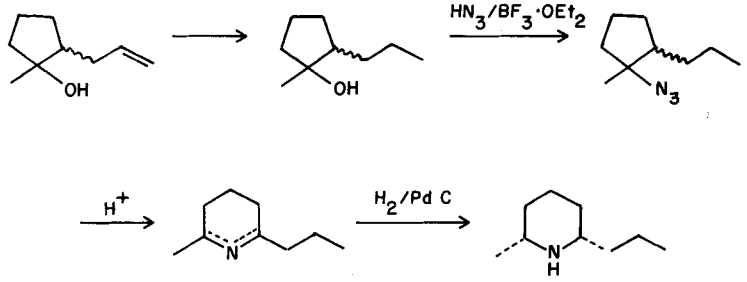
Synthesis of the unnatural enantiomer (2*R*,6*S*)-(−)-dihydropinidine from (*S*)-(+)-6-methyl-2-piperidone confirms that the natural pinidine possesses the (2*R*,6*R*) configuration assigned previously.

An analogous approach was followed for synthesis of the fire-ant venom solenopsin-A (*trans*-6-methyl-2-undecylpiperidine) (see below). The low yield of the Mundy rearrangement of the required precursor, *N*-lauryl-6-methyl-2-piperidone, and the preponderance of cis reduction product, even when the piperideine intermediate was reduced with sodium borohydride, detracts from the usefulness of the approach for long-chain *trans*-piperidine alkaloids such as the solenopsins.



SCHEME 12

Acid-catalyzed reaction of cyclopentane tertiary azides affords α-substituted piperideines in good yield, and this rearrangement has been exploited for the synthesis of racemic dihydropinidine (Scheme 13) and related alkaloids [γ-coniceine, (±)-coniine] (*53*).



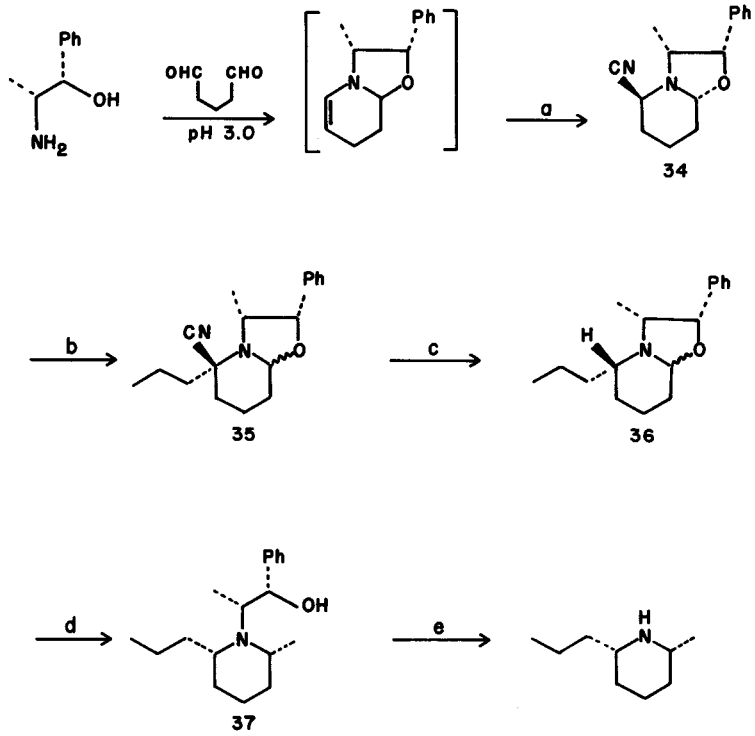
SCHEME 13

The overall yield for the sequence in Scheme 13 is about 60%.

An enantiospecific route to (+)- and (−)-dihydropinidine and (+)- and (−)-coniine, using (+)-norephedrine or (−)-phenylglycinol as chiral auxiliary, has been developed by Husson and collaborators (Scheme 14) (*54*).

The high stereoselectivity observed in the conversion of **35** to **36** is believed to result from a mechanism involving formation of an iminium ion by elimination of the cyano group and subsequent approach of hydride under stereoelectronic control from the upper face. Reaction of **36** with methylmagnesium iodide gives predominantly (>95%) the cis product **37**, and removal of the chiral auxiliary by treatment with 70% sulfuric acid afforded optically pure (2*S*,6*R*)-(+)-dihydropinidine (natural configuration).

The unnatural (−)-enantiomer was synthesized from the analog of **34** in which



SCHEME 14. (a) KCN, (b) LDA, *n*-C_3H_7Br, (c) $AgBF_4$–$Zn(BH_4)_2$, (d) CH_3MgI, (e) 70% H_2SO_4.

the chiral component was derived from (−)-phenylglycinol, i.e., with methyl and phenyl substituents replaced by phenyl and hydrogen, respectively. This material was first alkylated with methyl halide and the product was selectively reduced as above. The propyl chain was introduced cis to the methyl group by reaction with propylmagnesium bromide, and the chiral auxiliary was removed by hydrogenolytic cleavage.

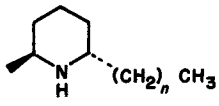
V. Other 2,6-Disubstituted Piperidines

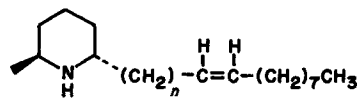
A most interesting series of papers describing the chemistry and biology of fire-ant venoms has emanated from the laboratories of M. S. Blum and colleagues at the University of Georgia.

The red form of the fire ant, *Solenopsis saevissima*, owes its trivial name to the potency of its venom, which exhibits hemolytic, insecticidal, and antibiotic activity. The venom was found to be composed of five constituents, designated

solenopsins, and seems to be the only known nonproteinaceous venom delivered by bite or sting.

Gas chromatography, combined gas chromatography–mass spectrometry, and mass spectrometry (including chemical ionization mass spectrometry) were used in separation and partial characterization of the five solenopsins (**38–42**) (*55*).





38 Solenopsin A $n = 10$

39 Solenopsin B $n = 12$

40 Solenopsin C $n = 14$

41 Dehydrosolenopsin B $n = 3$

42 Dehydrosolenopsin C $n = 5$

The base peak in the mass spectra of all of the solenopsins at *m/e* 98 ($C_6H_{12}N^+$) results from cleavage of the long side chain. The gas chromatogram of the venom mixture after hydrogenation exhibits only three peaks. Ions corresponding to $C_{19}H_{37}N$ and $C_{21}H_{41}N$ disappeared, and the intensity of the $C_{19}H_{39}N^+$ and $C_{21}H_{43}N^+$ ions increased, suggesting that the unsaturated components are olefinic analogs of solenopsins B and C, respectively.

Additional structural evidence was obtained by "carbon skeleton chromatography" applied to the venom mixture. In this technique, recently developed by Beroza (*56*), the alkaloids are swept by hydrogen gas through a hot tube, containing a palladium catalyst on a gas chromatographic support, prior to entering the injection port of a gas chromatograph. The hydrogen serves both as carrier gas and reactant, and the compounds are degraded hydrogenolytically to the hydrocarbons possessing the same carbon skeleton. The venom mixture gave rise to the alkanes pentadecane, heptadecane, nonadecane, and heneicosane. Thus the presence of *N*-methyl groups or methyl or other branches is excluded.

These data, plus additional spectral information, allowed plane structures to be advanced for solenopsins A–C. Comparison with synthetic material confirmed these assignments and demonstrated the trans relationship of the substituents on C-2 and C-6. The synthetic reference compounds were obtained by reduction of the appropriate 2-methyl-6-alkylpyridines. Catalytic hydrogenation of the latter affords cis-2,6-disubstituted piperidines, while reduction with sodium in alcohol also yields the trans isomers as minor products.

Location of the double bond in the unsaturated solenopsins was accomplished, inter alia, by ozonolysis of the total venom mixture, which gave nonanal as the sole volatile product. The structures of these alkaloids were also confirmed by synthesis.

A subsequent paper from Blum's laboratory indicated that the venoms from *individual* ants may be analyzed by combined gas chromatography–mass spectrometry (*57*).

Comparative analysis of the venom components of *Solenopsis geminata, S. invicta, S. richteri,* and *S. xyloni* revealed patterns of alkaloid distribution characteristic of each species, thus demonstrating the taxonomic value of such analysis.

The five trans-2,6-disubstituted piperidine alkaloids isolated from *S. saevissima* (see above) were found in these species, as well as the corresponding cis isomers.

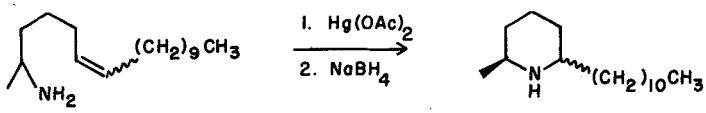
It was observed that the venoms of workers of *S. invicta* and *S. richteri* contain alkaloidal constituents that are not present in their alate queens or in either the workers or alate queens of *S. geminata* or *S. xyloni* (*58*). Thus in venom from *S. richteri* and *S. invicta* workers, alkaloids with trans C_{13} side chains predominate, while C_{11} (trans) alkaloids are minor components. *Solenopsis invicta* venom is also rich in trans C_{15} alkaloids, apparently absent in other species. *Solenopsis xyloni* and *S. geminata* workers on the other hand produce venom containing essentially only C_{11} compounds (mainly cis) as do the queens of all four species.

Careful analysis of the distribution of alkaloids in the venoms of the different castes of the four species led to the development of an interesting model for the biochemical evolution of these alkaloids in *Solenopsis* species (*58*).

The components of venoms from a large number of Neotropical *Solenopsis* species exhibit the same molecular weight range as do those from the venom of *S. invicta* (*59*). One *Solenopsis* species from Brazil, however, produced venom containing *only* C_9-side-chain solenopsins, with the trans isomer predominating (*59*). It was then found that venom from alate females of *S. geminata* and *S. richteri* also contain traces of the C_9 alkaloid (cis in the case of the former species, both cis and trans in the latter case).

Bioassays have shown that those solenopsins that have antibacterial properties are more inhibitory to gram-positive than gram-negative bacteria (*60*).

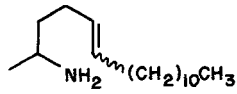
Besides the synthetic work conducted by Blum's group in connection with the structural studies, several additional syntheses of solenopsins have been reported. Thus solenopsin A has been prepared by intramolecular aminomercuration of the aminoolefin **43** (Scheme 15) (*61*).



43

11% trans (solenopsin A)
41% cis
31% recovered 43

SCHEME 15



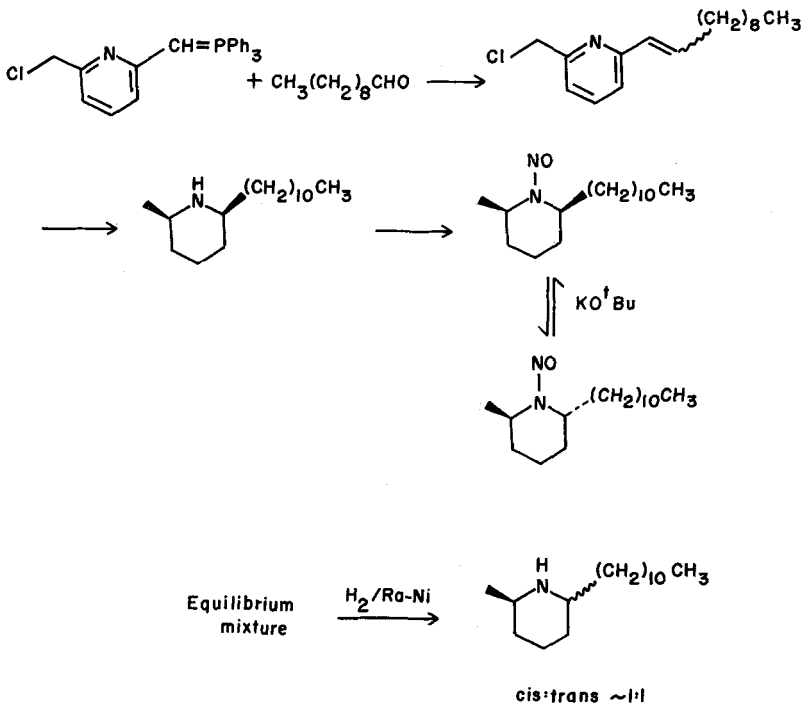
44

It is interesting to note that aminomercuration of the isomeric aminoolefin **44** led to the formation of pyrrolidines (cis and trans) rather than piperidines (*61*).

An analogous cyclization was employed by this group in the synthesis of *Prosopis* alkaloids (*42*).

The Mundy *N*-acyllactam rearrangement provides a short route to solenopsin A, but the overall yield is meager (see above) (*52*).

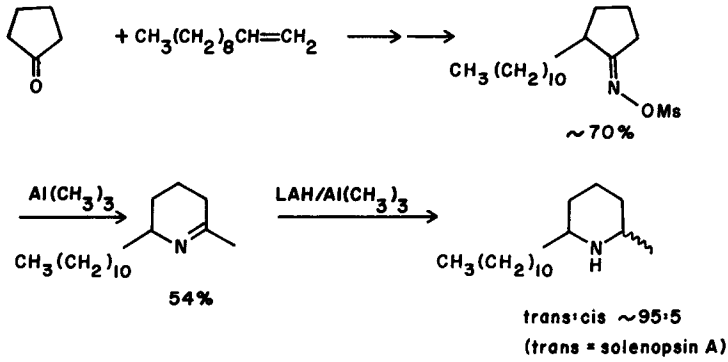
The fact that hydrogenation or reduction of 2,6-disubstituted pyridines or piperideines tends to give a preponderance of the cis products proved a major obstacle in the early syntheses of trans-2,6-disubstituted piperidine alkaloids. Fumita and colleagues (*62*) have been able to synthesize racemic solenopsin A from the cis isomer by base-catalyzed equilibration of the *N*-nitroso derivative (Scheme 16).



SCHEME 16

The yields in all steps are good, and the recovered cis isomer can, in principle, be recycled.

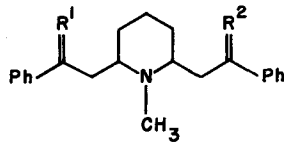
The first stereoselective synthesis of solenopsins was accomplished by Yamamoto and colleagues (*63*), via stereocontrolled reduction of 2,6-disubstituted piperideine precursors (Scheme 17) through the agency of lithium aluminum hydride in the presence of trimethylaluminum—a valuable contribution to the field. Solenopsin B was prepared in a like manner.



SCHEME 17

Alkaloids from both *Lobelia* and *Sedum* species might also be included in this section under the heading 2,6-disubstituted pyridines, but the latter are considered instead in the following section along with other bases from the same genus.

Isolation of lobeline (**45**) from four Appalachian lobelias (*64*) and Indian lobelia (*65*) has been reported. Lobelanine (**46**) and lobelanidine (**47**) were also detected in the North American species (*64*).



45 R^1 = H, OH
R^2 = O

46 $R^1 = R^2 = O$

47 $R^1 = R^2$ = H, OH

A method of estimating lobelanine in lobelia extracts, using thin-layer chromatography and colorimetric analysis, has been described (*66*), and an efficient procedure for isolating lobeline using ion-exchange resins, has been developed (*67*).

The biosynthesis of lobeline was investigated in *Lobelia inflata* plants growing hydroponically or in soil (*68*). Chemical degradation of lobeline isolated after administration of ^{14}C-labeled phenylalanine showed that this amino acid contributes the C_6—C_2 side-chain units of the alkaloid. Labeled cinnamic acid and 3-hydroxy-3-phenylpropionic acid were similarly and even more efficiently incorporated, implicating benzoylacetic acid as the immediate precursor of the side chains (*68*).

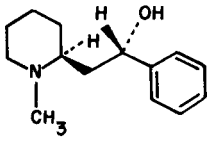
Incorporation of lysine-2-^{14}C in another experiment gave rise to labeled lobeline in which half of the radioactivity was located at C-2, and the other half resided (presumably) at C-6 (*68*).

A general scheme for the biosynthesis of piperidine alkaloids from lysine is shown in Section VI (Scheme 18) (*71*). The distribution of activity at C-2 and C-6 of lobeline can be rationalized by the assumption that one of the intermediates between lysine and lobeline is symmetrical. One possible candidate is free cadaverine (cf. Scheme 18), however, this compound is not readily incorporated into lobeline, and the symmetrical intermediate responsible for the observed labeling pattern has, in fact, been identified as lobelanine (**46**) (*68*).

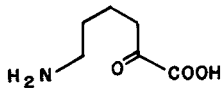
VI. Sedum Alkaloids

The period under review has seen considerable research activity in the areas of isolation, structure elucidation, biosynthesis, and synthesis of *Sedum* alkaloids.

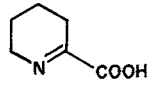
Tracer experiments by Spenser (*69*) showed that lysine is a precursor of sedamine (**48**) in *Sedum acre*. It was observed that lysine-*2-t-6*-^{14}C was incorporated into sedamine without loss of tritium relative to carbon-14. This observation excludes compounds such as **49** and **50** as intermediates on the biosynthetic pathway from lysine to sedamine (and similar alkaloids) (*69,70*).



48

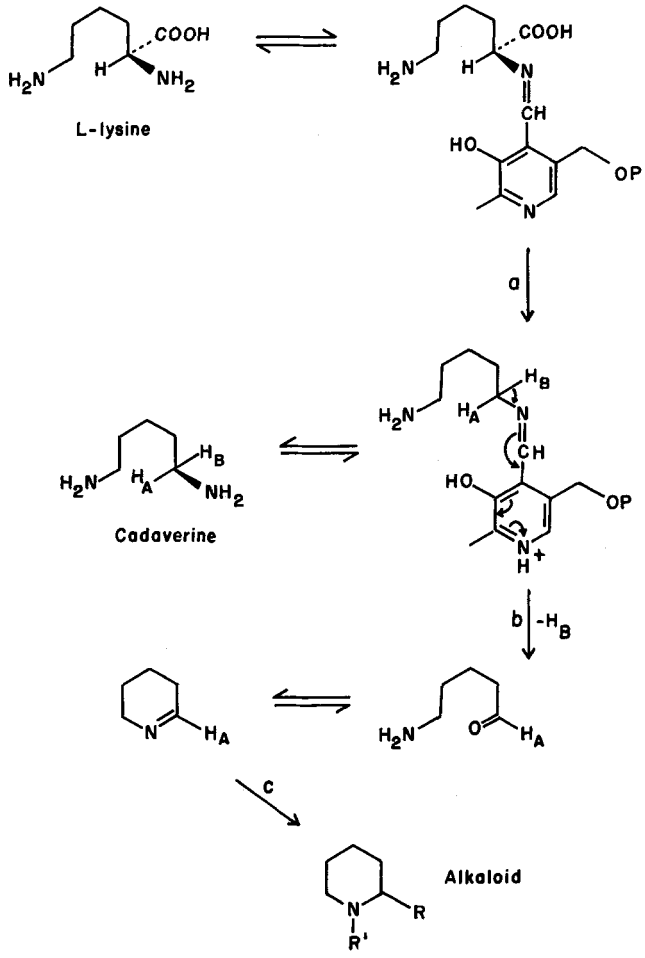


49



50

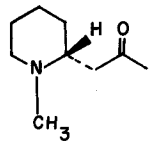
The accumulated data of Spenser, Leete, and other workers appear to be accommodated most satisfactorily by the model depicted in Scheme 18 for the



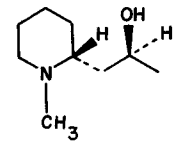
SCHEME 18. (a) L-Lysine decarboxylase (stereospecific decarboxylation), (b) diamine oxidase (stereospecific oxidative deamination), (c) stereospecific entry of side chain at C-2: benzoyl acetic acid (re-face) → → sedamine, acetoacetic acid (si-face) → → pelletierine, dihydronicotinic acid (re-face) → → anabasine.

biosynthesis of sedamine and other piperidine alkaloids, including pelletierine and anabasine (*71*). In an elegant study, Leistner and Spenser, using cadaverine chirally tritiated at C-1 through the agency of L-lysine decarboxylase from *Bacillus cadaveris,* demonstrated that in the biosynthesis of *N*-methylpelletierine (**51**) and *N*-methylallosedridine (**52**) in *Sedum sarmentosum,* the 1-pro-*R* hydrogen of the diamine is retained at C-2 of the alkaloids and the 1-pro-*S* proton is lost (*71,72*).

It was established that L-lysine decarboxylase from *B. cadaveris* effects decar-



51



52

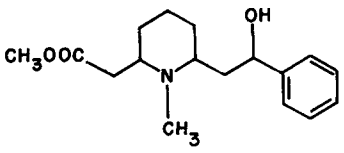
boxylation with retention of configuration, such that L-lysine-*2-t* affords (1*S*)-cadaverine-*1-t* (*72*). During the biosynthesis of alkaloids **51** and **52** from the latter substrate (mixed with cadaverine-*1*-^{14}C) in *Sedum sarmentosum,* tritium is lost from the site that becomes C-2 of the alkaloids and retained only at C-6.

The stereospecific oxidative deamination occurring during the alkaloid biosynthesis finds a parallel in the behavior of diamine oxidase from hog kidney. Using chirally deuterated cadaverines, Richards and Spenser (*73*) showed by ^2H-NMR analysis that this enzyme system also mediates removal of the pro-*S* hydrogen from C-1 of cadaverine, and that the product of the oxidative deamination, 5-aminopentanal (hence, the derived Δ^1-piperideine) retains the pro-*R* hydrogen at the sp^2 carbon (*73*).

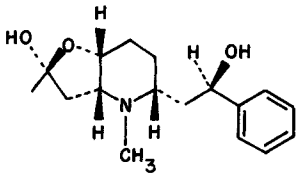
Subsequent experiments by Gerdes and Leistner (*74*) confirmed that L-lysine decarboxylase from *B. cadaveris* effects decarboxylation with retention of configuration, as does the enzyme from *Escherichia coli.* The diamine oxidase from pea seedlings, like that from hog kidney, removes the 1-pro-*S* hydrogen from cadaverine during the formation of Δ^1-piperideine. The observation that DL-lysine-2-*t* (L component) is incorporated into sedamine (**48**) in *Sedum acre* with complete retention of tritium (*69*) implies that the stereochemical course of one of the transformations between lysine and Δ^1-piperideine is reversed in this system. Further study of the biosynthesis of alkaloids by *S. acre,* possibly using cell-free extracts, may shed light on this apparent anomaly (*74*).

While comparison of incorporation efficiencies of labeled enantiomers and racemates may indicate the configuration of a precursor in the biosynthesis of a natural product [cf. (*75*)], the results are not unequivocal. A general and more reliable method was developed by Spenser's group (*76*) and used to establish that sedamine, *N*-methylpelletierine, and *N*-methylallosedridine from two *Sedum* species are derived from L-lysine, whereas pipecolic acid from these plants is derived from D-lysine. The use of mixed, differently labeled (^3H and ^{14}C) enantiomers and racemates provides, in effect, an internal standard. Comparison of the isotope ratios of substrate and product indicates which enantiomer is utilized as the biosynthetic precursor.

The structures of two new minor bases from *S. acre* have been determined by a Belgian research group. The formulation **53** was advanced for sederine on the basis of spectroscopic and chemical data (*77*). Its stereochemistry remains to be determined.



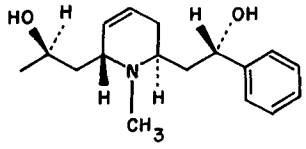
53



54

The structure of sedacryptine was established as **54** by X-ray analysis (*78*). Sedacryptine may be identical with a previously isolated alkaloid, designated hydroxysedinone (*79*), however direct comparison was not possible.

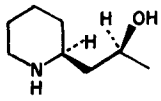
Hootele and co-workers (*80*) have also established that the alkaloid sedinine is correctly depicted as **55,** rather than an isomeric formulation as previously proposed (*81*), in which the disubstituted double bond in the heterocycle occupies the alternative position. Sedinine, first isolated from *S. acre,* has been shown to occur in a number of *Sedum* species.



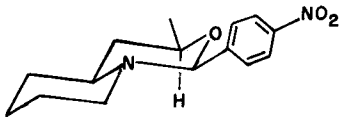
55

The structure was established by X-ray analysis of the free base and its hydrochloride. The absolute configuration was determined by application of Horeau's method to 10-deoxydihydrosedinine, the hydrogenolysis product of the alkaloid (*80*).

In another investigation of the alkaloid content of *Sedum acre,* Gulubov and Bozhkova (*82*) have reported the isolation of sedinine, sedamine, and sedridine from this species.

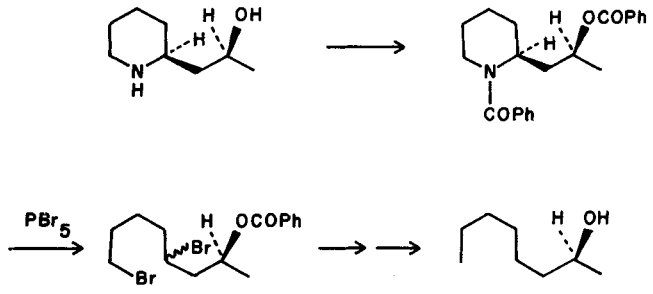


56



57

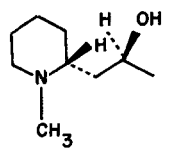
Beyerman's group advanced the (2*S*,2′*S*) configuration **56** for (+)-sedridine in 1965 (*4*,*83*). In order to check the configuration at C-2′, which had been based on NMR analysis of oxazine derivatives of racemic sedridine and allosedridine, and which was considered to be at variance with other chemical and spectroscopic data (*84*), Fodor's group (*85*) degraded (+)-sedridine via von Braun degradation of its *O*,*N*-dibenzoyl derivative to an acyclic dibromide. The latter, (+)-4,8-dibromo-2-octyl benzoate, afforded, on hydrogenolysis and hydrolysis, (*S*)-(+)-octan-2-ol, in accord with the original assignment of the Dutch researchers (*83*) (Scheme 19).



SCHEME 19

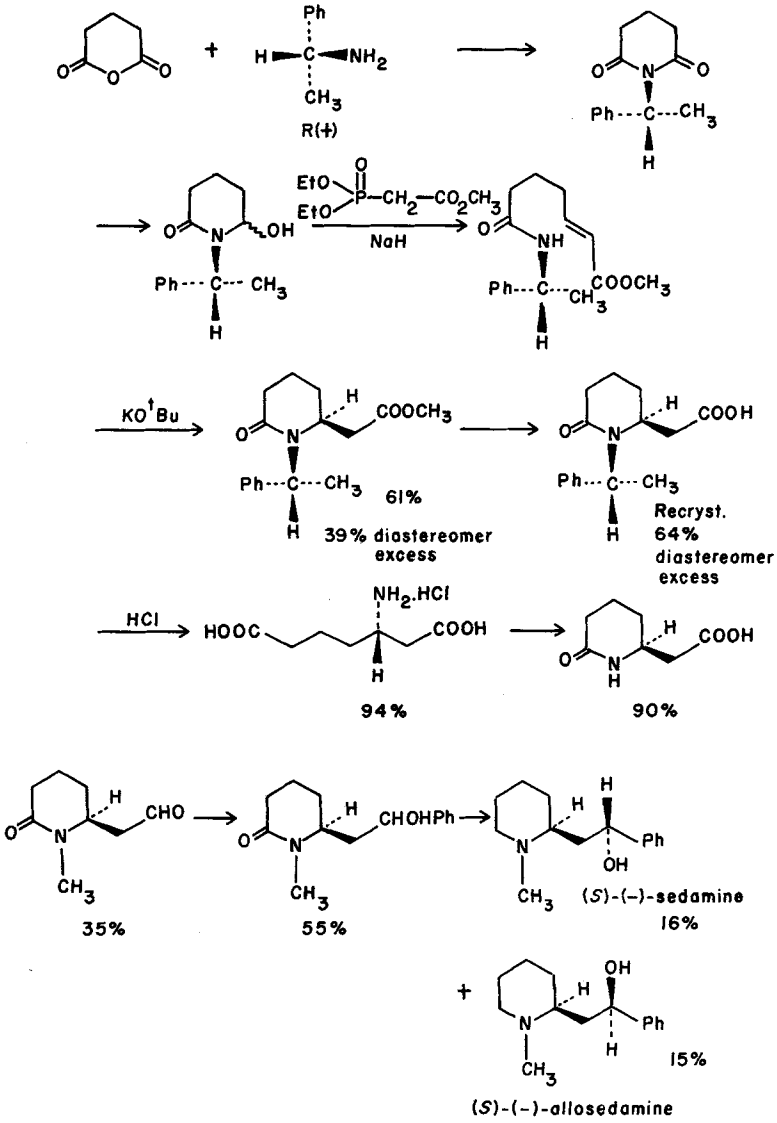
Further support for the assigned configuration was derived from ORD and CD studies on (−)-sedridine and (+)-allosedridine hydrochloride (*86*). X-Ray analysis (*85*) of the oxazine **57** derived from (−)-allosedridine by treatment with *p*-nitrobenzaldehyde, was also in accord with the previous findings

In order to determine the configuration of (+)-2-(2-hydroxypropyl)-1-methylpiperidine, an alkaloid isolated from *Sedum sarmentosum* Bunge (*87*), the four possible stereoisomers were synthesized from 2-(2-hydroxypropyl)pyridine (*88*). Resolution could be effected after separation of the diastereoisomers obtained from catalytic hydrogenation of the *N*-methylpyridinium salt. Alternatively, and preferably, the 2-(2-hydroxypropyl)pyridines (**58**) could be resolved prior to N-methylation and hydrogenation.



58

Since the absolute configurations of the 2-(2-hydroxypropyl)-pyridines are known (*89*), and the threo configuration of *N*-methylsedridine was determined by correlation with racemic sedridine, the configurations of all four isomers were established. The stereochemical assignments were confirmed by ORD measurements in neutral and acidic media.

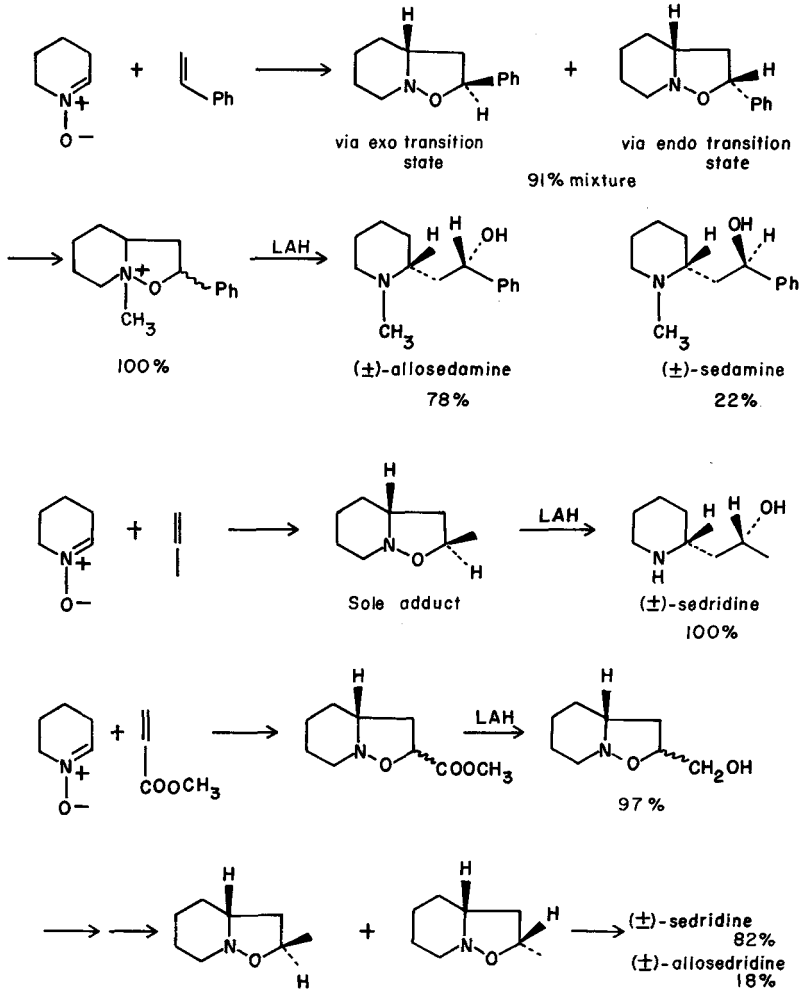


SCHEME 20

The configuration of the natural product from *S. sarmentosum* was found to be (2*R*,2′*S*), i.e., the compound is (+)-*N*-methylallosedridine, (**58**).

An asymmetric intramolecular Michael reaction has been applied in the synthesis of (*S*)-(−)-sedamine and (−)-allosedamine (*90*). Chiral induction is achieved via a phenylethyl group attached to the nucleophilic nitrogen atom (Scheme 20).

Associated with a study of the stereochemical outcome of 1,3-dipolar cycloadditions of cyclic nitrones with monosubstituted olefins, Tufariello (*91*) has devel-

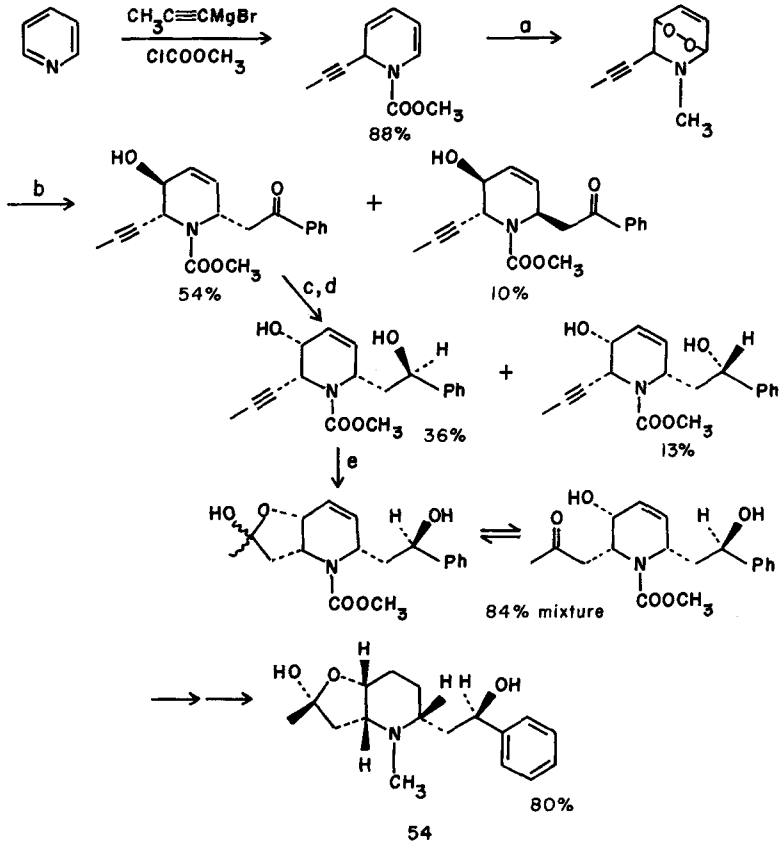


SCHEME 21

oped short efficient syntheses of (±)-allosedamine and (±)-sedridine (Scheme 21).

Mixtures of endo and exo addition, with the latter mode predominating, were observed for styrene and methyl acrylate, activated monosubstituted olefins capable of secondary orbital interactions. The unactivated olefin propylene apparently gave only exo addition with 2,3,4,5-tetrahydropyridine 1-oxide, attributed to steric interactions between ring hydrogens and the methyl group in the disfavored endo transition state (*91*).

Natsume and Ogawa (*92*) have applied the $SnCl_2$-mediated reaction of endo peroxides with nucleophiles [see above, Section II, (*34–37*)] to the synthesis of sedacryptine (**54**) (*78*) (Scheme 22).



SCHEME 22. (a) $O_2/h\nu$/sensitizer, (b) CH_2=C(Ph)OTMS, $SnCl_2$, (c) Jones' reagent, (d) $LiBH_4$, (e) $HgSO_4$.

VII. Tobacco Alkaloids, Related Compounds, and Other Nicotinic Acid Derivatives

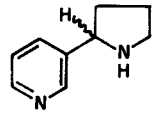
Tobacco continues to be a popular drug, although its use has abated somewhat in recent years as a consequence of the demonstrated adverse effects of smoking on health. The economic importance of tobacco cultivation in many countries, together with increasing concern about the physiological effects of smoking, has brought about a dramatic expansion of the already abundant literature on nicotine and other tobacco constituents, as well as their pyrolysis and combustion products. This chemistry is reviewed in a large number of publications; see, for example, references *93–103*.

Because of the volume of the literature, much of which is of somewhat specialized interest, and since excellent reviews already exist, no attempt is made in this section to provide comprehensive coverage of the field of tobacco alkaloids. Some topics not considered here include procedures for separation and analysis of nicotine and related alkaloids, variations in alkaloid content associated with different tobacco varieties, culture conditions or processing, and the isolation of known tobacco alkaloids from other genera. Rather, the emphasis is placed on selected recent developments in the chemistry of those compounds considered likely to be of interest to the natural products chemist.

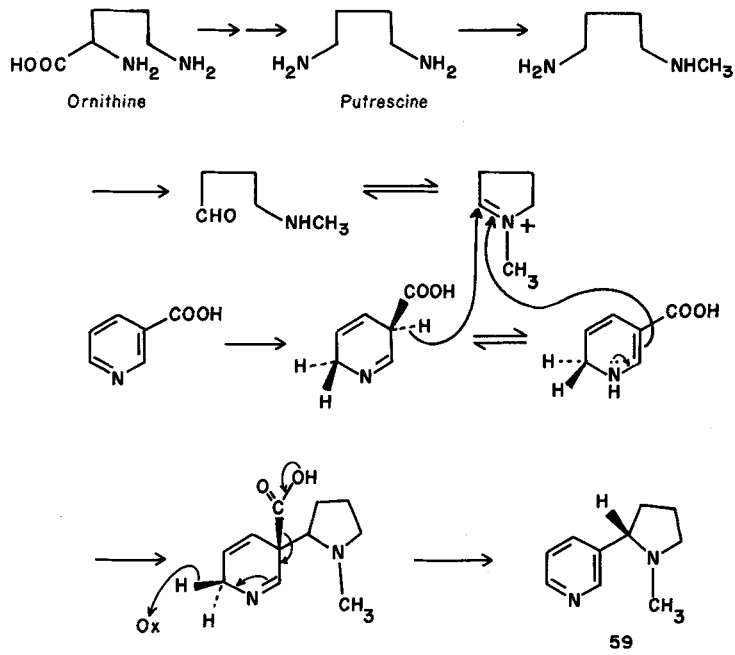
The results of extensive research by R. F. Dawson, E. Leete, R. U. Byerrum, S. Mizusaki, and others (references cited in *100*) on the biosynthesis of nicotine (**59**), which takes place in the roots of *Nicotiana tabacum,* can be summarized by the sequence depicted in Scheme 23 (*100–105*).

This pathway received support from the isolation and partial purification by the Japanese research group of three enzymes catalyzing crucial early steps, namely, ornithine decarboxylase (*106*), putrescine *N*-methyltransferase (*107*), and *N*-methylputrescine oxidase (*108*).

Incorporation of ornithine-*2*-^{14}C or ornithine-*5*-^{14}C into the pyrrolidine ring of nicotine (and nornicotine) results in equal labeling at C-2′ and C-5′ of the alkaloid, but only the δ nitrogen of ornithine is utilized in the formation of the pyrrolidine ring (references cited in *100*). Further evidence for the symmetrical incorporation of ornithine into nicotine and nornicotine (**60**) was provided by tracer experiments with doubly labeled ornithine-*2,3*-$^{13}C_2$ (*109*).



60



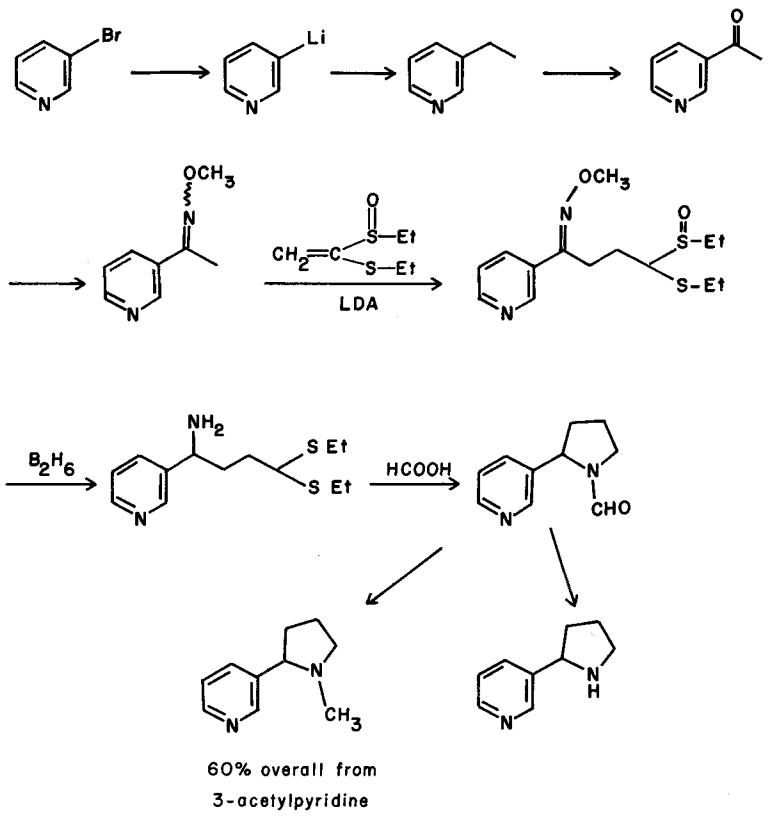
SCHEME 23

During the 1960s, Rapoport published a series of papers asserting that the labeling pattern of nicotine obtained after short-term exposure of intact *N. glutinosa* to $^{14}CO_2$ was at variance with the symmetrical intermediate hypothesis for the biosynthesis of the *N*-methylpyrrolidine ring. Using ^{13}C-NMR techniques, Hutchinson has reexamined the incorporation of label from CO_2 (^{13}C) (*110,111*).

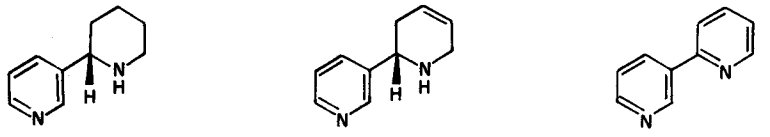
His observation of unequal intramolecular labeling in the *N*-methylpyrrolidine moiety of nicotine can be rationalized in biochemical terms (*111*), but further experimental clarification of the phenomenon is desirable. In the course of this study, Hutchinson (*111*) developed a new synthesis of nornicotine, tailored to the preparation of nicotine-2′,3′,*N*-methyl-$^{13}C_3$ (Scheme 24).

The alkaloid nornicotine (**60**) a minor component of *N. tabacum,* but the major alkaloid of other *Nicotiana* species, has been shown to be a demethylation product of nicotine (references cited in *100* and *102*) and does not appear to be biosynthesized directly from putrescine. Consistent with the accepted pathway was the observation that no differences were observed in the enzymatic oxidation of *N*-methylputrescine and putrescine by extracts of *N. tabacum* cultivars in which either nicotine or nornicotine predominated (*112*).

Anabasine (**61**), first isolated from *Anabasis aphylla* is the major alkaloid of *N. glauca,* and a minor constituent of *N. tabacum* (*100*).



SCHEME 24

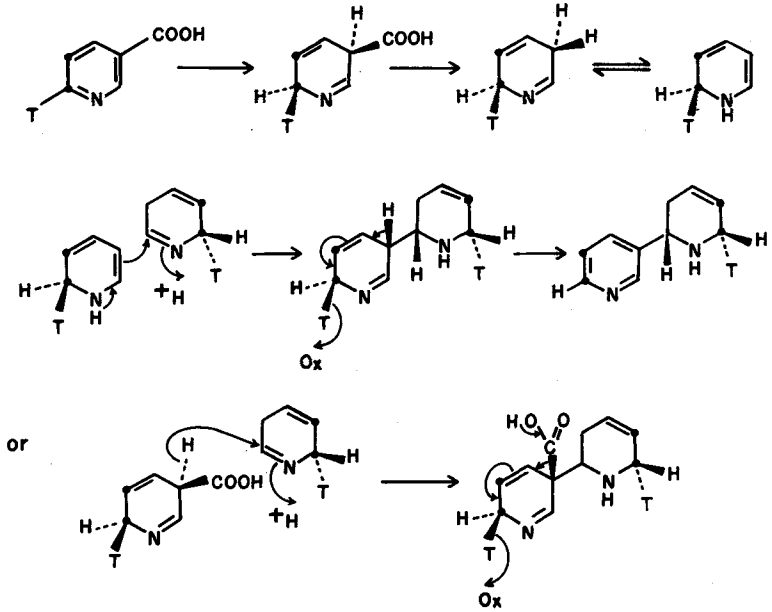


61 62 63

Lysine is the precursor of the piperidine ring (*113*) via Δ^1-piperideine (cf. Scheme 18), and the pyridine ring has its origin in nicotinic acid (*114*) via dihydronicotinic acid, as in the biosynthesis of nicotine (Scheme 23) (*102*).

(−)-Anatabine (**62**), a minor co-metabolite in several *Nicotiana* species, is Δ^4-dehydroanabasine, and might be expected to be derived from the same biosynthetic precursors. It was found, however, that lysine is not incorporated into

anatabine but that both heterocyclic rings are derived from nicotinic acid. Label from nicotinic-*6*-^{14}C acid was found at C-6 and C-6′ of anatabine produced by *N. glutinosa,* while administration of nicotinic-2-^{14}C acid to *N. tabacum* plants afforded anatabine labeled at C-2 and C-2′ (115,116). Administration of a mixture of nicotinic-*5,6*-$^{14}C,^{13}C_2$ acid and nicotinic-*6-t* acid to *N. glauca* plants yielded anatabine, which was labeled equally in both rings with ^{13}C, was almost devoid of tritium in the pyridine ring and retained 100% of tritium at C-6′. The pro-*S* configuration of this tritium indicated that in the reduction of nicotinic acid, hydrogen was introduced at C-6 in the pro-*R* position (*117*). The results of all of the tracer experiments are accommodated in a biosynthetic pathway to anatabine such as depicted in Scheme 25 (*102,115–117*).

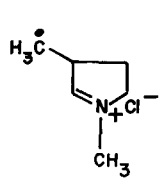


SCHEME 25

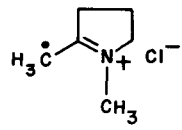
The alkaloid α,β-dipyridyl (**63**), isolated from several *Nicotiana* species after air-drying, appears to be formed in the plants from anatabine during the drying process.

The incorporation of unnatural precursors, specifically methyl-substituted pyrrolinium derivatives, into nicotine analogs by *N. glutinosa* was studied to probe, inter alia, the specificity of the enzyme system catalyzing the condensation with the appropriate dihydronicotinic acid derivative (see above) (*119*).

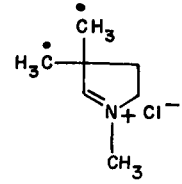
The ^{14}C-labeled unnatural precursors **64, 65,** and **66** were synthesized by



64

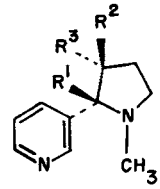


65



66

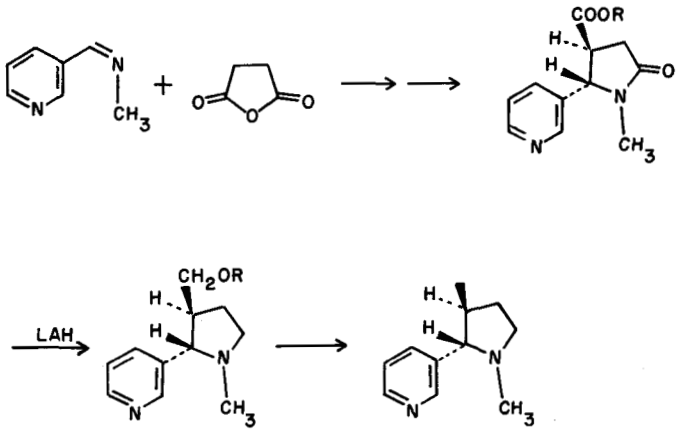
conventional methods from 1-methyl-2-pyrrolidinone. Plants were grown in aerated hydroponic solution to which the precursors were added. The uptake of activity was monitored continually, and all activity could be accounted for: no metabolism of precursors to respired $^{14}CO_2$ was evident. After suitable periods, incorporation of **64, 65,** and **66** into the corresponding nicotine derivatives (**67**) was estimated at 6.4–13.8, 0.04, and 0.77%, respectively. The differences in incorporation (approximate ratio 360:1:20) were attributed, at least in part, to steric hindrance in the condensation reaction with the dihydronicotinic acid derivative.



67

To facilitate characterization of the products, the nicotine analogs **67** ($R^1 = R^3 = H$, $R^2 = CH_3$), ($R^1 = R^2 = H$, $R^3 = CH_3$), and ($R^1 = H$, $R^2 = R^3 = CH_3$), among others, were synthesized by reaction of 3-pyridyllithium with the appropriate 2-pyrrolidinone and reduction of the resulting iminium salt. Analysis of their NMR spectra shows that the protons of a C-3′ methyl group cis with respect to the pyridine ring are shielded relative to the hydrogens on a trans methyl group. Furthermore, the presence of a methyl group at C-3′, cis to the C-2′ hydrogen, causes the signal for the latter to undergo a marked shift upfield relative to its position in nicotine. While the absolute configuration of the nicotine analog from **64** was rigorously established as (2′*S*,3′*S*) by CD and ORD analysis in conjunction with spectroscopic data, the configurations of the analogs from **65** and **66** were assigned tentatively on the basis of biogenetic considerations (*119*).

Rapoport's assignment of structure and stereochemistry to the nicotine analog biosynthesized from **64** was supported by a second synthesis of this product by

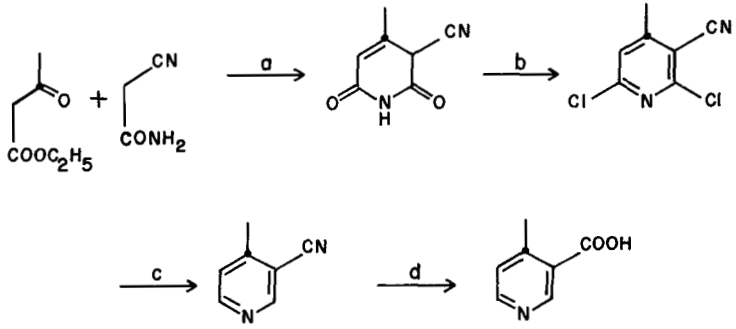


SCHEME 26

Cushman and Castagnoli (*120*) (Scheme 26). The overall yield was 17%. The use by these authors of a pseudocontact shift reagent allowed detailed assignment of all of the NMR signals.

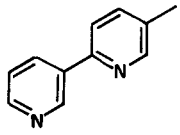
While a methyl substituent at C-2 or C-3 of the pyrrolinium component hindered but did not prevent its incorporation into the corresponding nicotine analog, labeled 4-methylnicotinic acid failed entirely to be elaborated to 4-methylnicotine by *N. tabacum* (*121*).

The nonsubstrate, 4-methylnicotinic-*4*-^{14}C acid was synthesized by a modification of Bobbit's route (Scheme 27) (*122*).

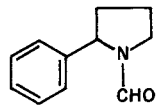


SCHEME 27. (a) KOH–CH_3OH, (b) $POCl_3$, (c) H_2–Pd, (d) NaOH.

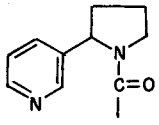
The anticipated product, 4-methylnicotine, was prepared in racemic form by modifications of three published nicotine syntheses. It could also be made in optically active form in low yield by reaction of nicotine with methyllithium according to Haglid (*123*).



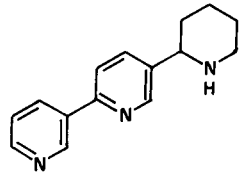
68



69



70



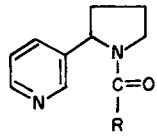
71

After something of a hiatus in isolation of new *Nicotiana* alkaloids, two publications in 1972 reported the identification of new minor alkaloids from *N. tabacum*. Three alkaloids, **68, 69,** and **70,** were isolated by preparative GLC from extracts of aged burley tobacco after removal of the large excess of nicotine by vacuum distillation (*124*).

The structure of **68** was established by spectrometric methods, and by comparison with some isomeric methyl 2,3′-bipyridines synthesized from 3-aminopyridine and the appropriate picoline, using the Gomberg–Bachman reaction. The assignment was further supported by spectral comparison with anabasamine (**71**) isolated from *Anabasis aphylla* (*125*).

N-Formylnornicotine (**69**) and *N*-acetylnornicotine (**70**) were characterized by spectral analysis and by comparison with synthetic materials. Since the same *N*-acyl compounds were obtained using mild extraction and separation techniques, it is improbable that they are artifacts. Extracts of both aged and unaged burley tobacco contained these bases.

Other *N*-acylnornicotines (**72,** R = n-C_5H_{11}, and **72,** R = n-C_7H_{15}) were found in the resin fraction of flue-cured *N. tabacum* and in air-cured burley tobacco (*126*). The levels of these bases in the flue-cured tobacco samples were estimated at about 1.5 and 5 ppm, respectively. The more abundant base (**72,** R = n-C_7H_{15}), was characterized by analysis of its IR and mass spectra and by



72

comparison with a synthetic specimen, and the structure of the lower homolog (**72**, R = *n*-C_5H_{11}) was then readily deduced from its mass spectrum.

Identification of minor components of tobacco and tobacco smoke, as well as their mammalian metabolites, is very important in relation to the physiological effects of smoking and requires analytical techniques capable of furnishing structural information on trace amounts of material. Mass spectrometry, particularly when coupled with gas chromatography, is an invaluable tool in this context (cf. Ref. *126*). A review on the application of mass spectrometry to the structure elucidation of alkaloids (pre-1972) contains references to investigations of a number of nicotine-type bases (*127*).

In a more recent paper, Glenn and Edwards (*128*) describe detailed studies on the mass spectral fragmentations of a series of 2-, 3-, and 4-pyridyl analogs in relation to their structures.

In a review of applications of ^{13}C-NMR spectroscopy in structure studies on alkaloids, Wenkert *et al.* (*129*) tabulate spectral data for the tobacco alkaloids anabasine, 1-methylanabasine, nornicotine, and nicotine as well as, inter alia, some piperidine bases including arecoline and coniine. Spectroscopic measurements and assignments in the case of nicotine have been made by Roberts *et al.* (*130*) and Pitner and co-workers (*131*).

X-Ray studies (*132*) have provided detailed information about the structure of nicotine (as its dihydroiodide) in the crystalline state. Just as relevant in the context of understanding the nature of its interaction with receptors associated with its physiological effects is knowledge about the preferred conformation(s) of the alkaloid in solution. Three stereochemical aspects must be considered in defining the conformation of nicotine. These are the rotational arrangement of the two heterocyclic rings about the C-3—C-2′ bond, the orientation of the pyrrolidine *N*′-methyl group, and the conformation of the pyrrolidine ring. Using various NMR techniques, a group at the Philip Morris Research Center has made important contributions in this area.

The orientation of the *N*′-methyl group was investigated by analysis of NMR spectra of nicotine measured in strongly acid media, under conditions where the rate of deprotonation–inversion is slow relative to the NMR time scale (*133*). Peaks assignable to the *N*-methyl protons of the major and minor diastereomeric salt forms were observed at δ3.13 and 2.82, respectively. Irradiation of the signal at δ3.13 resulted in large nuclear Overhauser effect (NOE) enhancement for the signals corresponding to two of the hydrogens α to the pyrrolidine nitrogen, but no enhancement in the pyridyl proton region, indicating that the methyl group of the major species is trans to the pyridine ring.

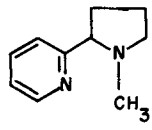
On the basis of gas-phase kinetic quenching experiments it was estimated that nicotine-free base exists with its *N*-methyl group preferentially (>90%) trans to the pyridine ring (*133*).

The high resolution ^{1}H-NMR spectrum of nicotine was analyzed in detail to

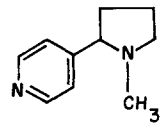
extract information concerning the other two conformational aspects (*134*). Analysis of the pyrrolidine ^1H resonances was facilitated by studying the spectra of several selectively deuterated nicotine analogs, and the ^2H-NMR chemical shifts of these analogs allowed the unambiguous assignment of ^1H chemical shifts. The vicinal coupling constants of the protons on the pyrrolidine ring suggest that the ring adopts an envelope conformation with the (trans) pyridine and methyl substituents both equatorial. Previous indications that the pyridine and pyrrolidine rings are perpendicular about the C-3—C-2′ bond (references cited in *134*) were supported by the observation of long-range coupling between H-2′ and H-6, as well as by NOE measurements (*134*).

Analysis of the ^{13}C-NMR spin–lattice relaxation times of nicotine in terms of anisotropic rotational diffusion constants suggested a conformation in which the H-2′–C-2′–C-3–C-2 dihedral angle is approximately 0° (*135*). The most probable conformation of the alkaloid in solution is thus approximately defined with respect to all three aspects. An excellent discussion of the conformational studies is contained in the review article by Seeman (*103*).

The conformations of the nicotine analogs **73** and **74** in $CDCl_3$ solution were found to be virtually identical with that of nicotine by ^1H, ^2H, ^{13}C, and ^{15}N-NMR spectroscopy (*136*).



73

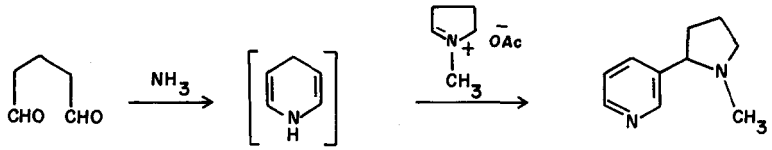


74

An investigation of *N*′-(β-hydroxyethyl)anabasine and related compounds by IR and NMR spectroscopy indicated that the substituents on the piperidine ring assume a diequatorial conformation, with intramolecular hydrogen bonding evident between the hydroxylic proton and the nitrogen of the second heterocycle (*137*).

Current interest in the biosynthesis of nicotine and related compounds, their metabolic fates, and pharmacological structure–activity relationships has provided the stimulus for many of the syntheses that have been reported in recent years. In several cases, the syntheses have been tailored to incorporate label in specific positions (*111,141,142,147*). Like other relatively simple natural products, nicotine has also been a vehicle for testing synthetic methodology (e.g., *140,150,153,157,159*).

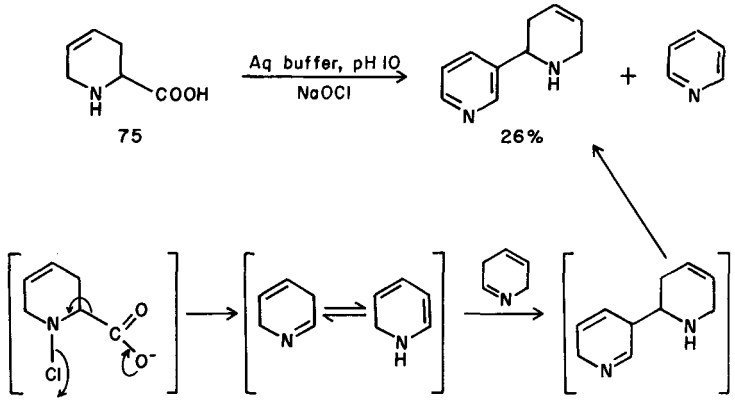
An interesting biosynthetically patterned synthesis of nicotine was accomplished by Leete (Scheme 28) (*138*). The alkaloid was formed on stirring an aqueous mixture containing glutaraldehyde, ammonia, and 1-methyl-Δ^1-pyr-



SCHEME 28

rolinium acetate at ambient temperature without exclusion of air. The maximum radiochemical yield (21.2%) using 1-methyl-Δ^1-pyrrolinium-2-^{14}C acetate was obtained at pH 10.3.

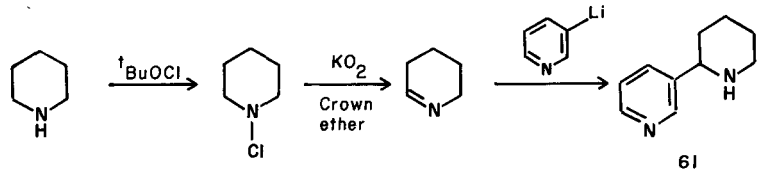
Another noteworthy biomimetic synthesis by Leete (*139*), that of anatabine, is depicted in Scheme 29. The starting material was the natural product baikiain **75.**



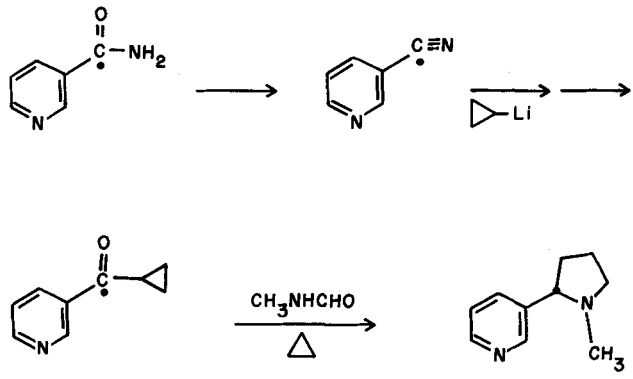
SCHEME 29

Primary and secondary organic chloramines react with potassium superoxide to produce imines in good yield (*140*). This reaction was employed to generate Δ^1-piperideine from *N*-chloropiperidine, and the former with 3-pyridyllithium gave (±)-anabasine (**61**) (Scheme 30). This approach, again, is somewhat reminiscent of the latter stages of the biosynthetic pathway.

A modification of the Cloke–Stevens rearrangement of cyclopropyl imines



SCHEME 30

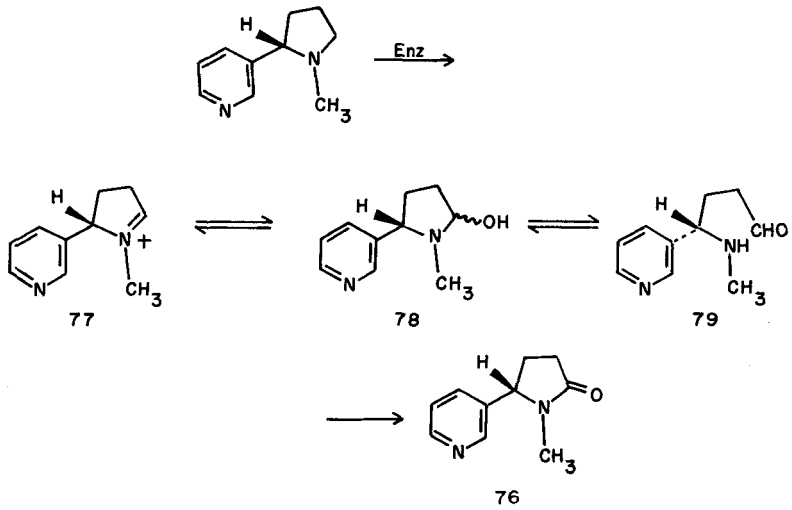


SCHEME 31

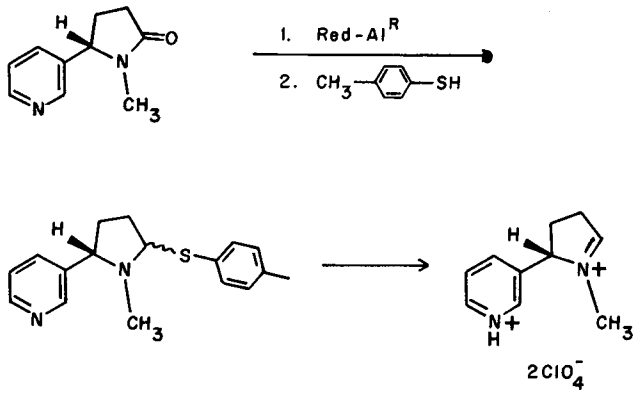
(see below) has been used to synthesize (±)-nicotine-2′-^{14}C (Scheme 31) (*141*).

Nicotine labeled in the pyrrolidine ring with ^{15}N was prepared from ^{15}N-nornicotine by methylation with formic acid–formaldehyde (*142*). The labeled ^{15}N-nornicotine was synthesized by reductive amination of 4-oxo-4-(3′-pyridyl)butanal, using $NaBH_3CN$-[^{15}N]H_4Br.

It has been demonstrated that the major pathway for the metabolism of (−)-nicotine in man involves the formation of (−)-cotinine (**76**) (references cited in *143*). It is likely that the latter is formed via the iminium ion (**77**), which, depending on conditions, may be in equilibrium with the carbinolamine **78** and possibly the amino aldehyde **79** (Scheme 32).



SCHEME 32



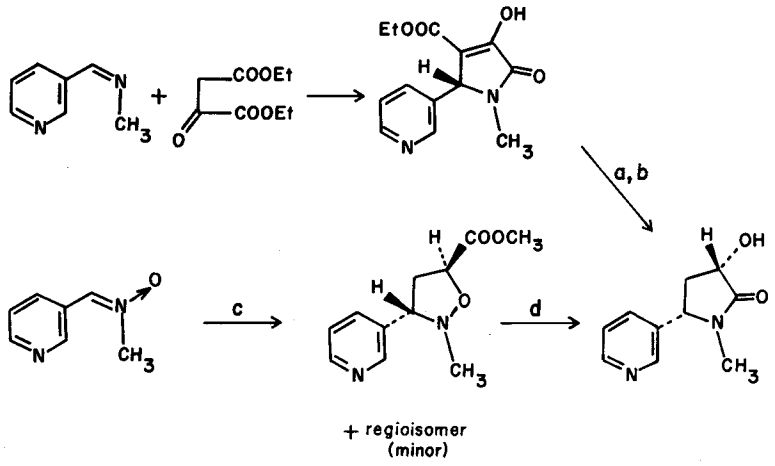
SCHEME 33

To acquire further understanding of these equilibria, the iminium salt (perchlorate) was prepared from (−)-cotinine by the route depicted in Scheme 33, and its behavior in aqueous solutions at different pH was investigated by NMR spectroscopy (*143*). In freshly prepared acidic or neutral solutions, it was found that the iminium ion is the principal or only species present, while in strongly alkaline solution the carbinolamine was the sole species observed. In weakly alkaline solution both forms were present. Under the latter conditions, the gradual formation of a dimer was observed. The amino aldehyde potentially derivable via the carbinolamine did not appear to be present.

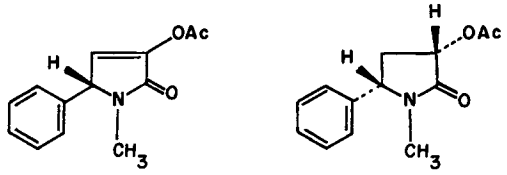
The mammalian metabolites of nicotine are in general more polar and pharmacologically less active than the alkaloid itself. The major metabolite cotinine (**76**) can undergo further enzymatic oxidation, and a hydroxylated cotinine was isolated from the urine of smokers and of various mammals after administration of cotinine. This metabolite was identified as 3′-hydroxycotinine by spectroscopic analysis (*144*). Comparison with a synthetic sample confirmed the structural assignment, and NMR analysis, using models with known stereochemistry, established the configuration of the metabolites (*144*).

3′-Hydroxycotinine was synthesized by two routes (Scheme 34) both of which produced a product epimeric with the natural metabolite. Epimerization at C-3′, via S_N2 displacement, led to the correct stereochemistry.

Assignment of configuration was based on comparison of NMR signals with those of model compounds. Thus the synthetic 3′-epihydroxycotinine showed a pattern of signals very similar to those of **81,** the hydrogenation product of **80.** Reduction of **80** with deuterium provided strong confirmatory evidence. It can be concluded that the pyridyl and hydroxy groups are trans in the natural metabolite, which thus possesses a (3′*R*,5′*S*) configuration (*144*).



SCHEME 34. (a) H_3O^+, (b) $NaBH_4$ (or HI–HOAc–NaH_2PO_2), (c) CH_2=$CHCOOCH_3$, (d) H_2–Raney Ni.



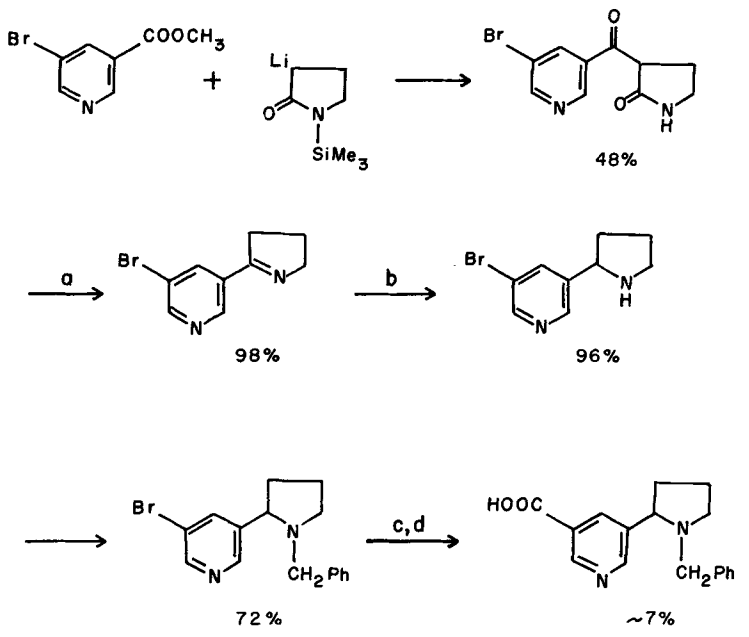
80 81

Cotinine *N*-oxide was also isolated as a mammalian metabolite of cotinine by these investigators (*145*).

With a view to the development of radioimmunoassays, analogs of several N′-substituted nornicotines associated with tobacco were synthesized, all of which possess a hydroxymethyl group at C-3′ through which they may be linked to macromolecules for antibody production (*146*). A modification of Castagnoli's synthesis (*120*) was employed for preparation of the 3′-hydroxymethylnornicotine precursor. The pyrrolidine nitrogen was acylated with appropriate anhydrides, and the concomitantly formed ester was selectively hydrolyzed, and the alcohol was converted to a hemisuccinate.

An approach to 5-carboxy derivatives of nornicotine via the 5-bromo analog is outlined in Scheme 35 (*146*).

Myosmine (**82**) is a minor component among the alkaloids of *N. tabacum* and has also been isolated from tobacco smoke. It can be reduced to nornicotine.



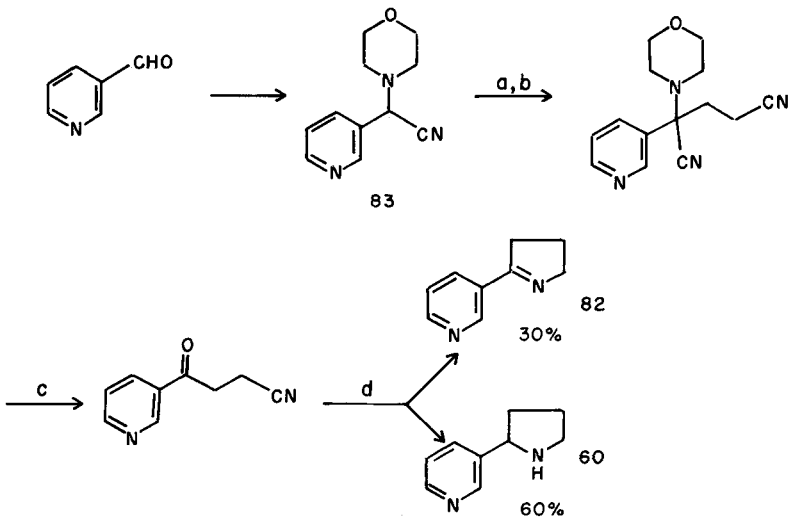
SCHEME 35. (a) H_3O^+, (b) $NaBH_4$, (c) *n*-BuLi, (d) CO_2.

Several syntheses of the alkaloid have been reported, some of which are described below. A route developed by Leete and coworkers (*147*) is well suited to the introduction of isotopic label at specific positions for studies on metabolism of tobacco alkaloids. The key step is 1,4-addition of an acyl anion equivalent (**83**) to acrylonitrile (Scheme 36).

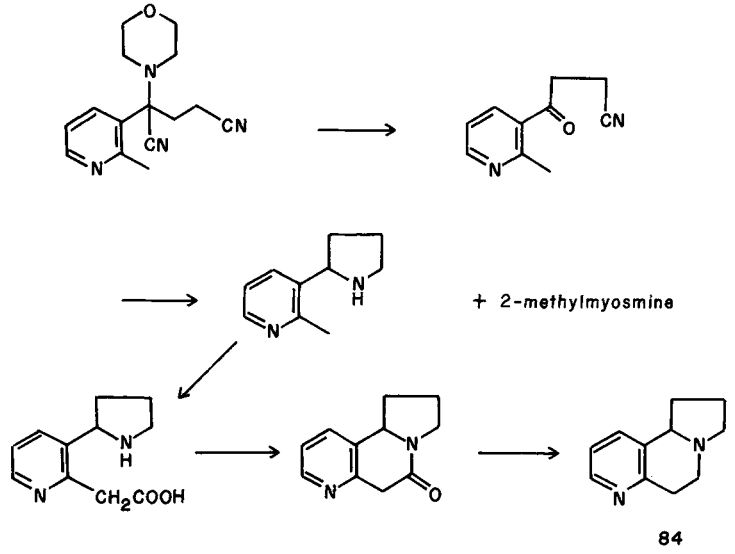
The nicotine analog **84** was prepared, using the same methodology, to investigate the pharmacological effects of freezing the rotation about the C-3—C-2′ bond of nicotine by insertion of an extra bridging methylene group (Scheme 37) (*148*). The 2-methylnornicotine intermediate was also converted to 2-methylnicotine, another analog of pharmacological interest.

An alternative interesting approach to 2-methylnornicotine and other 2-alkylnicotinoids utilizes as an acyl anion equivalent an α-cyanoamine generated by sigmatropic rearrangement of an ylide (Scheme 38) (*149*).

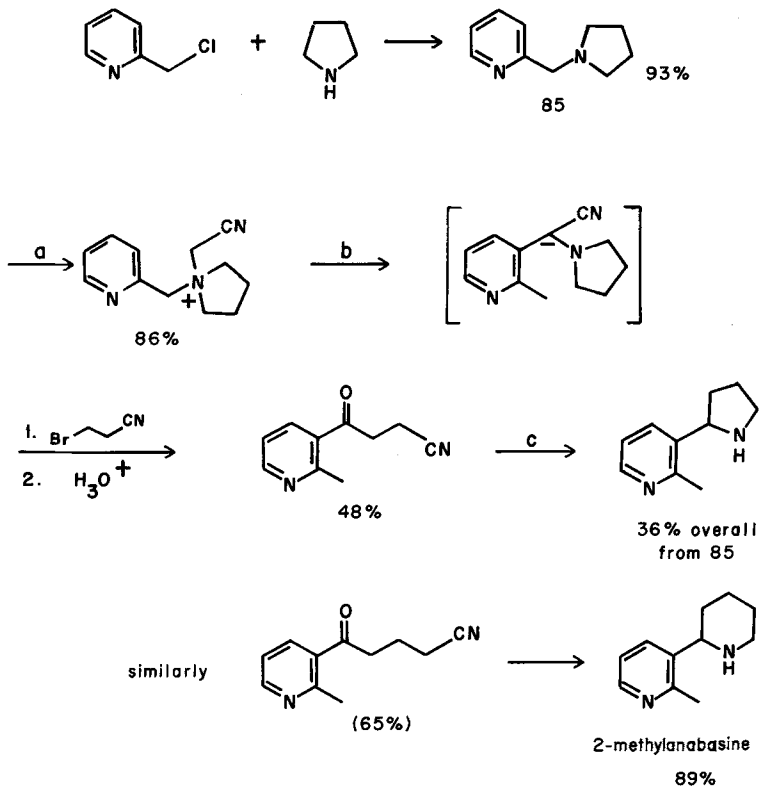
2-Ethylnornicotine was prepared similarly. An α-cyanoamine acyl-anion equivalent was used initially to extend the side chain of pyridine-2-carboxaldehyde (Scheme 39) (*149*). This sequence was complicated by competition between the desired Sommelet–Hauser rearrangement and Stevens-type rearrangement of **87** on base treatment. The former pathway could be made to predominate by using sodium amide in ammonia as base.



SCHEME 36. (a) KOH–*t*-BuOH, (b) CH_2=CHCN, (c) H_3O^+, (d) H_2–Raney Ni (overall yield combined alkaloids, 67%).



SCHEME 37



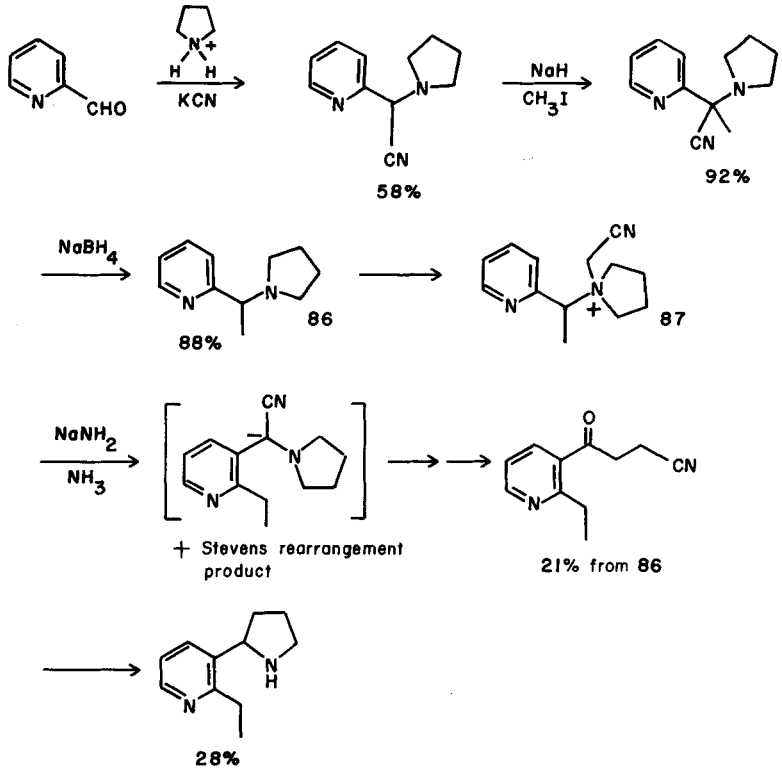
SCHEME 38. (a) $PhSO_3CH_2CN$, (b) 2 × NaH, THF, DMSO, (c) H_2–Raney Ni (EtOH–NH_3).

A modified direct approach to 2-substituted nicotinoids, again exploiting the Sommelet–Hauser rearrangement and the reactivity of α-cyanoamines, was conceived (*149*) on the basis of the results described above (Scheme 40).

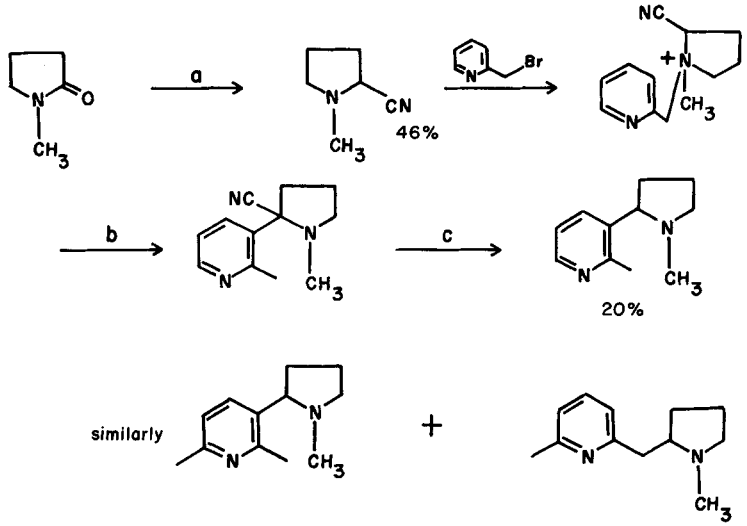
In a paper demonstrating the scope of palladium-catalyzed vinylic substitution reactions with heterocyclic bromides, Heck *et al.* have described a four-step synthesis that affords nornicotine in some 24% overall yield (Scheme 41) (*150*).

In 1929, Cloke (*151*) reported the thermal rearrangement of a cyclopropylimine, which afforded a Δ^1-pyrroline (*152*). Stevens (*153*) reinvestigated the reaction, which he found to require acid catalysis, and has demonstrated its utility for the synthesis of alkaloids (*154*). The synthesis of myosmine (**82**) using this methodology is depicted in Scheme 42. Apoferrorosamine (**88**), a degradation product of the *Pseudomonas roseus fluorescens* metabolite ferrorosamine, was synthesized by an analogous sequence.

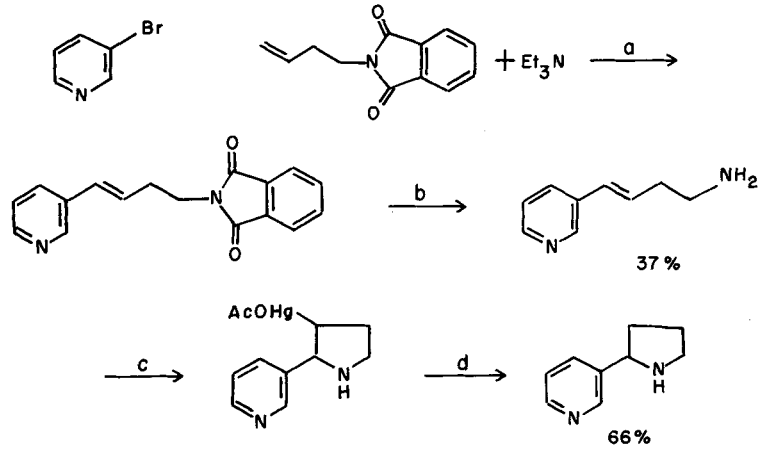
N-Vinylpyrrolidone is the commercially available precursor for a short, efficient synthesis of myosmine by Swedish researchers (*155*). The vinyl group serves as a convenient acid-labile NH protecting group (Scheme 43).



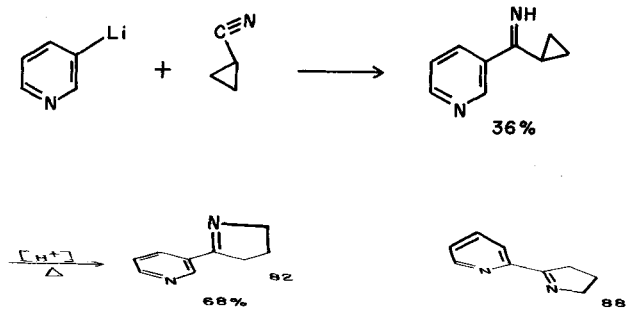
SCHEME 39



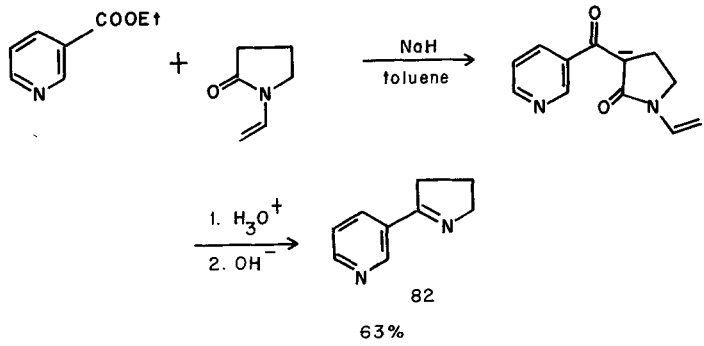
SCHEME 40. (a) Red-Al®–NH_4CN, (b) KO-*t*-Bu, DMSO, THF, (c) LAH.



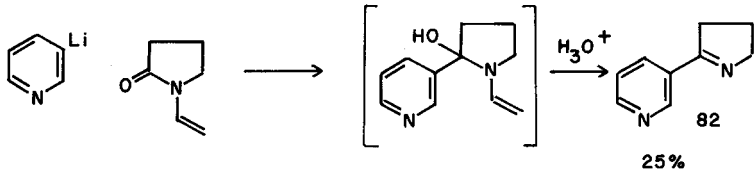
SCHEME 41. (a) $Pd(OAc)_2$–(*o*-toluene)$_3$P, (b) NH_2NH_2, (c) $Hg(OAc)_2$, (d) $NaBH_4$.



SCHEME 42



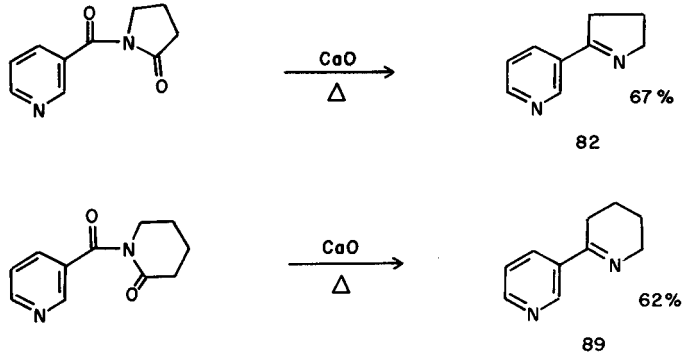
SCHEME 43



SCHEME 44

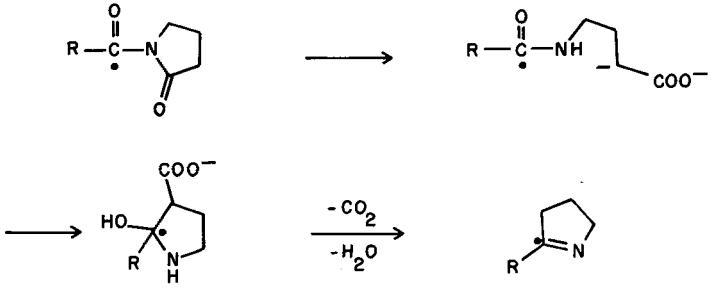
Another short synthesis, employing *N*-vinylpyrrolidone, is shown in Scheme 44 (*156*). An analogous sequence, using 2-lithiopyridine, gives apoferrorosamine (**88**) in 28% yield.

The Mundy *N*-acyllactam rearrangement (*157*) has been used to good effect for the synthesis of myosmine (**82**), anabaseine (**89**), and other alkaloids (Scheme 45) (*158*).



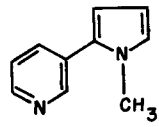
SCHEME 45

The results of a labeling experiment are in accord with the proposed mechanism of the rearrangement (Scheme 46) (*157*).



SCHEME 46

Nicotyrine (**90**) is a minor alkaloid, probably formed after harvesting of tobacco (*102*). The alkaloid was synthesized in high yield (72%) by the photolysis of 3-iodopyridine in the presence of 1-methylpyrrole (*159*). The yield of nornicotyrine formed from the analogous reaction with pyrrole was only 12% (*159*).



90

The metabolism of nicotine to cotinine (**76**), 3′-hydroxycotinine, and cotinine *N*-oxide in man and other mammals has been mentioned earlier in this section. Both cis and trans diastereomeric nicotine 1′-*N*-oxides were also identified as mammalian metabolites of the alkaloid, and the possible physiological significance of the predominance of one or other metabolic pathway has been noted (references cited in *160*).

The five possible *N*-oxides of (*S*)-(−)-nicotine were prepared by oxidative methods previously described and were used as references in an examination of extracts of roots, stems, and leaves of *Nicotiana tabacum, N. affinis,* and *N. sylvestris* to determine which nicotine *N*-oxides are plant metabolites (*160*). Detailed spectroscopic analysis of the synthetic *N*-oxides was also undertaken. Only the *cis*- and *trans*-nicotine 1′-*N*-oxides were found in the *Nicotiana* species investigated, and the relative concentrations of these metabolites and the parent alkaloid were estimated. The *N*-oxides are apparently not intermediates in the demethylation of nicotine to nornicotine, and their role in nicotine metabolism was discussed (*160*).

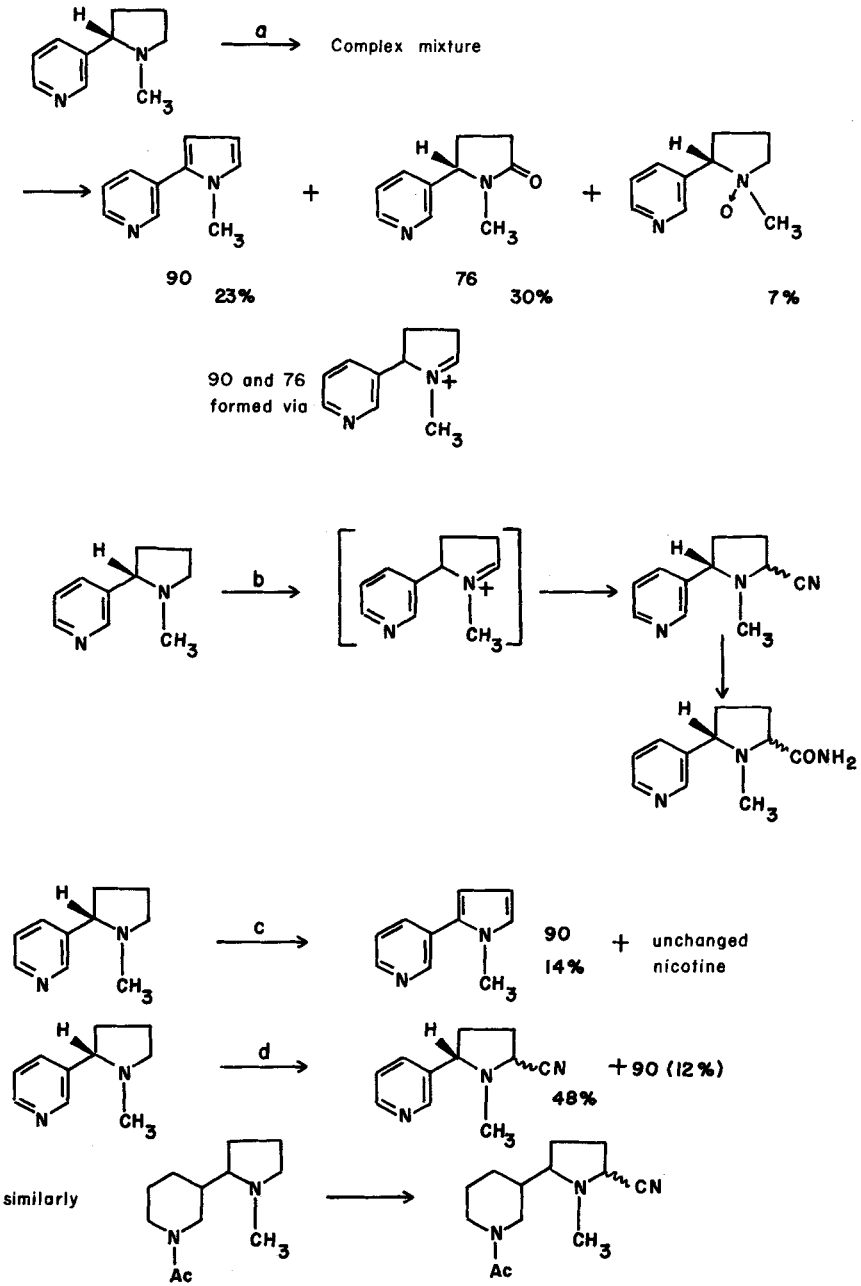
Studies on the dye-sensitized photochemical oxidation of nicotine and *N*-methylanabasine have revealed interesting differences in behavior of the *N*-methylpyrrolidine and *N*-methylpiperidine systems (*161*).

Nicotine, under various conditions, undergoes photochemical oxidations only in the pyrrolidine ring (Scheme 47) (see also Ref. *162*).

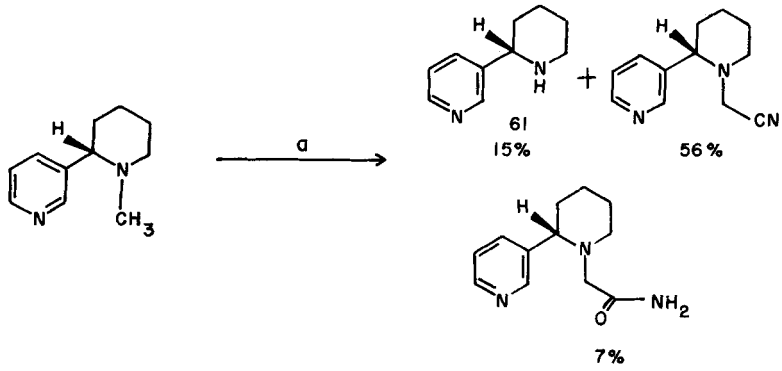
In contrast, *N*-methylanabasine underwent oxidation solely at the methyl group of the *N*-methylpiperidine (Scheme 48) (*161*).

The regioselectivity observed in the photooxidation of nicotine does not necessarily apply in enzymatic oxidation of the alkaloid, however. Thus incubation of nicotine with rabbit liver in the presence of cyanide ion was found to yield both 5′-cyanonicotine and *N*-(cyanomethyl)nornicotine (*163*).

Nitrosamines, in particular *N*′-nitrosonornicotine (**91**) and the ring-opened derivative (**92**) are formed from nicotine during the curing and smoking of tobacco and may be included among the substances implicated in the development of cancers associated with smoking (*164*). To furnish further information about the nitrosamines derivable from nicotine, reaction of the alkaloid with sodium nitrite



SCHEME 47. (a) O_2–$h\nu$–methylene blue, (b) O_2–$h\nu$–methylene blue–KCN [in presence of sodium pyruvate, reaction stops at nitrile stage (79%)], (c) $h\nu$–N_2–eosine; (d) $h\nu$–N_2–eosine–KCN.



SCHEME 48. (a) $h\nu$–O_2–methylene blue–KCN–sodium pyruvate.

was studied under a variety of conditions (*165*). The results are summarized in Scheme 49.

In an important paper, Hecht and co-workers (*164*) review the structures and properties of nitrosamines derived from nicotine and related tobacco alkaloids. Their modes of formation are discussed, as well as their metabolism, with particular emphasis on the reactive electrophilic species produced via α hydroxylation and their significance in relation to carcinogenicity.

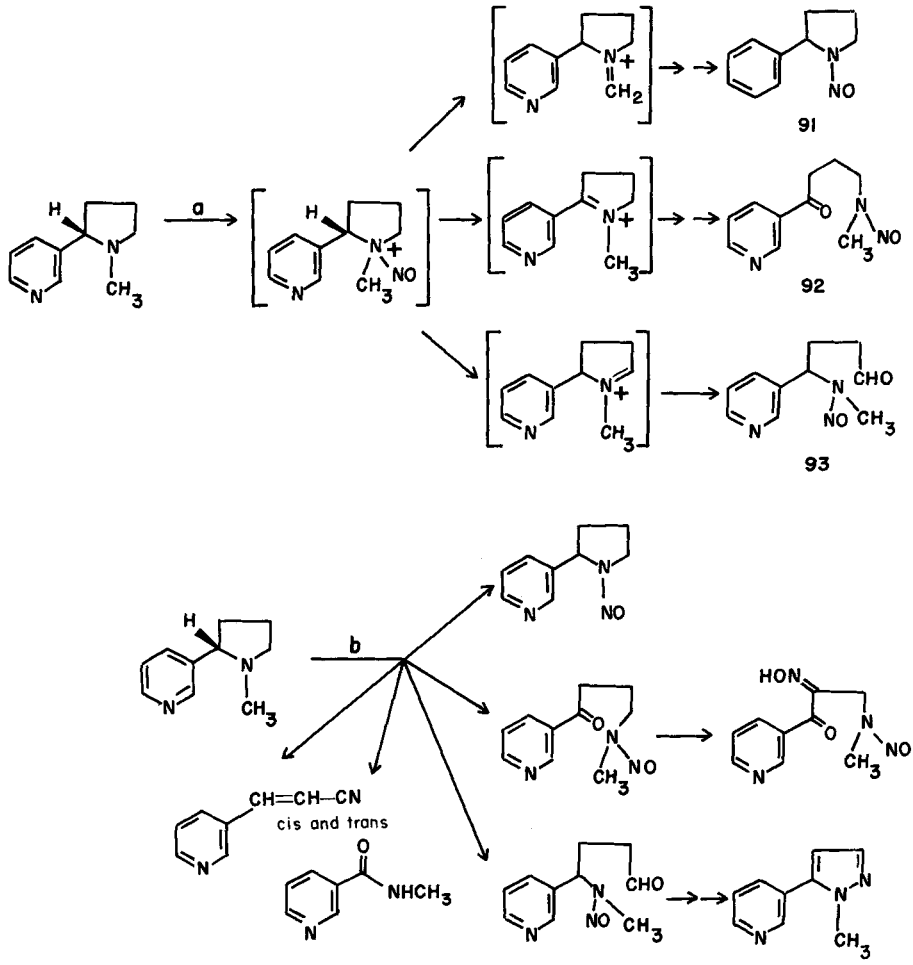
Seeman and Whidby demonstrated that nicotine, on treatment with methyl iodide, undergoes alkylation at the pyridine and pyrrolidine nitrogen atoms in the ratio 11:5 (*166*). To investigate factors influencing the regio- and stereochemical outcome of the Menschutkin reaction, which should have some general relevance to the chemistry of nicotine, these authors and their colleagues have conducted NMR studies on the products of alkylation of nicotine and its azetidine, piperidine, and perhydroazepine analogs with CH_3I, CD_3I, and $^{13}CH_3I$ (*167*).

Among other aspects of nicotine chemistry that have received attention recently, may be mentioned its reactions with methyl and hydroxymethyl radicals, generated by chemical means (*168*). The former affords 4- and 6-methylnicotine in yields of 6.5 and 28.6%, respectively, while the hydroxymethyl group enters only in the 6 position to give the corresponding analog in 12.6% yield.

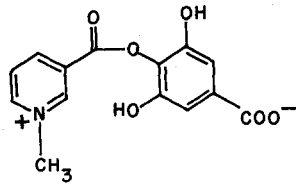
The formation of quinolizine and indolizine derivatives from nicotinoids and acetylenic esters has been investigated by Acheson and co-workers (*169*).

The remainder of this section is focused on alkaloids derived from nicotinic acid from sources other than tobacco.

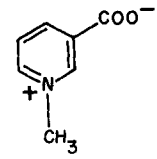
Among the bases isolated in a systematic examination of the seeds, leaves, stems, and roots of *Abrus praecatorius,* a plant used in Indian medicine was precatorine, identified as the gallic acid ester **94** of trigonelline (**95**) (*170*). The parent betaine trigonelline was also present in the extracts and was found as well among alkaloids from the leaves of the Indian medicinal plant *Desmondium triflorum* (*171*).



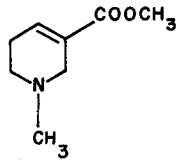
SCHEME 49. (a) $NaNO_2$–20°C–17 hr (under these conditions, most nicotine recovered unchanged; yields of nitrosamines 0.1–2.8%), (b) 5 × $NaNO_2$–90°C.



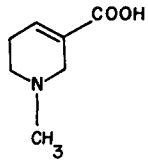
94



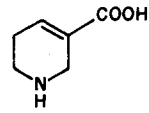
95



96



97

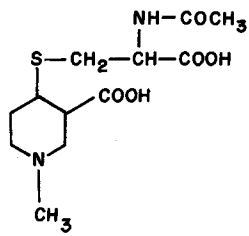


98

Arecoline (**96**) is a constituent of the fruit of the palm *Areca catechu* L. (Palmae), along with arecaidine (**97**), guvacine (**98**), and other compounds.

The pronounced cholinergic activity of arecoline is responsible for some of the effects associated with chewing of betel nuts. Among its other pharmacological effects, arecoline has anthelmintic activity. The chemistry and pharmacology of arecoline have been reviewed (*172,173*). The base may be synthesized by partial reduction of the methiodide of methyl nicotinate, and an improved procedure for effecting this transformation, using potassium borohydride, has been published (*174*).

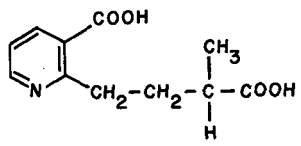
The mammalian metabolism of arecoline was investigated by administration of tritium-labeled base (as hydrochloride) to rats (*175*). Almost 20% of the administered radioactivity was excreted in the urine during an 18-hr period. Besides unchanged arecoline, labeled metabolites found in urine extracts included arecoline *N*-oxide, arecaidine, arecaidine *N*-oxide, *N*-acetyl-*S*-(3-carboxy-1-methylpiperid-4-yl)-L-cysteine (**99**) and an unidentified metabolite.



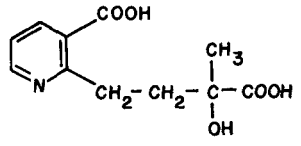
99

Administration of arecoline-*t* *N*-oxide afforded the same compounds (in different relative amounts) showing that *in vivo* deoxygenation of the *N*-oxide(s) was occurring. The binding of arecoline to rat tissues and macromolecules was also investigated (*175*).

The Chinese plant *Tripterygium wilfordii* produces complex insecticidal ester alkaloids whose structures have not been completely elucidated, but which give rise on alkaline hydrolysis to wilfordic acid (**100**) and hydroxywilfordic acid



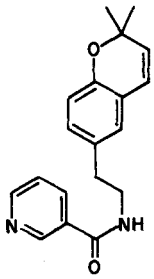
100



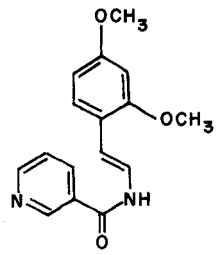
101

(**101**) (*176*). The structures of these degradation products were confirmed by mass spectrometry, and it was shown that nicotinic-*6*-^{14}C acid and the nicotinamide portion of *carbonyl*-^{14}C-NAD are both incorporated efficiently by the plant into these moieties (*177*). The precursors were incorporated with comparable efficiency into the alkaloids of leaves and stems, but nicotinic acid was incorporated much more readily into the root alkaloids. These and other aspects of the metabolism of nicotinic acid and NAD in *T. wilfordii* are discussed by Lee and Waller (*177*).

Nicotinamides were among the bases isolated from Jamaican *Amyris plumieri* D.C. (Rutaceae) (*178*). The structure of the chromene nicotinamide **102** was advanced on the basis of spectroscopic analysis, in which NMR and mass spectrometry figured dominantly.



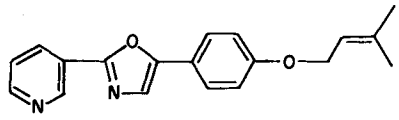
102



103

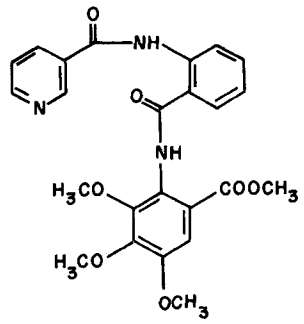
A biogenetic-type synthesis via prenylation of the nicotinamide derivative of tyramine confirmed the proposed structure (*178*). A second metabolite was identified as **103** by spectroscopy and chemical degradation, which included ozonolysis to give 2,4-dimethoxybenzaldehyde. Synthesis of the dihydro derivative of **103** confirmed the structural assignment.

Also found in *A. plumieri* was *O*-dimethylallylhalfordinol (**104**), previously isolated, in a mixture with its *O*-isopentenyl isomer, from *Aeglopsis chevalieri* Swing (Rutaceae) (*179*).



104

The nicotinic acid amide **105** was one of the metabolites isolated from *Aspergillus terreus* strain IFO 8835 by Yamamoto's group (*180*). The structure was elucidated by spectroscopy and chemical degradation. Thus treatment of **105**

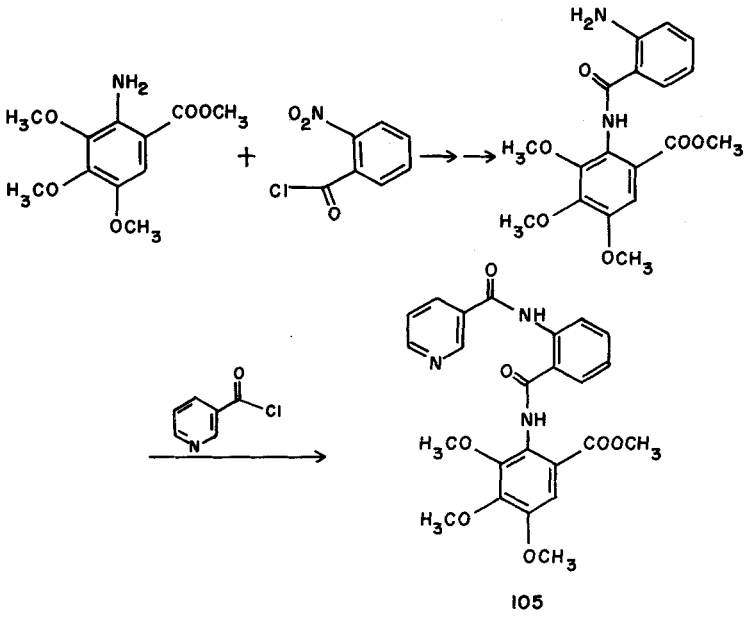


105

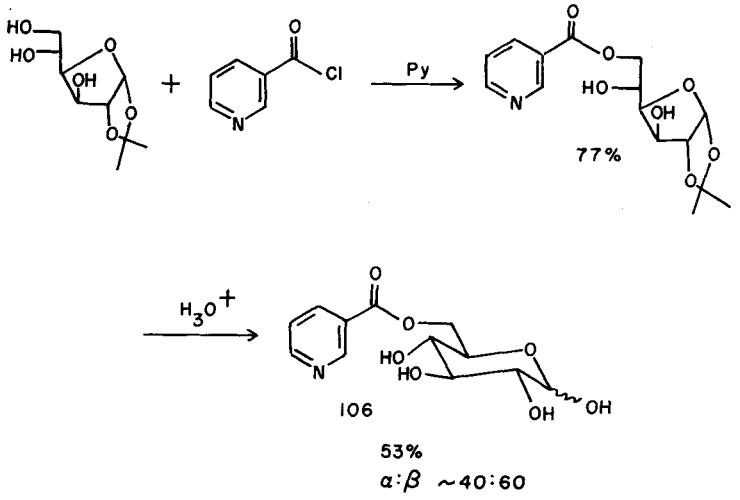
with alkali under mild conditions merely hydrolyzed the methyl ester functionality, while somewhat more vigorous alkaline hydrolysis afforded nicotinic acid plus the corresponding dipeptide. The latter was cleaved by alkali under more forcing conditions to anthranilic acid and 3,4,5-trimethoxyanthranilic acid. The metabolite was synthesized by a route summarized in Scheme 50 (*180*). In pharmacological tests, the metabolite showed contractive activity for smooth muscle, but it had no antiinflammatory activity (*180*).

Buchananine (**106**) (Scheme 51), a nicotinic ester of glucose, is isolated from the plant *Cryptolepis buchanani*, which has been used in Indian medicine for the treatment of rickets (*181*).

The reducing properties of the base indicated that the C-1 hydroxy group of glucose is not involved in the ester linkage, while the failure to detect formaldehyde on periodic acid oxidation indicated that the glucose unit is esterified through its C-6 primary hydroxy group (*181*). On the basis of NMR evidence derived from a 60-MHz spectrum, it was proposed that the anomeric carbon of the glucose unit possesses the α configuration (*181*). This assignment was later challenged (*182*) on the grounds that the rate of mutarotation of certain sugars in water is greatly enhanced by the presence of pyridines, leading to the expectation



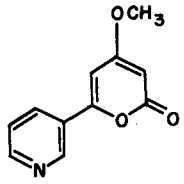
SCHEME 50



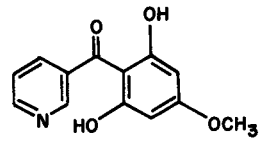
SCHEME 51

that buchananine should exist as an anomeric mixture. That this is in fact the case was evident from the NMR spectrum of synthetic material run at 100 or 360 MHz. The synthesis of buchananine is depicted in Scheme 51 (*182*).

Aniba duckei Kosterm., an Amazonian Lauraceae species, is the source of commercial rosewood oil. Anibine (**107**) has been identified among the chemical constituents of its trunk wood, several of which are 2-pyrones (reference cited in *183*). Chromatographic fractionation of the mother liquor from crystallization of anibine afforded new compounds one of which, designated duckein, was identified on the basis of its spectroscopic characteristics as **108.**



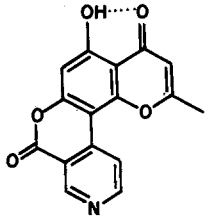
107



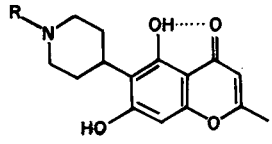
108

The biosynthesis of anibine and duckein is considered to involve chain extension of a nicotinoyl precursor by two and three acetate units, respectively (*183*).

The structures of three new alkaloids, **109, 110,** and **111,** from root bark of *Schumanniophyton problematicum* (Rubiaceae) were deduced on the basis of spectroscopic evidence and, in the case of the former, schumanniophytine, by degradative experiments (*184*). Noreugenine (**112**) was a useful spectroscopic model for **110** and **111.**

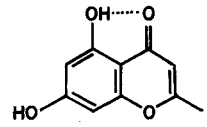


109



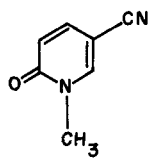
110 R = H

111 R = CH_3

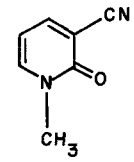


112

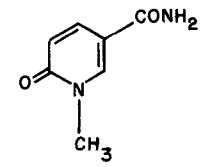
The alkaloids nudiflorine (**113**) (*185*) and ricinidine (**114**) (*186*) are produced by *Trewia nudiflora,* a tropical plant native to India. On administration of nic-



113



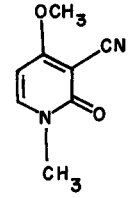
114



115

otinic-6- or 7-^{14}C acid to young *T. nudiflora* plants, six compounds were detected in the radioactive alkaloid fraction from the plant extract (*187*). Three of these were identified as nudiflorine (**113**) (trace), trigonelline (**95**), and *N*-methyl-5-carboxamide-2-pyridone (**115**). The latter is a normal mammalian metabolite of nicotinic acid but had not previously been isolated from plants (*187*). It is proposed that the biosynthesis of nudiflorine (**113**) involves *N*-methylnicotinamide and the pyridone **115** as intermediates (*187*).

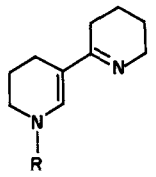
The rapid translocation of ricinine-3,5-^{14}C (**116**) to young developing tissues,



116

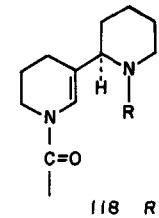
when it is administered to senescent leaves of the castor bean plant *Ricinus communis*, suggests that the compound has a specific physiological or metabolic function in growth processes, since it seems unlikely that a metabolic "waste product" would be transported into seeds and other vitally important tissues from a leaf about to be abscised (*188*).

Alkaloids are known to play a significant ecological role in contributing to the relative resistance of the plants which produce them to the depradations of phytophagous insects and herbiverous animals. As part of a study undertaken in this context, the alkaloid contents of several Colorado *Lupinus* species were examined (*189*). The major alkaloids found in extracts of *L. formosus* Greene were histrine (**117**) and (+)-ammodendrine (**118**). *N*-Acetylhistrine (**119**) and (+)-*N'*-methylammodendrine (**120**), hitherto unreported as natural products, were also present. By gas chromatography–mass spectrometry and preparative gas chromatography, it was possible to detect and identify (−)-anabasine (**61**), (−)-*N*-methylanabasine, *N*-methylpelletierine (**51**), and lupinine, the only conventional lupine alkaloid present in this species.



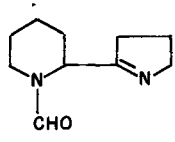
117 R = H

119 R = $COCH_3$

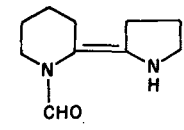


118 R = H

120 R = CH_3



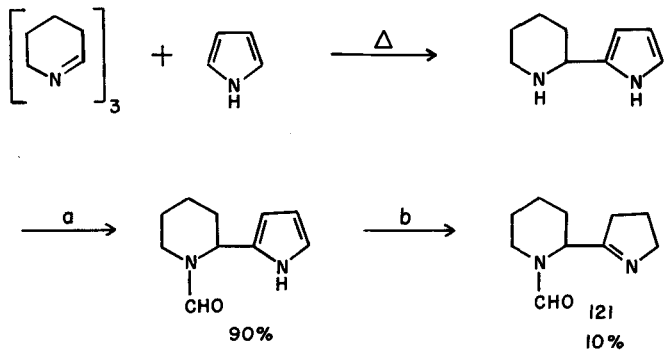
121



121a

The novel alkaloid smipine was identified as **121** by spectroscopic analysis of the base and some derivatives. Distinctive spectral features were IR absorption at 1670 and 1645 cm^{-1}, attributed to the tertiary amide and isolated imine groups, respectively. Evidence for the *N*-formyl group was found in the NMR signal at δ8.15 and the ion at *m/e* 151 (M − CHO) in the mass spectrum. An ion at *m/e* 112 (M − C_4H_6N) indicated the presence of a five-membered nitrogen heterocycle containing one degree of unsaturation. A synthesis of smipine confirmed the assigned structure (Scheme 52) (*189*).

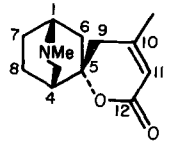
The lack of optical activity of the natural alkaloid is not surprising in view of the possibility of equilibrium with the tautomeric form **121a.** It is suggested (*189*) that the biosynthesis of smipine may involve oxidative ring cleavage and rearrangement of ammodendrine or a tetrahydroanabasine derivative.



SCHEME 52. (a) Cl_3CCHO–$CHCl_3$–0°C, (b) Zn–HCl.

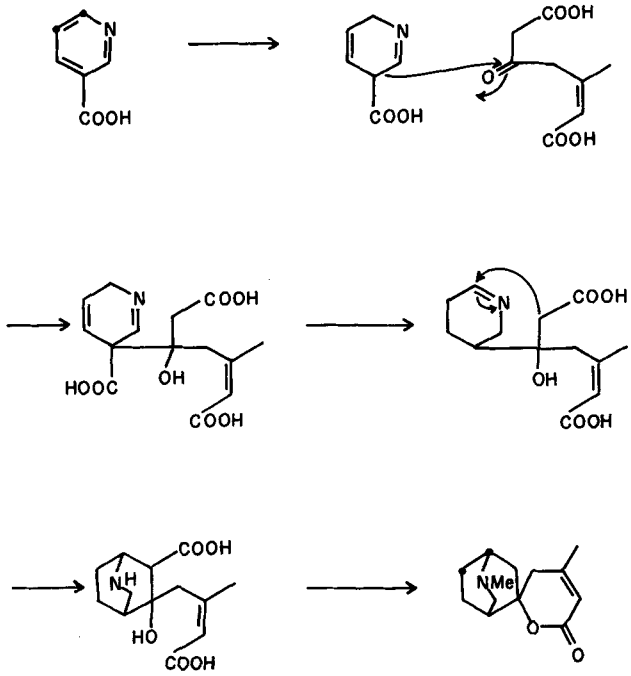
The mass spectra of bipiperidyl bases of the ammodendrine type display ions associated with some interesting fragmentations and rearrangements. These are analyzed in detail and discussed in another publication from the same laboratory (*190*).

Dioscorine (**122**) is an alkaloid found in the tropical yam *Dioscorea hispida*



122

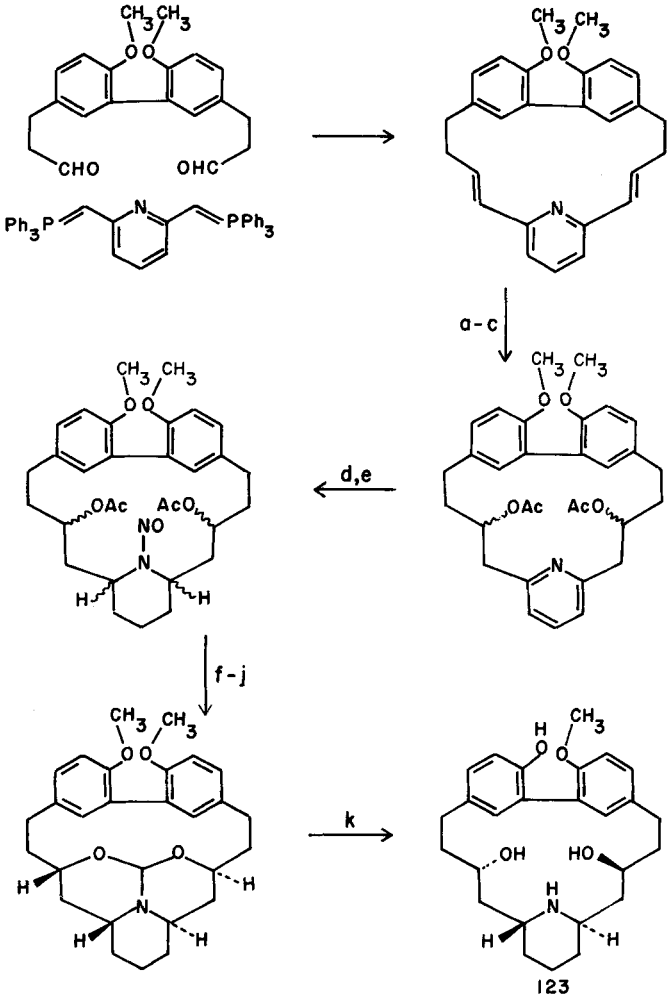
Dennst. and related species (references cited in *191*). Incorporation of label from acetate-*1*-^{14}C at carbons 5, 10, and 12 established the biosynthetic origin of the unsaturated lactone moiety (*191*). Earlier speculations on the origin of the isoquinuclidine portion of dioscorine have been laid to rest by the observation that label from both nicotinic-*2*-^{14}C acid and nicotinic-*5,6*-$^{14}C, {}^{13}C_2$ acid is incorporated in a manner consistent with the biosynthetic pathway shown in Scheme 53 (*191,192*).



SCHEME 53

VIII. Piperidine Metacyclophane Alkaloids

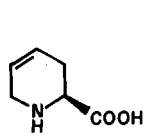
The piperidine metacyclophane alkaloids are a subgroup of the Lythraceous alkaloids, which have been the subject of extensive reviews by Gołębiewski and Wróbel in this series (*193*) and others (*194*). Lythranidine (**123**), a representative of this class, has been synthesized in racemic form by Fuji *et al.* (*195*). The synthesis, which is the first for this type of alkaloid, is outlined in Scheme 54.



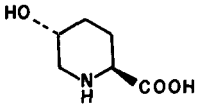
SCHEME 54. (a) MCPBA, CH_2Cl_2, (b) H_2, Pd–charcoal, MeOH, (c) Ac_2O, Et_3N, (d) H_2, PtO_2, Raney Ni, MeOH, (e) isopentyl nitrite, CH_2Cl_2, (f) DMSO, Δ, N_2, *t*-BuOK, (g) H_2, Raney Ni, MeOH, (h) KOH, MeOH, H_2O, (i) $CH(OEt)_3$, PTSA, (j) $HSCH_2CH_2SH$, $AlCl_3$, CH_2Cl_2, (k) HCl, H_2O, MeOH, Δ.

IX. Pipecolic Acid Derivatives

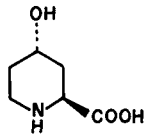
Examples of pipecolic acid derivatives have been noted from a variety of sources. L-Baikiain (**124**), first isolated from Rhodesian teak *Baikiaea plurijuga* (*196*), has been found in a number of plants including the seaweed *Corallina officinalis* (*197*).



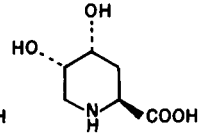
124



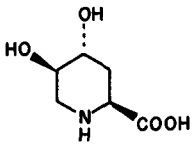
125



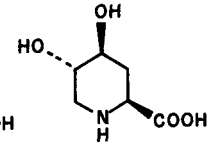
126



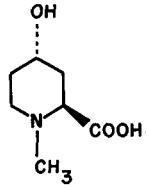
127



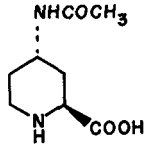
128



129

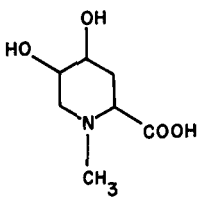


130

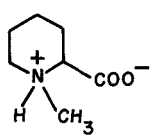


131

The hydroxypipecolic acids (**125,126,127,128,** and **129**) have been noted in various species of Brachystegioideae (*198*) and the structures of the dihydroxypipecolic acids (**127,128,129**) have been confirmed by synthesis in optically active form (*199*). A 4-hydroxy-L-pipecolic acid has been found in *Peganum harmala* (*200*). Ovalin, an *N*-methyl-4-hydroxypipecolic acid isolated from *Milletia ovalifolia* seed, has been assigned structure **130** and its absolute configuration was proposed on the basis of the similarity of its Cotton effect curve with that of (−)-*trans*-4-hydroxy-L-pipecolic acid (*201*). *trans*-4-Acetylamino-L-pipecolic acid (**131**) has been isolated from the leaves of the legume *Calliandra haematocephala,* and its structure was deduced from chemical and spectroscopic data (*202*). An *N*-methyl-4,5-dihydroxypipecolic acid, glabrin (**132**), of un-



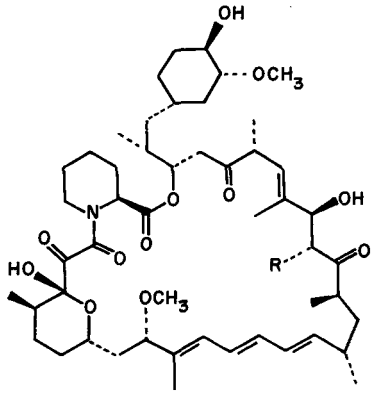
132



133

known configuration, has been obtained from the Indian tree *Pongamia glabra* (*203*), whose extracts are reputed to possess curative action against various diseases (*204*).

The *N*-methylpipecolic acid betaine homarine (**133**) has been isolated from marine sources (*205*). Hydroxy- and ketopipecolic acids have been noted in the hydrolysis products of certain peptides (*206,207*). Hydrolysis of the antitumor antibiotic rapamycin ($C_{56}H_{79}NO_{13}$, **134**) yielded L-(−)-pipecolic acid, which revealed the absolute configuration of the macrolide whose structure was determined by X-ray methods (*208*) in conjunction with chemical and spectroscopic information (*209*). Demethoxyrapamycin obtained from the same source, *Streptomyces hygroscopicus*, has been assigned structure **135** on the basis of spectroscopic data and comparison with rapamycin (*210*).



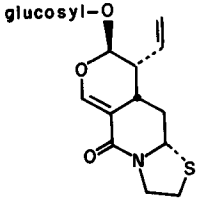
134 R = OCH_3

135 R = H

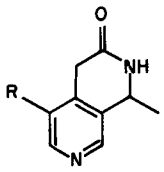
X. Terpenoid Alkaloids

A. Monoterpenoid Alkaloids

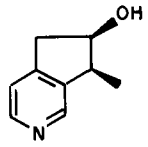
The monoterpene alkaloids have been the subject of extensive reviews in this series (*211*) and elsewhere (*212*). Notable among recent additions to this class is the novel sulfur-containing glucoside xylostosidine (**136**) whose structure was deduced from NMR and mass-spectral data (*213*). The corresponding sulfoxides loxylostosidine A (S—O bond β) and B (S—O bond α) have been isolated from the same source, i.e., *Lonicera xylosteum* L. (*214*).



136

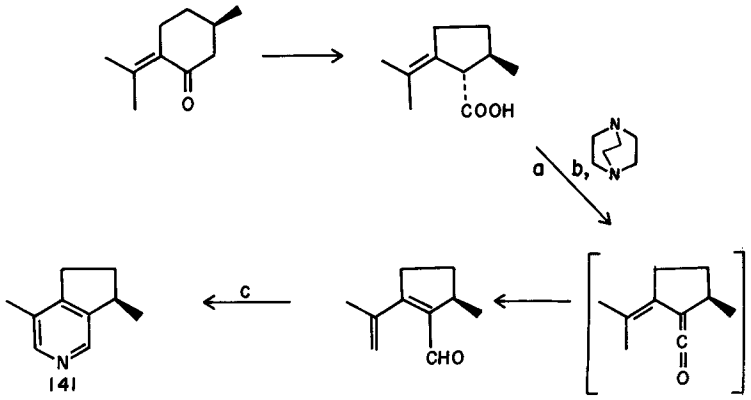


137 R = H
138 R = $COOCH_3$
139 R = OCH_3



140

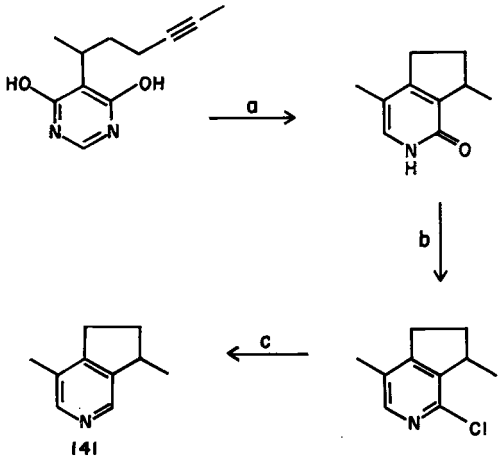
A new alkaloid, jasminidine (**137**), has been isolated, together with jasminin (**138**), from *Syringa vulgaris* L. (Oleaceae), and its structure was deduced from spectroscopic data (*215*). Jasminin was previously isolated from *Jasminium gracile, J. lineare,* and *Ligustrum novoguineense* (*216*). Ripperger has proposed that both jasminin (**138**) and jasminidin (**137**) possess the (*S*) configuration in view of their negative Cotton effects in comparison with those of venoterpene (**140**) and actinidine (*215*). The dextrorotatory enantiomer of actinidine (**141**) has been synthesized from (+)-pulegone as outlined in Scheme 55 (*217*).



SCHEME 55. (a) $(COCl)_2$, (b) benzene, Δ, (c) NH_2OH, Δ.

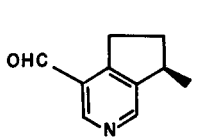
A novel synthesis of (±)-actinidine (**141**) involving the intramolecular cycloaddition of an acetylenic pyrimidine, as indicated in Scheme 56, has been reported (*218*).

Structure **139** has been proposed for acanthicifoline, a new alkaloid from *Acanthus ilicifolius* (*219*). Recently venoterpene (**140**) has been found in *Striga hermonteca* (*220*), actinidine in *Valeriana officinalis* L. (*221*), and boschniakine

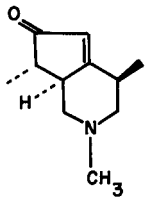


141

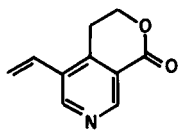
SCHEME 56. (a) Δ, −isocyanic acid, (b) phosphoryl chloride, (c) H_2, Pd–charcoal, KOH, MeOH.



142



143



144

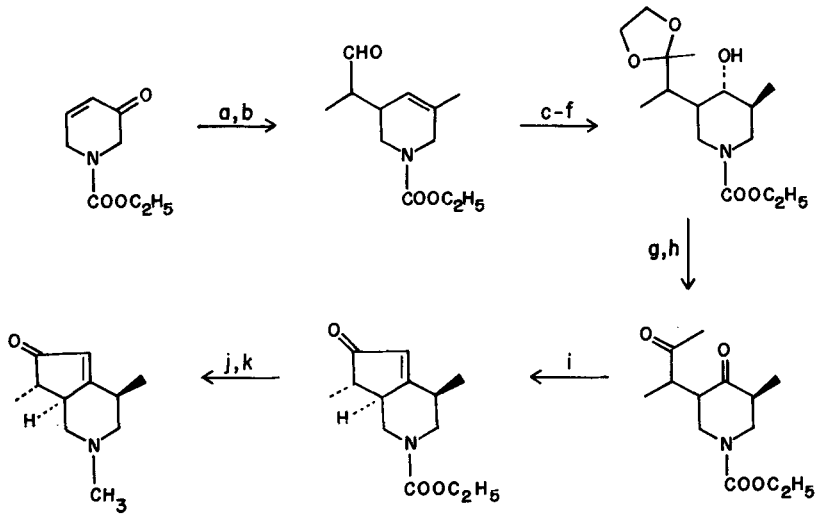
(**142**) in *Plantago sempervirens* (*222*). The absolute configuration of the latter has been established by ORD methods (*222*).

Tecomanine (**143**), an alkaloid from *Tecoma stans* Juss., whose salts show hypoglycemic activity, has been synthesized in racemic form via the stereoselective route shown in Scheme 57 (*223*) and a synthesis of (±)-7-desmethyltecomanine in racemic form has been recorded (*224*).

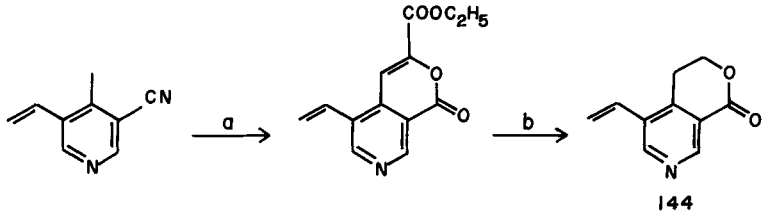
A new synthesis of gentianine (**144**) has been reported and is outlined in Scheme 58 (*225*).

B. Sesquiterpenoid Alkaloids

Gaillardia pulchella is the source of some novel sesquiterpenoid alkaloids possessing antiinflammatory activity. Following extensive chemical and spectroscopic studies Yanagita *et al.* (*226*) have established the structures of pulchellidine (**145**) and neopulchellidine (**146**). These assignments were confirmed by the X-ray analysis (*227*) of the dibromide of the nonnitrogenous analog pulchellin (**147**), which was isolated from the same source and could be obtained by mild Hofmann degradation of pulchellidine (*228*).

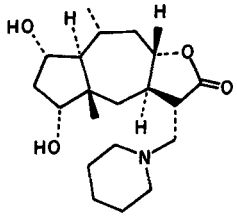


SCHEME 57

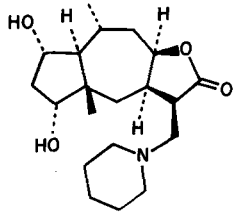


144

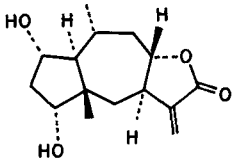
SCHEME 58



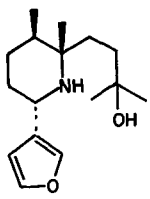
145



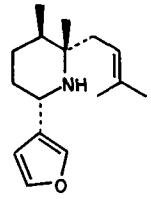
146



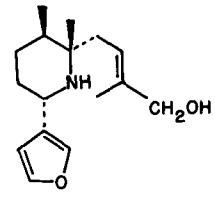
147



148



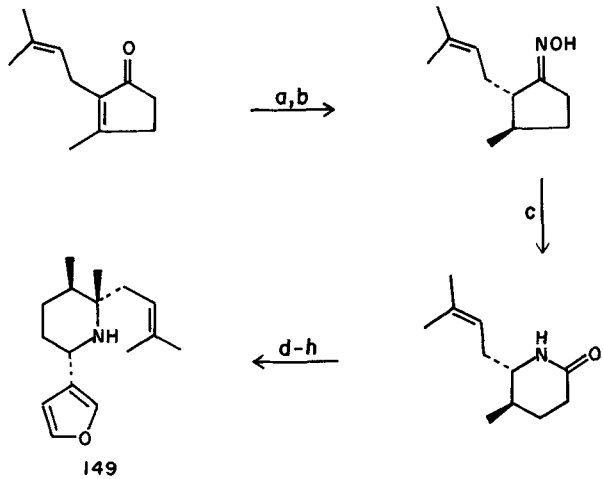
149



150

The nuphar alkaloids, which include several substituted piperidines such as nupharamine (**148**), 3-epinupharamine, anhydronupharamine (**149**), nuphamine (**150**), and 3-epinuphamine, have been the subject of a review in this series from a chemical perspective (*229*) and elsewhere from a chemotaxanomic point of view (*230*).

Szychowski *et al.* (*231*) completed a total synthesis of a mixture of (±)-nupharamine (**148**) (minor) and (±)-3-epinupharamine (major), which are separated by chromatography following a final step that involves hydration of the (±)-anhydronuphuramine (**149**) intermediate. The latter has been the object of a total synthesis by Lalonde and co-workers (*232*) as outlined in Scheme 59. The key step in the control of configurations at C-2 and C-3 is a Li–NH_3 reduction of a cyclopentenone to give a trans ketone converted via Beckmann rearrangement of its oxime to a six-membered amide. This product on elaboration through five further steps resulted in a mixture of the stereoisomers (±)-anhydronupharamine (**149**) (85%), nuphenine, its C-3 epimer, and the 2,6-trans isomer.



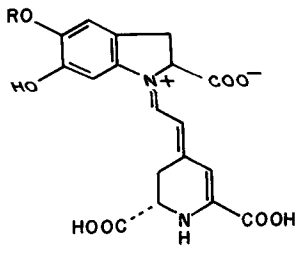
149

SCHEME 59. (a) Li, NH_3, (b) NH_2OH, (c) PCl_5, (d) Me_2SO_4, KOH, (e) LiH, 3-furoylchloride, (f) KOH, H_2O, (g) CaO, Δ, (h) $NaBH_4$, EtOH.

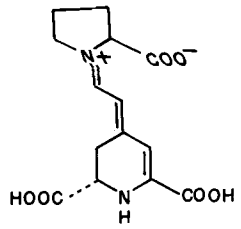
XI. Miscellaneous Pyridine Alkaloids

A. Alkaloids from Higher Plants

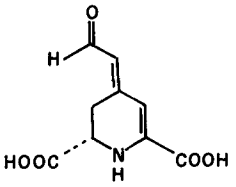
The relationship between the yellow betaxanthin and red betacyanin plant pigments was firmly established when Dreiding and co-workers (*233*) achieved the chemical transformation of betanidine (**151,** R = H), the aglycone of the red beet *Beta vulgaris* pigment (**151,** R = β-D-glucose) to indicaxanthin (**152**) from the cactus *Opuntia ficus indica* Mill. A precursor of the 1,7-diazaheptamethinium moiety in these pigments is the alkaloid betalamic acid (**153**) (*234*). The latter has been synthesized from *N*-benzylnorteloidinone (*235*). Another alkaloid belonging to this group, but of fungal origin, is muscaflavin (**154**) from Amanita muscaria (236).



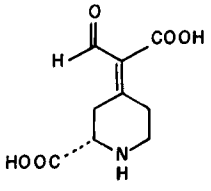
151



152



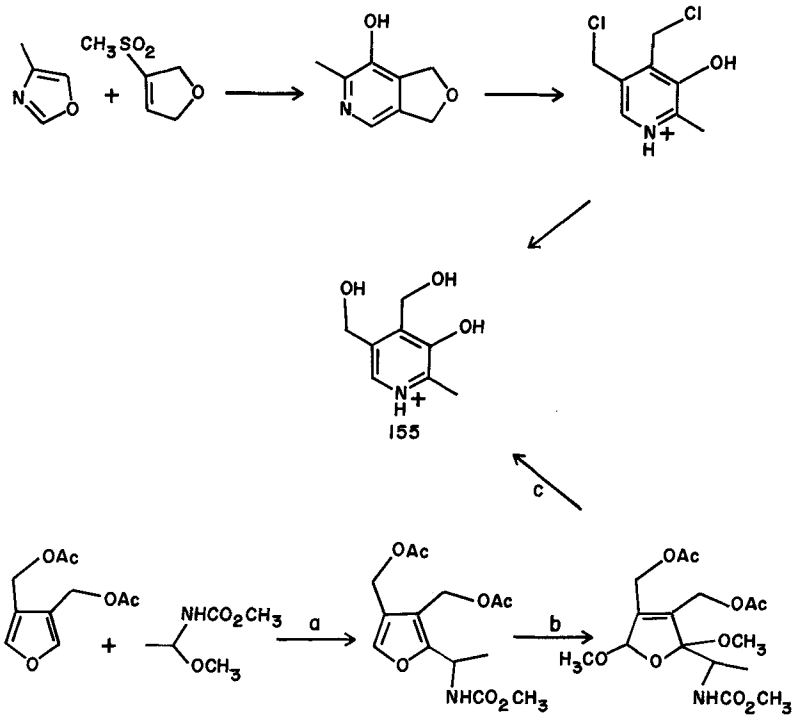
153



154

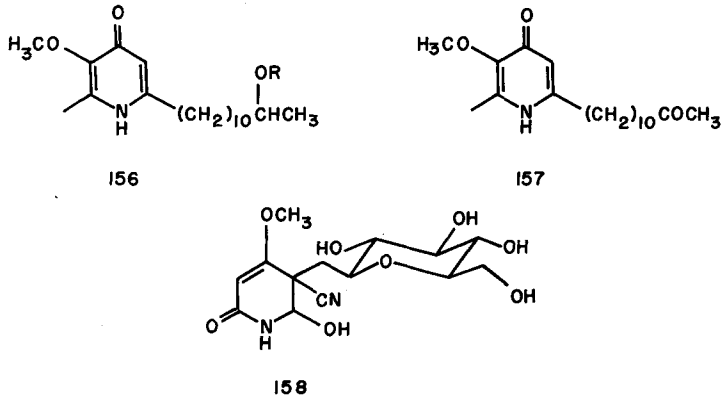
Two new syntheses of vitamin B_6 (**155**) have been reported recently. An efficient pathway featuring a Diels–Alder approach by Böll and König (*237*) is outlined in Scheme 60, while another, which exploits the potential of α-aminoalkyl furans, is due to Shono and co-workers (*238*).

Several examples of a new type of 4-pyridone alkaloids have been isolated from the leaves of *Melochia pyramidata* L. (Sterculiaceae). The structures of melochinine (**156,** R = H), melochinine D-glucoside (**156,** R = glucose), and melochinone (**157**) were deduced by Medina and Spiteller (*239,240*), based on spectroscopic and chemical studies. A cyanogenic glucoside, acalyphin (**158**),

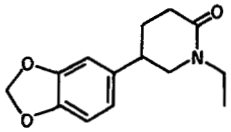


SCHEME 60. (a) PTSA, (b) anodic oxidation, MeOH, (c) HCl, H_2O.

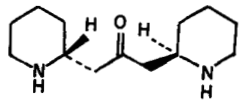
has been isolated from the medicinal plant *Acalypha indica*. Its structure was deduced largely from ^1H- and ^{13}C-NMR data (*241*). The configuration of chiral carbons α and β to the nitrogen have yet to be ascertained.



Campedine (**159**), whose structure was assigned on the basis of chemical and spectroscopic data, was isolated from *Campanula medium* (*242*). The structure of anaferine (**160**), from *Withania somnifera,* has been confirmed by synthesis (*243*), and evidence was presented for the (*R,R*) configuration (*244*).

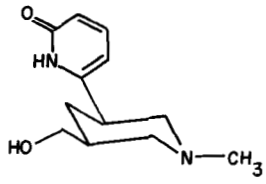


159

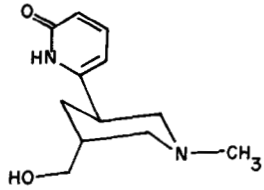


160

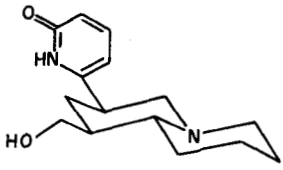
Kuraramine (**161**) and isokuraramine (**162**), in addition to 16 known lupine alkaloids, have been isolated from *Sophora flavescens* by Murakoshi and coworkers (*245*). Based on study of the concentrations of **161** and (+)-mamanine (**163**) in the growing plant, these authors suggest that (+)-kuraramine and (+)-mamanine (**163**) may be oxidative metabolites of (−)-*N*-methylcytisine (**164**) and (−)-anagyrine (**165**). The structures of these new pyridine alkaloids were



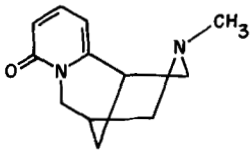
161



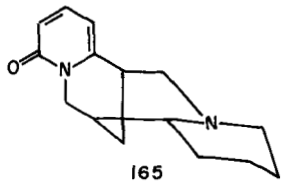
162



163



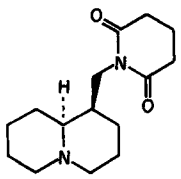
164



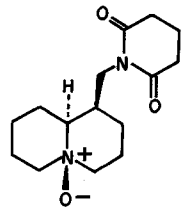
165

determined by spectroscopic data, and the absolute configurations have yet to be determined.

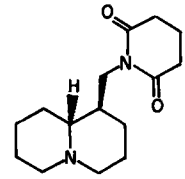
(−)-Epilamprolobine (**166**) and (+)-epilamprolobine *N*-oxide (**167**) have been isolated from *Sophora tomentosa* by Murakoshi and co-workers (*246*). Their structures were established from spectroscopic data and by comparison with synthetic (+)-epilamprolobine prepared by transformation from (−)-lupinine. (−)-Epilamprolobine (**166**) is a diastereomer of (+)-lamprolobine (**168**), isolated from *Lamprolobium fruticosum*. These authors have also proposed a biosynthetic pathway for (−)-epilamprolobine.



166

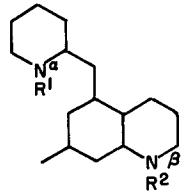


167



168

Nyembo *et al.* (*247*) have isolated four novel alkaloids from *Lycopodium* species and have proposed that their skeleton, represented by phlegmarine (**169**), may feature as a biogenetic intermediate in the pathway to the lycopodium alkaloids. Phlegmarine and N_{β}-methylphlegmarine (**170**) were obtained from *Lycopodium phlegmaria* while N_{α}-methylphlegmarine (**171**) was isolated from *L. cernuum* and N_{α}-acetyl-N_{β}-methylphlegmarine (**172**) from *L. clavatum var. borbonicum*. The structures of these compounds have been assigned on the basis of chemical and spectroscopic data, but their stereochemistry remains unresolved, although synthesis of stereoisomers of **172** features in the structural studies.

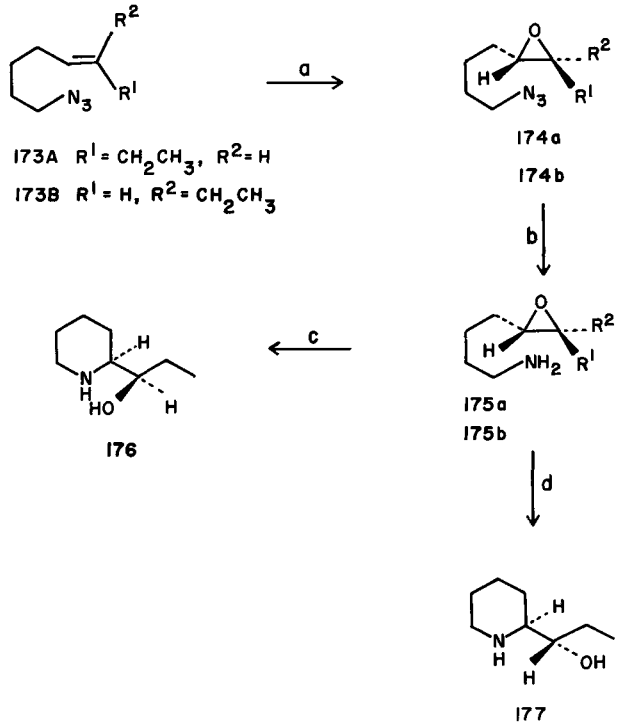


169 $R^1, R^2 = H$

170 $R^1 = H, R^2 = CH_3$

171 $R^1 = CH_3, R^2 = H$

172 $R^1 = COCH_3, R^2 = CH_3$



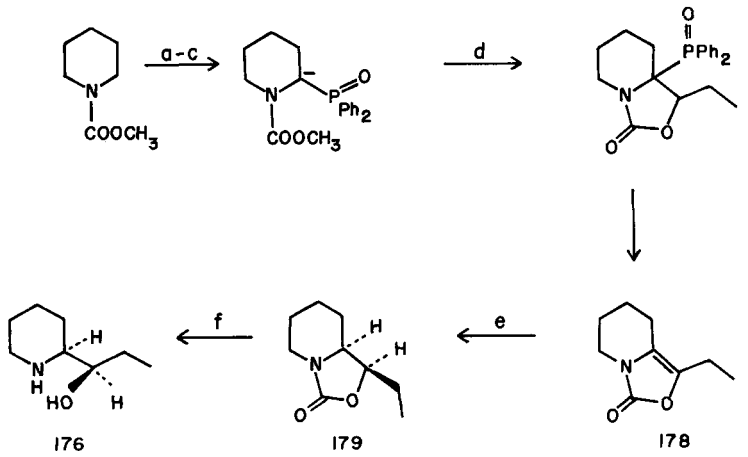
SCHEME 61. (a) MCPBA, CH_2CH_2, (b) Ph_3P, THF, H_2O, (c) toluene, Δ, (d) benzene, Δ.

An efficient stereospecific synthesis of (±)-α-conhydrine (**176**) and (±)-β-conhydrine (**177**) has been executed by Pilard and Vaultier (*248*) (Scheme 61) in which the epoxy azides **174a** and **174b**, prepared from the corresponding olefin azides **173a** and **173b**, are transformed to the corresponding amines **175a** and **175b**, which on refluxing in an aromatic solvent are converted to (±)-α-conhydrine and (±)-β-conhydrine in 59 and 65% overall yields, respectively.

A synthesis of (±)-α-conhydrine (**176**) from *N*-carbomethoxypiperidine by Shono *et al.* (*249*) features a highly stereoselective catalytic reduction of the 2-oxazolone **178** to give the erythro isomer (>98.5%) **179**, which on hydrolysis afforded (±)-α-conhydrine in 33% overall yield (Scheme 62).

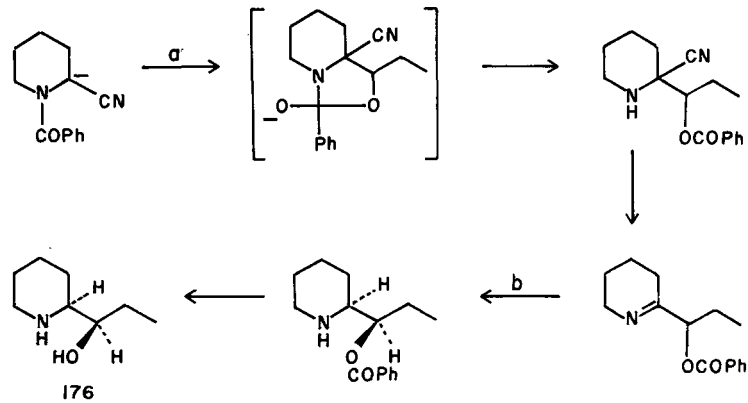
A high-yield synthesis of (±)-α-conhydrine (**176**) by Stork *et al.* (*250*) has been achieved via a general procedure developed by the Columbia group for alkylation α to amines via α-cyano derivatives. Application of their method to 2-cyanopiperidine afforded **176** in 77% yield from propionaldehyde and with excellent stereoselectivity (Scheme 63).

Three chiral syntheses of (+)-coniine (**183**) have been reported (*251–253*). The most recent route by Husson *et al.* (*253*) involves the condensation of (+)-

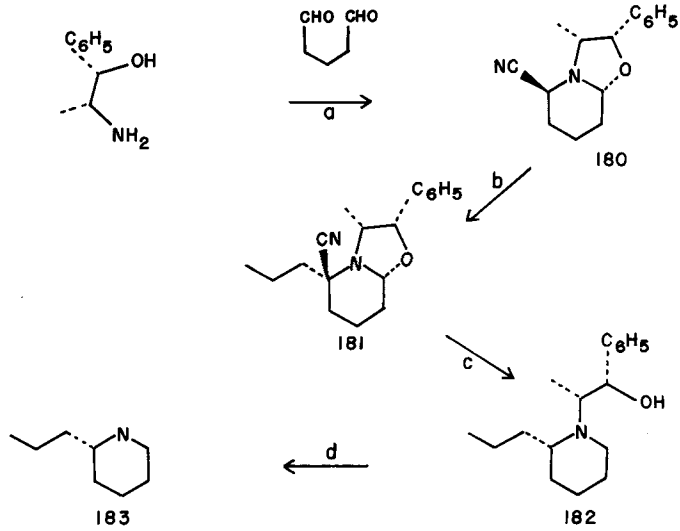


SCHEME 62. (a) anodic oxidation, MeOH, (b) Ph_2PCl, AcOH, (c) LDA, (d) CH_3CH_2CHO, (e) H_2, PtO_2, AcOH, 20 atm, (f) OH^-.

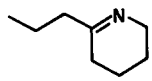
norephedrine and glutaraldehyde with addition of KCN to provide the 2-cyano-6-oxazolopiperidine **180** in one step. Alkylation of the anion of **180** with propyl bromide and reduction with $NaBH_4$ gave the alcohol **182,** which on hydrogenolysis was cleaved to give (+)-coniine (**183**) in excellent overall yield. The synthon **180** has also been employed to prepare (−)-coniine. Two enzymes have been isolated from *Conium maculatum,* which catalyze the conversion of 5-oxooctanal plus alanine to γ-coniceine (**184**) (*254*). From the same source an enzyme has been isolated, which effects the conversion of γ-coniceine to coniine (*255*).



SCHEME 63. (a) Li *N,N*-diisopropylamide, THF, CH_3CH_2CHO, (b) $NaBH_4$, MeOH.



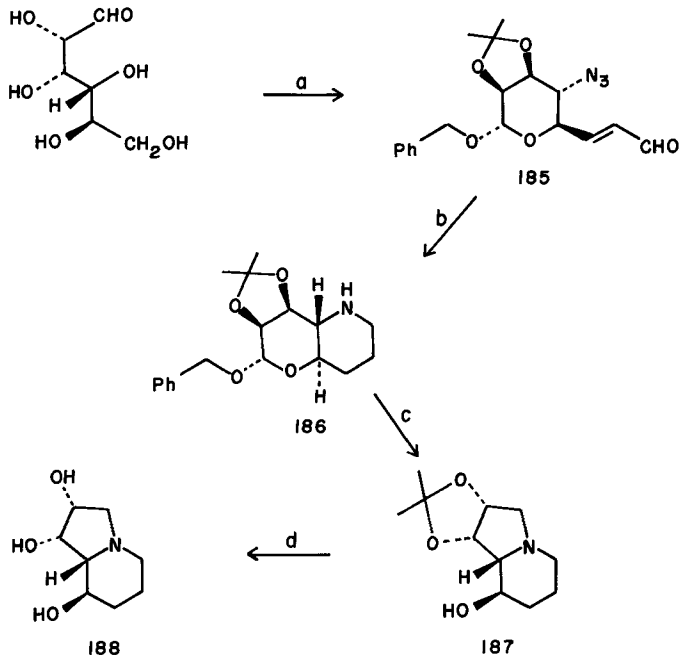
SCHEME 64. (a) pH 3, KCN, (b) LDA, n PrBr, (c) $NaBH_4$, EtOH, (d) H_2SO_4, Δ.



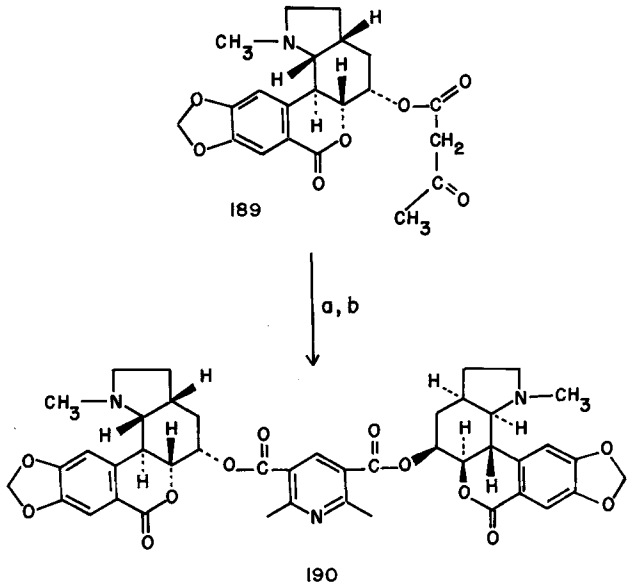
184

Structure **188** for swainsonine, a potent α-mannosidase inhibitor from *Swainsonia canescens* (Benth.) A. Lee, proposed by Colegate *et al.* (*256*) based on chemical and spectroscopic data, has been confirmed by X-ray analysis of its diacetate (*257*). The alkaloid has also been isolated from *Rhizoctonia leguminicola* (*258*) and was originally incorrectly designated as 3,4,5-trihydroxyoctahydro-1-pyrindine (*259*). An elegant enantiospecific synthesis of swainsonine from D-mannose by Fleet *et al.* (*260*), outlined in Scheme 65, proceeds via the azidoenal **185,** which on hydrogenation in the presence of 10% palladium on charcoal in methanol gave the secondary amine **186.** Subsequent treatment of **186** with hydrogen in acetic acid, using palladium black, led to the acetonide **187** of swainsonine in 87% yield from **180.** Dissolution of acetonide **187** in trifluoroacetic acid–water led to swainsonine (**188**).

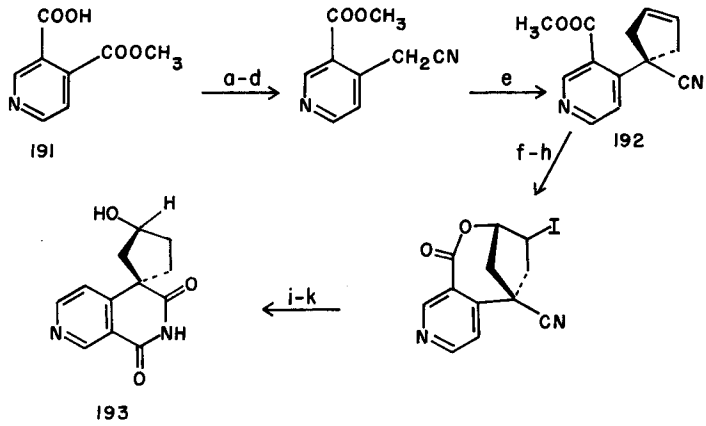
Clivimine (**190**) (*261*), a unique Amaryllidaceae alkaloid (*262*) from *Clivia miniata* Regel, has been synthesized by applying the Hantzch pyridine synthesis to the alkaloid clivacetine (**189**), a possible biogenetic precursor of **190.** The



SCHEME 65. (a) Several steps, (b) 10% Pd–charcoal, H_2, MeOH, (c) Pd black, H_2, AcOH, (d) CF_3COOH, H_2O.



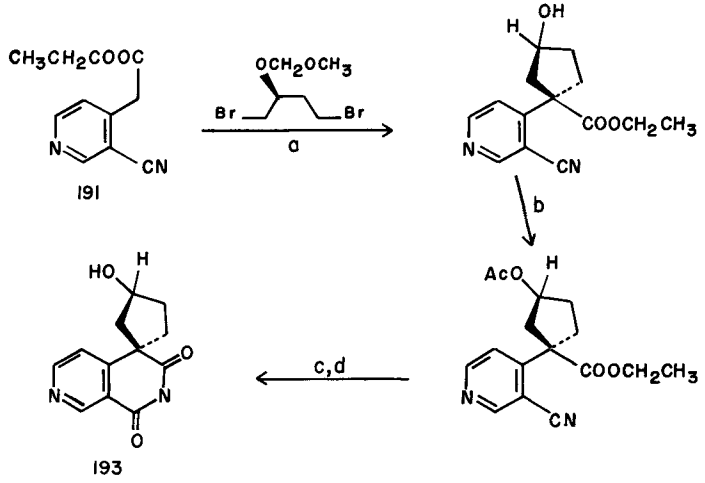
SCHEME 66. (a) H_2CO, NH_3, (b) $NaNO_2$, AcOH.



SCHEME 67. (a) $LiAlH_4$, THF, (b) PCl_5, CH_2Cl_2, (c) MeOH, (d) NaCN, Aliquat 336, CH_2Cl_2, (e) (Z)-1,4-dichlorobut-2-ene, NaH, THF, (f) NaOH, THF, H_2O, (g) KI, I_2, $NaHCO_3$, H_2O, CH_2Cl_2, (h) *n*-Bu_3SnH, AIBN, benzene, (i) NH_3, MeOH, (j) NaH, *i*-PrOH, (k) H_3O^+.

two-step transformation conducted by Kobayashi and co-workers (*263*) is outlined in Scheme 66.

Cytotoxic sesbanine (**193**) was isolated from the ethanol extract of the seeds of *Sesbania drummondii*, a source reported to possess potent antileukemic activity (*264a*). The structure and relative stereochemistry were established by X-ray techniques (*264b*). In view of its potential as an antileukemic agent and its novel structure, sesbanine has been the target of two total syntheses to date. The first

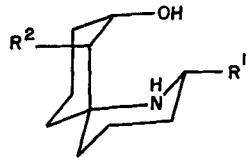


SCHEME 68. (a) NaH, DMF, HMPA, (b) diethyl azodicarboxylate, $(C_6H_5)_3P$, AcOH, THF, (c) K_2CO_3, EtOH, (d) H_2O_2, NaOH, EtOH.

synthesis by Bottaro and Berchtold (*265*) provided racemic sesbanine in ~3.5% overall yield starting from 4-(methoxycarbonyl)-nicotinic acid (**191**) in an 11-step sequence featuring a stereospecific introduction of the hydroxyl group via the iodolactonization of the cyano ester **192** (see Scheme 67). A synthesis by Tomioka and Koga (*266*) outlined in Scheme 68 employs a similar strategy for the development of the spirocyclic ring system but utilizes (−)-1,4-dibromobutan-2-ol to provide, after a stereoinversion step, (+)-sesbanine in ~4.4% overall yield. This synthetic material displays $[\alpha]_D^{23}$ +43.1°, while natural sesbanine is reported to show $[\alpha]_D^{23}$ +14.6°.

B. Alkaloids from Animals

Since the report in 1971 (*267*) on the spiropiperidines, histrionicotoxin (**194**), and dihydrohistrionicotoxin (**195**), isolated from the skin of the poisonous Colombian frog *Dendrobates histrionicus*, there has been considerable interest on both the pharmacological and synthetic fronts. In addition, a number of new related minor bases (**196,197**) have been found in the same source, and it has been learned that the nature of the side chain is an important factor for cholinolytic activity and sodium–potassium ion membrane transport phenomena (*268*). Several syntheses of (±)-perhydrohistrionicotoxin (**196**) (*269, 270, 271,273–277*) and one of (±)-octahydrohistrionicotoxin (**197**) (*271*) have been reported, while a synthetic approach to the skeleton of histrionixotoxin (**194**) and dihydrohistrionicotoxin (**195**) has been described (*278*).



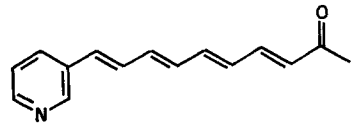
194 $R^1 = CH_2CH\overset{cis}{=}CHC{\equiv}CH$, $R^2 = CH\overset{cis}{=}CHC{\equiv}CH$

195 $R^1 = CH_2CH_2CH{=}C{=}CH_2$, $R^2 = CH\overset{cis}{=}CHC{\equiv}CH$

196 $R^1 = CH_2CH_2CH_2CH_2CH_3$, $R^2 = CH_2CH_2CH_2CH_3$

197 $R^1 = CH_2CH_2CH_2CH{=}CH_2$, $R^2 = CH_2CH_2CH{=}CH_2$

One of three components of the alarm pheromone system of the carnivorous hermaphroditic sea slug *Navanox inermis* Cooper has been shown to be the pyridyl ketone **198** (*279*). It is interesting to note that the other two components

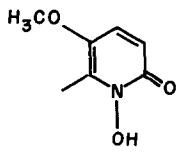


198

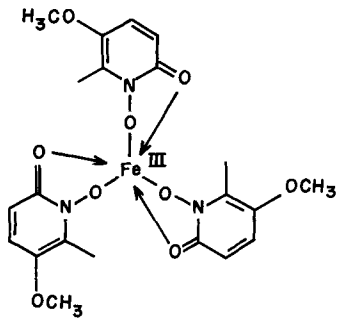
are analogs in which the pyridine ring is replaced by a phenyl and a *p*-hydroxyphenyl group.

C. Alkaloids from Microorganisms

Microorganisms have been the source of a number of alkaloids featuring one or more pyridine or piperidine nuclei. These range in complexity from the simple pyridone antibiotic **199** to the antitumor macrolide rapamycin **134.** The former structure (**199**) was proposed by Itoh *et al.* (*280*) for a new antifungal antibiotic isolated from the culture broth of *Pseudomonas* sp. (strain BN-227) and simultaneously by Barker *et al.* (*281*) for a compound designated G1549 from *Pseudomonas alcaligenes* cultures. Both groups described another antibiotic (**200**) prepared by treatment of **199** with ferric chloride and also isolated from *Pseudomonas* sp. (BN-227) by the Japanese group. The structure of **199,** designated antibiotic BN-227, originally deduced from chemical and spectroscopic data, was subsequently confirmed by X-ray studies (*282*).



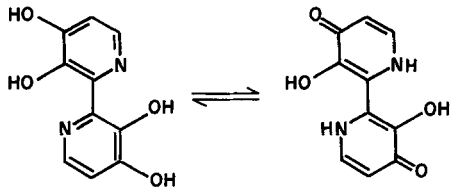
199



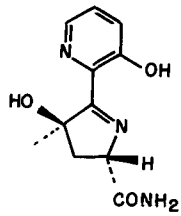
200

Orelline, a toxic alkaloid from the mushroom *Cortinarius orellanus* Fries, has been assigned the tautomeric structures **201** and **202,** and the accompanying toxic orellanine is the corresponding bis-*N*-oxide (*283*).

Liu and co-workers (*284*) have reported that siderochelin A, a ferrous ion-chelating metabolite from the fermentation broth of *Norcardia* sp. SC 11,340, shows modest activity against an array of aerobic and anaerobic microorganisms. Its structure and relative stereochemistry (**203**) were revealed by X-ray



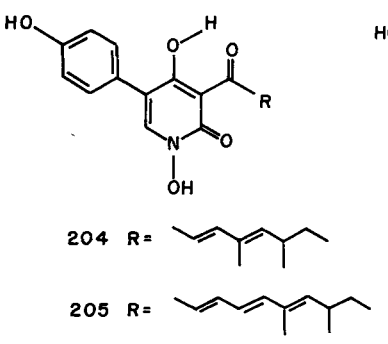
201 202



203

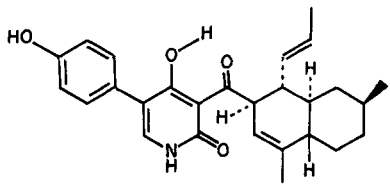
crystallography. The absolute configuration was determined on *N*-bromoacetyldihydrosiderochelin A monohydrate by Okuyama *et al.* (*285*), who also reported that siderochelin B, a diastereomer of **203,** could be obtained by base-catalyzed epimerization of siderochelin A. In contrast to the pioneering Squibb group, these authors did not find siderochelin B to accompany siderochelin A in their strain *Norcardia* sp. MG 254-CF5 and noted that the ^{1}H-NMR signal for the methine-bearing carboxamide disappears when the epimerization is conducted in deuterated methanol.

The structures of two novel fungal-derived pigments, tenellin and bassianin, have been established as **204** and **205,** respectively, on the basis of extensive chemical and spectroscopic data including NMR studies on tenellin following



204 R=

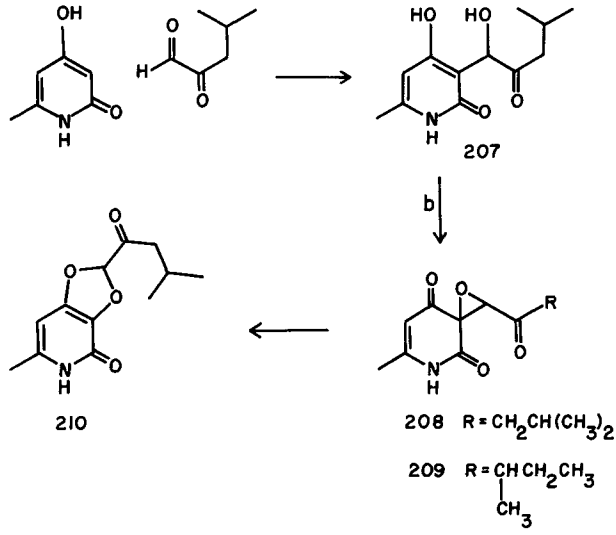
205 R=



206

biosynthetic enrichment with ^{13}C- and ^{15}N-labeled precursors (*286*). These pigments were isolated from cultures of the insect pathogen *Beauveria bassiana* (Bals.) Vuill. and *B. tenella* (Delacroix) Siem. A related antifungal antibiotic pigment, ilicicolin H (**206**), has been isolated from the imperfect fungus *Cylindrocladium ilicicola* (*287*). Tenellin (**204**) has been synthesized in racemic form by Williams and Sit (*288*).

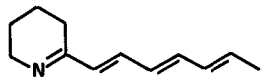
Structure **208,** proposed by Findlay *et al.* (*289*) for the antibiotic flavipucine, a metabolite of *Aspergillus flavipes,* has been confirmed by X-ray studies (*290*) on synthetic racemic flavipucine. The latter was prepared via the two-step sequence outlined in Scheme 69 by Findlay *et al.* (*291*). Condensation of 4-hydroxy-6-



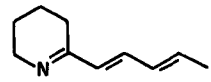
SCHEME 69

methyl-2-pyridone with isobutylglyoxal gave the intermediate **207,** which on oxidation with *tert*-butyl hydroperoxide provided racemic flavipucine plus its diastereomer (1:1) in 63% yield. Fractional crystallization provided the X-ray sample whose oxiran geometry was revealed in the analysis. Flavipucine is accompanied in isolation by some 20–26% of isomer **209** and substantial amounts of isoflavipucine (**210**), to which it can be rearranged in high yield by boiling in nonanhydrous xylene or less efficiently by treatment with aqueous sodium carbonate (*292*). The synthon **207** has been exploited by another group in effecting a flavipucine synthesis very similar to the pioneering one (*293*).

Nigrifactin (**211**) from *Streptomyces* strain FFD-101 (*294*) has been the subject of two syntheses (*295,296*) and a biosynthetic study (*297*), which showed it to be derived from six acetate units in linear combination. The alkaloid displays anti-



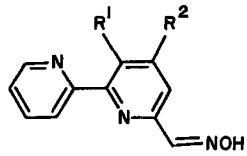
211



212

histaminic properties and affects blood pressure (*298*). A related compound (**212**) has been isolated from *Streptomyces* sp. NA-337 (*299*).

The alkaline-dependent actinomycete *Streptomyces caeruleus* has provided four closely related dipyridyl aldoximes designated caerulomycin A, B, C, and D. A 4-methoxy-2,2′-dipyridyl-6-(*E*)-aldoxime (**213**) was isolated by Funk and Divekar in 1959 (*300*), who reported its antibiotic activity, and its structure was deduced by Divekar *et al.* in 1967 (*301*) from chemical and spectroscopic evidence. A decade later the structures of B (**214**) and C (**215**) were established (*302*). Caerulomycin D (**216**) is reported to be a glycoside of 3,4-dihydroxy-2,2′-dipyridyl-6-(*E*)-aldoxime. Biosynthetic studies have revealed that these unique metabolites are derived in part from lysine and acetate (*303*).



213 R^1 = H, R^2 = OCH_3

214 R^1 = OH, R^2 = OCH_3

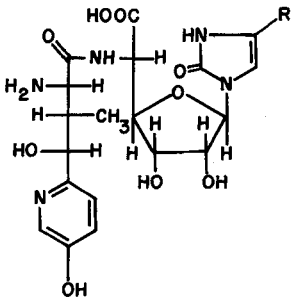
215 R^1 = OCH_3, R^2 = OCH_3

216 R^1, R^2 = OH, O-glucose

The structures and absolute configurations of neopolyoxins A (**217**), B (**218**), and C (**219**) were deduced from chemical and spectroscopic data (*304*). These compounds, isolated from *Streptomyces cacaoi* subsp. *asoensis*, are potent inhibitors of fungal cell-wall chitin synthetase, and A and C are reported to be isomeric with the nikkomycins X and Z, respectively, obtained from *Streptomyces tendae* (*305*).

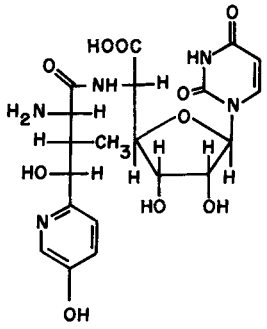
Rubradirin (**220**), an inhibitor of bacterial protein synthesis, was isolated from *Streptomyces achromogenes* var. *rubradiris* (*306*), and its structure, which is related to the ansamycins, was deduced from chemical and spectroscopic data (*307*).

The anticancer antibiotic streptonigrin (**221**) was first isolated from cultures of *Streptomyces flocculus* (*308*) and later from a strain of *Actinomyces albus* var.

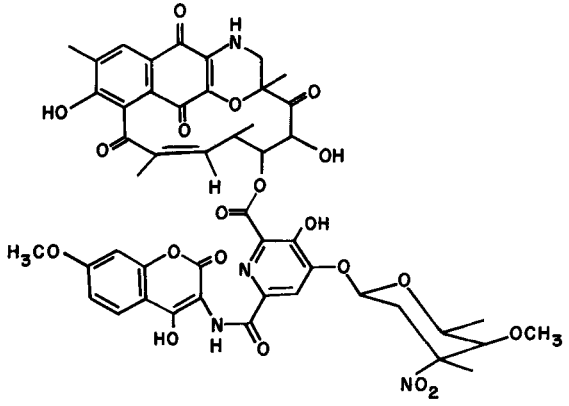


217 R = CHO

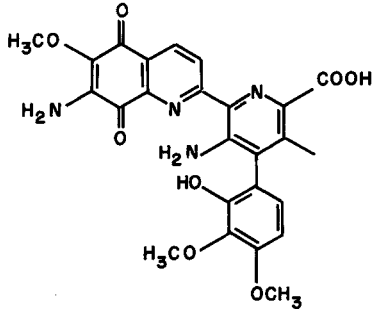
218 R = COOH



219



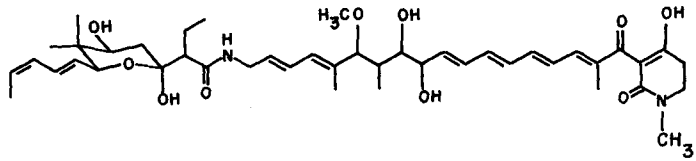
220



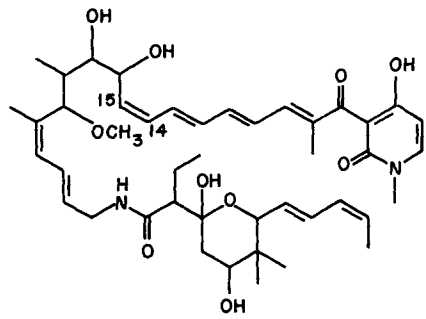
221

bruneomycini (*309*) and from *Streptomyces rufochromogenes* (and *S. echinatus*). Isolates from the latter sources were named bruneomycin and rufochromomycin, respectively (*310*). Structure **221** was elucidated by Rao, Biemann, and Woodward (*311*), on the basis of degradative and spectroscopic studies and confirmed by X-ray crystallography, in 1975 (*312*). An extensive review of the chemistry, biosynthesis, and mechanism of action of streptonigrin by Gould and Weinreb has recently appeared (*313*), and the compound has been the objective of two successful total syntheses (*314,315*).

From *Streptomyces cinnamomeus* Zeeck *et al.* (*316*) have isolated kirrothricin, whose gross structure (**222**) was deduced from chemical degradation and spectroscopic studies. Gullo *et al.* (*317*) have proposed structure **223** for factumycin, a broad spectrum antibiotic from the culture broth of *S. lavendulae* and have noted that kirrothricin may be dihydrofactumycin if the 14,15 double bond proves to possess the *Z* configuration.



222



223

References

1. M. Hesse, "Alkaloid Chemistry." Wiley, New York, 1981.
2. S. W. Pelletier, ed., "Alkaloids: Chemical and Biological Perspectives," Vol. 1. Wiley, New York, 1983.
3. M. Shamma, *J. Am. Chem. Soc.* **105**, 6769 (1983).

4. W. A. Ayer and T. E. Habgood, *Alkaloids (N.Y.)* **11,** 459.
5. Reviews *in Alkaloids (London):* V. A. Snieckus, **1,** (1971) through **5,** (1975); A. R. Pinder, **6,** (1976) through **12,** (1982); R. B. Herbert (Biosynthesis), **1,** (1971) through **12,** (1982).
6. R. K. Hill *in* "Chemistry of the Alkaloids" (S. W. Pelletier, ed.), Van Nostrand-Reinhold, New York, 1970.
7. V. A. Snieckus, *Alkaloids (London)* **1,** 48(1971).
8. R. J. Highet and P. F. Highet, *J. Org. Chem.* **31,** 1275 (1966); W. Y. Rice and J. L. Coke, *J. Org. Chem.* **31,** 1010 (1966).
9. I. Christofidis, A. Welter, and J. Jadot, *Tetrahedron* **33,** 977 (1977).
10. I. B. Gianinetto, J. L. Cabrera, and H. R. Juliani, *J. Nat. Prod.* **43,** 632 (1980).
11. D. Lythgoe and M. J. Vernenge, *Tetrahedron Lett.,* 1133 (1967).
12. I. Christofidis, A. Welter, and J. Jadot, *Tetrahedron* **33,** 3005 (1977).
13. Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, *Bull. Soc. Chim. Belg.* **81,** 425, 443 (1972).
14. D. Lythgoe, A. Busch, N. Schvarzberg, and M. J. Vernengo, *An. Asoc. Quim. Argent.* **60,** 317 (1972); *Chem. Abstr.* **77,** 164901 (1972).
15. V. U. Ahmad, A. Basha, and W. Haque, *Z. Naturforsch. B.: Anorg. Chem., Org. Chem.* **33,** 347 (1978).
16. K. Jewers, M. J. Nagler, K. A. Zirvi, F. Amir, and F. H. Cottee, *Pahlavi Med. J.* **5,** 1 (1974); *Chem. Abstr.* **81,** 23097 (1974).
17. R. Ott-Longoni, N. Viswanathan, and M. Hesse, *Helv. Chim. Acta* **63,** 2119 (1980).
18. J. Bruneton and A. Cavé, *Tetrahedron Lett.,* 739 (1975).
19. R. J. Highet and P. F. Highet, *Tetrahedron Lett.,* 1803 (1970).
20. H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Am. Chem. Soc.* **92,** 1590 (1970).
21. T. M. Smalberger, G. J. H. Rall, H. L. de Waal, and R. R. Arndt, *Tetrahedron* **24,** 6417 (1968), and references cited therein.
22. J. L. Coke and W. R. Rice, Jr., *J. Org. Chem.* **30,** 3420 (1965); T. R. Govindachari, *J. Indian Chem. Soc.* **45,** 945 (1968), and references cited therein.
23. A. U. Ogan, *Phytochemistry* **10,** 2544 (1971).
24. E. M. Burdick, *Econ. Bot.* **25,** 363 (1971).
25. C.-S. Tang, *Phytochemistry* **18,** 651 (1979).
26. G. Fodor, J.-P. Fumeaux, and V. Sankaran, *Synthesis,* 464 (1972).
27. E. Brown and A. Bourgouin, *Tetrahedron* **31,** 1047 (1975).
28. E. Brown and R. Dahl, *Bull. Soc. Chim. Fr.,* 4292 (1972).
29. E. Brown and A. Bonte, *Tetrahedron Lett.,* 2881 (1975).
30. R. J. Highet, unpublished, cited as personal communication in Ref. *29.*
31. D. Lythgoe and M. J. Vernenge, *Tetrahedron Lett.,* 1133 (1967).
32. E. Brown and A. Bourgouin, *Chem. Lett.,* 109 (1974).
33. E. Brown and R. Dhal, *J. Chem. Soc., Perkin Trans. 1,* 2190 (1976).
34. M. Natsume and M. Ogawa, *Heterocycles* **12,** 159 (1979).
35. M. Natsume and M. Ogawa, *Heterocycles* **14,** 169 (1980).
36. M. Natsume and M. Ogawa, *Heterocycles* **14,** 615 (1980).
37. M. Natsume and M. Ogawa, *Heterocycles* **16,** 973 (1981).
38. S. Hanessian and R. Frenette, *Tetrahedron Lett.,* 3391 (1979).
39. N. S. Narasimhan, *Chem. Ind. (London),* 1526 (1956).
40. E. J. Corey, K. C. Nicoleau, and L. S. Melvin, Jr., *J. Am. Chem. Soc.* **97,** 654 (1975).
41. A. J. G. Baxter and A. B. Holmes, *J. Chem. Soc., Perkin Trans. 1,* 2343 (1977); A. B. Holmes, J. Thompson, A. J. G. Baxter, and J. Dixon, *J. Chem. Soc., Chem. Commun.,* 37 (1985).

42. Y. Saitoh, Y. Moriyama, T. Takahashi, and Q. Khuong-Huu, *Tetrahedron Lett.*, **21,** 75 (1980); Y. Saitoh, Y. Moriyama, H. Hirota, T. Takahashi, and Q. Khuong-Huu, *Bull. Chem. Soc. Jpn.* **54,** 488 (1981).
43. E. Brown, R. Dhal, and J. Lavoue, *Tetrahedron Lett.*, 2767 (1971); E. Brown, J. Lavoue, and R. Dhal, *Tetrahedron* **29,** 455 (1973).
44. K. E. Harding and S. R. Burks, *J. Org. Chem.* **49,** 40 (1984).
45. M. F. Roberts and R. T. Brown, *Phytochemistry* **20,** 447 (1981).
46. A. D. Harmon, U. Weiss, and J. V. Silverton, *Tetrahedron Lett.*, 721 (1979).
47. P. A. Taylor, H. K. Schnoes, and R. D. Durbin, *Biochim. Biophys. Acta* **286,** 107 (1972). Other references cited in Lee and Rapoport (*48*).
48. D. L. Lee and H. Rapoport, *J. Org. Chem.* **40,** 3491 (1975).
49. C. Tang and H. Rapoport, *J. Am. Chem. Soc.* **94,** 8615 (1972).
50. E. Leete and R. A. Carver, *J. Org. Chem.* **40,** 2151 (1975).
51. E. Leete and K. N. Juneau, *J. Am. Chem. Soc.* **91,** 5614 (1969); E. Leete, J. C. Lechleiter, and R. A. Carver, *Tetrahedron Lett.*, 3779 (1975).
52. R. K. Hill and T. Yuri, *Tetrahedron* **33,** 1569 (1977), and references cited herein.
53. A. Astier and M. M. Plat, *Tetrahedron Lett.*, 2051 (1978).
54. L. Guerrier, J. Royer, D. S. Grierson, and H.-P. Husson, *J. Am. Chem. Soc.* **105,** 7754 (1983).
55. J. G. MacConnell, M. S. Blum, and H. M. Fales, *Tetrahedron* **26,** 1129 (1971).
56. M. Beroza, *Acc. Chem. Res.* **3,** 33 (1970).
57. J. M. Brand, M. S. Blum, H. M. Fales, and J. G. MacConnell, *Toxicon* **10,** 259 (1972).
58. J. M. Brand, M. S. Blum, and H. H. Ross, *Insect Biochem.* **3,** 45 (1973).
59. J. G. MacConnell, R. N. Williams, J. S. Brand, and M. S. Blum, *Ann. Entomol. Soc. Am.* **67,** 134 (1974).
60. D. P. Jouvenaz, M. S. Blum, and J. G. MacConnell, *Antimicrob. Agents Chemother.* **2,** 291 (1972).
61. Y. Moriyama, D. Doan-Huynh, C. Monneret, and Q. Khuong-Huu, *Tetrahedron Lett.*, 825 (1977).
62. K. Fuji, K. Ichikawa, and E. Fujita, *Chem. Pharm. Bull. Jpn.* **27,** 3183 (1979).
63. Y. Matsumura, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.* **23,** 1929 (1982).
64. A. Krochmal, L. Wilken, and M. Chien, *Lloydia* **35,** 303 (1972).
65. C. S. Shah, J. S. Qadry, and M. G. Bhatt, *Phytochemistry* **11,** 2884 (1972).
66. M. S. Karawya, S. M. Abdel-Wahab, and A. Y. Zaki, *J. Assoc. Off. Anal. Chem.* **54,** 1423 (1971).
67. Y. V. Shostenko, S. K. Mushinskaya, I. S. Simon, and E. S. Vysotskaya, see *Chem. Abstr.* **78,** 101929 (1973); Y. V. Shostenko and I. S. Simon, *Tr. Voronezh. Gos. Univ.* **72,** 213 (1969), see *Chem. Abstr.* **77,** 156308 (1972).
68. M. F. Keogh and D. G. O'Donovan, *J. Chem. Soc. (C),* 2470 (1970); D. G. O'Donovan and T. Forde, *J. Chem. Soc. (C),* 2889 (1971); D. G. O'Donovan, D. J. Long, E. Forde, and P. Geary, *J. Chem. Soc., Perkin Trans. 1,* 415 (1975).
69. R. N. Gupta and I. D. Spenser, *Phytochemistry* **9,** 2329 (1970).
70. E. Leete, *Acc. Chem. Res.* **4,** 100 (1971).
71. E. Leistner and I. D. Spenser, *J. Am. Chem. Soc.* **95,** 4715 (1973), and references cited therein.
72. E. Leistner and I. D. Spenser, *J. Chem. Soc., Chem. Commun.*, 378 (1975).
73. J. C. Richards and I. D. Spenser, *J. Am. Chem. Soc.* **100,** 7402 (1978).
74. H. J. Gerdes and E. Leistner, *Phytochemistry* **18,** 771 (1979).
75. T. J. Gilbertson, *Phytochemistry* **11,** 1737 (1972).
76. E. Leistner, R. N. Gupta, and I. D. Spenser, *J. Am. Chem. Soc.* **95,** 4040 (1973).

77. C. Hootelé, J. P. Etienne, and B. Colau, *Bull. Soc. Chim. Belg.* **88,** 111 (1979).
78. C. Hootelé, B. Colau, F. Halin, J. P. Declercq, G. Germain, and M. van Meerssche, *Tetrahedron Lett.* **21,** 5061 (1980).
79. J. H. Kooy, *Planta Med.* **30,** 295 (1976).
80. C. Hootelé, B. Colau, F. Halin, J. P. Declercq, G. Germain, and M. van Meerssche, *Tetrahedron Lett.* **21,** 5063 (1980).
81. B. Franck, *Chem. Ber.* **93,** 2360 (1960).
82. As. Z. Gulubov and I. Z. Bozhkova, *Nauchn. Tr. Plovdivski Univ., Mat. Fiz. Khim., Biol.* **10,** 101 (1972), see *Chem. Abstr.* **78,** 13761 (1973).
83. H. C. Beyerman, L. Maat, A. van Veen, A. Zweistra, and A. von Phillipsborn, *Rec. Trav. Chim. Pays-Bas* **84,** 1367 (1965).
84. G. A. Cooke and G. Fodor, *Can. J. Chem.* **46,** 1105 (1968).
85. D. Butruille, G. Fodor, C. Saunderson Huber, and F. Letourneau, *Tetrahedron* **27,** 2055 (1971).
86. H. C. Beyerman, L. Maat, J. P. Visser, J. Cymerman Craig, R. P. Chan, and S. K. Roy, *Rec. Trav. Chim. Pays-Bas* **88,** 1012 (1969).
87. L. Marion and M. C. Raput, *Can. J. Res. Sect. B* **27,** 215 (1949).
88. H. Beyerman, B. S. L. Bordes, L. Maat, and F. M. Warnaar, *Rec. Trav. Chim. Pays-Bas* **91,** 1441 (1972).
89. G. Fodor and G. A. Cooke, *Tetrahedron* **22,** Suppl. 8, 113 (1966).
90. T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, *Chem. Lett.*, 223 (1977).
91. J. J. Tufariello and S. A. Ali, *Tetrahedron Lett.*, 4647 (1978).
92. M. Natsume and M. Ogawa, *Heterocycles* **20,** 601 (1983).
93. R. A. W. Johnstone and J. R. Plimmer, *Chem. Rev.* **59,** 885 (1959).
94. L. D. Quin, *Sel. Chim.* **20,** 37 (1962).
95. U. S. von Euler, ed., "Tobacco Alkaloids and Related Compounds." Macmillan, New York, 1965.
96. F. Haglid, *Acta Pharm. Suec.* **4,** 117 (1967).
97. J. Schormueller, "Handbook of Food Chemistry, Vol. 6: Alkaloid-containing food substances, spices, salt." Springer-Verlag, Berlin, 1970.
98. R. W. Ryall, *in* "Neuropoisons, Their Pathophysiological Actions" (L. L. Simpson and D. R. Curtis, eds.). Plenum, New York, 1974.
99. P. S. Larson and H. Silvette, "Tobacco, Experimental and Clinical Studies," Supplement III. Williams & Wilkins, Baltimore, Md., 1975.
100. C. R. Enzell, I. Wahlberg, and A. J. Aasen, *Prog. Chem. Org. Nat. Prod.* **34,** 1 (1977).
101. I. Schneltz and D. Hoffmann, *Chem. Rev.* **77,** 295 (1977).
102. E. Leete, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 1. p. 85. Wiley, New York, 1983.
103. J. I. Seeman, *Heterocycles* **22,** 165 (1984).
104. D. Gross, *in* "Biosynthese der Alkaloide" (K. Mothes and H. R. Schütte, eds.). VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.
105. G. A. Cordell, "Introduction to Alkaloids: a Biogenetic Approach." Wiley, New York, 1981.
106. S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tomaki, *Plant Cell Physiol.* **14,** 103 (1973).
107. S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tomaki, *Plant Cell Physiol.* **12,** 633 (1971).
108. S. Mizusaki, Y. Tanabe, M. Noguchi, and E. Tomaki, *Phytochemistry* **11,** 2757 (1972).
109. E. Leete and M. L. Yu, *Phytochemistry* **19,** 1093 (1980).
110. C. R. Hutchinson, M. T. S. Hsia, and R. A. Carver, *J. Am. Chem. Soc.* **98,** 6006 (1976), and references cited therein.
111. M. Nakane and C. R. Hutchinson, *J. Org. Chem.* **43,** 3922 (1978).
112. J. W. Saunders and L. P. Bush, *Plant Physiol.* **64,** 236 (1979).

113. E. Leete, *J. Am. Chem. Soc.* **78,** 3520 (1956).
114. M. L. Solt, R. F. Dawson, and D. R. Christman, *Plant Physiol.* **35,** 887 (1960).
115. E. Leete, *J. Chem. Soc., Chem. Commun.*, 9 (1975).
116. E. Leete and S. A. Slattery, *J. Am. Chem. Soc.* **98,** 6326 (1976).
117. E. Leete, *J. Chem. Soc., Chem. Commun.*, 610 (1978).
118. E. Leete, K. C. Ranbom, and R. M. Riddle, *Phytochemistry* **18,** 75 (1979).
119. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.* **93,** 7021 (1971).
120. M. Cushman and N. Castagnoli, Jr., *J. Org. Chem.* **37,** 1268 (1972).
121. E. Leete and S. A. S. Leete, *J. Org. Chem.* **43,** 2122 (1978).
122. J. M. Bobbit and D. A. Scola, *J. Org. Chem.* **25,** 560 (1960).
123. F. Haglid, *Acta Chem. Scand.* **21,** 329 (1967).
124. A. H. Warfield, W. D. Galloway, and A. G. Kallianos, *Phytochemistry* **11,** 3371 (1972).
125. S. Z. Mukhamedzhanov, K. A. Aslanov, A. S. Sadykov, V. B. Leont'ev, and V. K. Kiryukhin, *Khim. Prir. Soedin.* **4,** 158 (1968).
126. A. J. N. Bolt, *Phytochemistry* **1,** 2341 (1972).
127. S. D. Sastry, *in* "Biochemical Applications of Mass Spectrometry" (G. R. Waller, ed.). Wiley (Interscience), New York, 1972.
128. D. F. Glenn and W. B. Edwards, *J. Org. Chem.* **43,** 2860 (1978).
129. E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.* **7,** 46 (1974).
130. W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Am. Chem. Soc.* **93,** 990 (1971).
131. T. P. Pitner, J. I. Seeman, and J. F. Whidby, *J. Heterocycl. Chem.* **15,** 585 (1978).
132. C. H. Koo and H. S. Kim, *Taehan Hwahakhoe Chi* **9,** 134 (1965).
133. J. F. Whidby and J. I. Seeman, *J. Org. Chem.* **41,** 1585 (1976), and references cited therein.
134. T. P. Pitner, W. B. Edwards, R. L. Bassfield, and J. F. Whidby, *J. Am. Chem. Soc.* **100,** 246 (1978).
135. T. P. Pitner, J. F. Whidby, and W. B. Edwards, *J. Am. Chem. Soc.* **102,** 5149 (1980).
136. J. F. Whidby, W. B. Edwards, and T. P. Pitner, *J. Org. Chem.* **44,** 794 (1979).
137. M. Karimov, A. S. Sadykov, K. A. Aslanov, V. B. Leont'ev, F. G. Kamaev, and T. K. Yunusov, *Khim. Prir. Soedin.*, 207 (1972); *Chem. Abstr.* **77,** 48677 (1972).
138. E. Leete, *J. Chem. Soc., Chem. Commun.*, 1091 (1972).
139. E. Leete, *J. Chem. Soc., Chem. Commun.*, 1055 (1978).
140. F. E. Scully, Jr., *J. Org. Chem.* **45,** 1515 (1980).
141. R. A. Comes, M. T. Core, M. D. Edmonds, W. B. Edwards, III, and R. W. Jenkins, Jr., *J. Labelled Compds.* **9,** 253 (1973).
142. E. Leete, H. V. Isaacson, and H. D. Durst, *J. Labelled Compds.* **7,** 313 (1971).
143. S. Brandänge and L. Lindblom, *Acta Chem. Scand. Ser. B,* **33,** 187 (1979).
144. E. Dagne and N. Castagnoli, Jr., *J. Med. Chem.* **15,** 356 (1972), and references cited therein.
145. E. Dagne and N. Castagnoli, Jr., *J. Med. Chem.* **15,** 840 (1972).
146. A. Castonguay and H. van Vunakis, *J. Org. Chem.* **44,** 4332 (1979).
147. E. Leete, M. R. Chedekal, and G. R. Bodem, *J. Org. Chem.* **37,** 4465 (1972).
148. T. E. Catka and E. Leete, *J. Org. Chem.* **43,** 2125 (1978).
149. E. B. Sanders, H. V. Secor, and J. I. Seeman, *J. Org. Chem.* **43,** 324 (1978).
150. W. C. Frank, Y. C. Kim, and R. H. Heck, *J. Org. Chem.* **43,** 2947 (1978).
151. J. B. Cloke, *J. Am. Chem. Soc.* **51,** 1174 (1929).
152. P. M. Maginnity and J. B. Cloke, *J. Am. Chem. Soc.* **73,** 49 (1951).
153. R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Am. Chem. Soc.* **90,** 5576 (1968).
154. R. V. Stevens, *Acc. Chem. Res.* **10,** 193 (1977).
155. S. Brandänge and L. Lindblom, *Acta Chem. Scand. Ser. B,* **30,** 93 (1976).
156. D. Spitzner, *Synthesis,* 242 (1977).

157. B. P. Mundy, B. R. Larsen, L. F. McKenzie, and G. Braden, *J. Org. Chem.* **37,** 1635 (1972); B. P. Mundy, K. B. Lipkowitz, M. Lee, and B. R. Larsen, *J. Org. Chem.* **39,** 1963 (1974).
158. B. P. Mundy and B. R. Larsen, *Synth. Commun.* **2,** 197 (1972).
159. H.-S. Ryang and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 594 (1972).
160. J. D. Phillipson and S. S. Handa, *Phytochemistry* **14,** 2683 (1975).
161. Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron* **31,** 3049 (1975).
162. J. Cossy and J. P. Pete, *Tetrahedron Lett.*, 4941 (1978).
163. T. L. Nguyen, L. D. Gruenke, and N. Castagnoli, *J. Med. Chem.* **22,** 259 (1979).
164. S. S. Hecht, C.-H. B. Chen, and D. Hoffmann, *Acc. Chem. Res.* **12,** 92 (1979).
165. S. S. Hecht, C.-H. B. Chen, R. M. Ornaf, E. Jacobs, J. D. Adams, and D. Hoffmann, *J. Org. Chem.* **43,** 72 (1978).
166. J. I. Seeman and J. F. Whidby, *J. Org. Chem.* **41,** 3824 (1976).
167. J. I. Seeman, H. V. Secor, J. F. Whidby, and R. L. Bassfield, *Tetrahedron Lett.*, 1901 (1978).
168. H. Itokawa, T. Inaba, R. Haruta, and S. Kameyama, *Chem. Pharm. Bull.* **25,** 1295 (1978).
169. R. M. Acheson, M. J. Ferris, and N. M. Sinclair, *J. Chem. Soc., Perkin Trans. 1*, 78 (1980).
170. S. Ghosal and S. K. Dutta, *Phytochemistry* **10,** 195 (1971).
171. S. Ghosal, R. S. Srivastava, P. K. Banerjee, and S. K. Dutta, *Phytochemistry* **10,** 3312 (1971).
172. R. T. Coutts and J. R. Scott, *Can. J. Pharm. Sci.* **6,** 78 (1971).
173. R. B. Burrows, *in* "Progress in Drug Research" (E. Jucker, ed.), Vol. 17, pp. 108–210. Birkhäuser Verlag, Basel, 1973.
174. I. A. Kozello, A. Y. Gasheva, and V. I. Khmelevskii, *Khim. Farm. Zh.* **10,** 90 (1976); *Chem. Abstr.* **86,** 171205 (1977).
175. R. Nery, *Biochem. J.* **122,** 503 (1971).
176. M. Beroza, *J. Org. Chem.* **28,** 3562 (1963).
177. H. J. Lee and G. R. Waller, *Phytochemistry* **11,** 2233 (1972).
178. B. A. Burke and H. Parkins, *Tetrahedron Lett.*, 2723 (1978).
179. D. L. Dreyer, *J. Org. Chem.* **33,** 3658 (1968).
180. K. Arai, S. Shimizu, and Y. Yamamoto, *Chem. Pharm. Bull.* **29,** 1005 (1981).
181. S. K. Dutta, B. N. Sharma, and P. V. Sharma, *Phytochemistry* **17,** 2047 (1978).
182. R. Somanathan, H. D. Tabba, and K. M. Smith, *J. Org. Chem.* **45,** 4999 (1980).
183. D. de Barros Corêa and O. R. Gottlieb, *Phytochemistry* **14,** 271 (1975).
184. E. Schlittler and U. Spitaler, *Tetrahedron Lett.*, 2911 (1978).
185. R. Mukherjee and A. Chatterjee, *Tetrahedron* **22,** 1461 (1966).
186. S. N. Ganguli, *Phytochemistry* **9,** 1667 (1970).
187. S. D. Sastry and G. R. Waller, *Phytochemistry* **11,** 2241 (1972).
188. G. R. Waller and L. Skursky, *Plant Physiol.* **50,** 622 (1972).
189. W. L. Fitch, P. M. Dolinger, and C. Djerassi, *J. Org. Chem.* **39,** 2974 (1974).
190. W. L. Fitch and C. Djerassi, *J. Am. Chem. Soc.* **96,** 4917 (1974).
191. E. Leete and A. R. Pinder, *Phytochemistry* **11,** 3219 (1972).
192. E. Leete, *J. Am. Chem. Soc.* **99,** 648 (1977); E. Leete, *Phytochemistry* **16,** 1705 (1977).
193. W. M. Gołębiewski and J. T. Wróbel, *Alkaloids (N.Y.)* **18,** 263 (1981).
194. E. Fujita and K. Fuji, *Int. Rev. Sci.: Org. Chem., Ser. 2* **9,** 119 (1976).
195. K. Fuji, K. Ichikawa, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1066 (1980).
196. F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950).
197. J. C. Nadgwick, B. J. Ralph, J. S. Shannon, and J. J. Simes, *Arch. Biochem. Biophys.* **141,** 766 (1970).
198. P. R. Shewry and L. Fowden, *Phytochemistry* **15,** 1981 (1976).
199. M. Marlier, G. Dardenne, and J. Casimir, *Phytochemistry* **15,** 183 (1976).
200. V. V. Ahmed and M. A. Khan, *Phytochemistry* **10,** 3339 (1971).
201. R. K. Gupta and M. Krishnamurti, *Phytochemistry* **18,** 2021 (1979).

202. M. Marlier, G. Dardenne, and J. Casimir, *Phytochemistry* **18,** 479 (1979).
203. P. S. Sampath Kumar, W. S. Murti, and T. R. Seshadri, *Tetrahedron Lett.* **45,** 4451 (1971).
204. Watt, *Dictionary of Economic Products of India* **6**(1), 322 (1892).
205. E. Premuzic, *Fortschr. Chem. Org. Naturst.* **29,** 417 (1971).
206. J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Am. Chem. Soc.* **80,** 3349 (1958).
207. H. Vanderhaege and G. Parmentier, *J. Am. Chem. Soc.* **82,** 4414 (1960).
208. D. C. N. Swindells, P. S. White, and J. A. Findlay, *Can. J. Chem.* **56,** 2491 (1978).
209. J. A. Findlay and L. Radics, *Can. J. Chem.* **58,** 579 (1980).
210. J. A. Findlay, Jia-Sen Liu, D. J. Burnell, and T. T. Nakashima, *Can. J. Chem.* **60,** 2046 (1982).
211. G. A. Cordell, *Alkaloids (N.Y.)* **16,** 432 (1977).
212. V. Snieckus *in* "Alkaloids" (Organic Chemistry Series Two) (K. Wiesner, ed.), Vol. 9, p. 191. Butterworths, London, 1976.
213. R. K. Chaudhuri, O. Sticher, and T. Winkler, *Helv. Chim. Acta* **53,** 1045 (1980).
214. R. K. Chaudhuri, O. Sticher, and T. Winkler, *Tetrahedron Lett.* **22,** 559 (1981).
215. H. Ripperger, *Phytochemistry* **17,** 1069 (1978).
216. N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.* **21,** 1321 (1968).
217. J. D. Wuest, A. M. Madonik, and D. C. Gordon, *J. Org. Chem.* **42,** 2111 (1977).
218. L. B. Davies, S. G. Greenberg, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1,* 1909 (1981).
219. K. P. Tiwara, P. K. Minocha, and M. Masood, *Pol. J. Chem.* **54,** 857 (1980).
220. M. Baoua, J. M. Bessiere, B. Pucci, and J. P. Rigaud, *Phytochemistry* **19,** 718 (1980).
221. M. M. Janot, J. Guilhem, O. Contz, G. Venera, and E. Cionga, *Ann. Pharm. Fr.* **37,** 413 (1979).
222. H. Ripperger, *Pharmazie* **34,** 577 (1979).
223. T. Imanishi, N. Yagi, and M. Hanaoka, *Tetrahedron Lett.* **22,** 667 (1981).
224. T. Momose, M. Kinoshita, and T. Imanishi, *Heterocycles* **12,** 243 (1979).
225. T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles* **3,** 627 (1975); T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *J. Org. Chem.* **41,** 2542 (1976).
226. M. Yanagita, S. Inayami, and T. Kawamata, *Tetrahedron Lett.*, 131 (1970); *ibid.*, 3007 (1970).
227. T. Sekita, S. Inayama, and Y. Iitaka, *Tetrahedron Lett.*, 135 (1970).
228. T. Kawamata and S. Inayana, *Chem. Pharm. Bull.* **19,** 643 (1971).
229. J. T. Wróbel, *Alkaloids (N.Y.)* **16,** 181 (1977).
230. Peura Pekka, *Acta Pharm. Fenn.* **91,** 175 (1982); Peura Pekka, *Acta Pharm. Fenn.* **89,** 205 (1980).
231. J. Szychowski, J. T. Wróbel, and A. Leniewski, *Can. J. Chem.* **55,** 3105 (1977).
232. R. T. Lalonde, N. Muhammad, and C. F. Wong, *J. Org. Chem.* **42,** 2113 (1977).
233. H. Wyler, M. E. Wilcox, and A. S. Dreiding, *Helv. Chim. Acta* **48,** 361 (1965); M. Piatelli, L. Minale, and R. H. Nicolaus, *Phytochemistry* **4,** 817 (1965).
234. L. Kimler, R. A. Larsen, L. Messenger, J. B. Moore, and T. J. Mabry, *Chem. Commun.*, 1329 (1971).
235. G. Buchi, H. Fliri, and R. Shapiro, *J. Org. Chem.* **42,** 2192 (1977).
236. H. Dopp and H. Musso, *Chem. Ber.* **106,** 3473 (1973).
237. W. Böll and H. König, *Justus Liebigs Ann. Chem.*, 1657 (1979).
238. T. Shono, Y. Matsumura, K. Tsubata, and J. Takata, *Chem. Lett.*, 1121 (1981).
239. E. Medina and G. Spiteller, *Chem. Ber.* **112,** 376 (1979).
240. E. Medina and G. Spiteller, *Justus Liebigs Ann. Chem.* **1981,** 538 (1981).
241. A. Nahrstedt, J.-D. Kant, and V. Wray, *Phytochemistry* **21,** 101 (1982).
242. W. Doepke and G. Fritsch, *Pharmazie* **25,** 128 (1970).

243. C. Schopf, G. Benz, F. Braun, H. Hinkel, G. Krueger, R. Rokohl, and A. Hutzler, *Justus Liebigs Ann. Chem.* **737,** 1 (1970).
244. H. C. Beyerman, L. Maat, and C. A. Moerman, *Rec. Trav. Chim. Pays-Bas* **90,** 1326 (1971).
245. I. Murakoshi, E. Kidoguchi, J. Haginiwa, S. Ohmiya, K. Higashiyama, and H. Otomasu, *Phytochemistry* **20,** 1407 (1981); I. Murakoshi, E. Kidoguchi, J. Haginiwa, S. Ohmiya, K. Higashiyama, and H. Otomasu, *Phytochemistry* **21,** 2379 (1982).
246. I, Murakoshi, E. Kidoguchi, M. Nakamura, J. Haginawa, S. Ohmiya, K. Higashiyama, and H. Otomasu, *Phytochemistry* **20,** 1725 (1981).
247. L. Nyembo, A. Goffin, C. Hootelé, and J.-C. Braekman, *Can. J. Chem.* **56,** 851 (1978).
248. S. Pilard and M. Vaultier, *Tetrahedron Lett.* **25,** 1555 (1984).
249. T. Shono, Y. Matsumura, and T. Kanazawa, *Tetrahedron Lett.* **24,** 4577 (1983).
250. G. Stork, R. M. Jacobson, and R. Levitz, *Tetrahedron Lett.* **9,** 771 (1979).
251. J. F. Archer, P. R. Boyd, W. R. Jackson, M. F. Grundon, and W. A. Khan, *J. Chem. Soc. C,* 2560 (1971).
252. K. I. Aketa, S. Terashima, and S. I. Yamada, *Chem. Pharm. Bull.* **24,** 621 (1976).
253. L. Guerrier, J. Royer, D. S. Grierson, and H.-P. Husson, *J. Am. Chem. Soc.* **105,** 7754 (1983).
254. M. F. Roberts, *Phytochemistry* **17,** 107 (1978).
255. M. F. Roberts, *Phytochemistry* **14,** 2393 (1975).
256. S. M. Colegate, P. R. Darling, and C. R. Huxtable, *Aust. J. Chem.* **32,** 2257 (1979).
257. B. W. Skelton and A. H. White, *Aust. J. Chem.* **33,** 435 (1980).
258. M. J. Schneider, F. S. Ungemach, H. P. Broquist, and T. M. Harris, *Tetrahedron* **39,** 29 (1983).
259. F. P. Guengerich, S. J. DiMari, and H. P. Broquist, *J. Am. Chem. Soc.* **95,** 2055 (1973).
260. G. W. J. Fleet, M. J. Gough, and P. W. Smith, *Tetrahedron Lett.* **25,** 1853 (1984).
261. W. Döpke, M. Bienert, A. L. Burlingame, H. K. Schnoes, P. W. Jeffs, and P. S. Farrer, *Tetrahedron Lett.*, 451 (1967).
262. Claudio Fuganti, *Alkaloids (N.Y.)* **15,** 83 (1975).
263. S. Kobayashi, Y. Imakura, H. Ishikawa, and E. Sasakawa, *Heterocycles* **14,** 751 (1980).
264a. R. G. Powell, C. R. Smith, R. V. Madrigal, *Planta Med.* **31,** 1 (1976).
264b. R. G. Powell, C. R. Smith, D. Weisleder, D. A. Muthard, and J. J. Clardy, *J. Am. Chem. Soc.* **101,** 2784 (1979).
265. J. C. Bottaro and G. A. Berchtold, *J. Org. Chem.* **45,** 1176 (1980).
266. K. Tomioka and K. Koga, *Tetrahedron Lett.* **21,** 2321 (1980).
267. J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Nat. Acad. Sci. U.S.A.* **68,** 1870 (1971).
268. B. Witkop and E. Goessinger, *Alkaloids (N.Y.)* **21,** 139 (1983).
269. M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.* **40,** 2009 (1975).
270. T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *J. Org. Chem.* **40,** 2012 (1975).
271. E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.* **97,** 430 (1975).
272. E. J. Corey, M. Petrzilka, and Y. Ueda, *Tetrahedron Lett.*, 4343 (1975).
273. E. J. Corey, M. Petrzilka, and Y. Ueda, *Helv. Chim. Acta* **60,** 2294 (1977).
274. H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1515 (1978).
275. E. J. Corey, Y. Uyada, and R. A. Ruden, *Tetrahedron Lett.*, 4347 (1975).
276. H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 4841 (1978); H. E. Schoemaker and W. N. Speckamp, *Tetrahedron* **36,** 951 (1980).
277. D. A. Evans and E. W. Thomas, *Tetrahedron Lett.*, 411 (1979).
278. J. J. Tufariello and E. J. Trybulski, *J. Org. Chem.* **39,** 3378 (1974).
279. H. L. Sleeper and W. Fenical, *J. Am. Chem. Soc.* **99,** 2367 (1977).

280. J. Itoh, S. Miyadoh, S. Takahashi, S. Amano, N. Ezaki, and Y. Yamada, *J. Antibiot.* **32,** 1089 (1979).
281. W. R. Barker, C. Callaghan, L. Hill, D. Noble, P. Acred, P. B. Harper, M. A. Sowa, and R. A. Fletton, *J. Antibiot.* **32,** 1096 (1979).
282. J. Itoh, S. Amano, Y. Ogawa, Y. Kodama, N. Esaki, and Y. Yamada, *J. Antibiot.* **33,** 377 (1980).
283. W. Z. Antkowiak and W. P. Gessner, *Tetrahedron Lett.*, 1931 (1979).
284. W.-C. Liu, S. M. Fisher, J. Scott Wells, Jr., C. S. Ricca, P. A. Principe, W. H. Trejo, D. P. Bonner, J. Z. Gougoutas, B. T. Toeplitz, and R. B. Sykes, *J. Antibiot.* **34,** 791 (1981).
285. D. Okuyama, H. Hakanura, H. Naganawa, T. Takita, H. Umezawa, and Y. Iitaka, *J. Antibiot.* **35,** 1241 (1982).
286. C.-K. Wat, A. G. McInnes, Donald G. Smith, J. L. C. Wright, and L. C. Vining, *Can. J. Chem.* **55,** 4090 (1977).
287. M. Matsumoto and H. Minato, *Tetrahedron Lett.*, 3827 (1976).
288. D. R. Williams and S.-Y. Sit, *J. Org. Chem.* **47,** 2846 (1982).
289. J. A. Findlay and L. Radics, *J. Chem. Soc., Perkin Trans. 1,* 2071 (1972).
290. P. S. White, John A. Findlay, and W. H. J. Tam, *Can. J. Chem.* **56,** 1904 (1978).
291. J. A. Findlay and F. Y. Shum, *Synth. Commun.* **3,** 355 (1973); J. A. Findlay, J. W. H. Tam, and J. Krepinsky, *Synth. Commun.* **7,** 149 (1977).
292. J. A. Findlay, *Heterocycles* **12,** 389 (1979).
293. N. N. Girotra, Z. S. Zelawski, and N. L. Wendler, *J. Chem. Soc., Chem. Commun.*, 566 (1976).
294. T. Terashima, Y. Kuroda, and Y. Kaneko, *Tetrahedron Lett.*, 2535 (1969).
295. M. Pailer and E. Haslinger, *Monatsh. Chem.* **101,** 508 (1970).
296. H. W. Gschwend, *Tetrahedron Lett.*, 2711 (1970).
297. T. Terashima, E. Idaka, Y. Kishi, and T. Goto, *J. Chem. Soc., Chem. Commun.*, 75 (1973).
298. Y. Kaneko, T. Terashima, and Y. Kuroda, *Agric. Biol. Chem.* **32,** 783 (1968).
299. M. Onda, Y. Konda, Y. Narimatsu, H. Tanaka, J. Awaya, and S. Omura, *Chem. Pharm. Bull.* **23,** 2462 (1975).
300. A. Funk and P. V. Divekar, *Can. J. Microbiol.* **5,** 317 (1959).
301. P. V. Divekar, G. Read, and L. C. Vining, *Can. J. Chem.* **45,** 1215 (1967).
302. A. G. McInnes, D. G. Smith, J. L. C. Wright, and L. C. Vining, *Can. J. Chem.* **55,** 4159 (1977).
303. A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *Can. J. Chem.* **57,** 3200 (1979).
304. M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, and T. Miyazawa, *Tetrahedron Lett.* **21,** 3395 (1980).
305. H. Hagenmaier, A. Keckeisen, H. Zähner, and W. A. König, *Liebigs Ann. Chem.* **1979,** 1494 (1979); U. Dähn, H. Hagenmaier, H. Höhne, W. A. König, G. Wolf, and H. Zähner, *Arch. Microbiol.* **107,** 143 (1976).
306. F. Reusser, *J. Antibiot.* **32,** 1186 (1979).
307. H. Hoeksema, S. A. Mizsak, C. Chidester, and L. Baczynsky, *Abstr. 18th Intersci. Conf. Antimicrob. Agents Chemother.*, #170 (1978); H. Hoeksema, C. Lewis, S. A. Mizsak, J. A. Shiley, D. R. Wait, H. A. Whaley, and G. E. Zurenko, *J. Antibiot.* **31,** 945 (1978).
308. K. V. Rao and W. P. Cullen, *Antibiot. Annu. (1959–1960),* 950 (1960).
309. E. S. Kudrina, O. L. Olkhovatova, L. I. Muravieva, G. F. Gauze, *Antibiotiki (Moscow)* **11,** 400 (1966); H. G. Brazhnikova, V. I. Ponomarenko, I. N. Kovsharova, E. B. Kruglyak, and V. V. Proshylakova, *Antibiotiki (Moscow)* **13,** 99 (1968).
310. Société des usines chimiques Rhone-Poulenc, Br. Patent 872,261 (1961); *Chem. Abstr.* **55,** 25158 (1961).

311. K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.* **85,** 2532 (1963).
312. Y.-Y. Chiu and W. N. Lipscomb, *J. Am. Chem. Soc.* **97,** 2525 (1975).
313. S. J. Gould and S. M. Weinreb, *Prog. Chem. Org. Nat. Prod.* **41,** 77 (1982).
314. F. Z. Basha, S. Hibino, D. Kim, W. E. Pye, T.-T. Wu, and S. M. Weinreb, *J. Am. Chem. Soc.* **102,** 3962 (1980); S. M. Weinreb, F. Z. Basha, S. Hibino, N. A. Khatri, D. Kim, W. E. Pye, and T.-T. Wu, *J. Am. Chem. Soc.* **104,** 536 (1982).
315. A. S. Kende, D. P. Lorah, and R. J. Boatman, *J. Am. Chem. Soc.* **103,** 1271 (1981).
316. A. Zeeck, H.-U. Hoppe, and I. Hummel, *Tetrahedron Lett.* **22,** 2357 (1981).
317. V. P. Gullo, S. B. Zimmerman, R. S. Dewey, O. Hensens, and P. J. Cassidy, *J. Antibiot.* **35,** 1705 (1982).

This Page Intentionally Left Blank

— CHAPTER 4 —

BENZOPHENANTHRIDINE ALKALOIDS

V. ŠIMÁNEK

Institute of Chemistry
Palacký University
Olomouc, Czechoslovakia

I. Introduction

The benzo[*c*]phenanthridine alkaloids, commonly referred to as benzophenanthridine alkaloids, were discussed in this series in 1970 (*1*) and in 1979 (*2*) in chapters on "Papaveraceae Alkaloids" by Šantavý. The reviews by Mester, on the occurrence of benzophenanthridine alkaloids in Rutaceae, cover the periods 1960–1973 (*3*) and 1973–1976 (*4*). Recently, a list of all the benzophenanthridine alkaloids and some of their synthetic derivatives has been published (*5*). This compilation includes their occurrence and spectral data. A series of

THE ALKALOIDS, VOL. 26

Annual Reports included these alkaloids in the chapters on "β-Phenylethylamines and the Isoquinoline Alkaloids" by Bentley, beginning in 1971 (*6*). The last review in this series covers the literature up to June 1982. There are several books on isoquinoline alkaloids available, where chapters on benzophenanthridine alkaloids, their occurrence, and their general chemistry are included (*7–10*). Two reviews were devoted exclusively to benzophenanthridine alkaloids (*11,12*). The methods of synthesis of benzophenanthridines have been summarized (*13,14*). The biological activity of some benzophenanthridine alkaloids also has been reviewed (*15–18*).

The past few years have seen a tremendous growth in interest in benzophenanthridine alkaloids, and studies regarding chemistry and biological activity were intensified. Improved methods for the detection and chromatographic separation of quaternary benzophenanthridines were developed, new alkaloids were isolated, and their structures were assigned. There has been an increasing reliance on spectral data—mainly ^{1}H- and ^{13}C-NMR spectra. X-Ray diffraction analyses of (+)-chelidonine (**1**), (+)-corynoline (**9**), and (+)-14-epicorynoline (**18**) were reported. Several total syntheses of different types of benzophenanthridines were accomplished. The knowledge of the conformation and chemical reactivity of benzophenanthridine alkaloids helps in better understanding the mode of action and the biosynthesis of these compounds. Progress has been made in determining the biosynthetic pathways of chelidonine, sanguinarine (**52**), and macarpine (**63**).

This chapter presents a comprehensive survey of the occurrence, chemistry, biochemistry, and biological activity of benzophenanthridine alkaloids. The systematic numbering for benzophenanthridines and the accepted lettering for each individual ring are given for chelidonine to serve as an example (*12*). The benzophenanthridine alkaloids can be classified into the following six groups on the basis of structures and properties:

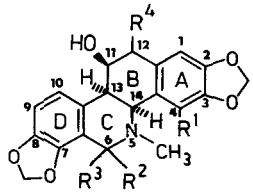
1. Hexahydrobenzophenanthridine alkaloids
2. Dihydrobenzophenanthridine alkaloids
3. *N*-Demethylbenzophenanthridine alkaloids
4. Quaternary benzophenanthridine alkaloids
5. Dimeric dihydrobenzophenanthridine alkaloids
6. Secobenzophenanthridine alkaloids

The group of hexahydrobenzophenanthridine alkaloids is subdivided into chelidonine and corynoline alkaloids, which have an additional 13-methyl group at the B/C ring junction. The largest group is represented with the alkaloids dihydro substituted at C-6. It is assumed that dihydrobenzophenanthridine alkaloids substituted at C-6 with oxygen or carbon and obtained by nucleophilic addition to the iminium double bond are artefacts. A third group comprises seven N-demethylated aromatic benzophenanthridines. The quaternary benzophe-

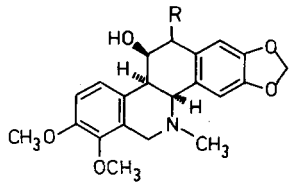
nanthridine group belongs to the most intensively studied among isoquinoline alkaloids. Some of these alkaloids possess a wide range of biological activity, including antifungal, antibacterial, antiinflammatory, and antitumor effects. Chelerythrine (**50**) and sanguinarine (**52**) find application in human medicine. The dimeric bases and alkaloids with an open C ring form the last two groups. The group of secobenzophenanthridines does not include alkaloids obtained by opening the B ring of corynoline (**9**).

II. Occurrence of Benzophenanthridine Alkaloids

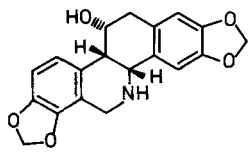
The benzophenanthridine alkaloids are known to exist in five plant families, namely, the Fumariaceae (genera *Corydalis, Dicentra,* and *Fumaria*), the Pa-



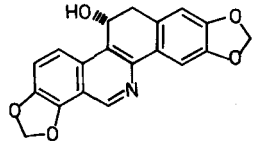
1 $R^1 = R^2 = R^3 = R^4 = H$ CHELIDONINE
2 $R^1 = R^4 = H$, $R^2 + R^3 = O$ OXOCHELIDONINE
4 $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$ 4-METHOXYCHELIDONINE
5 $R^1 = R^2 = R^3 = H$, $R^4 =$ ⁱⁱⁱⁱOH CHELAMINE



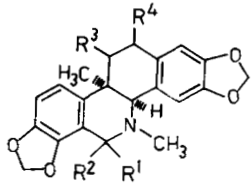
6 R = H HOMOCHELIDONINE
7 R = ⁱⁱⁱⁱOH CHELAMIDINE



3 (-)-NORCHELIDONINE



8 (+)-LUGUINE



9 $R^1=R^2=R^4=H$; $R^3=\alpha OH$ CORYNOLINE

10 $R^1=R^2=R^4=H$; $R^3=\alpha OCOCH_3$ O-ACETYLCORYNOLINE

11 $R^1=R^2=R^4=H$; $R^3=\alpha SO_3H$ (+)-CORYNOLINE 11-O-SULFATE

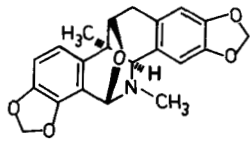
13 $R^1+R^2=O$; $R^3=\alpha OH$; $R^4=H$ 6-OXOCORYNOLINE

14 $R^1=R^2=H$; $R^3=\alpha OH$; $R^4=\beta OH$ 12-HYDROXYCORYNOLINE

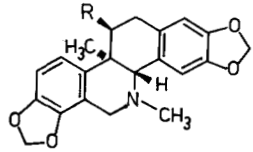
15 $R^1=CH_2OH$; $R^2=R^4=H$; $R^3=\alpha OH$ CORYNOLAMINE

16 $R^1=CH_2COCH_3$; $R^2=R^4=H$; $R^3=\alpha OCOCH_3$ CONSPERINE

17 $R^1=R^2=R^4=H$; $R^3=\beta OH$ 11-EPICORYNOLINE

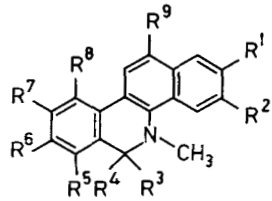


12 CORYNOLOXINE



18 R=OH (+)-14-EPICORYNOLINE

19 $R=OCOCH_3$ (+)-11-O-ACETYL-14-EPICORYNOLINE



20 $R^1 + R^2{=}OCH_2O$; $R^3{=}R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ Dihydrochelerythrine

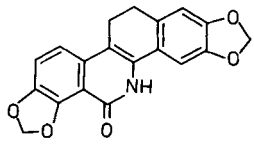
21 $R^1 + R^2{=}OCH_2O$; $R^3+R^4{=}O$; $R^5{=}R^6{=}OCH_3$; $R^7{=}R^8{=}R^9{=}H$ Oxochelerythrine

22 $R^1 + R^2{=}OCH_2O$; $R^3{=}OH$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ 6-Hydroxydihydrochelerythrine

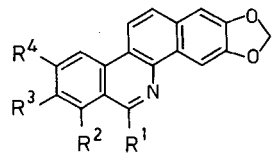
23 $R^1 + R^2{=}OCH_2O$; $R^3{=}OCH_3$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ 6-Methoxydihydrochelerythrine

24 $R^1 + R^2{=}OCH_2O$; $R^3{=}CH_2OH$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ Bocconoline

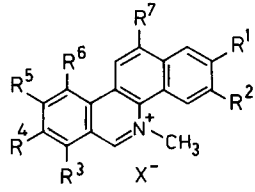
25 $R^1 + R^2{=}OCH_2O$; $R^3{=}CH_2COCH_3$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ 6-Acetonyldihydrochelerythrine
26 $R^1 + R^2{=}OCH_2O$; $R^3{=}CH_2COCH_2CH_3$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}R^6{=}OCH_3$ 6-(2'-Ketobutane)dihydrochelerythrine
27 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}R^4{=}R^7{=}R^8{=}R^9{=}H$ Dihydrosanguinarine
28 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3 + R^4{=}O$; $R^7{=}R^8{=}R^9{=}H$ Oxosanguinarine
30 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}OCH_3$; $R^4{=}R^7{=}R^8{=}R^9{=}H$ 6-Methoxydihydrosanguinarine
31 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3 + R^4{=}NH$; $R^7{=}R^8{=}R^9{=}H$ 6-Iminosanguinarine
32 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}CH_2OH$; $R^4{=}R^7{=}R^8{=}R^9{=}H$ 6-Hydroxymethyldihydrosanguinarine
33 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}CH_2COCH_3$; $R^4{=}R^7{=}R^8{=}R^9{=}H$ 6-Acetonyldihydrosanguinarine
34 $R^1 + R^2{=}OCH_2O$; $R^3{=}CH_2OH$; $R^4{=}R^7{=}R^8{=}R^9{=}H$; $R^5{=}OH$; $R^6{=}OCH_3$ 6-Hydroxymethyldihydrofagaridine
35 $R^1 + R^2{=}OCH_2O$; $R^3{=}R^4{=}R^5{=}R^8{=}R^9{=}H$; $R^6{=}R^7{=}OCH_3$ Dihydronitidine
36 $R^1 + R^2{=}OCH_2O$; $R^3 + R^4{=}O$; $R^5{=}R^8{=}R^9{=}H$; $R^6{=}R^7{=}OCH_3$ Oxonitidine
37 $R^1 + R^2{=}R^6 + R^7{=}OCH_2O$; $R^3{=}R^4{=}R^5{=}R^8{=}R^9{=}H$ Dihydroavicine
38 $R^1 + R^2{=}OCH_2O$; $R^3{=}R^4{=}R^7{=}R^9{=}H$; $R^5{=}R^6{=}R^8{=}OCH_3$ Dihydrochelilutine
39 $R^1{=}R^2{=}R^5{=}R^6{=}R^8{=}OCH_3$; $R^3{=}R^4{=}R^7{=}R^9{=}H$ Dihydrosanguilutine
40 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}R^4{=}R^7{=}R^9{=}H$; $R^8{=}OCH_3$ Dihydrochelirubine
41 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3 + R^4{=}O$; $R^7{=}R^9{=}H$; $R^8{=}OCH_3$ Oxochelirubine
42 $R^1 + R^2{=}R^5 + R^6{=}OCH_2O$; $R^3{=}R^4{=}R^7{=}H$; $R^8{=}R^9{=}OCH_3$ Dihydromacarpine



29 N-DEMETHYL-11,12-DIHYDROOXOSANGUINARINE



43 $R^1{=}R^4{=}H$; $R^2{=}OCH_3$; $R^3{=}OH$ DECARINE
44 $R^1{=}R^4{=}H$; $R^2{=}OH$; $R^3{=}OCH_3$ ISODECARINE
45 $R^1{=}R^4{=}H$; $R^2{=}R^3{=}OCH_3$ NORCHELERYTHRINE
46 $R^1{=}R^4{=}H$; $R^2 + R^3{=}OCH_2O$ NORSANGUINARINE
47 $R^1{=}OCH_3$; $R^2 + R^3{=}OCH_2O$; $R^4{=}H$ PANCORINE
48 $R^1{=}R^2{=}H$; $R^3{=}R^4{=}OCH_3$ NORNITIDINE
49 $R^1{=}R^2{=}H$; $R^3 + R^4{=}OCH_2O$ DES-N-METHYLAVICINE



50 R^1 + R^2=OCH_2O; R^3=R^4=OCH_3; R^5=R^6=R^7=H Chelerythrine
51 R^1 + R^2=OCH_2O; R^3=R^4=OCH_3; R^5=R^6=H; R^7=OC_2H_5 12-Ethoxychelerythrine
52 R^1 + R^2=R^3+R^4=OCH_2O; R^5=R^6=R^7=H Sanguinarine
53 R^1 + R^2=OCH_2O; R^3=R^4=OH; R^5=R^6=R^7=H 7,8-Demethylenesanguinarine
54 R^1 + R^2=OCH_2O; R^3=OH; R^4=OCH_3; R^5=R^6=R^7=H Fagaridine
55 R^1;R^2;R^3;R^4=3xOCH_3; 1xOH; R^5=R^6=R^7=H Punctatine
56 R^1 + R^2=OCH_2O; R^3=R^6=R^7=H; R^4=R^5=OCH_3 Nitidine
57 R^1 + R^2=R^4+R^5=OCH_2O; R^3=R^6=R^7=H Avicine
58 R^1=OH; R^2=R^4=R^5=OCH_3; R^3=R^6=R^7=H Fagaronine
59 R^1=R^2=R^6=OCH_3; R^3+R^4=OCH_2O; R^5=R^7=H Sanguirubine
60 R^1=R^2=R^3=R^4=R^6=OCH_3; R^5=R^7=H Sanguilutine
61 R^1 + R^2=R^3+R^4=OCH_2O; R^5=R^7=H; R^6=OCH_3 Chelirubine
62 R^1 + R^2=OCH_2O; R^3=R^4=R^6=OCH_3; R^5=R^7=H Chelilutine
63 R^1 + R^2=R^3+R^4=OCH_2O; R^5=H; R^6=R^7=OCH_3 Macarpine

paveraceae (several genera) and the Rutaceae (in the taxonomically closely related genera *Fagara* and *Zanthoxylum,* and in the genus *Toddalia*). In the Caprifoliaceae (genus *Symphoricarpos*) and Meliaceae (genus *Xylocarpus*), the occurrence of these alkaloids is restricted to chelidonine (**1**) and dihydrochelerythrine (**20**). Table I shows the genera of the plant families (according to Engler's classification) producing benzophenanthridine alkaloids. The occurrence of benzophenanthridine alkaloids in the Fumariaceae and Papaveraceae families has been reviewed up till 1977 (*1,2*), and in the Rutaceae up till 1976 (*3,4*). In the Fumariaceae and Papaveraceae these alkaloids occur together with several other types of isoquinoline alkaloids, in the Rutaceae with some isoquinoline and furoquinoline alkaloids.

In Table II, 70 naturally occurring benzophenanthridines have been listed. Nineteen of them are new alkaloids isolated during the past decade. With the exception of chelidonine (**1**), corynoline (**9**), dihydrochelerythrine (**20**), chelerythrine (**50**), and sanguinarine (**52**), the benzophenanthridines are mostly isolated as minor alkaloids. The 6-hydroxy (**22**), 6-methoxy (**23,30**), and 6-imino (**31**) derivatives of dihydrochelerythrine and dihydrosanguinarine (**27**) are probably artefacts arising during the isolation procedure (*30,76*). They may be easily prepared from naturally occurring quaternary alkaloids by addition of the nucleophile to the iminium bond (*77,78*).

TABLE I
PLANT GENERA CONTAINING BENZOPHENANTHRIDINE ALKALOIDS WITH NUMBER OF SPECIES INVESTIGATED

Family	Genera (number)
Caprifoliaceae	*Symphoricarpos* (1)
Fumariaceae	*Corydalis* (24)
	Dicentra (1)
	Fumaria (6)
Meliaceae	*Xylocarpus* (1)
Papaveraceae	*Argemone* (15)
	Chelidonium (2)
	Dicranostigma (3)
	Eschscholtzia (5)
	Glaucium (10)
	Hunnemannia (1)
	Hypecoum (4)
	Macleaya (Bocconia) (6)
	Meconopsis (1)
	Papaver (44)
	Platystemon (1)
	Pteridophyllum (1)
	Romneya (1)
	Sanguinaria (1)
	Stylomecon (1)
	Stylophorum (1)
Rutaceae	*Fagara* (23)
	Toddalia (2)
	Zanthoxylum (33)

It is difficult to assess the taxonomic significance of benzophenanthridine alkaloids (*79*). However, for certain genera the occurrence of some groups of these alkaloids is characteristic. Hexahydro-13-methylbenzophenanthridines occur only in the genus *Corydalis* (Fumariaceae). The 8,9-oxygenated alkaloids, i.e., nitidine (**56**), avicine (**57**), and fagaronine (**58**) derivatives and the group of secobenzophenanthridines are found in the Rutaceae. Chelerythrine (**50**) and sanguinarine (**52**) and their dihydro derivatives **20** and **27** are the most widely distributed benzophenanthridine alkaloids in the Fumariaceae, Papaveraceae, and Rutaceae families.

The effects of the cultivation and environmental factors on the quantity of benzophenanthridine alkaloids have been studied in *Chelidonium majus* (*80,81*). This plant is a source of chelerythrine and sanguinarine.

TABLE II
NATURALLY OCCURRING BENZOPHENANTHRIDINES IN PLANTS

Alkaloid[a]	Occurrence
Hexahydrobenzophenanthridines	
Chelidonine (**1**)	Caprifoliaceae
(+)-, (−)-isomer, racemate	*Symphoricarpos albus* (*19*)
	Fumariaceae (*2*)
	Papaveraceae (*1,2*)
	Glaucium corniculatum ssp. *refractum* (*20*)
	G. vitellinum Boiss. et Buhse (*21*)
Oxochelidonine (**2**)	Papaveraceae (*1*)
(−)-Norchelidonine (**3**)	Papaveraceae (*1,2*)
	Glaucium flavum var. *vestitum* (*22*)
4-Methoxychelidonine (**4**)	Papaveraceae (*1*)
Chelamine (12-hydroxychelidonine) (**5**)	Papaveraceae (*1*)
Homochelidonine (**6**)	Papaveraceae (*1*)
Chelamidine (12-hydroxyhomochelidonine) (**7**)	Papaveraceae (*1*)
(+)-Luguine (**8**)	Papaveraceae
	Glaucium flavum Cr. var. *vestitum* (*22*)
Corynoline (**9**)	Fumariaceae (*2*)
(+)-isomer, racemate	*Corydalis conspersa* (*23*)
	C. incisa (Thunb.) Pers. (*24*)
	C. lineariodes (*25*)
	C. melanochlora (*25*)
	C. mucronifera (*25*)
	C. stricta Steph. (*25*)
O-Acetylcorynoline (**10**)	Fumariaceae (*2*)
	Corydalis conspersa (*23*)
	C. lineariodes (*25*)
	C. melanochlora (*25*)
	C. mucronifera (*25*)
	C. stricta Steph. (*25*)
(+)-Corynoline 11-*O*-sulfate (**11**)	Fumariaceae
	Corydalis incisa (Thunb.) Pers. (*26*)
Corynoloxine (**12**)	Fumariaceae (*2*)
	Corydalis conspersa (*23*)
6-Oxocorynoline (**13**)	Fumariaceae (*2*)
12-Hydroxycorynoline (**14**)	Fumariaceae (*2*)
Corynolamine (**15**)	Fumariaceae
	Corydalis incisia (Thunb.) Pers. (*27*)
Consperine (6-acetonyl-11-*O*-acetylcorynoline) (**16**)	Fumariaceae
	Corydalis conspersa (*23*)
11-Epicorynoline (**17**)	Fumariaceae (*2*)
(+)-14-Epicorynoline (**18**)	Fumariaceae (*2*)
(+)-11-*O*-Acetyl-14-epicorynoline (**19**)	Fumariaceae (*2*)

TABLE II (*Continued*)

Alkaloid[a]	Occurrence
Dihydrobenzophenanthridines	
Dihydrochelerythrine (**20**)	Fumariaceae
	Corydalis ledebouriana (*28*)
	Papaveraceae (*1,2*)
	Eschscholtzia californica Cham. (*29*)
	Glaucium flavum Cr. var. *vestitum* (*30*)
	G. vitellinum Boiss, et Buhse (*21*)
	Meliaceae
	Xylocarpus granatum (*31*)
	Rutaceae (*3,4*)
	Fagara angolensis (*32*)
	F. chalybea Engl. (*31*)
	F. holstii (*31*)
	Toddalia asiatica Lamk. (*33*)
	Zanthoxylum coriaceum (*34*)
Oxochelerythrine (**21**)	Rutaceae
	Zanthoxylum arnottianum Maxim (*67*)
6-Hydroxydihydrochelerythrine (**22**)	Rutaceae
	Toddalia asiatica Lamk. (*35*)
6-Methoxydihydrochelerythrine (**23**)	Papaveraceae (*2*)
	Rutaceae (*3*)
	Toddalia asiatica Lamk. (*36*)
Bocconoline (**24**)	Papveraceae (*2*)
	Chelidonium japonicum Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*)
	Macleaya cordata (*38*)
	Rutaceae
	Fagara mayu (Bert. ex Hook. et Arn.) Engler (*39*)
6-Acetonyldihydrochelerythrine (**25**)	Rutaceae (*4*)
	Fagara ailanthoides (Sieb. et Zucc.) (*40*)
	Toddalia asiatica Lamk. (*33*)
6-(2′-Ketobutane) dihydrochelerythrine (**26**)	Rutaceae
	Fagara mayu (Bert. ex Hook. et Arn.) Engler (*39,41*)
Dihydrosanguinarine (**27**)	Fumariaceae (*2*)
	Fumaria parviflora Lam (*42*)
	F. vaillantii Loisl. (*43*)
	Corydalis gigantea Trautv. et Mey (*44*)
	C. ledebouriana (*28*)
	C. meifolia Wall. (*45*)
	C. paniculigera Rgl. (*46*)
	C. remota Fisch. (*44*)
	C. vaginans Royle (*44*)
	Papaveraceae (*1,2*)
	Eschscholtzia californica Cham. (*29*)

(*continued*)

TABLE II (*Continued*)

Alkaloid[a]	Occurrence
Dihydrosanguinarine (**27**)	*Glaucium flavum* Cr. var. *vestitum* (*30*) *G. vitellinum* Boiss. et Buhse (*21*) *Pteridophyllum racemosum* Sieb. et Zucc. (*71*) Rutaceae (*3,4*) *Fagara angolensis* (*32*)
Oxosanguinarine (**28**)	Fumariaceae (*1,2*) *Corydalis ledebouriana* (*28*) *C. paniculigera* Rgl. (*46*) *Fumaria indica* (Haussk.) Pugsley (*47*) *F. parviflora* Lam. (*42,48*) *F. vaillantii* Loisl. (*43*) Papaveraceae (*1,2*) *Hypecoum procumbens* L. (*49*) *Pteridophyllum racemosum* Sieb. et Zucc. (*71*)
N-Demethyl-11,12-dihydrooxosanguinarine (**29**)	Papaveraceae (*2*)
6-Methoxydihydrosanguinarine (**30**) (−)-isomer, racemate	Fumariaceae *Fumaria indica* (Haussk.) Puglsley (*47*) *F. vaillantii* Loisl. (*43*) Papaveraceae (*2*) *Hypecoum procumbens* L. (*49*)
6-Iminosanguinarine (**31**)	Papaveraceae *Glaucium flavum* Cr. var. *vestitum* (*30*)
6-Hydroxymethyldihydrosanguinarine (**32**)	Papaveraceae *Chelidonium japonicum* Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*)
6-Acetonyldihydrosanguinarine (**33**)	Fumariaceae *Fumaria vaillantii* Loisl. (*43*) Papaveraceae (*2*) *Glaucium flavum* Cr. var. *vestitum* (*30*) *Hypecoum procumbens* L. (*49*)
6-Hydroxymethyldihydrofagaridine (**34**)	Rutaceae *Zanthoxylum microcarpum* Griseb. (*50*)
Dihydronitidine (**35**)	Rutaceae (*3,4*) *Fagara angolensis* (*32*) *Toddalia asiatica* Lamk. (*36*)
Oxonitidine (**36**)	Rutaceae (*3,4*) *Fagara ailanthoides* (Sieb. et Zucc.) (*40*) *Zanthoxylum nitidum* (*72*)
Dihydroavicine (**37**)	Rutaceae (*3,4*) *Toddalia asiatica* Lamk. (*36*)
Dihydrochelilutine (**38**)	Papaveraceae (*2*)
Dihydrosanguilutine (**39**)	Papaveraceae (*2*)

TABLE II (*Continued*)

Alkaloid[a]	Occurrence
Dihydrochelirubine (**40**)	Papaveraceae (*2*) *Eschscholtzia californica* Cham. (*29*)
Oxochelirubine (**41**)	Papaveraceae *Glaucium flavum* Cr. var. *vestitum* (*30*)
Dihydromacarpine (**42**)	Papaveraceae (*2*) *Eschscholtzia californica* Cham. (*29*)
N-Demethylbenzophenanthridines	
Decarine (**43**)	Rutaceae (*3,4*) *Zanthoxylum microcarpum* Griseb. (*50*) *Z. viride* Waterm. (*51*)
Isodecarine (**44**)	Rutaceae *Zanthoxylum decaryi* H. Perr. (*73*)
Norchelerythrine (**45**)	Papaveraceae (*2*) *Chelidonium japonicum* Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*) Rutaceae *Fagara ailanthoides* (Sieb. et Zucc.) (*40*) *Toddalia asiatica* Lamk. (*74*)
Norsanguinarine (**46**)	Fumariaceae *Fumaria vaillantii* Loisl. (*43*) Papaveraceae (*2*) *Chelidonium japonicum* Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*) *Glaucium flavum* Cr. var. *vestitum* (*22*) *Hypecoum procumbens* L. (*49*) *Papaver somniferum* L. (*52*) *Pteridophyllum racemosum* Sieb. et Zucc. (*71*)
Pancorine (**47**)	Fumariaceae *Corydalis paniculigera* Rgl. (*53*)
Nornitidine (**48**)	Rutaceae *Zanthoxylum microcarpum* Griseb. (*50*)
Des-*N*-methylavicine (**49**)	Rutaceae *Zanthoxylum cuspidatum* (*54*)
Quaternary benzophenanthridines	
Chelerythrine (**50**)	Fumariaceae (*1,2*) *Corydalis ophiocarpa* Hook. et Thoms. (*55,56*) *Fumaria schramii* Pugsley (*57*) Papaveraceae (*1,2*) *Chelidonium japonicum* Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*) *Dicranostigma franchetianum* Fedde (*58*) *D. lactucoides* Hook. et Thoms. (*58*) *D. leptopodum* (Maxim.) Fedde (*58*)

(*continued*)

TABLE II (*Continued*)

Alkaloid[a]	Occurrence
Quaternary benzophenanthridines	
Chelerythrine (**50**)	*Stylophorum diphyllum* (Michx.) Nutt. (*70*)
	Rutaceae (*3,4*)
	Fagara chalybea Engl. (*31*)
	F. mayu (Bert. ex Hook. et Arn.) Engler (*39*)
	F. tessmanii (*59*)
	F. zanthoxyloides Lam. (*60*)
	Zanthoxylum coriaceum (*34*)
	Z. fagara (L.) Sarg. (*61*)
	Z. monophyllum (*61*)
	Z. williamsii (*61*)
12-Ethoxychelerythrine (**51**)	Rutaceae
	Zanthoxylum nitidum (*72*)
Sanguinarine (**52**)	Fumariaceae (*1,2*)
	Corydalis gigantea Trautv. et Mey (*44*)
	C. marshalliana Pers. (*44*)
	C. ophiocarpa Hook. et Thoms. (*55,62*)
	C. paniculigera Rgl. (*46*)
	C. remota Fisch. (*44*)
	C. rosea Leych. (*44*)
	C. vaginans Royle (*44*)
	Fumaria parviflora Lam. (*42,48*)
	F. schramii Pugsley (*57*)
	Papaveraceae (*1,2*)
	Chelidonium japonicum Thunb. (syn. *Hylomecon vernalis* Maxim.) (*37*)
	Dicranostigma franchetianum Fedde (*58*)
	D. lactucoides Hook. f. et Thoms. (*58*)
	D. leptopodum (Maxim.) Fedde (*58*)
	Pteridophyllum racemosum Sieb et. Zucc. (*71*)
7,8-Demethylenesanguinarine (**53**)	Papaveraceae
	Macleaya cordata Mil. R. Br. (*63*)
	M. microcarpa Maxim. Fedde (*63*)
Fagaridine (**54**)	Rutaceae (*4*)
	Fagara tessmanii (*59*)
Punctatine (**55**)	Rutaceae
	Zanthoxylum punctatum Vahl. (*75*)
Nitidine (**56**)	Rutaceae (*3,4*)
	Fagara chalybea Engl. (*31*)
	F. tessmanii (*59*)
	Zanthoxylum bouetense (*64*)
	Z. fagara (L.) Sarg. (*61*)

TABLE II (*Continued*)

Alkaloid[a]	Occurrence
Nitidine (**56**)	*Z. monophyllum* (*61*) *Z. williamsii* (*61*) *Z. cuspidatum* Champ. (*Fagara cuspidata* Engl.) (*54*)
Avicine (**57**)	Rutaceae (*3*)
Fagaronine (**58**)	Rutaceae (*3*)
Sanguirubine (**59**)	Papaveraceae (*1,2*)
Sanguilutine (**60**)	Papaveraceae (*1,2*)
Chelirubine (**61**)	Fumariaceae (*1*) Papaveraceae (*1,2*) *Dicranostigma franchetianum* Fedde (*58*) *D. lactucoides* Hook. f. et Thoms. (*58*)) *D. leptopodum* (Maxim.) Fedde (*58*) *Papaver oreophillum* (*65*)
Chelilutine (**62**)	Papaveraceae (*1,2*) *Pteridophyllum racemosum* Sieb. et Zucc. (*71*) Rutaceae (*3*)
Macarpine (**63**)	Papaveraceae (*1*)
Dimeric benzophenanthridines	
Chelerythridimerine[1,3-bis(6-hydrochelerythrinyl)acetone] (**64**)	Papaveraceae (*2*)
Sanguidimerine [(+)-1,3-bis(6-hydrosanguinarinyl)acetone] (**65**) (meso isomer = chelidimerine)	Papaveraceae (*2*)
Toddaldimerine[1,3-(6-hydrochelerythrinyl-6-hydro-*N*-norchelerythrinyl)acetone] (**66**)	Rutaceae *Toddalia asiatica* Lamk. (*33*)
Secobenzophenanthridines	
Arnottianamide (**67**)	Rutaceae (*2*) *Fagara chalybea* Engl. (*31*) *Toddalia asiatica* Lamk. (*35*) *Zanthoxylum arnottianum* Maxim. (*66,67*) *Z. cuspidatum* Champ. (*Fagara cuspidata* Engl.) (*66,67*)
Iwamide (**68**)	Rutaceae *Zanthoxylum arnottianum* Maxim. (**67**)
Isoarnottianamide (**69**)	Rutaceae (*2*) *Zanthoxylum cuspidatum* Champ. (*Fagara cuspidata* Engl.) (*66*)
Integriamide (**70**)	Rutaceae *Zanthoxylum integrifoliolum* (Merr.) [*Fagara integrifoliola* (Merr.)] (*68,69*))

(*continued*)

TABLE II (*Continued*)

ADDENDUM TO TABLE II

Alkaloid[a]	Occurrence
(+)-Chelidonine (**1**)	Papaveraceae *Glaucium squamigerum* Kar. et Kir. (*216*)
Dihydrochelerythrine (**20**)	Rutaceae *Zanthoxylum spinosum* Swingle (*210*) *Z. tessmannii* (*211*)
6-Methoxydihydrochelerythrine (**23**)	Rutaceae *Zanthoxylum rubescens* Planch. ex Oliv. (*212*) *Z. tessmannii* (*211*)
Dihydrosanguinarine (**27**)	Fumariaceae *Corydalis bulbosa* (L.) DC. (*213*) Papaveraceae *Dicentra peregrina* Rudolph (*214*) *D. spectabilis* L. (*214*)
Dihydronitidine (**35**)	Rutaceae *Zanthoxylum tessmannii* (*211*)
Norchelerythrine (**45**)	Rutaceae *Zanthoxylum spinosum* Swingle (*210*)
Norsanguinarine (**46**)	Fumariaceae *Fumaria indica* (Haussk) Pugsley (*215*)
Chelerythrine (**50**)	Papaveraceae *Dicentra peregrina* Rudolph (*214*) *Glaucium squamigerum* Kar. ET Kir. (*216*) Rutaceae *Zanthoxylum spinosum* Swingle (*210*)
Sanguinarine (**52**)	Papaveraceae *Dicentra peregrina* Rudolph (*214*) *D. spectabilis* L. (*214*) *Glaucium squamigerum* Kar. et Kir. (*216*)
Nitidine (**56**)	Rutaceae *Zanthoxylum rubescens* Planch. ex Oliv. (*212*) *Z. tessmannii* (*211*)
Chelirubine (**61**)	Papaveraceae *Glaucium squamigerum* Kar. ET Kir. (*216*)

[a] In alkaloids known under two names, preference is given to the most common name: (±)-chelidonine (diphylline) (**1**), (+)-14-epicorynoline [(+)-isocorynoline] (**18**), 6-methoxydihydrochelerythrine (angoline) (**23**), dihydrochelirubine (dihydrobocconine) (**40**), and chelirubine (bocconine) (**61**). Only the prefix oxo is used, e.g., 6-oxocorynoline (**13**) even though in the literature also the name 6-oxycorynoline is encountered.

III. Isolation and Analytical Methods

The nonquaternary benzophenanthridine alkaloids are isolated from plant material by the classical extraction procedure and separated mostly by column chromatography. Preparative scale liquid chromatography (LC) is used to separate the crude hexane extract of *Fagara chalybea* barks (*82*). Thus dihydrochelerythrine (**20**) is obtained. The preparative LC method brings about a great reduction of time and minimizes the risk of sample deterioration on the column. Compared to the LC method, the relative amount of dihydrochelerythrine obtained by conventional chromatography is smaller. On the open column, the dihydro analog is oxidized to quaternary chelerythrine (**50**). The influence of the isolation procedure on the composition of benzophenanthridine alkaloids from roots of *Glaucium flavum* has been reported (*30*). When dichloromethane was used to extract plant material moistened with ammonia, the extract yielded dihydrochelerythrine, dihydrosanguinarine (**27**), 6-iminosanguinarine (**31**), 6-acetonyldihydrosanguinarine (**33**), and oxochelirubine (**41**). Extraction of root material with hot methanol afforded, in addition to the alkaloids **20, 27, 33,** and **41,** the new compounds 6-formylmethyldihydrochelerythrine and bocconoline (6-hydroxymethyldihydrochelerythrine, **24**). In this plant material, 6-iminosanguinarine (**31**) could not be detected.

To isolate quaternary benzophenanthridine alkaloids, use is made of their reaction with hydroxide ions (*77*). After alkalization, the alkaloids of the chelerythrine group form pseudobases that pass into nonpolar organic solvents together with other tertiary bases. The benzophenanthridine alkaloids can be separated as pseudocyanides (*83,84*). The separation of quaternary benzophenanthridine alkaloids from each other is, however, rather difficult. The methods based on the crystallization of salts fail when more complex mixtures are to be separated (*85,86*). Thus it is also not possible to isolate the minor quaternary benzophenanthridine alkaloids. Slavík and Slavíková (*87*) elaborated an effective chromatographic method to separate quaternary acetates on a column of acidic alumina. Besides the perfectly separated chelerythrine (**50**) and sanguinarine (**52**), it is possible to isolate sanguirubine (**59**), sanguilutine (**60**), chelirubine (**61**), and chelilutine (**62**) (*87,88*).

The alkaloids of the nitidine group undergo disproportionation already in an alkaline medium (*89*), but they can be obtained directly from concentrated crude extracts—on extraction with methanol in the form of pseudocyanides (*61,89,90*), and on extraction with petroleum ether and chloroform as chlorides (*91–93*). The mixture of chlorides [often containing chelerythrine] has been separated further by column chromatography on alumina (*91*).

The quantitative determination of benzophenanthridine alkaloids was carried out to analyze the content of these alkaloids in *Herba chelidonii, Radix chelidonii,* and in tinctures of *Chelidonium majus* L. Scholz *et al.* (*94*) determined

chelidonine (**1**), chelerythrine (**50**), and sanguinarine (**52**) by photometry of the eluates from TLC separation zones. Freytag (*95*) developed a rapid method of quantitative determination of chelidonine, chelerythrine, and sanguinarine by direct remission measuring of HPTLC plates. This method eliminates the errors made during elution. Walterová *et al.* (*96*) used capillary isotachophoresis for qualitative and quantitative analyses of quaternary benzophenanthridine alkaloids. The method utilizes the different electromigration properties of quaternary ions for a quick and direct determination of chelerythrine and sanguinarine in extracts and crude fractions in the presence of quaternary protoberberines and tertiary bases (Fig. 1).

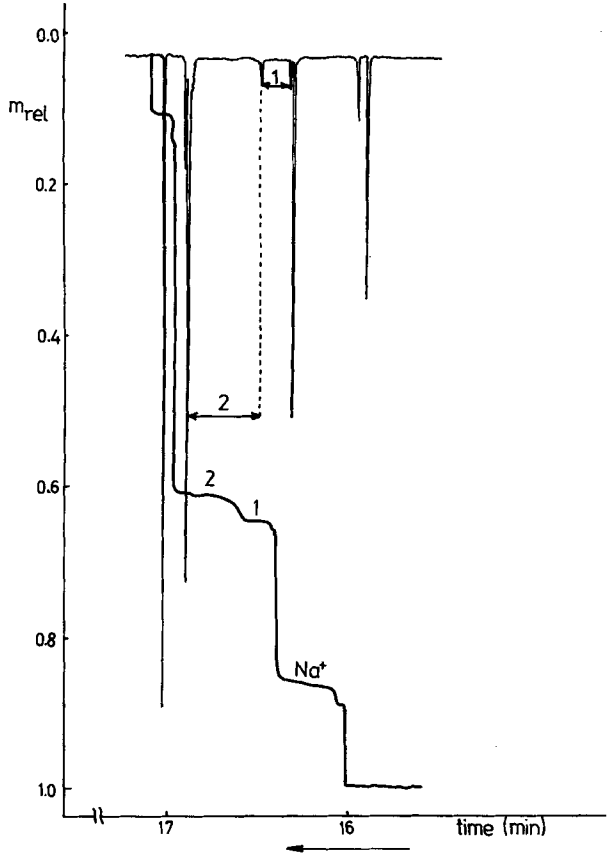


FIG. 1. Isotachopherogram of the quaternary benzophenanthridine fraction from *Chelidonium majus*. (1) Sanguinarine (**52**); (2) chelerythrine (**50**); m_{rel}, relative effective mobility.

IV. Stereochemistry and Spectral Characteristics

A. X-Ray Crystallography

X-Ray analysis of (+)-chelidonine (**1**) *p*-bromobenzoate revealed an equatorial *p*-bromobenzoxy group at C-11 and an axial *N*-CH_3 group (*97*). It confirmed the cis-B/C ring junction. In contrast to the one conformation of unesterified chelidonine in solution (*98*), two crystal forms of **1** *p*-bromobenzoate with B/C half-chair–twist-half-chair and B/C twist-half-chair–half-chair conformations have been established (*97*). The absolute configuration of (+)-chelidonine is 11*S*, 13*R*, and 14*S*. By X-ray studies of (+)-14-epicorynoline (**18**) bromoacetate, the trans-B/C ring junction, a B/C twist-half-chair–half-chair conformation, an axial *N*-CH_3 group, and the absolute configuration 11*S*, 13*R*, and 14*S* were determined (*99,100*). The absolute configuration 11*S*, 13*R*, and 14*R* for (+)-corynoline (**9**) was proposed (*99*) and confirmed by X-ray analysis (*24*).

B. ^{1}H- and ^{13}C-NMR Spectroscopy

Two recent reviews (*101,102*) and a collection of ^{13}C-NMR spectral data on isoquinoline alkaloids (*103*) including NMR spectra of benzophenanthridine alkaloids are available. A major study of ^{1}H- and ^{13}C-NMR spectra of hexahydrobenzophenanthridines was carried out by Takao *et al.* (*98,104*) (Tables III and IV). There was proposed a preferred B/C half-chair–half-chair conformation with a cis-B/C ring junction, an equatorial *N*-CH_3, and an axial 11-OH group for (+)-chelidonine (**1**), (±)-corynoline (**9**), and corynolamine (**15**). The acetylation of the 11-OH group of these alkaloids changes the B-ring conformation and that of the *N*-CH_3 group by breaking the intramolecular hydrogen bond between them. For (+)-14-epicorynoline (**18**) in solution, the same conformation was suggested as that found for the bromoacetate of **16** by X-ray studies (*99*). Twist-half-chair conformation for ring B in chelidonine was indicated on the basis of the coupling between C-11 and C-12 protons (J = 4.3 Hz) (*105*). In another paper (*106*), ^{1}H-NMR shifts for three stereoisomers of 12-hydroxycorynoline (**14**) were given. In six analogs of chelidonine, the influence of the configuration of the 11- and 12-OH groups on the B/C conformation was studied by chemical shifts and couplings between the protons at C-11, -12, -13, and -14 (*107*). The elucidation of the structure of (+)-corynoline 11-*O*-sulfate (**11**) (*26*) and that of (+)-luguine (**8**) (*22*) were achieved by ^{1}H- and ^{13}C-NMR spectroscopy. The determination of the structure of chelirubine (**61**) by total synthesis led to the clarification of the difference in chemical shifts between 9-H and 11-H in dihydrosanguinarine (**27**) and dihydrochelirubine (**40**) (*108*). The low-frequency shift of 9-H and the high-frequency shift of 11-H in the spectrum of dihydrocheli-

TABLE III

^{1}H CHEMICAL SHIFTS OF SOME BENZOPHENANTHRIDINE ALKALOIDS

Hydrogen	Hexahydrobenzophenanthridine alkaloid		
	(±)-Chelidonine (**1**)[a]	(±)-Corynoline (**9**)[b]	(±)-14-Epicorynoline (**18**)[b]
1-H	6.64s	6.65s	6.61s
4-H	6.66s	6.68s	7.17s
6-H_2	3.43d (*J* 15.7)	3.46d (*J* 15.4)	3.95d (*J* 17.0)
	4.08d (*J* 15.7)	4.05d (*J* 15.4)	4.26d (*J* 17.0)
9-H	6.76d (*J* 7.9)[c]	6.93d (*J* 8.3)[c]	6.88d (*J* 8.2)[c]
10-H	6.73d (*J* 7.9)[c]	6.81d (*J* 8.3)[c]	6.76d (*J* 8.2)[c]
11-H	4.23bs (W_H 7.9)	3.96m	4.32d (*J* 5.0)
12-H_2	3.08dd (*J* 17.5 and 4.3)	3.10dd (*J* 17.9 and 4.5)	3.21dd (*J* 18.3 and 5.0)
	3.21d (*J* 17.5)	3.16d (*J* 17.9)	2.82d (*J* 18.13)
13-H	2.98t (*J* 2.8)	—	—
14-H	3.57bs (W_H 6.8)	3.32bs	4.50s
13-CH_3	—	1.15s	1.10s
N-CH_3	2.27s	2.22s	2.48s
2,3-OCH_2O	5.95d (*J* 1.5)[c]	5.97d (*J* 1.5)[c]	5.90d (*J* 1.5)
	5.99d (*J* 1.3)[c]	6.00d (*J* 1.5)[c]	5.92d (*J* 1.5)
7,8-OCH_2O	5.927d (*J* 1.5)[c]	5.97s[c]	6.96s[c]
	5.934d (*J* 1.5)[c]		

	Dihydrobenzophenanthridine alkaloid		
	Dihydrosanguinarine (**27**)[d]	Dihydrochelirubine (**40**)[d]	Dihydromacarpine (**42**)[e]
1-H	7.10s	7.11s	7.57s
4-H	7.72s	7.72s	7.71s
6-H_2	4.14s	4.07s	4.11s
9-H	6.83d (*J* 8)	6.59s	6.64s
10-H	7.30d (*J* 8)	—	—
11-H	7.69d (*J* 9)	8.35d (*J* 9)	7.87s
12-H	7.46d (*J* 9)	7.47d (*J* 9)	—
N-CH_3	2.54s	2.54s	2.53s
10-OCH_3	—	3.81s	3.89s
12-OCH_3	—	—	4.00s
2,3-OCH_2O	5.99s	5.96s[c]	—
7,8OCH_2O	5.99s	6.00s[c]	—

[a]From Ref. *105*.

[b]From Ref. *146*.

[c]Assignments may be reversed.

[d]From Ref. *108*.

[e]From Ref. *109*, ^{1}H-NMR spectra measured in $CDCl_3$, chemical shifts given as δ values (ppm) and coupling constants *J* given in Hz.

TABLE IV
^{13}C-CHEMICAL SHIFTS OF SOME HEXAHYDROBENZOPHENANTHRIDINE ALKALOIDS[a]

Carbon	Alkaloid		
	(+)-Chelidonine (**1**)	(+)-Corynoline (**9**)	(+)-14-Epicorynoline (**18**)
1	107.4	107.7	107.3
2	145.3[b]	145.2[b]	145.3[b]
3	145.6[b]	145.4[b]	146.2[b]
4	111.9	112.8	106.8
4a	128.9	128.0	129.5
6	53.9	54.4	52.1
6a	117.1	116.9	117.6
7	143.1	142.9	145.3
8	148.2	148.2	146.5
9	109.2	109.4	108.8
10	120.4	118.7	117.6
10a	131.4	136.2	135.5
11	72.4	76.1	74.1
12	39.7	36.8	33.7
12a	125.8	125.3	126.9
13	42.1	40.8	39.4
14	62.9	69.8	58.3
13-CH_3	—	23.5	23.9
N-CH_3	42.4	43.2	38.1
2,3-OCH_2O	101.1[b]	101.0[b]	100.7[b]
7,8-OCH_2O	101.4[b]	101.4[b]	101.3[b]

[a]From Ref. *104*, ^{13}C-NMR spectra measured in $CDCl_3$, chemical shifts given as δ values (ppm).

[b]Assignments may be reversed.

rubine result from the 10-OCH_3 group. The structure of macarpine (**63**) was assigned by a comparison of the ^{1}H-NMR spectrum of its 5,6-dihydro derivative **42** with the spectra of dihydrosanguinarine (**27**) and dihydrochelirubine (**40**) (*109*) (Table III). Eu(dpm)$_3$-induced shifts of ^{1}H-NMR signals of some 6-oxobenzophenanthridine alkaloids were published (*11*).

C. ULTRAVIOLET, FLUORESCENCE, AND INFRARED SPECTROSCOPY

The UV data of some hexahydrobenzophenanthridine and aromatic benzophenanthridine alkaloids were reported (*104,110*). The UV spectra can be analytically utilized to differentiate between the 7,8- and the 8,9-oxygenated types of these alkaloids (*111*) (Table V). A pH-dependent spectral change of the longest

TABLE V
ULTRAVIOLET SPECTRA OF SOME QUATERNARY BENZOPHENANTHRIDINE ALKALOIDS

Alkaloid[a]	Solvent	Absorption λ_{max}(log ϵ)
Chelerythrine (**50**)[b]	EtOH	228 (4.45), 273sh (4.53), 282 (4.59), 315sh (4.21), 321 (4.229, 347sh (3.79), 400 (3.15), 435sh (3.13)
Sanguinarine (**52**)[b]	EtOH	236 (4.48), 285 (4.53), 328 (4.25), 352sh (3.85), 400 (3.07), 476 (3.12)
Chelirubine (**61**)[b]	EtOH	232 (4.50), 281 (4.46), 305sh (3.99), 341 (4.24), 354 (424), 413 (2.91), 508 (3.17)
Nitidine (**56**)[c]	MeOH	231 (4.42), 272 (4.49), 281sh (4.48), 303sh (4.40), 329 (4.38)

[a]In form of chlorides.
[b]From Ref. *110*.
[c]From Ref. *169*.

wavelength band was used to study the cation–pseudobase equilibrations of quaternary benzophenanthridines (*112,113*). The fluorescence spectra of chelerythrine (**50**), sanguinarine (**52**), and nitidine (**56**) were studied in different solvents and in dependence on pH values (*113*). Infrared spectral data in the 2600–2850-cm^{-1} region were used to assign the orientation of the *N*-CH_3 group in hexahydrobenzophenanthridines (*98*).

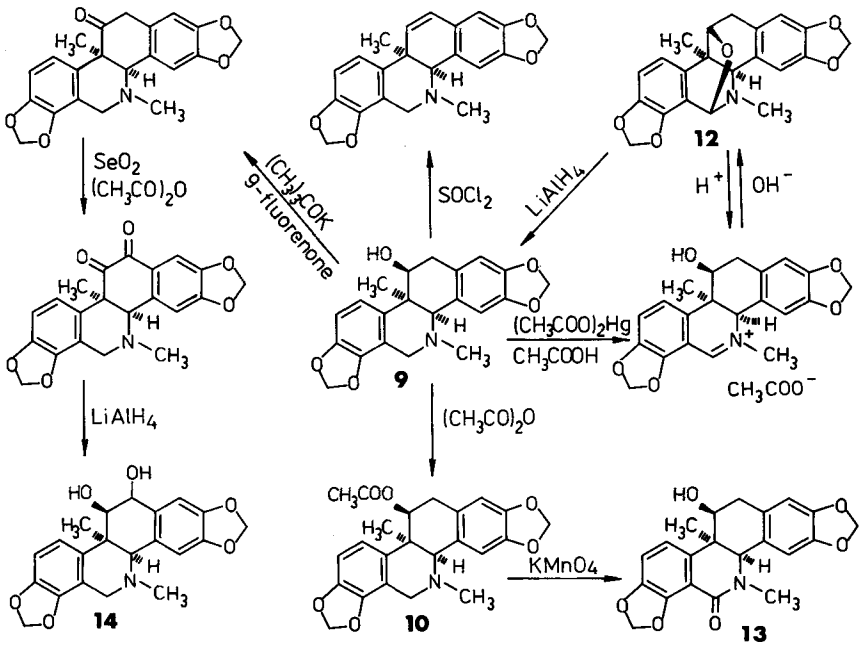
D. CIRCULAR DICHROISM

The aromatic chirality rule was used to explain the relationship between the sign of the Cotton effects and the absolute configurations of (+)-chelidonine (**1**), (+)-homochelidonine (**6**), (+)-corynoline (**9**), (+)-corynoloxine (**12**), (+)-14-epicorynoline (**18**), and their derivatives (*104*).

V. Chemical Reactivity and Conversions of Benzophenanthridine Alkaloids

A. HEXAHYDROBENZOPHENANTHRIDINE ALKALOIDS

Some simple transformations of these alkaloids provide confirmatory evidence of their structures, e.g., corynoline (**9**) (Scheme 1) (*114–116*). The oxidative transformation of (−)-norchelidonine (**3**) to (+)-luguine (**8**), carried out by using a one-electron oxidant, Fremy's salt [$\cdot ON(SO_3K)_2$, FS] under phase-transfer conditions, probably mimics the natural process in the *N*-demethylbenzophenanthridine series (Scheme 2) (*117*). The same authors reported the transforma-

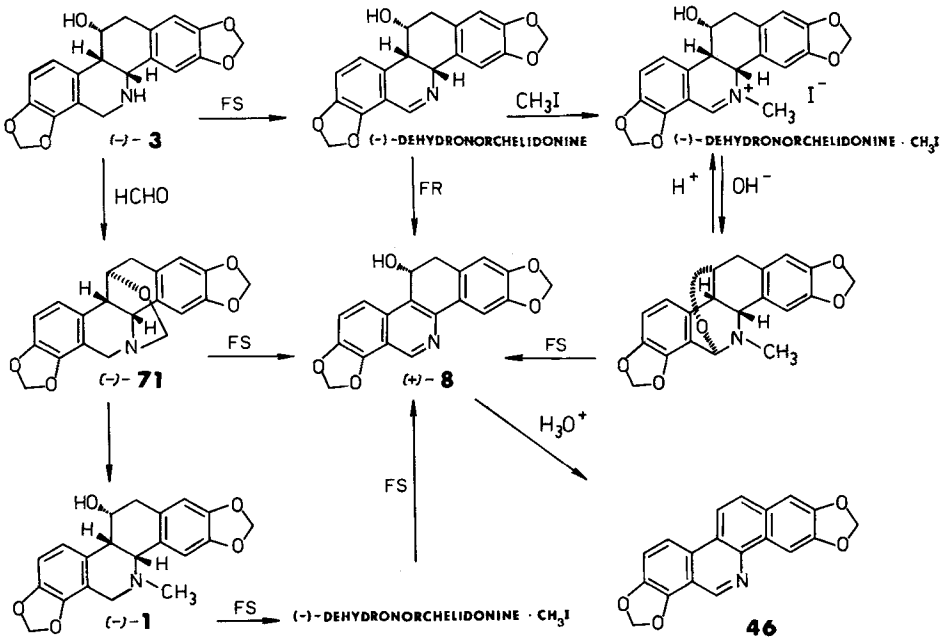


SCHEME 1. Chemical conversions of hexahydrobenzophenanthridine alkaloids.

tion of (−)-norchelidonine (**3**) to (+)-luguine (**8**) by using sodium acetate in the presence of iodine or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (*22*). A new derivative **71** (isodidehydrochelidonine) was obtained by reaction of **3** with formaldehyde (Scheme 2) (*117*).

B. DIHYDROBENZOPHENANTHRIDINE ALKALOIDS

An interesting reaction is the dehydrogenation of 5,6-dihydro derivatives to quaternary salts (*8*). It is carried out with mercuric acetate. The 7,8-oxygenated dihydro derivatives are unstable in solvents like chloroform, methanol, and ethanol. They are readily converted to quaternary salts by the action of air and light (*31*). The *O*-benzyl-*N*-methyldihydro derivative of decarine (**43**) was oxidized to a quaternary salt with DDQ (*118*). Dehydrogenation of dihydrochelirubine (**40**) with DDQ afforded chelirubine (**61**) (*108*). 6-Oxo derivatives can be prepared from 6-cyanodihydro derivatives (pseudocyanides) by their reduction with NaH in hexamethylphosphoric triamide (HMPA) following air oxidation (*11*). The photochemical reaction of dihydrochelerythrine (**20**) with methanol, using acetone as a sensitizer, gave bocconoline (**24**) (*38*).



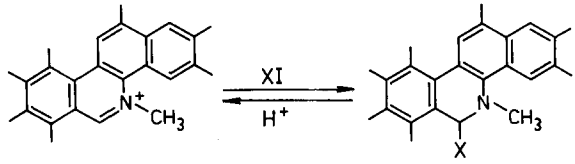
SCHEME 2. Transformations of benzophenanthridine alkaloids.

C. *N*-DEMETHYLBENZOPHENANTHRIDINE ALKALOIDS

In the *N*-demethylbenzophenanthridine alkaloids, the reactions studied were alkylations of the nitrogen atom. The standard alkylation method with dimethyl sulfate in xylene or nitrobenzene afforded quaternary benzophenanthridinium salts (*119*). Under strict reaction conditions, the quantitative methylation of nitrogen by the action of methyl fluorosulfonate takes place (*120*). *N*-Methyl-5,6-dihydro derivatives can be prepared in high yield from *N*-demethylbenzophenanthridines by reaction with $NaBH_4$ and dimethyl sulfate in HMPA (*118*) or with $NaBH_4$ and acetic acid or formic acid (*11*). Reductive alkylation of pancorine (**47**) with $NaBH_4$ in methanol gave dihydrosanguinarine (**27**) (*53*).

D. QUATERNARY BENZOPHENANTHRIDINE ALKALOIDS

Quaternary benzophenanthridine alkaloids are in protic solvents present as an equilibrium mixture of the quaternary iminium form and the nucleophilic solvent adduct (*77*) (Scheme 3). The adduct with the hydroxide ion is called a pseudobase (*78*). The relative susceptibility of the iminium bond to nucleophilic attack is mainly dependent on the position of the electron-donating substituents of the D ring (*121*). The substituent at position 7 destabilizes the cation via the electronic



SCHEME 3. Addition of the nucleophile to the benzophenanthridinium ion.

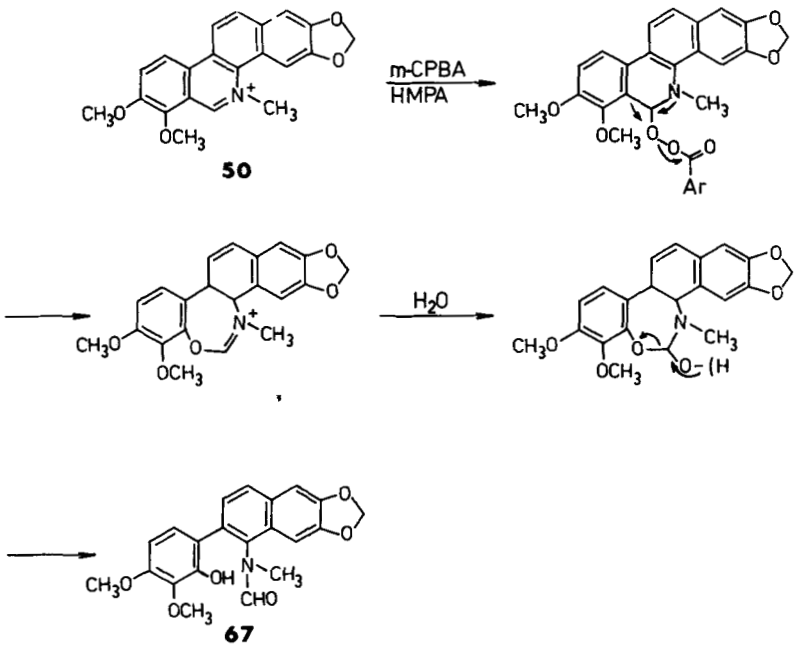
effect relative to the adduct (chelerythrine group), whereas the substituent at position 9 (nitidine group) stabilizes the cation. The pK_{R+} values of pseudobase formation for chelerythrine (**50**), sanguinarine (**52**), and nitidine (**56**) are given in Table VI (*113*). Solvation of the quaternary ion in water leads to a marked decrease in its acidity. The pK_{R+} values are significantly lower in the presence of bovine albumin and cationic detergents (*122*). They correlate with the biological activity of quaternary benzophenanthridine alkaloids (*122,123*). The stability constants in the formation of thiol adducts with chelerythrine and sanguinarine were measured (*123*). In strongly alkaline media, the quaternary benzophenanthridines disproportionate to 5,6-dihydro and 6-oxo derivatives (*89*). They are readily demethylated on heating above 200°C to give *N*-demethyl derivatives (*124,125*). Reduction of quaternary benzophenanthridines with $NaBH_4$ to 5,6-dihydro derivatives, oxidation with $K_3Fe(CN)_6$ to 6-oxo derivatives, alkylation with Grignard reagents to 6-alkyldihydro derivatives, and the formation of pseudocyanides with sodium or potassium cyanide are well-known reactions. Recrystallization of these alkaloids from methanol or ethanol gives rise to 6-alkoxydihydro derivatives, and treatment with acetone in alkaline medium yields 6-acetonyldihydro derivatives (*8*). Chelerythrine, when irradiated in methanol and acetone (1:1), affords bocconoline (**24**) in a sixfold higher yield than that obtained from the analogous photochemical reaction with dihydrochelerythrine (**20**) (*38*). 6-Iminosanguinarine (**31**) was synthetically prepared from 6-chlorosanguinarine and sodium amide (*30*).

The C ring of quaternary benzophenanthridines opens easily on oxidation

TABLE VI
pK_{R+} VALUES OF SOME BENZOPHENANTHRIDINES[a]

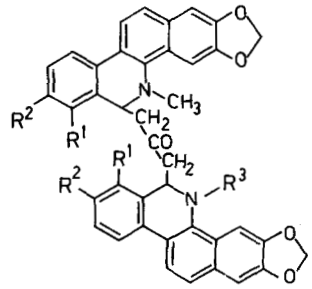
Compound	pK_{R+} [water– ethanol 1:1 (w/w)]	pK_{R+} (water)
Sanguinarine (**52**)	5.75 ± 0.18	7.92 ± 0.08
Chelerythrine (**50**)	6.67 ± 0.19	8.77 ± 0.07
Nitidine (**56**)	9.76 ± 0.15	12.10 ± 0.02

[a]From Ref. *113*.



SCHEME 4. The Baeyer–Villiger oxidation of quaternary benzophenanthridine alkaloids.

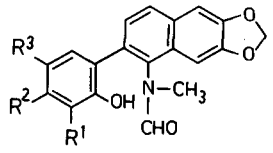
under Baeyer–Villiger-like conditions, with *m*-chloroperoxybenzoic acid (*m* CPBA) in HMPA, to give secobenzophenanthridines (*11*) (Scheme 4). Thus chemical evidence was provided for the structure of arnottianamide (**67**) by oxidation of chelerythrine (*66*), iwamide (**68**) by oxidation of the *O*-benzyl-*N*-



64 $R^1=R^2=OCH_3$; $R^3=CH_3$ CHELERYTHRIDIMERINE

65 $R^1+R^2=OCH_2O$; $R^3=CH_3$ SANGUIDIMERINE

66 $R^1=R^2=OCH_3$; $R^3=H$ TODDALDIMERINE



67 $R^1=R^2=OCH_3$; $R^3=H$ ARNOTTIANAMIDE

68 $R^1=OCH_3$; $R^2=OH$; $R^3=H$ IWAMIDE

69 $R^1=H$; $R^2=R^3=OCH_3$ ISOARNOTTIANAMIDE

70 $R^1=H$; $R^2+R^3=OCH_2O$ INTEGRIAMIDE

methyl derivative of decarine (**43**) (*118*), isoarnottianamide (**69**) by oxidation of nitidine (**56**) (*66*), and integriamide (**70**) by oxidation of avicine (**57**) (*68*).

E. Secobenzophenanthridine Alkaloids

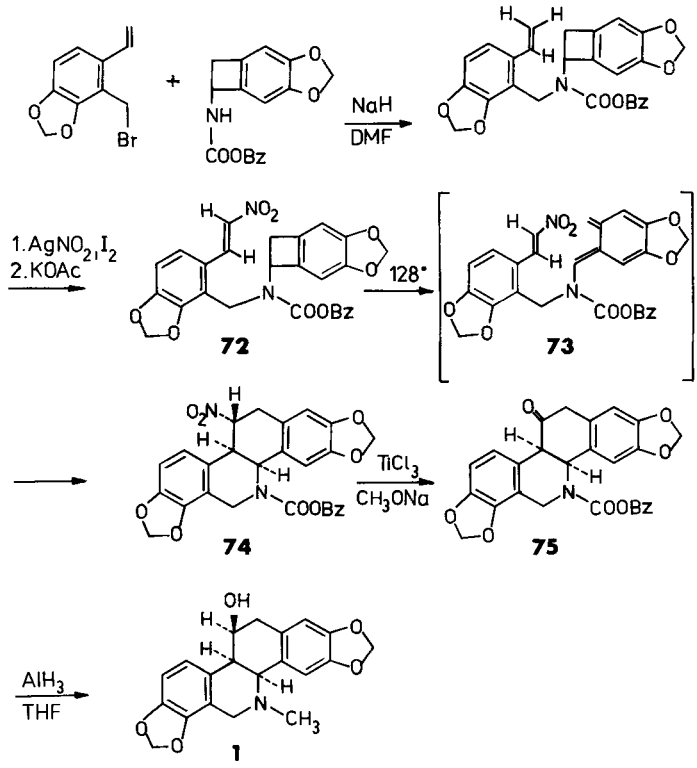
Treatment of isoarnottianamide (**69**) with the Rodinow reagent (trimethylphenylammonium ethoxide) afforded the *O*-methyl derivative of **69.** The Bischler–Napieralski reaction of this *O*-methyl derivative with phosphorus oxychloride in acetonitrile gave chelilutine (**62**) (*126*).

VI. Synthesis

The syntheses of benzophenanthridine alkaloids have been subdivided into those for the preparation of chelidonine, corynoline, chelerythrine (including alkaloids with five and six oxygen functions), and the nitidine groups of alkaloids.

A. Chelidonine Group

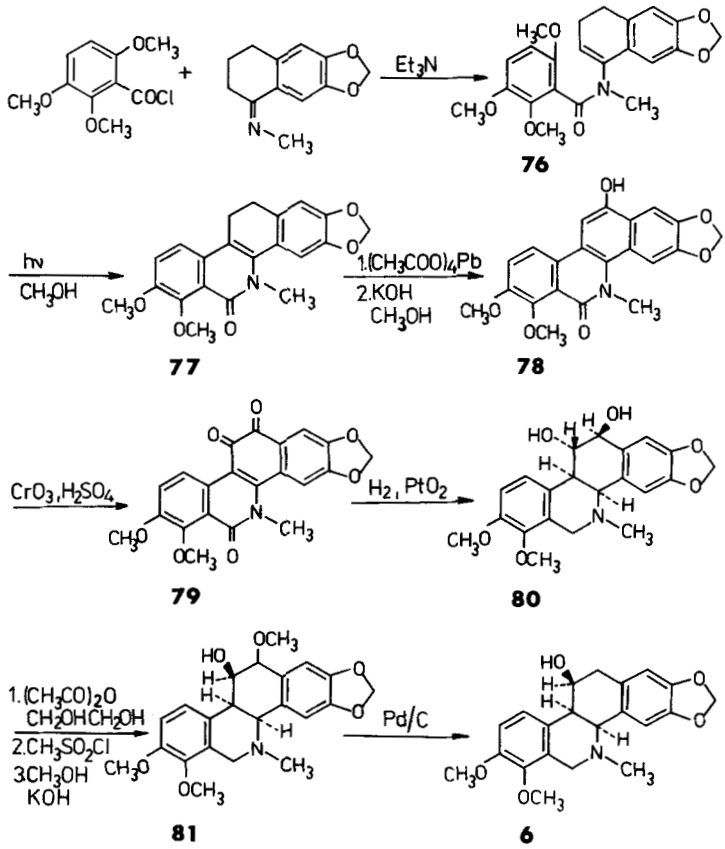
(+)-Chelidonine (**1**), the major alkaloid of this group, was isolated from *Chelidonium majus* as early as 1839 (*127*). The first synthesis of racemic chelidonine and its *N*-demethyl derivative norchelidonine (**3**) was described in 1971 (*128*). The initial compounds of the synthesis are 2-bromomethyl-3,4-methylenedioxystyrene and benzyl *N*-(4,5-methylenedioxybenzocyclobutene-1-yl)carbamate. The modification of the synthesis, through replacement of the acetylenic moiety by an olefinic dienophile with a nitro group in the intermediary product **72** (Scheme 5), results in 100% stereoselectivity of the key intramolecular cycloaddition transient (*E*)-quinodimethane **73** to give rise to the *cis*-B/C-hexahydrobenzophenanthridine skeleton (*129,130*). The replacement of the



SCHEME 5. The Oppolzer synthesis of (±)-chelidonine (**1**).

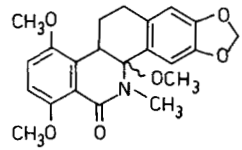
nitro group by an oxo group is carried out by treatment of compound **74** with $TiCl_3$ and sodium methoxide. The unstable ketone **75** is reduced with AlH_3 directly to (±)-chelidonine (**1**). On preparing (±)-norchelidonine (**3**), the 11-oxo group is reduced by $NaBH_4$, and the carbamate group is hydrogenolyzed with 10% palladium–charcoal in ethanol. The yield of (±)-chelidonine, calculated on benzocyclobutenylcarbamate, is 25%.

Acylation of 1-tetralonimines with *o*-methoxy substituted benzoyl chlorides gave stable enamides in good yield. These enamides underwent smooth photocyclization to afford the benzophenanthridine nucleus (*131,132*). This also provided a synthesis of homochelidonine (**6**) (*133,134*) (Scheme 6) and model compounds derived from chelidonine (*107,135*). The introduction of the oxygen function to position 11 was achieved by oxidation of the 12-hydroxy lactam **78** to afford the 11,12-quinone **79.** This compound was catalytically hydrogenated to the 11α,12β-glycol **80.** Conversion of the 11α-hydroxy group to the desired 11β-hydroxy group was accomplished by selective acetylation of the 12β-hydroxy group, followed by methane sulfonation of the 11α-hydroxy group. The

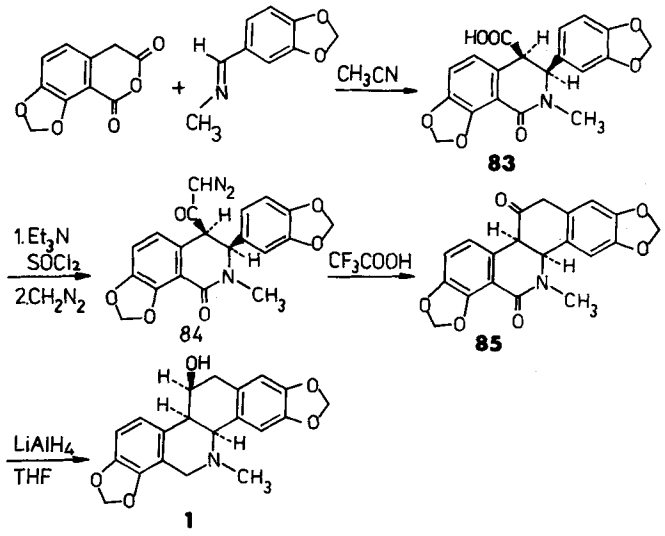


SCHEME 6. The Ninomiya synthesis of (±)-homochelidonine (**6**).

resulting methanesulfonate was then treated with methanolic potassium hydroxide to give the 11β-hydroxy-12-methoxy amine **81.** Hydrogenolysis of the 12-methoxy group with 40% palladium–charcoal afforded (±)-homochelidonine (**6**). The disadvantage of photocyclization of *o*-methoxy substituted enamides is the nonselectivity in the orientation of cyclization and the low yield (19%) of the desired lactam **77.** The second product of the photocyclization of enamide **76** is lactam **82** (18% yield).



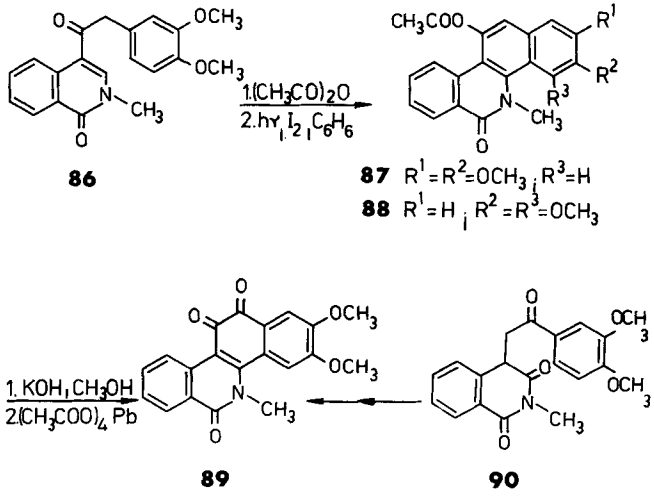
82



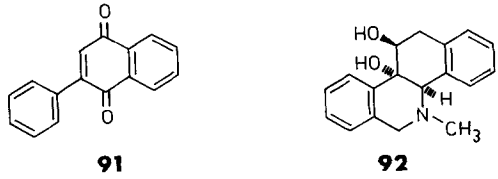
SCHEME 7. The Cushman synthesis of (±)-chelidonine (**1**).

Cushman *et al.* (*136,137*) have used the isoquinolone **83** as the starting material to carry out an elegant synthesis of (±)-chelidonine (Scheme 7). Compound **83** is formed by addition of 3,4-methylenedioxyhomophthalic anhydride to 3,4-methylenedioxybenzylidine methylamine. This key step of the synthesis (in dependence on the polarity of the used solvent) gives rise to a mixture of cis and trans diastereoisomers. The cis diastereoisomer **83** is thermodynamically less stable. When the condensation is carried out in acetonitrile, there arise 67% of the cis in addition to 33% of the trans isomer. The carboxyl group of **83** is converted to an acid chloride, followed by reaction with diazomethane to yield compound **84.** The diazo ketone **84** undergoes ring closure to compound **85,** which is stereospecifically reduced by $LiAlH_4$ to give (±)-chelidonine.

The preparation of some analogs of chelidonine was studied by Onda's group. By a two-step synthesis, 11-acetoxy-5,6-dihydro-2,3-dimethoxy-5-methyl-6-oxobenzophenanthridine (**87**) and its 3,4-dimethoxy isomer **88** were prepared from 4-(3′,4′-dimethoxyphenylacetyl)-2-methyl-1-isoquinolone (**86**) (*138*) (Scheme 8). The hydrolysis of the 11-acetoxy group of **87** to the 11-hydroxy group and subsequent oxidation afforded the quinone **89,** an intermediate in the synthesis of the chelidonine-like compound. The quinone **89** was also prepared from 12-acetoxy-5,6-dihydro-2,3-dimethoxy-5-methyl-6-oxobenzophenanthridine by a four-step synthesis from 4-(3′,4′-dimethoxyphenacyl)-2-methylhomophthalimide (**90**) (*139*) (Scheme 8). The optically active analog of 13-hydroxychelidonine, compound **92,** was synthesized from naphthoquinone **91** (*140,141*).

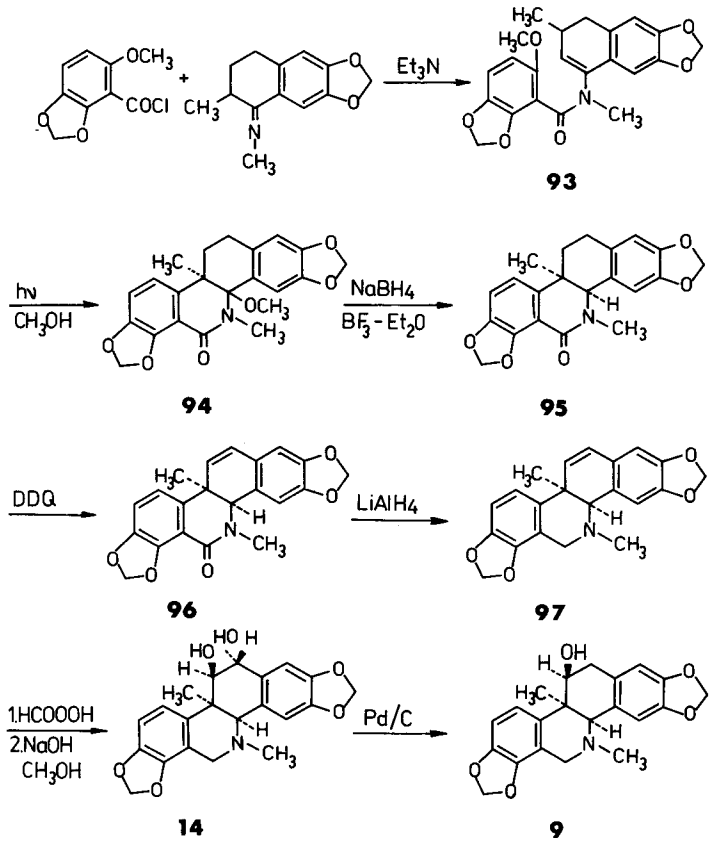


SCHEME 8. The Onda synthesis of quinone amides.

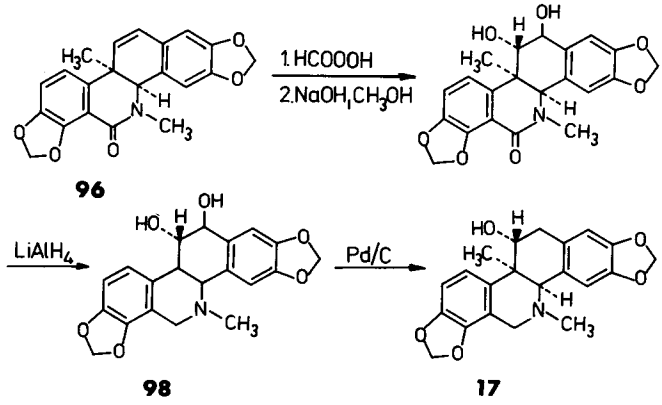


B. CORYNOLINE GROUP

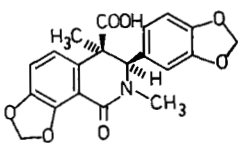
The first total synthesis of hexahydro-13-methylbenzophenanthridine alkaloids (±)-corynoline (**9**), (±)-12-hydroxycorynoline (**14**) (Scheme 9), and (±)-11-epicorynoline (**17**) (Scheme 10) was carried out by Ninomiya *et al.* (106,142,143). The key steps in this synthesis are photocyclization of enamide **93** and the stereoselective introduction of hydroxy groups to positions 11 and 12. Enamide **93** was prepared from 6-methoxy-2,3-methylenedioxybenzoyl chloride and 2-methyl-1-tetralonimine. Photocyclization of **93** gave lactam **94** in 20% yield. Reductive cleavage of the 14-OCH_3 group yielded the cis lactam **95,** which constitutes a common basic skeleton of hexahydrobenzophenanthridine. The different behavior of amine **97** (Scheme 9) and lactam **96** (Scheme 10) toward performic acid (in the first case affording 11β,12α-glycol **14,** in the second case a mixture of 11α,12α and 11α,12β-glycol **98**) is explained by the different steric course of the oxidation of the 11,12 double bond in compounds **97** and **96** (*106*).



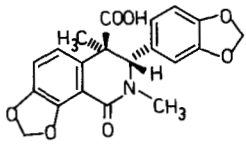
SCHEME 9. The Ninomiya synthesis of (±)-corynoline (**9**) and (±)-12-hydroxycorynoline (**14**).



SCHEME 10. The Ninomiya synthesis of (±)-11-epicorynoline (**17**).



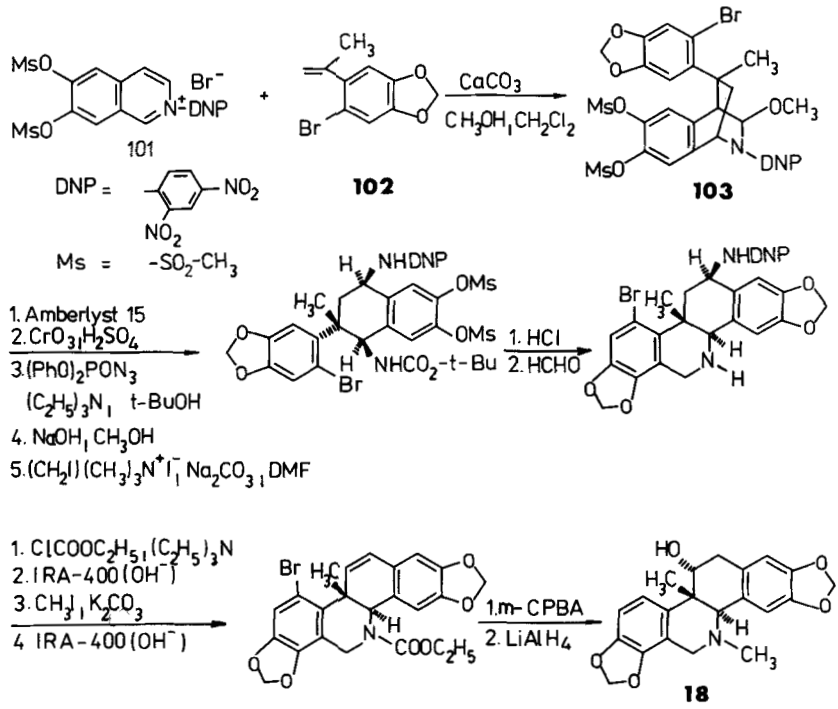
99



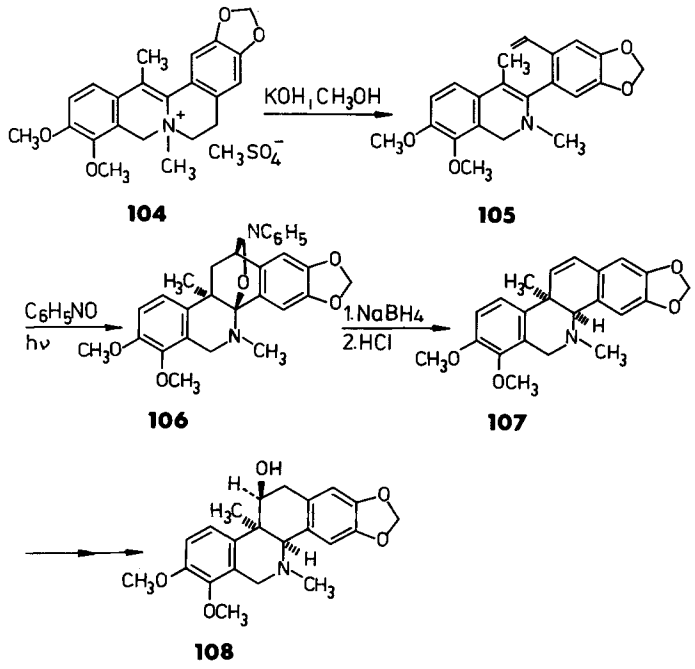
100

Cushman *et al.* (*144–146*) applied the same method as in the synthesis of (±)-chelidonine (*137*) for the total synthesis of (±)-corynoline, 6-oxocorynoline (**13**), and the only naturally occurring *trans*-B/C-hexahydrobenzophenanthridine alkaloid (±)-14-epicorynoline (**18**). The addition of 3,4-methylenedioxy-7-methylhomophthalic anhydride to 3,4-methylenedioxybenzylidene methylamine gave two diastereomeric isoquinolones **99** and **100.** (±)-Corynoline and its 6-oxo derivative **13** were synthetized by using the cis isomer **99,** and (±)-14-epicorynoline (**18**) was prepared from the trans isomer **100.**

Recently, (±)-14-epicorynoline was prepared by cycloaddition of 6,7-dimethanesulfoxy-2-(2′,4′-dinitrophenyl)isoquinolinium bromide (**101**) with α-methylstyrene **102** (*147*) (Scheme 11). The isomerically pure adduct **103** was transformed by 14 steps into the alkaloid **18.**

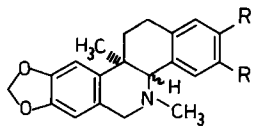


SCHEME 11. The Falck synthesis of (±)-14-epicorynoline (**18**).

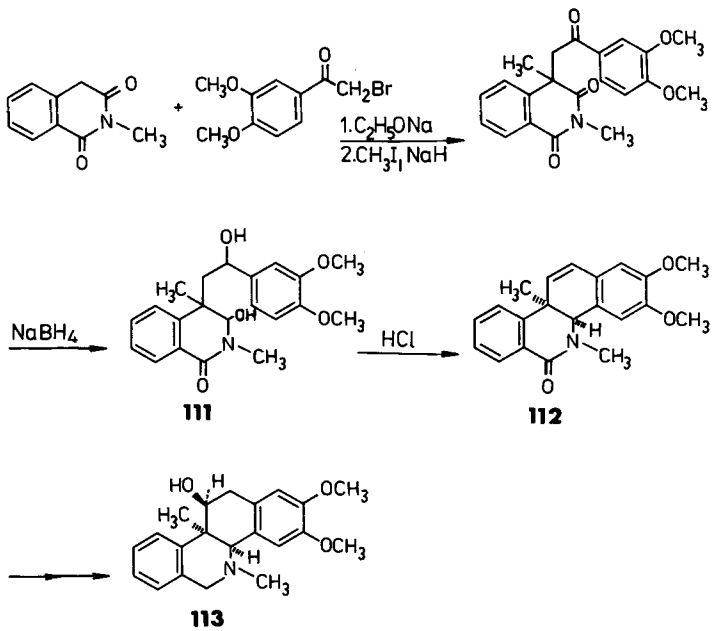


SCHEME 12. The Onda synthesis of (±)-corynoline analog **108.**

The 7,8-dimethoxy analog of corynoline, compound **108,** was synthetized from 7,13-dimethyl-7,8-dihydroberberine methylsulfate (**104**) by Onda *et al.* (*148–150*). In the last modification (Scheme 12), the crucial step of this synthesis (photolysis of the methine base **105**) is performed in the presence of nitrosobenzene (*150*). The photo product **106** has the trans-B/C ring junction. The 13-CH_3 group sterically prevents the approach of nitrosobenzene from the same side. Reduction of compound **106** gives stereoselectively hexahydrobenzophenanthridine **107** with cis-B/C ring junction. The 11-hydroxy group was introduced in a similar manner as in the case of (±)-corynoline (*106*). Cis- and trans-B/C-fused hexahydro-13-methylbenzophenanthridines **109** and **110** were prepared from 2-(3′,4′-methylenedioxyphenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene and its 6,7-dimethoxy derivative (*151*). The isocarbostyril



109 R = H
110 R = OCH_3



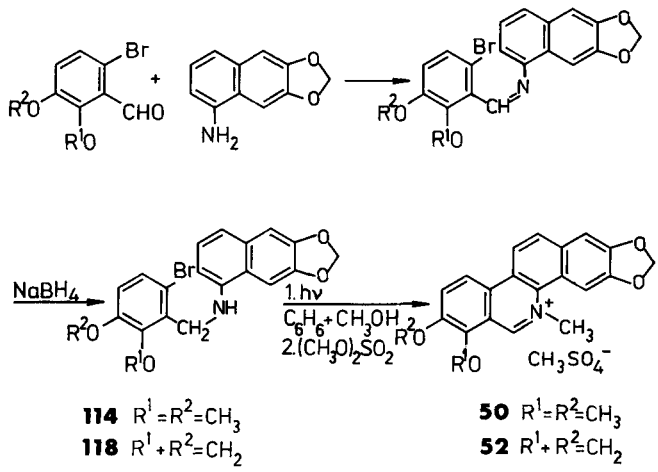
SCHEME 13. Synthesis of 2,3-dimethoxy-*trans*-11-hydroxy-13-methyl-*cis*-5,6,11,12,13,14-hexahydrobenzophenanthridine (**113**).

derivative **111,** obtained from 2-methylhomophthalimide and 3,4-dimethoxyphenacyl bromide via three steps, was stereoselectively cyclized to 11,12-didehydrolactam **112** (*152*) (Scheme 13). Compound **112** was converted to the analog of corynoline, compound **113,** by the method of Ninomiya (*106*).

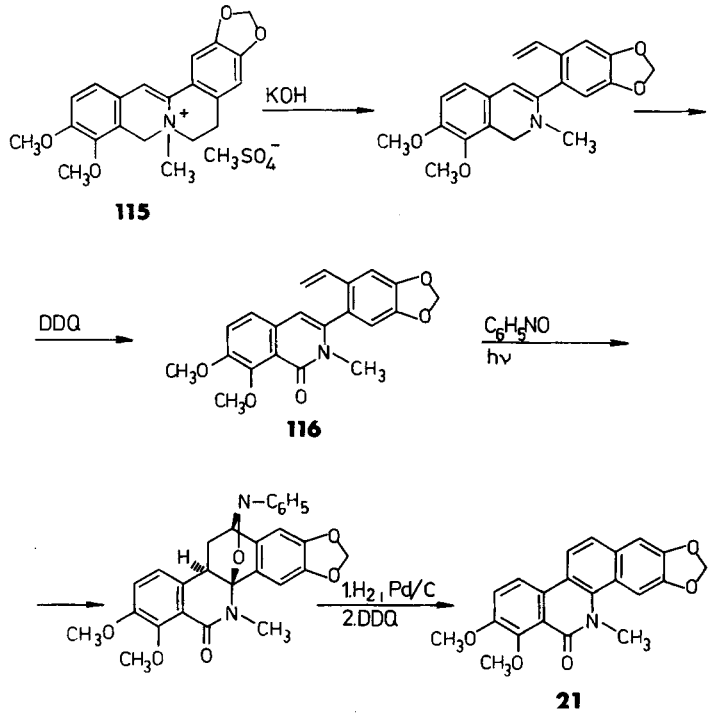
C. CHELERYTHRINE GROUP

There have been described five synthetic approaches to alkaloids of this group and some transformations of protopine and protoberberine alkaloids to chelerythrine (**50**) and sanguinarine (**52**) (*8,9,13,14*). Most of the total syntheses are very complex and give low overall yields. Some of these syntheses are limited to a particular substitution pattern. Recently, the interest in the medical applications of quaternary benzophenanthridine alkaloids and their *N*-demethyl and 5,6-dihydro derivatives has led to the modification of synthetic approaches to benzophenanthridines.

Chelerythrine was the first synthetically prepared quaternary benzophenanthridine alkaloid (*153*). Šmidrkal (*154*) used the Kessar method (*155*) for the synthesis of chelerythrine by photocyclization of bromo-substituted *N*-benzylnaphthylamine **114** (overall yield 7%) (Scheme 14). This synthesis starts from readily available compounds: 3-ethoxy-4-hydroxybenzaldehyde and 2,3-di-



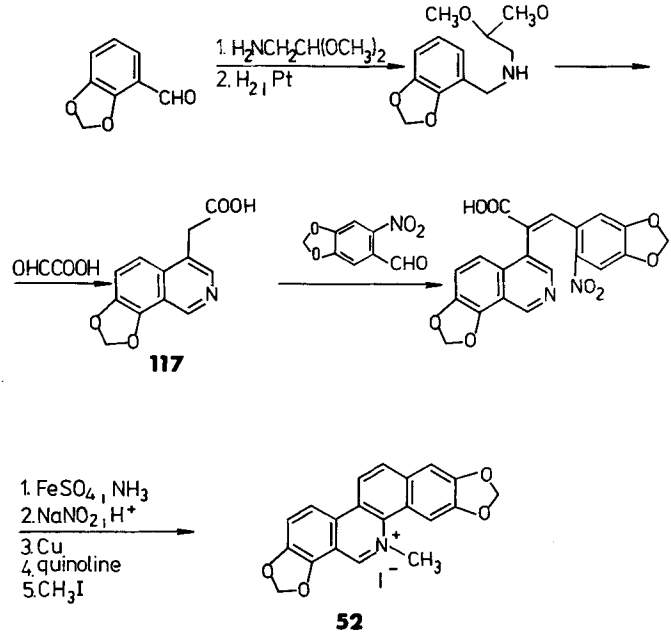
SCHEME 14. Syntheses of chelerythrine (**50**) and sanguinarine (**52**).



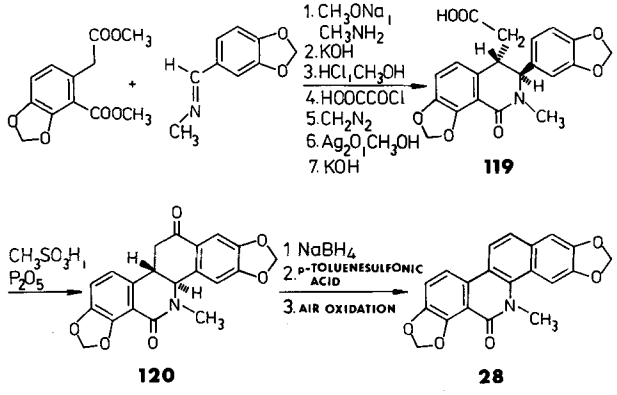
SCHEME 15. The Onda synthesis of 6-oxochelerythrine (**21**).

hydronaphthalene, from which 6-bromo-2,3-dimethoxybenzaldehyde and 1-amino-6,7-methylenedioxynaphthalene are prepared (*156,157*). It is of theoretical significance only that the photolysis of the methanolic solution of allocryptopine *N*-oxide gives rise to chelerythrine in a 2% yield (*158*). 6-Oxochelerythrine (**21**) was prepared by a four-step synthesis from dihydroberberine metho salt **115** (*159*) (Scheme 15). The crucial point of this transformation is the photolysis of isocarbostyril **116** in the presence of nitrosobenzene. 6-Oxochelerythrine (**21**) was also prepared by dehydrogenolysis of lactam **77** (Scheme 6) with lead tetraacetate (*134*).

The first synthesis of sanguinarine (**52**) by Dyke *et al.* (*160*) from 2,3-methylenedioxybenzaldehyde relies on the simple synthesis of 4-carboxymethylene-7,8-methylenedioxyisoquinoline (**117**) (Scheme 16). The two remaining rings are built by condensation of **117** with 6-nitro-3,4-methylenedioxybenzaldehyde and Pschorr cyclization to afford sanguinarine in 0.6% overall yield. The photocyclization of the bromo-substituted *N*-benzylnaphthylamine **118** (Scheme 14) proved useful in another synthesis of sanguinarine (8% yield) (*154*). The photolysis of protopine *N*-oxide afforded sanguinarine in a 1% yield (*158*). 6-Oxosanguinarine (**28**) was prepared from 3,4-methylenedioxyhomophthalic dimethylester and 3,4-methylenedioxybenzyl-

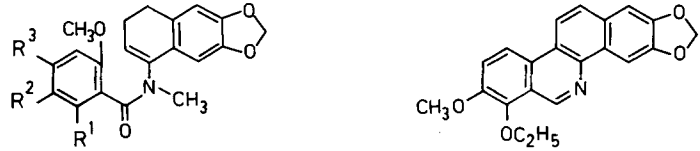


SCHEME 16. The Dyke synthesis of sanguinarine (**52**).



SCHEME 17. The Shamma synthesis of 6-oxosanguinarine (**28**).

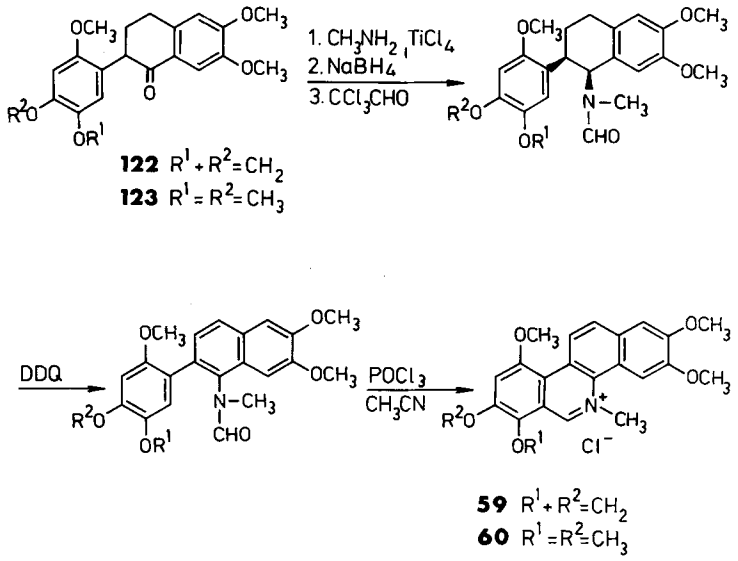
idenemethylamine (*161*) (Scheme 17). In the modified synthesis of **28**, starting from 3,4-methylenedioxyhomophthalic anhydride, the polyphosphoric ethyl ester was used for the cyclodehydration of acid **119** to ketone **120** (*154*) (Scheme 17). The yield of cyclization increased by 30%. The unpublished synthesis of 6-oxosanguinarine (**28**) by photocyclization of enamide **121** has been mentioned in the review (*131*).



121 $R^1+R^2=OCH_2O$, $R^3=H$
127 $R^1=H$, $R^2=R^3=OCH_3$
128 $R^1=H$, $R^2+R^3=OCH_2O$

124

The synthesis of benzophenanthridine alkaloids having five and six oxygen functions was carried out to confirm their structures. The synthesis of sanguilutine (**60**) and chelilutine (**62**) by Kessar *et al.* (*155*), using photocyclization of bromo-substituted *N*-benzylnaphthylamines as a crucial step, finds universal application in the preparation of fully aromatized benzophenanthridines. Ishii *et al.* (*162*) described the synthesis of sanguirubine (**59**) and sanguilutine (**60**). The intermediates 2-aryl-1-tetralones **122** and **123** were prepared according to Robinson (*163*) from 2-methoxy-4,5-methylenedioxy or 2,3,4-trimethoxybenzaldehyde and 3,4-dimethoxyacetophenone. The ensuing reaction sequence, affording



122 $R^1 + R^2 = CH_2$
123 $R^1 = R^2 = CH_3$

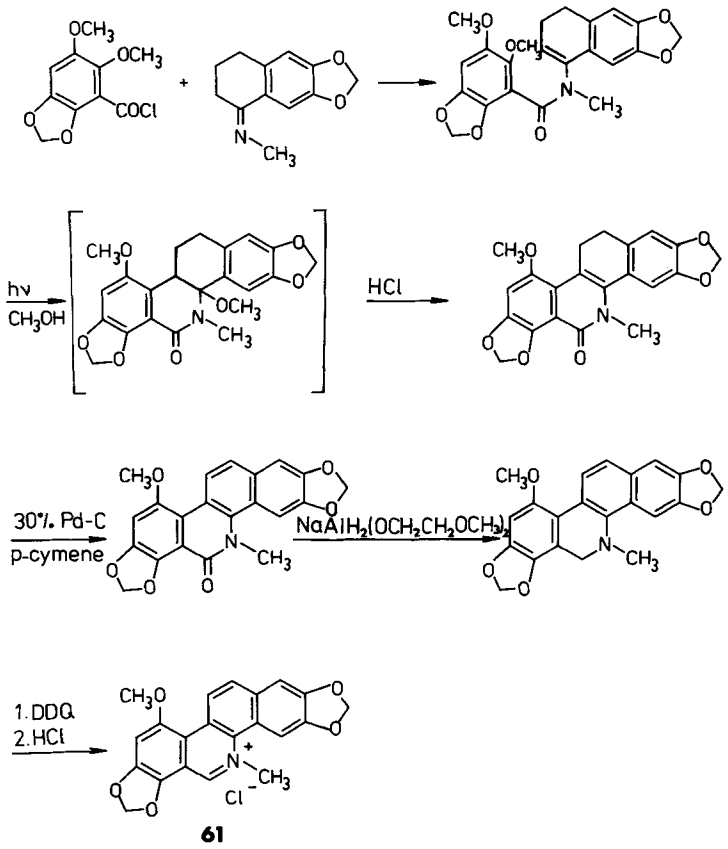
59 $R^1 + R^2 = CH_2$
60 $R^1 = R^2 = CH_3$

SCHEME 18. The Ishii synthesis of aromatic benzophenanthridines.

the benzophenanthridine nucleus, is different (Scheme 18). The overall yield for **59** is 42% and for **60** it is 60% from **122** and **123.** In the same manner, chelirubine (**61**) was prepared in 18% yield (*126*). The Ninomiya method of enamide photocyclization (*131*) was used in the total synthesis of chelirubine from 2,3-dimethoxy-5,6-methylenedioxybenzoyl chloride and *N*-methyl-6,7-methylenedioxy-1-tetralonimine (*108*) (Scheme 19). Methylation of isoarnottianamide (**69**), followed by Bischler–Napieralski cyclization, afforded chelilutine (**62**) (*126*). The Kessar photosynthetic method (*155*) was applied in the synthesis of dihydromacarpine (**42**) from 2-bromo-3-methoxy-5,6-methylenedioxybenzaldehyde and 1-amino-4-methoxy-6,7-methylenedioxynaphthalene (*109*). The analog of decarine (**43**) called ethyl isodecarine (**124**) was synthetized (*164*) by a reaction sequence developed for the synthesis of sanguinarine (**52**) (*160*).

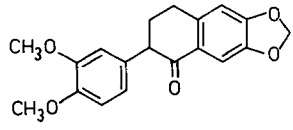
D. NITIDINE GROUP

The antitumor activity of nitidine (**56**) and fagaronine (**58**) stimulated several syntheses of these alkaloids (reviews *8–14*). Three syntheses of nitidine (*120,165,166*) were based on a common intermediate, the 2-aryl-1-tetralone **125,** known from the Robinson method for the preparation of the benzophenanthridine nucleus (*163*). The overall yields of these syntheses were from 7 to 16%. The unpublished synthesis of nitidine from this intermediate (overall yield 40%) was



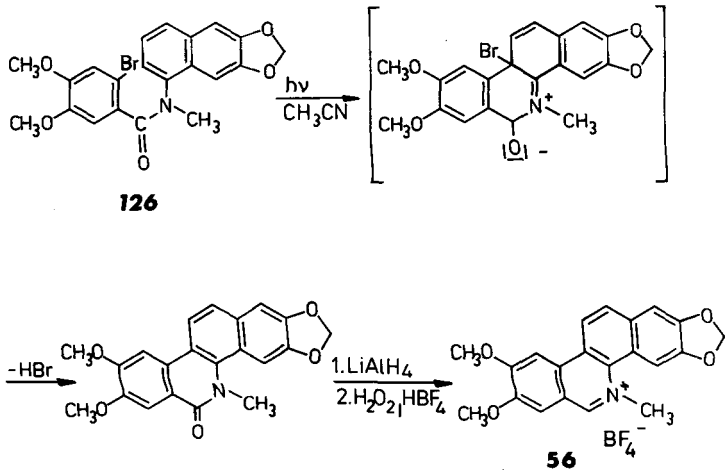
61

SCHEME 19. The Ninomiya synthesis of chelirubine (**61**).



125

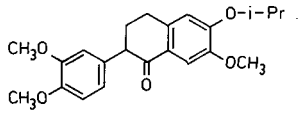
described in review *11*. The synthesis of nitidine involving a photocyclization of bromo-substituted *N*-benzoylnaphthylamine **126** gave a low yield (1.6%) (*167,168*) (Scheme 20). Cushman *et al.* (*169*) reported the seven-step synthesis of **56,** where the initial reaction was the addition of 4,5-dimethoxyhomophthalic anhydride to 3,4-methylenedioxybenzylidenemethylamine. The overall yield was



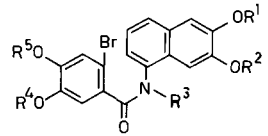
SCHEME 20. The synthesis of nitidine (**56**).

9.8%. Nornitidine (**48**) and de-*N*-methylavicine (noravicine) (**49**) were prepared by Dyke *et al.* (*170*) by a synthetic procedure analogous to that of sanguinarine (**52**) (*160*). Dihydronitidine (**35**) and dihydroavicine (**37**) were synthesized through photocyclization of the enamide **127** and **128,** prepared by condensation of 2,4,5-trimethoxy- or 2-methoxy-4,5-methylenedioxybenzoyl chloride and *N*-methyl-6,7-methylenedioxy-1-tetralonimine (*171*). Kessar *et al.* (*167*) prepared avicine (**57**) by photocyclization of bromo-substituted *N*-benzoylnaphthylamine **129.**

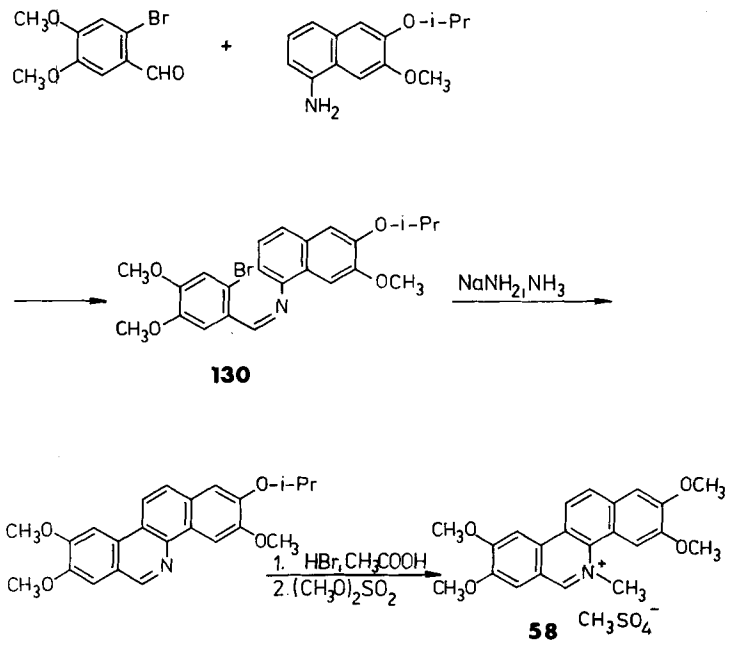
The first synthesis of fagaronine (**58**) was reported by Stermitz *et al.* (*119, 172*). The cyclization of the anil **130,** prepared by condensation of 1-amino-6-isopropoxy-7-methoxynaphthalene and 6-bromo-3,4-dimethoxybenzaldehyde, was carried out with sodium amide in liquid ammonia (Kessar benzyne cyclization) (Scheme 21). The overall yield from the starting compound 2,3-dihydroxynaphthalene was 5.2%. Ishii *et al.* (*173*) described the synthesis of fagaronine,



131



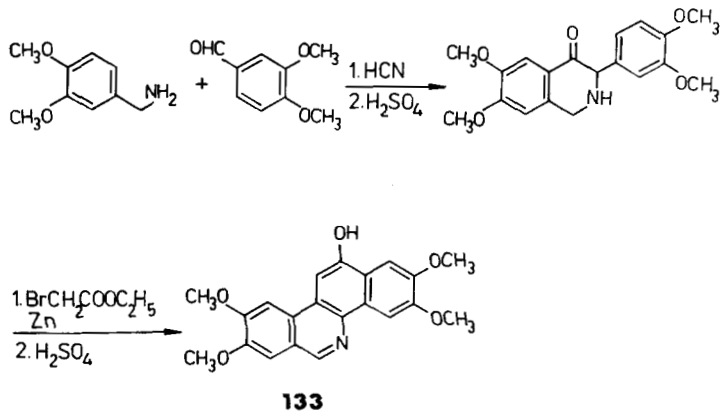
129 $R^1+R^2=R^5+R^4=CH_2$; $R^3=CH_3$
132 $R^1=COCH_3$; $R^2=R^4=R^5=CH_3$; $R^3=H$



SCHEME 21. The Stermitz synthesis of fagaronine (**58**).

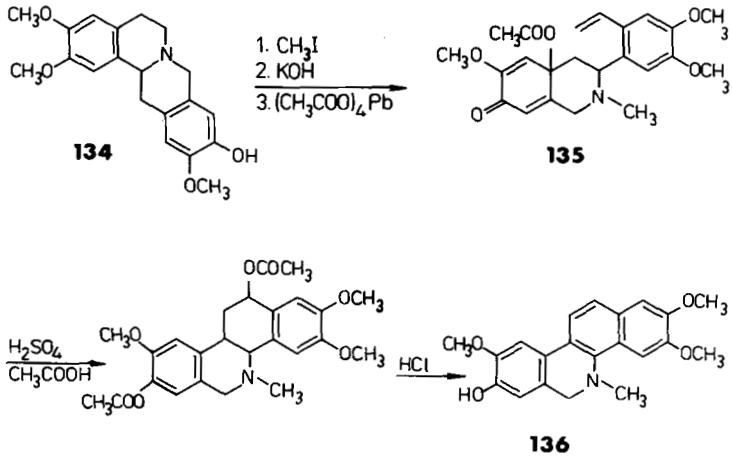
which involved formation of 2-aryl-1-tetralone **131.** This compound is converted to the alkaloid **58** in three steps (for the reaction sequence see Scheme 18). The Ishii modification of the Robinson pathway to the benzophenanthridine nucleus proved to be a profitable method for the preparation of benzophenanthridine alkaloids in sufficient yield, e.g., for fagaronine the overall yield was 15% based on the starting 3,4-dimethoxybenzaldehyde. The improved methods of preparation of some key intermediates for this type of synthesis are described (*174,175*). Most recently, Šmidrkal reported a synthetic route to fagaronine by photochemical cyclization of *N*-(6′-bromo-2′,3′-dimethoxybenzyl)-6-isopropoxy-7-methoxy-1-naphthylamine (Kessar photosynthetic method) (*176*). The synthesis of *N*-demethylfagaronine by photocyclization of a bromo-substituted *N*-benzoylnaphthylamine **132** was published by Ninomiya *et al.* (*177*).

From the syntheses of nitidine analogs the four-step synthesis of 12-hydroxy-2,3,8,9-tetramethoxybenzophenanthridine (**133**) is of interest (*178*) (Scheme 22). The starting compounds are easily available and the overall yield is 25%. 8-Hydroxy-5-methyl-2,3,9-trimethoxy-5,6-dihydrobenzophenanthridine (**136**) has been prepared from protoberberine **134** via the methine base **135** (*179*) (Scheme 23). This biometic approach to benzophenanthridines is of little significance from the viewpoint of a practical preparation.



133

SCHEME 22. Synthesis of 12-hydroxy-2,3,8,9-tetramethoxybenzophenanthridine (**133**).



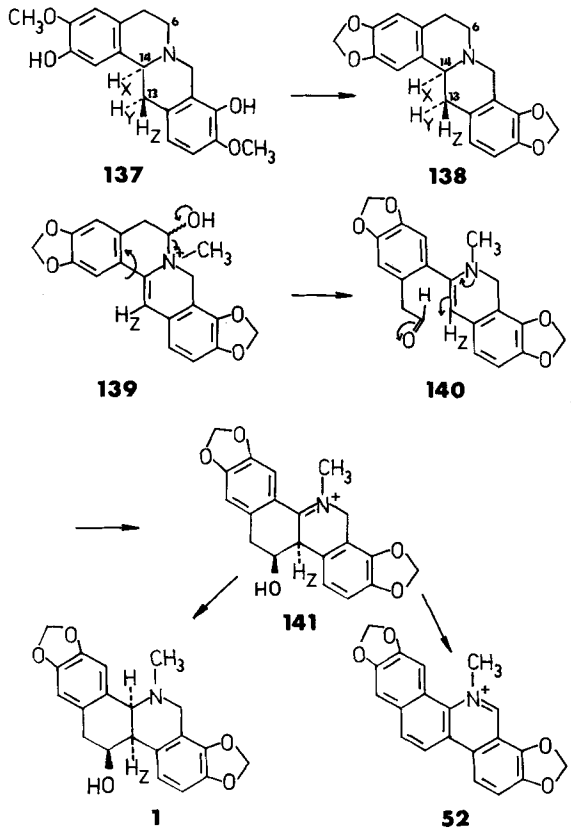
134 **135** **136**

SCHEME 23. Transformation of 10-hydroxy-2,3,11-trimethoxytetrahydroberberine (**134**) to 8-hydroxy-2,3,9-trimethoxy-5,6-dihydrobenzophenanthridine (**136**).

VII. Biosynthesis

The benzophenanthridine alkaloids arise from protoberberine precursors by cleavage of the N—C-6 bond and formation of a new bond between C-6 and C-13 (*180*).

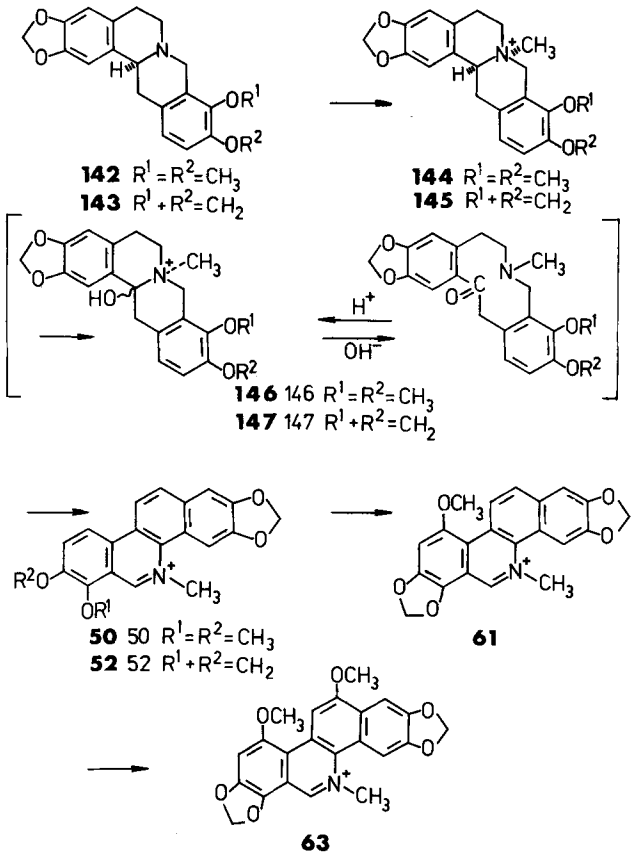
Battersby *et al.* (*181*) used specifically labeled compounds to establish the biogenesis of N-methylated benzophenanthridines in *Chelidonium majus*. The final stages of the pathway are shown in Scheme 24. After dopamine, the key



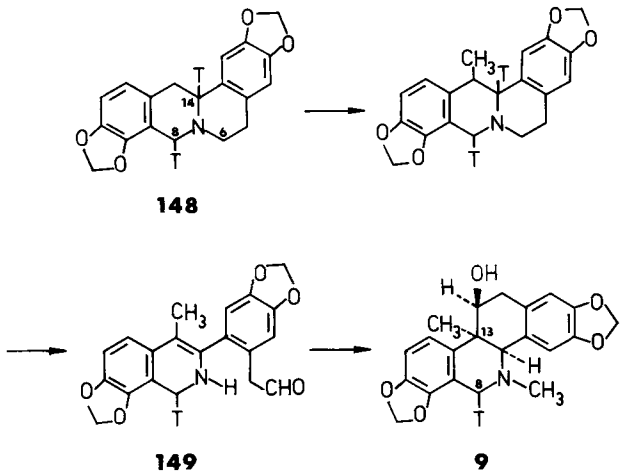
SCHEME 24. The Battersby pathway of biosynthesis of benzophenanthridine alkaloids.

intermediate is (+)-reticuline, which is cyclized oxidatively to (−)-scoulerine (**137**). The next step is formation of two methylenedioxy groups to produce stylopine (**138**). No intermediates have been isolated for the subsequent stages that are thought to involve N-methylation, 6-hydroxylation, and 13,14-dihydrogenation. The hydrogen atoms, removed from C-13 and C-14 of stylopine (**138**), are lost from the same face of this molecule. The subsequent rearrangement of compound **139** affords chelidonine (**1**) by cleavage of aldehyde enamine **140** and by reduction of the iminium intermediate **141** and then sanguinarine (**52**) by oxidative dehydration of **141.** Oxidation of the methylene group at C-6 to the aldehyde level involves stereospecific removal of the hydrogen atom in the *S* region. Pro-*R* hydrogen at C-13 is specifically retained in chelidonine. This is probably an example of stereospecific biosynthetic hydroxylation with retention of configuration.

Takao *et al.* (*182*) used the callus tissues of *Macleaya cordata* to study the stereospecifity of the pathway for the biosynthesis of chelerythrine (**50**), sanguinarine (**52**), chelirubine (**61**), and macarpine (**63**) from tetrahydroprotoberberine precursors. Predominantly the (−)-(*S*)-enantiomers and *cis*-*N*-methyl derivatives of tetrahydroprotoberberines can be stereospecifically metabolized to the benzophenanthridine skeleton. By incorporation experiments, the following biosynthetic pathways were defined: (−)-(*S*)-7,8,13,14-tetrahydroberberine (**142**) → (−)-*cis*-*N*-methyl-7,8,13,14-tetrahydroberberinium salt (**144**) → allocryptopine (**146**) → chelerythrine (**50**) and −)-7,8,13,14-tetrahydrocoptisine (**143**) → (−)-*cis*-*N*-methyl-7,8,13,14-tetrahydrocoptisinium salt (**145**) → → protopine (**147**) → sanguinarine (**52**) → chelirubine (**61**) → → macarpine (**63**) (Scheme 25). The conversion shown in Scheme 25 also takes place in intact *Macleaya cordata* plants.



SCHEME 25. Conversion of protoberberines to benzophenanthridines.



SCHEME 26. Suggested pathway for the biosynthesis of corynoline (**9**) from stylopine (**148**).

According to Yagi *et al.* (*183*), [8,14-^3H]stylopine (**148**) is a precursor of corynoline (**9**) in *Corydalis incisa* (Scheme 26). Stylopine (**148**) is transformed to corynoline (**9**) via the intermediate **149** by oxidative cleavage of the N—C-6 bond, followed by bond formation between the C-6 and C-13 atoms. The 14-^{3}H is specifically lost and one hydrogen at C-8 is retained in corynoline.

The biogenesis of N-demethylated benzophenanthridine alkaloids, e.g., norchelidonine (**3**) and luguine (**8**), is still unknown. Castedo *et al.* (*117*) found that the oxidative conversions (−)-norchelidonine (**3**) to (+)-luguine (**8**) are easily carried out by using a one-electron oxidant (Scheme 2). Their results may be of some relevance to future incorporation studies of the biogenetic origin of *N*-demethylbenzophenanthridines.

The callus tissues from 11 species of Papaveraceae were found to contain protopine and dihydrosanguinarine (**27**), oxosanguinarine (**28**), norsanguinarine (**46**), and sanguinarine (**52**) (*184*). Chelerythrine (**50**) and protoberberine alkaloids, which are present in intact plants, were not detected. The formation of sanguinarine and its derivatives **27**, **28**, and **46** in addition to protopine, was confirmed in the callus tissues of *Papaver bracteatum* Lindl. (*185*) and in those of *Papaver somniferum* (*52,186*). Recently, Forche *et al.* (*187*) reported that dihydrochelerythrine (**20**), dihydrosanguinarine (**27**), dihydrochelirubine (**40**), and dihydromacarpine (**42**) were obtained from a cell suspension culture of *Eschscholtzia californica*. The yields of alkaloids depended on the conditions of the media. This accumulation of benzophenanthridine alkaloids indicates that the simplest biogenetic pathway of alkaloid formation initiated from (+)-reticuline takes place in plant cells.

VIII. Biological Activity

The pharmacology of chelidonine (**1**), chelerythrine (**50**), sanguinarine (**52**), nitidine (**56**), and fagaronine (**58**) has been summarized (*15,16*), and their interactions with various biopolymers have been reviewed (*17,18*). In phytotherapy, extracts containing benzophenanthridine alkaloids from *Chelidonium majus, Sanguinaria canadensis,* and *Fagara zanthoxyloides* are used (*188*).

Recently, chelidonine has been retested because of its significant cytotoxicity in KB and P388 cell cultures (*137*). Chelidonine displays moderate *in vivo* activity against L-1210, P388 leukemia, and Walker carcinosarcoma (*189*). *In vitro* experiments showed that chelidonine *N*-oxide has a higher cytotoxicity than does chelidonine (*190*). These two compounds have also been tested for their antibiotic activity. The effects of chelidonine and its derivatives are, however, not so pronounced as to find practical application in human medicine.

At present, much interest centers on studies of biological activity of quaternary benzophenanthridine alkaloids. The main effects that may act on their biological activity are: the planarity of the molecule, the type of substitution on ring D, and the acidity of the quaternary cation (*121,191*).

Chelerythrine, sanguinarine, and their 6-cyano and 6-alkoxydihydro derivatives produce good antimicrobial effects (*60,192,193*). The alkaloids **50** and **52** have been tested for their antiinflammatory activity (*193*). Because of their low toxicity and high antiinflammatory effect, they are recommended for medical use in the treatment of oral inflammatory processes (*194*). The fraction of quaternary alkaloids from roots of *Chelidonium majus,* containing chelerythrine and sanguinarine, has an antifungal effect on some *Trichophyton* strains (*195*). The antitumor, analgesic, and antiinflammatory activities of some semisynthetic derivatives of sanguinarine and chelilutine (**62**) have also been tested (*196,197*).

Nitidine proved to be promising as a clinically useful antitumor agent; however, after preclinical pharmacologic and toxicologic evaluations, further studies had to be stopped (*16,198*). Fagaronine displayed an antitumor activity against L-1210 and P388 leukemia in mice and a lower toxicity than did **56** (*16*). However, fagaronine showed a narrow spectrum of activity in animal tumor systems. This group of alkaloids does not appear to be very promising for the further development of cancer research (*198*).

Quaternary benzophenanthridines interact with biopolymers by three main mechanisms, i.e., reaction of the iminium bond with nucleophilic groups of the receptor binding site, an intercalation of the alkaloid between pairs of DNA bases, or interaction of the quaternary cation with the anionic site of the biopolymers (*18*). Na^+/K^+-transporting ATPase, whose interaction with alkaloids has been investigated more profoundly, shows a high affinity to chelerythrine, sanguinarine, and their analogs and no affinity to nitidine and

fagaronine (*199–201*). Chelerythrine and sanguinarine inhibit rat liver L-alanine and L-aspartate aminotransferases (*123*). It is assumed that the inhibitory effect of these alkaloids on Na^+/K^+-transporting ATPase and aminotransferase activities may be brought about by formation of an adduct between the thiol groups of the enzyme and the iminium bond of the quaternary cation. Quaternary benzophenanthridine alkaloids serve as sensitive probes for anionic sites of acetylcholinesterase (*122,202*) and butyrylcholinesterase (*203*). Sanguinarine inhibits human plasma diamine oxidase (*204*). The mechanism of this inhibition is, however, still obscure. The binding mechanisms of sanguinarine and its pseudobase with DNA have been studied (*205*).

Nitidine, fagaronine and some of their derivatives inhibit reverse transcriptase activity of various RNA oncogenic viruses through binding to specific base pairs, e.g., A–T, of the template–primer (*206*). Fagaronine was found to be the most potent inhibitor. Nitidine, 6-methoxydihydronitidine, and *O*-methylfagaronine inhibit tRNA methyltransferase and catechol *O*-methyltransferase activities (*207*).

Addendum

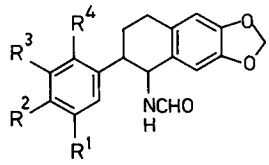
Recently, Ninomiya and Naito summarized the chemistry and syntheses of benzophenanthridine alkaloids (*208*). A survey of some benzophenanthridines constitutes a part of the review on taxonomy and known biological properties of *Toddalia asiatica* (*209*). Isodecarine (**44**) (Table II and Ref. *73*) is, according to one of the authors (J. Vaquette), identical with decarine (**43**). The addendum to Table II shows the benzophenanthridines isolated for the first time from plant species studied in 1984 (*210–216*).

Walterová (*217*) reported the application of capillary isotachophoresis for the determination of chelerythrine (**50**), sanguinarine (**52**), sanguilutine (**60**), and chelilutine (**62**). Sanguinarine in dental plaque and saliva was determined by reversed-phase HPLC analysis (*218*).

The new high-field NMR studies of a variety hexahydrobenzophenanthridines and their salts demonstrated an agreement of the solution and solid state conformations in this class of alkaloids (*219*). Specifically, the B-ring twist half-chair solid-state conformation for (+)-14-epicorynoline (**18**) *p*-bromobenzoate (*100*) is identical to the B-ring twist half-chair solution conformation of (+)-11-*O*-acetyl-14-epicorynoline (**19**). The B-ring twist half-boat solid-state conformation of (±)-corynoline (**9**) *p*-bromobenzoate (*220*) is identical to the B-ring twist half-boat solution conformation of (±)-*O*-acetylcorynoline (**10**), and the B-ring half-chair solid-state conformation of (+)-chelidonine (**1**) *p*-bromobenzoate (*97*) is identical to the B-ring half-chair solution conformation of (+)-*O*-acetylchelido-

nine (*219*). Two crystal forms of (+)-chelidonine *p*-bromobenzoate show only minor differences in their conformations (*97*).

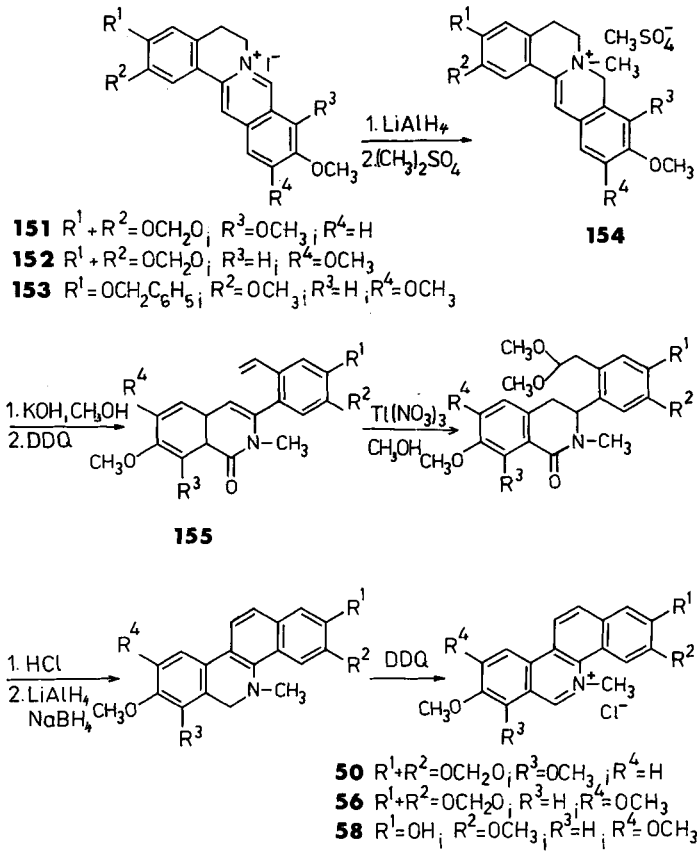
A full report about reductive N-methylation of *N*-demethylbenzophenanthridines (see Refs. *11* and *118*) has been published (*221*). The *N*-methyldihydro bases are readily convertible to the corresponding quaternary benzophenanthridines by oxidation with Jones reagent or DDQ in yields of 70–93%. Experimental conditions for the air oxidation of 6-cyanodihydrobenzophenanthridines (see Ref. *11*) to the corresponding 6-oxo bases are also described. Ishii *et al.* (*222*) reported on a detailed examination of Bayer–Villiger type oxidation of quaternary alkaloids chelerythrine (**50**), nitidine (**56**), avicine (**57**), and the *O*-benzyl-*N*-methyl derivative of decarine (**43**) with *m*-CPBA in HMPA to naturally occurring secobenzophenanthridines (see Refs. *11,66,68,* and *118*).



150a $R^1=R^2=R^3=OCH_3$; $R^4=H$
b $R^1=R^4=H$; $R^2+R^3=OCH_2O$
c $R^1=OCH_3$; $R^2=H$; $R^3+R^4=OCH_2O$
d $R^1+R^2=OCH_2O$; $R^3=H$; $R^4=OCH_3$

The pK_{R+} values of pseudobase formation 7.53 for chelerythrine and 7.32 for sanguinarine in water were published (*223*). These values were obtained potentiometrically at alkaloid concentrations of 10^{-3} *M*. The difference between pK_{R+} of **50** and **52** in Table VI and the later values is probably caused by an unsuitable method (*223*).

Further examination of Bischler–Napieralski cyclization of the formamide derivatives **150a–d,** key intermediates in the Robinson synthetic sequence for benzophenanthridine alkaloids, was described (*224*). Ishii *et al.* (*225*) published the experimental conditions of the synthesis of sanguirubine (**59**) and sanguilutine (**60**) from 2-aryl-1-tetralones (see Scheme 18 and reference *162*). Application of Bischler–Napieralski cyclization of *O*-methyl derivatives of isoarnottianamide (**69**) and integriamide (**70**) to chelilutine (**62**) and chelirubine (**61**) is also reported. Hanaoka *et al.* (*226,227*) converted berberine (**151**), pseudoberberine (**152**) and *O*-benzyldehydrodiscretine (**153**) to chelerythrine (**50**), nitidine



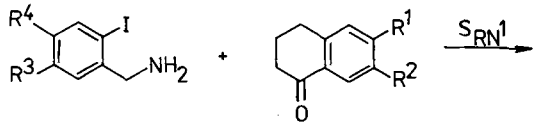
151 $R^1+R^2=OCH_2O$; $R^3=OCH_3$; $R^4=H$
152 $R^1+R^2=OCH_2O$; $R^3=H$; $R^4=OCH_3$
153 $R^1=OCH_2C_6H_5$; $R^2=OCH_3$; $R^3=H$; $R^4=OCH_3$

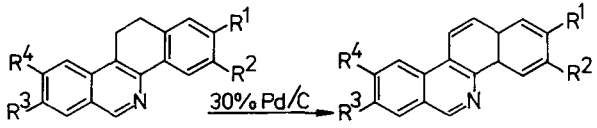
154 **155**

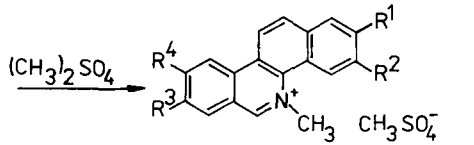
50 $R^1+R^2=OCH_2O$; $R^3=OCH_3$; $R^4=H$
56 $R^1+R^2=OCH_2O$; $R^3=H$; $R^4=OCH_3$
58 $R^1=OH$; $R^2=OCH_3$; $R^3=H$; $R^4=OCH_3$

SCHEME 27. Transformation of protoberberines to benzophenanthridines.

(**56**) and fagaronine (**58**) via Hofmann degradation of quaternary salt **154** to the anamide **155,** followed by cyclization, reduction, and dehydrogenation (Scheme 27). Beugelmans *et al.* (*228*) describe a generally applicable synthesis of nitidine-type alkaloids (yields 16–25%). The radical nucleophilic substitution reaction ($S_{RN}1$) between *o*-iodobenzylamine and 1-tetralone enolate affords 11,12-dihydrobenzophenanthridine whose dehydrogenation and quaternization yield the corresponding alkaloid (Scheme 28). Thus, nitidine (**56**), avicine (**57**), fagaronine (**58**), and allonitidine (**156**) were prepared (*228*). A study of the course of pericyclic reaction of the oxo derivative of compound **105** (see Scheme 12 and Ref. *150*) in the presence of nitrosobenzene was published by Onda *et al.* (*229*). The stereochemistry of the photoadducts obtained by this reaction is discussed on the basis of ^1H- and ^{13}C-NMR spectral data in Ref. *230*. The indenoisoquinoline analog **157** of nitidine has been prepared (*231*) (Scheme 29).







56 $R^1 + R^2 = OCH_2O$; $R^3 = R^4 = OCH_3$

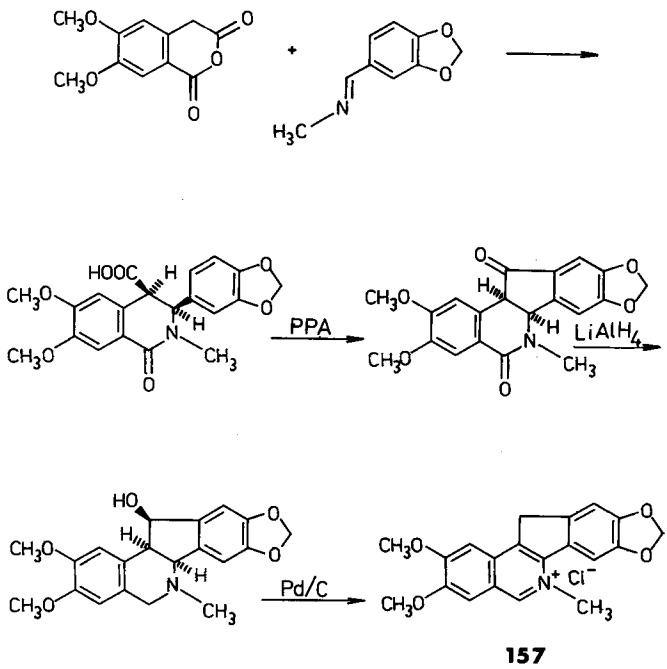
57 $R^1 + R^2 = R^3 + R^4 = OCH_2O$

58 $R^1 = OH$; $R^2 = R^3 = R^4 = OCH_3$

156 $R^1 = R^2 = OCH_3$; $R^3 + R^4 = OCH_2O$

SCHEME 28. Syntheses of benzophenanthridines by radical nucleophilic substitution reaction ($S_{RN}1$) between *o*-iodobenzylamine and 1-tetralone enolate.

Sanguinarine showed antiplaque activity in humans (*218*). For plaque-retentive properties in combination with antimicrobial and antiinflammatory actions, sanguinarine forms a component of toothpastes and oral rinses sold in the United States since 1984. Fagaronine, *N*-demethylfagaronine, and some derivatives were tested for antitumor activity (*232*). The results showed the activity of quaternary salt **58** to differ from that of N-demethylated bases, which are explainable by a different mechanism of action on the molecular level. The mechanism of interaction of fagaronine with nucleic acids is studied in Ref. *233*. The most likely mode of interaction is intercalation. Compound **157** has significant antitumor activity against L1210 lymphoid leukemia, P388 lymphocytic leukemia, and B16 melanocarcinoma (*231*). Antitumor properties of the benzophenanthridine alkaloids nitidine (**56**) and fagaronine (**58**) were described by Suffness and Cordell in Vol. 25 of this series.



157

SCHEME 29. Synthesis of the indenoisoquinoline analog of nitidine (**56**).

Acknowledgment

I would like to thank Dr. Padam N. Sharma, Central Drug Research Institute, Lucknow, India, for help in collection of literature on benzophenanthridine alkaloids.

REFERENCES

1. F. Šantavý, *Alkaloids (N.Y.)* **12,** 417 (1970).
2. F. Šantavý, *Alkaloids (N.Y.)* **17,** 493 (1979).
3. I. Mester, *Fitoterapia* **44,** 123 (1973).
4. I. Mester, *Fitoterapia* **48,** 268 (1977).
5. B. D. Krane, M. O. Fagbule, M. Shamma, and B. Gözler, *J. Nat. Prod.* **47,** 1 (1984).
6. K. W. Bentley, series of reviews in *Alkaloids (London)* **1,** 136 (1971); **2,** 161 (1972); **3,** 149 (1973); **4,** 174 (1974); **5,** 155 (1975); **6,** 150 (1976); **7,** 139 (1977); **9,** 122 (1979); **10,** 120 (1981); **11,** 113 (1981); **12,** 131 (1982); **13,** 155 (1983).
7. T. Kametani, *in* "The Chemistry of the Isoquinoline Alkaloids," Vol. 2. Kinkodo Inc., Sendai, 1974.
8. M. Shamma, *in* "The Isoquinoline Alkaloids," p. 317. Academic Press, New York, 1972.
9. M. Shamma and J. L. Moniot, *in* "Isoquinoline Alkaloids Research: 1972–1977," p. 261. Plenum, New York, 1978.

10. T. Kametani, ed., *Heterocycles, Suppl. 1,* 363 (1983).
11. H. Ishii and T. Ishikawa, *Yakugaku Zasshi* **101,** 663 (1981).
12. S. D. Phillips and R. N. Castle, *J. Heterocyc. Chem.* **18,** 223 (1981).
13. S. F. Dyke, *in* "Rodd's Chemistry of Carbon Compounds" (S. Coffey, ed.), Vol. IV, p. 173. Elsevier, Amsterdam, 1978.
14. M. J. Hearn and S. L. Swanson, *J. Heterocycl. Chem.* **18,** 207 (1981).
15. V. Preininger, *Alkaloids (N.Y.)* **15,** 241 (1975).
16. G. A. Cordell and N. R. Farnsworth, *Heterocycles* **4,** 393 (1976).
17. D. Walterová, V. Preininger, and V. Šimánek, *Acta Univ. Palacki. Olomuc., Fac. Med.* **97,** 121 (1984).
18. J. Ulrichová, D. Walterová, and V. Šimánek, *Acta Univ. Palacki. Olomuc., Fac. Med.* **106,** 31 (1981).
19. M. Szaufer, H. Kowalewski, and J. D. Phillipson, *Phytochemistry* **17,** 1446 (1978).
20. A. Ghanbarpour, A. Shafiee, and M. Parchami, *J. Nat. Prod.* **41,** 472 (1978).
21. A. Shafiee, A. Ghanbarpour, I. Lalezari, and S. Lajevardi, *J. Nat. Prod.* **42,** 174 (1979).
22. L. Castedo, D. Dominguez, J. M. Saá, and R. Suau, *Tetrahedron Lett.*, 2923 (1978).
23. Fang Qicheng, Lin Mao, and Weng Qingmei, *Planta Med.* **50,** 25 (1984).
24. N. Takao, M. Kamigauchi, and K. Iwasa, *Tetrahedron* **35,** 1977 (1979).
25. Fang Qicheng, Lin Mao, and Weng Qingmei, *Yaoxue Xuebao* **16,** 708 (1981); *Chem. Abstr.* **96,** 31687 (1982).
26. K. Iwasa, N. Takao, G. Nonaka, and I. Nishioka, *Phytochemistry* **18,** 1725 (1979).
27. N. Takao and K. Iwasa, *Chem. Pharm. Bull.* **27,** 2194 (1979).
28. Kh. Sh. Khusainova and Yu. D. Sadykov, *Khim. Prir. Soedin.*, 670 (1981).
29. J. Berlin, E. Forche, and V. Wray, *Z. Naturforsch. C* **38,** 346 (1983).
30. L. Castedo, D. Dominguez, M. Pereira, J. Saá, and R. Suau, *Heterocycles* **16,** 533 (1981).
31. F. Y. Chou, K. Hostettman, I. Kubo, K. Nakanishi, and M. Taniguchi, *Heterocycles* **7,** 969 (1977).
32. P. G. Waterman and S. G. Khalid, *Biochem. Syst. Ecol.* **9,** 45 (1981).
33. P. N. Sharma, A. Shoeb, R. S. Kapil, and S. P. Popli, *Phytochemistry* **20,** 2781 (1981).
34. J. A. Swinehart and F. R. Stermitz, *Phytochemistry* **19,** 1219 (1980).
35. P. N. Sharma, A. Shoeb, R. S. Kapil, and S. P. Popli, *Phytochemistry* **21,** 252 (1982).
36. P. N. Sharma, A. Shoeb, R. S. Kapil, and S. P. Popli, *Indian J. Chem. Sect. B.* **17,** 299 (1979).
37. H. Itokawa, A. Ikuta, N. Tsutsui, and I. Ishigura, *Phytochemistry* **17,** 839 (1978).
38. H. Ishii, T. Ishikawa, K. Hosoya, and N. Takao, *Chem. Pharm. Bull.* **26,** 166 (1978).
39. E. M. Assem, I. A. Benages, and S. M. Albonico, *Planta Med.* **48,** 77 (1983).
40. H. Ishii, T. Ishikawa, M. Mihara, and M. Akaike, *Yakugaku Zasshi* **103,** 279 (1983).
41. E. M. Assem, I. A. Benages, and S. M. Albonico, *Phytochemistry* **18,** 511 (1979).
42. M. Alimova, I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 642 (1982).
43. B. Sener, B. Gözler, R. D. Minard, and M. Shamma, *Phytochemistry* **22,** 2073 (1983).
44. N. N. Margvelashvili, O. N. Tolkachev, N. P. Prisyazhnyuk, and A. T. Kiryanova, *Khim. Prir. Soedin.*, 592 (1978).
45. D. S. Bhakuni and R. Chaturvedi, *J. Nat. Prod.* **46,** 466 (1983).
46. M. Alimova, I. A. Israilov, M. S. Yunusov, N. D. Abdullaev, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 727 (1982).
47. V. B. Pandey, A. B. Ray, and B. Dasgupta, *Phytochemistry* **18,** 695 (1979).
48. M. E. Popova, V. Šimánek, L. Dolejš, B. Smysl, and V. Preininger, *Planta Med.* **45,** 120 (1982).
49. T. Gözler, M. A. Önür, R. Minard, and M. Shamma, *J. Nat. Prod.* **46,** 414 (1983).

50. R. T. Boulware and F. R. Stermitz, *J. Nat. Prod.* **44,** 200 (1981).
51. H. Ishii and T. Ishikawa, *Yakugaku Zasshi* **97,** 890 (1977).
52. E. Forche and B. Frantz, *Planta Med.* **42,** 137 (1981).
53. M. Alimova, I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 671 (1981).
54. H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Yakugaku Zasshi* **96,** 1458 (1976).
55. V. Preininger, L. Dolejš, B. Smysl, and V. Šimánek, *Planta Med.* **36,** 213 (1979).
56. K. Iwasa and N. Takao, *Phytochemistry* **21,** 611 (1982).
57. M. E. Popova, A. N. Boeva, L. Dolejš, V. Preininger, V. Šimánek, and F. Šantavý, *Planta Med.* **40,** 156 (1980).
58. E. Táborská, F. Věžník, L. Slavíková, and J. Slavík, *Collect. Czech. Chem. Commun.* **43,** 1108 (1978).
59. I. Addae-Mensah and E. A. Sofowora, *Planta Med.* **35,** 94 (1979).
60. O. O. Odebiyi and E. A. Sofowora, *Planta Med.* **36,** 204 (1979).
61. F. R. Stermitz, M. A. Caolo, and J. A. Swinehart, *Phytochemistry* **19,** 1469 (1980).
62. C. Tani, N. Nagakura, and C. Kuriyama, *Yakugaku Zasshi* **98,** 1658 (1978).
63. O. E. Lasskaja and O. N. Tolkachev, *Khim. Prir. Soedin.*, 764 (1978).
64. J. Vaquette, A. Cave, and P. G. Waterman, *Plant. Med. Phytother.* **12,** 235 (1978).
65. F. Věžník, E. Táborská, and J. Slavík, *Collect. Czech. Chem. Commun.* **46,** 926 (1981).
66. H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Tetrahedron Lett.*, 1203 (1976).
67. H. Ishii, T. Ishikawa, and J. Haginiwa, *Yakugaku Zasshi* **97,** 890 (1977).
68. H. Ishii, I.-S. Chen, T. Ishikawa, M. Ishikawa, and S.-T. Lu, *Heterocycles* **12,** 1037 (1979).
69. H. Ishii, I.-S. Chen, M. Akaike, T. Ishikawa, and S.-T. Lu, *Yakugaku Zasshi* **102,** 182 (1982).
70. J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.* **49,** 704 (1984).
71. A. Ikuta and H. Itokawa, *Phytochemistry* **15,** 577 (1976).
72. M. H. Wang, *Yao Hsueh Tung Pao* **16,** 48 (1981); *Chem. Abstr.* **95,** 192260 (1981).
73. J. Vaquette, A. Cavé, P. G. Waterman, T. Sévenet, and J. Pusset, Colloques Internationaux du CNRS, No. 298: "Substances Naturelles d'Interet Biologique du Pacifique," p. 137. edition du CNRS, (1980).
74. P. D. Desai, T. R. Govindachari, K. Nagarajan, and N. Vishwanathan, *Indian J. Chem.* **5,** 41 (1967).
75. F. R. Stermitz and I. A. Sharifi, *Phytochemistry* **16,** 2003 (1977).
76. N. Decaudain, N. Kunesch, and J. Poisson, *Ann. Pharm. Fr.* **35,** 521 (1977).
77. V. Šimánek and V. Preininger, *Heterocycles* **6,** 475 (1977).
78. J. W. Bunting, *Adv. Heterocycl. Chem.* **25,** 1 (1979).
79. D. S. Seigler, *Alkaloids (N.Y.)* **16,** 1 (1978).
80. M. Turowska, *Herba Pol.* **15,** 18 (1969).
81. C. Franz and D. Fritz, *Herba Hung.* **18,** 245 (1979).
82. K. Hostettmann, M. J. Pettei, I. Kubo, and K. Nakanishi, *Helv. Chim. Acta* **60,** 670 (1977).
83. P. Karrer, *Ber. Dtsch. Chem. Ges.* **50,** 212 (1917).
84. J. Gadamer and A. Stichel, *Arch. Pharm.* **262,** 488 (1924).
85. E. Späth and E. Kuffner, *Ber. Dtsch. Chem. Ges.* **64,** 1123 (1931).
86. R. A. Konovalova, S. Yunusov, and A. P. Orechov, *Chem. Zentralbl.* **1,** 2530 (1941).
87. J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.* **20,** 21 (1955).
88. J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.* **25,** 1667 (1960).
89. H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, 1840 (1959).
90. H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, 4007 (1959).
91. F. Fish and P. G. Waterman, *Phytochemistry* **10,** 3322 (1971).
92. F. Fish and P. G. Waterman, *Phytochemistry* **10,** 3325 (1971).
93. P. G. Waterman, *Phytochemistry* **15,** 578 (1976).

94. C. Scholz, R. Hänsel, and C. Hille, *Pharm. Ztg.* **121,** 1571 (1976).
95. W. E. Freytag, *Planta Med.* **40,** 278 (1980).
96. D. Walterová, V. Preininger, and V. Šimánek, *Planta Med.* **50,** 149 (1984).
97. N. Takao, N. Morita, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and S. Fujii, *Tetrahedron Lett.*, 495 (1979); *Acta Crystallogr. Sect. B.* **37,** 2043 (1981).
98. N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.* **26,** 1880 (1978).
99. N. Takao, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and A. Wakahara, *Tetrahedron Lett.*, 805 (1974).
100. N. Takao, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and A. Wakahara, *Tetrahedron* **35,** 1099 (1979).
101. D. W. Hughes and D. B. MacLean, *Alkaloids (N.Y.)* **18,** 217 (1981).
102. T. A. Crabb, *in* "Annual Reports on NMR Spectroscopy" (G. A. Webb, ed.), Vol. 13, p. 60. Academic Press, London, 1982.
103. M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids." Plenum, New York, 1979.
104. N. Takao, M. Kamigauchi, K. Iwasa, and N. Morita, *Arch. Pharm.* **317,** 223 (1984).
105. M. Cushman and T.-C. Choong, *Heterocycles* **14,** 1935 (1980).
106. I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Perkin Trans. 1,* 212 (1980).
107. I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Perkin Trans. 1,* 2165 (1983).
108. H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K.-I. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.* **26,** 864 (1978).
109. N. Takao, M. Kamigauchi, M. Sugiura, I. Ninomiya, O. Miyata, and T. Naito, *Heterocycles* **16,** 221 (1981).
110. L. Hruban, F. Šantavý, and S. Hegerová, *Collect. Czech. Chem. Commun.* **35,** 3420 (1970).
111. F. Šantavý, *Heterocycles* **14,** 1159 (1980).
112. V. Šimánek, V. Preininger, S. Hegerová, and F. Šantavý, *Collect. Czech. Chem. Commun.* **37,** 2746 (1972).
113. D. Walterová, V. Preininger, F. Grambal, V. Šimánek, and F. Šantavý, *Heterocycles* **14,** 597 (1980).
114. N. Takao, *Chem. Pharm. Bull.* **19,** 247 (1971).
115. G. Nonaka, H. Okabe, I. Nishioka, and N. Takao, *Yakugaku Zasshi* **93,** 87 (1973).
116. G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.* **23,** 521 (1975).
117. L. Castedo, D. Dominguez, A. Puga, J. M. Saá, and R. Suau, *Heterocycles* **20,** 1895 (1983).
118. T. Ishikawa and H. Ishii, *Heterocycles* **5,** 275 (1976).
119. J. P. Gillespie, L. G. Amoros, and F. R. Stermitz, *J. Org. Chem.* **39,** 3239 (1974).
120. R. K.-Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.* **18,** 66 (1975).
121. M. A. Caolo and F. R. Stermitz, *Heterocycles* **12,** 11 (1979).
122. J. Ulrichová, D. Walterová, V. Preininger, J. Slavík, J. Lenfeld, M. Cushman, and V. Šimánek, *Planta Med.* **48,** 111 (1983).
123. D. Walterová, J. Ulrichová, V. Preininger, J. Lenfeld, J. Lasovský, and V. Šimánek, *J. Med. Chem.* **24,** 1100 (1981).
124. K. Haisová, J. Slavík, and L. Dolejš, *Collect. Czech. Chem. Commun.* **38,** 3312 (1973).
125. M. Tin-Wa, C. L. Bell, C. Bevelle, H. H. S. Fong, and N. R. Farnsworth, *J. Pharm. Sci.* **63,** 1476 (1974).
126. H. Ishii, T. Ishikawa, Y.-I. Ichikawa, and M. Sakamoto, *Chem. Pharm. Bull.* **25,** 3120 (1977).
127. J. M. Probst, *Ann. Pharm.* (Lemgo, *Ger.*) **29,** 113 (1839).
128. W. Oppolzer and K. Keller, *J. Am. Chem. Soc.* **93,** 3836 (1971).
129. W. Oppolzer, *Heterocycles* **14,** 1617 (1980).
130. W. Oppolzer and C. Robbiani, *Helv. Chim. Acta* **66,** 1119 (1983).

131. I. Ninomiya and T. Naito, *Heterocycles* **15,** 1433 (1981).
132. I. Ninomiya and T. Naito, *Alkaloids (N.Y.)* **22,** 214–224 (1983).
133. I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles* **7,** 137 (1977).
134. I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Perkin Trans. 1,* 2171 (1983).
135. I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles* **7,** 131 (1977).
136. M. Cushman, T.-C. Choong, J. T. Valko, and M. P. Koleck, *Tetrahedron Lett.* **21,** 3845 (1980).
137. M. Cushman, T.-C. Choong, J. T. Valko, and M. P. Koleck, *J. Org. Chem.* **45,** 5067 (1980).
138. M. Onda, Y. Harigaya, and T. Suzuki, *Chem. Pharm. Bull.* **25,** 2935 (1977).
139. Y. Harigaya, S. Takamatsu, H. Yamaguchi, T. Kusano, and M. Onda, *Chem. Pharm. Bull.* **28,** 2029 (1980).
140. Y. Harigaya, K. Yotsumoto, S. Takamatsu, H. Yamaguchi, and M. Onda, *Chem. Pharm. Bull.* **29,** 2557 (1981).
141. Y. Harigaya, S. Takamatsu, H. Yamaguchi, and M. Onda, *Chem. Pharm. Bull.* **30,** 1244 (1982).
142. I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Chem. Commun.,* 437 (1976).
143. I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles* **5,** 67 (1976).
144. M. Cushman and Y. P. Gupta, *Heterocycles* **19,** 1431 (1982).
145. M. Cushman, A. Abbaspour, and Y. P. Gupta, *Heterocycles* **19,** 1587 (1982).
146. M. Cushman, A. Abbaspour, and L. P. Gupta, *J. Am. Chem. Soc.* **105,** 2873 (1983).
147. J. R. Falk, S. Manna, and C. Mioskowski, *J. Am. Chem. Soc.* **105,** 631 (1983).
148. M. Onda, K. Yuasa, J. Okada, K. Kataoka, and K. Abe, *Chem. Pharm. Bull.* **21,** 1333 (1973).
149. M. Onda, K. Yuasa, and J. Okada, *Chem. Pharm. Bull.* **22,** 2365 (1974).
150. M. Onda, H. Yamaguchi, and Y. Harigaya, *Chem. Pharm. Bull.* **28,** 866 (1980).
151. M. Onda, Y. Harigaya, and J. Horie, *Chem. Pharm. Bull.* **26,** 3330 (1978).
152. H. Iida, I. Endo, M. Narimiya, and T. Kikuchi, *Heterocycles* **14,** 1325 (1980).
153. A. S. Bailey and C. R. Worthington, *J. Chem. Soc.,* 4535 (1956).
154. J. Šmidrkal, *Collect. Czech. Chem. Commun.* **49,** 1412 (1984).
155. S. V. Kessar, Y. P. Gupta, K. Dhingra, G. S. Sharma, and S. Narula, *Tetrahedron Lett.,* 1459 (1977).
156. J. Šmidrkal, *Collect. Czech. Chem. Commun.* **47,** 2140 (1982).
157. J. Šmidrkal, private communication.
158. K. Iwasa and N. Takao, *Heterocycles* **20,** 1535 (1983).
159. M. Onda and H. Yamaguchi, *Chem. Pharm. Bull.* **27,** 2076 (1979).
160. M. Sainsbury, S. F. Dyke, and B. J. Moon, *J. Chem. Soc. C,* 1797 (1970).
161. M. Shamma and H. H. Tomlinson, *J. Org. Chem.* **43,** 2852 (1978).
162. H. Ishii, T. Watanabe, and T. Ishikawa, *Chem. Pharm. Bull.* **26,** 3252 (1978).
163. T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.,* 835 (1937).
164. H. Ishii, T. Ishikawa, and Y.-I. Ichikawa, *Chem. Pharm. Bull.* **26,** 514 (1978).
165. T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocycl. Chem.* **10,** 31 (1973).
166. R. K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.* **10,** 85 (1973).
167. S. V. Kessar, G. Singh, and P. Balakrishnan, *Tetrahedron Lett.,* 2269 (1974).
168. W. J. Bengley and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 1,* 2324 (1977).
169. M. Cushman and L. Cheng, *J. Org. Chem.* **43,** 286 (1978).
170. S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron* **24,** 1467 (1968).
171. I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Neda, and K. Harada, *J. Chem. Soc., Perkin Trans. 1,* 762 (1975).
172. F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, and T. A. Stermitz, *J. Med. Chem.* **18,** 708 (1975).
173. H. Ishii, I.-S. Chen, and T. Ishikawa, *Chem. Pharm. Bull.* **31,** 2963 (1983).

174. H. Ishii, T. Ishikawa, T. Deushi, K. Harada, T. Watanabe, E. Ueda, T. Ishida, M. Sakamoto, E. Kawanabe, T. Takahashi, Y. Ichikawa, K. Takizawa, T. Masuda, and I.-S. Chen, *Chem. Pharm. Bull.* **31,** 3024 (1983).
175. H. Ishii, E. Kawanabe, K. Harada, T. Deushi, E. Ueda, T. Watanabe, Y. Ichikawa, M. Sakamoto, T. Ishida, T. Takanashi, K. Nakajima, and T. Ishikawa, *Chem. Pharm. Bull.* **31,** 3039 (1983).
176. J. Šmidrkal, *Collect. Czech. Chem. Commun.* (in press).
177. I. Ninomiya, T. Naito, and H. Ishii, *Heterocycles* **3,** 307 (1975).
178. T. A. Olugbade and R. D. Waigh, *J. Pharm. Pharmacol.*, 81 (1981).
179. T. Kametani, M. Takemura, M. Ihara, K. Fukumoto, and K. Takahashi, *Heterocycles* **6,** 99 (1977).
180. E. McDonald, *Chem. Heterocycl. Compds.* **38,** 275 (1981).
181. A. R. Battersby, J. Staunton, M. C. Summers, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1,* **45,** (1979).
182. N. Takao, M. Kamigauchi, and M. Okada, *Helv. Chim. Acta* **66,** 473 (1983).
183. A. Yagi, G. Nonaka, S. Makayama, and I. Nishioka, *Phytochemistry* **16,** 1197 (1977).
184. A. Ikuta, K. Syōno, and T. Furuya, *Phytochemistry* **13,** 2175 (1974).
185. I. N. Kuzovkina and S. A. Rabinovich, *Rastit. Resur.* **17,** 553 (1981); *Chem. Abstr.* **96,** 3669 (1982).
186. E. Forche, L. Witte, A. Bishoff, and J. Berlin, *Planta Med.* **45,** 165 (1982).
187. J. Berlin, E. Forche, V. Wray, J. Hammer, and W. Hoesel, *Z. Naturforsch., C Biosci.* **38,** 346 (1983).
188. W. H. Lewis and M. P. F. Elvin-Lewis, *in* "Medical Botany." Wiley, New York, 1977.
189. J. Zbierska and Z. Kowalewski, *Herba Pol.* **25,** 209 (1979).
190. J. Zbierska and Z. Kowalewski, *Herba Pol.* **26,** 61 (1980).
191. K. Y. Zee-Cheng, Y. Shon-Yen, and C. C. Cheng, *J. Med. Chem.* **21,** 199 (1978).
192. L. A. Mitscher, Y. H. Park, D. Clark, G. W. Clark, P. D. Hammesfahr, W.-N. Wu, and J. L. Beal, *J. Nat. Prod.* **41,** 145 (1978).
193. J. Lenfeld, M. Kroutil, E. Maršálek, J. Slavík, V. Preininger, and V. Šimánek, *Planta Med.* **43,** 161 (1981).
194. H. Černá, B. Fiala, J. Lenfeld, E. Maršálek, V. Preininger, and V. Šimánek, *Acta Univ. Palacki. Olomuc., Fac. Med.* **107,** 159 (1984).
195. N. Hejtmánková, D. Walterová, V. Preininger, and V. Šimánek, *Fitoterapia* **55,** 291 (1984).
196. J. M. G. Pereira and J. R. Madureira, Ger Offen. DE 3,236,455; *Chem. Abstr.* **99,** 71065 (1983).
197. W. Mowicky, PCT Int. Appl. WO 8300, 486; *Chem. Abstr.* **99,** 71067 (1983).
198. M. Suffness and J. D. Douros, *Med. Chem. (Academic)* **16,** 474.
199. H. G. Cohen, E. E. Seifen, K. D. Straub, C. Tiefenback, and F. R. Stermitz, *Biochem. Pharmacol.* **27,** 2555 (1978).
200. E. E. Seifen, R. J. Adams, and R. K. Riemer, *Eur. J. Pharmacol.* **60,** 373 (1979).
201. L. R. Meyerson, K. D. McMurtney, and V. E. Davis, *Neurochem. Res.* **3,** 239 (1978).
202. J. Ulrichová, J. Kovář, and V. Šimánek, *Collect. Czech. Chem. Commun.* **50,** 978 (1985).
203. J. Ulrichová, D. Walterová, V. Preininger, and V. Šimánek, *Planta Med.* **48,** 174 (1983).
204. A. B. Vaidya, T. G. Rajagopalan, A. G. Kale, and R. J. Levine, *J. Postgrad. Med. (Bombay)* **26,** 28 (1980).
205. E. Smékal, N. Kubová, and V. Kleinwächter, *Stud. Biophys.*
206. M. L. Sethi, *J. Nat. Prod.* **42,** 187 (1979).
207. J. W. Lee, J. O. MacFarlane, K. Y. Zee-Cheng, and C. C. Cheng, *J. Pharm. Sci.* **66,** 986 (1977).
208. I. Ninomiya and T. Naito, *Rec. Dev. Chem. Nat. Carbon Compds.* **10,** 11 (1984).

209. J. C. Gaignault and G. Combes, *Fitoterapia* **55,** 37 (1984).
210. A. I. Gray and K. M. Ng, International Symposium, "The Chemistry and Biology of Isoquinoline Alkaloids," p. 20. London, April 16–18, 1984.
211. A. J. Foyere, B. T. Ngadini, B. L. Soudengam, and E. Tsamo, *Planta Med.* **50,** 210 (1984).
212. J. O. Moody and A. Sofowora, *Planta Med.* **50,** 101 (1984).
213. H. G. Kiryakov and E. S. Iskrenova, *Planta Med.* **50,** 136 (1984).
214. I. A. Israilov, F. M. Melikov, and D. A. Murav'eva, *Khim. Prir. Soedin.*, 79 (1984).
215. B. Dasgupta, K. K. Seth, V. B. Pandey, and A. B. Ray, *Planta Med.* **50,** 481 (1981).
216. J. Slavík, L. Slavíková, and L. Dolejš, *Collect. Czech. Chem. Commun.* **49,** 1318 (1984).
217. D. Walterová, Z. Stránský, V. Preininger, and V. Šimánek, *Electrophoresis* **6,** 128 (1985).
218. G. L. Southard, R. T. Boulware, D. R. Walborn, W. J. Groznik, E. E. Thorne, and S. L. Yankell, *J. Am. Dent. Assoc.* **108,** 338 (1984).
219. M. Cushman, A. Abbaspour, K. Iwasa, and N. Takao, *J. Nat. Prod.* **47,** 630 (1984).
220. T. Kametani, T. Honda, M. Ihara, M. Shimanouchi, and Y. Sasada, *J. Chem. Soc., Perkin Trans. 2,* 1605 (1978).
221. H. Ishii, T. Ishikawa, Y.-I. Ichikawa, M. Sakamoto, M. Ishikawa, and T. Takahashi, *Chem. Pharm. Bull.* **32,** 2984 (1984).
222. H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *J. Chem. Soc., Perkin Trans. 1,* 1769 (1984).
223. M. E. Perel'son, I. V. Persiyanova, T. S. Semenova, and I. E. Konylova, *Khim. Prir. Soedin.*, 337 (1984).
224. H. Ishii, K. I. Harada, T. Ishida, T. Deushi, T. Masuda, M. Sakamoto, Y. I. Ichikawa, T. Takahashi, M. Ishikawa, and T. Ishikawa, *Chem. Pharm. Bull.* **32,** 2971 (1984).
225. H. Ishii, T. Ishikawa, T. Watanabe, Y. I. Ichikawa, and E. Kawanabe, *J. Chem. Soc., Perkin Trans. 1,* 2283 (1984).
226. M. Hanaoka, T. Motonishi, and Ch. Mukai, *J. Chem. Soc., Chem. Commun.*, 718 (1984).
227. M. Hanaoka, H. Yamagishi, M. Marutani, and Ch. Mukai, *Tetrahedron Lett.* **25,** 5169 (1984).
228. R. Beugelmans, M. Bois-Choussy, J. Chastanet, H. Ginsburg, and L. Quintero-Cortes, unpublished results.
229. M. Onda, A. Hatano, H. Yamaguchi, and N. Sato, *Chem. Pharm. Bull.* **32,** 2503 (1984).
230. H. Yamaguchi, and M. Onda, *Chem. Pharm. Bull.* **32,** 909 (1984).
231. M. Cushman, P. Mohan, and E. C. R. Smith, *J. Med. Chem.* **27,** 544 (1984).
232. M. Arisawa, J. M. Pezzuto, C. Bevelle, and G. A. Cordell, *J. Nat. Prod.* **47,** 453 (1984).
233. J. M. Pezzuto, S. K. Antosiak, W. M. Messmer, M. B. Slaytor, and G. R. Honig, *Chem.-Biol. Interact.* **43,** 323 (1983).

— CHAPTER 5 —

LYCOPODIUM ALKALOIDS

D. B. MACLEAN

Department of Chemistry
McMaster University
Hamilton, Ontario, Canada

I. Introduction

The two previous reviews of the lycopodium alkaloids published in this series covered the literature until the end of 1972 (*1,2*). Since then many new alkaloids have been isolated and characterized. Some of them are simple variants of already known structures, but a surprisingly large number of new ring systems has been discovered. Particularly noteworthy is the finding of a new group of alkaloids in *Lycopodium lucidulum* containing a basic skeleton of 27 carbon

THE ALKALOIDS, VOL. 26

atoms and 3 nitrogen atoms (*3,4*). The various structural types found in the Lycopodiaceae are illustrated in the figures accompanying the tables of Section II.

The ring systems found in the lycopodium alkaloids have continued to challenge chemists interested in organic synthesis. When the last review went to press, only annotinine and lycopodine had been synthesized (*2*). In the interim, new and improved routes to lycopodine and some of its simple derivatives have been developed, several of the $C_{16}N_2$ alkaloids have been synthesized, and the construction of a number of the other ring systems found in this family has been mastered. Details of these studies may be found in Section III of this review. However, fewer than half of the ring systems have yielded to synthesis, and many fascinating problems await solution.

Biosynthetic studies, unlike the synthetic studies, have not been vigorously pursued since 1972. An interesting proposal has, however, been put forward relating to the biogenesis of the alkaloids (Section IV) and the relationship between alkaloid content and botanical classification has been discussed (*5,6*) (Section V).

In the period since 1972, brief general reviews of current literature on the lycopodium alkaloids have appeared almost on an annual basis (*7,8*), and several reviews dealing exclusively with synthesis have been published (*9–12*).

II. The Alkaloids and Their Occurrence

A. Introduction

The alkaloids, their sources, and their structures are discussed in this section. For purposes of classification and easy reference, the alkaloids of established structure have been divided into four groups, based on the number of carbon and nitrogen atoms present in the structural framework. The three distinctive groups are those containing (i) 16 carbon atoms and 1 nitrogen atom, (ii) 16 carbon atoms and 2 nitrogen atoms, and (iii) 27 carbon atoms and 3 nitrogen atoms. The fourth group comprises those alkaloids that do not fit into any of the categories above. Alkaloids that have been isolated, but whose structures have not been clarified, are listed separately as are the molecular complexes that have been isolated.

All known alkaloids of established structure are included in the tables. References to the earlier reviews (*1,2*) are given if the particular compound was cited or discussed previously. In each of the tables of this section the alkaloids are listed within each ring system in order of increasing molecular weight. The tables provide the name, molecular formula, molecular weight, functionality (with respect to the ring system), and a reference or references to the structural elucida-

tion and source. For each of the groups $C_{16}N$, $C_{16}N_2$, and $C_{27}N_3$, the alkaloids in the tables are further subdivided according to ring system. All tables have an accompanying figure illustrating the ring system or systems under consideration.

A brief account of the structural elucidation of new alkaloids within each group is provided in the appropriate section. Many of the structures of new alkaloids have been established by X-ray crystallography and, in those cases, spectral data have been largely omitted unless they are unusual in some respect. Readers are referred to the original articles for details.

B. The $C_{16}N$ Alkaloids

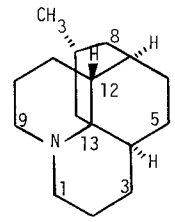
1. Introduction

This is the largest group of lycopodium alkaloids, containing over 60 members. The alkaloids are listed in three tables. The first table contains alkaloids that are derivatives of lycopodane, that is, they have the ring system present in lycopodine (Table I). The second table lists the alkaloids with an alopecurane skeleton and those $C_{16}N$ alkaloids that have a unique structure. Alkaloids in Table II have present in their ring systems a hexahydrojuloidine skeleton in common with those of the lycopodane group. The third table lists alkaloids of the fawcettimane, fawcettidane, serratinane, and magellanane skeleta. All members of Table III have a five-membered ring, an oxygen at C-5, and a quaternary carbon center at C-12, which set them apart from other groups. The tricyclic system of the fawcettimane skeleton is present in the other three ring systems.

2. The Lycopodane Group

Inspection of Table I shows that many new species have been examined since the last review and that lycopodine is present in the majority of them. Lycodoline and clavolonine are also widely distributed alkaloids of this group. The lycopodane ring system is represented in Fig. 1. The origin of the numbering system used for the lycopodane system and for other ring systems has been described elsewhere (*1*) and is commonly used.

The chirality assigned to lycopodine on the basis of ORD evidence (*1,2*) has been confirmed by an X-ray crystallographic study (*27,28*). It is represented in Fig. 1. The configuration of most other alkaloids of the series has been established either by correlation with lycopodine, using chemical methods or by chiroptical or X-ray methods. Alkaloids belonging to the other enantiomeric series have never been reported. In cases where the absolute configuration has not been established but the relative configuration is known, the assumption is made that the alkaloid has the same chirality as lycopodine. A case in point is lycophlegmine.



lycopodane skeleton

FIG. 1. The ring system of the lycopodane alkaloids.

The structures of the eight new alkaloids of this group are discussed separately below.

The structure of gnidioidine ($C_{16}H_{23}NO_2$, **7**), isolated from *Lycopodium gnidioides* and from *L. phlegmaria,* was based on spectral examination and on comparison of the data obtained with the spectra of other alkaloids of this series (*14*). The NMR spectrum of **7** established the presence of a trisubstituted double bond, a secondary alcohol, and a $CHCH_3$ group. The IR spectrum showed the presence of a ketonic carbonyl group in a six-membered ring and an OH group. The presence of the secondary OH function was confirmed by conversion of **7** to an *O*-acetate and by oxidation of the alcohol to a ketone; both the *O*-acetate and the ketone displayed the expected spectral properties. Sodium borohydride reduction of **7** yielded a product whose spectral properties were similar to those of lycofoline (**16**), but a direct comparison was not made. Thus gnidioidine is either 5-hydroxy-8-oxo-$\Delta^{11,12}$-dehydrolycopodane or the isomeric 5-oxo-8-hydroxy compound. The mass spectra of neither gnidioidine nor its *O*-acetyl derivative showed fragment ions at M − 28 or M − 70, characteristic of $\Delta^{11,12}$-lycopodanes with a carbonyl at C-8. Thus the 5-oxo-8-hydroxy-$\Delta^{11,12}$-lycopodane structure was favored for the alkaloid. Further support of this structure came from a mass spectrometric examination of the catalytic hydrogenation product of **7;** its mass spectrum showed a base peak at M − 115, similar to that of *O*-acetylclavolonine (**11**-Ac) but unlike that of *O*-acetylannofoline (**10**-Ac) where the base peak of the spectrum appeared at M − 71. The methyl and the acetoxy groups at C-15 and C-8, respectively, in *O*-acetylgnidioidine, have been shown to be trans to one another on the basis of the coupling constants between the vicinal hydrogen atoms at the corresponding positions. On these grounds gnidioidine has been assigned structure **7.** The relative configuration at C-4 and the absolute configuration were not established but very likely conform to the pattern already established in this series.

Lycognidine ($C_{27}H_{39}NO_5$, **36**) has been reported only in *L. gnidioides* (*14,15*). Hydrolysis of the alkaloid in methanolic KOH yielded 3,4-dimethoxyphenylpropionic acid and deacetyllycoclavine (**19**), identified by comparison

TABLE I

$C_{16}N$ ALKALOIDS WITH A LYCOPODANE SKELETON

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Anhydrodihydrolycopodine (**1**)	$C_{16}H_{25}N$	231	$\Delta^{4,5}$;	(*1*)	(*1*)
Anhydrolycodoline (**2**)	$C_{16}H_{23}NO$	245	$\Delta^{11,12}$; 5, =O	(*1*)	(*1,2*); *Lycopodium carolinum* (Lawalree) Symoens (*6,13*); *L. clavatum* var. *borbonicum* (*5*); *L. gnidioides* L.f. (*14,15*); *L. inundatum* L. (*6,15*); *L. phlegmaria L. (5) L. saururus* Lam (*6,13*)
Anhydrodeacetylpaniculine (P5) (**3**)	$C_{16}H_{25}NO$	247	$\Delta^{4,5}$; 10, OH (*R*)	(*16,17*)	*L. paniculatum* Desvaux (*16,18*)
Lycopodine (**4**)	$C_{16}H_{25}NO$	247	5, =O	(*1,2*)	(*1,2*); *L. carolinum* (*13,19*); L. *cernuum* L. (*19*); *L. clavatum* L. (*19,20*); *L. clavatum* var. *borbonicum* (*5*); *L. clavatum* var. *inflexum* (*21*); *L. contiguum* Klotzsch. (*15,19,22*); *L. erythraeum* (*13*); *L. inundatum* (*15*); L. *issleri* (Rouy) Lawalree (*15,19*); *L. magellanicum* (Palisot de Beauvois) (*23,24*); *L. paniculatum* (*18*); *L. phlegmaria* (*5*); *L. saururus* (*13,19*); *L. sitchense* (Rubr.) (*15,19*); *L. thyoides* H. B. Willd (*15,19,22*)

(*continued*)

TABLE I (*Continued*)

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Dihydrolycopodine (L1)(**5**)	$C_{16}H_{27}NO$	249	5, OH(*R*)	(*1,2*)	*L. carolinum* (*19*); *L. clavatum* (*20*); *L. clavatum* var. *borbonicum* (*5*); *L. clavatum* var. *inflexum* (*21*); *L. contiguum* (*15,19*); L. *paniculatum* (*18*); L. *saururus* (*13*); *L. thyoides* (*15*)
Acrifoline (**6**)	$C_{16}H_{23}NO_2$	261	$\Delta^{11,12}$; 5, OH(*R*); 8, =O	(*1*)	(*1,2*)
Gnidioidine (**7**)	$C_{16}H_{23}NO_2$	261	$\Delta^{11,12}$; 5, =O; 8, OH(*R*)	(*14*)	*L. gnidioides* (*14,15*); *L. phlegmaria* (*5*)
Lycophlegmine (**8**)	$C_{16}H_{23}NO_2$	261	$\Delta^{11,12}$; 5, =O; 10, OH(*S*)	(*25*)	*L. phlegmaria* L. (*25*)
Serratidine (**9**)	$C_{16}H_{23}NO_2$	261	$\Delta^{11,12}$; 5, =O; 7, OH(*R*)	(*2*)	(*2*)
Annofoline (**10**)	$C_{16}H_{25}NO_2$	263	5, OH(*R*), 8, =O	(*1*)	(*1,2*)
Clavolonine (**11**)	$C_{16}H_{25}NO_2$	263	5, =O; 8, OH(*R*)	(*1*)	(*1,2*); *L. clavatum* L. (*2*); *L. contiguum* (*15,22*); *L. inundatum* (*15*); *L. megellanicum* (*23*); *L. saururus* (*13*); *L sitchense* (*15,19*); *L. thyoides* (*15*)
Flabelliformine (**12**)	$C_{16}H_{25}NO_2$	263	4, OH(*R*); 5, =O	(*1*)	(*1*)
L 20 (**13**)	$C_{16}H_{25}NO_2$	263	5, =O; 6, OH(*S*)	(*1*)	(*1,2*)
Lucidioline (**14**)	$C_{16}H_{25}NO_2$	263	$\Delta^{11,12}$; 5, OH(*S*); 6, OH(*S*)	(*2*)	(*2*); *L. gnidioides* (*14,15*); *L. ophioglossoides* (*15*)

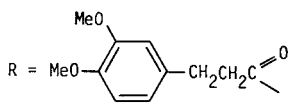
Lycodoline (L8, L30) (**15**)	$C_{16}H_{25}NO_2$	263	5, =O; 12, OH(*S*)	(*1*)	(*1,2*); *L. carolinum* (*13*); *L. clavatum* var. *barbonicum* (*5*); *L. clavatum* var. *inflexum* (*21*); *L. clavatum* (*20*); L. *inundatum* (*15*); *L. phlegmaria* (*5*); *L. saururus* (*13*)
Lycofoline (Base H) (**16**)	$C_{16}H_{25}NO_2$	263	$\Delta^{11,12}$; 5, OH(*R*), 8 OH(*R*)	(*1*)	(*1*)
Pseudoselagine (L23) (**17**)	$C_{16}H_{25}NO_2$	263	5, =O; 12 OH(*R*)	(*2*)	(*1,2*)
Deacetylfawcettiine (Base D) (**18**)	$C_{16}H_{27}NO_2$	265	5, OH(*R*); 8, OH (*R*)	(*1*)	(*1*); *L. contiguum* (*15,19*); *L. magellanicm* (*23*) *L. thyoides* (*15*)
Deacetyllycoclavine (P4) (**19**)	$C_{16}H_{27}NO_2$	265	5, OH (*S*): 6, OH(*S*)	(*16*)	*L. paniculatum* (*16,18*)
Deacetylpaniculine (**20**)	$C_{16}H_{27}NO_2$	265	5, OH(*R*); 10, OH(*R*)	(*16,17*)	*L. confertum* (*17,26*); *L. paniculatum* (*16*)
Flabelline (**21**)	$C_{18}H_{28}N_2O$	288	$\Delta^{4,5}$; 5, NHAc	(*1*)	(*1*)
Acetyldihydrolycopodine (**22**)	$C_{18}H_{29}NO_2$	291	5, OAc(*R*)	(*1*)	(*1*); *L. clavatum* var. *borbonicum* (*5*); *L. contiguum* (*15,19*); *L. magellanicum* (*24*); *L. paniculatum* (*18*); *L. thyoides* (*15,19,22*)
Acetylacrifoline (L12) (**23**)	$C_{18}H_{25}NO_3$	303	$\Delta^{11,12}$; 5, OAc(*R*); 8, =O	(*1*)	(*1*)
Lycoverticine (**24**)	$C_{18}H_{28}N_2O_2$	304	$\Delta^{4,5}$; 5, NHAc; 12, OH(*S*)	(*14*)	*L. verticillatum* L. (*14*)
Acetyllycofoline (Base M) (**25**)	$C_{18}H_{27}NO_3$	305	$\Delta^{11,12}$; 5, OAc(*R*); 8, OH(*R*)	(*1*)	(*1*)
Fawcettiine (β-Lofoline) (Base C and J) (**26**)	$C_{18}H_{29}NO_3$	307	5, OAc(*R*); 8, OH(*R*)	(*1*)	(*1*); *L. clavatum* (*19*); *L. contiguum* (*15,19,22*); *L. magellanicum* (*23*); *L. saururus* (*19*); *L. thyoides* (*15,19,22*)

(*continued*)

TABLE I (*Continued*)

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
α-Lofoline (**27**)	$C_{18}H_{29}NO_3$	307	5, OAc(*R*); 8, OH(*R*)	(*1*)	(*1*)
Lycoclavine (**28**)	$C_{18}H_{29}NO_3$	307	5, OAc(*S*); 6, OH(*S*)	(*1*)	(*1,2*); *L. gnidioides* (*14,15*); *L. paniculatum* (*16*)
Paniculine (P2) (**29**)	$C_{18}H_{29}NO_3$	307	5, OAc(*R*); 10, OH(*R*)	(*16,17*)	*L. confertum* (*17*); *L. paniculatum* (*16,18*)
Lycofawcine (Base L) (**30**)	$C_{18}H_{29}NO_4$	323	5, OAc(*R*); 8, OH(*R*); 12, OH(*S*)	(*1*)	(*1*)
Diacetyllycofoline (Base N) (**31**)	$C_{20}H_{29}NO_4$	347	$\Delta^{11,12}$; 5, OAc(*R*); 8, OAc(*R*)	(*1*)	(*1*)
Acetylfawcettiine (Base K) (**32**)	$C_{20}H_{31}NO_4$	349	5, OAc(*R*); 8, OAc(*R*)	(*1*)	(*1*); *L. clavatum* (*19*); *L. contiguum* (*15,19,22*); *L. magellanicum* (*24*); *L. saururus* (*19*); *L. thyoides* (*15,19,22*)
Acetyllofoline (L9?) (**33**)	$C_{20}H_{31}NO_4$	349	5, OAc(*R*); 8, OAc(*S*)	(*1*)	(*1*)
Acetyllycoclavine (Base O) (**34**)	$C_{20}H_{31}NO_4$	349	5, OAc(*S*); 6, OAc(*S*)	(*1*)	(*1*)
Acetyllycofawcine (**35**)	$C_{20}H_{31}NO_5$	365	5, OAc(*R*); 8, OAc(*R*); 12, OH(*S*)	(*1*)	(*1*)
Lycognidine (**36**)[a]	$C_{27}H_{39}NO_5$	457	5, OR(*S*); 6, OH(*S*)	(*14*)	*L. gnidioides* (*14,15*)

[a]Lycognidine



with an authentic sample prepared by reduction of alkaloid L 20 (**13**). Esterification of lycoclavine with an excess of 3,4-dimethoxyphenylpropionic anhydride yielded a diester that gave lycognidine on partial hydrolysis. The assignment of the ester function of **36** to C-5 is based on analogy with studies carried out earlier (*1*) on the hydrolysis of acetyllycoclavine (**34**), which undergoes selective hydrolysis at C-6. A comparison of the NMR spectra of lycoclavine, lycognidine, and the phenylpropionate diester confirmed this assignment. Since L 20 has been prepared from lycopodine (*1,2*), the absolute configuration of **36** is known.

The structure of lycoverticine ($C_{18}H_{28}N_2O_2$, **24**) was deduced from its spectral properties and confirmed by its hydrolysis to and synthesis from lycodoline (**15**). The synthesis was achieved by reduction of the oxime of lycodoline over Ra-Ni in the presence of acetic anhydride. Thus lycoverticine is (*S*)-12-hydroxyflabelline.

Lycophlegmine ($C_{16}H_{23}NO_2$, **8**) has been found as one of many components present in *L. phlegmaria* harvested in Sri Lanka (*25*). It has been assigned the structure designated in Table I on the basis of its spectral properties. The IR spectrum indicated the presence of an OH group and a ketone in a six-membered ring. The ^{1}H-NMR spectrum indicated that the alcohol function was secondary and that a secondary C—CH_3 group and a trisubstituted double bond were present. Double irradiation studies demonstrated that the alcohol was allylic and situated at C-10. The mass spectrum suggested that the compound belonged to the lycopodane group and that the double bond was located at $\Delta^{11,12}$ of the lycopodane skeleton. Reduction (H_2/Pt) gave a dihydro derivative that had Bohlmann bands in its IR spectrum; these bands are present in all 12-epilycopodane derivatives that have been previously examined (*1,2*). The 12-epi compounds are normally formed on reduction of lycopodium alkaloids having a $\Delta^{11,12}$ double bond. The assignment of configuration of the CH_3 group at C-15 and the placement of the carbonyl at C-5 was based on analogy to other lycopodium systems and on comparison of the spectral data of **8** with those of other alkaloids of this series.

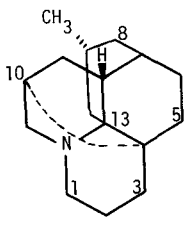
Paniculine ($C_{18}H_{29}NO_3$, **29**) and deacetylpaniculine ($C_{16}H_{27}NO_2$, **20**) occur in *L. paniculatum* (*16,18*) and in *L. confertum* (*17*) but anhydrodeacetylpaniculine ($C_{16}H_{25}NO$, **3**) has been reported only in the former (*16,18*). Hydrolysis of paniculine yielded the deacetyl compound, which in turn was dehydrated readily to **3** (*16*). The presence of an *O*-acetyl group and an OH group in **29,** two OH groups in **20,** and one OH group and one trisubstituted double bond (deduced by NMR) in **3** was apparent (*16,18*) from a spectral examination of the three bases. The ring system of the three alkaloids was established by conversion of paniculine to acetyldihydrolycopodine, a transformation that also showed that the *O*-acetyl group of **29** was located at C-5 in the lycopodane ring system. The only remaining structural problem with respect to **29** was the site and configuration of the OH group. In the initial report (*16*) on the structures of these alkaloids, the OH group of paniculine was considered to be tertiary because of its

behavior toward oxidizing agents. It was assigned to C-7 because its placement at other tertiary sites on the lycopodane skeleton was precluded on the basis of arguments that will not be outlined here. A subsequent investigation (*17*), in which detailed ^{1}H- and ^{13}C-NMR studies were conducted on **29** and on several related alkaloids, showed that the OH group was secondary, that it was located at C-10, and that it had the (*S*) configuration. This study resolved the structure of **29.** Deacetylpaniculine is therefore (5*R*,10*S*),-5,10-dihydroxylocopodane and anhydrodeacetylpaniculine is (*S*)-10-hydroxy-$\Delta^{4,5}$-dehydrolycopodane.

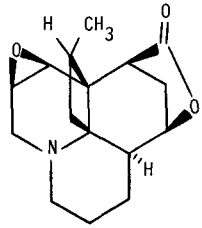
Deacetyllycoclavine (P4) ($C_{16}H_{27}NO_2$, **19**) has been found in *L. paniculatum* (*16,18*). Its structure was established by comparison of its spectral properties with those of the previously reported hydrolysis product of lycoclavine (**28**) (*1*) and by its transformation to alkaloid L 20 (**13**) by oxidation with Sarett's reagent (*16*).

3. The Alopecurane Group and Four Alkaloids of Unique Structure

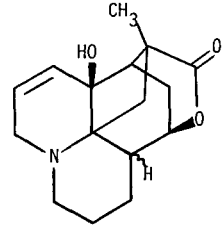
The alopecurane group and four alkaloids of unique structure are listed in Table II, and the ring systems present in them are shown in Fig. 2. Not a single



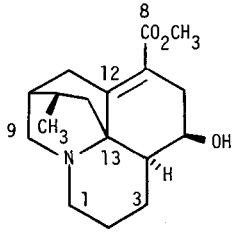
alopecurane skeleton



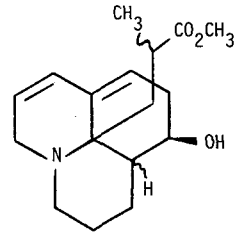
annotinine



annotine



annopodine



lyconnotine

FIG. 2. The ring systems of the alopecurane alkaloids and four $C_{16}N$ alkaloids with unique structures.

TABLE II

$C_{16}N$ ALKALOIDS WITH AN ALOPECURANE SKELETON AND FOUR $C_{16}N$ ALKALOIDS OF UNIQUE STRUCTURE

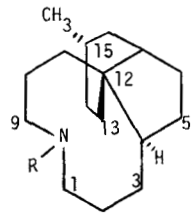
Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Alkaloids with the alopecurane skeleton					
Dehydrolycopecurine (**37**)	$C_{16}H_{23}NO$	245	5, =O	(*2*)	(*2*); *Lycopodium inundatum* (*15*)
Lycopecurine (**38**)	$C_{16}H_{25}NO$	247	5, OH(*R*)	(*2*)	(*2*)
Inundatine (**39**)	$C_{16}H_{23}NO_2$	261	2, OH(*R*); 5, =O	(*2*)	(*2*); *L. inundatum* (*15*)
Isoinundatine (**40**)	$C_{16}H_{23}NO_2$	261	2, =O, 5, OH(unassigned)	(*2*)	(*2*); *L. inundatum* (*15*)
Debenzoylalopecurine (**41**)	$C_{16}H_{25}NO_2$	263	2, OH(*S*); 5, OH(*R*)	(*2*)	(*2*)
Acetyldebenzoylalopecurine (**42**)	$C_{18}H_{27}NO_3$	305	2, OAc(*S*); 5, OH(*R*)	(*2*)	(*2*)
Alopecurine (**43**)	$C_{23}H_{29}NO_3$	367	2, OBz(*S*); 5, OH(*R*)	(*2*)	(*2*)
Alkaloids of unique structure					
Annotinine (**44**)	$C_{16}H_{21}NO_3$	275		(*1*)	(*1*)
Annotine (**45**)	$C_{16}H_{21}NO_3$	275		(*1*)	(*1*)
Annopodine (**46**)	$C_{17}H_{25}NO_3$	291		(*2*)	(*2*)
Lyconnotine (**47**)	$C_{17}H_{25}NO_3$	291		(*1*)	(*1*)

new alkaloid in any of the five ring systems has been reported. Three alopecurane alkaloids of established structure were isolated in an examination of *L. inundatum* (*15*).

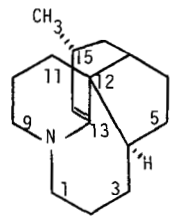
4. The Fawcettimane, Fawcettidane, Serratinane, and Magellanane Groups

The fawcettimane, fawcettidane, serratinane, and magellanane groups are collected together in Table III, and the four ring systems are shown in Fig. 3. The tricyclic ring system of the fawcettimane group is incorporated intact into the three tetracyclic systems of the other groups. Relative to fawcettimine, the fawcettidane system has a bond between N and C-13, the serratinane system a bond between N and C-4, and the magellanane system a bond between C-3 and C-10. The formulas of Fig. 3 illustrate the structural relationship among the four ring systems and between them and the lycopodane group but fail to provide an insight into the geometry of the compounds. Stereostructures for some of the alkaloids of the group may be found in the sections that follow.

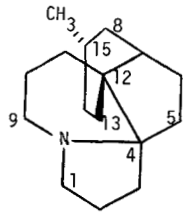
The magellanane system is new since the last review, and new alkaloids of all the other ring systems have been isolated. The relative and absolute configurations of all members of the group are known.



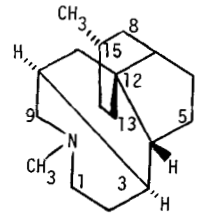
fawcettimane skeleton



fawcettidane skeleton



serratinane skeleton



magellanane skeleton

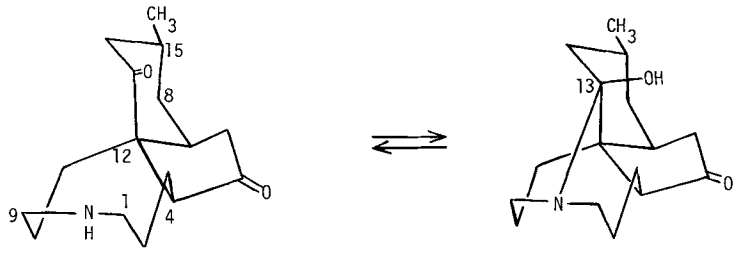
FIG. 3. The ring systems of the fawcettimane, fawcettidane, serratinane, and magellanane alkaloids.

TABLE III

$C_{16}N$ ALKALOIDS WITH THE FAWCETTIMANE, FAWCETTIDANE, SERRATINANE, AND MEGELLANANE SKELETA

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Alkaloids with the fawcettimane skeleton					
Lycothunine (**48**)	$C_{16}H_{23}NO_2$	261	$\Delta^{10,11}$; 5, =O; 13, =O	(*29*)	(*2*)
Fawcettimine (**49**)	$C_{16}H_{25}NO_2$	263	5, =O; 13, =O; R = H	(*2,29*)	(*1*); *Lycopodium clavatum* var. *inflexum* (*21*)
Alopecuridine (**50**)	$C_{16}H_{25}NO_3$	279	4, OH(*R*); 5, =O; 13, =O; R = H	(*30*)	(*2*)
Lycophlegmarine (**51**)	$C_{18}H_{27}NO_3$	305	$\Delta^{3,4}$; $\Delta^{14,15}$; 5, OH(*S*); 13, =O; 14, OCH_3; R = CH_3	(*29*)	(*1,2*); *L. phlegmaria* (*25*)
Alkaloids with the fawcettidane skeleton					
Fawcettidine (**52**)	$C_{16}H_{23}NO$	245	$\Delta^{13,14}$; 5, =O	(*2,29*)	(*1,2*); *L. phlegmaria* (*25*)
Epidihydrofawcettidine (**53**)	$C_{16}H_{25}NO$	247	$\Delta^{13,14}$; 5, OH(*S*)	(*25,31*)	*L. phlegmaria* (*25*)
Alolycopine (**54**)	$C_{16}H_{21}NO_2$	259	$\Delta^{3,4}$; $\Delta^{13,14}$; 5, =O, 8, OH(*S*)	(*2*)	(*2*)
Anhydroaposerratinine (**55**)	$C_{16}H_{23}NO_2$	261	$\Delta^{13,14}$; 5, =O; 8, OH(*S*)	(*14*)	*L. verticillatum* (*14*)
8-Deoxyserratinidine (**56**)	$C_{18}H_{28}N_2O$	288	$\Delta^{13,14}$; 5, NHAc(*S*)	(*25,31*)	*L. phlegmaria* (*25*)
Serratinidine (**57**)	$C_{18}H_{28}N_2O_2$	304	$\Delta^{13,14}$; 5, NHAc(*S*); 8, OH(*S*)	(*2,31*)	(*2*)
Alkaloids with the serratinane skeleton					
8-Deoxy-13-dehydroserratinine (**58**)	$C_{16}H_{23}NO_2$	261	5, =O; 13, =O	(*25*)	*L. phlegmaria* (*25*)
8-Deoxyserratinine (**59**)	$C_{16}H_{25}NO_2$	263	5, =O; 13, OH(*S*)	(*2*)	(*2*)
Serratine (**60**)	$C_{16}H_{25}NO_3$	279	5, =O; 13, OH(*S*); 15, OH(*S*)	(*2*)	(*2*)
Serratinine (**61**)	$C_{16}H_{25}NO_3$	279	5, =O; 8, OH(*S*); 13, OH(*S*)	(*2*)	(*2*)
Serratanidine (**62**)	$C_{16}H_{25}NO_4$	295	5, =O; 8, OH(*R*); 13, OH(*S*); 15, OH(*R*)	(*2*)	(*2*)
Alkaloids with the magellanane skeleton					
Megellaninone (**63**)	$C_{17}H_{23}NO_2$	273	$\Delta^{14,15}$; 5, =O; 13, =O	(*24*)	*L. magellanicum* (*24*)
Magellanine (**64**)	$C_{17}H_{25}NO_2$	275	$\Delta^{14,15}$; 5, OH(*S*); 13, =O	(*23*)	*L. magellanicum* (*23*)
Lycopaniculatine (**65**)	$C_{17}H_{27}NO_2$	277	5, =O; 13, OH(*S*)	(*18*)	*L. paniculatum* (*18*)

Alkaloids of the fawcettimane group are secondary amino ketones, which may exist in principle in two tautomeric forms: either as the amino ketone A or the carbinolamine B, as illustrated for fawcettimine. The latter form is dominant as judged by IR spectroscopy. They have been classified in this review as amino ketones in order to differentiate them clearly from the fawcettidane group and to accentuate the relationship of the secondary amines to lycophlegmarine, the only tertiary amine of the group. Three alkaloids of this type have been investigated in the period under review. Two of them, alopecuridine (**50**) and lycophlegmarine (**51**) are new bases, while the third, lycothunine (**48**) (*2*), was reported previously, but its structure at the time was unknown.



Fawcettimine

Alopecuridine has been shown to be (*R*)-4-hydroxyfawcettimine (*30*). The nature of its ring system was established by its reduction with Ca in NH_3 to a mixture of fawcettimine and dihydrofawcettimine from which fawcettimine was isolated as its perchlorate. Acetylation of the reduction mixture also yielded the known *N*-acetylfawcettimine as one of the products. The hydroxy function was considered to be α to the carbonyl, because of its hydrogenolysis with Ca/NH_3, and tertiary, because it was unaffected by Jones's reagent. These conclusions were verified by an X-ray crystallograpic study of *N*-acetylalopecuridine that established at the same time the configuration at C-4 (*30*). Structure **50** also represents the absolute configuration because earlier studies (*2*) had established that fawcettimine and serratinine (of known absolute configuration) belonged to the same enantiomeric series.

An X-ray crystallographic examination of *O*-acetyllycothunine (*29*) was carried out that indicated that lycothunine was **48.** It was now obvious that lycothunine had the same basic skeleton as that of fawcettimine, and indeed upon reduction with H_2/Pt it yielded fawcettimine. Acetylation of dihydrolycothunine yielded *N*-acetylfawcettimine, providing further confirmation that lycothunine is $\Delta^{10,11}$-dehydrofawcettimine. Lycothunine formed an *O*-acetyl derivative upon acetylation in contrast to the behavior of fawcettimine and alopecuridine, both of which yielded *N*-acetyl derivatives upon similar treatment. In the former case, *O*-acetylation occurred at the 13-hydroxy group in the carbinolamine form.

The correlation of lycothunine with fawcettimine has resolved the stereochemistry at C-4 of fawcettimine. The configuration at this position was the only feature of the stereochemistry of fawcettimine that had not already been clarified.

Lycophlegmarine (**51**) was converted to its *p*-bromobenzoyl derivative and examined by X-ray crystallography (*29*) which showed that it had the structure and relative stereochemistry represented in **51.** The (*S*) configuration at C-5 was deduced by application of Brewster's rule (*32*) to the alkaloid and its *p*-bromobenzoate. Thus lycophlegmarine belongs to the same enantiomeric series as other alkaloids of this group.

Three new representatives of the fawcettidine group of alkaloids have been reported, namely, anhydroaposerratinine (**55**), from *L. verticillatum,* and two bases from *L. phlegmaria,* epidihydrofawcettidine (**53**), and 8-deoxyserratinidine (**56**). The stereochemistry of fawcettidine (**52**) and serratinidine (**57**) has been clarified, and the structure and stereochemistry of the new alkaloids have been established.

In the case of **55,** the structure was determined by acetylation of the base to *O*-acetylanhydroaposerratinine (*14*), a compound of known structure and configuration (*2*).

The structure of 8-deoxyserratinidine (**56**) rests on its derivation from fawcettidine (**52**). The latter was converted to its oxime, the oxime was reduced with H_2 over Ra-Ni, and the resulting primary amine was acetylated with Ac_2O/py to yield **56** (*25*). Epidihydrofawcettidine (**53**) yielded fawcettidine (**52**) upon Jones oxidation (*25*), thereby establishing its structure. The compound was epimeric with dihydrofawcettidine prepared synthetically.

Because of their derivation from or conversion to fawcettidine, the stereochemistry of **53** and **56** is known except at C-4 and C-5. An X-ray examination of 8-deoxyserratinidine showed that the configuration at C-5 was (*S*) ($NHCOCH_3$ is α) and that at C-4 was also (*S*) (H is α) (*31*). An NMR examination of the proton at C-5 of 8-deoxyserratinidine, dihydrofawcettidine, and serratinidine showed that all three showed a similar half-band width for the multiplet attributed to this signal in each of the three compounds. In contrast, the half-band width of the proton at C-5 in epidihydrofawcettidine was different. These data suggested that **56, 57,** and dihydrofawcettidine had the same configuration at C-4 and C-5 but differed from **53** at C-5 (*31*). Application of Brewster's benzoate rule (*32*) to **53** and to dihydrofawcettidine and their respective benzoates in chiroptical studies confirmed the stereochemical assignments (*31*).

In the previous section, evidence was presented that established the configuration at C-4 of fawcettimine. Earlier studies had demonstrated that fawcettimine may be transformed to fawcettidine (*33*) from which it seems likely that the configuration at C-4 is the same in both bases. Thus the relative and absolute configurations of all six bases in this series appear secure.

One new alkaloid of the serratinane ring system has been reported, namely, 8-

deoxy-13-dehydroserratinine (**58**) from *L. phlegmaria* (*25*). The structure was deduced from an analysis of its mass spectrum, which was characteristic of 13-dehydroserratinines. Comparison with an authentic sample of 8-deoxy-13-dehydroserratinine prepared from serratinine revealed the identity of the two compounds (*25*).

Only three representatives of the magellanane ring system have been reported, namely, lycopaniculatine* (**65**) (*18,34*), magellanine (**64**) (*23*), and magellaninone (5-dehydromagellanine) (**63**) (*24*). The structures of **64** and **65** were determined by X-ray crystallography carried out on the methobromide of **64** and the hydrobromide of **65**, while **63** has been prepared from **64** by a Jones oxidation, thereby establishing its structure (*24*). These alkaloids have a characteristic fragmentation pattern (*18,23,24*) in their mass spectra that sets them apart from other classes of lycopodium alkaloids and which should assist future workers in recognizing new members of this group.

The X-ray investigations (*18,23*) established the relative configurations of lycopaniculatine and magellanine but not their absolute configurations, a matter that has since been resolved. The configurations at C-5 of magellanine and C-13 of lycopaniculatine were determined by two methods (*24*), namely, Horeau and Kagan's method with (±)-α-phenylbutyric acid (*35*) and Brewster's benzoate method (*32*). By both procedures the respective centers were established to have the (*S*) configuration. Therefore these alkaloids belong to the same enantiomeric series as that of all the $C_{16}N$ alkaloids that have so far been examined. This is not surprising in view of their close structural relationship to the fawcettimane group.

C. The $C_{16}N_2$ Alkaloids

The alkaloids of the four ring systems found in the $C_{16}N_2$ alkaloids are recorded in Table IV, and the ring systems are illustrated in Fig. 4. Within this group two new ring systems, represented by the phlegmarines and Base R, have been discovered since the last review. The phlegmaranes are interesting structures in a biosynthetic context (see Section IV for a full discussion). Base R is closely related in structure to the fawcettimine and fawcettidine alkaloids. No new representatives of the flabellidane group have been reported, but the occurrence of these alkaloids in newly investigated species has been reported. In the cernuane group, dihydrodeoxycernuine (**79**) and dihydrodeoxylycocernuine (**82**) have been found in *L. carolinianum* (*15,19*). Both compounds had been pre-

* The name paniculatine originally used for this alkaloid has also been used for an alkaloid of the Aconite family (*36*) that was first isolated in 1921 (*37*). Since the name paniculatine has precedence in the Aconite series, it is suggested that in future the lycopodium alkaloid be renamed lycopaniculatine.

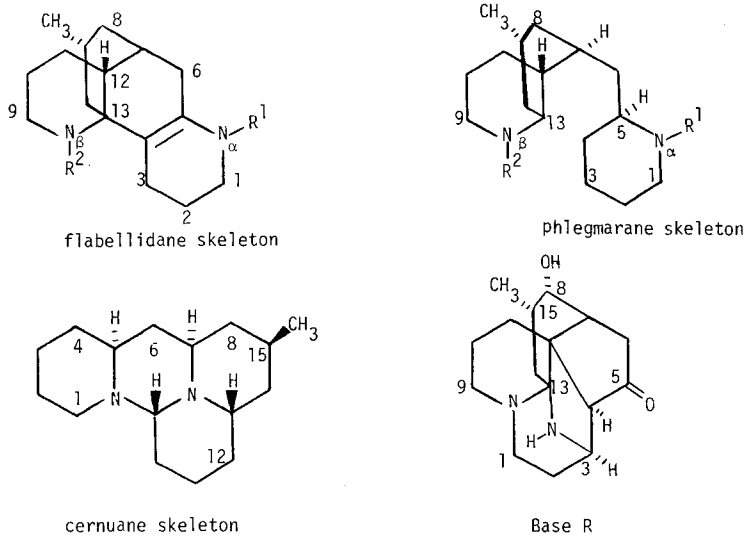


FIG. 4. The ring systems of the $C_{16}N_2$ alkaloids.

viously prepared by reduction of cernuine and lycocerniune, respectively, with lithium aluminum hydride (LAH) (*1*).

The structure and relative configuration of Base R was determined by an X-ray crystallographic study of its monoperchlorate, and the absolute configuration was established by ORD measurements on the base (*38*). The formation of Base R from a $\Delta^{3,4}$ dehydro derivative of fawcettimine (**49**) by the action of ammonia is easily envisaged.

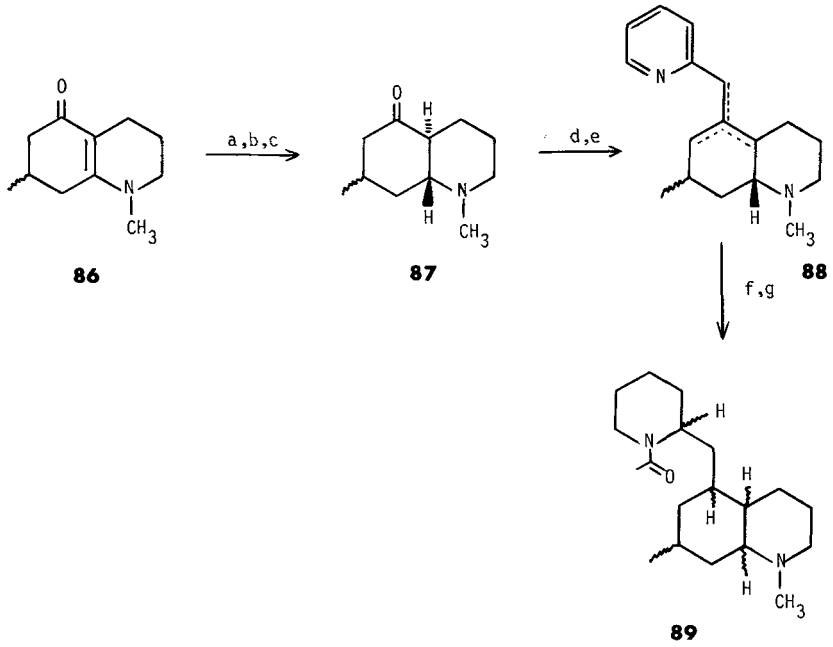
There are five bases with the phlegmarine skeleton that differ from one another in the nature of the substituents on the two nitrogen atoms. They have been reported in only three species (*5,25*) and are abundant in none. In view of their possible biosynthetic significance a search for their presence in other members of the Lycopodiaceae would be in order.

The skeletal structure of these alkaloids was deduced by Nyembo *et al.* (*5*) on the basis of a spectroscopic examination of four alkaloids and on biogenetic analogy. The mass spectra of the alkaloids provided the first insight into the nature of the ring system and revealed the substitution pattern on the two nitrogen atoms. The ring system was then synthesized in an unequivocal manner, yielding a mixture of bases diastereomeric with the alkaloids. The mass spectra of the synthetic compounds clearly indicated that their ring systems were identical with the natural bases. The natural and synthetic compounds were examined by conventional electron-impact methods and by mass-analyzed kinetic energy spectroscopy (MIKES) and by collision-induced decomposition (CID) of selected

TABLE IV
LYCOPODIUM ALKALOIDS WITH A $C_{16}N_2$ SKELETON

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Alkaloids with the flabellidane skeleton					
Lycodine (**66**)	$C_{16}H_{22}N_2$	242	$\Delta^{N\alpha,1}$; $\Delta^{2,3}$; $R^2 = H$	(*1*)	(*1,2*); *Lycopodium clavatum* (*15*); *L. magellanicum* (*24*)
N-Methyllycodine (**67**)	$C_{17}H_{24}N_2$	256	$\Delta^{N\alpha,1}$; $\Delta^{2,3}$; $R^2 = CH_3$	(*1*)	(*1*); *L. erythraeum* (*13*); *L. magellanicum* (*24*)
De-*N*-methyl-α-obscurine (**68**)	$C_{16}H_{24}N_2O$	260	1, =O; $R^1 = R^2 = H$	(*1*)	(*1,2*); *L. clavatum* (*20*)
β-Obscurine (**69**)	$C_{17}H_{24}N_2O$	272	$\Delta^{2,3}$; 1, =O; $R^1 = H$; $R^2 = CH_3$	(*1*)	(*1,2*)
α-Obscurine (**70**)	$C_{17}H_{26}N_2O$	274	1, =O; $R^1 = H$; $R^2 = CH_3$; 12(*R*)	(*1*)	(*1,2*); *L. clavatum* (*20*); *L. magellanicum* (*23*); *L. sitchense* (*15,19*); *L. thyoides* (*15*)
Sauroxine (**71**)	$C_{17}H_{26}N_2O$	274	1, =O; $R^1 = H$; $R^2 = CH_3$; 12(*S*)	(*1*)	(*1*); *L. saururus* (*13*)
Hydroxy-de-*N*-methyl-α-obscurine (**72**)	$C_{16}H_{24}N_2O_2$	276	1, =O; 12, OH(*S*); $R^1 = R^2 = H$	(*1*)	(*1*)

Flabellidine (L5) (**73**)	$C_{18}H_{28}N_2O$	288	$R^1 = COCH_3$; $R^2 = H$	(*1*)	(*1*); *L. paniculatum* (*16*); *L. thyoides* (*15,19*)
Alkaloids with the phlegmarane skeleton					
Phlegmarine (**74**)	$C_{16}H_{30}N_2$	250	$R^1 = R^2 = H$	(*5*)	*L. phlegmaria* (*5*)
N_β-Methylphlegmarine (**75**)	$C_{17}H_{32}N_2$	264	$R^1 = H$; $R^2 = CH_3$	(*5*)	*L. phlegmaria* (*5*)
N_α-Methylphlegmarine (**76**)	$C_{17}H_{32}N_2$	264	$R^1 = CH_3$; $R^2 = H$	(*5*)	*L. cernuum* (*5*)
N_5,N_β-Dimethylphlegmarine (**77**)	$C_{18}H_{34}N_2$	278	$R^1 = R^2 = CH_3$	(*25*)	*L. phlegmaria* (*25*)
N_α-Acetyl-N_β-methylphlegmarine (**78**)	$C_{19}H_{34}N_2O$	306	$R^1 = COCH_3$; $R^2 = CH_3$	(*5*)	*L. clavatum* var. *borbonicum* (*5*)
Alkaloids with the cernuane skeleton					
Dihydrodeoxycernuine (**79**)	$C_{16}H_{28}N_2$	248		(*1*)	*L. carolinianum* var. *affine* (*15,19*)
Anhydrolycocernuine (**80**)	$C_{16}H_{24}N_2O$	260	$\Delta^{12,13}$; 1, =O	(*2*)	(*2*); *L. carolinianum* (*15,19*)
Cernuine (L32) (**81**)	$C_{16}H_{26}N_2O$	262	1, =O	(*1,2*)	(*1,2*); *L. cernuum* (*15,19*); *L. carolinianum* (*15,19*)
Dihydroeoxylycocernuine (**82**)	$C_{16}H_{28}N_2O$	264	12, OH(*R*)	(*1*)	*L. carolinianum* (*15,19*)
Carolinianine (**83**)	$C_{16}H_{24}N_2O_2$	276	$\Delta^{14,15}$; 1, =O; 12, OH(*R*)	(*2*)	*L. carolinianum* (*15,19*)
Lycocernuine (**84**)	$C_{16}H_{26}N_2O_2$	278	1, =O; 12, OH(*R*)	(*1,2*)	*L. carolinianum* (*15,19*); *L. cernuum* (*15,19*)
Base R					
Base R (**85**)	$C_{16}H_{24}N_2O_2$	276		(*38*)	(*1*)



SCHEME 1. (a) Isopropyl iodide; (b) $NaBH_4$; (c) HCl, H_2O; (d) α-picolyllithium; (e) $SOCl_2$, py; (f) H_2/Pt, AcOH; (g) Ac_2O, py.

ions. The MIKES and CID studies established that the ions from both the natural and synthetic compounds were of the same structure.

The synthesis of Nyembo *et al.* (*5*) is outlined in Scheme 1. Compound **86,** previously used in an attempted synthesis of lycopodine (*1*), was converted in three steps to the perhydroquinolone **87** to which the authors assigned a trans ring junction. Treatment of **87** with α-picolyllithium, followed by dehydration, gave a mixture (by GLC) of three isomeric dehydration products represented in **88.** Reduction gave a mixture of perhydro compounds, which were partially separated and examined spectroscopically. The separated fractions gave mass spectra almost identical with the spectrum of **78** but none of the fractions corresponded exactly with the natural base in all of its spectral properties.

The relative stereochemistry of the phlegmarines has been examined in the author's laboratory. The stereochemical assignments shown in Fig. 4 were made on the basis of a synthesis (*39*) and on a detailed NMR examination of the synthetic material (*40*). This work is discussed in Section III,F. The absolute configuration of the bases is unknown.

N,N-Dimethylphlegmarine (**77**) has been recently identified in *L. phlegmaria* (*25*). Its structure was assigned on the basis of spectroscopic data, but a direct comparison with other phlegmarines has not been made.

D. The $C_{27}N_3$ Alkaloids

Ayer *et al.* (*3,4*) have found a new class of lycopodium alkaloids in the weak bases derived from *L. lucidulum*. The compounds are listed in Table V, and the two ring systems are illustrated in Fig. 5. An X-ray analysis of a derivative of oxolucidine B revealed its structure and stereochemistry and by inference that of oxolucidine B (**93**) itself. The structures of the other alkaloids of this ring system were deduced by correlation with the structure of oxolucidine B (*3*). The structure of spirolucidine was also revealed by an X-ray crystallographic study (*4*). The $C_{27}N_3$ alkaloids incorporate within their structures elements of both the phlegmarine (Section II,C) and the lucidiuline ring systems (Section II,E) suggesting a close biosynthetic relationship among the three structural types.

Lucidine B (**92**) was known from spectroscopic and chemical examination to contain an *N*-acetyl group, an *N*-methyl group, and a fully substituted imino group. Upon air oxidation, an OH group was introduced at C-14, yielding oxolucidine B (**93**) as shown in the partial structures of Scheme 2. Reduction of **93** with LAH yielded tetrahydrodeoxyoxolucidine B (**95**), which was converted to the crystalline *O,N*-di-*p*-bromobenzoyl derivative **96.** The X-ray study revealed the structure and stereochemistry of **96** from which it followed that oxolucidine B had structure **93** and lucidine B structure **92,** but the configuration at C-14 in the latter remains undetermined. The X-ray study also resolved the absolute configuration, which corresponds to that shown in Fig. 5.

The presence of a 2,3,6-trisubstituted pyridine unit in dihydrolycolucine (**91**) was inferred from spectroscopic examination. It was also a product, among others, obtained on dehydrogenation of lucidine B. Barring rearrangement during dehydrogenation, it follows that dihydrolycolucine has structure **91.** Lyco-

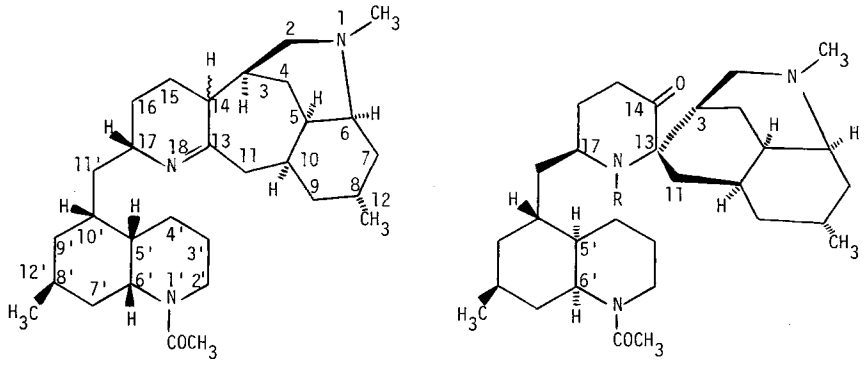
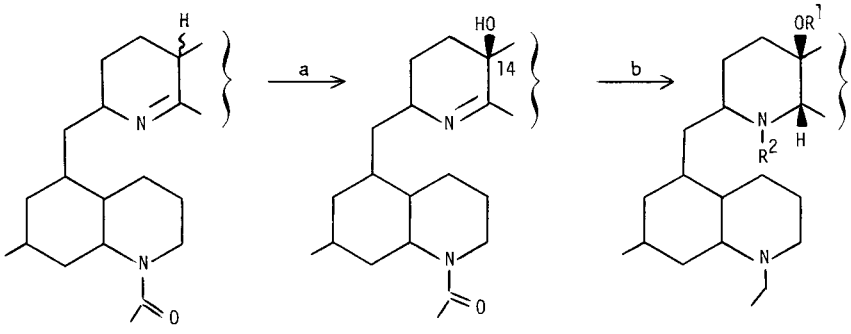


FIG. 5. The structures of lucidine B and spirolucidine.

TABLE V

LYCOPODIUM ALKALOIDS WITH A $C_{27}N_3$ SKELETON

Compound	Molecular formula	Molecular weight	Functionality	Structure elucidation	Source
Alkaloids related in structure to lucidine B					
Lycolucine (**90**)	$C_{30}H_{43}N_3O$	461	$\Delta^{14,15}$; $\Delta^{16,17}$; $\Delta^{10,11}$	(*3*)	*Lycopodium lucidulum* (*3*)
Dihydrolycolucine (**91**)	$C_{30}H_{45}N_3O$	463	$\Delta^{14,15}$; $\Delta^{16,17}$	(*3*)	*L. lucidulum* (*3*)
Lucidine B (serratanine A) (**92**)	$C_{30}H_{49}N_3O$	467	See Fig. 5	(*3,41*)	*L. lucidulum* (*3*); *L. serratum* (*41*)
Oxolucidine B (serratanine B) (**93**)	$C_{30}H_{49}N_3O_2$	483	14, OH(*S*)	(*3,41*)	*L. lucidulum* (*3*); *L. serratum* (*41*)
Spirolucidine (**94**)	$C_{30}H_{49}N_3O_2$	483	R = H; see Fig. 5	(*4*)	*L. lucidulum* (*4*)



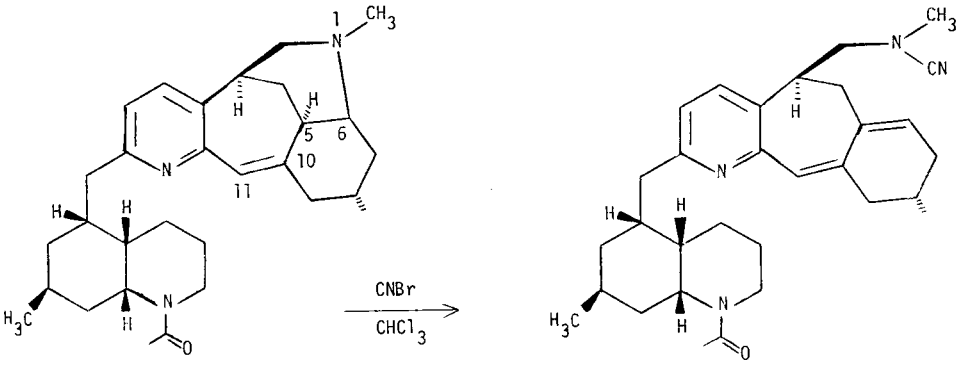
92 **93** **95** $R^1 = R^2 = H$

96 $R^1 = R^2 =$ *p*-bromobenzoyl

SCHEME 2. (a) Air; (b) LAH.

lucine (**90**) was converted to **91** by mild catalytic hydrogenation; the changes in the UV spectrum accompanying this reduction indicated that the double bond was conjugated to the pyridine ring. Its position at $\Delta^{10,11}$ was established when it was demonstrated that **90** was converted to diene **97** by treatment with CNBr, as shown in Scheme 3.

Shortly after these structures were published, Inubushi *et al.* (*41*) reported that the previously isolated serratanine (*1*) was a mixture of lucidine B (serratanine A) and oxolucidine B (serratanine B).



90 **97**

SCHEME 3

More recently, Ayer *et al.* (*4*) have elucidated the structure of spirolucidine (**94**), another $C_{27}N_3$ alkaloid closely related in structure to the lucidines and isolated from the same source. The structure rests ultimately on an X-ray examination of a derivative. The X-ray study established the relative but not the absolute configuration of **94.** The authors were able to deduce many of the structural features through spectroscopic and chemical examination of the base and several derivatives. For example, the presence of two $CHCH_3$ groups, one NCH_3, one *N*H, one $NCOCH_3$, and one carbonyl group situated α to an amino group was established. The X-ray analysis was carried out on tetrahydrodeoxyspirolucidine, obtained by reduction of **94** with LAH. In the reduction, the *N*-acetyl group was converted to *N*-ethyl and the carbonyl to a secondary alcohol with the (*S*) configuration (in terms of Fig. 5).

Aside from the structural difference between **92** and **94** resulting from a 1,2 bond migration, there are surprising differences in stereochemistry at C-17 and at C-5′ and C-6′. Ayer *et al.* (*4*) postulated that the spirolucidine ring system might be a precursor of alkaloids of the lucidine B-ring system, but the converse seems equally probable.

E. Alkaloids with Other than 16 or 27 Carbon Atoms in Their Structural Framework

Four distinct structural types are represented within the group of alkaloids having other than 16 or 27 carbon atoms (Table VI, Fig. 6). The ring system present in luciduline (**98**) is exceptional and only one simple derivative of it has been found in nature. Elements of the luciduline system are however incorporated into the $C_{27}N_3$ alkaloids discussed in the previous section.

The ring systems found in lycoflexine (**100**) and megastachine (**101**) are closely related to fawcettimine (**49**) and fawcettidine (**52**), respectively. They represent two of the new structural types reported since the previous review. The occurrence of selagine (**102**) in species other than *L. selago* (*1,2*) has been reported.

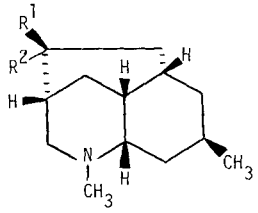
Lycoflexine is present in several *Lycopodium* species but derives its name from its isolation from *L. clavatum* var. *inflexum* (*21*). Its isolation from this source and its structural elucidation were reported simultaneously. In the interim, it has been found in five other species. It has been demonstrated recently that lycoflexine is identical with lycobergine, an alkaloid isolated from *L. serratum* (*2,25*) some years earlier than the isolation of lycoflexine from *L. clavatum.* Nevertheless it is proposed that the name lycoflexine be retained for this alkaloid because of its well-established use in the literature.

The structure of lycoflexine was determined by an X-ray crystallographic study on lycoflexine hydrobromide (*21*). It is evident that the alkaloid is closely related in structure to fawcettimine, differing from the latter by virtue of a

TABLE VI

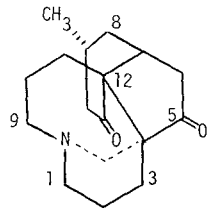
LYCOPODIUM ALKALOIDS THAT HAVE OTHER THAN 16 OR 27 CARBON ATOMS IN THEIR STRUCTURAL FRAMEWORK

Compound	Molecular formula	Molecular weight	Structure elucidation	Source
Alkaloids containing one nitrogen atom				
Luciduline (L21) (**98**)	$C_{13}H_{21}NO$	207	(*2*)	(*1,2*)
Dihydroluciduline (**99**)	$C_{13}H_{23}NO$	209	(*2*)	*Lycopodium lucidulum* (*15,42*)
Lycoflexine (lycobergine) (**100**)	$C_{17}H_{25}NO_2$	275	(*21*)	*L. carolinum* (*13*); *L. clavatum* var. *borbonicum* (*5*); *L. clavatum* var. *inflexum* (*21*); *L. inundatum* (*15*); *L. phlegmaria* (*25*)
Megastachine (**101**)	$C_{20}H_{29}NO_3$	331	(*43*)	*L. megastachyum* (*43*)
Selagine (**102**)	$C_{15}H_{18}N_2O$	242	(*1*)	*L. erythraeum* (*13*); *L. gnidioides* (*14,15*); *L. saururus* (*13*)

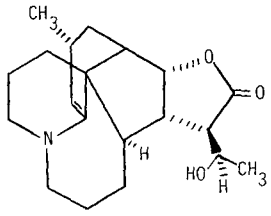


$R^1+R^2=O$, luciduline

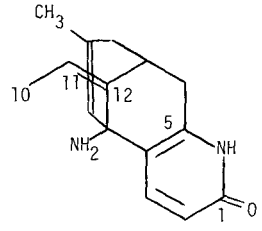
$R^1=H$, $R^2=OH$, dihydroluciduline



lycoflexine



megastachine



selagine

FIG. 6. Lycopodium alkaloids with other than 16 or 27 carbon atoms in their ring systems.

methylene bridge between the nitrogen and C-4. Lycoflexine has been prepared from fawcettimine by treatment with formaldehyde in methanol in the presence of HBr. This transformation established the absolute configuration of lycoflexine, since the absolute configuration of fawcettimine was known (Section II,B,4). Circular dichroism studies on several derivatives of **100** are in agreement with this assignment. The facile transformation of fawcettimine to lycoflexine raised the possibility that lycoflexine might be an artefact of isolation, but experiments described by the authors have ruled out this possibility (*21*).

The spectroscopic properties of lycoflexine have been examined, but only its mass spectrum deserves comment. The alkaloid shows a strong molecular ion peak in its spectrum and a base peak at *m/z* 84. The presence of a peak at *m/z* 84 of such strong intensity sets lycoflexine apart from other alkaloids of this family.

Megastachine, from *L. megastachyum*, is unusual among the lycopodium alkaloids in that it has the elements of an acetoacetate unit fused to a $C_{16}N$ skeleton of the fawcettidane type (*43*). The structure of **101** was elucidated by an X-ray crystallographic study on megastachine methiodide. This study established its relative but not its absolute configuration. The spectroscopic properties of the base and several derivatives have been reported. Megastachine is, at the time of writing, the sole representative of its class.

F. Alkaloids of Undetermined Structure and Molecular Complexes of the Alkaloids

The *Lycopodium* alkaloids whose structures or identity, as the case may be, remain to be resolved are collected together in Table VII. They constitute a formidable group, and it is unfortunate that many of them, especially those isolated more than 30 years ago, may never be reexamined. It is noteworthy that there are 11 alkaloids containing 3 nitrogen atoms and 28–33 carbon atoms within this group. These alkaloids are very likely related in structure to the $C_{27}N_3$ alkaloids recently investigated by Ayer (Section II,D) and thus constitute a rewarding group for future study.

TABLE VII
Alkaloids of Undetermined Structure

Compound	Molecular formula	Molecular weight	Source
Saururine	$C_{10}H_{19}N$	153	*Lycopodium saururus* (*1*)
—	$C_{10}H_{19-21}NO$	169 (171)	*L. annotinum* (*1*)
L 18	$C_{11}H_{19}NO$	181	*L. clavatum* (*1*)
L 26	$C_{15}H_{25}NO$	235	*L. sabinaefolium* (*1*)
L 35	$C_{14}H_{21}NO_2$	235	*L. densum* (*1*)
Base IV	$C_{16}H_{23}NO$	245	*L. annotinum* (*1*)
—	$C_{16}H_{23-25}NO$	245 (247)	*L. annotinum* (*1*)
Lycoserrine	$C_{16}H_{26}NO_2$	246	*L. serratum* (*2*)
L 16	$C_{16}H_{25}NO$	247	*L. obscurum* (*1*)
L 24	$C_{16}H_{25}NO$	247	*L. lucidulum* (*1*)
Pillijanine	$C_{15}H_{24}N_2O$	248	*L. saururus* (*1*)
L 10	$C_{16}H_{27}NO$	249	*L. annotinum* (*1*)
L 22	$C_{16}H_{27}NO$	249	*L. lucidulum* (*1*)
L 29	$C_{16}H_{23}NO_2$	261	*L. annotinum* (*1*)
Base VI	$C_{16}H_{23}NO_2$	261	*L. annotinum* (*1*)
Base 258	—	263	*L. clavatum* L. (*20*)
L 25	$C_{16}H_{25}NO_2$	263	*L. lucidulum* (*1*)
Lycoserramine	$C_{16}H_{25}NO_2$	263	*L. serratum* (*2*)
—	$C_{16}H_{25-27}NO_2$	263 (265)	*L. clavatum* (*1*)
Erythreine	$C_{17}H_{22}N_2O$	270	*L. erythraeum* (*13*)
Erythreidine	$C_{17}H_{22}N_2O$	270	*L. erythraeum* (*13*)
Borbonicine	$C_{17}H_{24}N_2O$	272	*L. clavatum* var. *borbonicum* (*13*)
Base E	$C_{17}H_{25}NO_2$	275	*L. fawcettii* (*1*)
Base VIII	$C_{16}H_{21}NO_3$	275	*L. annotinum* (*1*)
Base IX	$C_{17}H_{25}NO_2$	275	*L. annotinum* (*1*)
Base 168	$C_{16}H_{23}NO_3$	277	*L. clavatum* L. (*20*)
Base V	$C_{17}H_{27}NO_2$	277	*L. annotinum* (*1*)
L 28	$C_{17}H_{27}NO_2$	277	*L. annotinum* (*1*)
Base X	$C_{17}H_{25}NO_3$	291	*L. annotinum* (*1*)
Saururidine	$C_{17}H_{25}NO_3$	291	*L. saururus* (*13*)

(*continued*)

TABLE VII (*Continued*)

Compound	Molecular formula	Molecular weight	Source
Base XI	$C_{18}H_{25}NO_3$	303	*L. annotinum* (*1*)
—	$C_{18}H_{27}NO_3$	305	*L. contiguum* (*22*), *L. thyoides* (*22*)
Base G	$C_{18}H_{27}NO_3$	305	*L. fawcettii* (*1*)
L 17	$C_{18}H_{27}NO_3$	305	*L. obscurum* (*1*)
Base XII	$C_{18}H_{25}NO_4$	319	*L. annotinum* (*1*)
Base VII	$C_{20}H_{29}NO_4$	347	*L. annotinum* (*1*)
L 31	$C_{20}H_{29}NO_4$	347	*L. annotinum* (*1*)
L 15	$C_{20}H_{31}NO_4$	349	*L. tristachyum* (*1*)
LV1	$C_{29}H_{45}N_3$	435	*L. verticillatum* (*13*)
LO3	$C_{29}H_{49}N_3$	439	*L. obtusifolium* (*44*)
Gnidine	$C_{29}H_{51}N_3$	441	*L. gnidioides* (*15*)
LE1	$C_{28}H_{47}N_3O$	441	*L. erythraeum* (*13*)
Gnidinine	$C_{29}H_{51}N_3O$	457	*L. gnidioides* (*15*)
LO2	$C_{30}H_{49}N_3O$	467	*L. obtusifolium* (*44*)
LS14	$C_{30}H_{49}N_3O$	467	*L. saururus* (*13*)
Lucidine A	$C_{30}H_{49}N_3O$	467	*L. lucidulum* (*3*)
Dehydrolycocaroline	$C_{32}H_{51}N_3O$	493	*L. carolinianum* (*15*)
LO1	$C_{31}H_{39}N_3O_2$	495	*L. obtusifolium* (*44*)
Lycocaroline	$C_{32}H_{53}N_3O$	495	*L. carolinianum* (*15*)
Lycodiflexine	$C_{35}H_{50}N_2O_4$	562	*L. clavatum* var. *borbonicum* (*15*)

The six binary molecular complexes described in the literature are recorded in Table VIII. Five of them, comprising alkaloids of the lycopodane ring system, have been reported before (*1,2*). The sixth, more recently isolated, is made up of two alkaloids of undetermined structure, each containing two nitrogen atoms. It is the first example of a molecular complex in other than the lycopodane series.

TABLE VIII
MOLECULAR COMPLEXES

Compound	Molecular formula	Components	Source
Isolycopodine	$C_{32}H_{48}N_2O_3$	Lycopodine (**4**) + acrifoline (**6**)	(*2*)
—	$C_{32}H_{52}N_2O_3$	Dihydrolycopodine (**5**) + flabelliformine (**12**)	(*1*)
Clavatoxine	$C_{32}H_{50}N_2O_4$	Lycodoline (**15**) + flabelliformine (**12**)	(*2*)
Annotoxine	$C_{34}H_{44}N_2O_5$	Acrifoline (**6**) + annotine (**45**)	(*1*)
Isoerythreine	$C_{34}H_{44}N_4O_2$	Erythreine + erythreidine	*Lycopodium erythraeum* (*13*)
L9	$C_{36}H_{56}N_2O_5$	Lycopodine (**4**) + acetyllofoline (**33**)	(*1*)

G. Physical Properties of the Alkaloids

Modern physical methods have been widely used in the examination of the lycopodium alkaloids, but only a few attempts (*2*) have been made to correlate physical properties with structural type. A recent study of this nature has however been carried out by Nakashima *et al.* (*45*) who have examined the ^{13}C-NMR spectra of several alkaloids of the lycopodane and flabellidane series. As a result of their investigation, they were able to assign many of the resonances in the spectra of the alkaloids to specific carbon centers and also gained new insights into the stereochemistry of the alkaloids in solution. For example, they found that the *N*-methyl groups in α-obscurine (**70**), *N*-methyllycodine (**67**), and sauroxine (**71**) occupy axial positions. They also found distinct differences in the ^{13}C-NMR spectra of alkaloids epimeric at C-12, e.g., for lycodoline (**15**) and pseudoselagine (**17**) and for α-obscurine (**70**) and sauroxine (**71**). Thus ^{13}C NMR may have diagnostic value in assigning configuration at this center in new alkaloids of each series.

III. Synthesis of the Alkaloids

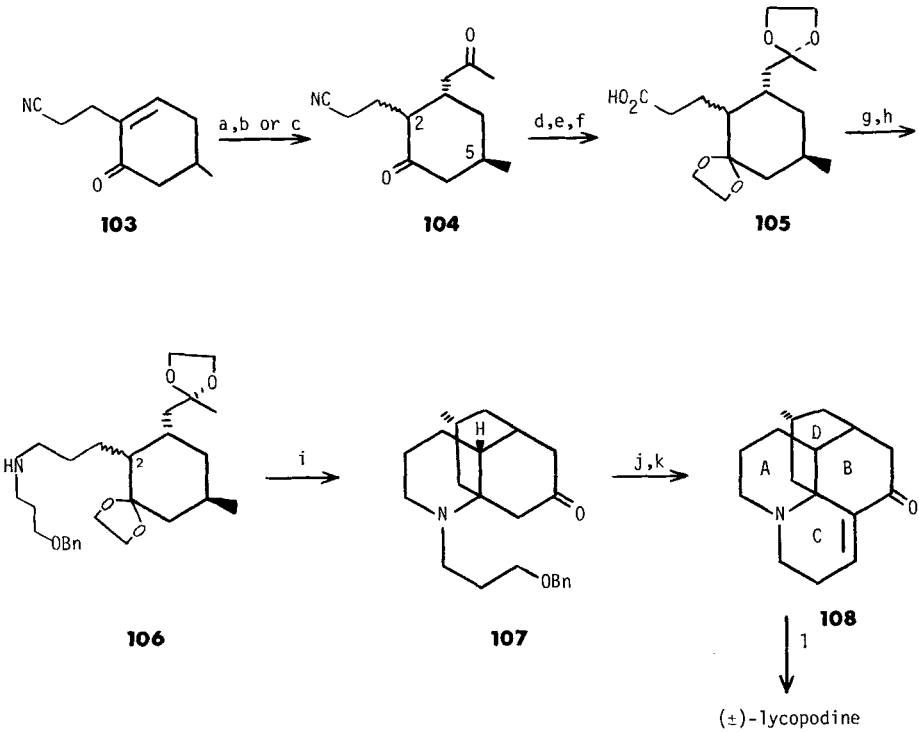
A. Introduction

Major advances have been made in the area of synthesis since the previous review (*2*). New and improved routes to lycopodine have been developed, and other alkaloids of the lycopodane ring system have been synthesized. In two cases, intermediates used to synthesize the lycopodane alkaloids have been adapted to the synthesis of the flabellidane alkaloids having a $C_{16}N_2$ skeleton. The synthesis of fawcettimine, fawcettidine, serratinine, and related alkaloids has been achieved, beginning from the hydrindane system that is a common feature of the ring systems present in these alkaloids. Four syntheses of luciduline have been reported, one of which is enantioselective. The phlegmarine system has been prepared, using a strategy employed in one synthesis of luciduline. Progress has been reported by two groups in the synthesis of selagine, and a diastereomer of the cernuane system has been prepared by a new route. The synthetic studies enumerated above will be reviewed in separate sections of this chapter, beginning with the lycopodane alkaloids.

B. The Lycopodane Alkaloids

1. The Heathcock Synthesis of (±)-Lycopodine and of (±)-Lycodoline

Lycopodine (**4**) is the most abundant and most widely distributed of all the lycopodium alkaloids. Moreover it has a ring system that is common to more than one-third of all of the alkaloids of established structure of the family. It is



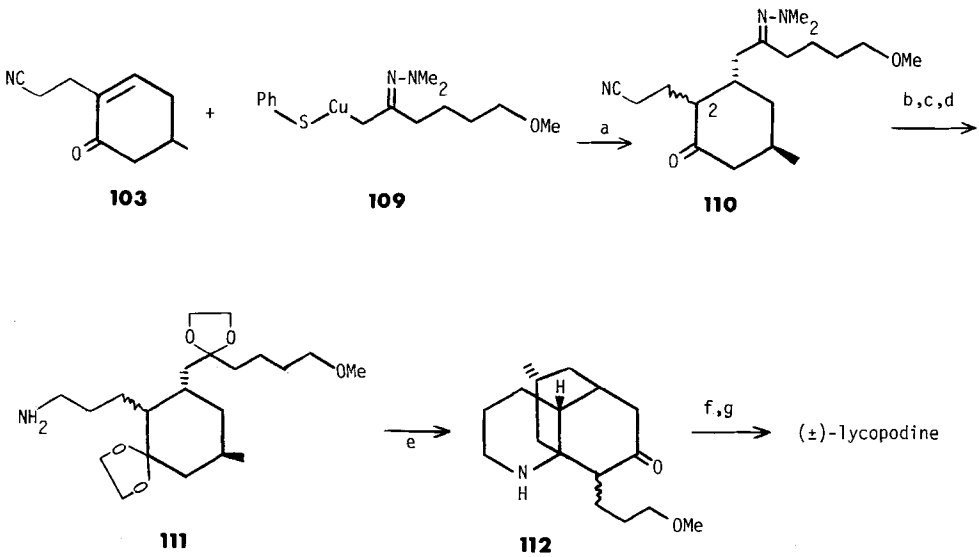
SCHEME 4. (a) (i) $(\text{Li})_2\text{CuLi}$, THF, (ii) O_3, MeOH; (b) (i) $(\text{Li}^{NNMe_2})_2$ CuLi, THF, (ii) H_2O, $CuCl_2$, pH 7; (c) (i) Li^{SiMe_3}, $TiCl_4$, THF, (ii) O_3, MeOH; (d) $(CH_2OH)_2$, TsOH, C_6H_6; (e) KOH, EtOH; (f) acidify; (g) $ClCO_2Et$, Et_3N, $NH_2(CH_2)_3OBn$; (h) LAH, THF; (i) 3 *M* HCl, MeOH, 65°C, 14 days; (j) H_2, Pd/C, HCl, EtOH; (k) $(C_6H_5)_2C{=}O$, *t*-BuOK, C_6H_6; (l) H_2, Pt.

not surprising, therefore, that its synthesis has engendered so much interest. Two related and ingenious routes to **4** have been devised by Heathcock and his collaborators (*46,47*), and one of these routes has been adapted to an equally elegant synthesis of (±)-lycodoline (*47,48*). The three syntheses are outlined separately below.

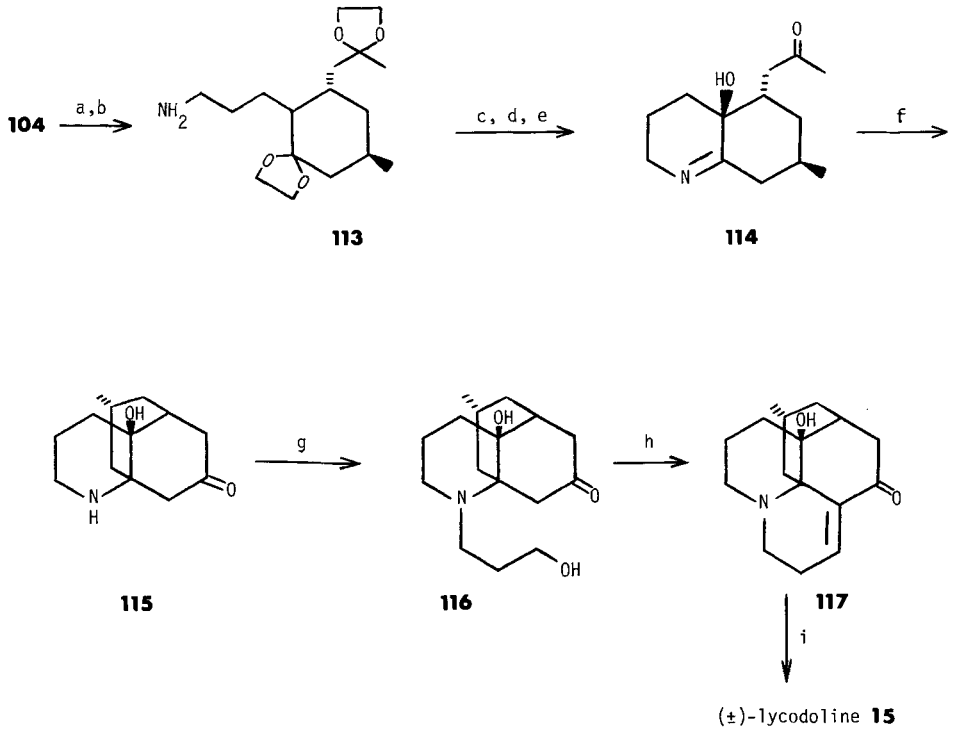
The enone **103,** prepared in three steps and in an overall yield of 60% from 5-methyl-1,3-cyclohexanedione (*49*), was used as the starting material in the three syntheses described in this section. In the first of these, outlined in Scheme 4, the three carbon unit required to complete ring B of lycopodine was introduced at C-3 of the enone **103.** The authors described three routes to accomplish this end. In the conjugate addition to the enone system, the entering group in each case assumed the requisite position trans to the methyl at C-5. The product was a mixture of epimers (~1:1) at C-2 but this presented no problem (see below). The carbonyl groups of **104** were protected by ketalization, and the cyano group was

hydrolyzed in base to the carboxylic acid **105.** The nitrogen atom and the three carbon atoms necessary to complete ring C of lycopodine were added next. The product **106** was then converted to the tricyclic compound **107** in a one-step operation under mildly acidic conditions that involved hydrolysis of the ketal groups and a Mannich condensation. The authors offer an explanation on conformational grounds for the fact that only one epimer at C-2 of the dione derived from **106** is capable of cyclization. However, since the epimers at C-2 of the intermediate dione may equilibrate under the conditions used in the Mannich reaction, it is possible for the yield in the cyclization reaction to exceed 50%. The tricyclic compound **107** was debenzylated, and the liberated primary alcohol was oxidized to an aldehyde, which cyclized spontaneously to the tetracyclic enone **108;** (±)-lycopodine was obtained by reduction of **108.**

In the second synthesis, the Cu reagent **109** was added stereoselectively to enone **103,** yielding **110** as a mixture of epimers at C-2. The mixture of dimethylhydrazones was hydrolyzed to a mixture of diketones, the latter was converted to a mixture of diketals, and the product was reduced with LAH, yielding the amines **111.** These amines were subjected to acid treatment in the same way as the corresponding mixture of Scheme 4. The product **112** was converted readily to (±)-lycopodine by standard methods, as shown in Scheme 5. The overall yield in the 8 steps was ~13%, which was lower than in the alternative route where the yield was 16.6% in 13 steps, but considerably shorter.



SCHEME 5. (a) THF, −78°C; (b) $CuCl_2$, H_2O, pH 7; (c) $(CH_2OH)_2$, TsOH, C_6H_6; (d) LAH, THF; (e) 3 *M* HCl, MeOH, 18 days, reflux; (f) 25% HBr in AcOH, 25°C, 22hr; (g) K_2CO_3.



SCHEME 6. (a) $(CH_2OH)_2$, TsOH, C_6H_6; (b) LAH, THF; (c) (i) 10% HCl, (ii) NaOH, (iii) EtOAc; (d) O_2; (e) H_2, Pd/C; (f) (i) toluene:3-bromo-1-propanol = 5:1, 120°C, 24hr; (ii) 1 *M* NaOH; (g) 3-iodo-1-propanol, acetone, K_2CO_3, Δ; (h) KH, $(C_6H_5)_2C{=}O$, toluene; (i) H_2, Pt.

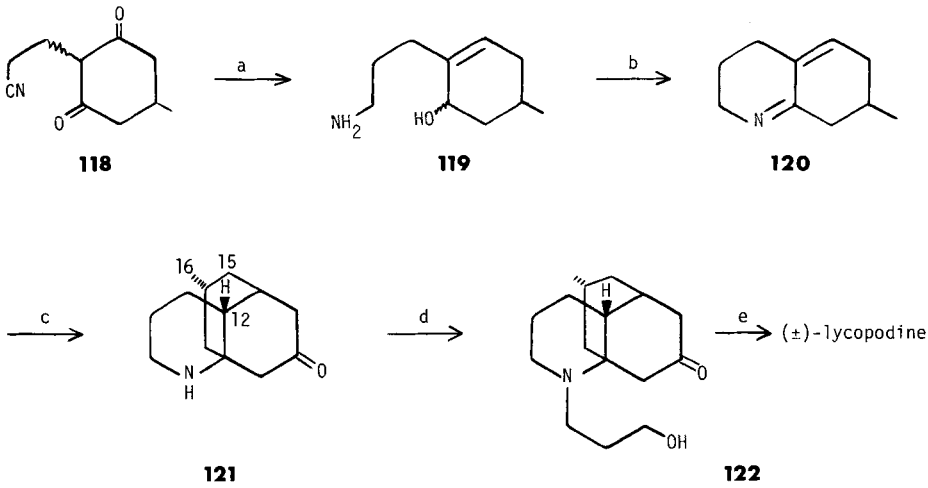
(±)-Lycodoline (**15**) was synthesized by the Heathcock group (*47,48*) in a modification of their lycopodine synthesis by introducing at an early stage the eventual OH group of lycodoline. To this end they took advantage of a reaction discovered by Cohen and Witkop (*50*) who had found that a hydroperoxide group was easily introduced at the bridgehead position (C-10) of $\Delta^{1,9}$ octahydroquinolines by autooxidation.

The starting material for the lycodoline synthesis was compound **113** (Scheme 6) obtained in two steps from **104.** When compound **113** was treated for a short period with 10% HCl, the solution basified, and the organic material taken up into ethyl acetate, an unstable imine was extracted into the solution. Treatment of the solution with O_2 presumably furnished a hydroperoxide (not isolated), which was reduced with hydrogen over Pd providing the bicyclic imine **114.** Conversion of **114** to the tricyclic amine **115** required carefully controlled conditions and was achieved in good yield by heating **114** in toluene with 3-bromo-1-propanol. Apparently the concentration of acid in the medium is crucial to the

condensation reaction. The conditions used provided a slow release of HBr as a result of slow polymerization of 3-bromo-1-propanol. The three carbon atoms required to complete the structural framework of lycodoline were introduced by reaction of **115** with 3-iodo-1-propanol. When the product **116** was oxidized with potassium hydride and benzophenone in toluene, the aldol condensation product **117** was isolated; it was easily converted to lycodoline. It is noteworthy that **116** reverted to **115,** presumably in an inverse Michael reaction of the intermediate aldehyde, upon similar treatment with potassium *t*-butoxide and benzophenone. The authors attribute the success of the KH/benzophenone procedure to the fact that the hydride abstracts the hydroxy hydrogen, preventing the intramolecular delivery of hydrogen to nitrogen from the OH group at C-12, an apparent requirement of the inverse Michael reaction.

2. Schumann Synthesis of (±)-Lycopodine

Schumann *et al.* (*51*) have prepared (±)-lycopodine in six steps from 2-(2-cyanoethyl)-5-methyl-1,3-cyclohexanedione (**118**), as outlined in Scheme 7. The key step in the synthesis was the 1,3 annulation of enimine **120** (derived from **118** through **119**) with acetonedicarboxylic acid. The annulation proceeded stereoselectively, providing **121,** which had the required relative configuration at C-12 and C-15 for elaboration to lycopodine. Compound **121** had been prepared by a different route by Heathcock *et al.* (*46,47*) in model studies leading up to their synthesis of lycopodine. The three carbon atoms required to complete the



SCHEME 7. (a) LAH, Et_2O, Δ; (b) (i) pyridinium dichromate, DMF, −5°C, (ii) NaOH; (c) (i) $O{=}C(CH_2CO_2H)_2$, dioxane, Δ, (ii) Na_2CO_3; (d) $Br(CH_2)_3OH$, NaOAc, 60°C; (e) see Scheme 6.

framework of lycopodine were introduced by treatment of **121** with 3-bromo-1-propanol. The product **122** was converted to (±)-lycopodine by the procedure developed by Heathcock *et al.* (*47,48*) to convert **116** to lycodoline.

3. Wenkert Synthesis of (±)-Lycopodine (4) and Four Lycopodane Alkaloids Oxygenated at C-5 and C-8

In 1973 Wenkert *et al.* (*52*) prepared the enone **123** from dimethyl quinolinate (*53*) with the objective of using **123** as a starting material for the synthesis of lycopodine and related alkaloids. This objective has now been realized in the synthesis of (±)-lycopodine and four racemic lycopodane alkaloids carrying oxygen at C-5 and C-8 (*54*) as shown in Scheme 8.

Enone **123** was reduced with LAH to **124,** and the latter was converted to **125** by treatment with 2-ethyl-2-lithio-1,3-dithiane in THF–HMPTA. The CH_2OH group of **125** was oxidized to an aldehyde, and the product was hydrolyzed to the tricarbonyl compound **126.** Cyclization of **126** in acidic medium afforded the tetracyclic enone **127,** which was readily reduced to the diketone **128.** The carbonyl group at C-8 was selectively converted to a thioketal and then reduced with Ra-Ni, yielding (±)-lycopodine.

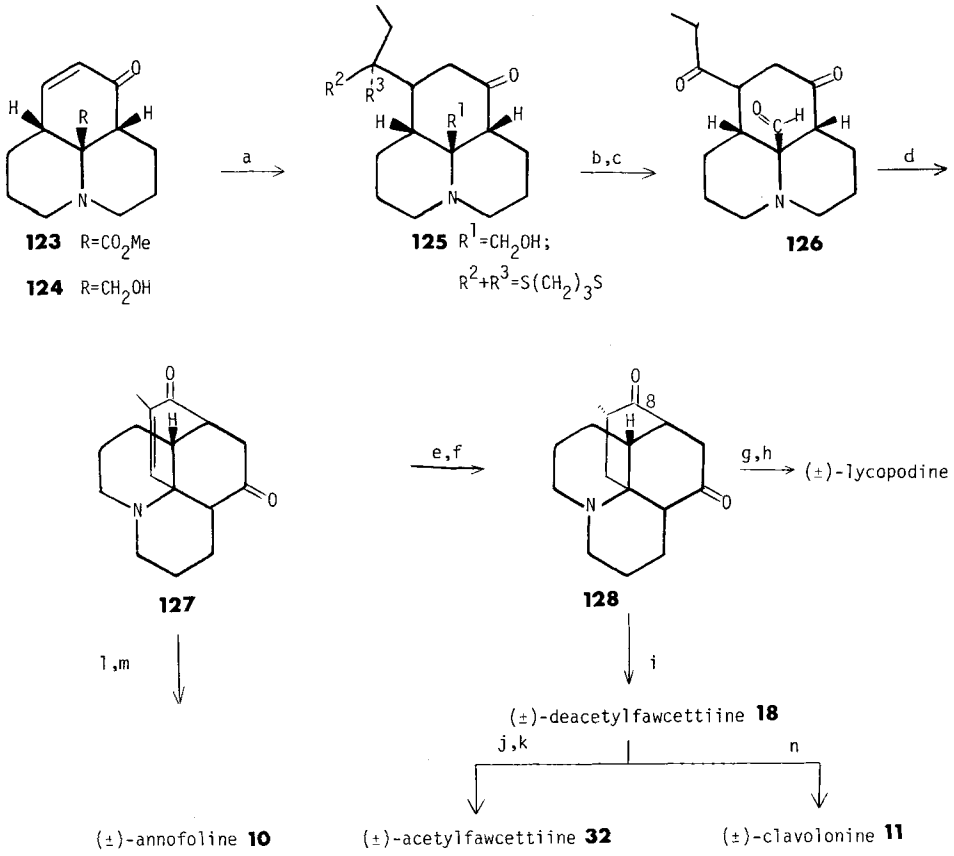
Three lycopodane alkaloids oxygenated at C-5 and C-8 were readily derived from **128.** (±)-Deacetylfawcettiine (**18**) was obtained on hydride reduction and (±)-acetylfawcettiine (**32**) by acetylation of **18.** (±)-Clavolonine (**11**) was prepared from **18** by selective acetylation at C-8, oxidation at C-5, and hydrolysis of the acetyl group according to a known procedure (*55*).

(±)-Annofoline (**10**) was derived from **127** in two reduction steps. The carbonyl group at C-5 was selectively reduced to the β alcohol with potassium tri-*sec*-butylboron hydride, and in a subsequent step the double bond in the bridge was reduced catalytically.

The Wenkert synthesis provides the first route to lycopodane alkaloids oxygenated on the bridge carbon atoms.

4. Synthesis of (±)-Anhydrolycodoline (2)

(±)-Anhydrolycodoline has been prepared (*56,57*) from the tricyclic enol **129** (*2*) by the route outlined in Scheme 9. The authors had attempted to synthesize lycodoline (**15**) by a Michael-type cyclization of **130** (available from **129** in five steps), but the cyclization failed under a variety of experimental conditions. An explanation for this failure came from model studies, which showed that *trans-N*-acrylyldecahydro-7-quinolones cyclized but that the cis isomers did not (*58,59*). Rational stereoelectronic arguments were proposed to account for the difference in behavior between the two isomers. It was argued that **130,** which has a cis AB

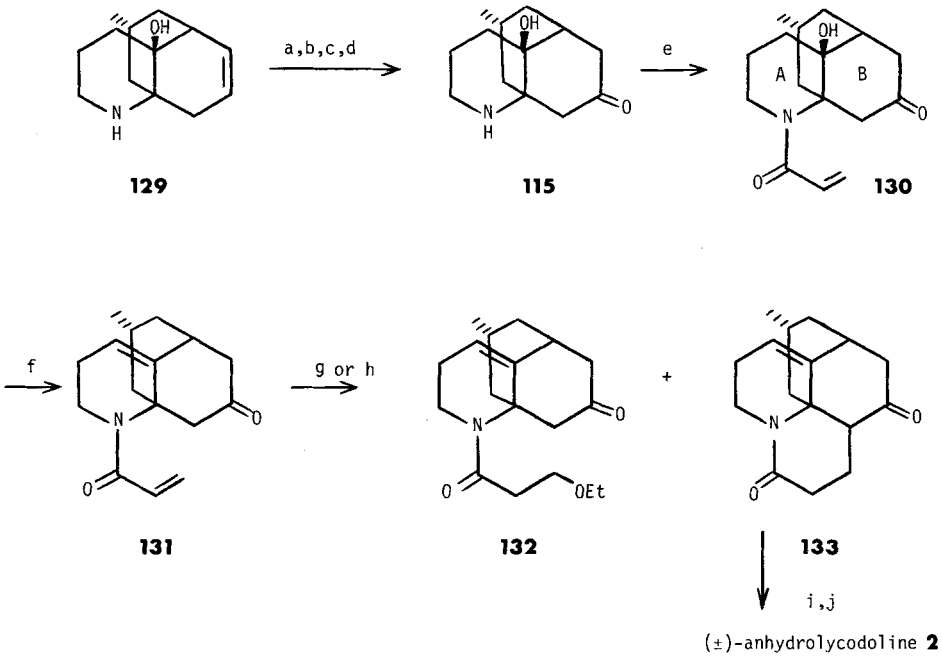


SCHEME 8. (a) 2-Ethyl-2-lithio-1,3-dithiane, THF, HMPTA; (b) DMSO, DCC; (c) $HgCl_2$, HgO, MeOH, H_2O; (d) HOAc:HCl = 9:1, 3.5 hr; (e) H_2/Pd, EtOAc; (f) NaOMe, C_6H_6, 30 min; (g) $(CH_2SH)_2$, HCl, AcOH; (h) Ra-Ni, EtOH, 18hr; (i) LAH, Et_2O; (j) MeLi, THF, 0°C; (k) Ac_2O, 20°C; (l) KB(*sec*-Bu)$_3$H, THF, −78°C, 4 hr; (m) H_2/Pd–C, EtOAc; (n) see Ref. *55*.

ring juncture, failed to cyclize for the same reasons as the model compound.

The synthesis of lycodoline was abandoned at this point, and attention was directed to the synthesis of **2.** Stereoelectronic considerations indicated that **131** should cyclize, and accordingly it was prepared from **130** by dehydration. Treatment of **131** with NaOEt in EtOH gave a mixture of **132** and **133,** but under modified conditions, using a crown ether, **133** was the sole product; it was readily converted to anhydrolycodoline (**2**) in two steps.

It has been noted that this synthetic route constitutes a formal synthesis of (±)-lycopodine (**4**) (*56,57*) and of (±)-lycodoline (**15**) (*60*). Ayer and Iverach (*61*) previously converted **2** to **4** by catalytic hydrogenation, albeit in low yield, and



SCHEME 9. (a) BnOCOCl, K_2CO_3, C_6H_6; (b) (i) B_2H_6, THF, (ii) H_2O_2, OH^-; (c) Jones' reagent; (d) H_2, Pd/C, EtOH; (e) CH_2=CHCOCl, Et_3N, $CHCl_3$; (f) CH_2Cl_2, H_2SO_4; (g) EtONa, EtOH, Δ; (h) NaOEt, dicyclohexyl-18-crown-6, DMF, Δ; (i) LAH, dioxane; (j) Jones' reagent.

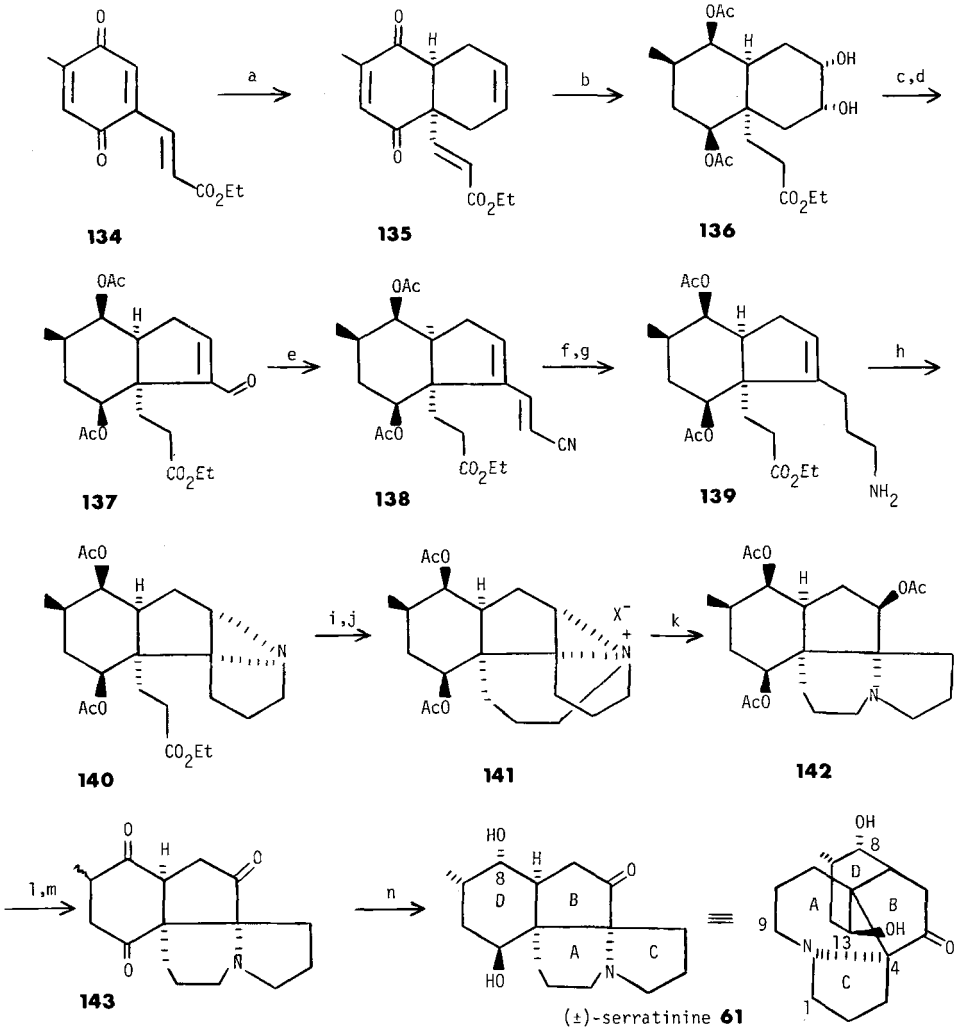
the intermediate **115** was a key compound in Heathcock's synthesis of **15** (Section III,B,1).

C. SYNTHESIS OF (±)-SERRATININE (**61**), (±)-FAWCETTIMINE (**49**), AND (±)-8-DEOXYSERRATININE (**59**)

Serratinine represents a formidable synthetic challenge to the chemist because of its six chiral centers and its two adjacent quaternary carbon atoms. Its synthesis has, however, been accomplished by Inubushi *et al.* (*62–65*) (Scheme 10). Their strategy involved the generation of the hydrindane system of rings **B** and **D** of the alkaloid, suitably functionalized for elaboration to the target molecule. In their initial paper (*62*) they described the synthesis of **135** from the quinone **134** and butadiene, and in their second paper (*63*), the elaboration of **135** to **137**, a compound in which the substituents on the potential D ring of serratinine are in the correct regiochemical array. Cleavage of the diol **136** gave an unstable dialdehyde, which was converted in an aldol condensation under carefully controlled conditions to the conjugated enal **137** and a regioisomer. A Wittig reac-

tion on the mixture provided **138** (8 parts), which was separated from its regioisomer (1 part). All of the carbon atoms and the nitrogen atom necessary to complete the ring system of **61** were now in place.

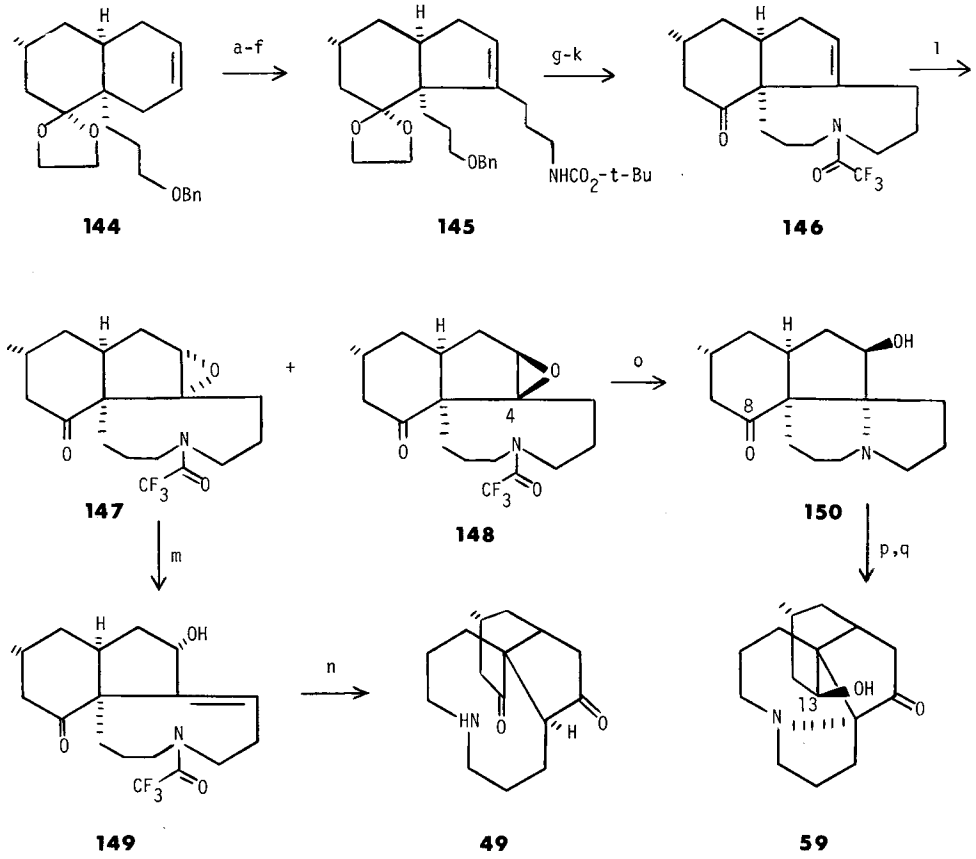
The completion of the synthesis (*64,65*) from **138** began with two reduction steps: first, a selective reduction of the exocyclic bond of the conjugated nitrile and second, of the nitrile group itself to the primary amine. The product **139** was



SCHEME 10. (a) Butadiene; (b) various steps, see Ref. *63;* (c) HIO_4; (d) pyrrolidine, AcOH, MeOH; (e) $CNCH_2PO(OC_2H_5)_2$, NaH; (f) $[Ph_3P]_3RhCl$, H_2; (g) $NaBH_4$, $CoCl_2$; (h) *N*-chlorosuccinimide, Cu_2Cl_2, CH_2Cl_2; (i) $LiBH_4$, EtOH; (j) TsCl, pyridine; (k) KOAc, EtOH; (l) KOH, MeOH; (m) Jones' oxidation; (n) $NaBH_4$.

converted to the aziridine **140** (a small amount of its stereoisomer was also formed by attack on the opposite face of the double bond) and the latter, in two steps, to the aziridinium salt **141.** The aziridine ring was opened with KOAc in EtOH, providing the triacetate **142,** and in two additional steps the trione **143,** as a mixture of epimers at C-15, was obtained. Finally, reduction of the trione yielded a mixture of (±)-serratinine (**61**) and its epimer at C-8.

The synthesis of the tricyclic alkaloid fawcettimine (**49**) has also been achieved by Inubushi *et al.* (*66,67*), using a strategy similar to that employed for serratinine. The starting material for the synthesis was compound **144** (Scheme



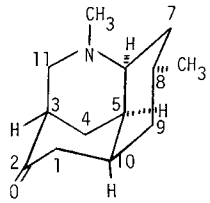
SCHEME 11. OsO_4, *N*-methylmorpholine *N*-oxide; (b) H_5IO_6; (c) morpholine, camphoric acid, Et_2O, HMPTA, 0°C, 20hr; (d) $(EtO)_2POCH_2CN$, NaH, C_6H_6; (e) H_2, $(Ph_3P)_3RhCl$, C_6H_6; (f) (i) $LiAlH_4$, THF, (ii) EtOAc, N_3CO_2-*t*-Bu; (g) (i) Na/liq NH_3, (ii) Jones' reagent, (iii), *N*-hydroxysuccinimide NOH, DCC, (iv), CF_3CO_2H; (h) Bu_3N, CH_3CN, Δ; (i) $LiBH_4$, THF; (j) (i) $LiAlH_4$, (ii) $(CF_3CO)_2O$, pyridine; (k) Jones' reagent; (l) MCPBA, CH_2Cl_2; (m) BF_3–Et_2O/CH_2Cl_2; (n) (i) Jones' reagent, (ii) H_2/Pd, EtOAc, (iii) KOH/MeOH; (o) KOH/MeOH; (p) Jones' reagent; (q) $NaBH_4$/EtOH.

11), which was prepared regioselectively and stereoselectively by a Diels–Alder reaction (*68,69*). In a sequence of steps reminiscent of those used in converting **135** to **139** (Scheme 10), compound **144** afforded the hydrindane **145** containing the 16 carbon atoms and one nitrogen atom required to form **49.** After the side chains of **145** were suitably functionalized, the nine-membered ring of fawcettimine was formed as a lactam, which was then reduced to the amine. Protection of the secondary amino function as an *N*-trifluoroacetamide gave **146,** which was converted to a mixture of epoxides, **147** and **148.** Upon treatment with BF_3–Et_2O, the α-epoxide **147** yielded the allylic alcohol **149** from which (±)-fawcettimine (**49**) was readily obtained.

(±)-8-Deoxyserratinine was prepared from the β-epoxide **148.** Hydrolysis of the amide gave directly the tetracyclic alcohol **150,** formed by intramolecular nucleophilic attack at C-4 of the epoxide by the liberated secondary amino group. Oxidation of the hydroxy ketone to a dione, followed by a selective reduction at C-13, gave (±)-8-deoxyserratinine (**59**).

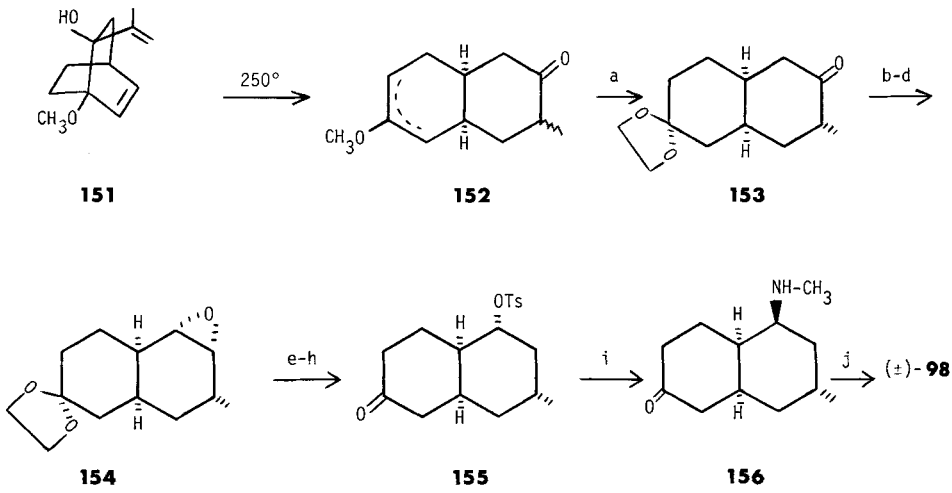
D. Synthesis of Luciduline (98)

Four syntheses of luciduline have been reported of which one, that of Oppolzer and Petrzilka, is enantioselective. The molecule poses an interesting synthetic problem because of its five chiral centers and the cis fusion of the ring system. The four routes to **98** will be discussed in order of their appearance in the literature.



Luciduline

In the approach of Scott and Evans (*70*), outlined in Scheme 12, the strategy was to synthesize the decalone **156** and to introduce the final carbon atom and the third ring in an intramolecular Mannich reaction. Their starting material was the bicyclic dienol **151,** which underwent an oxy-Cope rearrangement to **152.** Ketalization of **152** provided **153** as a mixture of epimers at the C—CH_3 group, but it was possible to isolate the desired epimer in high yield by crystallization. A three-step conversion of **153** to **154** was effected in good yield, using standard procedures. The epoxide ring of **154** was opened with thiophenoxide, the product was desulfurized with Ra-Ni, the alcohol group was tosylated, and the ketal was



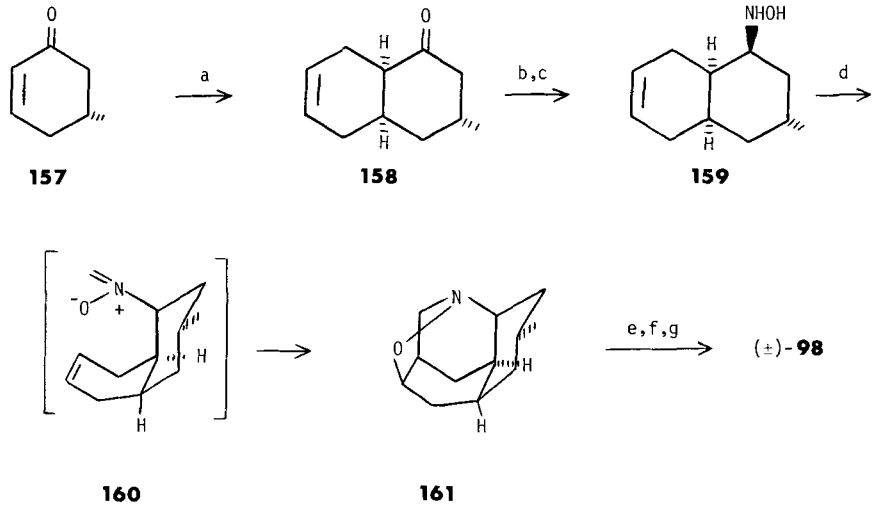
SCHEME 12. (a) $(CH_2OH)_2$, H^+; (b) $TsNHNH_2$; (c) MeLi (2 eq), Et_2O; (d) MCPBA, $CHCl_3$; (e) C_6H_5SNa, MeOH, Δ; (f) Ra-Ni, EtOH, Δ; (g) TsCl, pyridine, 10 hr; (h) $Me_2C{=}O$, HCl, 50°C, 0.75hr; (i) $MeNH_2$, C_6H_6, 75°C, 24hr, sealed tube; (j) paraformaldehyde, *i*-AmOH, Δ, 20hr.

hydrolyzed, yielding **155.** The resulting tosylate provided **156** on treatment with methylamine in benzene in a sealed system. The authors postulated that the displacement of tosylate may have occured intramolecularly through an aminal, formed by reaction of the ketone with methylamine. The final step was achieved in the anticipated fashion; (±)-luciduline was isolated as its hydrochloride.

Oppolzer and Petrzilka (*71,72*) developed an enantioselective synthesis of (±)-**98,** beginning with (*R*)-5-methylcyclohex-2-en-1-one **157.** The key intermediate in their approach (Scheme 13) was the hydroxylaminooctalin **159.** The hydroxylamino function was converted with formaldehyde to a transient nitrone, which added regioselectively to the $\Delta^{6,7}$ double bond of the octalin. The adduct was then converted to dihydroluciduline and luciduline. (±)-Luciduline was also prepared, using (±)-**157** as starting material.

Compound **157** was derived from (*R*)-3-methylcyclohexanone [available commercially or from (±)-pulegone] in a standard manner. Diels–Alder addition of butadiene to **157** gave a mixture of octalones **158** in which the trans isomer predominated (cis:trans = 1:2.5). By taking advantage of the observation that the cis isomer forms an oxime much faster than the trans, it was possible to devise conditions to convert the mixture mainly to the *cis*-oxime (cis:trans = 5:1). The oxime underwent reduction stereoselectively to the desired hydroxylamine **159.**

In the final steps of the synthesis, the hydroxylamine was converted through the intermediacy of the transient nitrone **160** to the cycloaddition product **161.** Methylation, followed by hydride reduction, gave dihydroluciduline, which was



157 158 159

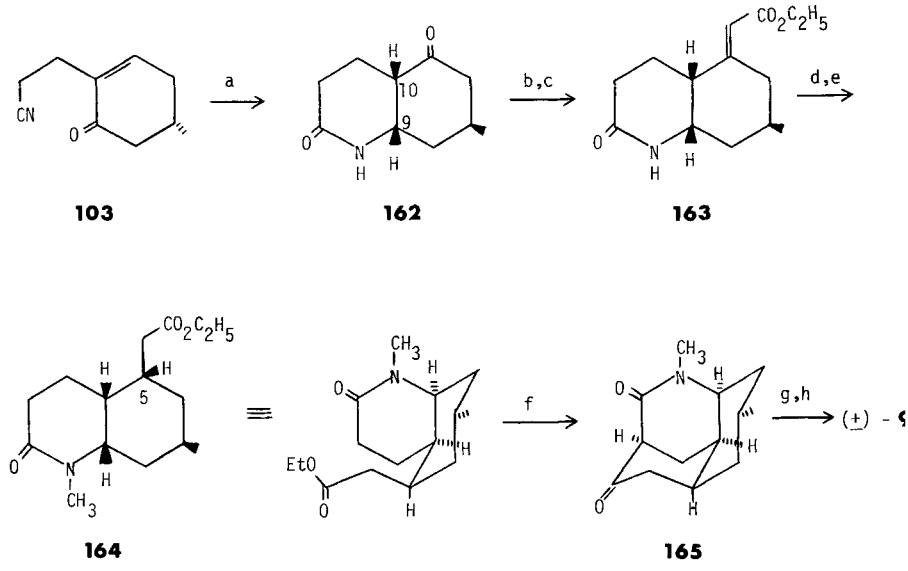
160 161

SCHEME 13. (a)⁄⁄⁄⁄, $SnCl_4$, 25°C; (b) NH_2OH, HCl, MeOH; (c) $NaCNBH_3$, pH 3–4; (d) paraformaldehyde, toluene, Δ, molecular sieves; (e) CH_3OSO_2F, Et_2O; (f) LAH, THF; (g) Jones' oxidation.

converted to luciduline by Jones' oxidation. The overall yield in seven steps beginning from **157** was 33%. This constitutes the first and only enantioselective synthesis of a lycopodium alkaloid.

Szychowski and MacLean (*73*) synthesized luciduline by a route in which the C-2—C-3 bond of luciduline was the final step in the construction of the carbon skeleton (Scheme 14). The starting material in their synthesis was 2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (**103**), the same substance used by Heathcock *et al.* (Section III,B,1) in their synthesis of lycopodine. Compound **103** was converted upon prolonged treatment with methanolic sodium hydroxide to a mixture of lactams **162,** epimeric at C-9 (cis:trans = 5:1). The isomer mixture was allowed to react with lithium ethyl trimethylsilylacetate in a Peterson reaction from which **163** was isolated. Hydrogenation, followed by N-methylation, gave a separable mixture (1:1) of the desired isomer **164** and its epimer at C-5. Cyclization of **164** to luciduline lactam **165** was effected with base in THF, and the lactam was converted by hydride reduction to dihydrolucidiuline and then by oxidation to (±)-luciduline by established methods.

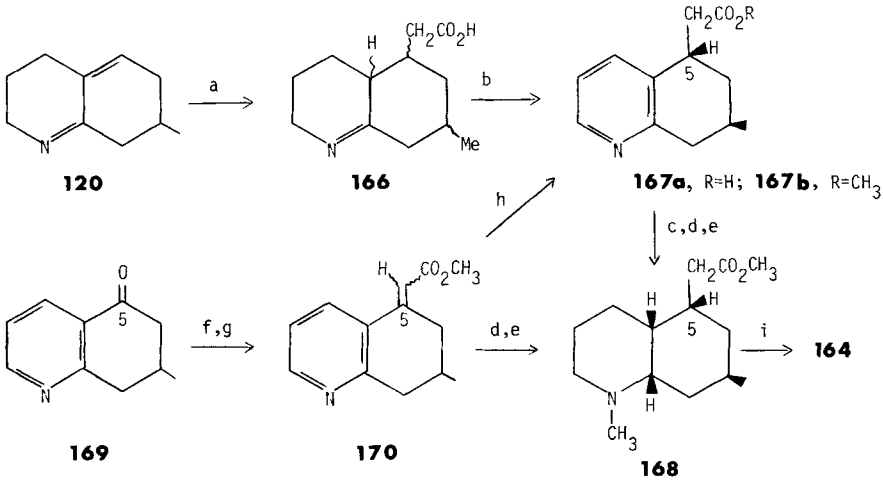
The enimine **120,** used so successfully in the synthesis of (±)-lycopodine (Section III,13,2), (±)-α-obscurine, and (±)-*N*-acetylflabellidine (Section III,E) by Schumann *et al.*, has been investigated by the same group (*74*) as a starting material for the synthesis of (±)-**98.** It turned out that **120** was impractical in this respect, but as a result of their study an alternative route to (±)-luciduline was developed. Their work is outlined in Scheme 15.



SCHEME 14. (a) NaOH, MeOH, Δ, 44 hr; (b) $(Me_3SiCHCO_2Et)Li^+$, −60°C, THF; (c) H_2O, H^+ (d) H_2/Pt, EtOH; (e) ($\bigcirc$–$\tilde{N}CH(CH_3)_2)Li^+$, Me_2SO_4; (f) ($\bigcirc$–$\tilde{N}CH(CH_3)2)Li^+$, THF, 0.5 hr, −60°C; (g) LAH, Et_2O; (h) Jones' oxidation.

Treatment of **120** with malonic acid gave **166** as a mixture of diastereomers. Conversion of the acids to their methyl esters, followed by reduction with $NaBH_4$, gave a complex mixture of stereoisomers that contained only traces of the compound required for continuation of the synthesis. It was found, however, that pyrolysis of the diastereomeric acids **166** led to a disproportionation reaction in which part of the enimine was oxidized to the pyridine **167a** (14% based on **120**), and another part was reduced to a mixture of diastereomeric perhydro compounds with inappropriate configurations for this synthesis. Reduction of the pyridine ring of ester **167b** gave stereoselectively a perhydro ester, which was N-methylated to **168.** This compound had the requisite stereochemistry for elaboration to luciduline, but this route to **168** was impractical because of low yield.

It was found that **168** was more conveniently prepared from the tetrahydroquinolone **169.** The two-carbon chain at C-5 was introduced by the Horner–Wittig reaction, yielding the diastereomeric esters **170** after ester exchange in a 1:1 ratio of *E* and *Z* isomers. Reduction of **170** could be carried out stepwise, first to **167b** and then to **168,** or in one step to de-*N*-methyl-**168.** In both cases a mixture of epimers at C-5 was formed, which was separated chromatographically. Oxidation of **168** yielded the previously prepared lactam **164,**



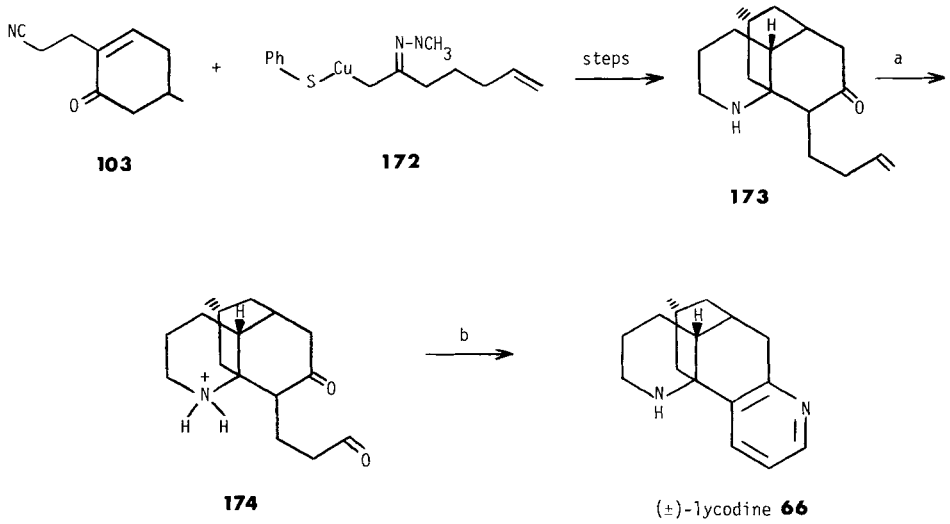
SCHEME 15. (a) $CH_2(CO_2H)_2$, C_6H_6, Δ; (b) Δ, 175°C, 20 hr; (c) MeOH, HCl, 5hr; (d) PtO_2, H_2, AcOH; (e) HCO_2H, $CH_2{=}O$; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, $C_6H_5CH_3$; (g) CH_3OH, HCl; (h) H_2, PtO_2, EtOH; (i) $KMnO_4$, dicyclohexano-[18]-crown-6, C_6H_6, 12hr.

and the synthesis was completed by the method of Szychowski and MacLean, as shown in Scheme 14.

E. SYNTHESIS OF (±)-LYCODINE (66), (±)-*N*-ACETYLFLABELLIDINE (171), (±)-DE-*N*-METHYL-α-OBSCURINE (68), AND (±)-α-OBSCURINE (70)

The title compounds belong to the same ring system but differ in oxidation state or in substitution. Three of them, lycodine and the two α-obscurines, are naturally occurring, and the third is a simple derivative of the natural compound **73.** Lycodine has been synthesized by Heathcock *et al.* (*47,75*) in an adaptation of their lycopodine synthesis, while *N*-acetylflabellidine (*76*) and the obscurines (*77*) have been made by Schumann *et al.* from the enimine **120** in a 1,3-annulation reaction similar to that used by them to prepare (±)-lycopodine.

Heathcock *et al.* prepared lycodine in good yield from **103** and **172** using a route analogous to that employed in one of their two syntheses of lycopodine (see Scheme 5, Section III,B,1). The reactions are sketched out in Scheme 16 beginning from compound **173,** an analog of **112** (Scheme 5). Ozonization of **173** as its bisulfate salt in MeOH at −78°C, followed by decomposition of the ozonide with Me_2S, provided the aldehyde **174** in methanolic solution. Without isolation of the aldehyde, the solution was treated with excess hydroxylamine hydro-

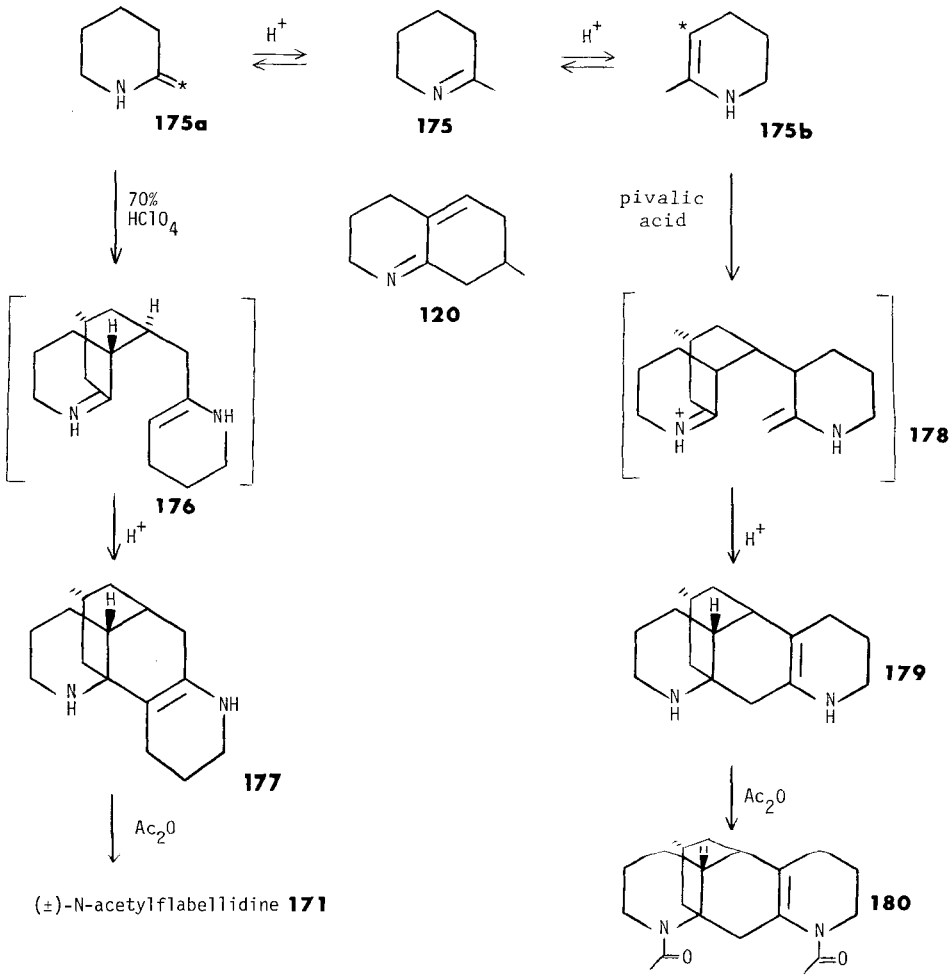


SCHEME 16. (a) (i) H_2SO_4, O_3, MeOH, −78°C, (ii) $(CH_3)_2S$; (b) (i) NH_2OH, HCl, 65°C, 48 hr, (ii) NaOH, H_2O.

chloride and boiled for 2 days; (±)-lycodine was obtained on workup in an overall yield of 13% based on 5-methyl-1,3-cyclohexanedione, a precursor of **103.**

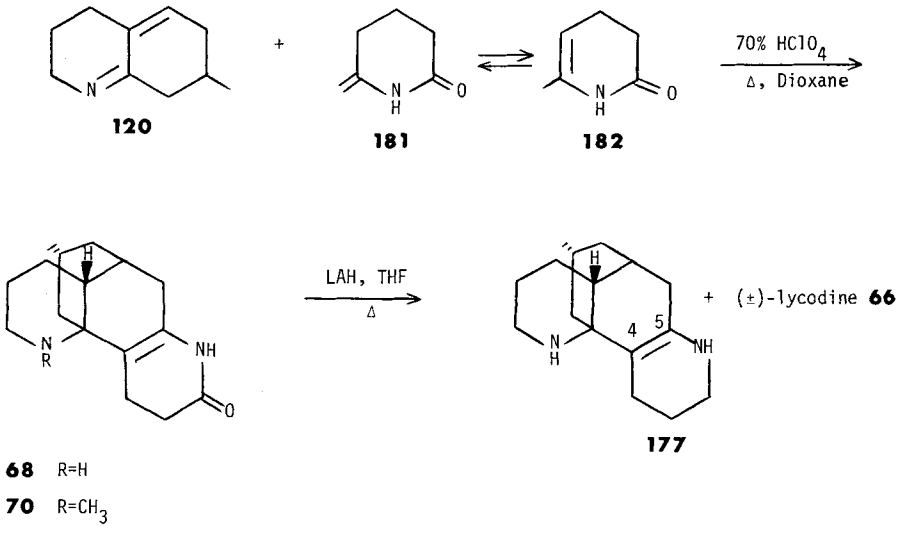
In an ingenious synthesis of *N*-acetylflabellidine (**171**), Schumann *et al.* (*76*) have employed as starting material the same enimine **120** that they used in the synthesis of lycopodine (Section III,B,2). They reasoned that 2-methylpiperideine **175** in one or both of its two enamine forms, **175a** or **175b,** would condense with **120,** as shown in Scheme 17, at either of the two starred carbon atoms. Condensation at the exocyclic double bond would lead after acetylation to **171,** while condensation at the endocyclic double bond would lead in a similar manner to the regioisomer **180.** In the actual reaction both products were formed, but the ratio was dependent on the cyclization conditions. In the presence of 70% perchloric acid, the major product was **171** (**171**:**180** = 3:2), and its formation through the transient intermediate **176** and the intermediate **177** is readily visualized. In pivalic acid, the major product was **180** (**180**:**171** = 9:1), and its formation was considered to proceed similarly through **178** and **179.** The relative stereochemistry of **180** was not established, but its formation might be expected to proceed with the same stereochemical outcome at the corresponding chiral centers as in the case of **171.**

In a further continuation of their work with enimine **120,** Schumann and Naumann (*77*) condensed it with 6-methyl-1,2,3,4-tetrahydro-2-oxopyridine (Scheme 18). They obtained (±)-de-*N*-methyl-α-obscurine (**68**) in 67% yield,



SCHEME 17

apparently formed by condensation with the exocyclic tautomer **181,** but none of the regioisomer expected from condensation with **182.** N-Methylation of (±)-**68** by literature methods gave (±)-α-obscurine (**70**). Reduction of **68** with LAH yielded a mixture of deacetylfalbellidine (**177**) and lycodine in a ratio **177:66** ≈ 5:1. 3,4-Dihydrolycodine was postulated to be an intermediate in the hydride reduction and to disproportionate to the two products as well as to undergo reduction to **177.** *N*-Acetyl derivatives of **177** and **66** were also prepared, and **177** was reduced with $NaBH_4$ to 4,5-dihydro-**177,** which was isolated as its di-*N*-acetyl derivative.

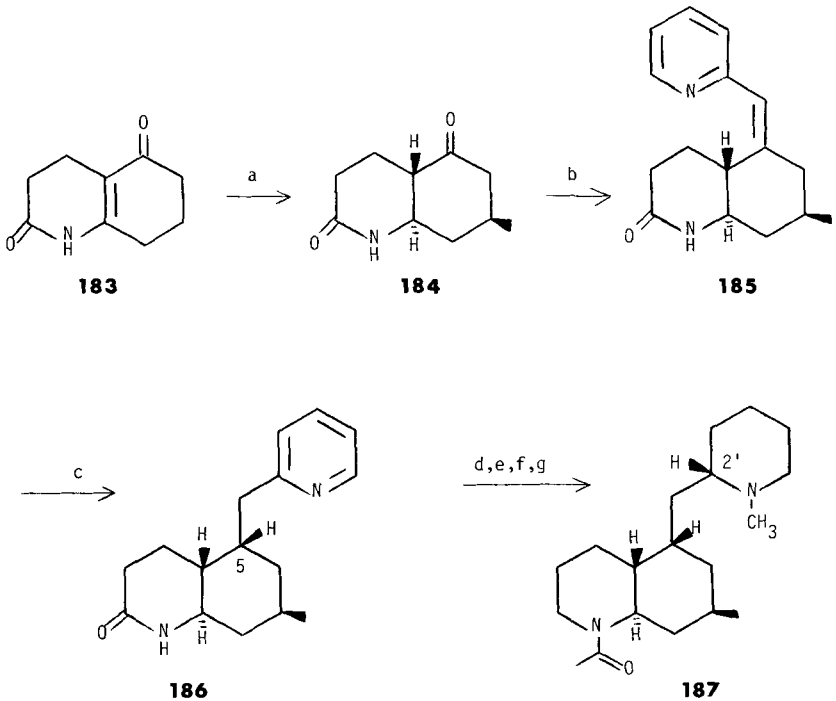


SCHEME 18

F. SYNTHESIS OF (±)-N_α-METHYL-N_β-ACETYLPHLEGMARINE (187)

Nyembo *et al.* (*5*) carried out the first synthesis of the ring system present in the phlegmaranes as part of the structural investigation of the five alkaloids of the group. Their work, which led to a mixture of diastereomers, is described in Section II,C. Leniewski *et al.* (*39*) synthesized **187** in a manner that defined four of the five chiral centers of the molecule and deduced the relative configuration of the fifth center by analysis of the ^{13}C-NMR spectrum of **187** and several of its stereoisomers (*40*).

The strategy used in the synthesis was the same as that used in the synthesis of luciduline (Section III,D) (*73*). The trans keto lactam **184** (Scheme 19) of defined stereochemistry (*73*) was prepared in two steps from **118** (Section III,B,2) by treatment first with 50% acetic acid, yielding **183,** and second with Li/NH_3. Treatment of **184** with 2-trimethylsilylmethylpyridine in the presence of base gave **185** along with about 2% of the *E* isomer. Reduction of the double bond of **185** gave approximately a 1:1 mixture of **186** and its epimer at C-5, which were easily differentiated by their ^{13}C-NMR spectra. A separation of the isomers could not be achieved, but their *N*-oxides presented no problem in this regard; the *N*-oxides were converted back to the bases with PCl_3. Compound **186** was then converted to a separable 1:1 mixture of **187** and its epimer at C-2′ in straightforward steps. Similarly, the epimer of **186** at C-5 was taken through the same



SCHEME 19. (a) (i) NH_3, Li, −33°C, 1 min; (ii) NH_4Cl; (b) 2-trimethylsilylmethylpyridine, *n*-BuLi, THF; (c) H_2, PtO_2, EtOH; (d) CH_3I, $(CH_3)_2C{=}O$; (e) H_2, PtO_2, H_2O; (f) LAH, Et_2O; (g) pyridine, AcCl.

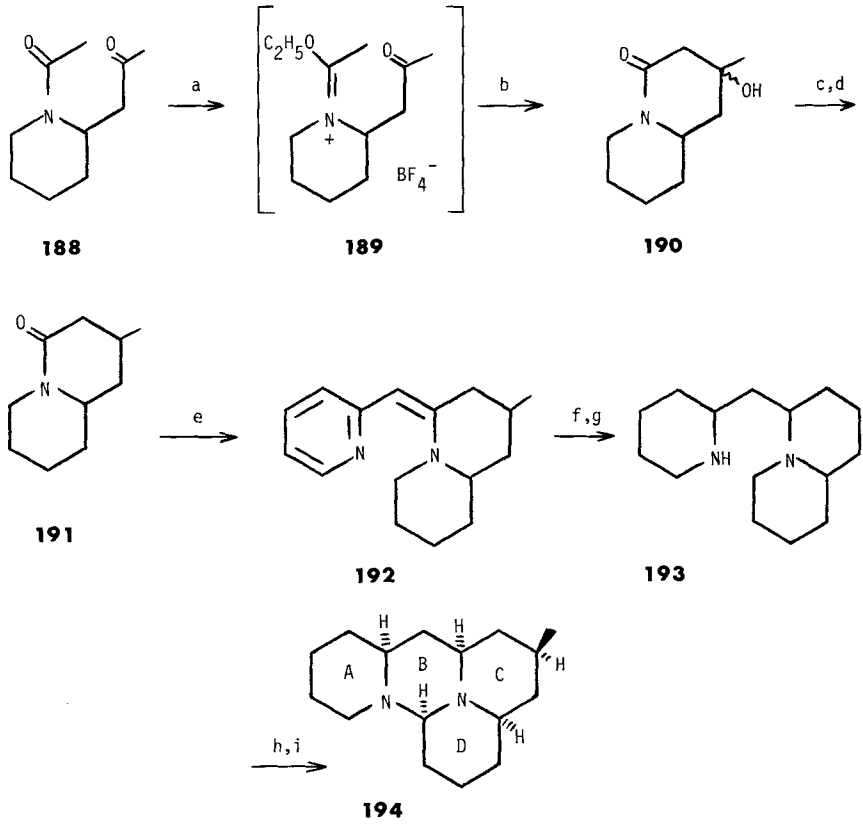
series of reactions so that four diastereomers differing only at C-5 and C-2′ were prepared. The configurations at C-2′ relative to C-5 were assigned by calculating the ^{13}C-NMR chemical shifts for each pair of epimers and comparing the calculated and observed values, using a method originally developed for acyclic hydrocarbons (*78*). The compound with the configuration corresponding to **187** was found to have properties similar to those of the compound formed by acetylation of **76** (*5*).

G. SYNTHESIS OF (±)-DIHYDRODEOXYEPIALLOCERNUINE (194)

N-Acetylpelletierine (**188**) has been used by Ban *et al.* (*79–81*) in a synthesis of (±)-dihydrodeoxyepiallocernuine (**194**), a compound previously prepared by Ayer *et al.* (*2*). Treatment of **188** (Scheme 20) with Meerwein's reagent gave the

iminium salt **189,** which, without isolation, was converted to **190** in the presence of BF_3–Et_2O. The elements of water were removed in a base-catalyzed β elimination, and the resulting conjugated lactam was reduced to **191,** comprising rings C and D of the target molecule.

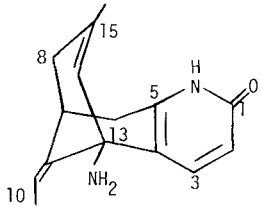
Compound **192,** containing all of the carbon and nitrogen atoms of **194,** was obtained on reaction of **191** with α-picolyllithium. Two reduction steps gave **193,** which was then treated with *N*-chlorosuccinimide, yielding an *N*-chloro derivative; irradiation yielded **194.** The authors point out that the photochemical step does not follow the usual regiochemical course observed in Hofmann–Loeffler cyclizations and may proceed by a different mechanism. The authors do not comment on the favorable stereochemical outcome of the synthesis nor on the stereochemistry of the intermediates.



SCHEME 20. (a) Et_3O^+ BF_4^-, CH_2Cl_2, Δ; (b) BF_3–Et_2O, Δ, K_2CO_3; (c) *t*-BuOK, *t*-BuOH, 90°C, 3 hr; (d) H_2, PtO_2, 60 psi; (e) -CH_2Li, THF, −40°C; (f) H_2, Pd/C, MeOH; (g) H_2, PtO_2, AcOH; (h) *N*-chlorosuccinimide, Et_2O; (i) *hv*, Et_2O.

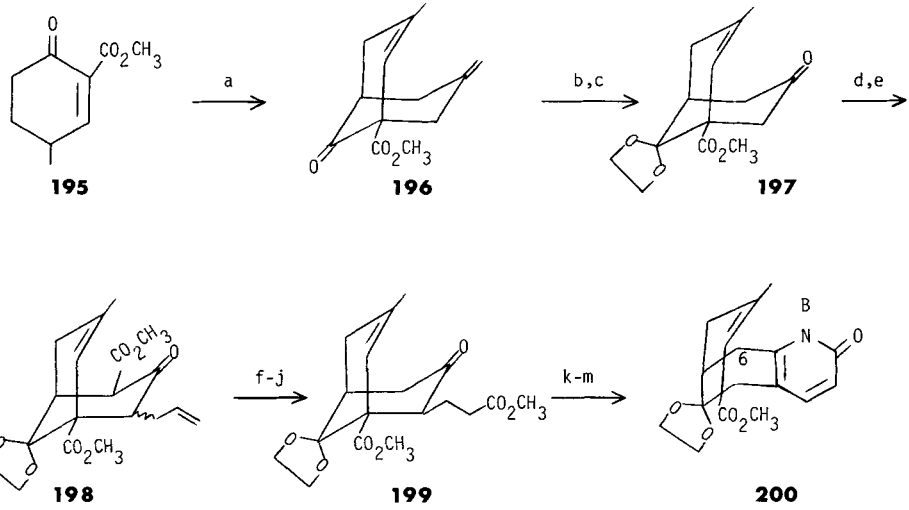
H. Approaches to the Synthesis of Selagine (102)

At the time of this writing, the synthesis of selagine was not complete, but two groups, those of Gravel and Kende, had made considerable progress in this direction. The initial objective of both groups was the construction of the bicyclo[3.3.1]nonene system of selagine with the eventual $\Delta^{14,15}$ double bond fixed in position and with the bicyclic compound suitably functionalized to complete the synthesis. Both groups have now reached this objective with the synthesis of **197** (Scheme 21) by different pathways. The group of Gravel have extended their work to add the pyridone ring.



selagine

The Gravel synthesis (*82*) (Scheme 21) began with 2-carbomethoxy-4-methyl-2-cyclohexenone, which was prepared from 4-methylcyclohexanone in conventional steps. Treatment of the dianion of **195** with methallyl dichloride gave



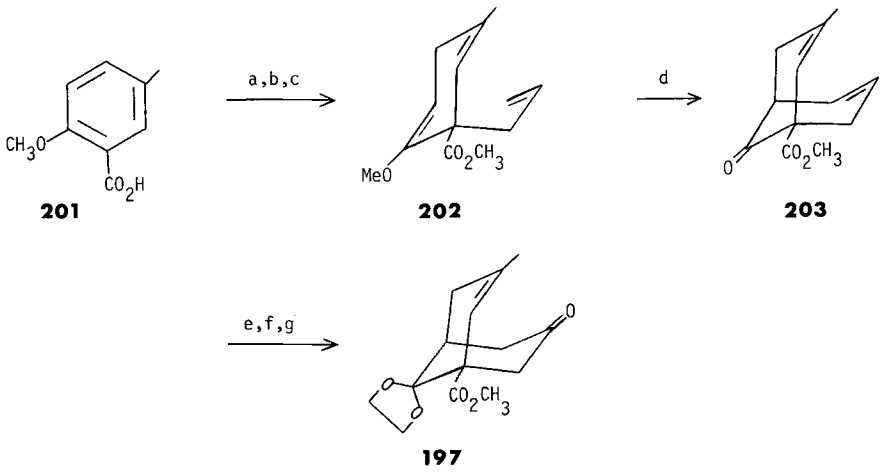
195 **196** **197** **198** **199** **200**

Scheme 21. (a) NaH, DMF, $CH_2{=}C(CH_2Cl)_2$; (b) $(CH_2OH)_2$, TsOH, C_6H_6, Δ; (c) O_3, CH_2Cl_2 −78°C, Zn, AcOH; (d) $(MeO)_2C{=}O$, NaH, THF; (e) LDA, THF, Br; (f) 10% aq NaOH, dioxane, Δ; (g) SiBH, THF, 0°C; (h) H_2O_2, OH^-; (i) Jones' oxidation; (j) CH_2N_2; (k) $BnNH_2{\cdot}AcOH$, *n*-BuOH, Δ, 20 hr; (l) Br_2, CH_2Cl_2; (m) Bu_3SnH, AIBN.

196, which was in turn ketalized and subjected to ozonolysis, yielding **197.** The latter was transformed to **198,** first by introducing a carbomethoxy group and second, an allyl group by alkylation of the dianion of the carbomethoxy intermediate. In a series of steps, **198** was decarboxylated, and the allyl group was changed to a carbomethoxyethyl group, providing **199.** The heterocyclic ring was formed by treatment with benzylamine, and the initially formed piperidone, with a $\Delta^{5,6}$ exocyclic double bond, (selagine numbering) was converted to the pyridine **200** by bromination, dehydrobromination, and finally replacement of the remaining bromine at C-6 by hydrogen.

The Kende synthesis (*83*) of **197** is outlined in Scheme 22. The product of Birch reduction of 2-methoxy-5-methylbenzoic acid (**201**) was alkylated without isolation with allyl chloride and then esterified to **202.** The treatment of **202** with $Pd(OCOCF_3)_2$ under the conditions outlined gave **203** in excellent yield, and its conversion to **197** was accomplished without difficulty.

With the groundwork so firmly in place, the total synthesis of (±)-selagine should shortly be a reality.



SCHEME 22. (a) Li, NH_3; (b) ~Cl; (c) MeI, K_2CO_3; (d) $Pd(CO_2CF_3)_2$ (0.5 eq) CH_3CN:CH_2Cl_2 = 1:1, $CuCl_2$ (1.0 eq), aerate for 2 hr; (e) $(CH_2OH)_2$, TsOH; (f) thexylborane; (g) $Na_2Cr_2O_7$, aq H_2SO_4.

IV. Biosynthesis and Biogenesis

Investigations of the biosynthesis of lycopodine and cernuine (*2*) have established that lysine **204** and acetate are the fundamental building units used in the synthesis of both alkaloids. This is illustrated in Fig. 7 where the heavy lines denote the lysine-derived carbon atoms and the light lines the acetate-derived

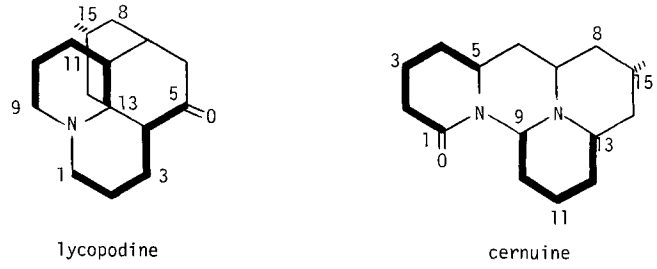
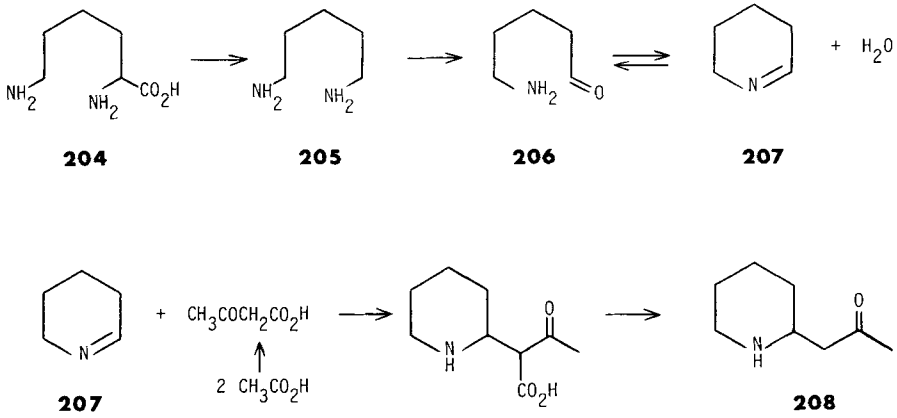


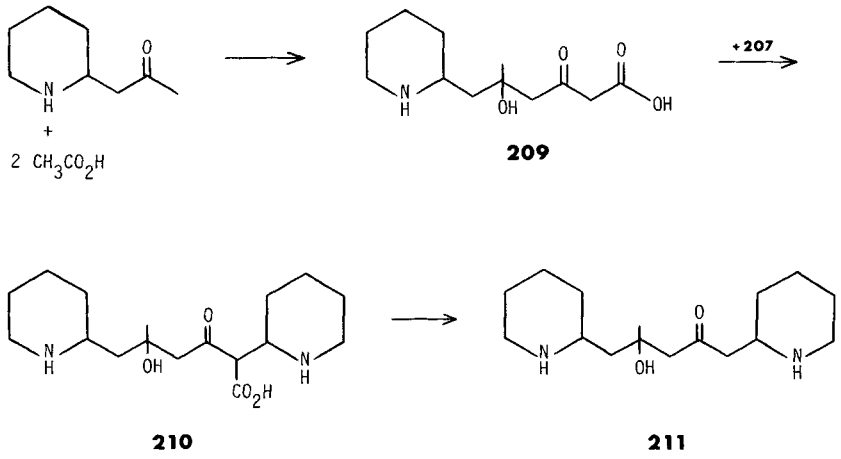
FIG. 7. Incorporation of lysine (heavy lines) and acetate (light lines) into lycopodine and cernuine.

carbon atoms of lycopodine and cernuine. It was also shown that cadaverine (**205**) and Δ^1-piperideine (**207**) were incorporated into both molecules in a manner similar to that of lysine and that pelletierine (**208**) (formation from lysine outlined in Scheme 23) was incorporated intact into both molecules at positions C-9 to C-16 inclusive but not into positions C-1 to C-8 inclusive. At the time that this work was carried out it was proposed that 2-piperidineacetoacetic acid might be the species incorporated into C-1 to C-8 and that 2-piperidineacetic acid would be an intermediate along the pathway (*2*). Experiments designed to test the intermediacy of 2-piperidineacetic acid indicated that it was not involved in the biosynthesis of lycopodine (*84*). In the same paper it was shown that malonic acid was incorporated as expected into lycopodine at the same carbon centers as in acetic acid.

A rationalization of the apparent anomaly that pelletierine is incorporated only into "one-half" of lycopodine whereas lysine, cadaverine, and Δ^1-piperideine are incorporated into both halves has been offered by the Braekman group (*5,6*). They proposed, without going into mechanistic detail, that pelletierine might



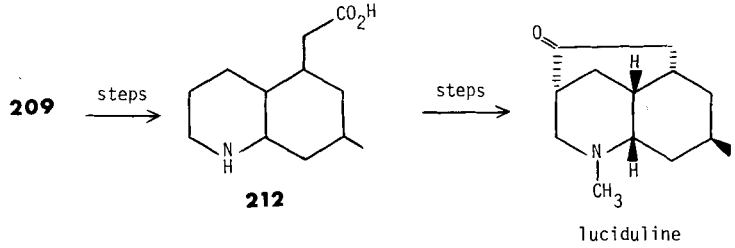
SCHEME 23



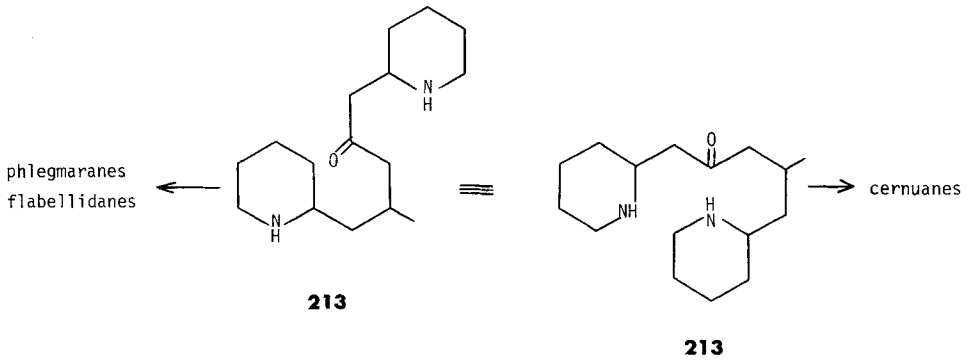
SCHEME 24

react with two further moles of acetate before condensing with a second lysine-derived fragment (Scheme 24). Structures **209–211** may be considered to be hypothetical intermediates along this pathway to the alkaloids. Intermediate **209** could lead directly without loss of carbon, through **212,** to the luciduline system (Scheme 25), whereas **211,** after removal of the OH group, would provide **213,** which could serve as a common precursor of the skeleta of the $C_{16}N_2$ alkaloids shown in Scheme 26. The $C_{16}N$ alkaloids could then be derived from the $C_{16}N_2$ alkaloids, such as the phlegmaranes or flabellidanes, in appropriate steps as originally suggested (*2*). The $C_{27}N_3$ alkaloids are also readily accommodated within the Braekman proposal. Dalton (*85*) has proposed an analagous pathway to lycopodine and the $C_{16}N_2$ alkaloids.

In view of the widespread distribution and the high abundance of the $C_{16}N$ alkaloids in the Lycopodiaceae, it would seem more likely that this group of alkaloids are primary products of biosynthesis and not derived from $C_{16}N_2$ precursors, which are less abundant and not as prevalent. The Braekman pro-



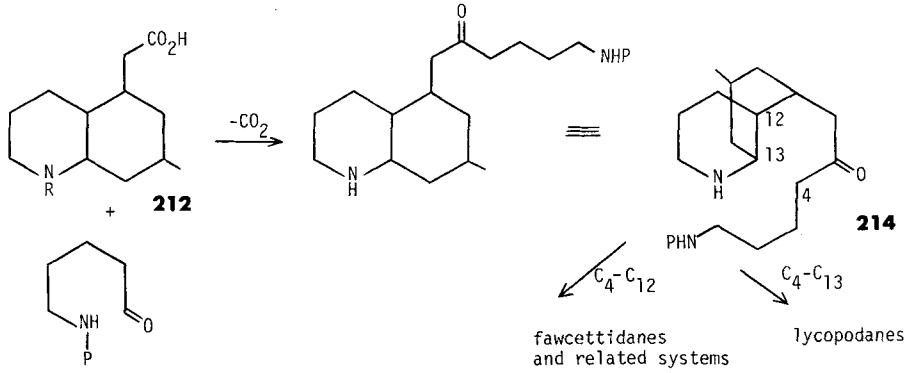
SCHEME 25



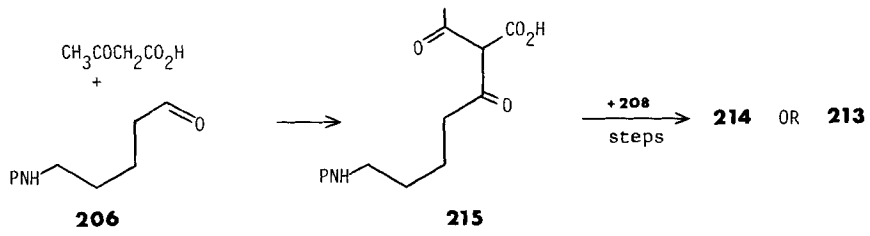
SCHEME 26

posal can be easily modified to accommodate this end (Scheme 27). Condensation of **212** with **206** (amino group protected) would provide **214,** an intermediate not unlike that prepared by Heathcock in his lycopodine synthesis (Scheme 5). Condensation between C-4 and C-13 would lead to lycopodane alkaloids and between C-4 and C-12 to the fawcettimane and related alkaloids of Fig. 3. The $C_{16}N_2$ alkaloids could also be formed from the same intermediate.

An alternative route to the $C_{16}N$ and also the $C_{16}N_2$ alkaloids is shown in Scheme 28 in which a protected 5-aminopentanal unit reacts first with an acetoacetate unit, yielding **215,** and then with pelletierine. Both of the hypothetical intermediates, **214** (Scheme 27), leading to the $C_{16}N$ alkaloids, and **213** (Scheme 26), leading to the $C_{16}N_2$ alkaloids, could be derived in this way. However this route would not provide a pathway to luciduline and the $C_{27}N_3$ alkaloids although it could provide, with modification, an attractive route to the ring systems found in annotinine (**44**) and annopodine (**46**). It is also of interest



SCHEME 27



SCHEME 28

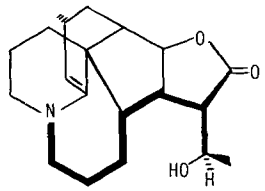


FIG. 8. The hypothetical derivation of megastachyine from **215** (heavy lines) and **212**—CO_2 (light lines).

that megastachyine (**101**) has intact within its structure the carbon framework of the hypothetical intermediate **215**, as illustrated in Fig. 8.

The biogenetic schemes discussed above account very well for nearly all of the structural types (annotine and lyconnotine being two exceptions) found within this family of alkaloids. The proposals are also in harmony with the biosynthetic studies already conducted (*2*), although one might not have expected an equal incorporation of lysine, cadaverine, and Δ^1-piperideine into both "halves" of lycopodine and cernuine. The testing of these proposals by experiment should now be undertaken.

V. Chemotaxonomy

The order Lycopodiales has been the subject of considerable controversy among taxonomists. Some specialists recognize five genera divided into two families, the family Urostachyaceae (*Huperzia*) and the family Lycopodiaceae (*Lycopodium, Lepidotis, Diphasium,* and *Phylloglosum*). A recent study by Wilce (*86*) based on an examination of lycopod spores suggests that one family, Lycopodiaceae, and two genera, *Lycopodium* and *Phylloglossum,* are adequate to describe the order. The genus *Lycopodium* may be divided, according to Wilce, into three subgenera, *Urostachys* (containing two sections, *Selago* and *Phlegmaria*), *Lepidotis* (containing three sections, *Cernua, Inudata,* and *Later-*

alia) and *Lycopodium*, containing seven sections. The seven sections of the subgenus *Lycopodium* are composed of *Lycopodium* and *Complanta* and five sections not formally named but representing the following elements: the Scariosum group, the Fastigiatum group, the Volubile group, *L. deuterodensum*, and *L. casuarinoides*. The latter two were placed in subgenus *Lycopodium* only tentatively.

Braekman *et al.* (*6,19*) have discussed the alkaloid content of the Lycopodiaceae in relation to their botanical classification. They point out that only ~10% of the known species have been examined, so that generalizations based on alkaloid content are tenuous at best. Nevertheless their findings, in so far as they go, are in harmony with the classification of Wilce. Species from all three subgenera have been examined and in all cases alkaloids have been isolated. They consider all alkaloids of the family to be derived from lysine, and this is probably a valid assumption; however, incorporation of lysine has been demonstrated experimentally only into the lycopodane and cernuane systems.

They noted that the subgenus *Urostachys*, the most primitive of the three subgenera, elaborated at least six different ring systems. (They combine the four ring systems of Fig. 3 into one category and do not consider ring systems that have only one representative such as those present in Fig. 2). It is the only subgenus from which $C_{27}N_3$ alkaloids have been isolated. The subgenus *Lepidotis*, the next in order of evolution, may be differentiated from the others by the presence of cernuane and alopecurane alkaloids; it also elaborates four other ring systems. Finally, in the subgenus *Lycopodium* the major components are lycopodane alkaloids accompanied by minor amounts of alkaloids of three other ring systems. It is noteworthy that the *Complanta* section, within this subgroup, elaborates mainly a single alkaloid, lycopodine. Braekman *et al.* have noted that the number of biosynthetic pathways operative in alkaloid synthesis in this family has apparently decreased in the course of evolution (*6*).

The lycopodane alkaloids are present in greater than trace quantity in all three subgenera. Also present but less abundant and less widely distributed in the three subgenera are alkaloids of the flabellidane, fawcettimane (and the three related systems), and the phlegmarane systems. In the last case they have been detected in only a single species in each subgenus.

As new species are examined it will be interesting to see if they fit into the pattern described by Braekman and his collaborators.

Acknowledgements

I wish to thank Gayle Griffin for typing the manuscript and especially for her patience and cheerfulness in dealing with the revisions involved in its preparation. My thanks are also extended to my students and postdoctoral associates who read the manuscript and helped in many ways in its preparation. In particular I am indebted to R. V. Gerard for his assistance in tabulating the alkaloids.

References

1. D. B. MacLean, *Alkaloids (N.Y.)* **10,** 305 (1968).
2. D. B. Maclean, *Alkaloids (N.Y.)* **14,** 248 (1973).
3. W. A. Ayer, L. M. Browne, Y. Nakahara, M. Tori, and L. T. J. Delbaere, *Can. J. Chem.* **57,** 1105 (1979).
4. W. A. Ayer, L. F. Ball, L. M. Browne, M. Tori, L. T. J. Delbaere, and A. Silverberg, *Can. J. Chem.* **62,** 298 (1984).
5. L. Nyembo, A. Goffin, C. Hootelé, and J. C. Braekman, *Can. J. Chem.* **56,** 851 (1978).
6. J. C. Braekman, L. Nyembo, and J. J. Symoens, *Phytochemistry* **19,** 803 (1980).
7. V. A. Snieckus, *Alkaloids (London)* **3,** 227 (1973); **4,** 322 (1974); **5,** 228 (1975).
8. W. A. Ayer, *Alkaloids (London)* **6,** 252 (1976); **8,** 216 (1978); **10,** 205 (1980); **11,** 199 (1981); **13,** 277 (1983).
9. C. H. Heathcock, E. Kleinman, and E. S. Binkley, *Int. Cong. Ser. Excerpta Med.* **457,** 71 (1979).
10. Y. Inubushi and T. Harayama, *Heterocycles* **15,** 611 (1981).
11. P. Welzel, *Nachr. Chem., Tech. Lab.* **31,** 462 (1983).
12. D. Schumann, *GIT Fachz. Lab.* **28,** 185 (1984).
13. M. Kahindo, D.Sc. Thesis, Université Libre de Bruxelles, Bruxelles, Belgique.
14. L. Nyembo, N. Kahindo, J. C. Braekman, and C. Hootelé. *Bull. Soc. Chim. Belg.* **85,** 595 (1976).
15. L. Nyembo, D.Sc. Thesis, Université Libre de Bruxelles, Bruxelles, Belgique.
16. G. Morales, L. A. Loyola, and M. Castillo, *Phytochemistry* **18,** 1719 (1979).
17. O. Muñoz and M. Castillo, *Heterocycles* **19,** 2287 (1982).
18. M. Castillo, G. Morales, L. A. Loyola, I. Singh, C. Calvo, H. L. Holland, and D. B. MacLean, *Can. J. Chem.* **54,** 2900 (1976).
19. J. C. Braekman, L. Nyembo, P. Bourdoux, N. Kahindo, and C. Hootelé, *Phytochemistry* **13,** 2519 (1974).
20. W. J. Rodewald and G. Grynkiewicz, *Rocz. Chem.* **51,** 1271 (1977).
21. W. A. Ayer, Y. Fukazawa, P. P. Singer, and B. Altenkirk, *Tetrahedron Lett.,* 5045 (1973).
22. W. A. Ayer and S. Dikko, *Phytochemistry* **13,** 653 (1974).
23. M. Castillo, L. A. Loyola, G. Morales, I. Singh, C. Calvo, H. L. Holland, and D. B. MacLean, *Can. J. Chem.* **54,** 2893 (1976).
24. L. A. Loyola, G. Morales, and M. Castillo, *Phytochemistry* **18,** 1721 (1979).
25. Y. Inubushi and T. Harayama, *Yakugaku Zasshi* **102,** 434 (1982).
26. M. T. Garland and O. Muñoz, *J. Appl. Crystallogr.* **15,** 112 (1982).
27. D. Rogers, A. Quick, and M. Ul-Haque, *Acta Crystallogr. Sect. B* **30,** 552 (1974).
28. M. Ul-Haque and D. Rogers, *J. Chem. Soc., Perkin Trans. 2,* 93 (1975).
29. Y. Inubushi and T. Harayama, *Chem. Pharm. Bull.* **29,** 3418 (1981).
30. W. A. Ayer, B. Altenkirk, and Y. Fukazawa, *Tetrahedron* **30,** 4213 (1974).
31. T. Harayama, T. Taga, K. Osaki, and K. Kuriyama, *Heterocycles* **22,** 1327 (1984).
32. J. H. Brewster, *Tetrahedron* **13,** 106 (1961).
33. Y. Inubushi, H. Ishii, T. Harayama, R. H. Burnell, W. A. Ayer, and B. Altenkirk, *Tetrahedron Lett.,* 1069 (1967).
34. M. Castillo, G. Morales, L. A. Loyola, I. Singh, C. Calvo, H. L. Holland, and D. B. MacLean, *Can. J. Chem.* **53,** 2513 (1975).
35. A. Horeau and D. B. Kagan, *Tetrahedron* **20,** 2431 (1974).
36. A. Katz and E. Staehelin, *Tetrahedron Lett.* **23,** 1155 (1982).
37. G. E. Brunner, Diss. ETH Zurich 1921, p. 60 (quoted in Ref. *36*).

38. R. H. Burnell, A. Chapelle, J. Fischer, and L. Ricard, *J. Chem. Soc., Chem. Commun.*, 391 (1974).
39. A. Leniewski, J. Szychowski, and D. B. MacLean, *Can. J. Chem.* **59,** 2479 (1981).
40. A. Leniewski, D. B. MacLean, and J. K. Saunders, *Can. J. Chem.* **59,** 2695 (1981).
41. Y. Inubushi, H. Ishii, and T. Harayama, *Yakugaku Zasshi* **100,** 672 (1980).
42. R. V. Gerard and D. B. MacLean. Unpublished results, McMaster University.
43. J. C. Braekman, C. Hootelé, N. Miller, J. P. Declercq, G. Germain, and M. Van Meerssche, *Can. J. Chem.* **57,** 1691 (1979).
44. A. Goffin, Thesis. Licencié en Sciences Chimique, Université Libre de Bruxelles, 1973.
45. T. T. Nakashima, P. P. Singer, L. M. Browne, and W. A. Ayer, *Can. J. Chem.* **53,** 1936 (1975).
46. C. H. Heathcock, E. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.* **100,** 8036 (1978).
47. C. H. Heathcock, E. F. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.* **104,** 1054 (1982).
48. C. H. Heathcock and E. F. Kleinman, *J. Am. Chem. Soc.* **103,** 222 (1981).
49. R. D. Clark and C. H. Heathcock, *J. Org. Chem.* **41,** 636 (1976).
50. L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.* **77,** 6595 (1955).
51. D. Schumann, H.-J. Müller, and A. Naumann, *Liebigs Ann. Chem.*, 1700 (1982).
52. E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Am. Chem. Soc.* **95,** 8427 (1973).
53. E. Wenkert, B. Chauncy, and S. H. Wentland, *Synth. Commun.* **3,** 77 (1973).
54. E. Wenkert and C. A. Broka, *J. Chem. Soc., Chem. Commun., 714 (1984).*
55. *R. H. Burnell and D. R. Taylor, Tetrahedron* **15,** 173 (1961).
56. S.-W. Kim, Y. Bando, and Z. Horii, *Tetrahedron Lett.*, 2293 (1978).
57. S.-W. Kim, Y. Bando, N. Takahashi, and Z. Horii, *Chem. Pharm. Bull.* **26,** 3150 (1978).
58. T. Momose, S. Uchida, T. Imanishi, S.-W. Kim, N. Takahashi, and Z. Horii, *Heterocycles* **6,** 1105 (1977).
59. T. Momose, S. Uchida, and T. Imanishi, *Chem. Pharm. Bull.* **26,** 972 (1978).
60. S.-W. Kim, I. Fujii, K. Nagao, and Y. Ozaki, *Heterocycles* **16,** 1515 (1981).
61. W. A. Ayer and G. G. Iverach, *Can. J. Chem.* **42,** 2514 (1964).
62. T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* **21,** 25 (1973).
63. T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* **21,** 1061 (1973).
64. T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *J. Chem. Soc., Chem. Commun.*, 827 (1974).
65. T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* **23,** 1511 (1975).
66. T. Harayama, M. Takatani, and Y. Inubushi, *Tetrahedron Lett.*, 4307 (1979).
67. T. Harayama, M. Takatani, and Y. Inubushi, *Chem. Pharm. Bull.* **28,** 2394 (1980).
68. T. Harayama, M. Takatani, and Y. Inubushi, *Chem. Pharm. Bull.* **27,** 726 (1979).
69. T. Harayama, M. Takatani, and Y. Inubushi, *Chem. Pharm. Bull.* **28,** 1276 (1980).
70. W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.* **94,** 4779 (1972).
71. W. Oppolzer and M. Petrzilka, *J. Am. Chem. Soc.* **98,** 6722 (1976).
72. W. Oppolzer and M. Petrzilka, *Helv. Chim. Acta* **61,** 2755 (1978).
73. J. Szychowski and D. B. MacLean, *Can. J. Chem.* **57,** 1631 (1979).
74. D. Schumann and A. Naumann, *Liebigs Ann. Chem.*, 1519 (1984).
75. E. Kleinman and C. H. Heathcock, *Tetrahedron Lett.*, 4125 (1979).
76. D. Schumann, H.-J. Müller, and A. Naumann, *Liebigs Ann. Chem.*, 2057 (1982).
77. D. Schumann, and A. Naumann, *Liebigs Ann. Chem.*, 220 (1983).
78. H. Beierbeck and J. K. Saunders, *Can. J. Chem.* **58,** 1258 (1980).
79. Y. Ban, M. Kimura, and T. Oishi, *Heterocycles* **2,** 323 (1974).
80. Y. Ban, M. Kimura, and T. Oishi, *Chem. Pharm. Bull.* **24,** 1490 (1976).

81. M. Kimura and Y. Ban, *Synthesis,* **201** (1976).
82. D. Gravel, L. Bordeleau, G. Ladouceur, J. Rancourt, and D. Thoraval, *Can. J. Chem.* **63** (1985).
83. A. S. Kende, R. A. Battista, and S. B. Sandoval, *Tetrahedron Lett.* **25,** 1341 (1984).
84. W. D. Marshall, T. T. Nguyen, D. B. MacLean, and I. D. Spenser, *Can. J. Chem.* **53,** 41 (1975).
85. D. R. Dalton, "The Alkaloids." Dekker, New York, 1979.
86. J. H. Wilce, *Am. Fern. J.* **62,** 65 (1972).

— CHAPTER 6 —

PEPTIDE ALKALOIDS*

ULRICH SCHMIDT
ALBRECHT LIEBERKNECHT

Institute for Organic Chemistry, Biochemistry and Isotope Research
University of Stuttgart
Stuttgart, West Germany

AND
ERNST HASLINGER

Institute for Organic Chemistry
University of Vienna
Vienna, Austria

I. Introduction

We define cyclic peptide alkaloids (*1,2*) as basic compounds embodying an ansa structure, in which a 10- or 12-membered peptide-type bridge spans the 1,3 or 1,4 positions of a benzene ring. Compounds that fit this definition have so far been isolated from Rhamnaceae, Sterculiaceae, Pandaceae, Rubiaceae, Urticaceae, Hymenocardiaceae, and Celastraceae (*2*). In an expansion of this definition, "linear peptide alkaloids" are defined as those compounds that can be formally derived from cyclic peptide alkaloids by scission of the bridge in an elimination reaction. Most of such compounds have been isolated from marine sponges (*3,4*).

*Translated by Dr. Adrian Stephen, Sandoz Research Institute, Vienna, Austria.

THE ALKALOIDS, VOL. 26

The following classification (*1,2*) of peptide alkaloids has proved useful:

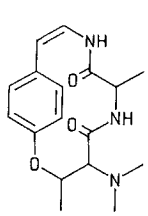
Type I: *p*-ansa compounds with a 14-membered ring incorporating a 10-membered bridge (e.g., frangulanine, amphibine B, integerrine).

Type II: *m*-ansa compounds with a 13-membered ring incorporating a 10-membered bridge (e.g., zizyphine A, B).

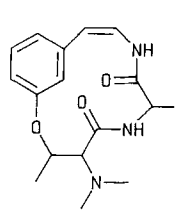
Type III: *m*-ansa compounds with a 15-membered ring incorporating a 12-membered bridge (e.g., mucronine A).

Type IV: linear compounds with a free phenolic group and dehydroamino acid (e.g., lasiodine A from Rhamnaceae and celenamides A–D from Pacific sponges (*3,4*)).

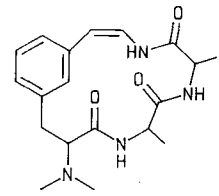
Almost all compounds feature a styrylamide group, which may arise by decarboxylation of a phenylalanine unit: this reaction can be easily carried out in vitro



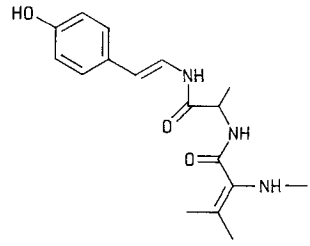
Type I



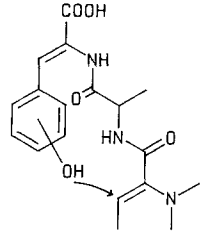
Type II

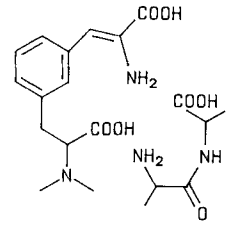


Type III



Type IV





SCHEME 1. The characteristic types of peptide alkaloids and the proposed biosynthetic pathway.

(*5*). A β=phenoxyamino acid unit is a characteristic feature of types I and II. It is plausible to assume that these types are formed biogenetically from a tripeptide containing two dehydroamino acids by addition of a phenolic group to the double bone of one of the latter (Scheme 1). This assumption is supported by the isolation from Rhamnaceae of a linear alkaloid shown to have both a free phenolic group and a dehydroamino acid unit (lasiodine A) (*6*). Compounds of type III contain no β-phenoxyamino acid, the bridge being linked to the benzene ring through carbon atoms only. Biogenesis of such compounds may involve a *m*-phenylenedialanine precursor or the corresponding dehydro compound (Scheme 1).

The trivial nomenclature of peptide alkaloids is derived from the botanical names of the plants from which they are isolated, a system which, unfortunately, causes confusion. In spite of this drawback, we shall not adopt a recently suggested nomenclature (*7*) because the latter is not applicable to the 13- and 15-membered compounds, which together comprise about 30% of all peptide alkaloids. Since the last comprehensive review of peptide alkaloids appeared in this series (*2*), about 30 new representatives have been isolated and their structures have been identified. The most surprising report has been of the isolation (*3,4*) of linear peptide alkaloids from Pacific sponges. Several attempts at synthesis have been published. Total syntheses of a 14-membered (type I; zizyphine A), a 15-membered (type III; mucronine B), and a linear (type IV) peptide alkaloid have been performed in Stuttgart (*8–16*), where the dihydro compounds of types I and II have been synthesized as well.

II. Structural and Conformational Studies

Mass spectrometry has played a central role in structural studies of peptide alkaloids. Tschesche *et al.* recognized early that the fragmentation of such compounds conforms to distinct rules. Analysis of mass spectra therefore permits conclusions to be drawn about the structural units present in these alkaloids and the manner in which they are linked together. This topic has already been discussed in detail (*2,17,18*).

Conformational studies of cyclic peptides have aroused great interest recently because the restricted molecular mobility of these compounds severely limits the numbers of possible conformers. Conformations of peptide alkaloids have been investigated by a variety of physicochemical techniques such as circular dichroism, NMR spectroscopy, and X-ray structural analysis.

NMR spectroscopy supplied the first clues to the simultaneous existence of two conformations in solution, which was deduced from the spectra of members of this class of compounds in which the chemical shift of individual groups is influenced by the proximity of the hydroxyphenylalanine group. Tschesche *et al.* (*19*) described a pair of N—CH_3 signals in the ^{1}H-NMR spectra of integerrenine

(**1**) and integerressine (**2**). Compounds **1** and **2**, and also their corresponding dihydro derivatives, exist as mixtures of two conformers in trifluoroacetic acid solution. In contrast, only a single NCH_3 signal is found in the NMR spectrum of **1** measured in deuterochloroform. Pais *et al.* (*20*) made similar observations on adouétine Y (**3**) and adouétine Z (**4**), but not on adouétine X (**5**), which contains no hydroxyphenylalanine group. Compound **4** also exists as a mixture of two conformers in CCl_4 (*20*). Spiteller and Medina (*21*) were able to show by ^{13}C-NMR spectroscopy that cis–trans isomerism about the C—Pro peptide bond is the reason for the existence of conformers. The chemical shift of the γ carbon atom of proline is characteristic of the cis or trans conformation, respectively (*22*).

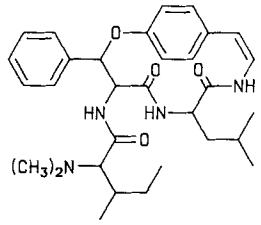
A detailed study has been made (*23*) of the solvent dependence of the conformation of frangulanine (**6**). It could be shown that in $CDCl_3$ the carbonyl group of the dimethylisoleucine side chain is hydrogen bonded to the NH group of leucine. Important evidence for this hydrogen bond is the extremely slow exchange of this proton against deuterium in $CDCl_3$. The increasing mobility of side chains as a function of their distance from the relatively rigid macrocycle has been studied, using relaxation measurements (*24,25*). The configuration of the β-hydroxyleucine unit in **6** was identified by NMR measurements as L-*erythro*-β-hydroxyleucine (*1,2,23*), a result that could be confirmed by chemical degradation of the product of enzymatic oxidation (*26*) and by X-ray structural analysis of trimethyl frangulanine methiodide (*27,28*). X-Ray diffraction shows **6** to have largely the same conformation whether in crystal form or in solution.

Measurement of optical activity complements the nuclear magnetic resonance data on conformational changes. Optical rotation values for zizyphine D (**7**) are strongly influenced by the solvent: $[\alpha]_D^{20}$ 236° (c = 0.1, $CHCl_3$); $[\alpha]_D^{20}$ −121° (c = 0.1, CH_3OH) (*29*). A significant indication of conformational changes in **7** resulting from a change of solvent are the strongly solvent-dependent coupling constants of the NH proton of the hydroxyisoleucine unit (*29*).

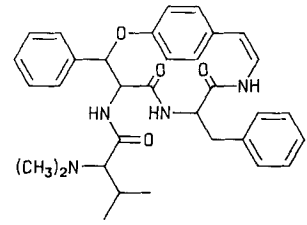
^{13}C-NMR spectroscopy has also been exploited for the study of peptide alkaloids. The first paper to be published on this subject describes the assignment of the ^{13}C frequencies of frangulanine (**6**). Conformational changes that result on substituting one solvent for another are reflected in the ^{13}C-NMR spectrum by distinct signal shifts, an effect that permitted the aromatic signals of **6** to be assigned (*23*). The ^{13}C-NMR spectra of a large number of peptide alkaloids have so far been measured, and their resonance signals have been assigned (*30–33*).

Assignment of the resonance frequencies of the olefinic carbon atoms of the styrylamine unit represented a major problem until Shamma *et al.* (*32*) found that the direct C—H coupling ($^1J_{^{13}C,^1H}$) is a reliable criterion. In zizyphine A, the carbon atom bound to the electronegative nitrogen atom has the larger coupling constant by about 15 Hz. The same is true for alkaloids with a 14-membered ring, as could be shown with frangulanine (**6**) as an example (*34*).

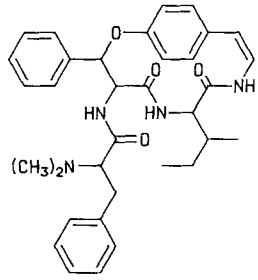
Rapoport *et al.* (*35*) undertook an exact analysis of ^{1}H-NMR spectra, including the spectra of model compounds, as part of their studies of conformation. By comparing the UV, IR, CD, and ^{1}H-NMR spectra of the model compounds **9** and **10,** they concluded that the conformation of the 14-membered ring system is the same in both compounds and that C-2 in **9** has the (*R*) configuration. It is possible to deduce from ^{1}H-NOE studies and ^{13}C-NMR spectra that both amide bonds in **11** have the (*S*)-trans configuration (*36*). X-Ray structural analysis of **11** reveals a conformation in the crystal similar to that already determined for frangulanine (**6**) (*27,28*). An interesting observation is that small divalent cations, such as Mg^{2+} and Ca^{2+}, induce a conformational change in **10,** which resembles that described for ceanothine B (**12**), although **10** can make available only two amide bonds as ligands. Similar interactions have been described for frangulanine (**6**), a



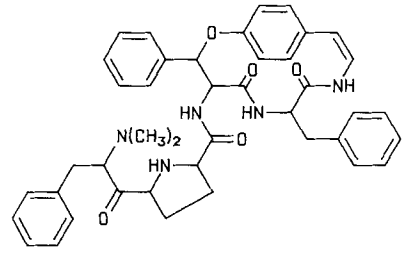
Integerrinine (1)



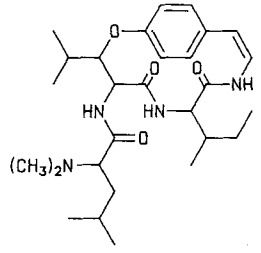
Integerrissine (2)



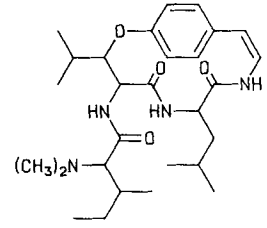
Adouétine Y (3)



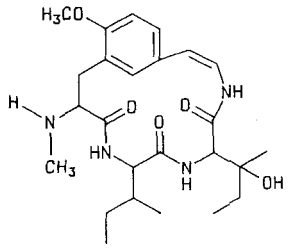
Adouétine Z (4)



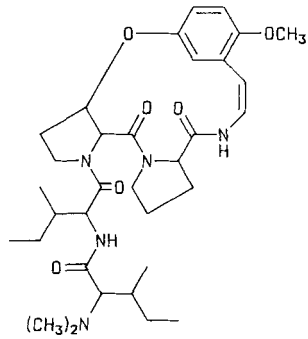
Adouétine X (5)



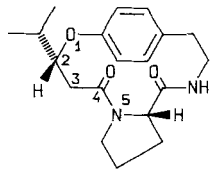
Frangulanin (6)



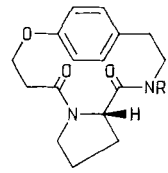
Zizyphine D (**7**)



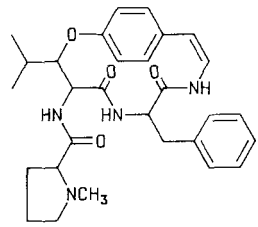
Zizyphine A (**8**)



9



10 R = H
11 R = CH_3



Ceanothine B (**12**)

compound that is reported to possess ionophoric properties in biological membranes owing to interaction with K^+ and Rb^+. Interaction with Li^+ and Na^+ can not be detected (*37,38*).

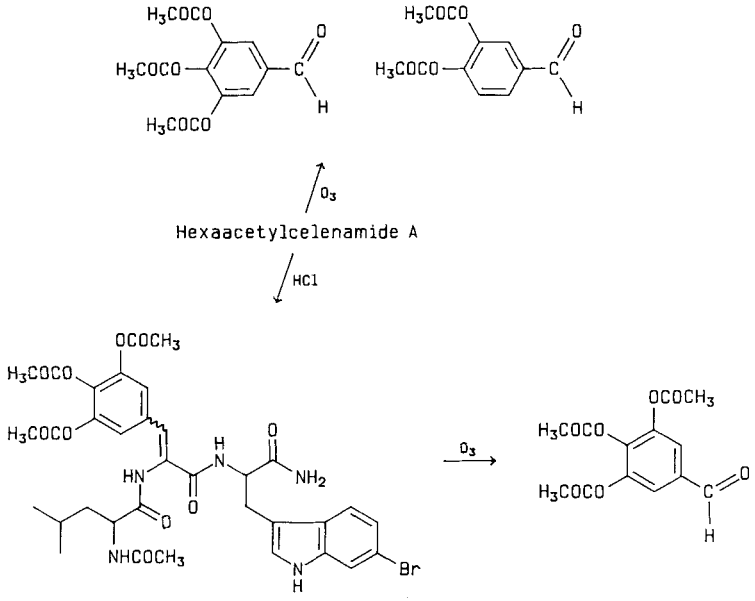
III. New Peptide Alkaloids Isolated and Elucidated

In the following classification of recently identified cyclic peptide alkaloids we have adopted the system suggested by R. Tschesche and E. U. Kaussmann. Compounds are first grouped according to ring size (13-, 14-, and 15-membered rings). An additional criterion is the identity of the β-hydroxyamino acid present

in the 13- and 14-membered ring systems. *trans*-3-Hydroxyproline is found in the 13-membered systems (zizyphine A type). The 14-membered systems contain either β-hydroxyleucine (frangulanine type), *trans*-3-hydroxyproline (amphibine B type), or β-hydroxyphenylalanine (integerrine type). Two cyclopeptide alkaloids are listed separately because of structural anomalies in the exocyclic region (addendum to Table III). The new cyclopeptides are listed in Tables I–IV. Structural elucidation and isolation are dealt with in the following subsection, where the structures of the open-chain peptides are also considered.

Linear Peptide Alkaloids

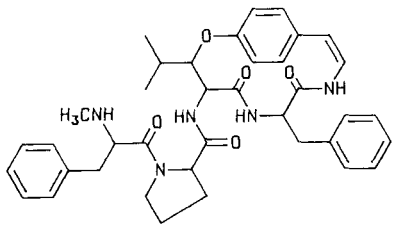
Andersen isolated linear peptide alkaloids from the sponge *Cliona celata* (Table V). Three closely related compounds containing 6-bromotryptophane, (celenamides A–C,) were isolated as peracetyl derivatives, and their structures were determined by NMR and mass spectroscopy and by the degradation steps shown in Scheme 2 (*3*). Acylation with acetic anhydride-d_6 and isolation of the corresponding hexaacetylcelenamides-d_{18} provided evidence that these natural products occur as free phenols with a free amino group. A fourth linear peptide alkaloid, isolated from *Cliona celata* as nonaacetylcelenamide D, contains dehydrotrihydroxyphenylalanine in place of 6-bromotryptophan (*4*). The E configuration in the triacetoxydehydrophenylalanine unit was proved by the total synthesis.



SCHEME 2. Degradative structure determination of linear peptide alkaloids by R. J. Andersen (*3*).

TABLE I

FRANGULANINE-TYPE: 14-MEMBERED RING WITH *p*-HYDROXYSTYRYLAMINE UNIT AND β-HYDROXYLEUCINE



Scutianin F

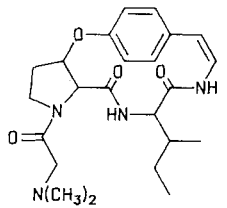
Compound and source[a]	Ring bond amino acid	Intermediate amino acid	Basic end	Molecular formula	MW	mp (°C)	$[\alpha]_D$[b]	Ref.
Scutianine F (a)	Phe	Pro	Monomethyl-Phe	$C_{38}H_{45}N_5O_5$	651	208	−132, m	*39*
Scutianine G (a)	Pse	—	Dimethyl-Phe	$C_{34}H_{40}N_4O_5$	584	162	−112,, m	*40*
Scutianine H (a)	Pse	—	Dimethyl-Ile	$C_{31}H_{42}N_4O_5$	550	242–243	−233, c	*31*
Nummularine K (b)	Leu	—	Dimethyl-Trp	$C_{33}H_{43}N_5O_4$	573	237–239	−45, m	*41*
Melonovine A (c)	Leu	—	Dimethyl-Val	$C_{27}H_{42}N_4O_4$	486	295	−285, c	*42*
Melonovine B (c)	Tyr	—	Dimethyl-Val	$C_{30}H_{40}N_4O_5$	536	200–206	—	*42*
5-β-Indolylmethyl-8-*N*,*N*-dimethylvalyl-9-isopropylphencyclopeptine (d)	Trp	—	Dimethyl-Val	$C_{32}H_{41}N_5O_4$	559	233	—	*7*
5-*sec*-Butyl-8-*N*-(*N*'-methylphenylalanyl)-9-isopropylphen cyclopeptine (e)	Ile	—	Monomethyl-Phe	$C_{30}H_{40}N_4O_4$	520	229	—	*43*

[a]Plant sources (indicated in parenthesis) are keyed to the following list: (a) *Scutia buxifolia*, (b) *Ziziphus nummularia*, (c) *Melochia tomentosa*, (d) *Ceanothus integerrimus*, (e) *Ceanothus sanguineus*, (f) (*Zizyphus nummularia*) and *Z. Oenoplia*, (g) *Zizyphus hysodrica*, (h) *Zizyphus mauritiana*, (i) *Discaria crenata* (rhamnaceae), (j) *Feretia apondanthera*, (k) *Araliorhamnus vaginata*, (l) *Zizyphus sativa*, and (m) *Zizyphus jujuba*.

[b]Solvents for $[\alpha]_D$: m = methanol, c = chloroform.

TABLE II

AMPHIBINE B-TYPE: 14-MEMBERED RING WITH A *p*-HYDROXYSTYRYLAMINE UNIT AND *trans*-3-HYDROXYPROLINE



Nummularin F

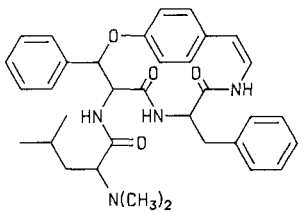
Compound and source[a]	Ring bond amino acid	Intermediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$[b]	Ref.
Nummularine F (f)	Ile	—	Dimethyl-Gly	$C_{23}H_{32}N_4O_4$	428	120	−204, m	*44*
Zizyphine G (f)	Pro	—	Ile	$C_{24}H_{32}N_4O_4$	440	130	−185, m	*45*
Hysodricanine A (g)	Pro	Phe	Dimethyl-Ile	$C_{35}H_{45}N_5O_5$	615	93–96	−215, c	*39*
Mauritine H (h)	Phe	Leu	Dimethyl-Ala	$C_{33}H_{43}N_5O_5$	589	212–215	−169, m	*39*

[a]Plant sources (indicated in parentheses) are listed in footnote *a* to Table I.

[b]Solvent for $[\alpha]_D$: m = methanol, c = chloroform.

TABLE III

INTEGERRINE-TYPE: 14-MEMEBERED RING WITH A *p*-HYDROXYSTYRYLAMINE UNIT AND β-HYDROXYPHENYLALANINE

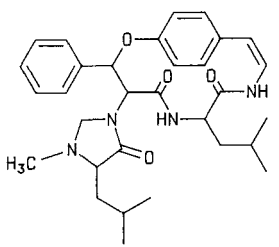


Creatine A

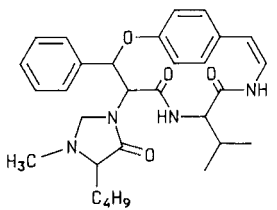
Compound and source[a]	Ring bond amino acid	Intermediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$[b]	Ref.
Crenatine A (i)	Phe	—	Dimethyl-Leu	$C_{34}H_{40}N_4O_4$	568	223	−292, c	*46a,b*
Feretine (j)	Phe	Pro	Monomethyl-Phe	$C_{41}H_{43}N_5O_5$	685	123	−139, c	*47*
Adouetine (j)	Phe	Pro	Dimethyl-Phe	$C_{42}H_{45}N_5O_5$	699	135–140	−183, c	*47*
Nummalarine D (b)	Leu	—	Monomethyl-Ile	$C_{30}H_{40}N_4O_4$	520	265–268	−186, c	*44*
Nummalarine E (b)	Leu	—	Dimethyl-Thr	$C_{29}H_{38}N_4O_5$	522	278–279	+12, m	*44*
Aralionine C (k)	Pse	—	Dimethyl-Ile	$C_{34}H_{40}N_4O_5$	584	95–97	−17, m	*39*
5-β-Indolylmethyl-8-*N*-methylvalyl-9-phenylphencyclopeptine (d)	Trp	—	Monomethyl-Val	$C_{34}H_{37}N_5O_4$	579	>350	—	*7*
5-Benzyl-8-*N*,*N*-dimethylisoleucyl-9-phenylphencyclopeptine (d)	Phe	—	Dimethyl-Ile	$C_{34}H_{40}N_4O_4$	568	>350	—	*7*

5-Isobutyl-8-*N*-methylisoleucyl-9-phenylphencyclopeptine (d)	Leu	—	Monomethyl-Ile	$C_{30}H_{40}N_4O_4$	520	213	—	*7*
Sativanine A (l)	Val	—	Dimethyl-Ile	$C_{30}H_{40}N_4O_4$	520	80	—	*48*

Addendum to Table III: Two Other 14-Membered Ring Peptide Alkaloids with a β-Hydroxyphenylalanine Unit



Nummularin G



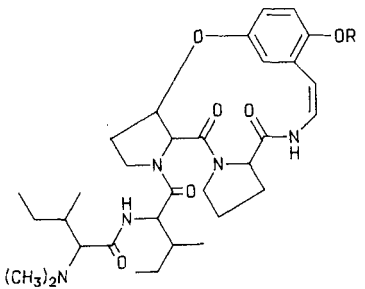
Sativanine B

Compound and source[a]	Molecular formula	MW	mp (°C)	$[\alpha]_D$[b]	Ref.
Nummularine G (b)	$C_{31}H_{40}N_4O_4$	532	174–175	−133, m	*41*
Sativanine B (l)	$C_{30}H_{38}N_4O_4$	518	amorphous	—	*48*

[a]Plant sources (indicated in parentheses) are listed in footnote *a* to Table I.
[b]Solvent for $[\alpha]_D$: m = methanol, c = chloroform.

TABLE IV

ZIZYPHINE A-TYPE: 13-MEMBERED RING WITH A β-(2-METHOXY-5-HYDROXYPHENYL)VINYLAMINE UNIT



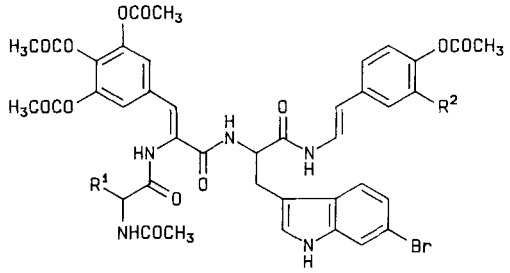
Zizyphine F, R = H

Compound and source[a]	Ring bond amino acid	Intermediate amino acid	R	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$[b]	Ref.
Zizyphine F (f)	Pro	Ile	H	Dimethyl-Ile	$C_{32}H_{47}N_5O_6$	597	235	−277, m	*45*
Nummularine A (b)	Ile	Leu	CH_3	Monomethyl-Phe	$C_{36}H_{49}N_5O_6$	647	235–240 decomp	−397, c	*49*
Nummularine B (b)	Phe	Val	CH_3	Monomethyl-Ala	$C_{32}H_{41}N_5O_6$	591	230–231	−390, c	*49*
Nummularine C (b)	Leu	—	CH_3	Dimethyl-Phe	$C_{31}H_{40}N_4O_5$	548	278–280	−371, c	*49*
Nummularine H (b)	Ile	Phe	CH_3	Monomethyl-Phe	$C_{39}H_{47}N_5O_6$	681	194–196	−343, m	*41*
Jubanine A (m)	Ile	Phe	CH_3	Dimethyl-Phe	$C_{40}H_{49}N_5O_6$	695	amorphous	−326, m	*50*
Jubanine B (m)	Phe	Phe	CH_3	Dimethyl-Phe	$C_{43}H_{47}N_5O_6$	729	amorphous	−218, m	*50*

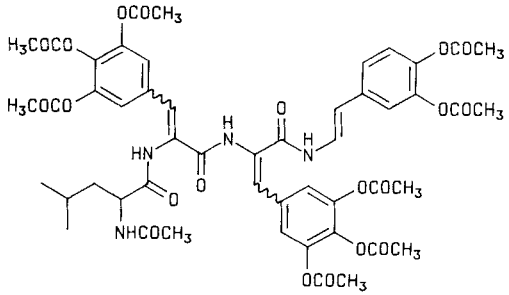
[a]Plant sources (indicated in parentheses) are listed in footnote *a* to Table I.

[b]Solvent for $[\alpha]_D$: m = methanol, c = chloroform.

TABLE V
CELENAMIDES FOUND IN THE MARINE SPONGE *Cliona celata*



Compound	R^1	R^2	Formula	MW	$[\alpha]_D{}^a$	Ref.
Hexaacetylcelenamide A	$CH_2CH(CH_3)_2$	CH_3COO	$C_{46}H_{48}BrN_5O_{14}$	975	+40	*3*
Hexaacetylcelenamide B	$CH(CH_3)_2$	CH_3COO	$C_{45}H_{46}BrN_5O_{14}$	961	+22	*3*
Pentaacetylcelenamide C	$CH_2CH(CH_3)_2$	H	$C_{44}H_{46}BrN_5O_{12}$	917	+14	*4*



Nonaacetylcelenamide D			$C_{50}H_{52}N_4O_{20}$	1029	−25	*4*

[a] $[\alpha]_D$ was measured in acetone.

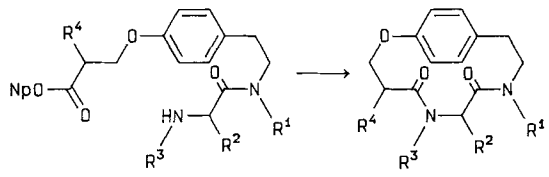
IV. Synthesis of Peptide Alkaloids

A. Early Approaches to the Synthesis of Peptide Alkaloids

First attempts to construct ansa-peptides as simple models of *p*-bridged peptide alkaloids were described by M. Pais (*51*) and H. Rapoport (*35,52*). The latter prepared active (nitrophenyl) esters **13a–13f** as linear precursors, which he was

TABLE VI

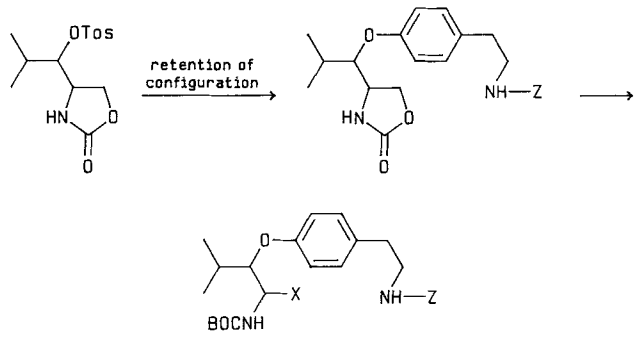
RING-CLOSURE REACTIONS OF NITROPHENYL ESTERS. YIELDS OF MONOMERIC AND DIMERIC CYCLOPEPTIDES



Dimer (%)	Monomer (%)	**14**	R^1	R^2	R^3	R^4
22	24	**a**	CH_3	$CH_2CH_2CH_2$	—	H
32	13	**b**	CH_3	$(CH_3)_2CHCH_2$	H	H
—	0.4	**c**	CH_3	$(CH_3)_2CHCH_2$	CH_3	H
34	24	**d**	H	$—CH_2CH_2CH_2—$	—	H
15	9	**e**	H	$(CH_3)_2CHCH_2$	H	H
—	36	**f**	H	$—CH_2CH_2CH_2—$	—	$(CH_3)_2CH$

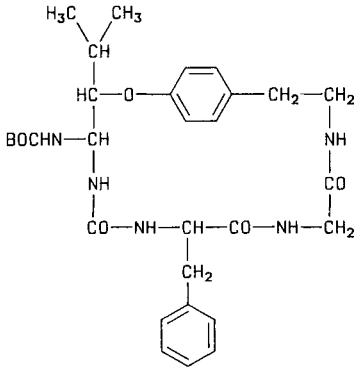
able to cyclize to the lactams **14a–14f** in low to moderate yields (Table VI). Cyclization was accompanied by the formation of dimers, these being usually the major reaction products. This series of experiments avoided the difficult synthesis of appropriate *erythro*-β-aryloxy-α-amino acids.

The elegant sequence of steps by which M. Pais (*53,54*) was able to construct the poorly accessible racemic β-aryloxy-α-amino acids is shown in Scheme 3. These derivatives were further converted to linear cyclization precursors. How-

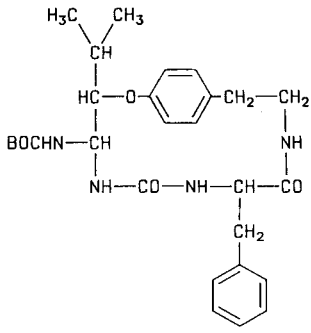


SCHEME 3. Stereoselective synthesis of *erythro*-β-phenoxyamino acids.

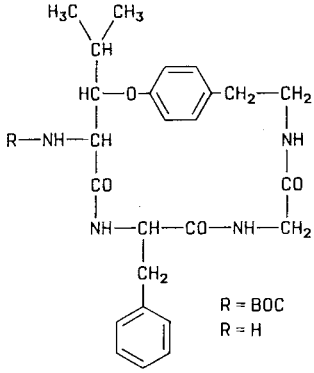
ever, attempts to prepare 14-membered *p*-ansa compounds of the dihydrofrangulanine type by ring closure of the corresponding linear azides or nitrophenyl esters were unsuccessful. In contrast, it was possible to effect ring closure of appropriate precursors to the 15-, 17-, and 18-membered rings (**15–17**), which are not natural products.



15



16



17

B. Model Reactions Directed Toward Total Synthesis

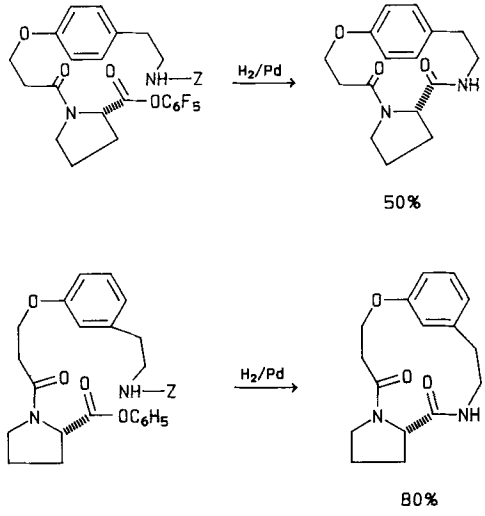
The concept underlying the approach adopted in Stuttgart was to close the ansa ring of the peptide alkaloids by formation of an amide group within the bridge. In total synthesis by this route the following difficulties may be expected:

(a) Formation of medium-sized, rigid peptide rings in good yield.

(b) Construction of *erythro*-β-phenoxyleucine compounds or *trans*-β-phenoxyproline compounds, respectively.
(c) Introduction of the styrylamide double bond.
(d) Attachment of the peptide side chain with a terminal *N,N*-dimethylamino acid.

1. Ring Closure Reactions

In preparation for the total synthesis of peptide alkaloids, a new method of preparing lactams was worked out (*12,13*), which is not only suitable for the synthesis of medium, relatively rigid rings (14-membered *p*-ansa-peptides) but can also be applied to large rings. The intermediate in this synthesis is an ω-benzyloxycarbonylamino carboxylic acid pentafluorophenyl ester, the Z-protective group of which is removed by catalytic hydrogenolysis under Ruggli–Ziegler dilution conditions. At high dilution the ω-amino carboxylic acid pentafluorophenyl ester thus formed undergoes ring closure. Results of model experiments carried out to optimize the reaction conditions are shown in Scheme 4.



SCHEME 4. Model ring-closure reactions with pentafluorophenyl esters (*12,13*).

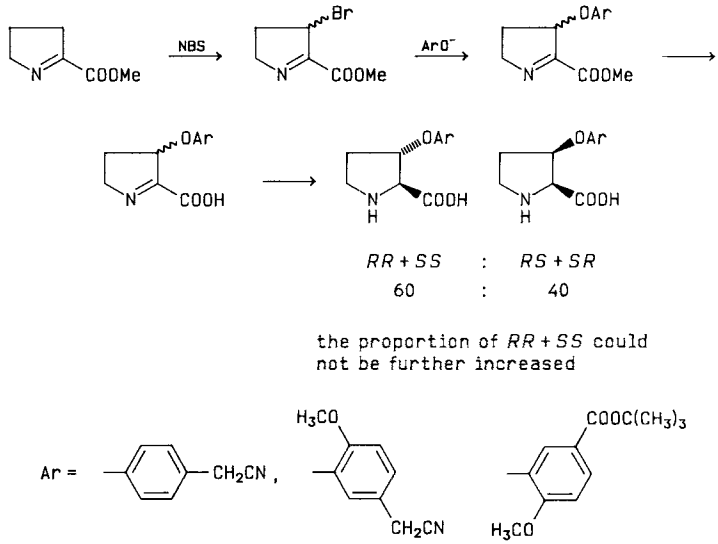
The best yields were obtained using dioxane as solvent, with the addition of 5 mol % 4-pyrrolidinopyridine as acylation catalyst, and 2% ethanol. The best conditions of temperature and dilution (i.e., dropwise addition time) depend on the size of the ring to be formed. The rigid, 14-membered ring can be prepared in 50% yield under the following reaction conditions: for the cyclization of 10

mmol of the amino acid in 300 ml solvent, dropwise addition should take about 5 hr, while a reaction temperature of 95°C is maintained. At lower temperatures, more dimer is formed and becomes the major product if ethyl acetate is chosen as the solvent. Formation of the *m*-ansa-cyclopeptide, which instead of being a rigid system is completely flexible, is complete in a much shorter time, only 3 hr at 50°C being required. Crude cyclization reaction mixtures can be worked up very simply: evaporation of the dioxane solvent is followed by removal of pentafluorophenol by steam distillation *in vacuo*. The catalyst, pyrrolidinopyridine, is strongly absorbed during subsequent chromatography on silica gel.

Predictably, this ring closure is also applicable to the corresponding ω-BOC-amino carboxylic acid pentafluorophenyl esters: after cleavage of the BOC group with trifluoroacetic acid and complete removal of excess acid by evaporation, a solution of the ω-amino carboxylic acid pentafluorophenyl ester trifluoroacetate is added under high dilution conditions to dioxane containing 1 mol of pyrrolidinopyridine and 5–50% *t*-butanol.

2. Synthesis of β-Phenoxyamino Acids

M. Pais has prepared racemic *erythro*-β-aryloxyleucines and *erythro*-β-aryloxyphenylalanines by an elegant, if lengthy, sequence (*54*). We made use of Häusler's synthesis of *trans*-β-aryloxyprolines (*55*) (Scheme 5), a route we also chose for the preparation of *trans*-β-aryloxyprolines substituted in the benzene ring. The ratio of trans to cis could not be improved above 60:40 (Scheme 5).



SCHEME 5. Synthesis of *trans*-β-phenoxyproline compounds (*55*).

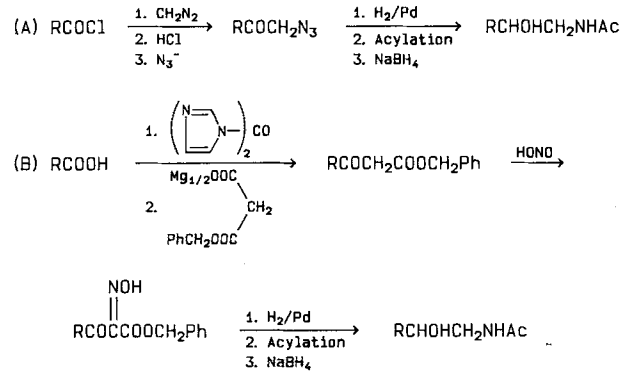
3. Construction of the Styrylamino Unit

Formation of the sensitive enamide double bond was postponed until after ring closure, and was effected by elimination from an *N*-acylphenylaminoethanol. Two routes were worked out for the elaboration of this function from the aromatic carboxy group (Scheme 6):

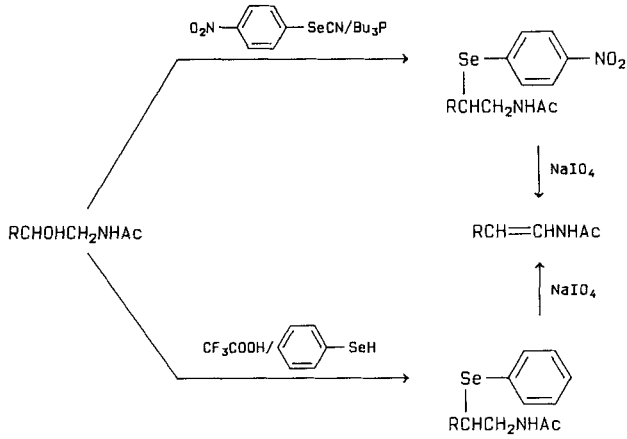
(a) The first route (A) starts from the acid chloride, which is converted via the diazo ketone and bromo ketone to the azido ketone. The latter can be readily converted to the aminoethanol derivative by reduction and acylation. However, the synthesis of zizyphine A later proved to be infeasible by this route, inasmuch as treatment of *O*-methoxydiazo ketones with HBr yielded furanones, not bromo ketones.

(b) The second route (B) makes use of Masamunes method (*56*) to convert the carboxylic acid to a β-keto acid benzyl ester, which is then oximated. Catalytic hydrogenation reduces the oxime to an amino group and cleaves the benzyl ester to the free β-keto acid, which decarboxylates, no intermediates being isolated. Acylation of the amino ketone and reduction of the keto group yielded the aminoethanol derivative.

Introduction of the double bond by selenium oxide elimination proved superior to the alternative elimination of HBr from the corresponding bromide (Scheme 7). The selenide precursors were obtained from the alcohols either by treatment with selenophenol and trifluoroacetic acid (*15*), or by redox condensation with selenocyanate and tributylphosphine (*57*). Oxidation and elimination yielded the olefin. When applied to linear aromatic hydroxyamides, the reaction afforded the *E*-enamides, while cyclic hydroxyamides were converted to the *Z* compounds.



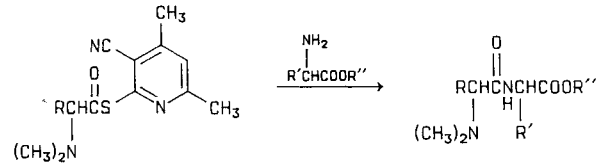
SCHEME 6. Synthesis of the *N*-acylphenylaminoethanol unit.



SCHEME 7. *N*-Acyl enamides from *N*-acylphenylaminoethanol compounds.

4. Synthesis of *N,N*-Dimethyl Peptides

Many peptide alkaloids contain a peptide side chain with an N-terminal *N,N*-dimethylamino acid. A number of methods developed for the activation of *N*-acylamino acids in peptide synthesis are based on proton catalysis, such as the use of carbodiimides, isonitriles, and Woodward's reagent, but all of these methods fail when applied to the activation of the carboxy group in these zwitterions. M. Pais studied the suitability of carbonate-ester mixed anhydrides (*58*) but found that reaction with an amino acid ester yielded both the dipeptide and the carbamic acid ester in equal amounts. Good acylation yields can be achieved with *N,N*-dimethylamino acid pentafluorophenyl esters, although partial racemization is often observed. A very rapid and completely racemization-free acylation method (Scheme 8) is based on the thiol esters (*59*) of 2-mercapto-3-cyano-4,6-dimethylpyridine, which themselves are readily prepared by a redox reaction from the corresponding disulfide, the *N,N*-dimethylamino acid, and triphenylphosphine:



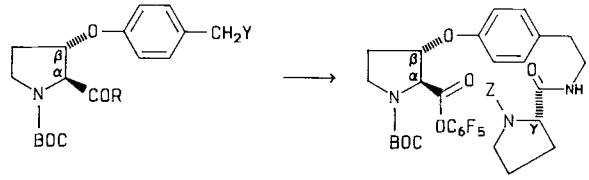
SCHEME 8. Peptide coupling via thiolesters of *N,N*-dimethylamino acids.

5. Isolation and Purification of Peptide Alkaloids

Naturally occurring peptide alkaloids are isolated by extracting the lipid-free substrate with alcohol, and are further purified by column and preparative thin-layer chromatography. In our synthetic work we used Lichroprep Si 60 (E. Merck AG) for the isolation and purification by preparative medium-pressure chromatography of lipophilic cyclopeptides obtained as ring closure products. The dimensions of the column were 50 × 4 cm. After removal of the pentafluorophenol and pyrrolidinopyridine, the column is loaded with up to 2 g of crude synthetic product. The eluant fractions are monitored with a UV detector, evaporated, and analyzed by mass spectroscopy for the target product. Using ethyl acetate/hexane as eluant, diastereomeric cyclopeptides could be separated. Basic end products of synthesis were purified by medium-pressure chromatography on Lichroprep Si 60, using ethyl acetate/ethanol as eluant.

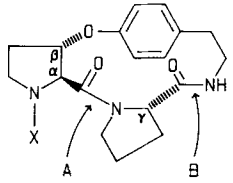
C. Synthesis of Dihydropeptide Alkaloids (*11,12*)

1. 14-Membered *p*-Ansa Compound Dihydrozizyphine G (**22a**) (Scheme 9)



	R	Y
18	OH	CN
19	OH	CH_2NH—Pro—Z

20



	α	β	Y
a	*S*	*S*	*S*
b	*R*	*R*	*S*

21 X = BOC
22 X = Ileu

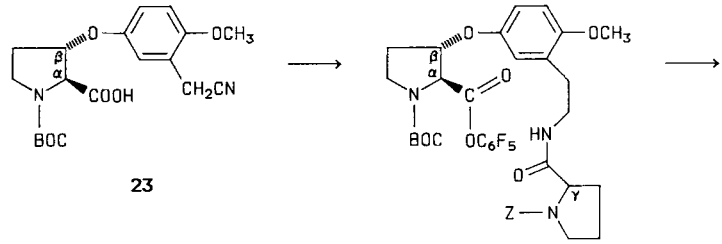
Ring-closure reaction: A 67% **21a**; 30% **21b**
B 35% **21a**; 10% **21b**

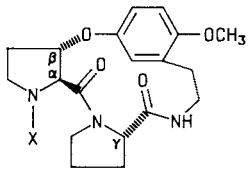
SCHEME 9. Synthesis of dihydrozizyphine G.

The racemic *trans*-β-aryloxyproline (**18**), prepared as outlined in Scheme 5, served as the starting material for the synthesis of the 14-membered ansa-peptide dihydrozizyphine G. Reduction of the nitrile group yielded the amine, and the latter was coupled with benzyloxycarbonylproline to yield a mixture of diastereomers **19a,b,** which in turn was converted to the diastereomers **20a,b.** Closure of the 14-membered *p*-ansa-peptide ring at position A was much superior to closure at B. The diastereomeric rings **21a** and **21b** could be separated without difficulty by medium pressure chromatography on silica gel. Here, as in all later syntheses of cyclopeptide alkaloids, the "correct" diastereomer with the configuration of the natural product (*SSS*) was formed in better yield than the (*RRS*) compound. Conventional methods were used to couple isoleucine with the ring compound **21a** to yield dihydrozizyphine G (**22a**) (*11,12*).

Two years later, the 14-membered dihydromauritine A was synthesized by American workers, who adopted an essentially similar approach (*60*). They too prepared the β-aryloxyproline, using the method of Häusler and Schmidt. However, the yield in the cyclization step was very poor, because they opted for the nitrophenyl ester procedure.

2. 13-Membered *m*-Ansa Compounds Dihydrozizyphine A (**27**) and B (**28**) (*10,14*) (Scheme 10)





	α	β	γ
a	*S*	*S*	*S*
b	*R*	*R*	*S*

25 X = BOC
26 X = H-Ileu
27 X = Me_2Ileu-Ileu
28 X = Me-Ileu-Ileu

Ring-closure reaction: 97% **25a;** 78% **25b**

SCHEME 10. Synthesis of dihydrozizyphine A.

In contrast to the rigid ring in a model of the *p*-ansa compound zizyphine G, the ring in the *m*-ansa compound zizyphine A (*8*) is flexible, a difference that is reflected in better yields on ring closure. Construction of these cyclopeptides starts with the β-aryloxyproline compound **23,** prepared as shown in Scheme 5. The trans compound could be separated from its cis isomer by medium-pressure chromatography. The ring closure that takes place after catalytic hydrogenation of the diastereomeric carbobenzoxypentafluorophenyl esters afforded the cyclic products **25a,b** in high yield. Once again, the diastereomer with the same configuration (*SSS*) as the natural compounds is found to be formed in higher yield (97%) than the (*RRS*) compound (78%). Facile separation of the two diastereomers was achieved by medium-pressure chromatography.

Compound **25** was converted to dihydrozizyphine A (**27**) and dihydrozizyphine B (**28**) by coupling it with the appropriate side chain by conventional methods. In the final step, **26** was acylated with the pentafluorophenyl ester of *N,N*-dimethylisoleucine (*10,14*).

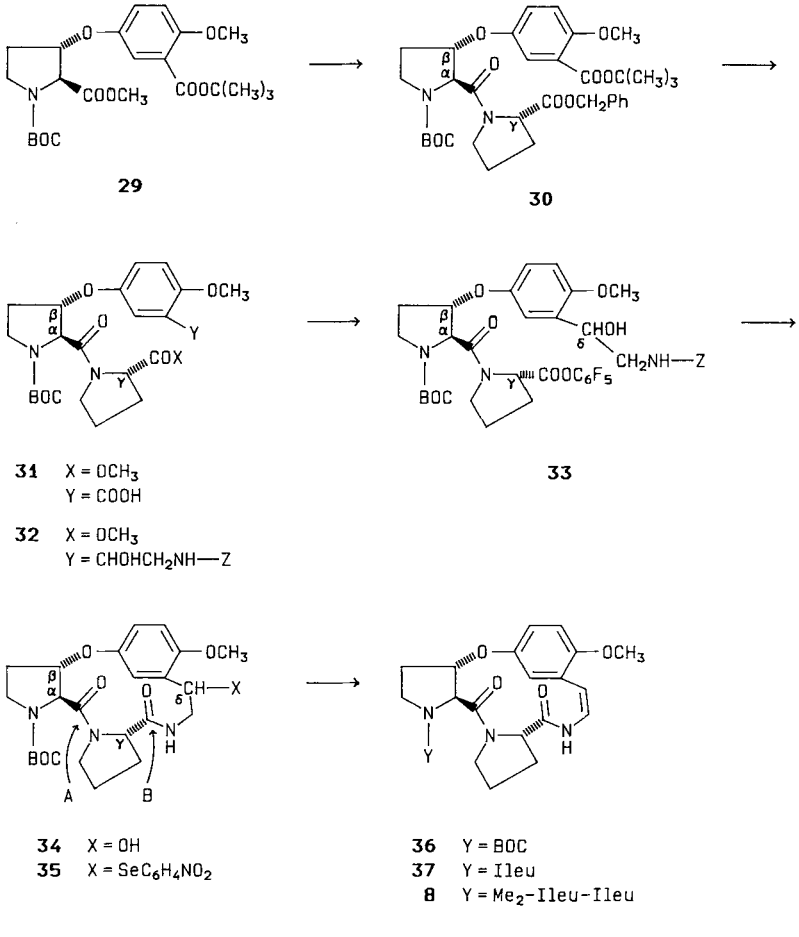
D. Total Synthesis of Peptide Alkaloids

1. Zizyphine A (**8**) (*12,16*) (Scheme 11)

The starting material for the synthesis of zizyphine A is the racemic *trans*-β-aryloxyproline derivative **29,** prepared by the well-established route outlined in Scheme 5 via the β-bromodehydroproline ester. Protection of the aromatic carboxylic acid by formation of the *t*-butyl ester permitted selective deprotection of this carboxy group for subsequent conversion to the aminoethanol group (corresponding to Scheme 6).

Both synthetic sequences, with ring closure at the alternative positions A and B, were carried out. Inasmuch as the ring of the *m*-ansa compound is flexible, in contrast to the rigid system of the *p*-ansa compound (dihydrozizyphine G), no difference is found between the yields of the reactions at positions A and B, over 80% being obtained in either case. The sequence in which ring closure of the pentafluorophenyl esters **33c** and **33d** is effected at position B offers the advantage that the acyclic diastereomeric precursors **30a** and **30b** can be separated before ring closure. If, on the other hand, the ring is closed at position A, a mixture of 4 diastereomeric products (**34**) is obtained, which is difficult to separate.

After separation from **30b,** the benzyl ester was converted to the methyl ester, and the *t*-butyl ester was cleaved to yield the carboxylic acid **31a.** The aminoethanol side chain was elaborated from the carboxy group, as illustrated in Scheme 6. Inasmuch as reduction of the carbonyl group is not selective, two diastereomeric alcohols **32c** and **32d** were obtained. Conversion of the cyclic alcohols **34c** and **34d** to the *p*-nitrophenylselenides **35c** and **35d,** followed by



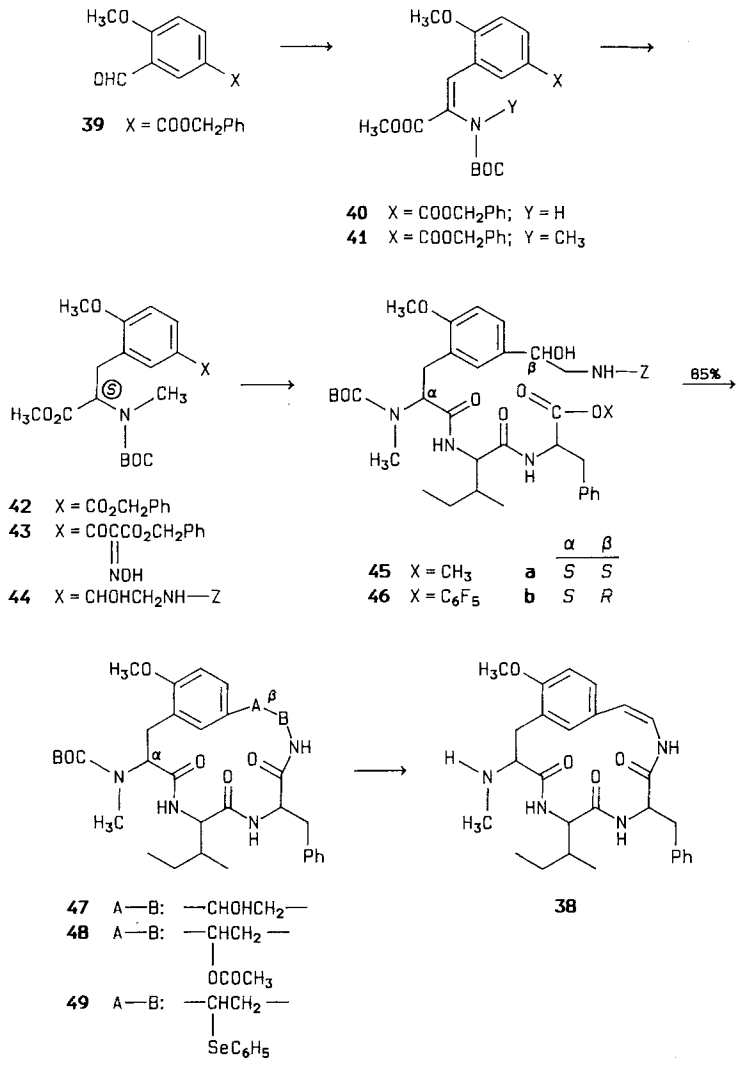
	α	β	Y	δ
a	*S*	*S*	*S*	
b	*R*	*R*	*S*	
c	*S*	*S*	*S*	*S*
d	*S*	*S*	*S*	*R*

SCHEME 11. Total synthesis of zizyphine A.

oxidative elimination, afforded the cis olefin **36.** The *N,N*-dimethylisoleucylisoleucine side chain was introduced via **37** as described in Section IV,B,4.

2. Mucronine B (**38**) (*15a,15b*) (Scheme 12)

The synthetic route planned for mucronine B also provided for formation of the styrylamide group by selenium oxide elimination and for ring closure at the



SCHEME 12. Total synthesis of mucronine B.

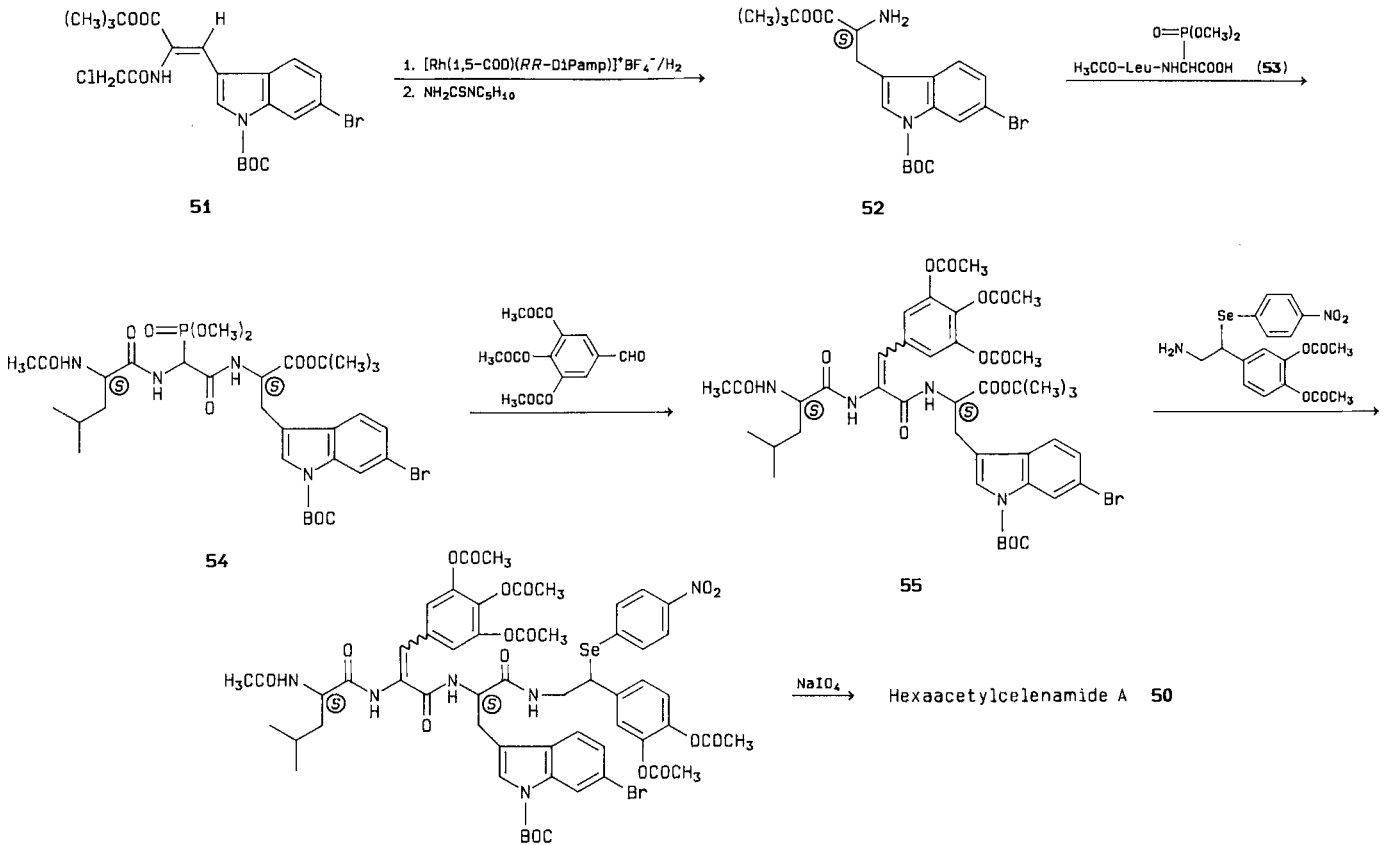
phenylethylamine nitrogen. Key fragments for the construction of this cyclopeptide are thus derivatives of (*S*)-2′-carboxy-5′-methoxyphenylalanine, with ester functions differentiated so as to permit selective cleavage. The aromatic carboxy group, protected as the benzyl ester, later served for construction of the styrylamide group. For preparation of the substituted phenylalanine, we chose the

sequence in which the dehydroamino acid ester is an intermediate, since this offered an opportunity for enantioselective hydrogenation to the substituted (*S*)-phenylalanine. In addition, the nitrogen atom of *N*-acyldehydroamino acid esters can easily be methylated.

In the dehydroamino acid synthesis that we developed, the aromatic aldehyde **39** was condensed with *N*-BOC-2-(dimethoxyphosphoryl)glycine methyl ester (*61,62*) to yield the dehydroamino acid ester **40,** predominantly the *Z* isomer, which was then smoothly methylated to **41.** Enantioselective hydrogenation on a rhodium–DiPAMP catalyst (*63*) yielded over 98% (ee >99%) of the (*S*) amino acid ester **42,** the benzyl ester group of which was hydrogenolyzed to the free carboxylic acid. Conversion to the β-keto ester, oximation, catalytic hydrogenation of **43** (corresponding to Scheme 6), and acylation with benzyloxycarbonyl chloride afforded **44a** and **44b.** After hydrolysis of the methyl ester, coupling with (*S*)-isoleucyl-(*S*)-phenylalanine ester gave the tripeptide ester **45a** and **45b.** Conversion of the latter to the pentafluorophenyl ester **46a** and **46b** supplied the educt for the ring-closure reaction, which was carried out by catalytic hydrogenation at high dilution (Section IV,B,1) to yield 85% of the cyclized products **47a** and **47b.** To facilitate purification, the diastereomeric alcohols were converted to the acetates **48a** and **48b,** and this mixture of diastereomers was treated directly with phenylselenol in trifluoroacetic acid to yield the selenides **49a** and **49b.** On subjecting the latter to oxidative elimination, the (*Z*) olefin mucronine B (**38**) was obtained exclusively.

3. Linear Peptide Alkaloid Hexaacetylcelenamide A (**50**) (*64*) (Scheme 13)

Condensation reactions with *N*-acyl-2-(dialkoxyphosphoryl)glycinates to build up dehydroamino acids and dehydropeptides are a characteristic feature of the synthesis of hexaacetylcelenamide A (*61,62*). Construction of the(*S*)-6-bromotryptophan **52**—which is evidently a characteristic amino acid in marine creatures—was achieved by enantioselective hydrogenation of the corresponding dehydroamino acid derivative **51,** prepared by a phosphonate condensation. Coupling the (*S*)-6-bromotryptophan-*t*-butyl ester **52** with the phosphoryl dipeptide **53** afforded the phosphoryl tripeptide **54,** which was condensed with triacetoxybenzaldehyde to yield a mixture of *cis*- and *trans*-dehydrotripeptides **55.** After separation of the latter, the remaining synthetic steps were carried out with the *E* and the *Z* isomers separately. Removal of the *t*-butyl groups from the *E* isomer and condensation with 2-*p*-nitrophenylseleno-3′,4′-(diacetoxyphenyl)ethylamine gave the seleno compound **56,** which underwent smooth oxidative elimination to yield the trans enamide hexaacetylcelenamide A (**50**) (see Table V).



SCHEME 13. Total synthesis of hexaacetylcelenamide A.

Acknowledgment

We gratefully appreciate the help of Dr. Ute Schanbacher and Gisela Kraschewski. Our synthetic work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

References

1. E. W. Warnhoff, *Fortschr. Chem. Org. Naturst.* **28,** 163 (1970).
2. R. Tschesche and E. U. Kaussmann, *Alkaloids* **15,** 191 (1975).
3. R. J. Stonard and R. J. Andersen, *J. Org. Chem.* **45,** 3687 (1980).
4. R. J. Andersen and R. J. Stonard, *Can. J. Chem.* **58,** 2121 (1980).
5. U. Schmidt and A. Lieberknecht, *Angew. Chem. Int. Ed. Engl.* **22,** 250 (1983).
6. J. Marchand, M. Pais, X. Monseur, and F. X. Jarreau, *Tetrahedron* **25,** 937 (1969).
7. J. C. Lagarias, D. Goff, F. K. Klein, and H. Rapoport, *J. Nat. Prod.* **42,** 220 (1979).
8. U. Schmidt, H. Griesser, A. Lieberknecht, and J. Talbiersky, *Angew. Chem. Int. Ed. Engl.* **20,** 280 (1981).
9. U. Schmidt, A. Lieberknecht, H. Griesser, and J. Häusler, *Angew. Chem. Int. Ed. Engl.* **20,** 281 (1981).
10. U. Schmidt, H. Bökens, A. Lieberknecht, and H. Griesser, *Tetrahedron Lett.* **22,** 4949 (1981).
11. U. Schmidt, A. Lieberknecht, H. Griesser, and . Häusler, *Liebigs Ann. Chem.*, 2153 (1982).
12. U. Schmidt, A. Lieberknecht, H. Bökens, and H. Griesser, *Angew. Chem. Int. Ed. Engl.* **20,** 1026 (1981).
13. U. Schmidt, A. Lieberknecht, H. Griesser, and J. Talbiersky, *J. Org. Chem.* **47,** 3261 (1982).
14. U. Schmidt, H. Bökens, A. Lieberknecht, and H. Griesser, *Liebigs Ann. Chem.*, 1459 (1983).
15a. U. Schmidt and U. Schanbacher, *Angew. Chem. Int. Ed. Engl.* **22,** 152 (1983).
15b. U. Schmidt and U. Schanbacher, *Liebigs Ann. Chem.*, 1205 (1984).
16. U. Schmidt, A. Lieberknecht, H. Bökens, and H. Griesser, *J. Org. Chem.* **48,** 2680 (1983).
17. R. Tschesche, E. U. Kaussmann, and H. W. Fehlhaber, *Chem. Ber.* **105,** 3094 (1972).
18. H. W. Fehlhaber, *Z. Anal. Chem.* **235,** 91 (1968).
19. R. Tschesche, J. Rheingans, H. W. Fehlhaber, and G. Legler, *Chem. Ber.* **100,** 3924 (1967).
20. M. Pais, J. Marchand, F. X. Jarreau, and R. Goutorel, *Bull. Soc. Chim. Fr.*, 1145 (1968).
21. E. Medina and G. Spiteller, *Liebigs Ann. Chem.*, 538 (1981).
22. O. Jardetzky and G. C. K. Roberts, "NMR in Molecular Biology," p. 162. Academic Press, New York, 1981.
23. E. Haslinger, *Tetrahedron* **34,** 685 (1978).
24. E. Haslinger, *Mh. Chem.* **109,** 523 (1978).
25. E. Haslinger and W. Robien, *Mh. Chem.* **110,** 1011 (1979).
26. M. G. Sierra, O. A. Mascaretti, F. J. Diaz, and E. A. Ruveda, *Chem. Commun.*, 915 (1972).
27. M. Takai, Y. Ogihara, Y. Iitaka, and S. Shibata, *Chem. Pharm. Bull.* **23,** 2556 (1975).
28. M. Takai, K. I. Kawai, Y. Ogihara, Y. Iitaka, and S. Shibata, *J. Chem. Soc., Chem. Commun.*, 653 (1974).
29. C. J. Chang and B. K. Cassels, *Contrib. Cient. Tecnol. (Univ. Tec. Estado, Santiago)* **28,** (1978).
30. M. Pais, F. X. Jarreau, G. M. Sierra, O. A. Mascaretti, E. A. Ruveda, C. J. Chang, E. W. Hagamann, and E. Wenkert, *Phytochemistry* **18,** 1869 (1979).
31. A. F. Morel, R. V. F. Bravo, F. D. A. M. Reis, and E. A. Ruveda, *Phytochemistry* **18,** 473 (1979).

32. D. M. Hindenlang, M. Shamma, G. A. Miana, A. H. Shah, and B. K. Cassels, *Liebigs Ann. Chem.*, 447 (1980).
33. T. A. Broadbent and E. G. Paul, *Heterocycles* **20,** 863 (1983).
34. E. Haslinger and W. Robien, *Mh. Chem.* **113,** 95 (1982).
35. D. Goff, J. C. Lagarias, W. C. Shik, M. P. Klein, and H. Rapoport, *J. Org. Chem.* **45,** 4813 (1980).
36. J. C. Lagarias, W. H. Yokoyama, J. Bordner, C. W. Shik, M. P. Klein, and H. Rapoport, *J. Am. Chem. Soc.* **105,** 1031 (1983).
37. R. A. Ravizzini, C. S. Andrev, and R. H. Vellejos, *Plant Cell Physiol.* **18,** 701 (1977).
38. K. Kowar, Y. Nozawa, and Y. Ogihara, *Experientia* **33,** 1454 (1977).
39. R. Tschesche, D. Hillebrand, H. Wilhelm, E. Ammermann, and G. Eckhardt, *Phytochemistry* **16,** 1025 (1977).
40. R. Tschesche and D. Hillebrand, *Phytochemistry* **16,** 1817 (1977).
41. R. Tschesche, M. Elgamal, and G. Eckhardt, *Chem. Ber.* **110,** 2649 (1977).
42. G. J. Kapadia, Y. N. Shukla, J. F. Morton, and H. A. Lloyd, *Phytochemistry* **16,** 1431 (1977).
43. J. C. Lagarias, D. Goff, and H. Rapoport, *J. Nat. Prod.* **42,** 663 (1979).
44. R. Tschesche, M. Elgamal, G. A. Miana, and G. Eckhardt, *Tetrahedron* **31,** 2944 (1975).
45. R. Tschesche, I. Khokhar, C. Spilles, G. Eckhardt, and B. K. Cassels, *Tetrahedron Lett.*, 2941 (1974).
46a. M. Silva, D. S. Bhakuni, P. G. Sammes, M. Pais, and F. X. Jarreau, *Phytochemistry* **13,** 861 (1974).
46b. P. Pacheco, S. M. Albomico, and M. Silva, *Phytochemistry* **12,** 954 (1973).
47. F. Bailleul and P. Delaveau, *Compt. Rend. C* **279,** 949 (1974).
48. R. Tschesche, A. H. Shah, and G. Eckhardt, *Phytochemistry* **18,** 702 (1979).
49. R. Tschesche, G. M. Miana, and G. Eckhardt, *Chem. Ber.* **107,** 3180 (1974).
50. R. Tschesche, J. Khokhar, H. Wilhelm, and G. Eckhardt, *Phytochemistry* **15,** 541 (1976).
51. F. Rocchiccioli, F. X. Jarreau, and M. Pais, *Tetrahedron* **34,** 2917 (1978).
52. J. C. Lagarias, R. A. Houghten, and H. Rapoport, *J. Am. Chem. Soc.* **100,** 8202 (1978).
53. J. Marchand, F. Rocchiccioli, M. Pais, and F. X. Jarreau, *Bull. Soc. Chim. Fr.* **12,** 4699 (1972).
54. F. Frappier, F. Rocchiccioli, F. X. Jarreau, and M. Pais, *Tetrahedron* **34,** 2911 (1978).
55. J. Häusler and U. Schmidt, *Liebigs Ann. Chem.*, 1881 (1979).
56. D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.* **18,** 72 (1979).
57. P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.* **41,** 1485 (1976).
58. M. Pais, F. X. Xavier, X. Lusiuchi, and R. Goutarel, *Liebigs Ann. Chim.*, 102 (1966).
59. U. Schmidt and K. Schefenacker, *Liebigs Ann. Chem.*, in press.
60. R. F. Nutt, K. N. Chen, and M. M. Joullier, *J. Org. Chem.* **49,** 1013 (1984).
61. U. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler, and J. Wild, *Angew. Chem. Int. Ed. Engl.* **21,** 776 (1982).
62. U. Schmidt, A. Lieberknecht, and J. Wild, *Synthesis*, 53 (1984).
63. B. D. Vinegard, W. S. Knowles, M. J. Sabaky, D. L. Bachman, and D. L. Weinkauff, *J. Am. Chem. Soc.* **99,** 5946 (1977).
64. U. Schmidt and J. Wild, *Angew. Chem. Int. Ed. Engl.* **23,** 991 (1984).

— CHAPTER 7 —

PYRROLIZIDINE ALKALOIDS

JERZY T. WRÓBEL

Department of Chemistry
University of Warsaw
Warsaw, Poland

I. Introduction

The interest in the chemistry, synthesis, and pharmacology of pyrrolizidine alkaloids (PAs) has increased considerably within the last decade. A review published in 1982 by D. J. Robins (*1*) covered the literature (up to early 1981) concerning the chemistry, biosynthesis, and pharmacology of alkaloids, necine bases, and necic acids. In 1981 Smith and Culvenor (*2*) wrote a chapter on the plant sources of hepatotoxic PAs. The present chapter extends the information provided by the two reviews to the literature that appeared mainly within the years 1981–1984, focusing on the new PAs, their structure, progress in the synthesis (particularly stereoselective) of alkaloids and necine bases, in spectrometry, biosynthesis, and pharmacology.

II. Pyrrolizidine Alkaloids: Structural Determinations, New Compounds

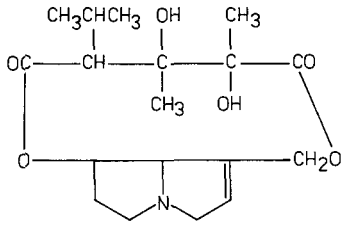
The damaging effects of pyrrolizidine alkaloids on liver and the concern about their presence in foodstuffs resulted in extensive studies of many plants that were

THE ALKALOIDS, VOL. 26

not previously tested. Monocrotaline (**41**), known for 50 years as a constituent of the Leguminosae family, was recently isolated (*3*) from *Crotalaria cephalotes*, *C. cunminghamii*, *C. nitens*, *C. paulina*, and *C. recta*.

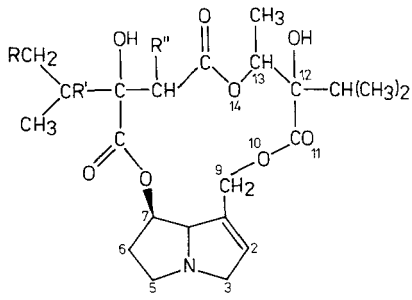
Owing to the discovery of PAs in livestock (*4*), hay and silage were studied for the presence of PAs using gas chromatography and mass spectrometry.

Earlier reports on the presence of PAs of the Compositae family in milk and honey led to the discovery of echimidine and its derivatives in honey from *Echium plantagineum* L. (0.27–0.95 ppm) (*5*). Also, trichodesmine (**1**) was isolated from *Trichodesma africanum* L. (*6*).

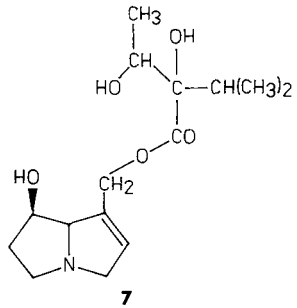


1

The species *Parsonia heterophylla* A. Cunn and *P. spiralis* Wall (Apocynaceae) were shown to be sources of new 14-membered ring PAs **2–6** and **8**.

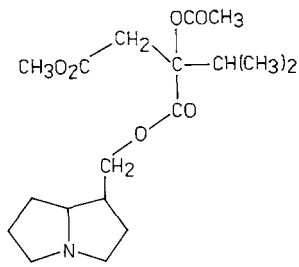


2 - 6



7

2 R = R' = R'' = H Parsonsine
3 R = CH_3, R' = R'' = H Heterophylline
4 R = R' = H, R' = OH Spiraline
5 R = CH_3, R' = H, R'' = OH Spiranine
6 R = CH_3 R' = R'' = OH Spiracine

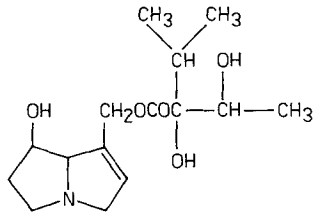


8

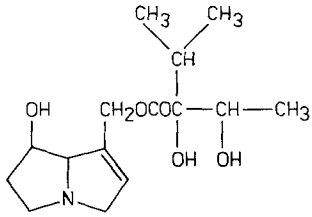
The structures were determined by ^{1}H-NMR and ^{13}C-NMR spectroscopy, by hydrogenolysis (Pt/MeOH) of the C-9 ester linkage, and by alkaline or acid hydrolysis, which resulted in trachelanthic and 2-isopropylmalic acids and retronecine (**57**). Partial hydrolysis of **2** gave the known alkaloid **7.** The structure of **8** was studied by ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy and acid hydrolysis.

Caterpillars of certain butterflies feed on *Parsonsia spiralis,* and the alkaloids present in this species can be found in the adult insects (*7*).

The separation of the two diastereoisomeric alkaloids intermedine (**9**) and lycopsamine (**10**) was effected thanks to their different tendencies to form borate complexes (*8*).

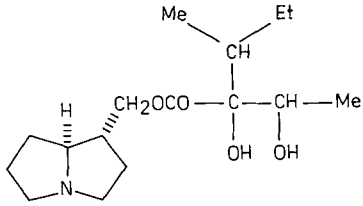


9

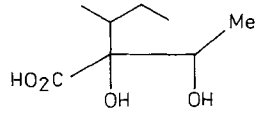


10

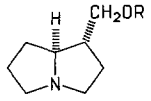
The following alkaloids were isolated from *Heliotropium curassavicium* L. (*9*): currasavine (**11**), trachelanthamidine (**82**) esterified by a new acid **12,** coromandaline (**13**), and heliovicine (**14**).

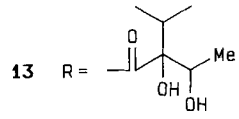


11

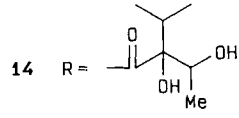


12





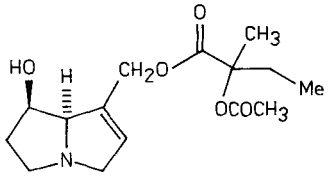
13 R =



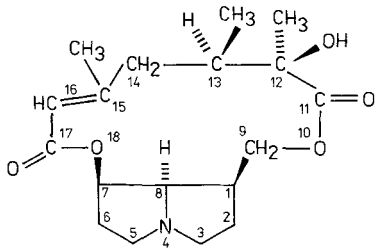
14 R =

Callimorphine (**15**) was isolated as a "metabolite" of the cinnabar moth. The structure of **15** was proposed on the basis of mass spectrometry and synthesis from 9-chlororetronecine hydrochloride and the sodium salt of (±)-α-acetoxy-α-methylbutyric acid (*10*).

An X-ray study of the (*R*,*R*)-(+)-bitartrate of bulgarsenine (**16**) has shown that the C-11 ester carbonyl group is directed upwards from the plane of the macro ring and is antiparallel to the C-17 ester carbonyl group (*11*).

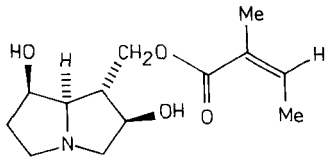


15



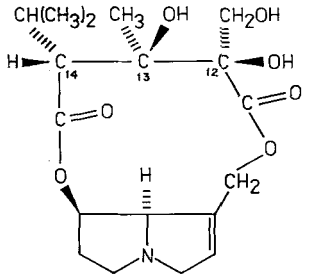
16

Helifoline (**17**) from *Heliotropium ovalifolium* (Boraginaceae) is a new example of an alkaloid derived from a triol necine base—croalbinecine (**145**). The structure of **17** was determined by spectroscopy and by hydrolysis, which resulted in **145** (*12*).

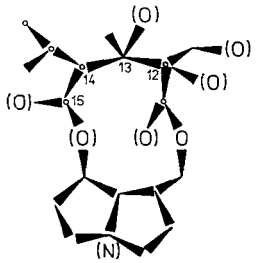


17

An X-ray study allowed the determination of the absolute configuration of junceine (**18**). Its pyrrolizidine ring is in an exo-puckered form, and the ester carbonyl bonds are synparallel and directed below the plane of the macrocyclic ring (**19**) (*13*).

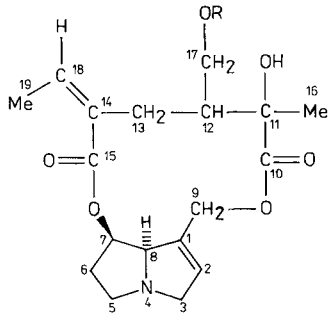


18



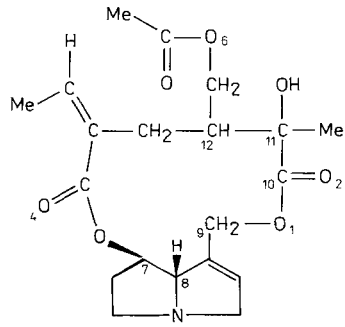
19

Two new alkaloids, gynuramine (**20**) and acetylgynuramine (**21**) were isolated from *Gynura scandens* (tribe Senecioneae), which is used in Africa as a medicinal herb. The structures of both alkaloids were determined by spectroscopy (IR, ^{1}H-NMR, ^{13}C-NMR, MS) (*14a*) along with the absolute configuration (*14b*) for (**21**).



20 R = H gynuramine

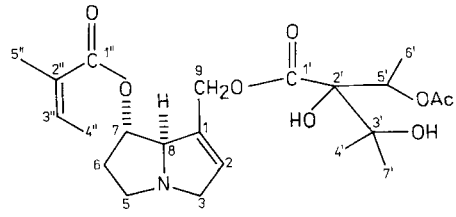
21 R = $-\overset{\overset{20}{\|}}{\underset{O}{C}}-\overset{21}{CH_3}$ acetylgynuramine



21

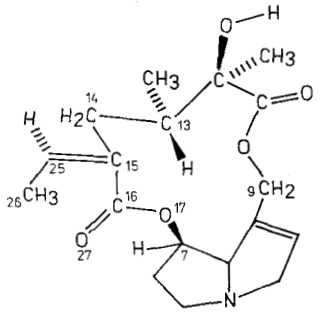
(−)-(7*R*, 8*R*, 11*S*, 12*R*)-

A revised structure has been assigned to acetylheliosupine, a minor alkaloid of *Cynoglossum officinale* L. (*15*). The revision concerns the acetyl group, which has been placed now on the secondary OH group at C-5′ instead of the previously suggested position at C-2′ (**22**).



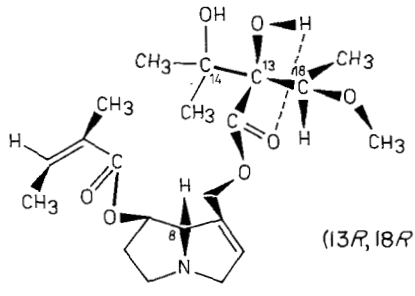
22

The X-ray analysis of senecionine (**23**) *has shown: the presence of the exo-puckered pyrrolizidine ring, a conformation of the 12-membered macrocyclic ring resembling that observed in crystalline retrorsine* (**185**), *the presence of antiparallel CO groups, and the presence of a C-15=C-25 bond cis-positioned to the CO group at C-16 (16a,16b).*



23

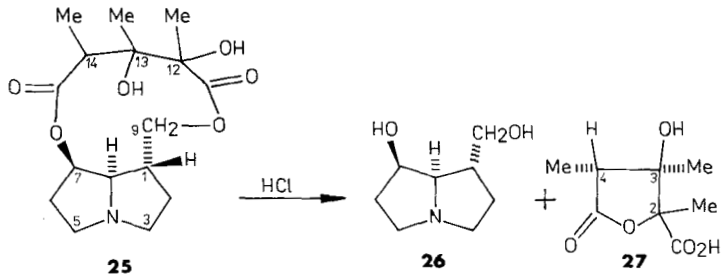
The absolute configuration assigned to lasiocarpine (**24**) includes an endo-puckered pyrrolizidine ring and CO groups out of H-8 on C-8 (*17*).



(13*R*, 18*R*)

24

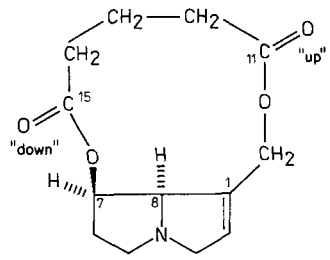
Cropodine (**25**) was isolated from *Crotalaria candicans* W. & A. (*18*). The structure was assigned on the basis of spectroscopic data and of acid hydrolysis, which resulted in turneforcidine (**26**) and monocrotalic acid (**27**).



25 **26** **27**

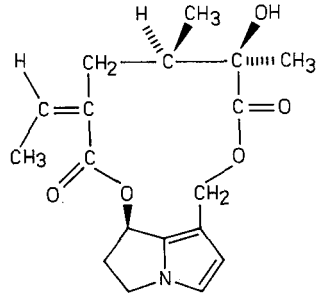
(2*R*,3*R*,4*R*)

The single-crystal structural analysis of 1,2-didehydrocrotalamine picrate (*19*) led to the absolute configuration of the alkaloid, indicating the antiparallel arrangement of carbonyl groups (**28**).



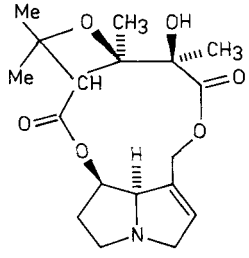
28

The conformation of dehydrosenecionine (**29**) was shown by X-ray analysis to resemble closely that of senecionine (**23**). The flattening of the pyrrolizidine ring causes a considerable distortion of the exocyclic angles (*20*).



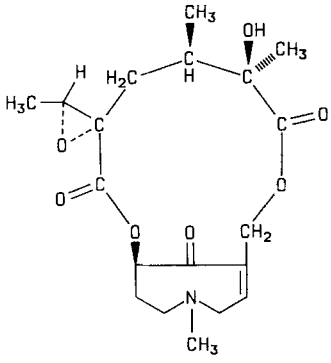
29

Grantaline (**30**), from *Crotalaria virgulata* [subspecies *grantiana* (Harvey) Polhill], was found to be a derivative of retronecine (**57**) and grantalinic acid (*21*). The structure and absolute configuration of **30** was determined by X-ray analysis.

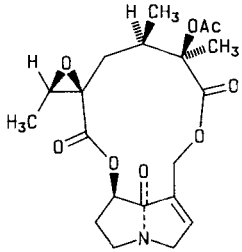


30

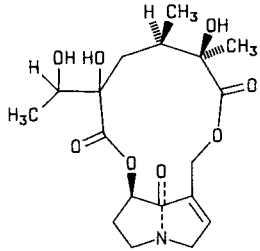
The species *Senecio aureus* L. (Asteraceae), used in American folk medicine, was reported (*22*) to contain the PA ostosenine (**31**). Florosenine (**32**) and flor-



31



32

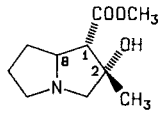


33

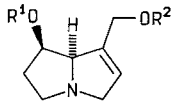
idanine (**33**) were isolated from the same species and characterized by spectroscopy (*23*).

The absolute configuration of tussilagine (**34**) was shown by X-ray analysis (*24*) to be (−)-(1*S*,2*S*,8*S*)-1α-methoxycarbonyl-2α-hydroxy-2β-methyl-1,2,3,5,6,8-hexahydro-7*H*-pyrrolizidine.

Four alkaloids were isolated from *Senecio triangularis* Hook: 7-angelylretronecine (**35**), 7-senecioylretronecine (**36**), 7,9-diangelylretronecine (**37**), 7-angelyl-



34



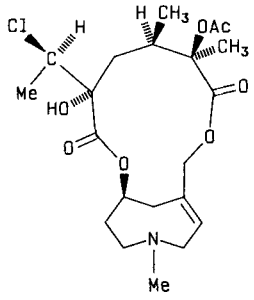
35 R^1 = (*Z*)-$CH_3CH{=}CCO(CH_3)$ R^2 = H

36 R^1 = $CH_3C(CH_3){=}CHCO$ R^2 = H

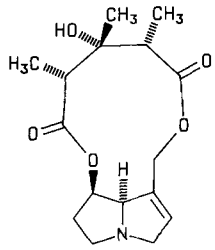
37 R^1 = (*Z*)-$CH_3CH{=}CCO(CH_3)$ R^2 = (*Z*)-$CH_3CH{=}CCO(CH_3)$

38 R^1 = $CH_3C(CH_3){=}CHCO$ R^2 = (*Z*)-$CH_3CH{=}CCO(CH_2OH)$

9-sarracinylretronecine (**38**). The three latter alkaloids have been isolated for the first time. Structural determinations were made using CD, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. Single-crystal structure X-ray analysis has shown the absolute configuration at C-12, C-13, C-15, and C-7 in doronine (**39**) to be (*R*) (*26*).

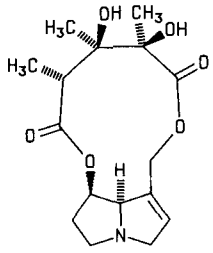


39

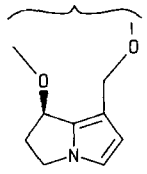


40

X-Ray determination of configuration and conformation of crispatine·H_2O (**40**) has shown, among other things, that its lactone ring resembles that of monocrotaline (**41**) and fulvine (**72**). A hydrogen bond was found between the hydroxyl group on C-13 and oxygen on carbon C-15 (*27*).



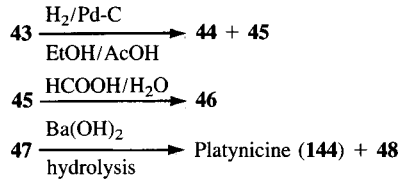
41

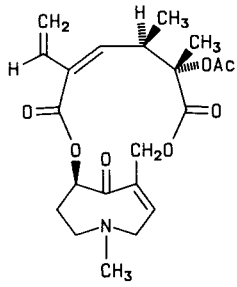


42

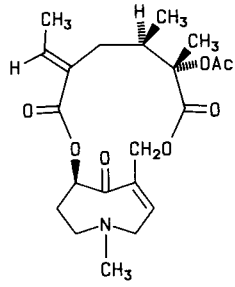
Significant changes in the conformation of the dilactone ring in dehydromonocrotaline (**42**) were demonstrated by X-ray analysis. The changes found predominantly around the primary ester system were explained in terms of the flattening of the pyrrolizidine nucleus (*28*).

Five alkaloids (four of them new) were isolated from *Ligularia dentata* Hara (Compositae), used as food in some areas of Japan (*29*). One of the known alkaloids, clivorine (**43**), was converted in a simple reaction sequence to new alkaloids. Hydrolysis of the unknown bases led to platynecine and necic acid (**48**) in support of the structural determinations.

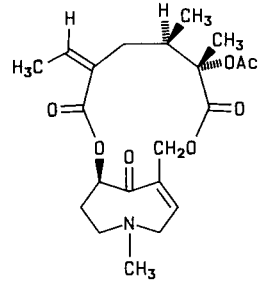




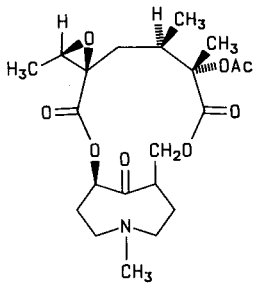
43



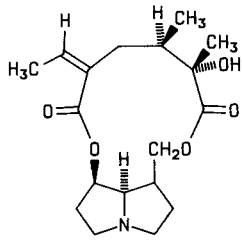
44



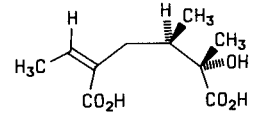
45



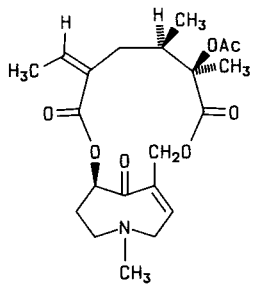
46



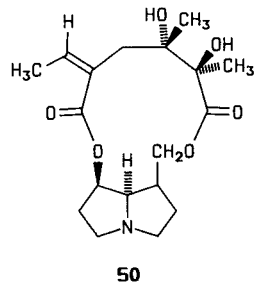
47



48



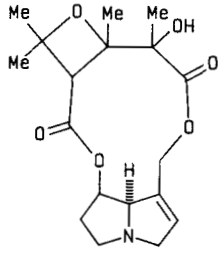
49



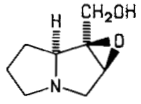
50

The four new alkaloids were described as liguralidine (**44**), neoligularidine (**45**), ligularizine (**46**), and ligularinine (**47**). Their spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, MS), which confirmed the proposed structures, show pronounced analogies with data found for known PAs of similar structure, such as acetylfukinotoxin (**49**), florosenine (**32**), and platyphilline (**50**).

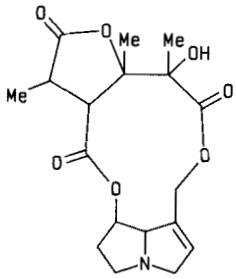
Crotalaria virgulata subsp. *grantiana* (of Australian origin) was a source of grantaline (**30**), grantianine (**52**), and necin base (**51**). Spectroscopic data (IR, ^{1}H-NMR, MS) confirmed the structures previously proposed for these alkaloids (*30*).



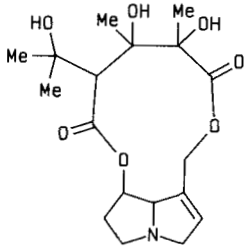
30



51



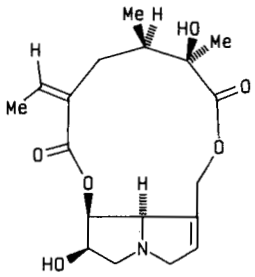
52



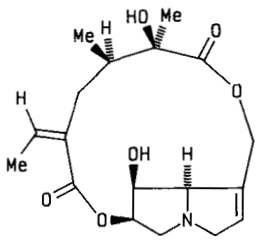
53

Globiferine (**53**) was isolated from *Crotalaria globifera* seeds together with known alkaloids trichodesmine (**1**), grantaline (**30**), and grantianine (**52**). Mass spectra have shown that globiferine differs from (**1**) only by the presence of one hydroxy group. The evidence for the location of the OH group was found in the ^{1}H-NMR spectrum (*31*). Similar conformations of lactone rings were found by X-ray analysis in isomeric alkaloids anacrotine (**54**) and madurensine (**55**) (*32*).

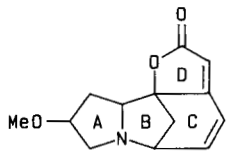
Structure **56** was proposed on the basis of spectroscopic data for a new PA (4-methoxynorsecurinine), isolated from *Phylanthus niruri* L. (Euphorbiaceae).



54



55



56

TABLE I

NEW PYRROLIZIDINE ALKALOIDS

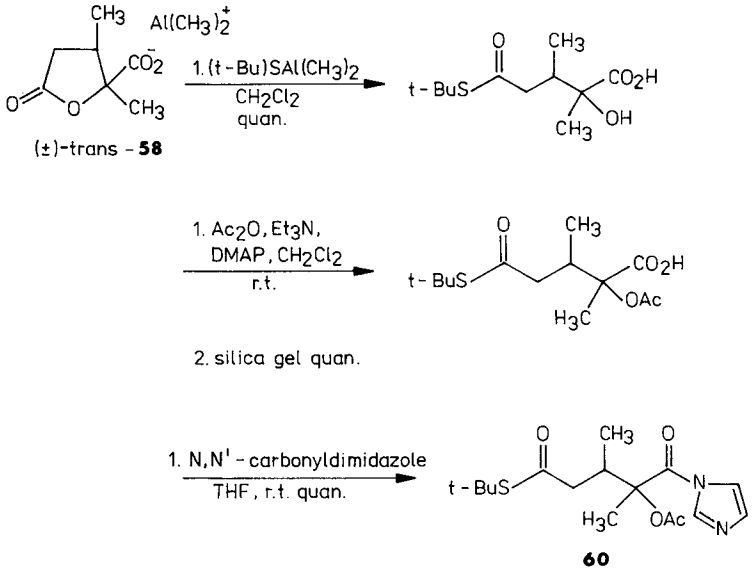
	Alkaloid	Formula (MW)	mp (°C)	$[\alpha]_D$ (solvent)	Source species	Ref.
15	Callimorphine	$C_{15}H_{23}NO_5$ (297)	—	—	Moth metabolite, *Tyria jacobeae*	*10*
17	Helifoline	$C_{13}H_{21}NO_4$ (255)	131–132	+25.4° ($CHCl_3$)	*Heliotropium ovalifolium* (Boroginaceae)	*12*
20	Gynuramine	$C_{18}H_{25}NO_6$ (351)	202–204	−16° ($CHCl_3$)	*Gynura scandens* (Senecioneae)	*14a,14b*
21	Acetylgynuramine	$C_{20}H_{27}NO_7$ (393)	153–155	−33° ($CHCl_3$)	*Gynura scandens* (Senecioneae)	*14a,14b*
25	Cropodine	$C_{16}H_{25}NO_3$ (327)	226–228	+70° (CH_3OH)	*Crotalaria candicans* W. & A.	*18*
36	7-Senecioylreronecine	$C_{13}H_{19}NO_3$ (237)	—	—	*Senecio triangularis* Hook	*25*
37	7-Angelyl-9-sarracinyl-retronecine	$C_{18}H_{25}NO_5$ (335)	139–140 (picrate)	+6.1° (CH_3OH) (picrate)	*Seneccio triangularis* Hook	*25*
38	7-Senecioyl-9-sarracinyl-retronecine	$C_{18}H_{25}NO_5$ (335)	112–113 (tartrate)	+11.0° (CH_3OH) (tartrate)	*Senecio triangularis* Hook	*25*
44	Ligularidine	$C_{21}H_{29}NO_7$ (407)	196	−49.8° (EtOH)	*Ligularia dentata* Hara	*29*
45	Neoligularidine	$C_{21}H_{29}NO_7$ (407)	117–119	−58° ($CHCl_3$)	*Ligularia dentata* Hara	*29*
46	Ligularizine	$C_{21}H_{29}NO_8$ (423)	210–211 (picrate)	−24.5° ($CHCl_3$) (picrate)	*Ligularia dentata* Hara	*29*
47	Ligularinine	$C_{18}H_{27}NO_5$ (337)	103–104	−88° ($CHCl_3$)	*Ligularia dentata* HaRa	*29*
53	Globiferine	$C_{18}H_{27}NO_7$ (369)	126–129	−8.6° ($CHCl_3$)	*Crotalaria globifera* E. Mey	*32*
56	4-Methoxynorsecurinine	$C_{13}H_{15}NO_3$ (233)	—	−47° (CH_3OH)	*Phyllanthus niruri* L. (Euphorbiaceae)	*33*

The only difference between **56** and a known alkaloid, phylanthine, is the presence of a five- instead of a six-membered ring "A" (*33*).

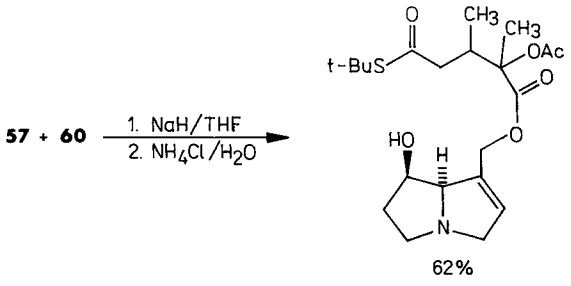
Properties of new PAs are summarized in Table I.

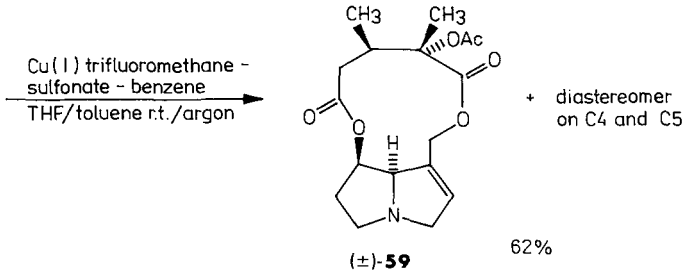
III. Syntheses of Pyrrolizidine Alkaloids

The effort to synthesize pyrrolizidine alkaloids was mainly directed toward the total stereospecific synthesis of PAs.

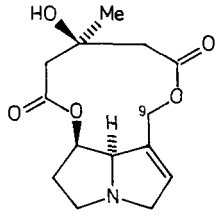


(±)-Retronecine (**57**) and (±)-*trans*-β-methyl-γ-carboxy-γ-valerolactone (**58**) served as reactants in the synthesis of crobarbatine acetate (**59**) (*34*). Acidic synthon **60** was prepared in three steps and treated with **57** (structure on p. 341). The alkaloid **59** was obtained with a 62% yield together with the diastereomer on carbons C-4 and C-5.

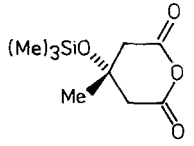




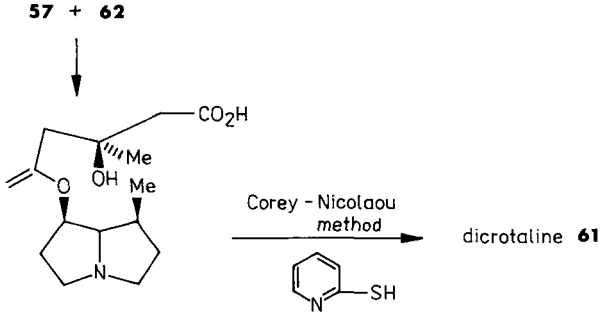
Dicrotaline (**61**) was synthesized in two simple steps from (+)-retronecine **57** and a derivative of dicrotalic acid (**62**) (*35*). The (13*S*) configuration of the synthetic **61** was confirmed by converting it to the optically active (*R*)-mevalone lactone **63** ($[\alpha]_D^{20}$ −20° in EtOH).



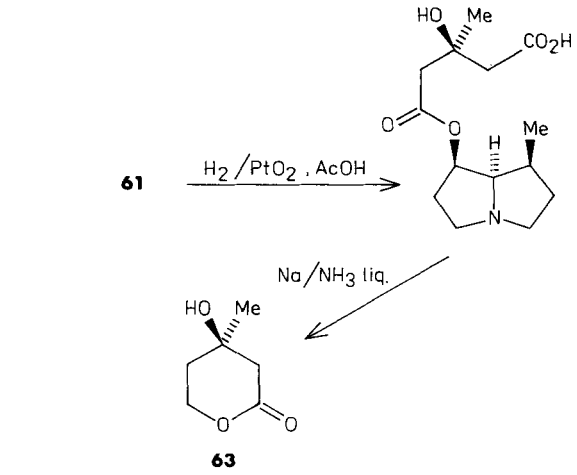
dicrotaline **61**

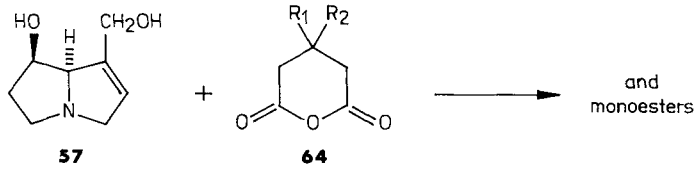


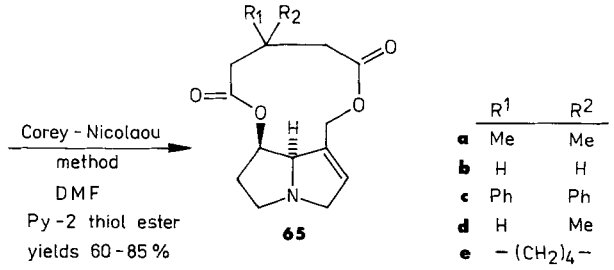
62



Eleven-membered macrocyclic dilactones **65** of retronecine (**57**) were synthesized from the latter and a derivative of glutaric anhydride **64.** The monoester mixture obtained in the first step was lactonized, using the Corey–Nicolaou method to obtain the dilactones **65** (*36*).

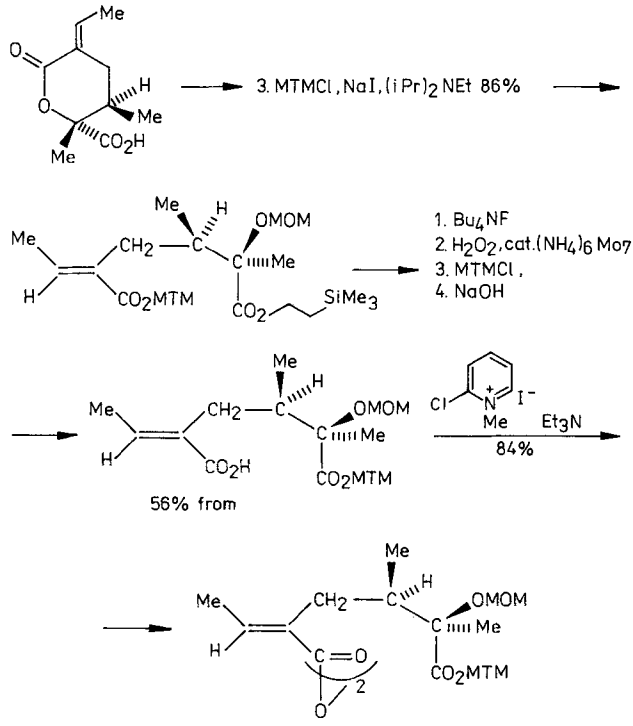


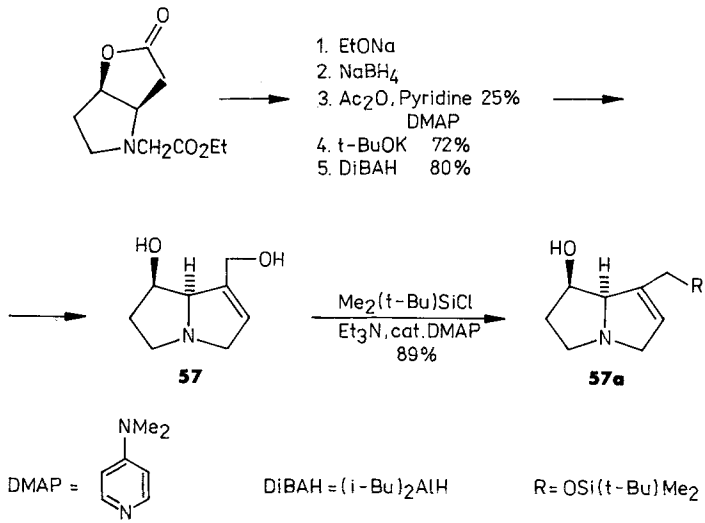


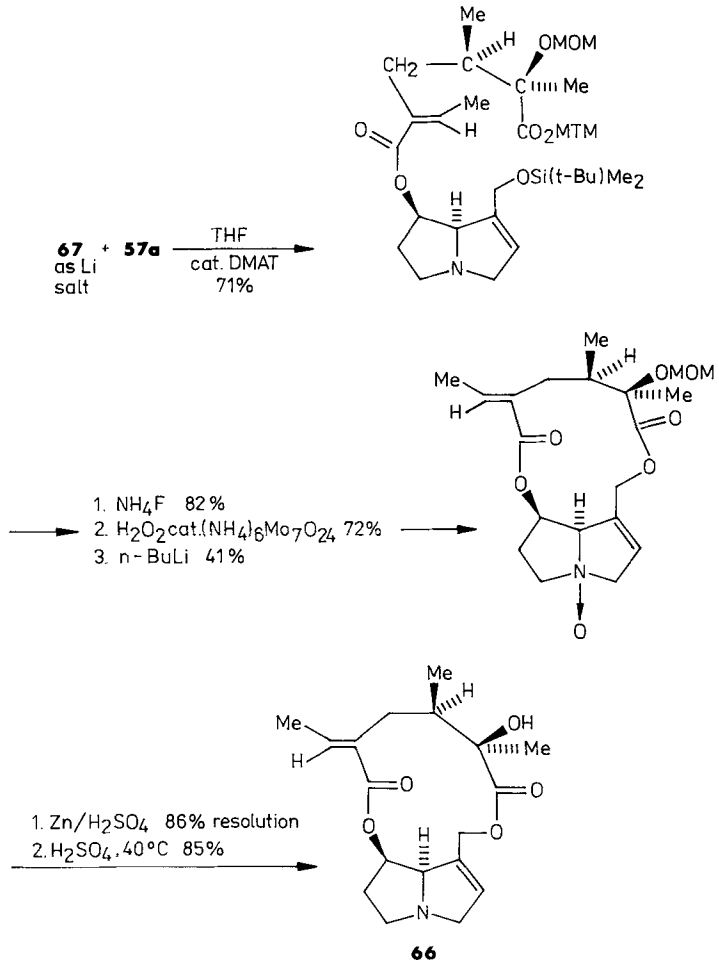


(±)-Intergerrimine (**66**) was synthesized from two synthons: necic acid (**67**), prepared in 11 steps in an overall yield of 24.7%, and retronecine (**57**), prepared by a modified Geissman method in an overall yield of 12.8%. The synthons were then converted in six steps to alkaloid **66** in a yield of 12.6% (*37*).

A semisynthetic PA (**68**) was prepared from retronecine (**57**) and (−)- and (+)-2-hydroxy-2-phenylbutyric acid in presence of CDD (*38*). Compound **68** is

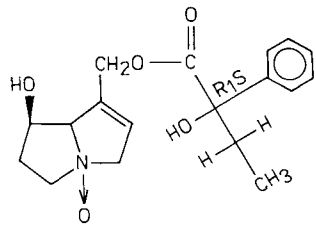

3. MTMCl, NaI, (iPr)2 NEt 86%
1. Bu4NF
2. H2O2, cat.(NH4)6 Mo7O24
3. MTMCl,
4. NaOH
Et3N
84%
56% from
67


1. EtONa
2. NaBH4
3. Ac2O, Pyridine 25%
DMAP
4. t-BuOK 72%
5. DiBAH 80%
Me2(t-Bu)SiCl
Et3N, cat. DMAP
89%
57
57a
DMAP =
DiBAH = (i-Bu)2AlH
R = OSi(t-Bu)Me2

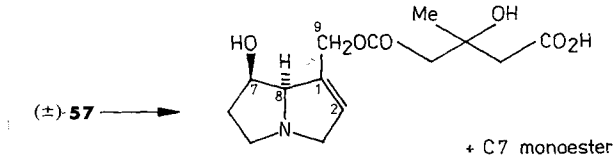


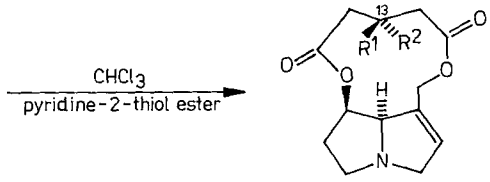
66

reported to have antitumor activity. (+)-Retronecine from natural sources was used in the total synthesis of dicrotaline (**61**) and 13-epidicrotaline (**69**). A mixture of the two alkaloids was obtained in a 32% overall yield from (+)-



68

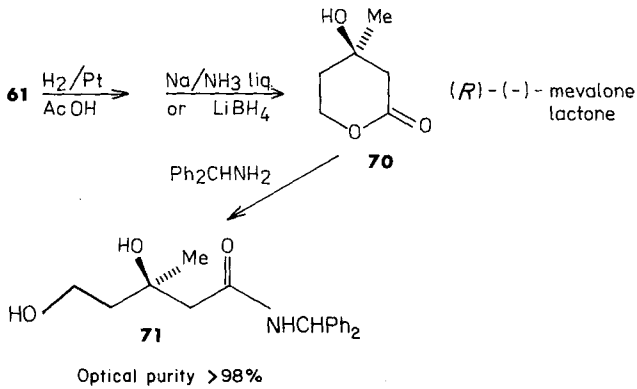




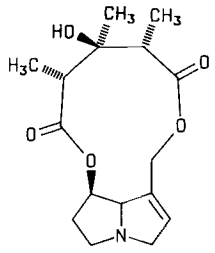
61 R^1=OH, R^2=Me

69 R^1=Me, R^2=OH

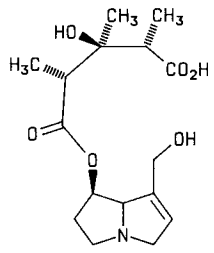
retronecine (**57**) and 3-hydroxy-3-methylglutaric anhydride in a two-step reaction. Compounds **61** and **69** were separated by chromatography (*39*). The absolute configuration at C-13 in **61** and **69** was established by a sequence of selective reactions of each epimer. An optically active (*R*)-(−)-mevalonelactone (**70**), obtained from **61**, was degraded to benzhydrylamide (**71**) of optical purity >98%. The absolute configuration at C-13 in dicrotaline (**61**) was then determined as (*S*). In a similar way, **69** was degraded to (*S*)-(+)-mevalonelactone, thus showing the (*R*) configuration at C-13 in (+)-13-epidictrotaline (**69**).



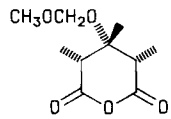
Two 11-membered pyrrolizidine alkaloids, fulvine (**72**) and crispatine (**40**) have been synthesized, using a new route of dilactone ring cyclization (*40*).



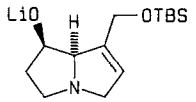
72



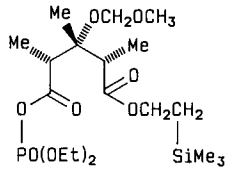
73



74

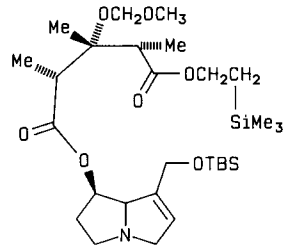


57



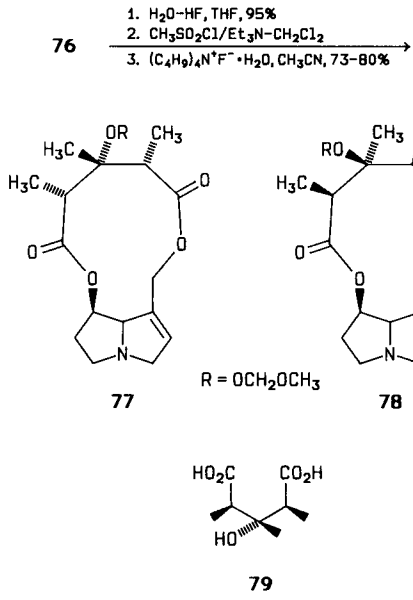
75

+ **57** ⟶



76

Carboxy and hydroxy groups in the key intermediate **73** were protected with trimethylsilylethane and mesyl groups, respectively, whereupon **73** was cyclized in three steps. The synthesis utilized two synthons: a protected crispatic anhydride (**74**) and monosilylated lithium alkoxide of synthetic (±)-retronecine (**57**). Crispatic anhydride (**74**) was first cleaved with $(CH_3)_2AlOCH_2CH_2Si(Me)_3$, resulting in a glutarate monoester, which was then treated so as to form a mixed phosphoric anhydride (**75**). The latter was coupled with **57** in the presence of DMAP. The product **76** was converted in three steps to a mixture of diastereomeric dilactones **77** and **78.** Reactions of **77** and **78** with $BF_3 \cdot Et_2O$/EtSH carried out under similar conditions led to **40** and to a crispatine diastereomer (isocrispatine), respectively. In a similar sequence *dl*-fulvine (**72**) and its di-



astereomer (±)-isofulvine were obtained from synthetic fulvinic acid (**79**) in 81% overall yield..

A total synthesis of an unusual PA containing sulfur, cassipourine (**80**), has been reported (*41*). A more detailed account of this synthesis is presented in the chapter on sulfur-containing alkaloids (*42*).

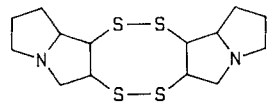
IV. Syntheses of Necine Bases

The syntheses described in this paragraph are arranged according to the structure of the starting compounds. An example of a synthetic approach that involves enzymatic reactions is discussed separately.

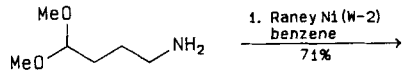
A. Syntheses from Open-Chain Precursors

4-Aminobutyral dimethyl acetal (**81**) was used in a simple synthesis of (±)- and (+)-trachelanthamidine (**82**). The dimeric product **83** was cyclized and reduced to racemic **82.** After treatment with *d*-camphor 10-sulfonate in aqueous solution at 100°C and subsequent reduction with $NaBH_4$, **83** was transformed to the (+)-epimer of **82** ($[\alpha]_D$ +5.1° in EtOH) with an optical purity of 33% (*43*).

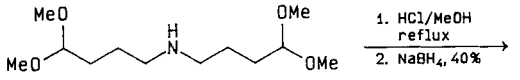
The synthesis of (+)-heliotridine (**84**) was reported (*44*) to start with (*S*)-malic acid (**85**). The key intermediate **86** was prepared from **85** by Mitsunobu coupling. After cyclization, **86** was transformed in four steps to the optically active necine base **84** in an overall yield of 8.1%.



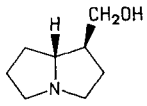
80



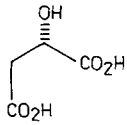
81



83

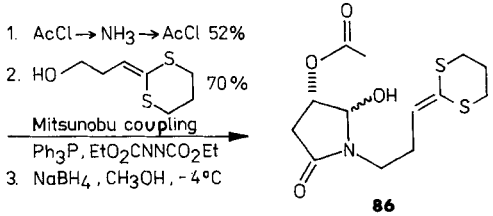


82
(±)-Trachelanthamidine

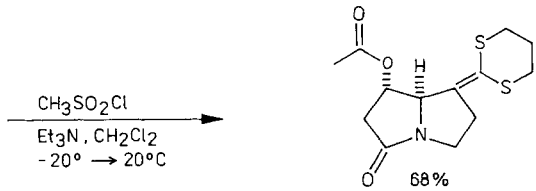


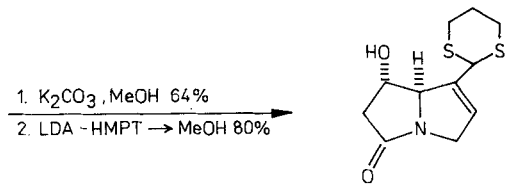
malic acid

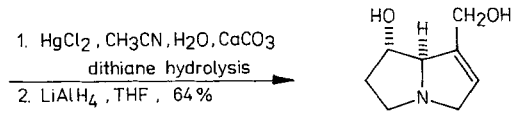
85



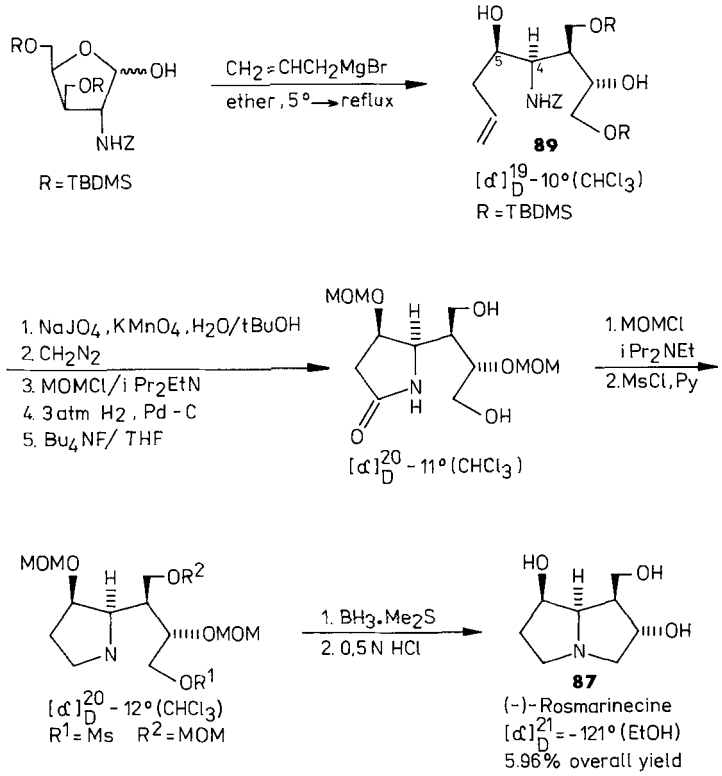
86







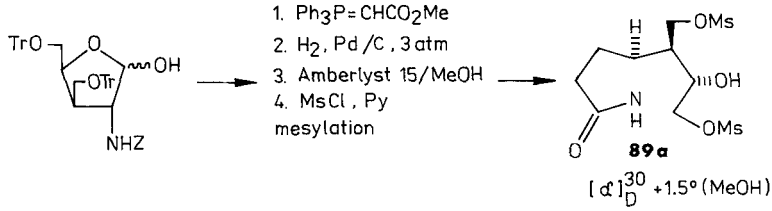
84
(+)-Heliotridine $[\alpha]_D^{20}$ +30.3°

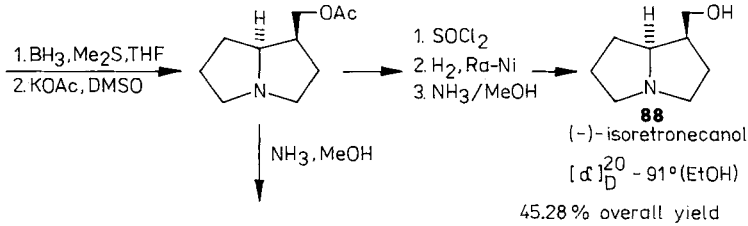


The open-chain precursor **89** for the synthesis of the optically active (−)-rosmarinecine (**87**) and (−)-isoretronecanol (**88**) was prepared from D-glucosamine. The necine base **87** was synthesized in 10 steps in an overall yield of 5.96%, $[\alpha]_D$ −121° (in EtOH).

(−)-Isoretronecanol (**88**) was synthesized in a similar way in five steps in an overall yield of 45.3%. This route might be suitable for the synthesis of optically active (−)-7-deoxyrosmarinecine (*45*).

The "crisscross annulation" was applied to compound **90** as the main step in the synthesis of (±)-dihydrodeoxyotonecine (**91**). The secopyrrolizidine system



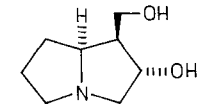


88

(-)-isoretronecanol

$[\alpha]_D^{20}$ - 91° (EtOH)

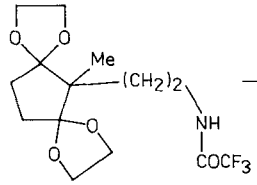
45.28% overall yield



(-)-7-deoxyrosmarinecine

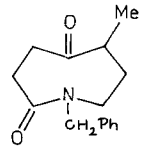
$[\alpha]_D^{25}$ - 115° (EtOH)

51.41% overall yield



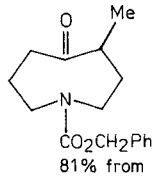
90

1. $PhCH_2Br$
2. HCl/AcOH 89%
3. K_2CO_3/H_2O/MeOH, 65%



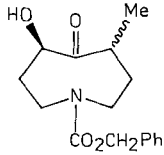
92

1. $CH(OMe)_3$/MeOH
cat. H_2SO_4
2. $LiAlH_4$/THF/D
3. $ClCO_2CH_2Ph/CHCl_3$

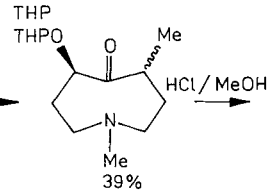


81% from

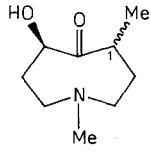
1. Br_2/MeOH
2. Et_4NOAc/Me_2CO, 83%
3. NH_3/MeOH, 77%



1. dihydropyran
CSA/CH_2Cl_2
2. $LiAlH_4$
3. PCC/CH_2Cl_2/NaOAc



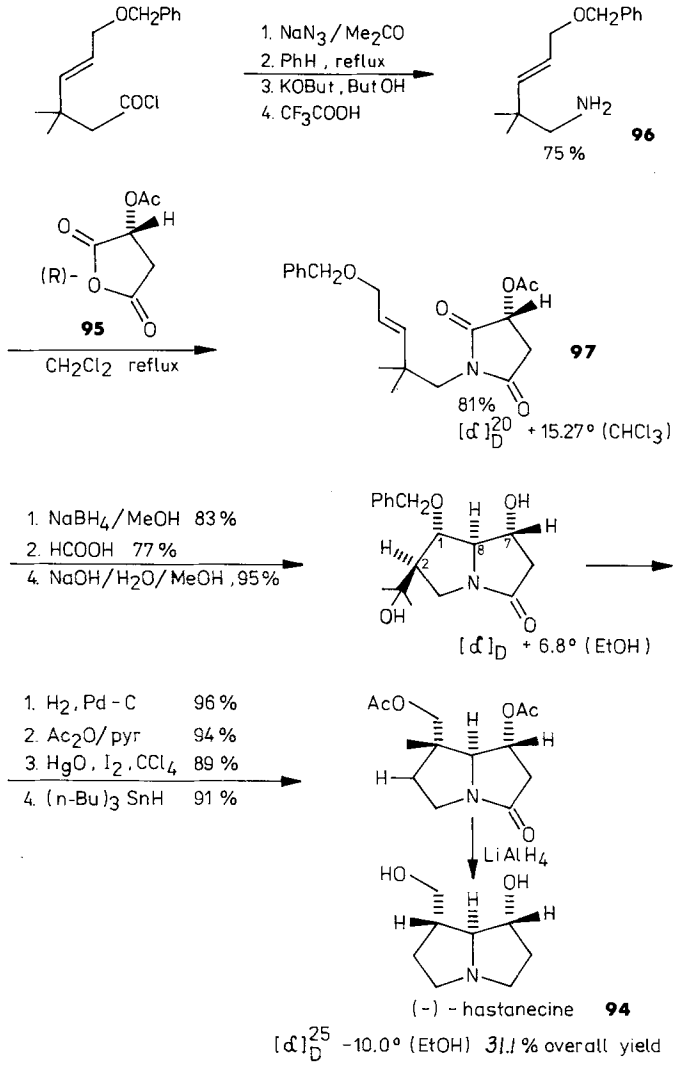
39%



91

92 thus obtained was transformed in 10 steps to the alkaloid **91** in an 11.6% overall yield (*46a*). The method was used to obtain (±)-heliotridane (**93**).

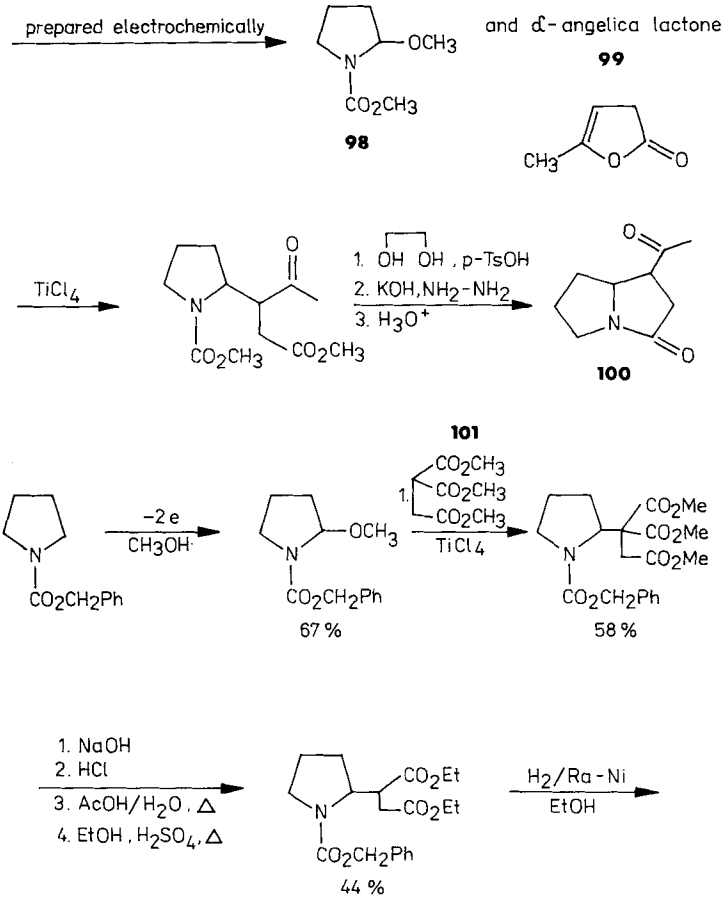
An enantioselective synthesis of (−)-hastanecine (**94**) was based on the optically active (*R*)-acetoxysuccinic anhydride (**95**). The latter was condensed with amine **96** resulting in a derivative of succinic acid imide (**97**). Its cyclization and transformations of functional groups were completed in eight steps, resulting in alkaloid **94** (31.1% overall yield ($[\alpha]_D^{25}$ −10.0°, EtOH).

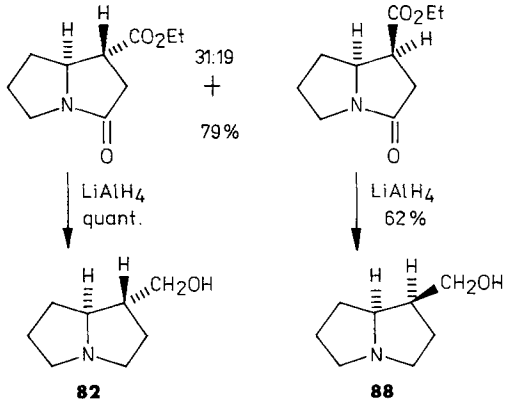


A similar reaction sequence led to the synthesis of (+)-hastanecine from (*S*)-acetoxysuccinic anhydride (*47*).

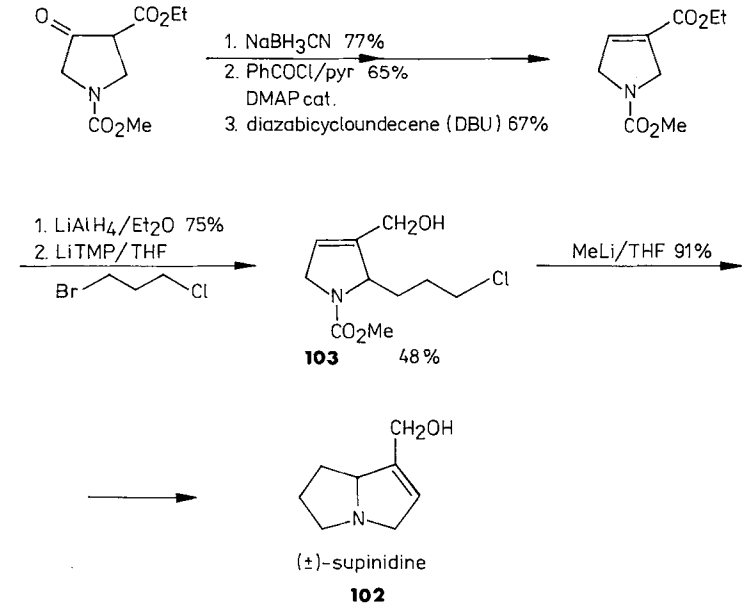
B. Syntheses from Pyrrole Derivatives and Simple Monocyclic Precursors

Syntheses of (±)-trachelanthamidine (**82**) and (±)-isoretronecanol (**88**) were based on the well-known reaction of tetrahydropyrrole derivative **98** with angelica lactone **99.** The reaction, carried out in the presence of $TiCl_4$, was followed by cyclization to yield pyrrolizidine derivative (**100**). In a similar way alkaloids **82** and **88** were obtained in 13.5 and 8.3% yields, respectively, from tricarboxylic acid **101** (*48*).

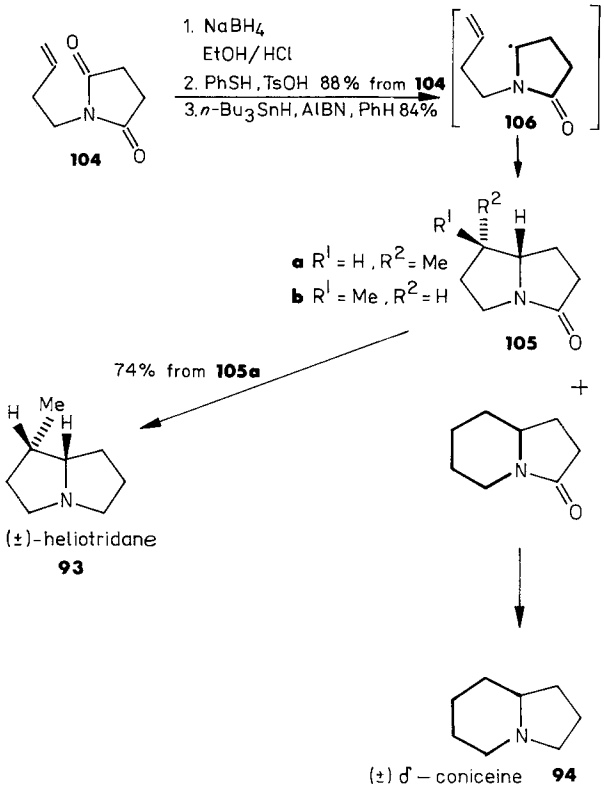


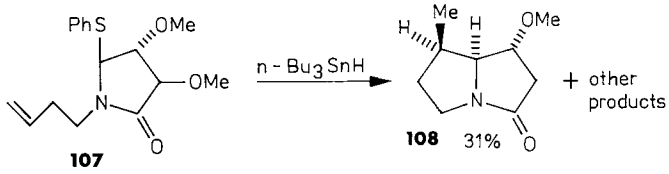


The main step in the synthesis of (±)-supinidine (**102**) involved a regioselective N-1—C-2 vicinal annulation of **103** prepared with 1,3-chlorobromopropane as shown in the scheme. The overall yield was 43.7% (*49*).



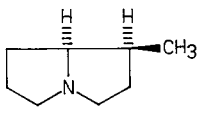
A new way of preparing necine bases (*50*) included the cyclization of the α-acylamino radical as the key step. Conversion of **104** to **105** was suggested to proceed via the intermediate α-acylamino radical **106.** Syntheses of (±)-heliotridane (**93**) and (±)-δ-coniceine (**94**) exemplify the new procedure.



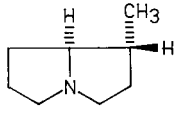


In general, any lactam derivative of the **107** type can be cyclized to a pyrrolizidine derivative (**108**) with stereochemistry at C-1, C-7, and C-8 corresponding to that of some more complex PAs. Thus the method described above may provide an enantioselective entry to this class of alkaloids.

Pyrrolidone **109** was used for a convenient synthesis of 1-methylpyrrolizidines: (±)-heliotridane (**93**) and (±)-pseudoheliotridane (**110**). This procedure provides better yields (61–65%) and requires fewer steps than do other synthetic methods (*51*).

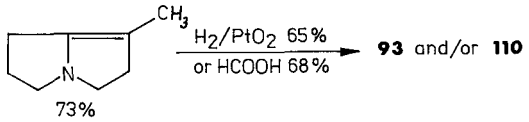


93

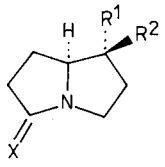


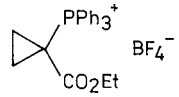
110

109



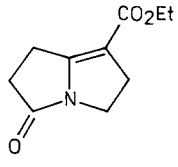
Another new approach (*52*) to the total synthesis of (±)-isoretronecanol (**88**) involves the reaction of sodium succinimide with tetrafluoroborate complex **111,** which results (in one step) in the pyrrolizidine derivative **112.** High stereoselectivity was observed in the catalytic reduction of **112,** which led to **88d** (2.5%)



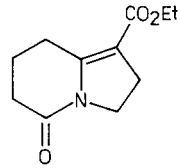


111

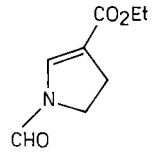
88 **a** $R^1 = H$, $R^2 = CH_2OH$, $X = H_2$
b $R^1 = CH_2OH$, $R^2 = H$, $X = H_2$
c $R^1 = H$, $R^2 = CO_2Et$, $X = O$
d $R^1 = CO_2Et$, $R^2 = H$, $X = O$



112

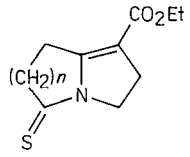


113

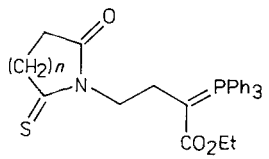


114

and **88c** (97.5%). Compound **88c** was reduced ($LiAlH_4$) to (±)-isoretronecanol (**88a**) in an 83.2% yield. Compound **88c** was epimerized to **88d;** this might provide a synthetic route to (±)-trachelanyhamidine (**82**). The synthetic pathway described above may also provide a route to prepare indolizidine **113** and pyrrolizidine **114** by treating **111** with anions of glutarimide and diformylimide, respectively. This approach to a synthesis of annelated bicycles from monothioimides was found to be unsatisfactory. Apart from the expected products, **112** and **113,** derivatives **115a** and **115b,** as well as **116a** and **116b**, were found in similar proportions in the reaction mixture.

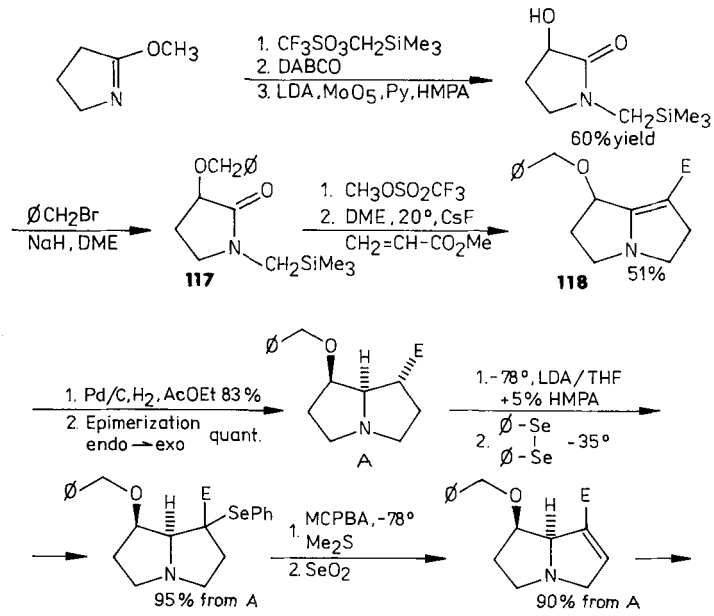


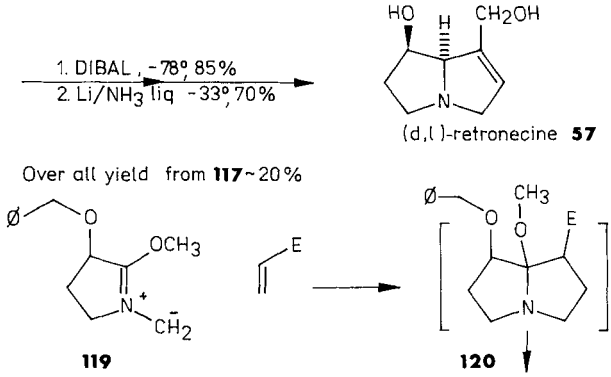
115 **a** $n = 1$
b $n = 2$



116 **a** $n = 1$
b $n = 2$

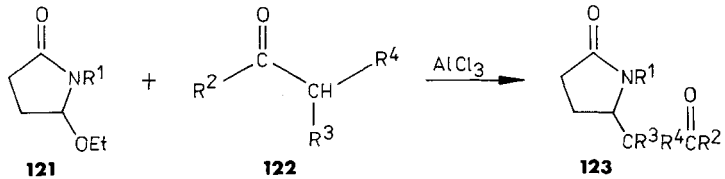
Cycloaddition to imidate methylide (nonstabilized) nitrogen ylide was used in the stereospecific synthesis of (±)-retronecine (**57**) (*53*). The key step in this procedure is the conversion of **117** to **118,** which proceeds through the formation of **119,** followed by a cycloaddition. The resulting intermediate **120** is then





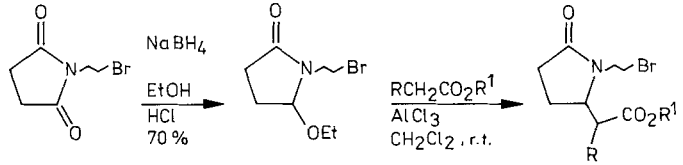
converted under the extant conditions to **118.** The overall yield of **57** from **117** was 20%.

Amidoalkylation with *N*-2-bromoethylsuccinimide was successfully used in the synthesis of isoretronecanol (**88**) and trachelanthamidine (**82**) (*54*). The first step, the reaction between **121** and **122,** resulted in the pyrrolizidine derivative **123.** The substituents in **121** and **122** were: R^1 = H or CH_2-CH_2Br; R^2 = alkoxy; R^3 and R^4 = H, CO_2R, NO_2, or CO_2CH_2Ph. The yields ranged between 51 and 70%. The synthesis of **88** and **82** is shown in the scheme. Both intermediates **124** and **125** result on cyclization in mixtures of **126** and **127.** Separated compounds were reduced by $LiAlH_4$ to (±)-isoretronecanol (**88**) and trachelanthamidine (**82**), respectively. The overall yield of the epimer mixture was 13.4%, and those of individual epimers were 1.35% (**88**) and 5.2% (*82*).



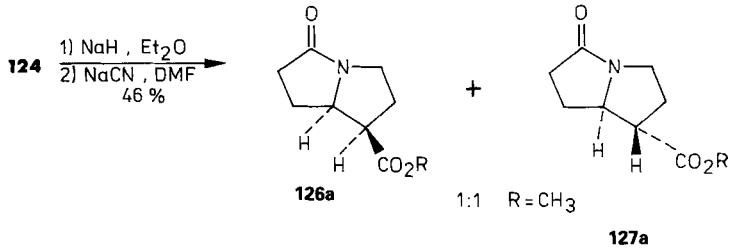
(±)-Supinidine (**102**) was synthesized from γ-butyrolactone (*55*). Here, the main step was a cationic cyclization to the pyrrolizidine system. A ketene thioacetal (**129**) (obtained from the **128** derivative) is essential in the five-membered ring formation. The overall yield of **102** from γ-butyrolactone was 19% and from **128,** 39%.

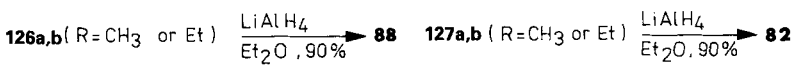
The rearrangement–cyclization of an *N*-acyliminium ion was used in the synthesis of trachelanthamidine (**82**) and supinidine (**102**) (*56*). It was based on the conversion of carbinolamine **130** to pyrrolizidinone derivative **131.** The key compound was the pyrrolizidine derivative **132,** prepared in six steps from aldehyde **133.** The last step in this preparation was the cyclization of open-chain amide **134** in formic acid. The hydroxypropyl side chain in **132** was removed in

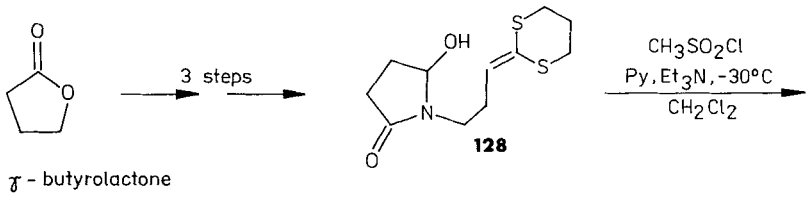


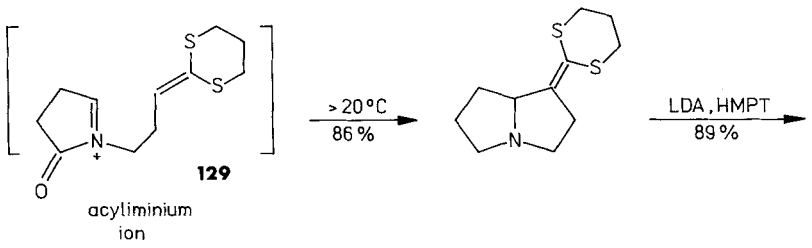
55 %, **124** R = CO_2CH_3 , R^1 = CH_3

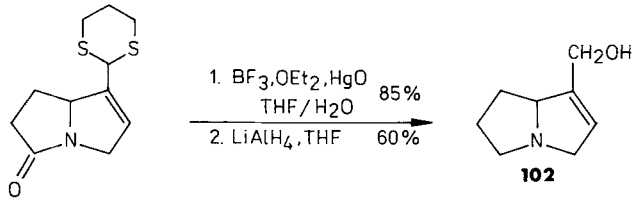
54 %, **125** R = $COCH_3$, R^1 = Et

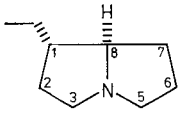






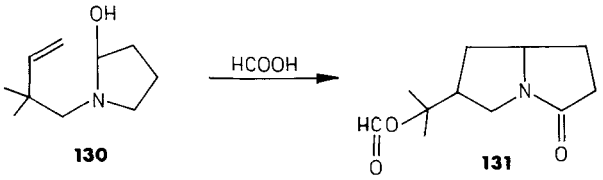




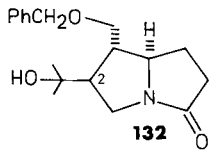


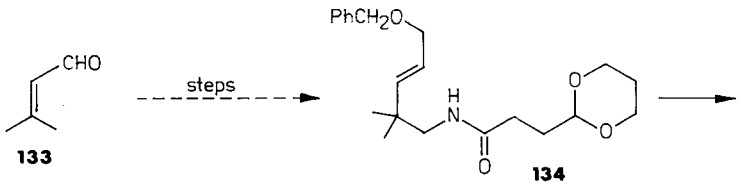
traechetanthamidine

(±)-**82**



three steps, resulting in compound **133** from which trachelanthamidine (**82**) and supinidine (**102**) were obtained in 17.3 and 15.4%, yields, respectively, by two different routes.

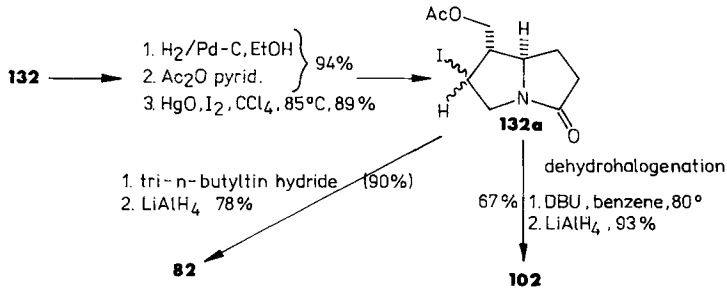




1. HCOOH, rt. Zn → **132**

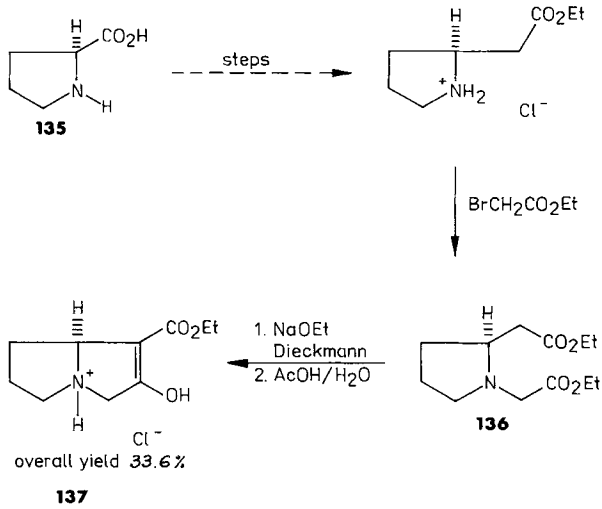
2. NaOH/MeOH/H_2O

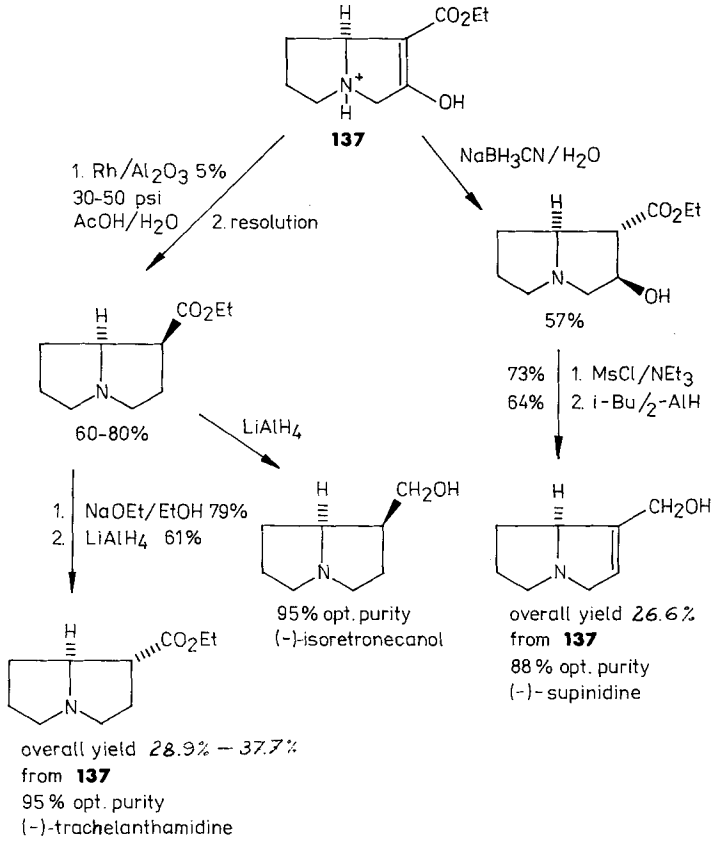
overall yield 29.6% from **133**

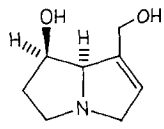


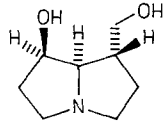
The optical purity of synthetic (−)-isoretronecanol (**88**), (−)-trachelanthamidine (**82**) and (−)-supinidine (**102**) was >80% (*57*). The key reaction was the preparation of the optically active necine base. This required a 10-step transformation of (*S*)-proline (**135**) to (*S*)-*N*,2-di(carboethoxymethyl)pyrrolidine (**136**). The Dieckmann condensation led then to (*S*)-1-carboethoxypyrrolizidin-2-one (**137**) in an overall yield of 33.6%. Compound **137** was then converted by three different pathways (cf. scheme) to the necine bases in the following overall yields: (−)-trachelanthamidine (optical purity 95%), 37.7% from **137** and 11.33% from **135;** (−)-isoretronecanol (optical purity 95%), 60% from **137** and 20.2% from **135;** (−)-supinidine (optical purity 88%), 26.6% from **137** and 8.9% from **135.**

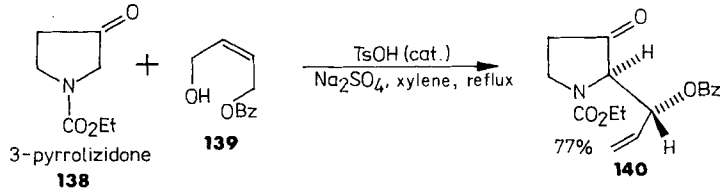
This approach demonstrates the feasibility of the chiral synthesis of necine bases from (*S*)-proline.

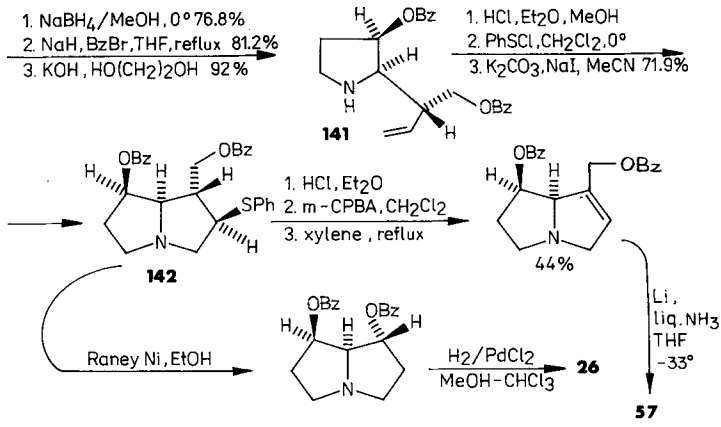



137
1. Rh/Al2O3 5%
30-50 psi
AcOH/H2O
2. resolution
NaBH3CN/H2O
57%
73%
64%
1. MsCl/NEt3
2. i-Bu/2-AlH
60-80%
LiAlH4
1. NaOEt/EtOH 79%
2. LiAlH4 61%
95% opt. purity
(-)-isoretronecanol
overall yield 26.6%
from 137
88% opt. purity
(-)-supinidine
overall yield 28.9% – 37.7%
from 137
95% opt. purity
(-)-trachelanthamidine


57


26

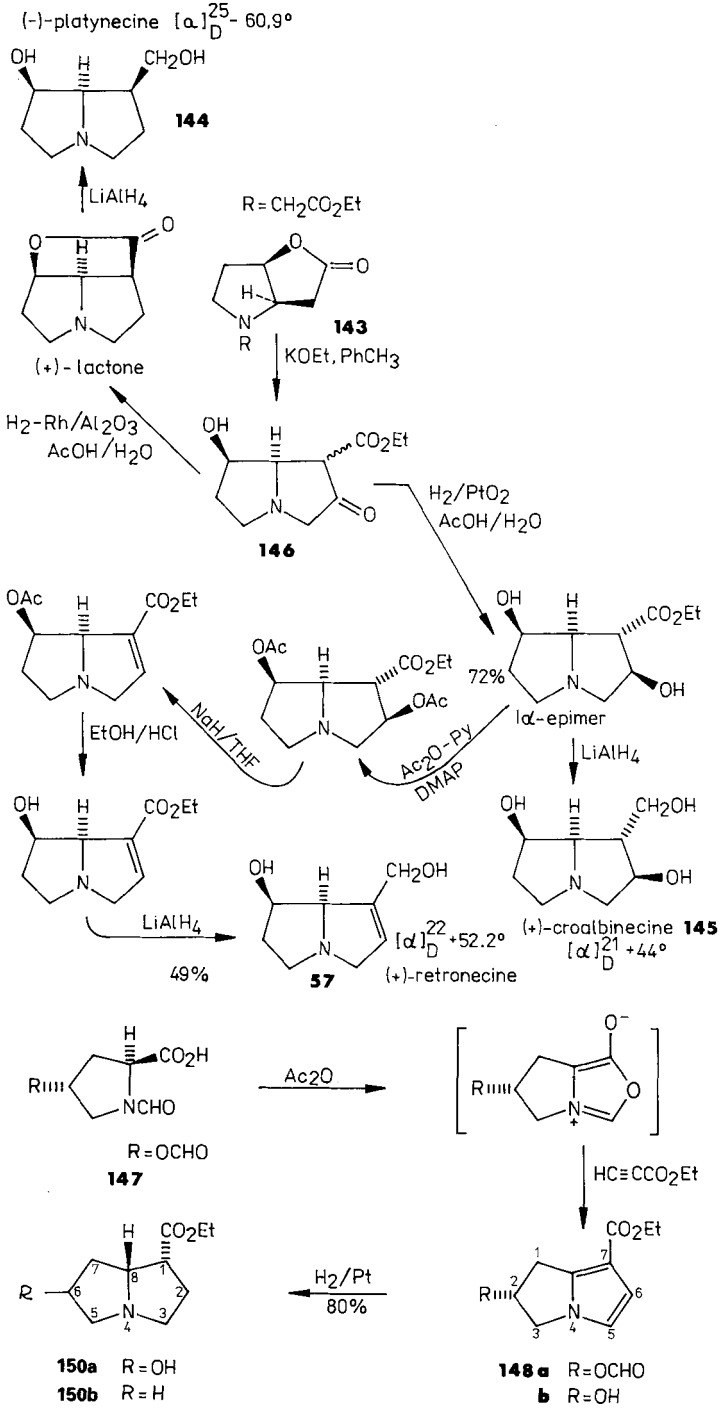

3-pyrrolizidone
138
139
TsOH (cat.)
Na2SO4, xylene, reflux
77%
140

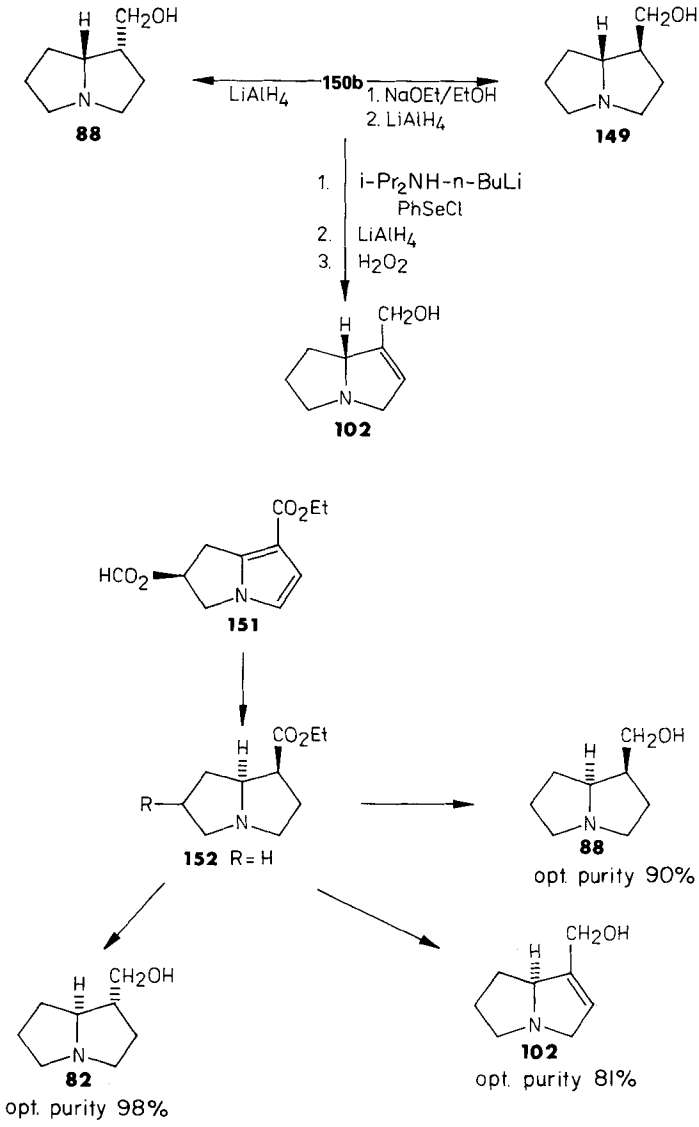


A new synthetic approach to the stereoselective synthesis of (±)-retronecine (**57**) and (±)-turneforcidine (**26**) was introduced (*58*) by combining the regioselective [3,3] sigmatropic rearrangement with a sulfenocycloamination. Treatment of 3-pyrrolizidine **138** with allylic compound **139** resulted in the formation of a chiral center on carbon C-3 in the reaction product **140.** The olefinic amine **141** was treated with benzenesulfenyl chloride, and a base-induced ring closure resulted in a pyrrolizidine derivative (**142**) having the required stereochemistry for both final products. Compound **142** was then transformed to necine base **57** or **26,** depending on the route used. The overall yields of (±)-retronecine and (±)-turneforcidine were 13.8 and 28.8%, respectively.

Enantioselective syntheses of (+)-retronecine (**57**), (−)-platynecine (**144**), and (±)-croalbinecine (**145**), were carried out, using (+)-6-aza-2-oxabicyclo[3.3.0]octan-2-one (**143**) (Geissman–Waiss lactone). Synthon **143** was rearranged (in one base-induced step) to pyrrolizidine derivative **146.** The latter was converted in three reasonably simple ways to the necine bases mentioned above. The specific rotations of **57, 144,** and **145** were $[\alpha]_D^{22}$ +52.2, $[\alpha]_D^{25}$ −60.9, and $[\alpha]_D^{21}$ +44°, respectively. The overall yield of retronecine (**57**) was best (49%) when prepared from **143** (*59*).

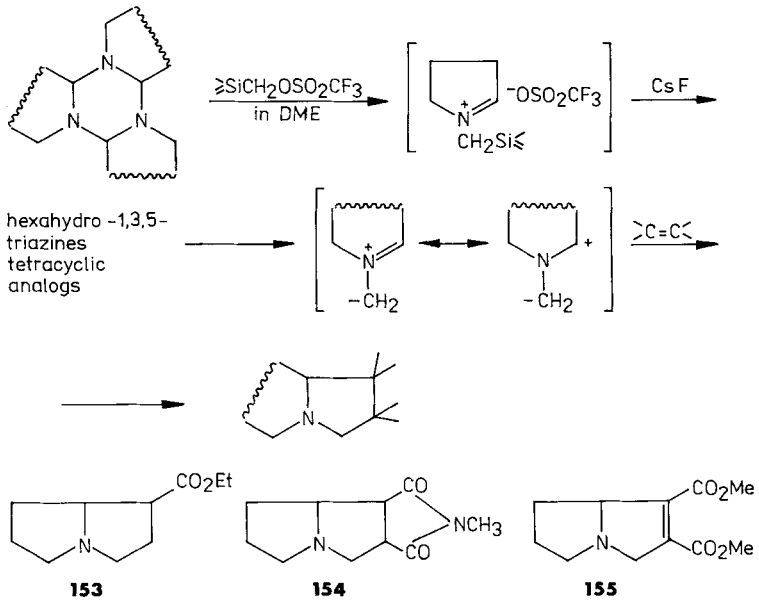
Six optically active necine bases were synthesized (*60*) by applying the regiospecific 1,3-dipolar cycloaddition of acetylenecarboxylic acid ester to the *N,O*-diformyl derivative **147.** The resulting pyrrolizidine derivatives **148a** and **148b** were the key compounds in the further synthesis. Their catalytic hydrogenation was highly stereospecific. The absolute configurations at C-1 and C-8 of **150a** were the same as those in (+)-isoretronecanol (**88**), (+)-laburnine (**149**), and (+)-supinidine (**102**), thus allowing the transformation of **150** to the necine bases discussed above. The epimerization of **148b** to **151,** followed by a catalytic

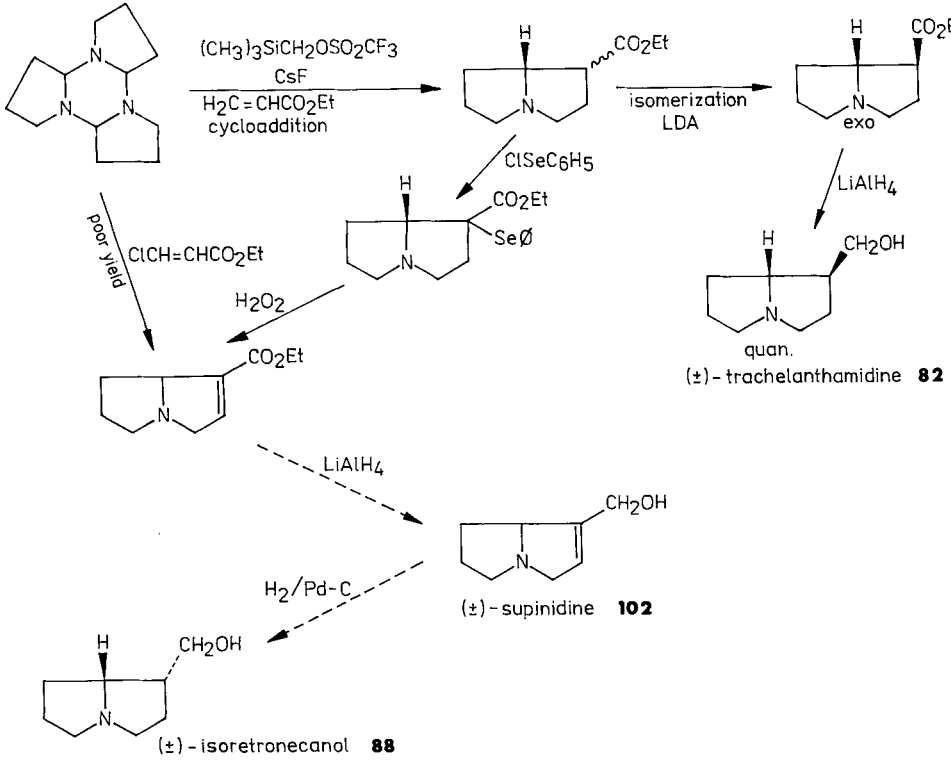

(-)-platynecine $[\alpha]_D^{25}$ - 60,9°
144
LiAlH4
(+)-lactone
R = CH2CO2Et
143
KOEt, PhCH3
H2-Rh/Al2O3
AcOH/H2O
146
H2/PtO2
AcOH/H2O
72%
1α-epimer
EtOH/HCl
NaH/THF
Ac2O-Py
DMAP
LiAlH4
LiAlH4
49%
57
$[\alpha]_D^{22}$ +52.2°
(+)-retronecine
(+)-croalbinecine 145
$[\alpha]_D^{21}$ +44°
Ac2O
R = OCHO
147
HC≡CCO2Et
H2/Pt
80%
150a R = OH
150b R = H
148a R = OCHO
b R = OH



hydrogenation, resulted in **152.** This opened the way to (−)-isoretronecanol (**88**), (−)-trachelanthamidine (**82**), and (−)-supinidine (**102**), which were obtained with optical purities of 90, 98, and 81%, respectively.

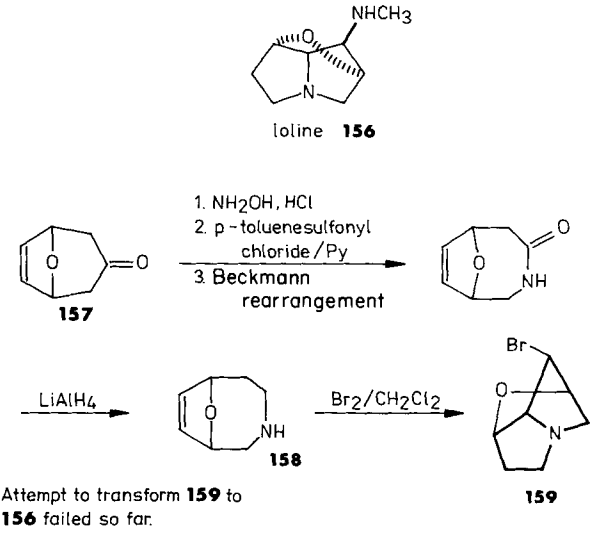
Another example of 1,3-dipolar cycloaddition is the synthesis of three necine bases (*61*), achieved by treating tetracyclic hexahydro-1,3,5-triazines with olefinic or acetylenic compounds in the presence of trimethylsilylmethyl tri-


≥SiCH2OSO2CF3
in DME
-OSO2CF3
CH2Si≤
CsF
hexahydro -1,3,5-
triazines
tetracyclic
analogs
-CH2
-CH2
≥C=C≤
CO2Et
CO
NCH3
CO
CO2Me
CO2Me
153
154
155


(CH3)3SiCH2OSO2CF3
CsF
H2C=CHCO2Et
cycloaddition
CO2Et
isomerization
LDA
exo
ClSeC6H5
LiAlH4
poor yield
ClCH=CHCO2Et
CO2Et
SeØ
CH2OH
H2O2
CO2Et
quan.
(±)-trachelanthamidine 82
LiAlH4
CH2OH
H2/Pd-C
(±)-supinidine 102
CH2OH
(±)-isoretronecanol 88

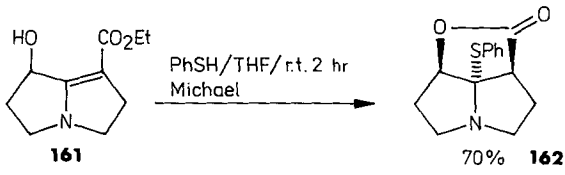
fluoromethanesulfonate and cesium fluoride. The reaction sequence is shown in the scheme. Compounds **153, 154,** and **155** were prepared, using acrylic acid ester, *N*-methylmaleic acid imide, and acetylenedicarboxylic acid, respectively. The route shown led also to (±)-trachelanthamidine (**55**), (±)-supinidine (**82**), and (±)-isoretronecanol (**88**).

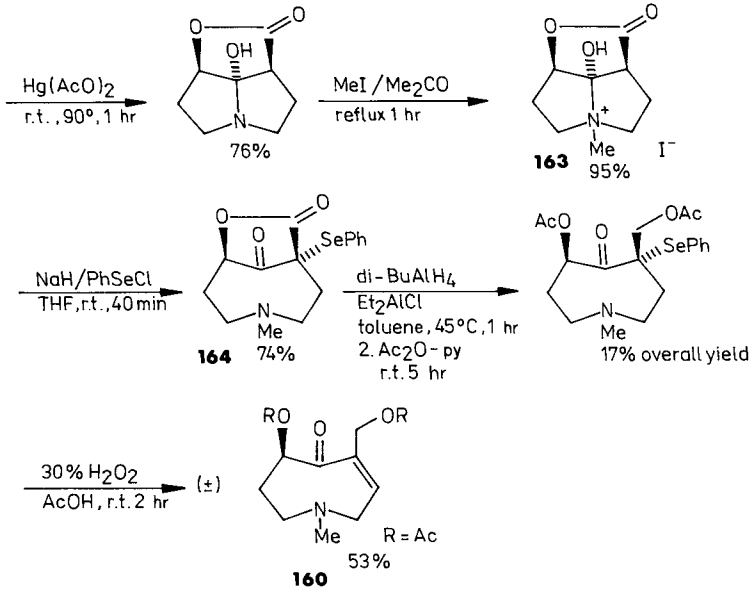
The synthesis of loline (**156**), an alkaloid with a unique oxygen bridge in the pyrrolizidine system, was attempted by a transannular cyclization of an amine. This resulted in the carbon skeleton of loline present in **159.** The key intermediate **158** was prepared in four simple steps from the ketone **157** derived from furan (*62*).

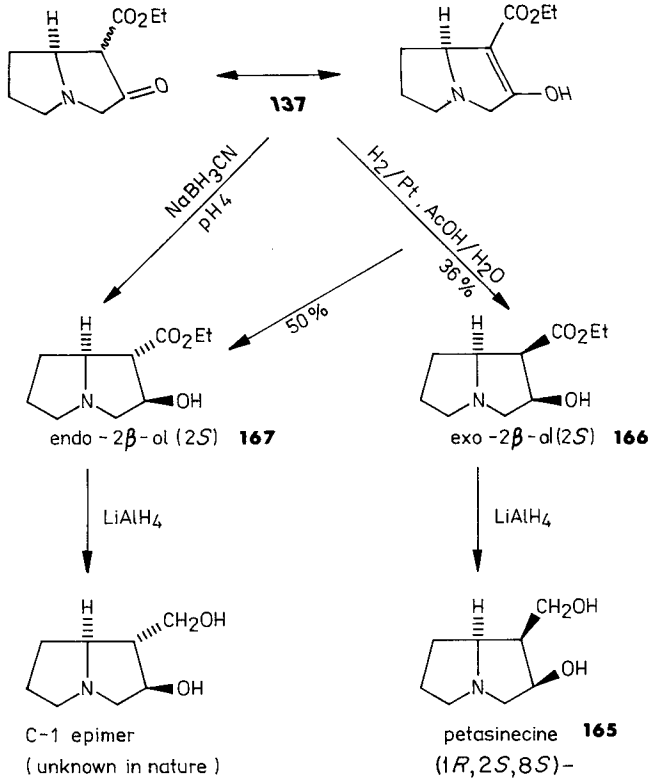


C. Syntheses from Pyrrolizidine Derivatives

(±)-Otonecine (**160**) was synthesized in seven steps in an overall yield of 9% (*63*). 1,8-Dihydropyrrolizidine derivative **161** was subjected to Michael condensation in which three chiral centers were formed, providing **162**. The secopyr-



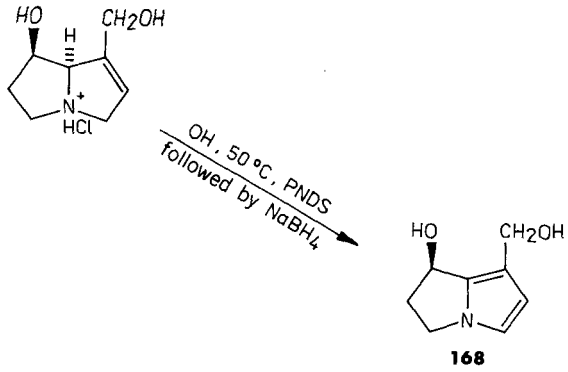

Hg(AcO)2
r.t., 90°, 1 hr
76%
MeI / Me2CO
reflux 1 hr
163
95%
NaH/PhSeCl
THF, r.t., 40 min
164
74%
di-BuAlH4
Et2AlCl
toluene, 45°C, 1 hr
2. Ac2O - py
r.t. 5 hr
17% overall yield
30% H2O2
AcOH, r.t. 2 hr
(±)
R = Ac
53%
160


137
NaBH3CN
pH4
H2/Pt, AcOH/H2O
36%
50%
endo - 2β - ol (2S) 167
exo - 2β - ol (2S) 166
LiAlH4
LiAlH4
C-1 epimer
(unknown in nature)
petasinecine 165
(1R, 2S, 8S) -

rolizidine system (**164**) was prepared from methiodide (**163**) and converted in three steps (cf. scheme) to (±)-otonecine (**160**).

Compound **137,** previously used in the synthesis of necine bases (*57*), was used for a stereoselective synthesis of petasinecine (1*R*,2*S*,8*S*) (**165**) and its C-1 epimer (*64*). The catalytic reduction of (8*S*)-ethoxycarbonylpyrrolizidin-2-one (**137**) resulted in a separable mixture of epimers **166** and **167.** Both epimers were easily reduced with $LiAlH_4$ to the corresponding diols, which included petasinecine (**165**).

The preparation of dehydroretronecine (**168**), a compound found in mammalian liver and possessing cytotoxic and carcinogenic properties was carried out in one step (*65*) from retronecine hydrochloride (**57**) · HCl and potassium nitrosodisulfonate [Fremy's salt, $(KSO_3)_2NO$].



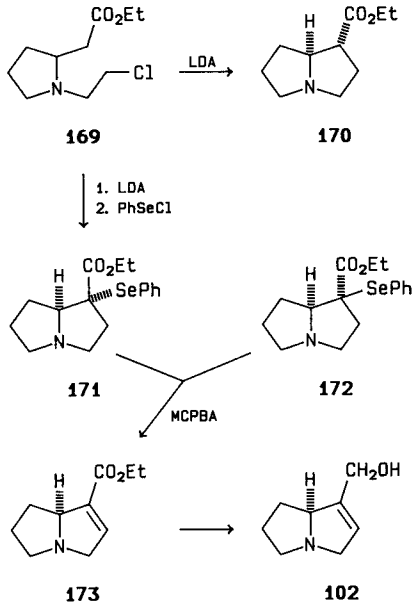
168

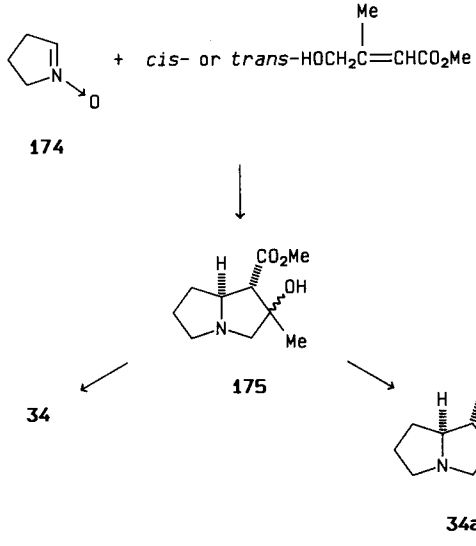
Pyrrolizidine derivative **169** was used for a novel and efficient synthesis of (±)-trachelanthamidine (**82**) and (±)-supinidine (**102**) (*66a,66b*). Alkylation of compound **169** with diisopropylamide (LDA) resulted in 1-carboethoxypyrrolizidine (**170**), which was converted to (±)-trachelanthimidine by a procedure described by Borch (*66a*). However, when compound **169** was treated with LDA and subsequently treated with phenylselenyl chloride, two diastereoisomeric selenides (**171** and **172**) were formed. Each of them, upon oxidative elimination, yielded ester **173,** which was converted to (±)-supinidine by a method previously used by Robins (*66b*).

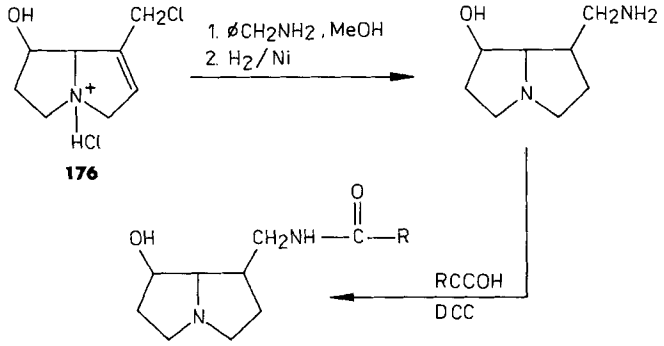
(±)-Tussilagine (**34**) and (±)-isotussilagine 1-oxide were synthesized from 1-pyrroline 1-oxide (**174**) and *trans*- or *cis*-$HOCH_2CMe{=}CHCO_2Me$ 2-butene ester. This cyclization resulted in two isomeric compounds, respectively. Both, on methylation and hydrolysis, resulted in **34** or **34a,** respectively.

A number of amides have been prepared from 9-chlororetronecine (**176**) (*68*).

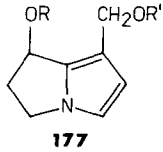
Pyrrolizidine alkaloids were found to be converted to their dehydro derivatives


CO2Et
Cl
LDA
H
CO2Et
169
170
1. LDA
2. PhSeCl
H
CO2Et
SePh
171
172
MCPBA
H
CO2Et
CH2OH
173
102


Me
+ cis- or trans-HOCH2C=CHCO2Me
O
174
H
CO2Me
OH
Me
175
34
H
CO2Me
OH
Me
34a

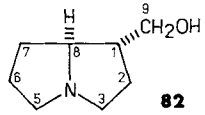


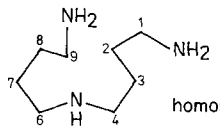
in human and animal liver. This stimulated a study of the alkylation kinetics of compounds similar to **177.** The reaction kinetics was described in terms of first-order and biexponential expressions (*69*).

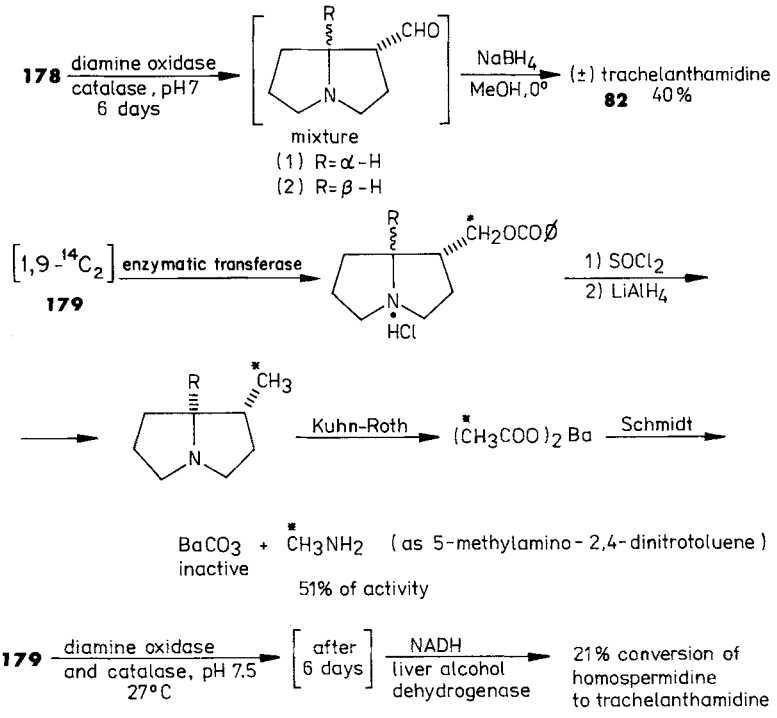


D. Syntheses Involving Enzymes

Biogenetic studies prompted a synthesis of (±)-trachelanthamidine (**82**), using enzymes under physiological conditions (*70*). Homospermidine (**178**) (precursor in the biosynthesis of necine bases) was incubated in a phosphate buffer (pH 7) at 27°C with diamine oxidase and catalase of pea seedlings. After reduction with sodium borohydride, alkaloid **82** was obtained in a 40% yield. Homospermidine-*1,9*-$^{14}C_2$ (**179**) was incorporated intact into trachelanthamidine (**82**), which retained 51% of the total activity at C-9. The possibility of one-pot conversion of **179** to **82** has also been demonstrated, and trachelanthamidine was isolated in a 40% yield together with 5% of isoretronecanol (**88**).

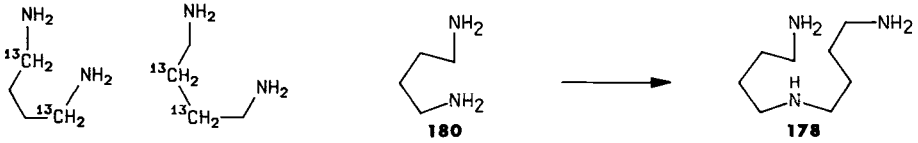


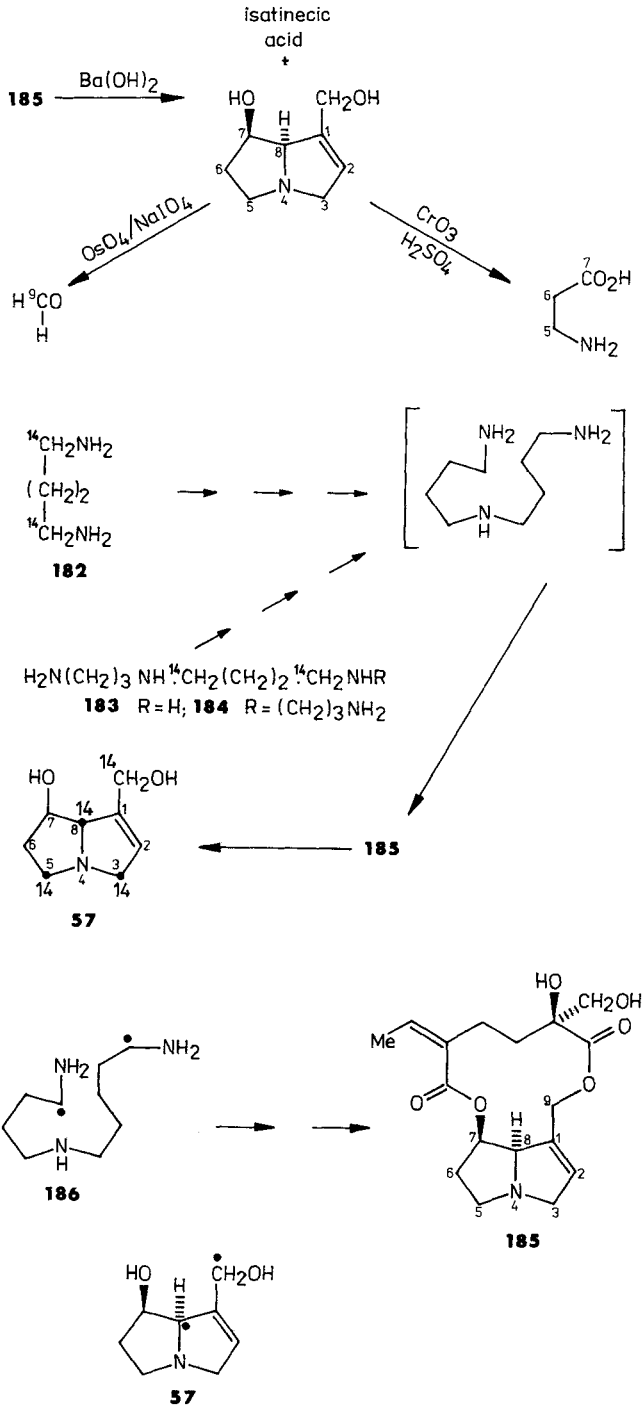




V. Biosynthesis

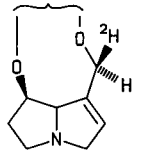
Robins *et al.* have continued their work on the biosynthesis of pyrrolizidine alkaloids and necine bases (*71–74*). 1-Amino-^{15}N-putrescine-*1*-^{13}C (**180**) was incorporated into retronecine (*57*) from retrorsine (**185**) in the *Senecio isatideus* plant. The incorporation of the precursor and its labeling pattern were consistent with the formation of a symmetrical intermediate, which was shown to be homospermidine (**186**). This finding was confirmed in experiments using ^{14}C-labeled compounds. The formation of homospermidine in the biosynthesis of retronecine was also demonstrated by incorporation of putrescine-*1,4*-$^{13}C_2$ (**181**) and -*2,3*-$^{13}C_2$ (**199**) into the same plant. In further studies, ^{14}C-labeled precursors



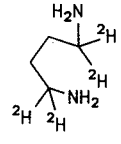

isatinecic acid
185
Ba(OH)2
OsO4/NaIO4
CrO3
H2SO4
182
183 R = H; 184 R = (CH2)3NH2
57
185
186
57

putrescine (**182**), spermidine (**183**), and spermine (**184**) were used to follow the biosynthesis of the necine portion in the alkaloid retrorsine (**185**) in the *Senecio isatideus* species. These experiments reconfirmed the formation of a symmetrical precursor from two molecules of each precursor. The symmetrical precursor C_4—N—C_4 was subsequently converted to retronecine. The ^{14}C activity has been distributed as follows: in retronecine, 22–24% at C-5, 6, 7; in putrescine-*2,3*-$^{14}C_2$, 22–25% at C-9 and 47% at C-5,6,7. This was consistent with the conclusions described above. Furthermore, the intact incorporation of homospermidine-*1,9*-$^{13}C_2$ (**186**) into retronecine (**57**) demonstrated homospermidine to be an intermediate in the biosynthesis of retronecine (**57**). Of the original activity, 44% was found on C-9 and 2% on C-5,6,7.

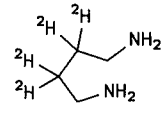
In addition to experiments with ^{13}C and ^{14}C precursors, Robins *et al.* (*72b*) used ^2H-labeled putrescines and ^2H-NMR spectroscopy to establish the labeling patterns in retrorsine (**185**). Putrescines-*1,4*-d_4 and -*2,3*-d_4 (**187** and **188**) were used to feed *Senecio isatideus*. The presence of ^2H at C-7d in retrorsine (**185a**), isolated from the plant, indicated the absence of intermediates with keto or enol groups. The majority of ^2H was located in one part of the pyrrolizidine system at C-1, C-2, C-3, and C-8. Thus the labeling pattern is consistent with the proposed biosynthetic pathway to retronecine (**57**), which includes formation of homospermidine (**178**). Moreover, the formation of (9*S*)-retrorsine-*9-d* (**185a**) indicated a stereospecific addition (from the re-face) of ^1H to the C=O group of the aldehyde precursor **189.** Other putrescines labeled (*R*)-*1-d* and (*S*)-*1-d* were used to study the biosynthetic route to retrorsine (**185**) in *Senecio isatideus* (*72c*). The labeling patterns found in retrorsines isolated from plants fed with these two precursors differed: equal label with ^2H was found at positions 3β, 5α, 8α, and 9-pro-*S* for the (*R*) precursor, while only the 3α and 5β positions were labeled with ^2H in the case of the (*S*) precursor. These results seem to point to the following conclusions: (1) oxidation of putrescine to 4-aminobutanol requires the



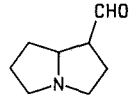
185a



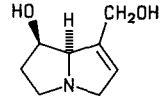
187



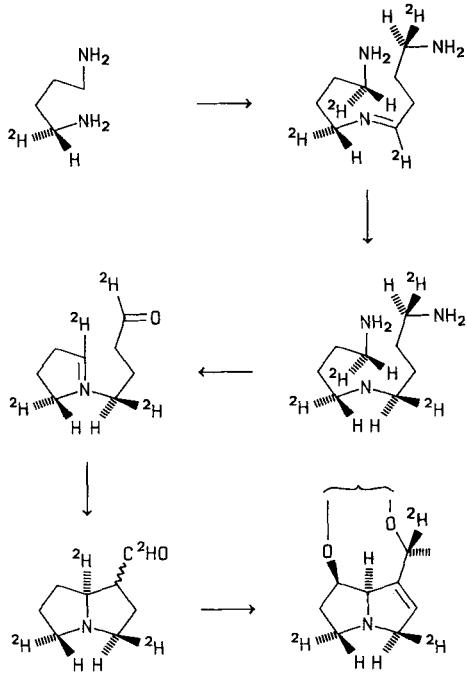
188



189



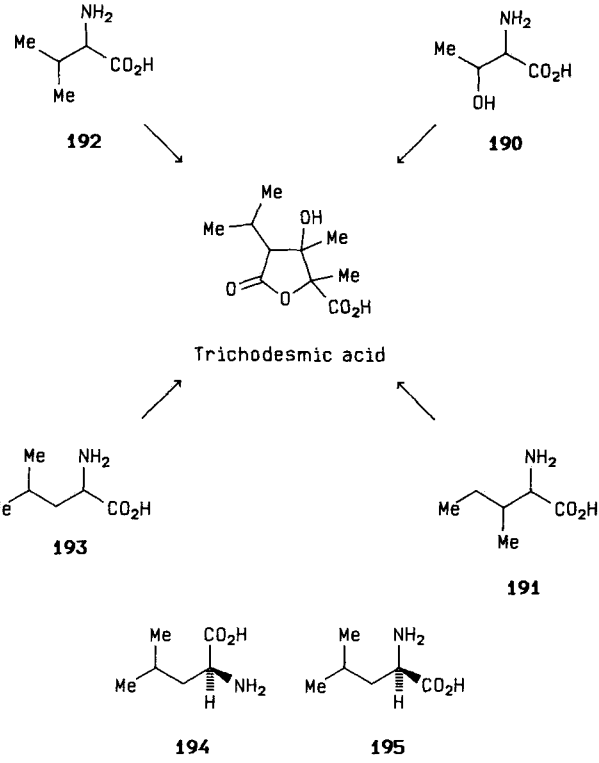
57



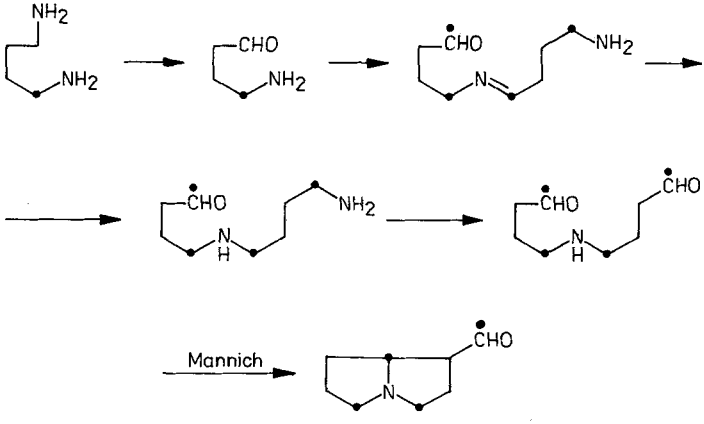
185

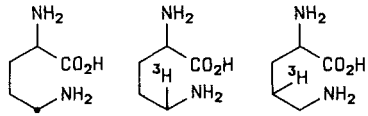
loss of the pro-*S* hydrogen, (2) reduction of the intermediate imine to homospermidine occurs at the si-face, (3) two oxidation steps leading to an aldehyde proceed with the removal of pro-*S* hydrogens, (4) cyclization of the iminium ion to 8α-pyrrolizidine proceeds at the re-face of the ion, and (5) reduction of the aldehyde occurs via the attack on the re-face of the carbonyl group.

Biosynthesis of trichodesmic acid (*73*) was studied, using ^{14}C labeled acids: (2*S*)-threonine-*U*-^{14}C (**190**), (2*S*)-isoleucine-*U*-^{14}C (**191**), (2*S*)-valine-*U*-^{14}C (**192**), (2*RS*)-valine-*4*-^{14}C (**193**), (2*S*)-leucine-*U*-^{14}C (**194**), and (2*RS*)-leucine-*2*-^{14}C (**195**). The feeding experiments were carried out with the *Crotalaria globifera* species, which produces the alkaloid trichodesmine (**1**). The degradation of trichodesmic acid, isolated from the plant fed with labeled amino acids, showed that the incorporation of valine and leucine labeled primarily carbons C-4, -5, -8, -9, and -10, whereas the label derived from threonine and isoleucine was mainly introduced at C-1, -2, -3, -6, and -7. Thus the two parts of trichodesmic acid are derived from different amino acids. Previous observations of the involvement of branched-chain amino acids in the biosynthesis of necic acids are supported.



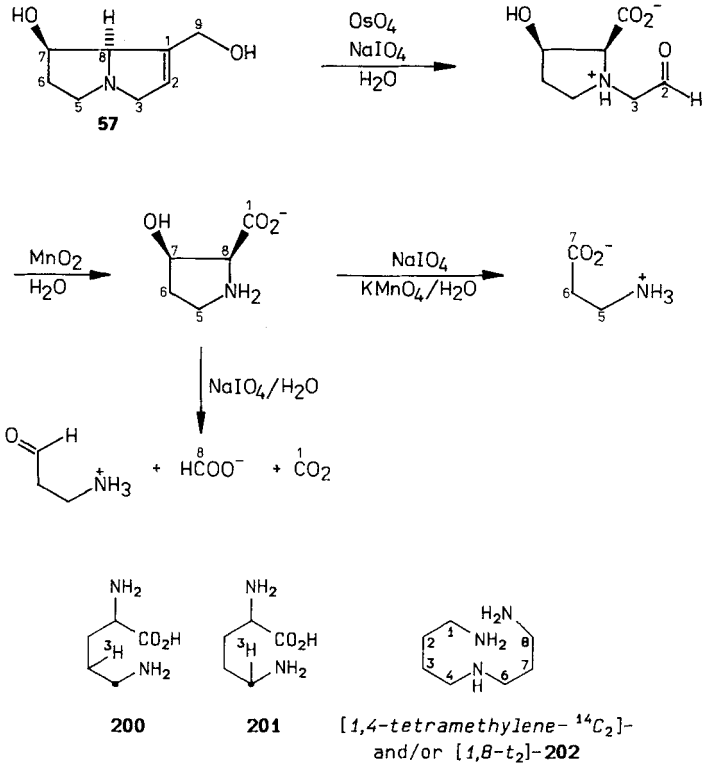
Spenser and Sorensen (*75,76*) have studied the biosynthesis of retronecine in *Senecio vulgaris,* using ^{13}C, putrescine-^{15}N (**180**), ornithine-5-^{14}C, *-5-t*, and *-4-t* (**196, 197,** and **198**). Although the results obtained were in agreement with the suggested biosynthetic pathway, including the C_4—N—C_4 symmetrical inter-





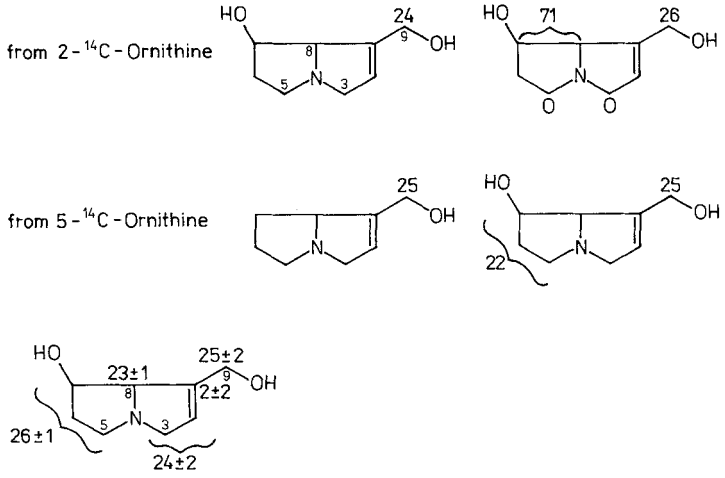
196 **197** **198**

mediate as the precursor of retronecine, the biosynthesis of the alkaloid was reinvestigated to clarify the distribution of label derived from ornithine. The incorporation mode into retronecine (**57**) of activity from ornithines-*5*-^{14}C, -*4*-*t*-*5*-^{14}C, and -5-*t*-5-^{14}C (**196, 200,** and **201**) and from ^{3}H,^{14}C-labeled spermidine (**202**) was determined by the degradation sequence shown in the scheme, together with the labeling pattern. Tritium was located in retronecine at positions C-2 (25%, 1H), C-6 (50%, 2H), and C-7 (25%, 1H). The stereochemistry of reactions involved in the biosynthesis of retronecine was studied by D NMR (*77*), using (*R*)-**203,** (*S*)-**204,** and putrescine-*1*-*d*. Retronecine from **203** was labeled with ^{2}H equally at positions 3-re, 5-re, 8, and 9-si, whereas retronecine from **204** was labeled with ^{2}H equally at positions 3-si and 5-si. The ster-

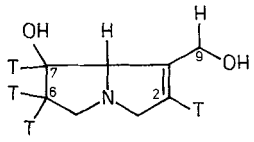


57

200 **201** [*1,4-tetramethylene*-$^{14}C_2$]- and/or [*1,8*-t_2]-**202**

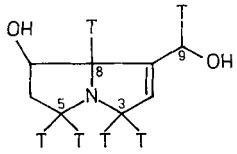


from [4-^{3}H,5-^{14}C]-ornithine

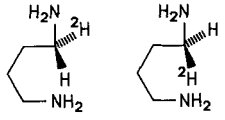


C-5,6,7,8	71±1
C-5,6	49±2
C-2,3	25±2 (by difference)
C-7	22±2 (by difference)

from [5-^{3}H,5-^{14}C]-ornithine



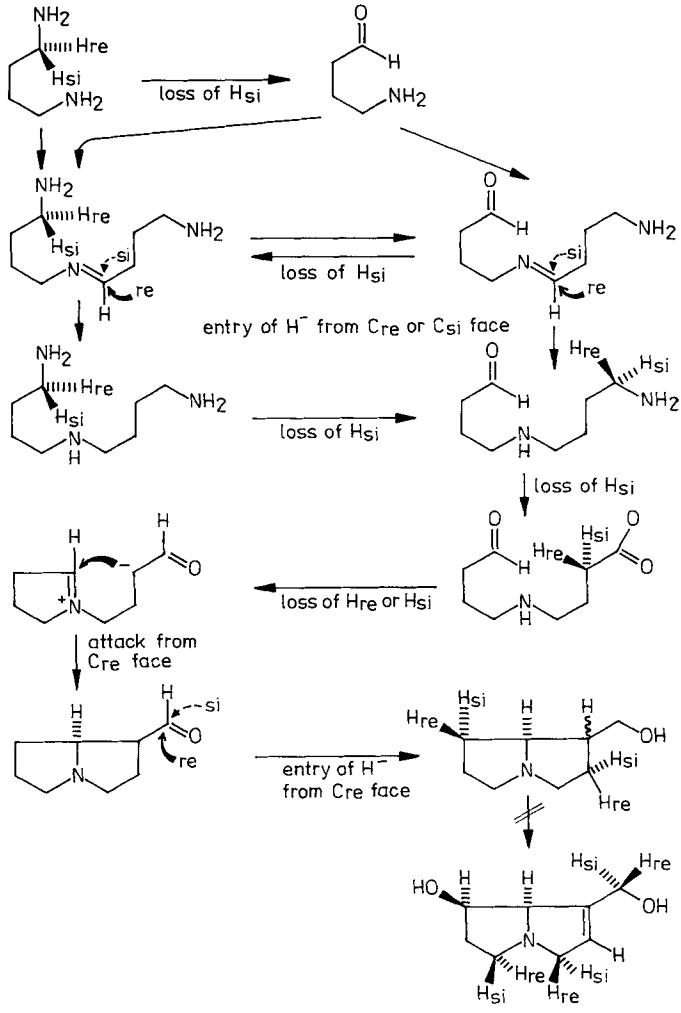
C-9	22±1
C-8	21±1
C-5,6,7,8	53±1
C-5,6	35±1
C-2,3	25±2



203 **204**

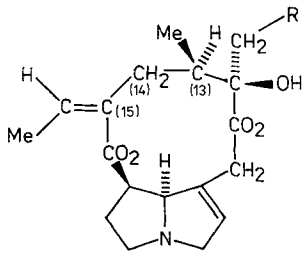
eochemistry of five steps in the biosynthetic conversion of putrescine to retronecine (**57**) is described in the scheme.

Cahill *et al.* studied the biosynthesis of the necic acid portion of PAs (*78*). Isoleucine (**205**) and necic acid (**206**) labeled stereospecifically with tritium at C-4 and C-3 were used for incorporation in the *Senecio* species. The configuration was shown to be retained in the ethyl group migration step during bio-

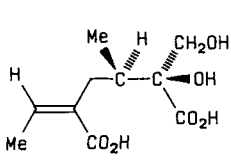


205 206

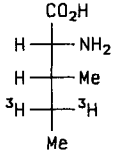
synthesis of isoleucine. It was also concluded that the formation of 10-carbon necic acid of type **206** is accompanied by a loss of C-4-pro-*R* hydrogen from both isoleucine components. Incorporation of tritium and ^{14}C-labeled **205** and **206** has



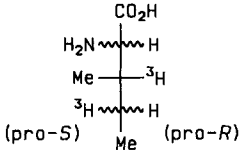
retrorsine R = OH **185**
senecionine R = H **23**



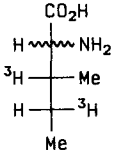
207



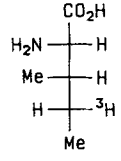
208



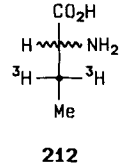
209



210



211



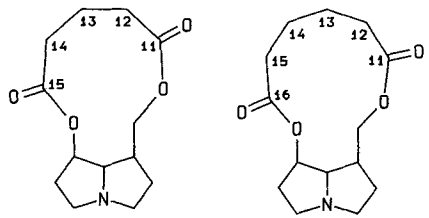
212

demonstrated that only (*S*)-isoleucine was a specific precursor of isatinecic acid (**207**) and that half of the tritium in (2*S*)-[4-$^3H_2$]-isoleucine (**208**) has been retained. Thus in retrorsine (**185**), two hydrogen atoms at C-13 and one of the C-15 ethylidene group are derived from C-4 methoxylene hydrogen atoms of (2*S*)-isoleucine. Next, two other doubly labeled isoleucines (**209** and **210**) were fed to *Senecio magnificus* to obtain senetionine (**23**), which contained no tritium. Thus the 4-pro=*S* hydrogen is lost during incorporation into necic acid, indicating that the C-3 and C-15 atoms in **23** are derived from the 4-pro-*R* hydrogen of L-isoleucine. Additional argument was obtained in feeding experiments with (2*S*,4*R*)-isoleucine-*4-t* (**211**) in which the 4-pro-*R* hydrogen atom was retained during incorporation into retrorsine (**185**). In addition, the experiment suggested an overall inversion of configuration at C-4 in isoleucine during formation of the C-13—C-14 bond. In the further study of the stereochemistry of the ethyl group migration in isoleucine during the rearrangement step, reductoisomerase was utilized as a catalyst. (*R*,*S*)-2-Aminobutanoic-*3*-^{14}*C*-*3*-t_2 acid (**212**) was incorporated into retrorsine (**185**); ^{14}C activity was found at the C-6,7 unit and all of the

tritium was lost. Thus the 3-pro-*S* hydrogen of 2-aminobutanoate was delivered to the 4-pro-*S* position in isoleucine, and the configuration was retained during the ethyl migration step. It has been independently shown that the enzymatic process converts both of the enantiomers (2*R* and 2*S*) of **212** to 2-oxobutanoate, but it was not established which process represents the natural metabolism in the *Senecio magnificus* plant.

VI. Spectroscopy

^{13}C-NMR spectroscopy is becoming an increasingly valuable tool in structural determinations of pyrrolizidine alkaloids. Its value is augmented by the limited information obtainable from ^{1}H-NMR spectra, particularly with respect to the differentiation between slight structural variations in the necic acid portion of PA molecules. The literature concerning ^{13}C-NMR spectra of individual PAs is included in references to Section II. The information given therein does not provide, however, a general view as to the rules that could be applicable to ^{13}C-NMR spectroscopy of the entire group of PAs. A more general approach can be found in three publications (*79–81*) that appeared during 1981 and 1982. The ^{13}C-NMR spectra of 42 PAs were analyzed, and the signal assignments were collected in a systematic way according to the type of the structure of both necin bases and necic acids in macrocyclic alkaloids. The data refer mainly to the crotalane (A) and senecane (B) series (*80*). It was concluded that the spectral characteristics of the single carbon atom are more readily deduced from ^{13}C–^{1}H coupling, and therefore measurements of the absolute magnitudes of the coupling constants are not always necessary. More informative is the signal multiplicity and the multiplet line shape for a particular group of compounds. This was exemplified by C-9, which gives a sharp triplet of doublets. Conversely, the signals of C-3, C-5, and C-6 are broadened, or their multiplicity is increased owing to long-range coupling. Both carbonyl carbon atoms were differentiated in a similar way: C-16 was recognized by its doublet when compared with a sharp,



coupled resonance for C-11. Methine atoms C-8 and C-7 were identified by the appearance of a doublet of doublets and of a more complex signal, respectively.

Criteria used in assignment of carbon resonances in PAs have been supplemented by the following generalizations.

- Absolute values of coupling constants (J_{CH}) were found to be reliable indications for the presence of ring strain or electronegative substituents. In strained macrocyclic rings, J_{CH} values for C-20 are ~170 Hz, whereas for the majority of members of the senecane series C-20 is characterized by $J_{CH} \approx 145$ Hz.
- Observation of isotopic shifts enables confirmation of the assignments for C-7, C-8, C-2′, C-3′, and C-6 since β- and γ-OD isotope shifts of 0.2(β), 0.1(γ), 0.06(β), 0.10(β) and 0.11(γ) ppm are observed at these carbon resonance sites, respectively.
- The stereochemistry at C-7 strongly reflects chemical shifts at C-1 and C-2 for noncyclic esters. For a β-OH substituent at C-7, average shifts at C-1 and C-2 are 132.8 and 130.8 ppm, whereas the values for α analogs are 136.2 and 126.4 ppm, respectively. Shifts of 2.4, −3.5 and 1.1 ppm were also observed for C-6, C-7, and C-8 in compounds having a β-OH at C-7, as opposed to an α-OH configuration.
- The saturation of the 1,2 double bond in the pyrrolizidine system accounts for the most significant shift for C-9 to a lower field by 5.5 ppm, larger than in the case of unsaturated compounds. Characteristic shifts to higher field are also observed for C-1, C-2, C-3, C-7, and C-8 in the pyrrolizidine ring.
- Conformational and configurational changes in substituent acids of alkaloids cause relatively small shift differences. However, in some cases a clear distinction between stereoisomers is evident. A good example is the inversion of configuration at C-3′ (*S*) (in the alkaloid rinderine) as opposed to the C-3′ (*R*) configuration in echinatine and lycopsamine. The induced shifts observed for C-1′, C-3′, and C-4′ are 3.0, −1.7, and 1.0 ppm, respectively, and provide good argument for configurational changes at C-3′. Similarly, the change in the configuration at C-13 in the alkaloid crispatine (*R*, meso) [which leads to fulvine (*S*, meso)] provides clear shift differences at C-11, C-12, C-13, C-14, C-17, and C-18, which are −2.7, 1.8, 1.6, 1.6. −3.6, and −1.5 ppm, respectively.
- Typical shieldings are observed for cis–trans isomerism about the exocyclic C-15=C-20 bond.

These general observations facilitate structural determinations of newly discovered PAs.

A specific and sensitive method of detection of PAs in foods consists in negative ion chemical ionization mass spectrometry, which was applied to 10 alkaloids (*82*). $(M - H)^-$ and $(M + OH)^-$ ions were observed together with ions representing necine bases and necin acids. Alkaloids of monoester-type structure did not form $(M + OH)^-$ ions.

VII. Toxicity and Pharmacology

Over 300 plants and plant products are known to contain pyrrolizidine alkaloids. At least 30 genera in 6 plant families have been identified as containing alkaloids which cause hepatotoxic effects in livestock and humans. Among the most poisonous are lassiocarpine (**24**), heliotrine, europine, monocrotaline (**41**), senecionine (**23**), retrorsine (**185**), and otonecine (**162**). Apart from acute and chronic hepatotoxicity, PAs have been reported to cause pneumotoxicity and a nucleotoxicity that includes mutagenesis, carcinogenesis, and a long-lasting antimitotic effect. The activation of PAs in the liver leads to toxic pyrrolic metabolites: dehydroalkaloids, which kill cells by alkylating cellular constituents thus causing necrosis of the liver and of the vascular endothelium of the lung, and secondary metabolites (dehydroamino alcohols), which are nucleotoxic and produce antimitotic, mutagenic, teratogenic, and carcinogenic effects.

According to Australian experience, recently described by Culvenor (*84*), sheep exposed to grazing on pastures infected with the weeds *Heliotropium europaeum* and *Echium plantagineum* may suffer shortening of productive life by as much as 2 years. Human poisoning is mostly due to consumption of poisoned cereal grains. It has not been established whether a continued low intake of PAs creates a health hazard for humans: the threshold level below which the health risk is sufficiently low has not been determined. Russian comfrey (*Symphytum* ×*uplandicum*), highly promoted in Australia as having medicinal value, was ingested in amounts reaching 5 mg/day. Pyrrolizidine alkaloids, present in the comfrey and similar alkaloids of *S. officinale* have been shown by Australian, European, and Japanese studies to be not only hepatotoxic but also carcinogenic in rats. No direct evidence exists for the effects carcinogenic PAs on humans.

Biochemical, NMR, and X-ray crystallographic studies have begun to throw some light on the influence of structure and conformation on toxic properties. Studies of the three principal metabolic reactions [pyrrole formation (activating), N-oxidation by microsomal oxidases, and hydrolysis by esterases (both detoxyfying) (*85,86*)] combined with other data led Culvenor (*84*) to suggest that the structures of hepatotoxic alkaloids are the outcome of an evolutionary drive toward a comparatively inert molecule, capable of rapid activation to a cytocidal alkylating action and with efficiency maintained by steric protection of the ester groups. Culvenor implies that this speculative picture may explain the function of PAs in the plants, in which they, more often than other alkaloids, occur in the non bitter *N*-oxide form. Since bitterness is said to cause mammals to reject feedstuff, this may offer survival advantage by permitting consumption in order to effect long-term reduction in herbivore population.

The available evidence contradicts the possible protection by PAs against insect predators. The possibility that PAs offer protection against microbial

attack is far from being proved. Culvenor suggests that PAs may function as built-in accelerators of mutation for the host plant.

Some PAs also show genotoxic effects both *in vitro* and *in vivo*. A recent review of the health hazards of PAs including chromosome aberrations and gene mutations is available (*83*). Although further evaluation *in vivo* of the actual genetic risk of these compounds is still required, it seems that the genetic damage is of lesser importance than the toxic and possible carcinogenic risk.

Few attempts have been made to develop useful pharmaceutical agents from PAs. Mild anticholinergic activity of the non-hepatotoxic esters of saturated amino alcohols of PAs allowed the use of sarracine and platyphylline (**50**) in the Soviet Union, where they were found to be beneficial in the treatment of gastrointestinal hypermotility and peptic ulceration. The free amino alcohols are reported to exert indirect cholinomimetic action involving release of acetylcholine from postganglionic sites in the guinea pig ileum.

More details on the toxicity, pharmacology, and biological activity of PAs can be found in the review by Suffness and Cordell in Volume 25 of *The Alkaloids* (*87*).

References

1. D. J. Robins, *Prog. Chem. Org. Nat. Prod.*, 115 (1982).
2. L. W. Smith and C. C. J. Culvenor, *J. Nat. Prod.* **44,** 129 (1981).
3. D. J. Pilbeam, A. J. Lyon-Joyce, and E. A. Bell, *J. Nat. Prod.* **46,** 601 (1983).
4. J. Luethy, U. Zweifel, B. Karlhuber, and S. Schlatter, *J. Agric. Food Chem.* **29,** 302 (1981).
5. C. C. J. Culvenor, J. A. Edgar, and L. W. Smith, *J. Agric. Food Chem.*, 958 (1981).
6. M. Omar, J. DeFeo, and H. W. Youngken Jr., *J. Nat. Prod.* **46,** 153 (1983).
7. J. A. Edgar, N. J. Eggers, A. J. Jones, and G. B. Russell, *Tetrahedron Lett.* **21,** 2657 (1980).
8. J. L. Frahn, C. C. J. Culvenor, and J. A. Mills, *J. Chromatogr.* **195,** 379 (1980).
9. P. S. Subramanian, S. Mohanraj, P. A. Cockrum, C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, and L. W. Smith, *Aust. J. Chem.* **33,** 1357 (1980).
10. J. A. Edgar, C. C. J. Culvenor, P. A. Cockrum, and L. W. Smith, *Tetrahedron Lett.* **21,** 1383 (1980).
11. K. Stoeckli-Evans, *Acta Crystallogr.* **1336,** 3150 (1980).
12. S. Mohanraj, P. Kulanthaivel, P. S. Subramanian, and W. Herz, *Phytochemistry* **20,** 1991 (1981).
13. H. Stoeckli-Evans, *Acta Crystallogr. Sect. B* **38,** 1614 (1982).
14a. H. Wiedenfeld, *Phytochemistry* **21**(11), 2767 (1982).
14b. H. Wiedenfeld, A. Kirfel, E. Roecher, and G. Will, *Phytochemistry,* 2065 (1983).
15. J. F. Resch and J. Meinwald, *Phytochemistry* (1982).
16a. M. F. Mackay and C. C. J. Culvenor, *Acta Crystallogr.* **1338,** 2754 (1982).
16b. Z. Hua, X. Xu, X. Wei, S. Tang, and Y. Wu, *Beijing-daxue Xuebao, Ziran Kexuae Ban* **4,** 89 (1983); *Chem. Abstr.* **100,** 139425 (1984).
17. D. G. Hay, M. F. Mackay, and C. C. J. Culvenor, *Acta Crystallogr.* **1338,** 155 (1982).
18. C. N. Haksar, O. P. Suri, R. S. Jamwall, and C. K. Atal, *Indian J. Chem. Sect. B* **21,** 492 (1982).

19. H. Stoecklii-Evans and D. J. Robins, *Helv. Chim. Acta* **66**(5), 1376 (1983).
20. M. F. Mackay, M. Sadek, C. C. J. Culvenor, and L. W. Smith, *Acta Crystallogr. Sect. C* **39,** 1230 (1983).
21. M. F. Mackay and C. C. J. Culvenor, *Acta Crystallogr. Sect. C* **39,** 1227 (1983).
22. J. F. Resch, S. A. Goldstein, and J. Meinwald, *Planta Med.* **47**(4), 255 (1983).
23. E. Roeder, H. Wiedenfeld, and A. Hoenig, *Planta Med.* **49**(1), 57 (1983).
24. H. Wiedenfeld, E. Roeder, A. Kirfel, and G. Will, *Arch. Pharm. (Weinheim, Ger.)* **316,** 367 (1983).
25. H. Rueger and M. H. Benn, *Can. J. Chem.* **61,** 2526 (1983).
26. R. Y. Wong and J. N. Roitman, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **400**(1), 163 (1984).
27. M. F. Mackay, M. Sadek, and C. C. J. Culvenor, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **40**(3), 470 (1984).
28. M. F. Mackay, M. Sadek, C. C. J. Culvenor, and L. W. Smith, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **40**(3), 473 (1984).
29. Y. Asada and T. Furuya, *Chem. Pharm. Bull.* **32**(2), 475 (1984).
30. L. W. Smith and C. C. J. Culvenor, *Phytochemistry* **23**(2), 473 (1984).
31. K. Brown, J. A. Devlin, and D. J. Robins, *Phytochemistry* **23**(2), 457 (1984).
32. M. F. Mackay, M. Sadek, and C. C. J. Culvenor, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **40**(6), 1073 (1984).
33. N. B. Mulchandani and S. A. Hassarajani, *Planta Med.,* 104 (1984).
34. J. Huang and J. Meinwald, *J. Am. Chem. Soc.* **103,** 861 (1981).
35. J. A. Devlin and D. J. Robins, *Chem. Commun.* **1272** (1981).
36. J. A. Devlin, D. J. Robins, and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1,* 1117 (1982).
37. K. Narasaka, T. Sakakura, T. Uchimaru, K. Morimoto, and T. Mukaiyama, *Chem. Lett.,* 455 (1982); K. Narasaka, T. Sakakura, T. Uchimaru, and D. Gueclin-Vuong, *J. Am. Chem. Soc.* **106**(10), 2954 (1984).
38. L. T. Gelbaum, M. M. Gordon, M. Miles, and L. H. Zalkow, *J. Org. Chem.* **47,** 2501 (1982).
39. K. Brown, J. A. Devlin, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1,* 1819 (1983).
40. E. Vedejs and S. D. Karsen, *J. Am. Chem. Soc.* **106**(10), 3031 (1984).
41. J. T. Wróbel *in* "Natural Sulfur Compounds" p. 353. Plenum, New York (1980); J. T. Wróbel and J. A. Glinski, *Can. J. Chem.* **59,** 1101 (1981).
42. J. T. Wróbel, *Alkaloids* **25,** (1985).
43. S. Takano, N. Ogawa, and K. Ogasawara, *Heterocycles* **16**(6), 915 (1981).
44. A. R. Chamberlin and J. Y. L. Chung, *J. Am. Chem. Soc.* **105,** 3653 (1983).
45. K. Tatsuda, H. Takahashi, Y. Amemiya, and M. Kinoshita, *J. Am. Chem. Soc.* **105,** 4096 (1983).
46a. T. Ohnuma, M. Nagasaki, M. Tabe, and Y. Ban, *Tetrahedron Lett.,* 4253 (1983).
46b. T. Ohnuma, M. Tabe, K. Shiiya, and Y. Ban, *Tetrahedron Lett.,* 4249 (1983).
47. D. J. Hart and T. K. Yang, *Chem. Commun.,* 135 (1983).
48. T. Shono, Y. Matsumura, K. Uchida, K. Tsubata, and A. Makino, *J. Org. Chem.* **49,** 300 (1984).
49. T. L. Macdonald and B. A. Narayanan, *J. Org. Chem.* **48,** 1129 (1983).
50. D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.,* 1430 (1982).
51. S. Miyano, S. Fujii, O. Yamashita, N. Toraishi, K. Sumuto, F. Satoh, and T. Masuda, *J. Org. Chem.* **46,** 1737 (1981).
52. W. Flitsch and P. Wernsmann, *Tetrahedron Lett.,* 719 (1981).
53. E. Wedejs and G. R. Martinez, *J. Am. Chem. Soc.* **102,** 7993 (1980).
54. G. A. Kraus and K. Neuenschwander, *Tetrahedron Lett.,* 3841 (1980).
55. A. R. Chamberlin and J. Y. L. Chung, *Tetrahedron Lett.,* 2619 (1982).

56. D. J. Hart and Teng-Kuei Yang, *Tetrahedron Lett.*, 2761 (1982).
57. H. Rueger and M. Benn, *Heterocycles* **19**(9), 1677 (1982).
58. T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *Heterocycles* **19**(11), 2075 (1982); T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *J. Org. Chem.* **48**(21), 3644 (1983).
59. H. Rueger and M. Benn, *Heterocycles* **20**(7), 1331 (1980).
60. D. J. Robins and S. Sakdarat, *J. Chem. Soc., Perkins Trans. 1*, 909 (1981).
61. Y. Terao, N. Imai, K. Achiwa, and M. Sekiya, *Chem. Pharm. Bull.* **30**(9), 3167 (1982).
62. S. R. Wilson, R. A. Sawicki, and J. C. Hufman, *J. Org. Chem.* **46,** 3887 (1981).
63. K. Niwa, Y. Vosaki, and K. Yamada, *Tetrahedron Lett.* **24**(51), 5731 (1984).
64. H. Rueger and M. Benn, *Heterocycles* **20**(2), 235 (1983).
65. R. Mattocks, *Chem. Ind. (London),* 251 (1981).
66. T. Kametani, K. Higashiyama, H. Otomasu, and T. Honda, *Heterocycles* **22**(4), 729 (1984).
67a. R. F. Borch and B. C. Ho, *J. Org. Chem.* **42,** 1225 (1977).
66b. D. J. Robins and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1*, 1734 (1979).
67. E. Roeder, H. Wiedenfeld, and E. J. Jost, *Arch. Pharm. (Weinheim Ger.)* **317**(5), 403 (1984).
68. R. S. Jamwal, K. A. Suri, O. P. Suri, C. N. Haksar, and C. K. Atal, *Indian J. Chem. Sect. B* **21**(3), 266 (1982).
69. J. J. Karchessy and M. L. Dainzer, *Heterocycles* **16**(4), 631 (1981).
70. D. J. Robins, *Chem. Commun.*, 1289 (1982).
71a. H. A. Khan and D. J. Robins, *Chem. Commun.*, 146 (1981).
71b. H. A. Khan and D. J. Robins, *Chem. Commun.*, 554 (1981).
72a. D. J. Robins and J. R. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 3083 (1981).
72b. J. Rana and D. J. Robins, *J. Chem. Soc., Chem. Commun.*, 1222 (1983).
72c. J. Rana and D. J. Robins, *J. Chem. Soc., Chem. Commun.*, 517 (1984).
73. J. A. Devlin and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1329 (1984).
74. J. Rana and D. J. Robins, *J. Chem. Res., (Synop.),* 146 (1983).
75. G. G. Sørensen and I. D. Spenser, *J. Am. Chem. Soc.*, 3208 (1981).
76. G. G. Sørensen and I. D. Spenser, *Can. J. Chem.* **60,** 643 (1982).
77. G. G. Sørensen and I. D. Spenser, *J. Am. Chem. Soc.*, 7401 (1983).
78. R. Cahill, D. H. G. Crout, M. V. M. Gregorio, M. B. Mitchell, and U. S. Mueller, *J. Chem. Soc. Perkin Trans. 1*, 173 (1983).
79. R. J. Molyneux, J. N. Roitman, M. Benson, and R. E. Lundin, *Phytochemistry* **21**(2), 439 (1982).
80. A. J. Jones, C. C. J. Culvenor, and L. W. Smith, *Aust. J. Chem.* **35,** 1173 (1982).
81. S. E. Drewes, J. Antonowitz, P. T. Kaye, and P. C. Coleman, *J. Chem. Soc., Perkin Trans. 1*, 287 (1981).
82. P. A. Dreifuss, W. C. Brumley, J. A. Sphon, and E. A. Caress, *Anal. Chem.* **55**(7), 1036 (1983).
83. O. Schimmer, *Dtsch. Apoth. Ztg.* **28,** 1361 (1983).
84. C. C. J. Culvenor, *TIPS* **January,** 18 (1985).
85. A. R. Mattocks, *Chem. Biol. Interact.* **35,** 301 (1981).
86. A. R. Mattocks and I. Bird, *Chem. Biol. Interact.* **43,** 209 (1983).
87. M. Suffness and G. A. Cordell, *Alkaloids (N.Y.)* **25,** 1 (1985).

Note Added in Proof

Racemic compounds are shown arbitrarily as one of the two enantiomers, and the other enantiomer of a particular optically active alkaloid would have the opposite configuration at the chiral centers.

CUMULATIVE INDEX OF TITLES

CUMULATIVE INDEX OF CONTRIBUTORS

SUBJECT INDEX

B

C

G

H

I

N

O

This Page Intentionally Left Blank