THE ALKALOIDS

Edited by

GEOFFREY A. CORDELL

VOLUME 52

ACADEMIC PRESS

THE ALKALOIDS

Chemistry and Biology

VOLUME 52

This Page Intentionally Left Blank

THE ALKALOIDS

Chemistry and Biology

Edited by

Geoffrey A. Cordell

College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois

VOLUME 52

Academic Press
San Diego London Boston New York
Sydney Tokyo Toronto

This book is printed on acid-free paper. ♾

Copyright © 1999 by ACADEMIC PRESS

All Rights Reserved.
No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the Publisher.
The appearance of the code at the bottom of the first page of a chapter in this book indicates the Publisher's consent that copies of the chapter may be made for personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. (222 Rosewood Drive, Danvers, Massachusetts 01923), for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Copy fees for pre-1998 chapters are as shown on the title pages. If no fee code appears on the title page, the copy fee is the same as for current chapters.
0099-9598/99 $30.00

Academic Press
a division of Harcourt Brace & Company
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
http://www.apnet.com

Academic Press Limited
24-28 Oval Road, London NW1 7DX, UK
http://www.hbuk.co.uk/ap/

International Standard Book Number: 0-12-469552-3

PRINTED IN THE UNITED STATES OF AMERICA
99 00 01 02 03 04 QW 9 8 7 6 5 4 3 2 1

CONTENTS

Chemistry and Biology of Steroidal Alkaloids from Marine Organisms

ATTA-UR-RAHMAN AND M. IQBAL CHOUDHARY

The Monoterpene Alkaloids

GEOFFREY A. CORDELL

CONTRIBUTORS

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

M. IQBAL CHOUDHARY (233), International Center for Chemical Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, Karachi 75270, Pakistan

GEOFFREY A. CORDELL (261), Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7230

A. A. LESLIE GUNATILAKA (1), Bioresources Research Facility, Office of Arid Lands Studies, University of Arizona, Tucson, Arizona 85706-6800

PIRJO HANHINEN (103), Laboratory of Organic and Bioorganic Chemistry, Technical University of Helsinki, Espoo, FIN-02150, Finland

MAURI LOUNASMAA (103), Laboratory of Organic and Bioorganic Chemistry, Technical University of Helsinki, Espoo, FIN-02150, Finland

PIOTR POPIK (197), Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Poland

ATTA-UR RAHMAN (233), International Center for Chemical Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, Karachi 75270, Pakistan

PHIL SKOLNICK (197), Neuroscience Discovery, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285

MINNA WESTERUND (103), Laboratory of Organic and Bioorganic Chemistry, Technical University of Helsinki, Espoo, FIN-02150, Finland

This Page Intentionally Left Blank

PREFACE

During the preparation of this volume of *The Alkaloids: Chemistry and Biology,* the death was announced of the Nobel Laureate, Sir Derek H. R. Barton, at the age of 79. A consummately dedicated natural product chemist, Barton contributed in many ways to the development of alkaloid chemistry. He was a founder of the concepts we now take for granted regarding the conformational analysis of polycyclic ring systems. His ideas about the biosynthesis of particular alkaloid groups, notably the importance of phenolic coupling reactions in isoquinoline alkaloid biosynthesis, were followed by some of the first biosynthetic experiments in plants testing his hypotheses. Undoubtedly, his legendary creativity will stand the test of time.

In Chapter 1 of this volume, Gunatilaka, a former Ph.D. student of Barton, reviews the work that has been conducted on the rich flora of Sri Lanka for alkaloids. The chemical diversity of the alkaloids is profound and is reflected in the biology associated with them.

In Chapter 2, Lounasmaa, Hanhinen, and Westersund present an extensive review of the isolation, spectroscopic characterization, and syntheses that have been conducted in the past 30 years on the sarpagine group of alkaloids. Revised concepts regarding the biogenesis of these alkaloids are discussed.

The recent substantial interest in ibogaine and its derivatives as potential anti-addictive agents is reviewed in Chapter 3 by Popik and Skolnick from the biochemical and pharmacological perspectives.

Chapter 4 offers an overview of the steroidal alkaloids from marine organisms by Atta-ur-Rahman and Choudhary. In addition to their unique sources and challenging structures, several of these alkaloids are currently of substantial biological interest.

In the final chapter, an update is presented of a review that I prepared almost 24 years ago on the substantial progress made regarding the isolation, systhesis, and biological activities of the monoterpene alkaloids.

Geoffrey A. Cordell
University of Illinois at Chicago

This Page Intentionally Left Blank

—CHAPTER 1—

ALKALOIDS FROM SRI LANKAN FLORA*

A. A. LESLIE GUNATILAKA

Bioresources Research Facility
Office of Arid Lands Studies
The University of Arizona
Tucson, AZ 85706

* This chapter is dedicated with great admiration to the memory of Professor Sir Derek H. R. Barton, a mentor who provided me with an unforgettable introduction to the world of natural products.

THE ALKALOIDS, VOL. 52
0099-9598/99 $30.00

Copyright © 1999 by Academic Press.
All rights of reproduction in any form reserved.

I. Introduction

Sri Lanka, formerly known as Ceylon, is an island about 65,600 km^2 in extent situated 29 km south of the southern tip of Peninsular India. The island is centrally located in the Indian Ocean between latitudes 5°55 minutes and 9°51 minutes north and longitudes 79°41 minutes and 81°53 minutes east. The tropical location of the island ensures uniform temperatures ranging from 78 to 85°F in the lowlands and about 55 to 70°F in the highest elevation of the country. Due to the absence of marked temperature differences, rainfall has become the conspicuous parameter in seasonal variations in the climate of Sri Lanka. The average rainfall varies from about 50 to 100 inches per year depending on local topography. Thanks to its geographic situation and climatic conditions, Sri Lanka has an abundant flora. From a total of about 3400 flowering plant species, about 830 are reported to be endemic to the country (*1–4*), and of this total about 750 species are claimed to have uses in indigenous systems of medicine (*2,3*) which provide primary health care for about 70% of the population (*5*). A number of local plants are also known to contain drugs described in the Western pharmacopeia. Distribution of these medicinal and/or drug yielding plants of Sri Lanka among the pteridophytes, gymnosperms, and angio-

sperms has been presented by Abeywickrema (*3*) and is summarized in Table I. Some of these plants may owe their pharmacological properties to the alkaloids contained in them.

Among the natural products, alkaloids constitute the largest single class of secondary metabolites. To date a total of about 16,000 alkaloids belonging to major classes are known (*6*). Many alkaloids display dramatic physiological activities and therefore find wide applications in medicine and as tools in pharmacological research; some alkaloids are toxic to humans and animals. Alkaloids occur mostly in higher plants belonging to angiosperm families and are absent or infrequent in gymnosperms, ferns, mosses, and lower plants. However, even in angiosperm families, alkaloid distribution is very uneven, and certain families are characteristically devoid of alkaloids. Angiosperm families of Sri Lanka that are particularly rich in alkaloids are presented in Table II, which also shows the approximate number of genera and species of each of these families found in Sri Lanka. In addition, Table II gives the number of these plants endemic to the country and the number employed in indigenous systems of medicine.

Pioneering work on the chemistry of Sri Lankan plants was carried out by research groups headed by J. P. C. Chandrasena, L. B. de Silva, M. U. S. Sultanbawa, G. P. Wannigama, and R. O. B. Wijesekera. Systematic studies on screening of Sri Lankan plants for alkaloids and studies on akaloid-containing plants of Sri Lanka were initiated in the early 1970s by Sultanbawa, Wannigama, and their co-workers. In 1974 a workshop on "Natural Products for Sri Lanka's Future" was organized by the National Science Council of Sri Lanka jointly with the National Academy of Sciences of the United States. This workshop was attended by almost all organic chemists in Sri Lanka and some leading natural product chemists from the United States, including Carl Djerassi and Norman Farnsworth, and highlighted the importance of studies on medicinal and related plants of Sri Lanka containing commercially important alkaloids (*7*). This meeting spurred a heightened interest in alkaloid-containing plants of Sri Lanka.

TABLE I
DISTRIBUTION OF MEDICINAL AND/OR DRUG-YIELDING PLANTS AMONG PTERIDOPHYTES, GYMNOSPERMS, AND ANGIOSPERMS IN SRI LANKA

	Total	Indigenous	Introduced	Endemic
Pteridophytes	5	5	0	0
Gymnosperms	1	1	0	0
Monocots	125	100	22	3
Angiosperms				
Dicots	619	564	44	11
Total	750	670	66	14

TABLE II
IMPORTANT ALKALOID-BEARING AND MEDICINALLY USEFUL PLANT FAMILIES OF SRI LANKA

Family	No. Reported from Sri Lanka			No. of Species Used in Indigenous Medicine	
	Genera	Species	Endemic	Nonendemic	Endemic
Amaryllidaceae[a,b]	4	10	—	5	—
Annonaceae[b]	17	45	18	2	—
Apocynaceae[b]	23	31	8	13	2
Compositae	60	115	20	21	1
Convolvulaceae	16	57	3	17	1
Cucurbitaceae	18	33	2	22	—
Euphorbiaceae	46	149	47	39	—
Flacourtiaceae	10	16	10	1	3
Gramineae[a]	122	295	21	35	—
Lauraceae[b]	10	33	23	6	—
Leguminosae	85	283	12	88	—
Liliaceae[a]	14	18	2	5	—
Loganiaceae[b]	5	18	10	3	1
Malvaceae	13	44	2	21	—
Menispermaceae[b]	11	13	—	12	—
Moraceae	11	34	5	20	—
Rubiaceae[b]	50	158	74	23	1
Rutaceae[b]	18	40	4	14	—
Solanaceae[b]	9	29	—	11	—
Verbenaceae	16	36	3	14	—
Zingiberaceae[a]	12	38	17	13	—

[a] Monocotyledons.
[b] Major alkaloid-bearing families.

The literature on the alkaloids of Sri Lankan plants up to mid-1977 was covered in a review by Gunatilaka (*8*) based on a lecture delivered at a workshop on phytochemical, pharmacological, and microbiological screening of Sri Lankan plants held as a prelude to the Third Asian Symposium on Medicinal Plants and Spices. Since the publication of this review, extensive studies on the alkaloids of Sri Lankan plants have been carried out by L. S. R. Arambewela, Atta-ur-Rahman, B. M. R. Bandara, K. T. D. De Silva, A. A. L. Gunatilaka, V. Kumar, P. Perera, J. Reisch, F. Sandberg, R. Verpoorte, G. P. Wannigama, E. M. K. Wijeratne, and their co-workers. This review covers the work published and presented at meetings up to mid-1997 and contains discussions on the distribution, structure elucidation, chemistry, biological activity, and biosynthetic aspects of alkaloids encountered in the Sri Lankan flora. Some of the studies on these plants were driven by their claimed medicinal uses, although many were of chemotaxo-

nomic and/or phytochemical nature. Of the 43 Sri Lankan plants from which alkaloids have been isolated, 17 have some claimed medicinal uses (*9*), and these are listed in Table III.

Each section in this chapter deals with a major class of alkaloids encountered in the Sri Lankan flora. Subsections under each section are dedicated to discussions on a particular group or subgroup of alkaloids. Alkaloids that do not belong to any of the major classes are considered in the section on miscellaneous alkaloids. This approach was preferred over a discussion based on plant taxonomy used in an earlier review on this subject (*8*). However, Table IV presents the Sri Lankan plant species (arranged in alphabetical order) from which alkaloids have been isolated, together with the families to which these plants belong and the alkaloids encountered. Some conclusions on the current status and future prospects are drawn at the end of the chapter.

II. Surveys for Alkaloids

Several systemic surveys of Sri Lankan plants for alkaloids have been reported. In 1973, Sultanbawa, Wannigama, and their co-workers reported a general survey of the Sri Lankan Annonaceae for alkaloids (*10*). In this study, crude basic fractions from leaves and twigs were subjected to Mayer's test and thin-layer chromatography (TLC) investigations. The endemic species examined included *Alphonsea coriacea* (Thw.) Finet and Gagnep, *Cyathocalyx zeylanicus* Champ. *ex* Hook. f. and Thoms., *Desmos elegans* (Thw). Safford, *Enicosanthum acuminatum* (Thw.) Airy-shaw, *Sageraea thwaitesii* Hook. f. and Thoms., *Xylopia championii* Hook. f. and Thoms., and *X. nigricans* Hook. f. and Thoms. The following nonendemic species were also tested; *Miliusa indica* Leschen *ex* A. DC. and *Uvaria semecarpifolia* Hook. f. and Thoms. All these nine species showed the presence of alkaloids, and some were subsequently subjected to detailed investigations.

Two extensive surveys of Sri Lankan plants for the occurrence of basic and quaternary alkaloids were reported by Sultanbawa and co-workers (*11,12*). In these studies 594 plant species, including 192 species endemic to Sri Lanka, were examined. Extracts derived by three different procedures were tested for the presence of alkaloids by Mayer's and/or Wagner's reagents, and the approximate number of alkaloids in each of the extracts giving a positive response in these tests was determined by TLC analysis utilizing Dragendorff's and iodoplatinate spray reagents. In these studies, 180 new plant species containing alkaloids were uncovered. Plant species giving positive tests for

TABLE III
MEDICINAL USES OF SOME SRI LANKAN PLANTS FROM WHICH ALKALOIDS HAVE BEEN ISOLATED

Plant Species	Part[a]	Reported Medicinal Uses
Adhatoda vasica Nees	Pl	Snakebite, wounds
	Lf	Diarrhea, dysentery, cough, asthma, rheumatic fevers, wounds
	Rt, Bk	Heart diseases, catarrah, eye diseases
	Rt	Malarial fever
Anamirta cocculus (L.) Wight and Arn.	Fr	Antidote for morphia poisoning
	Sd	Head lice, ringworm
	Bk	Snakebite wounds
Atalantia ceylanica (Arn.) Oliv.	Lf	Catarrah, bronchitis, chest complaints
	Rt	Ague
Catharanthus roseus (L.) G. Don	Lf	Diabetes, rheumatism, purgative
	Rt	Emmenagogue, antidysenteric purgative, depurative, hemostatic, toothache
Cyclea burmanii Miers	Pl	Expectorant, diuretic
	Lf	Wound healing, bleeding
Gloriosa superba L.	Tu	Bruises, sprains, blood diseases, swellings, wounds, abscesses, leprosy, piles, gonorrhea, impotency, ascites
Holarrhena mitis (Vahl.) R. Br. *ex* Roem & Schult.	Bk, Wd	Fevers, dysentery
	Bk	Antiperiodic
Limonia acidissima L.	Pl	Snakebite
	Bk	Biliousness
	Rt	Aromatic stimulant, stomachic, diarrhea, dysentery, throat ailments, insect bites
Mitragyna parvifolia (Roxb.) Korth.	Bk + Rt	Fever, colitis
Murraya koenigii (L.) Spreng.	Lf	Constipation, abdominal colic, diarrhea, dysentry, hoarseness, hiccough
	Bk + Lf + Rt	Tonic, stomachic
Pavetta indica L.	Rt	Visceral obstructions in children, dropsy
	Lf	Hemorrhoidal pains
	Wd	Rheumatism
Rauvolfia serpentina (L.) Benth. *ex* Kurz.	Lf	Eye diseases, snakebite
	Rt	Increase uterine contractions during childbirth, anthelmintic, fever, cholera, blood pressure, snakebite
Sida acuta Burm. f.	Lf	Boils, intestinal worms
	Sd	Inflammatory swellings
	Lf + Rt	Hemorrhoids, fevers, impotency, gonorrhea, rheumatism
Strychnos nux-vomica L.	Bk	Tonic for dyspepsia, pain after meals accompanied by diarrhea, leprosy, chronic syphilitic and other eruptions, intermittent fevers, epilepsy

(*continues*)

TABLE III (*Continued*)

Plant Species	Part[a]	Reported Medicinal Uses
	Lf	Ulcers
	Rt, Bk	Cholera
	Sd	Poisonous, given in small doses for paralytic and neuralgic affections, diarrhea, dysentery and debility of the spinal system
Tabernaemontana dichotoma Roxb.	Sd	Narcotic
	Lf	Purgative
Tabernaemontana divaricata R. Br. *ex* Roem & Schult.	Rt	Anthelmintic, toothache, eye diseases
	Ltx	Ophthalmia, sore eyes, skin diseases
Tylophora asthmatica Wight and Arn.	Lf + Rt	Dysentery, asthma, coughs, incipient tuberculosis
	Rt	Emetic, neuralgia, headache, substitute for ipecacuanha

[a] Bk, bark; Fr, fruit; Lf, leaf; Ltx, latex; Pl, whole plant; Rt, root; Sd, seed; Tu, tuber; Wd, wood.

alkaloids in these two surveys together with some useful information on their habitat and plant part(s) tested are presented in Table V.

A phytochemical screening of 104 plants used in the Sri Lankan traditional systems of medicine was reported by Gunatilaka and Sotheeswaran (*13*). Hot alcoholic extracts derived from plant material purchased from Ayurvedic shops were screened for alkaloids using Mayer's and Wagner's tests, and those showing positive responses were subjected to TLC examination. Of the 104 samples tested, 68 (ca. 65%) gave positive responses to all 3 alkaloid tests. This incidence is very much higher than the estimated occurrence of alkaloids in vascular plants and is not unexpected from a group of tropical plants with claims of pharmacological activity.

III. Quinoline Alkaloids

A. Distribution and Occurrence

Quinoline alkaloids are biogenetically derived from anthranilic acid and occur mainly in Rutaceous plants (*14*). These alkaloids were encountered in Sri Lankan plants of the families Annonaceae and Moraceae, in addition to the Rutaceae.

TABLE IV

ALKALOIDS FROM PLANTS OF SRI LANKA

Plant Source [Family]	Alkaloid(s) Encountered	Ref.
Actinodaphne speciosa Nees[a] [Lauraceae]	Laurotetanine (**30**)	*41*
	N-Methyllaurotetanine (**31**)	*41*
Adhatoda vasica Nees [Acanthaceae]	Vasicine (**212**)	*123*
Alseodaphne semicarpifolia Nees [Lauraceae]	Srilankine (**26**)	*38*
Alstonia macrophylla Wall. *ex* G. Don [Apocynaceae]	Alstomacrocine (**112**)	*84*
	(+)-Alstonamide (**146**)	*86,95*
	Alstonerine (**111**)	*79,82,88*
	Alstophylline (**110**)	*82,88*
	Alstopicralamine (**106**)	*85*
	Alstoumerine (**107**)	*86*
	Alstozine *N*-oxide (**104**)	*83*
	Anhydromacralstonine (**189**)	*82*
	Cabucraline (**103**)	*82*
	Demethoxyalstonamide (**147**)	*86*
	N_b-Demethylalstophylline oxindole (**160**)	*99*
	10-Hydroxystrictamine (**105**)	*84*
	19-Hydroxyvincamajine (**102**)	*82*
	Macralstonine (**188**)	*82,88*
	Macroxine-A (**159**)	*98*
	Talcarpine (**109**)	*82,88*
	Vincamajine (**101**)	*82*
	Vincorine (**145**)	*82*
	Yohimbine (**90**)	*79*
	β-Yohimbine (**91**)	*79*
Anamirta cocculus (L.) Wight & Arn. [Menispermaceae]	(−)-8-Oxo-tetrahydropalmatine (**62**)	*46*
	Oxypalmatine (**63**)	*46*
	Stepharine (**41**)	*44–46*
Ancistrocladus hamatus (Vahl.) Gilg.[a] [Ancistrocladaceae]	Ancistrocladine (**206**)	*117*
	Hamatine (**204**)	*117*
Annona reticulata L. [Annonaceae]	Cyathocaline (**53**)	*51*

Artabotrys zeylanicus Hook. f. & Thoms.[a] [Annonaceae]	Artabotrine (**50**)	*49*
	Atherospermidine (**42**)	*48,49*
	Lanuginosine (**43**)	*48*
	Liriodenine (**44**)	*48*
	8-Methoxyouregidione (**51**)	*48*
	Ouregidione (**52**)	*48*
	Oxobuxifoline (**45**)	*48*
	Oxocrebanine (**46**)	*48*
Atalantia ceylanica (Arn.) Oliv. [Rutaceae]	Atlanine (**21**)	*33*
	Ataline (**22**)	*33*
	5-Hydroxynoracronycine (**19**)	*34*
	5-Hydroxynoracronycine 5-(3-methylbut-2-enyl) derivative (**20**)	*34*
Broussonetia zeylanica (Thw.) Corner[a] [Moraceae]	Broussonetine (**4**)	*21*
	8-Hydroxyquinoline-4-carbaldehyde (**1**)	*15,16*
	8-Hydroxyquinoline-4-carbaldehyde oxime (**2**)	*19*
Cananga odorata (Lam.) Hook. f. & Thoms. [Annonaceae]	Cleistopholine (**6**)	*24*
	Eupolauridine (**55**)	*24,52*
	Liriodenine (**44**)	*24*
	Onychine (**54**)	*24*
	Oxopukateine (**49**)	*24*
Catharanthus pusillus (Murr.) G. Don [Apocynaceae]	Vincaleukoblastine (**186**)	*108*
	Vincristine (**187**)	*108*
Catharanthus roseus (L.) G. Don [Apocynaceae]	Vincaleukoblastine (**186**)	*108*
	Vincristine (**187**)	*108*
Cinchona ledgeriana Moens. [Rubiaceae]	5α-Carboxystrictosidine (**78**)	*70,71*
	Quinine (**9**)	*28*
Cyathocalyx zeylanica Champ. *ex* Hook. f. & Thoms.[a] [Annonaceae]	Cyathocaline (**53**)	*50*
Cyclea burmanii (DC.) Miers *ex* Hook. f. & Thoms. [Menispermaceae]	Phaeanthine (**23**)	*35*
	Tetrandrine (**24**)	*35*
	Limacine (**25**)	*37*
Diploclisia glaucescens (Bl.) Diels (syn: *Cocculus macrocarpus*) [Menispermaceae]	Glucescine (**40**)	*43*
	Stepharine (**41**)	*44*

(*continues*)

TABLE IV (*Continued*)

Plant Source [Family]	Alkaloid(s) Encountered	Ref.
Erythrina lithosperma Blume [Fabaceae]	Demethoxyerythratidinone (**59**)	*56,57*
	Erysotrine (**56**)	*56,57*
	Erythraline (**57**)	*56,57*
	Erythratidinone (**58**)	*56,57*
Gloriosa superba L. [Liliaceae]	Colchicine (**208**)	*118,120,122*
	2-Demethylcolchicine (**210**)	*120*
	N-Formyl-*N*-deacetylcolchicine (**209**)	*120*
	Lumicolchicine (**211**)	*120*
Glycosmis bilocularis Thw.[a] [Rutaceae]	Arborine (**214**)	*25*
	Arborinine (**10**)	*25*
	Glycorine (**213**)	*25*
	5-Hydroxyarborinine (**11**)	*25*
	Kokusaginine (**8**)	*25*
	Skimmianine (**7**)	*25*
Glycosmis mauritiana (Lam.) Tanaka [Rutaceae]	Des-*N*-methylacronycine (**18**)	*32*
	Glycomaurin (**70**)	*32*
	Glycomaurrol (**67**)	*32*
	Noracronycine (**17**)	*32*
Holarrhena mitis (Vahl.) R. Br. *ex* Roem. and Schult.[a] [Apocynaceae]	Conamine (**193**)	*113*
	Conessine (**190**)	*110,111,113*
	Conkurchine (**194**)	*111*
	N-Desmethylmitiphylline (**199**)	*112,114*
	Holadienmine (**195**)	*111*
	Holafebrine (**196**)	*111*
	Holarrhenine (**192**)	*111*
	Holarrhimine (**197**)	*111*
	Isoconessimine (**191**)	*111,113*
	N-3-Methylholarrhimine (**198**)	*111*
	Mitiphylline (**200**)	*112,114*
	Triacanthine (**215**)	*112–114*

Hunteria zeylanica (Retz.) Gardn. *ex* Thw.[a] [Apocynaceae]	Dihydrocorynantheol (**92**)	*78*
	(+)-Eburnamenine (**118**)	*78*
	Eburnamine (**113**)	*78*
	Epiyohimbol (**89**)	*78*
	O-Ethyleburnamine (**117**)	*78*
	Hydroxy-17-decarbomethoxy-16-dihydro-epiajmalicine (**87**)	*78*
	Isocorymine (**164**)	*78*
	Isoeburnamine (**114**)	*78*
	O-Methyleburnamine (**115**)	*78*
	O-Methylisoeburnamine (**116**)	*78*
	Pleiocarpamine (**167**)	*78*
	Tuboxenine (**169**)	*78*
	Vobasine (**138**)	*78*
	Yohimbol (**88**)	*78*
Limonia acidissima L. [Rutaceae]	Integriquinolone (**5**)	*23*
Litsea gardneri (Thw.) Hook. f.[a] [Lauraceae]	Actinodaphnine (**27**)	*41*
	Laurolitsine (**29**)	*41*
Luvunga angustifolia (Oliv.) Tan.[a] [Rutaceae]	5-Hydroxyarborinine (**11**)	*23*
	5-Methoxyarborinine (**12**)	*23*
Mitragyna parvifolia (Roxb.) Korth. [Rubiaceae]	Akuammigine N_4-oxide (**95**)	*80*
	Corynantheidol (**93**)	*80*
	Dihydrocorynantheol (**92**)	*80*
	Dihydrocorynantheol N_4-oxide (**94**)	*80*
	Isomitraphylline (**148**)	*97*
	Mitraphylline (**149**)	*96,97*
	Speciophylline *N*-oxide (**156**)	*80*
	Tetrahydroalstonine (**83**)	*80*
	Uncarine C (**152**)	*80*
	Uncarine D (**155**)	*80*
	Uncarine E (**151**)	*80*
	Uncarine F (**157**)	*80*
	Uncarine F *N*-Oxide (**158**)	*80*

(*continues*)

TABLE IV (*Continued*)

Plant Source [Family]	Alkaloid(s) Encountered	Ref.
Murraya gleniei Thw. *ex* Oliv. [Rutaceae]	Methyl 2-methyl-4-(*N*-2″β-methyl-1″,2″,3″,4″-tetrahydrocarbazol-1″α-yl-indol-3′-yl butanoate (**77**)	*67*
Murraya koenigii (L.) Spreng. [Rutaceae]	Girinimbol (**66**)	*61*
	Girinimbine (**68**)	*61,64*
	Koenimbine (**69**)	*64*
	Koenoline (**64**)	*60*
	Mahanimbilol (**73**)	*61*
	Mahanimbine (**75**)	*64*
	Murrayanine (**65**)	*60,61*
Neisosperma oppositifolia (Lam.) Fosberg & Sachet. (syn: *Ochrosia oppositifolia*) [Apocynaceae]	Bleekerine (**84**)	*76*
	3-Epirauvanine (**86**)	*76*
	Isocarapanaubine (**153**)	*75*
	Isoreserpiline (**82**)	*75,76*
	Neisosposinine (**154**)	*75*
	Ochroposinine (**85**)	*75,76*
	Reserpiline (**81**)	*75,76*
Neolitsea fuscata L.[a] [Lauraceae]	Isoboldine (**28**)	*42*
Neonauclea zeylanica (Hook. f.) Merr.[a] [Rubiaceae]	Neozeylanicine (**216**)	*124,125*
	6*S*-Hydroxy-7*R*-methyl-6,7-dihydro-2,5-pyrindene-4-carboxymethyl ester (**217**)	*124*
Petchia ceylanica (Wight) Livera[a] [Apocynaceae]	Ajmalicine (**80**)	*74*
	Demethylpeceyline (**182**)	*105*
	19*R*-Epimisiline (**143**)	*94*
	19*S*-Epimisiline (**144**)	*94*
	Lochnericine (**142**)	*74,106*
	Peceylanine (**184**)	*74,106*
	Peceyline (**183**)	*74,106*
	Pelankine (**185**)	*74,106*
Pleiospermium alatum (Wight and Arn.) Swingle [Rutaceae]	5,6-Dihydroxyarborinine (**13**)	*30*
	5,6-Dimethoxyarborinine (**15**)	*30*

	6-Hydroxy-5-methoxyarborinine (**14**)	*30*
	5-Hydroxyarborinine (**11**)	*23*
	5-Hydroxynoracronycine (**19**)	*30*
Rauvolfia serpentina (L.) Benth. *ex* Kurz. [Apocynaceae]	5α-Carboxystrictosidine (**78**)	*70,71*
	Strictosidine (**75**)	*70,71*
Sida acuta Burm. F. [Malvaceae]	Cryptolepine (**170**)	*102*
Sida cordifolia L. [Malvaceae]	Vasicine (**212**)	*102*
Strychnos nux-vomica L. [Loganiaceae]	5α-Carboxystrictosidine (**78**)	*70,71*
	Strictosidine (**75**)	*70,71*
Tabernaemontana dichotoma (L.) R. Br. *ex* Roem et Schult. (syn: *Ervatamia coronaria, E. divaricata, Tabernaemontana coronaria, Rejoua dichotoma*) [Apocynaceae]	*O*-Acetylvallesamine (**98**)	*81*
	(−)-Apparicine (**96**)	*81*
	Coronaridine (**119**)	*89*
	N_4-Demethyltabernamine (**174**)	*90,93*
	Dichomine (**160**)	*91,100*
	19*R*-Epiheyneanine (**127**)	*91*
	19*R*-Epiiboxygaine (**130**)	*92*
	19*R*-Epivoacristine (**124**)	*92*
	3′*R/S*-Hydroxy-N_4-demethylervahanine A (**179**)	*90,93*
	3′*R/S*-Hydroxy-N_4-demethylervahanine B (**180**)	*90,93*
	3′*R/S*-Hydroxy-N_4-demethyltabernamine (**176**)	*90,93*
	16*S*-Hydroxy-16,22-dihydroapparicine (**99**)	*81*
	3′*R/S*-Hydroxytabernamine (**177**)	*90,93*
	3′*R/S*-Hydroxyvoacamine (**178**)	*90*
	Ibogamine (**129**)	*89*
	Isomethuenine (**166**)	*92,93*
	3-Ketopropyl-coronaridine (**121**)	*91*
	3-Ketopropyl-epiheyneanine (**128**)	*93*
	12-Methoxyvoaphylline (**136**)	*91,92*
	Monogagaine (**181**)	*104*
	3,19*R*-Oxidocoronaridine (**131**)	*93*
	3-Oxocoronaridine (**120**)	*90*
	Perivine (**139**)	*92*
	(+)-Stemmadenine (**100**)	*81*

(*continues*)

TABLE IV (*Continued*)

Plant Source [Family]	Alkaloid(s) Encountered	Ref.
	Tabernamine (**173**)	*90*
	Tabersonine (**141**)	*89*
	Tubotaiwine (**168**)	*93,101*
	Vallesamine (**97**)	*81*
	Voacamine (**175**)	*90*
	Voacangine (**125**)	*89*
	Voacristine hydroxyindolenine (**132**)	*93*
	Voaphylline (**135**)	*89*
	Voaphylline hydroxyindolenine (**137**)	*89,91,92*
	Vobasine (**138**)	*91,92*
Tabernaemontana divaricata (syn: *Ervatamia coronaria, E. divaricata, Tabernaemontana coronaria*) [Apocynaceae]	Coronaridine (**119**)	*87*
	Isovoacangine (**126**)	*87*
	Isovoacristine (**123**)	*87*
	11-Methoxy-*N*-methyldihydropericyclivine (**108**)	*87*
	Tabernaemontanine (**140**)	*87*
	Voacristine (**122**)	*87*
	Vobasine (**138**)	*87*
Tylophora asthmatica Wight and Arn. [Asclepiadaceae]	Tylophorinidine (**203**)	*116*
	Tylophorine (**201**)	*116*
	Tylophorinine (**202**)	*116*
Uncaria elliptica (R. B. *ex* G. Dm.) [Rubiaceae]	Ajmalicine (**80**)	*72,73*
	Formosanine (Uncarine B) (**150**)	*73*
	Isomitraphylline (**148**)	*73*
	Mitraphylline (**149**)	*73,96*
	Roxburghine D (**171**)	*96*
	Roxburghine X (**172**)	*96*
Xylopia championii Hook. f. & Thoms.[a] [Annonaceae]	Dicentrinone (**47**)	*48*
	O-Methylmoschatoline (**48**)	*48*

[a] Endemic to Sri Lanka.

TABLE V

SRI LANKAN PLANT SPECIES GIVING POSITIVE TESTS FOR ALKALOIDS IN SURVEYS

Family Plant Name	Locality (Habitat)[c]	Part Tested[d]	Alkaloid Test[e]
ACANTHACEAE[a]			
Barleria prionitis L.	Naula (wgr)	Lf	M, W, T
Strobilanthes calycina Nees[b]	Horton Plains (mtf)	Lf	M
ALANGIACEAE[a]			
Alangium salviifolium (L. f.) Wangerin	Polonnaruwa (mdf)	Lf	M
AMARYLLIDACEAE[a]			
Crinum defixum Ker-Gawl.	Batticaloa (msh)	Fr	M, W, T
ANCISTROCLADACEAE			
Ancistrocladus hamatus (Vahl.) Gilg.[b]	Gilimale (raf)	Ft, Lf, Rt	M, W, T
ANNONACEAE[a]			
Alphonsea coriacea (Thw.) Finet & Gagnep.[b]	Kotiyagala (mtf)	Lf, Tw	M, T
Alphonsea lutea (Roxb.) Hook. f. & Thoms.	Wilpattu (mdf)	Lf, Tw	M, T
Alphonsea zeylanica Hook. f. & Thoms.	Peradeniya (clv)	Lf	M, T
Annona glabra L.	Negombo (mgr)	Lf, Tw	M, W, T
Annona squamosa L.	Colombo (wgr)	Tw	M, T
Artabotrys uncinatus (Lam.) Baill.	Ritigala (mdf)	Lf, Tw	M, T
Cananga odorata (Lam.) Hook. f. & Thoms.	Peradeniya (clv)	Lf	M, T
Desmos elegans (Thw.) Safford[b]	Kanneliya (raf)	Lf, Tw	M, T
Goniothalamus hookeri Thw.[b]	Hinidum kanda (raf)	Lf, Tw	M, T
Goniothalamus thwaitesii Hook. f. & Thoms.	Madugoda (smf)	Lf, Tw	M, T
Goniothalamus reticulatus Thw.[b]	Hinidum kanda (raf)	Lf, Tw	M, T
Miliusa zeylanica Gardn. *ex* Hook. f. & Thoms.	Madugoda (smf)	Lf, Tw	M, T
Mitrephora heyeana (Hook. f. & Thoms.) Thw.	Arankele (inf)	Lf	M, T
Polyalthia coffeoides (Thw. *ex* Hook. f. & Thoms.) Thw.	Ritigala (mdf)	Lf, Tw	M, T
Polyalthia korinti (Dunal) Thw.	Ratnapura (rfu)	Lf, Tw	M, T
Polyalthia longifolia (Sonnerat) Thw.	Ambalantota (clv)	Lf, Tw	M, T
Polyalthia suberosa (Roxb.) Thw.	Ambalantota (wgr)	Lf, Tw	M, T
Uvaria semecarpifolia Hook. f. & Thoms.[b]	Kanneliya (raf)	Lf, Tw	T
Uvaria sphenocarpa Hook. f. & Thoms.[b]	Kanneliya (raf)	Lf	M, T

(*continues*)

TABLE V (*Continued*)

Family Plant Name	Locality (Habitat)[c]	Part Tested[d]	Alkaloid Test[e]
Xylopia championii Hook. f. & Thoms.[b]	Kanneliya (raf)	Lf, Tw	M, T
Xylopia nigricans Hook. f. & Thoms.[b]	Peradeniya (clv)	Lf, Tw	M, T
Xylopia parvifolia Hook. f. Thoms.	Gilimale (raf)	Tw	M, T
APOCYNACEAE[a]			
Alstonia macrophylla Wall. *ex* G. Don	Udawatta-kelle (plf)	Lf	M, W, T
Alstonia scholaris R. Br.	Kitulgala (scf)	Lf, Tw	M, T
Ochrosia borbonica J. F. Gmel.	Galle (lwd)	Lf, Tw	M, T
Pagiantha dichotoma (Roxb.) Markgraf.	Badureliya (dsv)	Lf, Tw	M, W, T
Petchia ceylanica (Wight) Liverav.	Hanwella (wgr)	Tw	M, T
Rauvolfia densiflora (Wall.) Hook. f.	Ramboda (mtf)	Lf, Rt	M, T
Rauvolfia serpentina (L.) Benth. *ex* Kurz.	Peradeniya (clv)	Lf, Rt	M, T
ARACEAE[a]			
Amorphophallus dubius Bl.	Ambalangoda (wgr)	Co	M, T
ARALIACEAE[a]			
Schefflera racemosa (Wight) Harms	Illukkumbura (scf)	Lf, Tw, Fr	T
ARISTOLOCHIACEAE			
Apama siliquosa Lam.	Gilimale (raf)	Lf, Rt, Tw	M, W, T
ASCLEPIADACEAE			
Brachysteima srilankana Dassanayake & Jayasuriya[b]	Dikpatana (mtg)	Tu	T
Cryptolepis buchananii Roem. & Schult.	Madugoda (sfc)	Lf, Tw	M, T
Cryphostegia grandiflora R. Br.	Kalpitiya (cos)	Lf	M, T
Heterostemma tanjorense Wight & Arn.	Pottuvil (cos)	Lf, Tw	M, W, T
Tylophora flava Trim.[b]	Valaichennai (cos)	Pl	M, W, T
Tylophora indica (L.) Merr.	Arugam Bay (cts)	Lf, Tw	M, T
BEGONIACEAE[b]			
Begonia malabarica Lam.	Rattota (scf)	Lf, Tw	T
BERBERIDACEAE			
Berberis tinctoria Leschen	Nuwara-Eliya (scf)	Ft, Lf, Tw, Tm	M, W, T
BIGNONIACEAE[a]			
Stereospermum personatum (Hassk.) Chatterje	Rattota (scf)	Lf, Tw	M, T
BORAGINACEAE			
Heliotropium indicum L.	Tangalle (wgr)	Tw	T
Trichodesma indicum (L.) R. Br. *ex* A. DC.	Badulla/Mahiyangana (wgr)	Lf	M, T

BUXACEAE			
Sarcococca zeylanica Baill.	Horton Plains (mtf)	Lf, Tw	M, T
CAMPANULACEAE			
Lobelia nicotianifolia Heyne ex Roem	Ettampitiya (mtg)	Pl	M, T
CAPPARIDACEAE[a]			
Crataeva religiosa Forst. F.	Karathivu (cos)	Lf, Tw	M, W, T
CELASTRACEAE			
Elaeodendron glaucum (Rottb.) Pers.	Cheddikulam (mdf)	Lf	M, T
COMPOSITAE			
Artemisia dubia Wall. *ex* Bess.	Ambewela (clv)	Lf, Tw	T
Wedelia biflora L.	Arugam Bay (cod)	Lf, Tw	T
CONVOLVULACEAE			
Rivea ornata (Roxb.) Choisy	Pasikudah (tns)	Lf	T
ERYTHROXYLACEAE[a]			
Erythroxylum moonii Hochr.	Hinidum kanda (raf)	Lf, Tw	M, T
Erythroxylum obtusifolium (Wight) Hook. f.[c]	Madugoda (scf)	Lf, Tw	M, T
Erythroxylum zeylanicum O. E. Schultz[b]	Pasikudah (cos)	Lf, Tw	M, T
EUPHORBIACEAE			
Acalypha godseffiana Mast	Peradeniya (clv)	Lf, Tw	M, T
Excoecaria agallocha L.	Pottuvil (mgr)	Lf, Tw, Fr	T
Jatropha podagrica	Peradeniya (clv)	Lf, Tw	T
Macaranga indica Wight	Thangamalai (scf)	Lf, Tw	T
Phyllanthus cinereus Meull. Arg.	Ritigala (wgr)	Lf	T
Pedilathus tithymaloides (L.) Poit.	Peradeniya (clv)	Lf, Tw	T
Ricinus communis L.	Peradeniya (clv)	Fr, Tw	M, T
Sapium indicum Willd.	Peradeniya (clv)	Fr, Lf, Tw	T
FLACOURTIACEAE			
Casearia thwaitesii Briq.[b]	Horton Plains (mtf)	Lf, Tw	M, T
Erythrospermum zeylanicum (Gaertn.) Alston[c]	Morapitiya (raf)	Tw	M, T
Hydronocarpus octandra Thw.[b]	Hinidum kanda (raf)	Lf, Tw	T
GOODENIACEAE			
Scaevola plumieri (L.) Vahl.	Arugam Bay (cod)	Tw	M, T
GUTTIFERAE			
Garcinia echinocarpa Thw.[b]	Rangala (mtf)	Lf, Tw	T
HERNANDIACEAE[a]			
Gyrocarpus americanus Jacq.	Badulla (ddf)	Pl	M, T

(*continues*)

TABLE V (*Continued*)

Family Plant Name	Locality (Habitat)[c]	Part Tested[d]	Alkaloid Test[e]
HYDROPHYLLACEAE			
Hydrolea zeylanica (L.) Vahl.	Kekirawa (msh)	Lf, St	M, W, T
ICACINACEAE[a]			
Urandra apicalis Thw.[b]	Hinidum kanda (raf)	Lf, Tw	M, T
LAURACEAE			
Actinodaphne albifrons Kosterm.	Hinidum kanda (raf)	Lf, Tw	M, T
Actinodaphne elegans Thw.[b]	Hakgala (mtf)	Lf, Tw	M, T
Actinodaphne speciosa Nees[c]	Namunukula (mtf)	Lf, Tw	M, T
Actinodaphne stenophylla Thw.[b]	Rattota (scf)	Lf, Tw	M, T
Alseodaphne semecarpifolia Nees	Madugoda (scf)	Lf, Tw	M, T
Cinnamomum capparucoronde Kosterm.[b]	Hinidum kanda (raf)	Lf, Tw	M, T
Cinnamomum zeylanicum Bl.	Tangamalai (mtf)	Lf, Tw	M, T
Cryptocarya wightiana Thw.	Hinidum kanda (raf)	Tw	M, T
Litsea deccanensis Gamble	Mahakanda (scs)	Lf, Tw	T
Litsea glutinosa (Lour.) C. E. Rob	Madugoda (scf)	Lf, Tw	M, T
Litsea longifolia (Nees) Alston[b]	Kitulgala (raf)	Lf, Tw	T
Litsea ovalifolia (Wight) Hook. f.[b]	Namunukula (mtf)	Lf, Tw	T
Neolitsea fuscata (Thw.) Alston[b]	Hakgala (mtf)	Lf, Tw	M, T
LEGUMINOSAE			
Abrus precatorious L.	Argum Bay (cos)	Lf, Tw	M, T
Adenanthera agalosperma Alston	Gilimale (raf)	Lf, Tw	M, T
Crotolaria calycina Schrank	Godakawela (wgr)	Lf, Tw, Rt	M, T
Crotolaria juncea L.	Peradeniya (clv)	Sd	M, W, T
Crotolaria usaramoensis Bak. F.	Moneragala (wgr)	Lf, Tw	M, T
Crotolaria verrucosa L.	Pottuvil (cod)	Sd	M, W, T
Crotolaria walkeri Arn.[b]	Ambewela (mtf)	Lf, Tw	T
Dalbergia pseudo-sissoo Miq.	Ratnapura (raf)	Lf, Tw	T
Erythrina constantiana Micheli	Peradeniya (clv)	Lf, Tw	M, T
Erythrina lithosperma Miguel	Balangoda (clv)	Rt, Sd	M, T
Erythrina lysistemon Hutchinson	Peradeniya (clv)	Lf, Tw	M, T
Erythrina variegata L.	Balangoda (clv)	Lf, Tw	T
Pongamia pinnata (L.) Pierre	Madugoda (scf)	Lf, Tw	T

Sophora tomentosa L.	Kalkudah (tns)	Lf, Tw	M, W, T
Tephrosia maxima (L.) Pers.	Tangalle (cos)	Lf, Tw	M, W, T
LILIACEAE			
Asparagus racemosus Willd.	Arugam Bay (cos)	Lf, Tw	T
Gloriosa superba L.	Madugoda (scf)	Tu	T
Scilla hyacinthina (Roth) J. F. Macbr.	Puttalam (csg)	Bu	T
LOGANIACEAE[a]			
Fagraea ceilanica Thunb. (= *F. zeylanica* Thunb.)	Kanneliya (raf)	Fr	M, W, T
Fagraea obovata Wall.	Batticaloa (msf)	Ft, Lf, Tw	M, W, T
Strychnos nux-vomica L.	Arugam Bay (cos)	Lf, Tw	M, T
MALVACEAE			
Sida cordifolia L.	Adala-chinai (wgr)	Pl	T
MELIACEAE[a]			
Pseudocarapa championii (Thw.) Hemsl.[b]	Ratnapura (raf)	Lf, Tw	T
MENISPERMACEAE[a]			
Cocculus hirsutus (L.) Diels.	Madawela (scf)	Lf, Tw	M, T
Coscinium fenestratum (Gaertn.) Colebr.	Kanneliya (raf)	Lf, Tw	M, T
Cyclea burmanii (DC.) Miers *ex* Hook. f. & Thoms.	Madugoda (wgr)	Lf, Tw	M, T
Diploclisia glaucescens (Bl.) Diels	Madugoda (scf)	Lf, Tw	M, T
Pachygone ovata (Poir.) Miers *ex* Hook. f. & Thoms.	Cheddikulam (scf)	Lf, Tw	M
Tinospora malabarica (Lam.) Miers *ex* Hook. f. & Thoms.	Anuradhapura (msf)	Pl	M, W, Q
MONIMIACEAE[a]			
Hortonia angustifolia (Thw.) Trim.[b]	Kanneliya (raf)	Lf, Tw	M, T
Hortonia floribunda Wight & Arn.	Hakgala (mtf)	Lf, Tw	M, T
MORACEAE[a]			
Broussonetia zeylanica (Thw.) Corner[b] (= *Allaeanthus zeylanicus* Thw.)	Ettampitiya (scf)	Lf, Tw	T
Ficus hispidus L. f.	Balangoda (wgr)	Lf	M, T
Ficus nervosa Heyne *ex* Roth	Godakawela (wsd)	Lf	T
Streblus asper (Retz.) Lour	Teldeniya (scf)	L	M, T
MYRSINACEAE[a]			
Ardisia missionis Wall. *ex* DC.	Rattota (scf)	Lf, Tw	T
Maesa perrottetiana A. DC.	Ratnapura (wgr)	Lt, Tw	T
MYRTACEAE[a]			
Eugenia rotundata (Trim.) Trim.[b]	Rattota (scf)	Lf, Tw	T
Eugenia xanthocarpa Thw.[b]	Peradeniya (clv)	Tw	T
Rhodomyrtus parviflora Alston	Hakgala (mtf)	Lf, Tw	T

(*continues*)

TABLE V (*Continued*)

Family Plant Name	Locality (Habitat)[c]	Part Tested[d]	Alkaloid Test[e]
Syzgium neesianum Arn.[b]	Gilimale (raf)	Lf, Tw	T
Syzygium sclerophyllum Thw.[b]	Namunukula (mtf)	Lf, Tw	T
Syzygium spathulatum Thw.[b]	Rattota (scf)	Lf	T
OCHNACEAE[a]			
Ouratea zeylanica (Lam.) Alston	Hinidum kanda (raf)	Lf	T
		Tw	M, T
OLEACEAE			
Linociera zeylanica (L.) Gamble	Puttalam (tns)	Lf, Tw	M, W, T
ORCHIDACEAE			
Arundina graminifolia (D. Don) Hochr.	Godakawela (msh)	Lf, Tw	T
OXALIDACEAE[a]			
Biophytum reinwardtii (Zucc.) Klotzch.	Ambalangoda (wgr)	Pl	T
PALMAE[a]			
Borassus flabellifer L.	Jafna (clv)	Rz	T
PAPAVARACEAE			
Argemone mexicana L. (= *Argemone hispida* Gray)	Tangalle (wgr)	Lf, Tw	M, W, T
PASSIFLORACEAE[a]			
Adenia palmata (Lam.) Engl.	Porowagama (scf)	Lf, Tw	T
PEDLIACEAE[a]			
Pedalium murex L.	Arugam Bay (cod)	Rt, Tw	T
RANUNCULACEAE			
Ranunculus sagittifolius Hook.	Ambewela (msh)	Lf, Tw	T
RHAMNACEAE			
Ventilago maderaspatana Gaertn.	Balangoda (scs)	Lf	T
Zizyphus oenoplia (L.) Mill.	Madugoda (wgr)	Pl	M, T
RHIZOPHORACEAE[a]			
Anisophyllea cinnamomoides (Gardn. & Champ.) Alston[b]	Hinidum kanda (raf)	Lf	T
		Tw	M, T
Carallia brachiata (Lour.) Merr.	Madugoda (scf)	Lf, Tw	T
Cassipourea ceylanica (Gardn.) Alston	Arugam Bay (cos)	Lf, Tw	M, T
RUBIACEAE			
Allaeophania decipiens Thw.[b]	Horton Plains (mtf)	Lf, Tw	T

Canthium montanum Thw.[b]	Pattipola (mtf)	Lf, Tw	T
Gardenia fosbergii Tirv.[b]	Pethiyagoda (dsv)	Fr	M, W, T
Ixora arborea Roxb. *ex* Sm.	Cheddikulam (mdf)	Fr, Lf, Tw	T
Knoxia platycarpa Arn.[b]	Namunukula (mtg)	Lf, Tw	T
Lasianthus strigosus Wight[b]	Ratnapura (mtf)	Lf, Tw	T
Leucocodon reticulatum Gardn.	Rajamally (mtf)	Lf, Tw	T
Mitragyna parvifolia (Roxb.) Korth.	Dambulla (swf)	Lf, Tw	M, T
Morinda tinctoria Roxb.	Arugam Bay (cos)	Tw	T
Nauclea orientalis (L.) L.	Maha oya (swf)	Bk	T
Pavetta gleniei Thw. *ex* Hook. f.[b]	Madewala (mdf)	Lf, Tw	M, T
Pavetta indica L.	Arugam Bay (cos)	Lf, Tw	M, T
Pavetta indica var. *montana* Thw. (= *P. blanda* Bremek.)	Balangoda (wgr)	Lf, Tw	M, T
Randia dumetorum Lam.	Cheddikulam (tns)	Lf, Tw	T
Randia gardneri (Thw.) Hook. f.	Rattota (scf)	Lf	T
Uncaria thwaitesii (Hook. f.) Alston[b]	Kandy (scf)	Bk, Lf, Tm, Tw	M, T
Urophyllum zeylanicum (Wight) Thw.	Rajamally (mtf)	Lf, Tw	T
RUTACEAE			
Acronychia pedunculata (L.) Miq.	Madugoda (scf)	Lf, Tw	T
Atalantia ceylanica (Arn.) Oliv.[b]	Madugoda (scf)	Lf, Tw	T
Atalantia monophylla DC.	Madugoda (scf)	Lf, Tw	T
Clausena dentata (Willd.) M. Roem	Cheddikulam (mdf)	Lf, Tw	T
Clausena indica (Dalz.) Oliv.	Polonnaruwa (msf)	Bk, Ft, Lf, Sd, Tw	T
Euodia lunu-ankenda (Gaertn.) Merr.	Horton Plains (mtf)	Lf, Tw	T
Glycosmis bilocularis Thw.[b]	Cheddikulam (mdf)	Lf, Tw	T
Luvunga angustifolia (Oliv.) Tan.	Kanneliya (raf)	Lf	T
Micromelum ceylanicum Swingle	Madugoda (scf)	Lf, Tw	M, T
Murraya paniculata (L.) Jack	Balangoda (clv)	Lf, Tw	T
Paramignya monophylla Wight	Udawattakelle (plf)	Tw	T
Toddalia asiatica (L.) Lam.	Balangoda (scs)	Lf, Tw	T
SAPINDACEAE			
Lepisanthes tetraphylla (Vahl.) Radlk.	Amparai (msf)	Bk	M, W, T
SCROPHULARIACEAE			
Artanema longifolia (L.) Vahl.	Gilimale (msh)	Lf, Tw	M, W, T
SIMAROUBACEAE			
Samadera indica Gaertn.	Gilimale (raf)	Rt	M, W, T

(*continues*)

TABLE V (*Continued*)

Family Plant Name	Locality (Habitat)[c]	Part Tested[d]	Alkaloid Test[e]
SOLANACEAE			
Physalis minima L.	Kanneliya (wgr)	Pl	M, W, T
Solanum seaforthianum Andr.	Dambulla (scs)	Fr, Pl	M, W, T
STAPHYLACEAE			
Turpinia malabarica Gamble	Namunukula (mtf)	Lf, Tw	T
SYMPLOCACEAE			
Cordyloblaste pendula (Wight) Alston[b]	Namunukula (scf)	Lf, Tw	T
TACCACEAE[a]			
Tacca pinnatifida J. R. & G. Forst (= *T. leontopetaloides* (L.) Kuntze.)	Valaichenai (cos)	Rh	M, W, T
THEACEAE			
Gordonia ceylanica Wight[c]	Rangala (mtf)	Lf, Tw	T
THYMELAEACEAE			
Gnidia eriocephala Meisn.	Embilipitiya (scs)	Lf, Tw	T
TILIACEAE			
Grewia microcos L.	Balangoda (scs)	Lf, Tw	M, T
VERBENACEAE[a]			
Premna procumbens Moon	Arugam Bay (cos)	Lf, Tw	M, T
VIOLACEAE			
Hybanthus enneaspermus (L.) F. Muell.	*Batticoloa* (wgr)	Pl	M, W, T
VITACEAE			
Ampellocissus indica (L.) Planch	Hinidum kanda (raf)	Fr	M, T
ZINGIBERACEAE[a]			
Cyphostigma pulchellum (Thw.) Benth.[b]	Ratnapura (raf)	Lf, Pl, Rz, Tw	M, T T

[a] Tropical family.

[b] Species endemic to Sri Lanka.

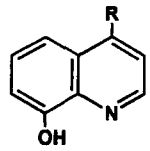
[c] aqt, aquatic; clv, cultivated; cod, coastal dune; cos, coastal scrub; csg, coastal grassland; cts, coastal thorn scrub; ddf, deciduous dry forest; dsf, disturbed forest; dsv, disturbed vegetation; ffd, fallow field; inf, intermediate forest; lwd, littoral woodland; mdf, mixed deciduous forest; mdfm, mixed deciduous forest margin; mgr, mangrove; mgs, mangrove swamp; msg, marshy ground; msh, marsh; mtf, montaine forest; mtg, montaine grassland; plf, planted forest; raf, rain forest; rfu, rain forest undergrowth; rvs, riverside; scs, secondary scrub; sfc, secondary forest clearing; smf, submontaine forest; svn, savannah; swf, swamp forest; tsc, thorn-scrub near coast; wgr, waste ground; wsd, wayside.

[d] Bk, stem bark; Bu, bulb; Fr, fruits; Lf, leaf; Pd, pod; Pl, whole plant; Rt, root; Rz, rhizome; Sd, seed; Tm, timber; Tw, twigs.

[e] M, Meyer's test; W, Wagner's test; T, TLC (Dragendorff's and/or Iodoplatinate spray reagent); Q, quaternary alkaloids.

B. Simple Quinolines and Quinolones

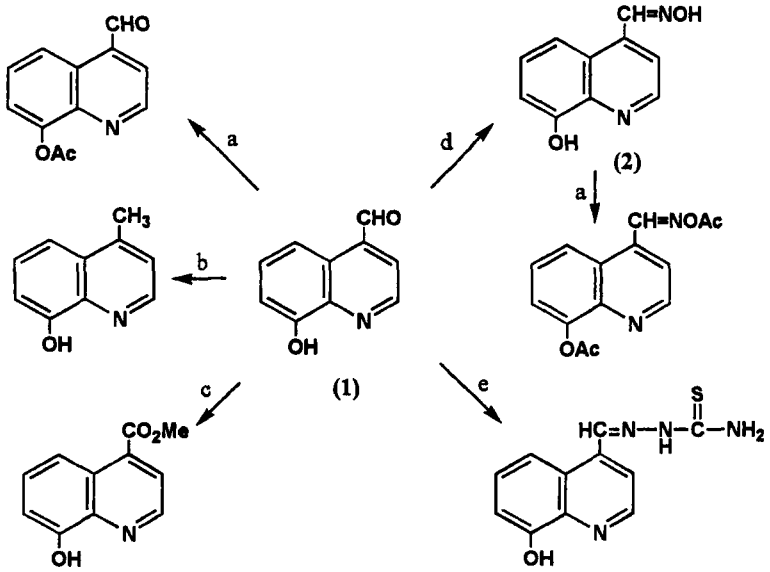
A series of simple, new 8-hydroxyquinoline (oxine) alkaloids was isolated from the timber of *Broussonetia zeylanica* Thw., an endemic plant of the family Moraceae. Fractionation led to the isolation of the major alkaloidal constituent, 8-hydroxyquinoline-4-carbaldehyde (**1**) $C_{10}H_7NO_2$, mp 155–156°C, in 0.25% yield from the dried timber (*15*). The structure of **1** was established with the aid of spectroscopic data and chemical derivatization



(1) R = CHO 8-Hydroxyquinoline-4-carbaldehyde

(2) R = CH=NOH 8-Hydroxyquinoline-4-carbaldehyde oxime

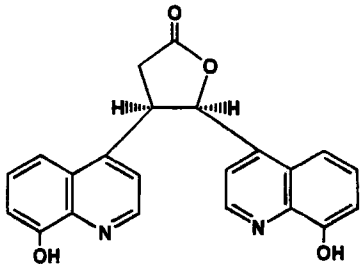
(3) R = $CH(OD)OCD_3$



SCHEME 1. Reagents: a. Ac_2O, pyridine, 25°C, 2 h; b. $NH_2NH_2 \cdot H_2O$, pyridine, reflux, 3 h; c. MnO_2, NaCN, MeOH, HOAc, 25°C, 2h; d. $NH_2OH \cdot HCl$, pyridine 100°C, 3h; e. $NH_2NHC(=S)NH_2$, EtOH, H_2O, 100°C, 0.5 h.

(Scheme 1). Changes observed in the ^{1}H NMR spectrum of **1** in methanol-d_4 were attributed to the *in situ* formation of its hemiketal **3** (*16,17*).

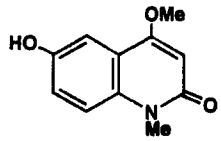
Two minor alkaloids were also isolated from *B. zeylanica* timber. The structure of one of these, $C_{10}N_8N_2O_2$, mp 223–224°C, was revised from 3,4-dihydroxy-2,2′-bipyridine (*18*) to 8-hydroxyquinoline-4-carbaldehyde oxime (**2**) based on synthetic, ^{1}H NMR and nuclear overhauser effect (NOE) difference NMR spectroscopic evidence (*19*). Natural occurrence of oximes, although rare in higher plants, is not without precedence, and the essential oil of *Ruta montana* L. has been reported to contain the bis-oxime of 3,4-hexanedione (*20*). The structure of the nonpolar minor alkaloid broussonetine, $C_{22}H_{16}N_2O_4$, mp 238–239°C, was elucidated as 3,4-bis(8-hydroxyquinolin-4-yl)-γ-butyrolactone (**4**) (*21*).



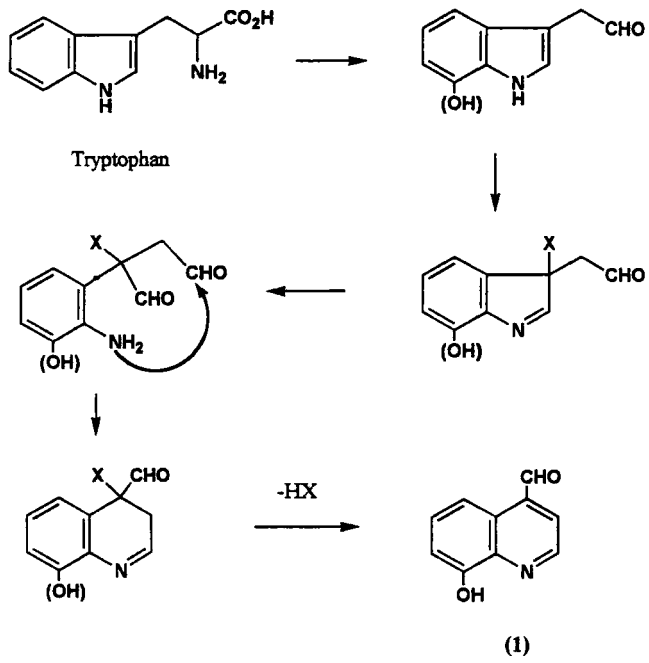
(**4**) Broussonetine

The isolation of alkaloids bearing the 8-hydroxyquinoline moiety prompted postulation (*17*) of a biosynthetic pathway to **1** from the amino acid tryptophan, for which chemical analogies are known (*22*) (Scheme 2). It should be noted, however, that, in general, quinolines are biosynthesized from anthranilic acid (*14*). Biosynthesis of broussonetine (**4**) would involve condensation of two molecules of **1** with a molecule of acetyl-CoA followed by cyclization, as depicted in Scheme 3.

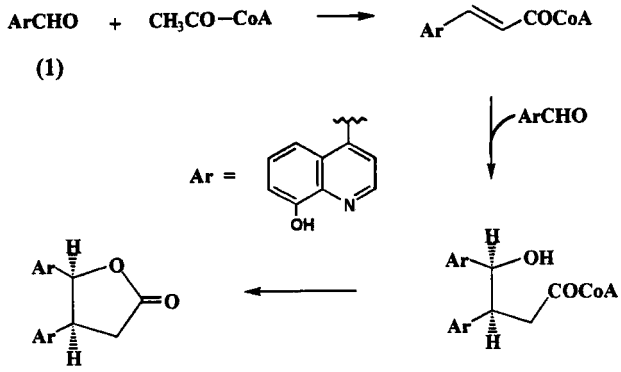
A known quinolone alkaloid, integriquinolone (**5**), has been reported from *Limonia acidissima* (L.) Swingle (syn: *Feronia limonia; Feronia elephantum*) of the family Rutaceae (*23*). The structure elucidation of **5** involved application of ^{1}H and ^{13}C NMR, NOE difference spectroscopy, and derivatization to its monoacetate.



(**5**) Integriquinolone



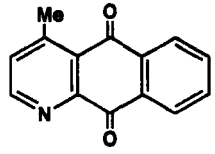
SCHEME 2.



SCHEME 3.

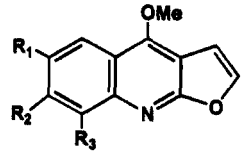
C. Benzo- and Furoquinolines

Cleistopholine (**6**), a simple benzoquinoline alkaloid first encountered in *Cleistopholis patens* (Annonaceae), was isolated from the Sri Lankan Annonaceae *Cananga odorata* (Lam.) Hook. f. and Thoms. (*24*). Furoqui-



(**6**) Cleistopholine

nolines, which are common in Rutaceous plants, were found to occur in *Glycosmis bilocularis* Thw., a rare species found in the dry zone of Sri Lanka. Two simple furoquinolines were isolated from the leaves of this plant and characterized as skimmianine (**7**) and kokusaginine (**8**) (*25*).

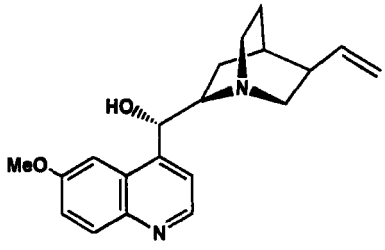


(**7**) $R_1 = H$; $R_2 = R_3 = OMe$ Skimmianine

(**8**) $R_1 = R_3 = OMe$; $R_2 = H$ Kokusaginine

D. *Cinchona* Alkaloids

Plants belonging to the genus *Cinchona* of the family Rubiaceae are not indigenous to Sri Lanka. *Cinchona ledgeriana* Moens. was introduced into Sri Lanka with the sole intention of exporting its bark (*26,27*) to extract the antimalarial quinoline alkaloid quinine (**9**) and its D-isomer, quinidine,



(**9**) Quinine

an alkaloid used in the treatment of cardiac arrhythmias. Wijesekara and co-workers recognized the necessity of devising a simple technique for demonstrating the distribution of these alkaloids in various specimens of *Cinchona* submitted by exporters (*28*). Their method involved a two-dimensional TLC analysis employing Si gel plates and the developing solvent systems $CHCl_3$–MeOH–17% NH_3 (24:6:0.05,v/v/v) and diethyl ether–diethylamine (17:1,v/v). This TLC method has been recently used to estimate the alkaloid contents of bark samples from over 100 *Cinchona* trees growing in Sri Lanka, and it was found that the highest alkaloid contents were observed in trees occurring at elevations of 1000–2500 m (*29*).

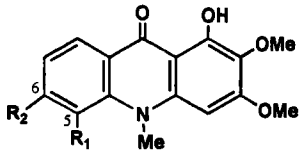
IV. Acridone Alkaloids

A. Distribution and Occurrence

Acridone alkaloids bear some resemblance to quinolines in that they have a common biosynthetic origin from anthranilic acid and are restricted to plants of the family Rutaceae. Sri Lankan species of Rutaceae in which acridone alkaloids have been encountered include *Atalantica ceylanica* (Arn.) Oliv., *Glycosmis bilocularis* Thw., *Glycosmis mauritiana* (Lam.) Tanaka, *Luvunga angustifolia* (Oliv.) Tan., and *Pleiospermium alatum* (Wight and Arn.) Swingle (syn: *Hesperethusa alata*).

B. Simple Acridones

Coincidentally, all alkaloids belonging to this class occurring in Sri Lankan plants bear a common 1-hydroxy-2,3-dimethoxy substitution. Arborinine [1-hydroxy-2,3-dimethoxy-10-methyl-9-acridone (**10**)], an



(**10**) $R_1 = R_2 = H$ Arborinine

(**11**) $R_1 = OH$, $R_2 = H$ 5-Hydroxyarborinine

(**12**) $R_1 = OMe$, $R_2 = H$ 5-Methoxyarborinine

(**13**) $R_1 = R_2 = OH$ 5,6-Dihydroxyarborinine

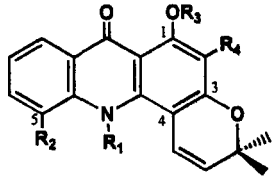
(**14**) $R_1 = OMe$, $R_2 = OH$ 6-Hydroxy-5-methoxyarborinine

(**15**) $R_1 = R_2 = OMe$ 5,6-Dimethoxyarborinine

acridone with only these substituents, was encountered in the leaves of *Glycosmis bilocularis* (*25*). 5-Hydroxyarborinine (**11**), $C_{16}H_{15}NO_5$, mp 206–207°C, is a new alkaloid first isolated from this plant (*25*), and subsequently from *Luvunga angustifolia* (*23*) and *Pleiospermium alatum* (*23,30*). The monomethylated derivative of **11**, 5-methoxyarborinine (**12**), $C_{17}H_{17}NO_5$, mp 130–132°C, is another new alkaloid encountered in *Luvunga angustifolia* (*23*). In addition to **11**, *Pleiospermium alatum* yielded two new simple acridone alkaloids, 5,6-dihydroxyarborinine (**13**), $C_{16}H_{15}NO_6$, mp 118–119°C, and 5,6-dimethoxyarborinine (**15**), $C_{18}H_{19}NO_6$, mp 198–200°C (*30*). Another derivative of arborinine, 6-hydroxy-5-methoxyarborinine (**14**), was also isolated from the same plant (*30*).

C. Pyranoacridones

Although the antitumor pyranoacridone alkaloid acronycine (**16**) has not been isolated from any Sri Lankan plant, several of its derivatives have been found to occur in those species investigated. It is noteworthy that the bark of *Acronychia laurifolia,* a plant of the genus from which acronycine has been encountered, is used in indigenous systems of medicine in Sri Lanka for the treatment of sores and ulcers (*9,31*). A report has appeared on the isolation of noracronycine (**17**) and des-*N*-methylacronycine (**18**) from the stem bark of *Glycosmis mauritiana* (*32*), a small tree growing in the dry zone of Sri Lanka. Two new pyranoacridones, 5-hydroxynoracronycine (**19**), $C_{19}H_{17}NO_4$, mp 252–254°C, and its 2-(3-methylbut-2-enyl) derivative (**20**), $C_{24}H_{25}NO_4$, mp 190–191.5°C, have been isolated from the bark of *Atalantia ceylanica* (*33,34*). 5-Hydroxynoracronycine (**19**) was also found to occur in the root bark of *Pleiospermium alatum* (*30*).

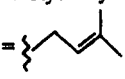


(16) $R_1 = R_3 = Me$, $R_2 = R_4 = H$ Acronycine

(17) $R_1 = Me$, $R_2 = R_3 = R_4 = H$ Noracronycine

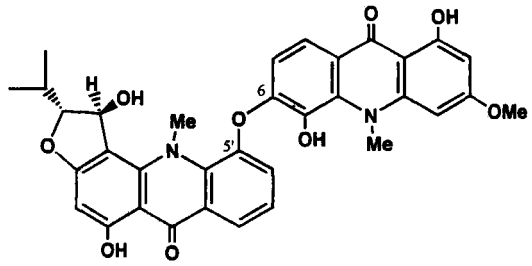
(18) $R_1 = R_2 = R_4 = H$, $R_3 = Me$ Des-*N*-methylacronycine

(19) $R_1 = Me$, $R_2 = OH$, $R_3 = R_4 = H$ 5-Hydroxynoracronycine

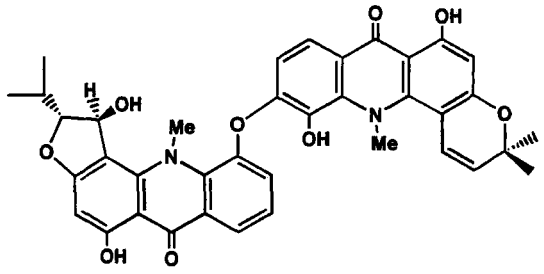
(20) $R_1 = Me$, $R_2 = OH$, $R_3 = H$, $R_4 =$ 

D. Binary Furanoacridone Alkaloids

Binary furanoacridones constitute a rare group of acridone alkaloids found restricted thus far to the Sri Lankan Rutaceae, *Atalantia ceylanica.* Two novel binary furanoacridones, atalanine (**21**), $C_{34}H_{30}N_2O_9$, mp 216.5–217.5°C, and ataline (**22**), $C_{38}H_{34}N_{20}O_9$, mp 209–210°C, were isolated from this plant and their structures were elucidated with the aid of spectroscopic



(21) Atalanine



(22) Ataline

data (*33*). A biogenetic pathway for these alkaloids via radical coupling has been proposed, and, based on these arguments, location of the ether linkage in both alkaloids was tentatively assigned to C-5′–C-6.

V. Isoquinoline Alkaloids

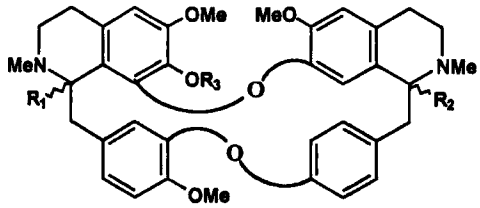
A. Distribution and Occurrence

Isoquinoline alkaloids are the second major class of alkaloids encountered in Sri Lankan flora and occur mainly in the families Annonaceae, Berberidaceae, Fabaceae, Lauraceae, and Menispermaceae. Plants of the Annonaceae have

been a recent focus of interest due to the occurrence of antitumor alkaloids in this family. *Erythrina* alkaloids, which are biosynthetically derived from benzylisoquinolines, are known from plants of the genus *Erythrina.*

B. Bisbenzylisoquinolines

Investigation of the roots of *Cyclea burmanii* (Menispermaceae) collected at Peradeniya (elevation: ca. 500 m) has afforded phaeanthine (**23**), $[\alpha]_D$ −214° (*35*). However, *C. burmanii* collected in Trivandrum (India) has been found to contain tetrandrine (**24**) (*36*), the enantiomer of phaeanthine (**23**). Noting this difference, Wannigama and co-workers were prompted to investigate *C. burmanii* collected in hot humid coastal plains



(23) R_1 = α-H, R_2 = β-H, R_3 = Me Phaeanthine

(24) R_1 = β-H, R_2 = α-H, R_3 = Me Tetrandrine

(25) R_1 = α-H, R_2 = β-H, R_3 = H Limacine

of Sri Lanka about 40 km south of Colombo, the environment being similar to that of Trivandrum, and this resulted in the isolation of tetrandrine (**24**) as the major alkaloid (*35*). Thus, the authors have emphasized the importance of the site of collection of a plant, especially when required for medicinal use. Further, the optical purity of phaeanthine (**23**) was established by the use of the chiral NMR shift reagent $Eu(tfc)_3$. The roots of *C. burmanii* are also known to contain the phenolic bisbenzylisoquinoline alkaloid limacine (**25**) (*37*).

C. Aporphine and Related Alkaloids

A variety of aporphine, proaporphine, oxoaporphine, and 4,5-dioxoaporphine alkaloids are known from plants of the families Annonaceae, Lauraceae, and Menispermaceae.

1. Aporphines

Srilankine, $C_{20}H_{23}NO_5$, $[\alpha]_D$ +122°, a new 4-hydroxylated aporphine alkaloid isolated from the endemic species *Alseodaphne semicarpifolia* Nees

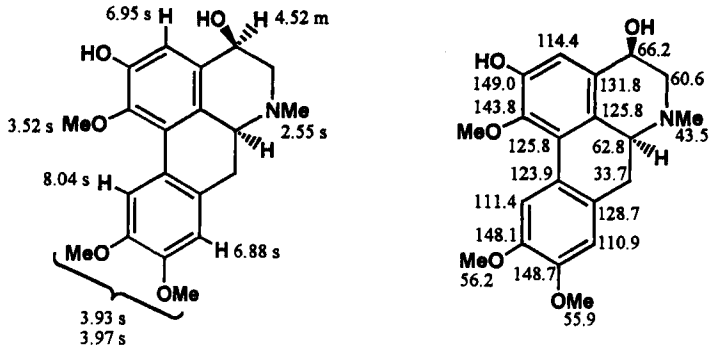
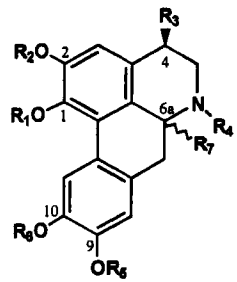


FIG. 1. ^{1}H and ^{13}C NMR data for srilankine (**26**).

(Lauraceae), was assigned the structure **26** based on spectroscopic evidence (*38*). The oxygenation pattern of the aromatic rings and the presence of a C-2 phenolic function were determined by its UV spectrum, coupled with base-induced bathochromic shifts. The location of the hydroxy function at C-4, its stereochemical disposition, and the stereochemistry of 6a-H were determined with the help of ^{1}H and ^{13}C NMR data and comparison with those of known compounds. The ^{1}H and ^{13}C NMR assignments for srilankine (**26**) are depicted in Fig. 1.



(**26**) $R_1 = R_2 = R_4 = R_5 = R_6 =$ Me, $R_3 =$ OH, $R_7 = \alpha$–H Srilankine

(**27**) $R_1, R_2 = CH_2$, $R_3 = R_4 = R_5 =$ H, $R_6 =$ Me, $R_7 = \alpha$–H Actinodaphnine

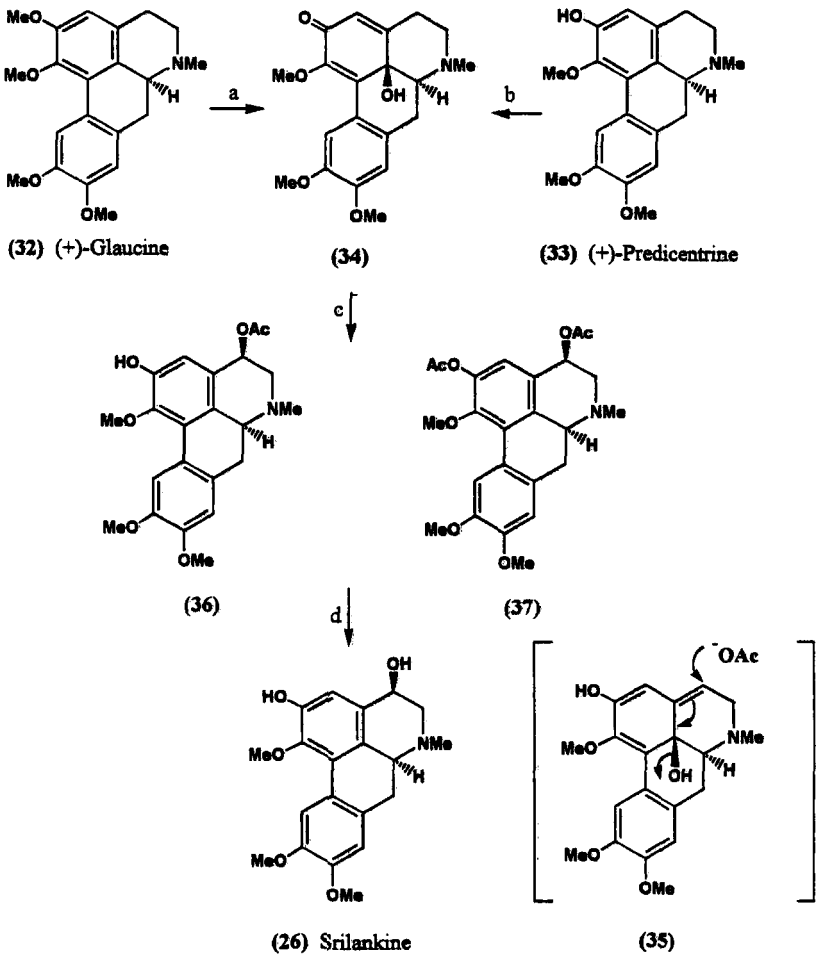
(**28**) $R_1 = R_3 = R_5 = R_7 =$ H, $R_2 = R_4 = R_6 =$ Me Isoboldine

(**29**) $R_2 = R_3 = R_4 = R_5 =$ H, $R_1 = R_6 =$ Me, $R_7 = \beta$–H Laurolitsine

(**30**) $R_1 = R_2 = R_6 =$ Me, $R_3 = R_4 = R_5 =$ H, $R_7 = \beta$–H Laurotetanine

(**31**) $R_1 = R_2 = R_4 = R_6 =$ Me, $R_3 = R_5 =$ H, $R_7 = \alpha$–H *N*-Methyllaurotetanine

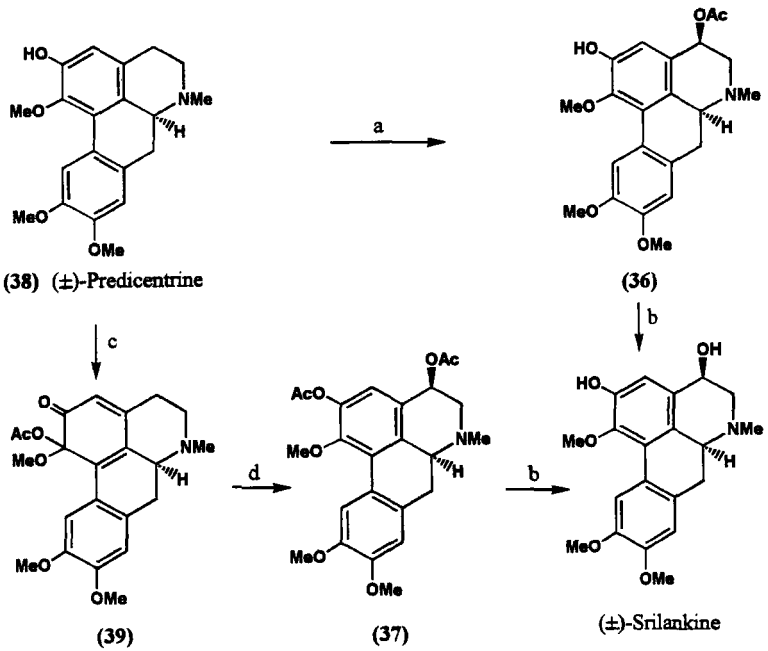
Following its isolation, two partial syntheses of srilankine (**26**) have been reported. As shown in Scheme 4, Philipov and co-workers synthesized **26** starting from either (+)-glaucine (**32**) or (+)-predicentrine (**33**) (*39*). Oxidation of either alkaloid with 30% H_2O_2 in 85% HCO_2H containing conc. H_2SO_4 afforded a common intermediate whose structure was elucidated as the glaucine quinol **34**. Treatment of **34** with Ac_2O and conc. H_2SO_4 afforded a mixture of mono- and diacetyl derivatives of srilankine (**36** and **37**, respec-



SCHEME 4. Reagents: a. 30% H_2O_2, 85% HCO_2H, conc. H_2SO_4, 5°C, 72 h; b. 30% H_2O_2, 85% HCO_2H, conc. H_2SO_4, 5°C, 3 h; c. Ac_2O, conc. H_2SO_4, 0.5 h; d. MeOH, KOH.

tively) presumably via the intermediate **35.** Alkaline hydrolysis of **36** and/or **37** yielded srilankine (**26**).

In a second synthesis of srilankine (**26**), Umezawa and co-workers applied their methodology to the oxidation of phenolic 1,2,3,4-tetrahydroisoquinolines (Scheme 5) (*40*). Consequently, lead tetraacetate oxidation of (±)-predicentrine (**38**) in HOAc at room temperature afforded (±)-4-*O*-acetylsrilankine (**36**) stereospecifically. The stereospecificity of this reaction was the result of the attack of HOAc from the lone-pair side of the nitrogen of the tetrahydroisoquinoline moiety due to hydrogen bonding. Acidic hydrolysis of **36** yielded (±)-srilankine. In an attempt to probe the mechanism of lead tetraacetate oxidation, these workers oxidized (±)-predicentrine (**38**) under controlled conditions, which resulted in the formation of the *O*-quinol acetate (**39**) as a mixture of two diastereoisomers. Treatment of **39** with Ac_2O–conc. H_2SO_4 afforded (+)-*O,O*-diacetylsrilankine (**37**), which, on hydrolysis, gave (±)-srilankine in an overall yield of 55%.

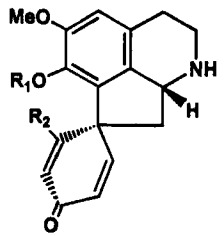


SCHEME 5. Reagents: a. $Pb(OAc)_4$, AcOH, room temp., 5 min; b. 10% HCl, room temp., 1 h; c. $Pb(OAc)_4$, CH_2Cl_2, 0°C, 1 min; d. Ac_2O, conc. H_2SO_4, 0°C → room temp., 30 min.

Several known aporphines have also been isolated from plants of the family Lauraceae, and these have been identified as actinodaphnine (**27**) [from the bark of *Litsea gardneri* (Thw.) Hook. f.] (*41*), isoboldine (**28**) [from the stem bark of *Neolitsea fuscata* (Thw.) Alston] (*42*), laurolitsine (**29**) [from the bark of *Litsea gardneri* (Thw.) Hook. f.] (*41*), and laurotetanine (**30**) and *N*-methyllaurotetanine (**31**) [from the leaves of *Actinodaphne speciosa* Nees] (*41*).

2. Proaporphines

Proaporphines, which are biosynthetic precursors of aporphine alkaloids, have been isolated from two Sri Lankan plants of the family Menispermaceae. Investigation of *Diploclisia glaucescens* (Bl.) Diels. (syn: *Cocculus macrocarpus* Wight and Arn.) has afforded a new alkaloid, glucescine (**40**) (*43*), and stepharine (**41**) (*44*). Stepharine (**41**) was also found to occur in *Anamirta cocculus* (*44–46*).

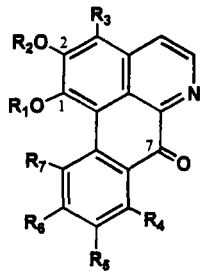


(40) $R_1 = H$, $R_2 = OMe$ Glucescine

(41) $R_1 = Me$, $R_2 = H$ Stepharine

3. Oxoaporphines

Despite the wide occurrence of oxoaporphines in members of the Annonaceae, Araceae, Hernandiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Monimiaceae, Papaveraceae, and Rananculaceae (*47*), this group of alkaloids has thus far been isolated from only three plants of Sri Lanka, all belonging to the Annonaceae. Wijeratne and co-workers recently reported (*48*) the isolation of five oxoaporphines from *Artabotrys zeylanicus* Hook. f. and Thoms. and two from *Xylopia championii* Hook. f. and Thoms. Investigation of *A. zeylanicus* stem bark afforded atherospermidine (**42**), lanuginosine (**43**), liriodenine (**44**), oxobuxifoline (**45**), and oxocrebanine (**46**), whereas the stem bark of *X. championii* resulted in the isolation of dicentrinone (**47**) and *O*-methylmoschatoline (**48**). The oxoaporphine alkaloids, liriodenine (**44**) and oxopukateine (**49**), were reported from the stem bark of *Cananga odorata* (Lam.) Hook. f. and Thoms. (*24*).



(42) $R_1,R_2 = CH_2$, $R_3 = OMe$, $R_4 = R_5 = R_6 = R_7 = H$ Atherospermidine

(43) $R_1,R_2 = CH_2$, $R_3 = R_4 = R_6 = R_7 = H$, $R_5 =$ OMe Lanuginosine

(44) $R_1,R_2 = CH_2$, $R_3 = R_4 = R_5 = R_6 = R_7 =$ H Liriodenine

(45) $R_1,R_2 = CH_2$, $R_3 = R_5 = OMe$, $R_4 = R_6 = R_7 = H$ Oxobuxifoline

(46) $R_1,R_2 = CH_2$, $R_3 = R_6 = R_7 = H$, $R_4 = R_5 = OMe$ Oxocrebanine

(47) $R_1,R_2 = CH_2$, $R_3 = R_4 = R_7 = H$, $R_5 = R_6 =$ OMe Dicentrinone

(48) $R_1 = R_2 =$ Me, $R_3 = OMe$, $R_4 = R_5 = R_6 = R_7 = H$ *O*-Methylmoschatoline

(49) $R_1,R_2 = CH_2$, $R_3 = R_4 = R_5 = R_6 = H$, $R_7 = OH$ Oxopukateine

4. 4,5-Dioxoaporphines

4,5-Dioxoaporphines constitute a relatively small group of aporphine alkaloids. Three 4,5-dioxoaporphines, namely, artabotrine (**50**), 8-methoxyouregidione (**51**), and ouregidione (**52**), have been isolated from the stem bark of *Artabotrys zeylanicus* (Annonaceae) (*48,49*). The structure of

(50) $R_1,R_2 = CH_2$, $R_3 = R_5 = H$, $R_4 =$ OMe Atrabotrine

(51) $R_1 = R_2 = Me$, $R_3 = R_5 = OMe$, $R_4 =$ H 8-Methoxyouregidione

(52) $R_1 = R_2 = Me$, $R_3 =$ OMe, $R_4 = R_5 = H$ Ouregidione

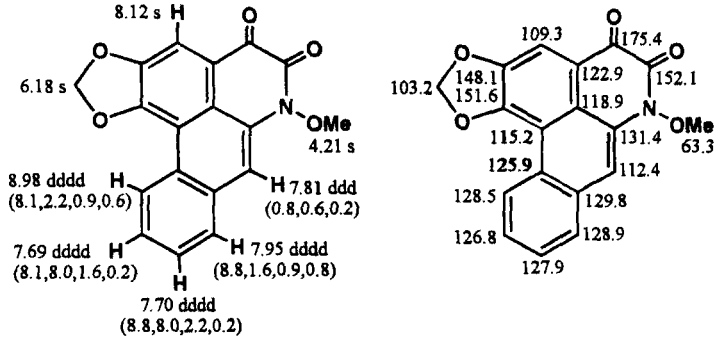
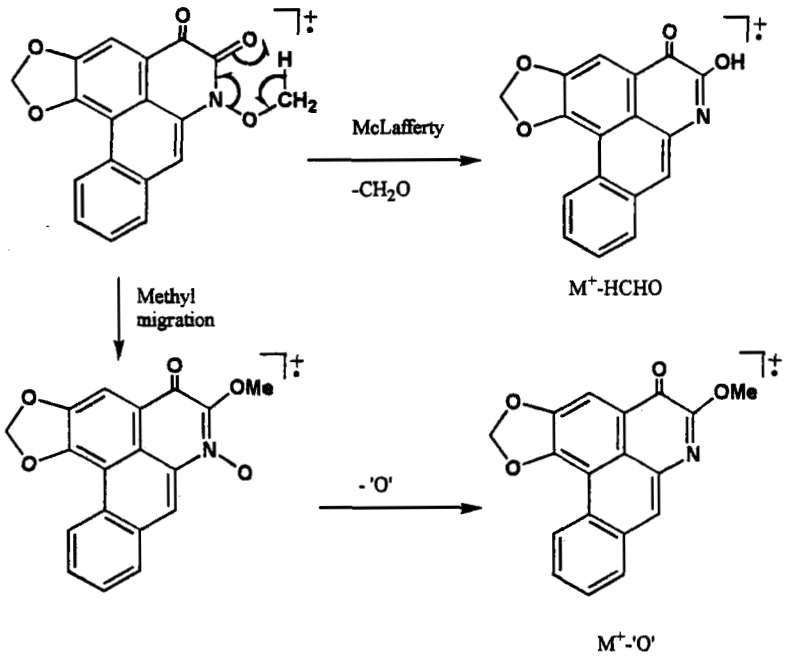


FIG. 2. ^{1}H and ^{13}C NMR data for artabotrine (**50**).

artabotrine, $C_{18}H_{11}NO_4$, mp 287–289°C, an unprecedented bioactive *N*-methoxylated 4,5-dioxoaporphine alkaloid, was deduced from spectral data and single-crystal X-ray analysis (*49*). ^{1}H and ^{13}C NMR spectral assignments for artabotrine were performed with the aid of distortionless enhancement by polarization transfer (DEPT), heteronuclear shift correlation (HETCOR), and heteronuclear shift correlations via multiple bond connectivities (HMBC) NMR techniques, and the coupling pattern and coupling constants of the aromatic protons were determined by spin simulation experiments. These assignments are depicted in Fig. 2. Although these data, together with UV, IR, and MS data, supported structure **50** for artabotrine, the unequivocal establishment of the presence of an unprecedented *N*-methoxy function had to be confirmed by X-ray diffraction analysis. Artabotrine (**50**) exhibited some unique MS fragmentations, which accounted for loss of oxygen and formaldehyde from the molecular ion, and these are shown in Scheme 6. 8-Methoxyouregidione (**51**), $C_{20}H_{17}O_6N$, mp 276–277°C, is another new alkaloid obtained from *A. zeylanicus,* the structure of which was determined by IR, UV, MS, and ^{1}H NMR spectroscopy (*48*). The 8-demethoxy analog of **51,** ouregidione (**52**), was also found to occur in the same extract (*48*).

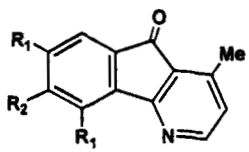
5. Azafluorenones and Diazafluoranthenes

Azafluorenone and diazafluoranthene alkaloids, which are biogenetically related to oxoaporphines, usually co-occur in plants of the family Annonaceae. Cyathocaline (**53**), $C_{14}H_{11}NO_4$, mp 222–224°, is a new azafluorenone alkaloid isolated from the stem bark of *Cyathocalyx zeylanica* Champ. *ex* Hook. f. and Thoms., a species of the Annonaceae endemic to Sri Lanka (*50*). Its structure was elucidated using spectroscopic techniques and by



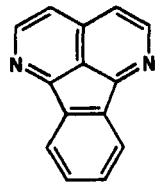
SCHEME 6.

chemical derivatization to its acetate. A TLC investigation has recently revealed the presence of cyathocaline (**53**) in *Annona reticulata* (*51*). Onychine (**54**) is an azafluorenone alkaloid encountered in the stem bark of *Cananga odorata* (*24*). The only diazafluoranthene alkaloid known in a Sri Lankan plant, eupolauridine (**55**), has also been isolated from the stem bark of *Cananga odorata* (*24,52*). Both onychine (**54**) and eupolauridine (**55**)



(53) R_1 = **OH**, R_2 = **OMe** Cyathocaline

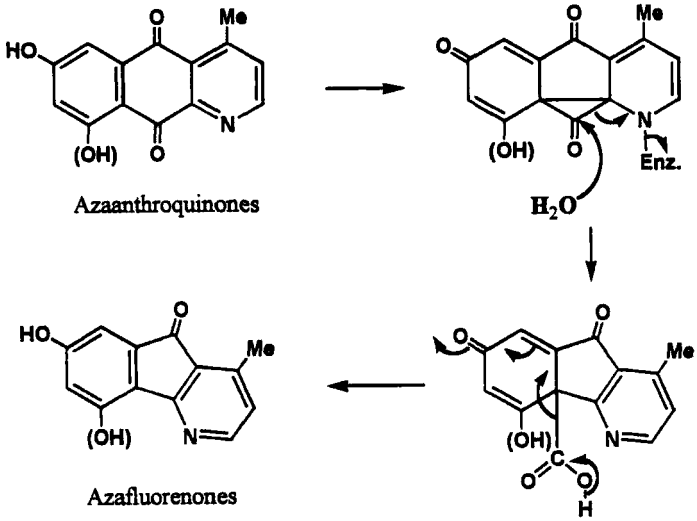
(54) $R_1 = R_2 =$ **H** Onychine



(55) Eupolauridine

obtained from different sources have been reported to exhibit antifungal activity against *Candida albicans* (*53*).

The natural azafluorenones and diazafluoranthenes thus far known are restricted in distribution to the plant family Annonaceae, which is known to elaborate a variety of alkaloids, including isoquinolines, aporphines, oxoaporphines, 4,5-dioxoaporphines, azanthraquinones, diazafluoranthenes, and azafluorenones. Cavé and co-workers have recently postulated a possible biogenetic relationship among the latter four classes of alkaloids (*54*). The proposed pathway from azaanthraquinones to azafluorenones involved a decarbonylation step for which they have suggested catalysis by a metalloenzyme producing a high-energy carbocationic species. For this biogenetic transformation an alternative pathway involving a Favorski-type intermediate has recently been suggested (see Scheme 7) (*50*).

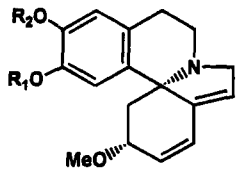


SCHEME 7. Biogenetic conversion of azaathraquinones to azaflurenones.

D. *ERYTHRINA* ALKALOIDS

Erythrina alkaloids, which are known to arise biogenetically from benzyltetrahydroisoquinolines, are found to occur in numerous *Erythrina* species of the family Fabaceae (Leguminosae), the only exception being their presence in the genus *Cocculus* (Menispermaceae) (*55*). *Erythrina* alkaloids are of wide interest because of their remarkable physiological action.

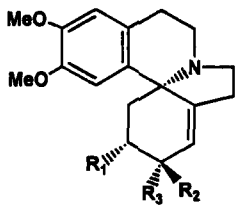
In a study of five different species of *Erythrina* collected from different countries, Barton, Widdowson, and co-workers reported the isolation of several new and known alkaloids from two Sri Lankan *Erythrina* species. The seeds of *Erythrina fusca* Lour. contained erysotrine (**56**). Erysotrine



(56) $R_1 = R_2 = Me$ Erysotrine

(57) $R_1,R_2 = CH_2$ Erythraline

was also isolated from the thorny variety of *E. lithosperma* Blume. A leaf extract of the smooth variety of *E. lithosperma* gave two new *Erythrina* alkaloids, in addition to erysotrine (**56**) and erythraline (**57**) (*56,57*). Structures for these two new alkaloids, erythratidinone (**58**), $C_{19}H_{23}NO_4$, mp 119–120°C, and 3-demethoxyerythratidinone (**59**), $C_{18}H_{21}NO_3$, mp 111–112°C (picrate, mp 200–202°C), were deduced by spectroscopic analysis and



(58) $R_1 = OMe, R_2,R_3 = O$ Erythratidinone

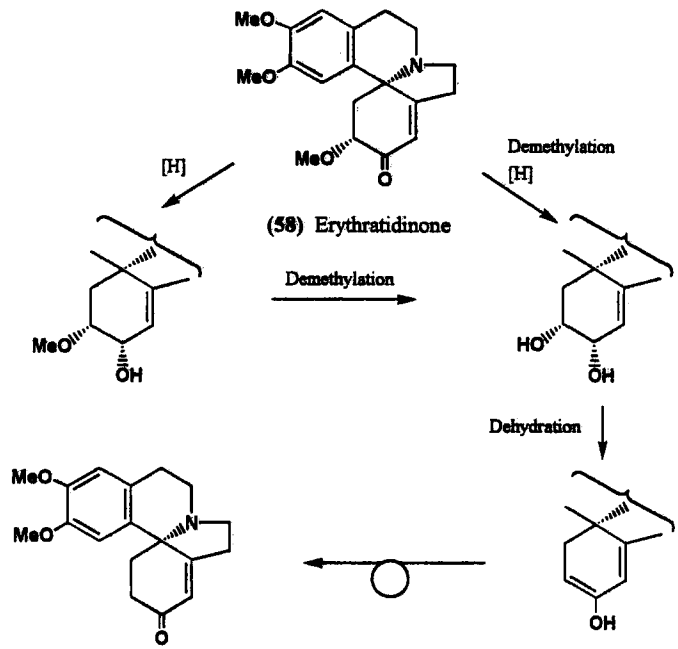
(59) $R_1 = H, R_2,R_3 = O$ 3-Demethoxyerythratidinone

(60) $R_1 = OMe, R_2 = H, R_3 = OH$ Erythratidine

(61) $R_1 = OMe, R_2 = OH, R_3 = H$ Epierythratidine

chemical interconversions. ^{1}H NMR spectral assignments of erythratidinone (**58**) were assisted by internuclear double resonance (INDOR) decoupling experiments (*57*). Reduction of **58** with $NaBH_4$ afforded two epimeric alcohols, **60** and **61.** The alcohol **60** was found to be identical with the previously known alkaloid erythratidine. Thus, **61** should be epierythratidine. The absolute configuration at C-3 of **60** was determined with the assistance of detailed ^{1}H NMR studies, and the configuration at C-5 was shown to be as in **59** by dehydration of erythratidine (**60**), albeit in low yield, to erysotrine (**56**), an alkaloid of known absolute stereochemistry.

3-Demethoxyerythratidinone (**59**) is unique to *E. lithosperma* in its lack of the 3-methoxy function. This implies a late stage modification of the normal biosynthetic pathway. Some plausible routes to **59** starting from erythratidinone (**58**), which co-occurs with **59** in *E. lithosperma,* are shown in Scheme 8.

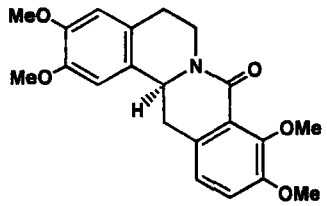


(**59**) 3-Demethoxyerythratidinone

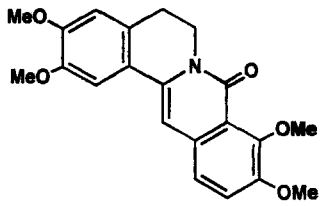
SCHEME 8.

E. Protoberberine Alkaloids

The protoberberines constitute a group of alkaloids that can theoretically be derived from benzylisoquinolines by condensation with *S*-adenosylmethionine. Protoberberine alkaloids occur in a wide variety of plant families, including the Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae, and Rutaceae. Investigation of the stem of *Anamirta cocculus* (L.) Wight and Arn. (Menispermaceae), a southeast Asian plant collected in Sri Lanka, has afforded two protoberberine alkaloids, (−)-8-oxotetrahydropalmatine (**62**) and oxypalmatine (**63**) (*46*), whereas the stems and roots of the same species occurring in Indonesia have yielded, in addition to **62,** berberine, palmatine, magnoflorine, and columbamine (*58*).



(62) (−)-8-Oxotetrahydropalmatine



(63) Oxypalmatine

VI. Carbazole Alkaloids

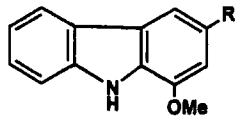
A. Classification and Occurrence

These alkaloids contain the basic carbazole nucleus derived from an indole and isoprene units in which one of the isoprenes is cyclized back to the indole to form a benzene ring. Carbazole alkaloids occur in plants of the family Rutaceae. Three basic groups of carbazole alkaloids are known (*59*). The murrayanine, or C_{13}, group contains one isoprene unit attached to an indole nucleus forming the parent carbazole ring system. The heptaphylline–glycomaurrol, or C_{18}, group has an additional isoprene group attached to C-1 or C-4 of the carbazole nucleus. The third, or C_{23}, group, which has two isoprene units on the carbazole nucleus, is represented by mahanimbine (**75**) and related alkaloids. Members of all three basic types of carbazole alkaloid occur in Sri Lankan Rutaceae. Binary carbazole–indole alkaloids are a complex group of carbazole alkaloids in which

an indole moiety is found attached to a tetrahydrocarbazole nucleus. A member of this group has been encountered in the Sri Lankan species, *Murraya gleniei.*

B. Murrayanine Group

This is the simplest known group of carbazole alkaloids. Fractionation of a bioactive $CHCl_3$ extract of the root bark of *Murraya koenigii* afforded the cytotoxic carbazole alkaloid, koenoline (**64**), $C_{14}H_{13}NO_2$, mp 130°C, together with murrayanine (**65**) (*60*). The structure of koenoline (**64**), which was obtained for the first time as a natural product, was established with the aid of spectroscopic data (UV, IR, ^1H and ^{13}C NMR and MS) accumulated for the parent alkaloid, as well as for its monoacetate. As anticipated, the $NaBH_4$ reduction product of murrayanine (**65**) was found to be identical with koenoline (**64**), further providing evidence for the proposed structure for the latter alkaloid. Murrayanine (**65**) has also been isolated from the stem bark of this plant (*61*).

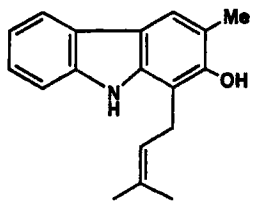


(64) $R = CH_2OH$ Koenoline

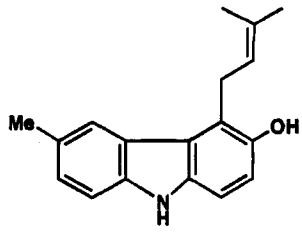
(65) $R = CHO$ Murrayanine

C. Heptaphylline-Glycomaurrol Group

This group contains carbazoles with a dimethylallyl substituent attached to C-1 or C-4, as well as those derived as a result of cyclization of this dimethyallyl group with a phenolic group at the *ortho* position. Girinimbilol (**66**), $C_{18}H_{19}NO$, mp 106°C, an alkaloid isolated from the stem bark of

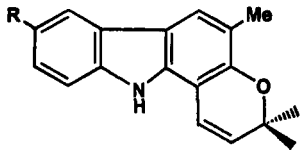


(66) Girinimbilol

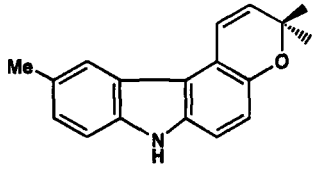


(67) Glycomaurrol

Murraya koenigii, although claimed to be new (*61*), appears to be identical with previously reported mukoenine A (*62*). Structure elucidation of **66** involved application of spectral data, conversion into its monoacetate, and HCO_2H-catalyzed cyclization to dihydrogirinimbine (dihydro-**68**). The stem bark of *M. koenigii* also afforded the known C_{18} carbazole, girinimbine (**68**) (*61*), which has previously been isolated from the seeds of the same



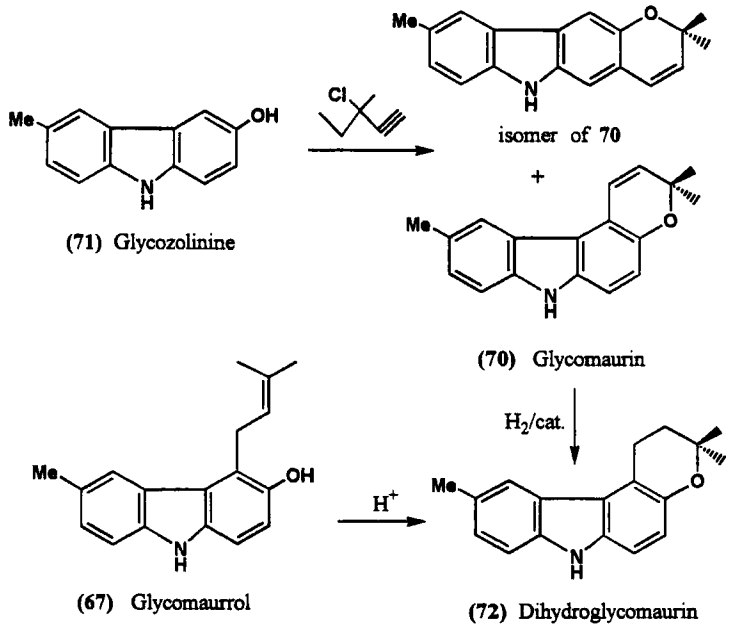
(68) R = H Girinimbine
(69) R = OMe Koenimbine



(70) Glycomaurin

plant collected in India (*63*). Extending their work on the seeds of *Murraya koenigii* into a chemotaxonomic study to identify different chemotypes of this plant growing in India and Sri Lanka, Reisch and co-workers have investigated the fruits and seeds collected in Sri Lanka (*64*). Their studies revealed the presence of girinimbine (**68**), koenimbine (**69**), and the C_{23} carbazole, mahanimbine (**75**), in the seeds of this plant collected at Nikawer-etiya. Interestingly, the seeds collected from a different locality, namely Marassana, in Sri Lanka did not contain any carbazole alkaloids. Some C_{23} carbazoles [murrayanol (**74**) and murrayazolidine (**76**)] encountered in the Indian seeds were found to be absent in Sri Lankan seeds.

From the CH_2Cl_2 extract of the stem bark of *Glycosmis mauritiana,* Kumar and co-workers have reported two new C_{18} carbazole alkaloids: glycomaurrol (**67**), $C_{18}H_{19}NO$, mp 149–150°C, and glycomaurin (**70**), $C_{18}H_{17}NO$, mp 195–196°C (*32*). Both compounds showed the color reactions characteristic of carbazole alkaloids, giving a violet coloration with conc. H_2SO_4, which turned green on dilution. The close similarity of the aromatic signals in the ^1H NMR spectra of the two alkaloids suggested an identical substitution pattern on the carbazole ring. The UV and ^1H NMR spectral data, together with the absence of a downfield shift of the benzylic olefinic proton in the ^1H NMR spectrum of glycomaurin on *N*-methylation, provided evidence for the presence of a novel ring system in this alkaloid. The final confirmation of the structure **70** proposed for glycomaurin was sought by a partial synthesis starting from glycozolinine [6-methylcarbazol-3-ol (**71**)]. As shown in Scheme 9, reaction of **71** with 3-chloro-3-methybutyne in the presence of tetrabutylammonium bromide as the phase transfer catalyst afforded glycomaurin (**70**) as the major product (*65*). The structure

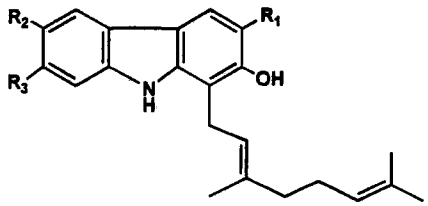


SCHEME 9. Semisynthesis of glycomaurin (**70**) and its structural relationship to glycomaurrol (**67**).

67 proposed for glycomaurrol with the help of spectroscopic data was confirmed by acidic cyclization of glycomaurrol (**67**) to yield **72,** which was found to be identical with dihydroglycomaurin obtained by catalytic hydrogenation of glycomaurin (**70**) (Scheme 9).

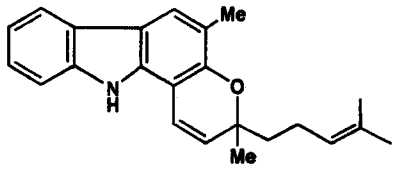
D. MAHANIMBINE GROUP

The new C_{23} carbazole alkaloid mahanimbilol (**73**), $C_{23}H_{27}NO$, has been obtained as a pale yellow oil from the stem bark of *Murraya koenigii* (*61*). The structure **73** was previously proposed for mahanimbilol isolated from the timber of Indian *M. koenigii* (*66*). However, the ^1H NMR (solvent not specified) and UV data reported by Rama Rao *et al.* (*66*) did not agree with those reported for **73** obtained by Reisch *et al.* (*61*) from the Sri Lankan sample, suggesting that the structure proposed for the Indian mahanimbilol may require revision. Treatment of mahanimbilol (**73**) with HCO_2H afforded bicyclomahanimbiline in which the geranyl side chain had cyclized into two fused rings (*61*).

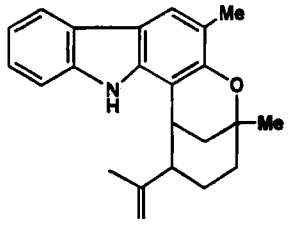


(73) R_1 = Me, R_2 = R_3 = H Mahanimbilol

(74) R_1 = H, R_2 = Me, R_3 = OMe Murrayanol



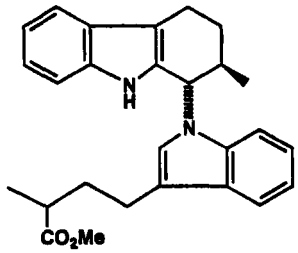
(75) Mahanimbine



(76) Murrayazolidine

E. Binary Tetrahydrocarbazole–Indole Alkaloid

A recent communication by Kumar and co-workers reported the isolation of a new binary tetrahydrocarbazole-indole alkaloid, methyl 2-methyl-4-(*N*-2″β-methyl-1″,2″,3″,4″-tetrahydrocarbazol-1″α-ylindol-3′-yl butanoate (**77**), $C_{27}H_{30}N_2O_2$ from the root timber of *Murraya gleniei* (*67*). It exhibited spectral data characteristic of an indole with an ester function. The mass spectral fragments having *m/z* 231 and 184 indicated that it was a binary alkaloid consisting of $C_{14}H_{17}NO_2$ and $C_{13}H_{14}N$ units. The structure and stereochemistry of **77** were established by the application of ^1H, ^{13}C, DEPT,



(77)

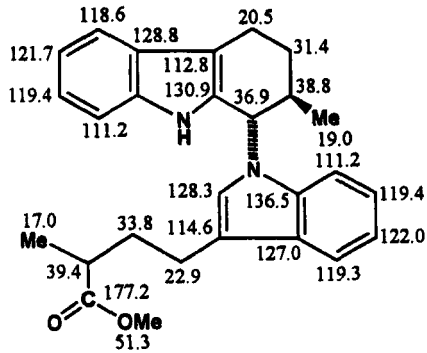


FIG. 3. ^{13}C NMR data for the binary tetrahydrocarbazole–indole alkaloid (77).

and ^{1}H–^{13}C HETCOR NMR techniques. Complete ^{13}C NMR assignments for this novel alkaloid are depicted in Fig. 3.

VII. Monoterpene Indole Alkaloids

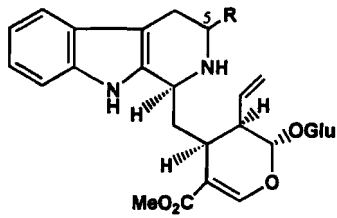
A. Distribution and Occurrence

Sri Lankan plants of the families Apocynaceae and Rubiaceae are rich sources of monoterpene indole alkaloids. A number of plants with claims of medicinal uses have been investigated, and a variety of alkaloids isolated. To date over 100 indole alkaloids have been isolated from Sri Lankan plants, about one-fourth of which are new records. Several alkaloids have been evaluated for their biological activities. However, the majority of

studies have involved conventional phytochemical and chemotaxonomic analysis. Variation in indole alkaloid content in the leaves of *Tabernaemontana dichotoma* collected from five different localities of Sri Lanka by a previously developed HPLC method (*68*) was evaluated by Perera and co-workers (*69*).

B. Strictosidine Group

In their studies on the biosynthesis of terpenoid indole alkaloids, De Silva and co-workers have carried out a screening of some indole alkaloid producing plants of Sri Lanka for the occurrence of the first nitrogenous monoterpenoid precursor (*70,71*). In this survey, *Rauvolfia serpentina, Strychnos nux-vomica, Cinchona ledgeriana,* and a number of *Mitragyna* and *Vinca* species were tested for the presence of vincoside and 5α-carboxyvincoside. Although these two proposed bio-intermediates (at the time) were not detected, macroisolation techniques revealed the occurrence of 5α-carboxystrictosidine (**78**), an isomer of 5α-carboxyvincoside, in all plants tested, and strictosidine (**79**), an isomer of vincoside, only in



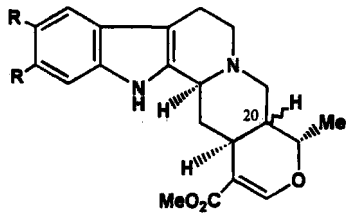
(**78**) **R** = CO_2H 5-Carboxystrictosidine

(**79**) **R** = **H** Strictosidine

Rauvolfia, Vinca, and *Strychnos* species. Strictosidine (**79**) and 5α-carboxystrictosidine (**78**) have been isolated from *R. serpentina* and *S. nux-vomica* and were characterized as the pentaacetate and the methoxycarbonyl pentaacetate derivatives, respectively.

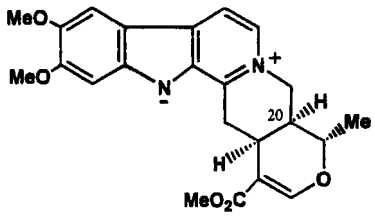
C. Ajmalicine–Corynantheine–Heteroyohimbine–Yohimbine Group

Ajmalicine (**80**) was found to occur in *Uncaria elliptica* (*72,73*) and *Petchia ceylanica* (*74*), whereas its 10,11-dimethoxy derivative, reserpiline (**81**), and the C-20 epimer of **81,** isoreserpiline (**82**), have been isolated from *Neiososperma oppositifolia* (*75,76*). Investigation of *N. oppositifolia* also

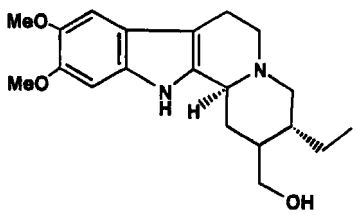


(80) R = H, 20β-H Ajmalicine
(81) R = OMe, 20β-H Reserpiline
(82) R = OMe, 20α-H Isoreserpiline
(83) R = H, 20α-H Tetrahydroalstonine

revealed the presence of bleekerine (10,11-dimethoxyalstonine) (**84**) (*76*), ochropposinine (**85**) (*75,76*), and the new natural product 3-epirauvanine (**86**) (*76*). A TLC survey of some local plants of the family Apocynaceae

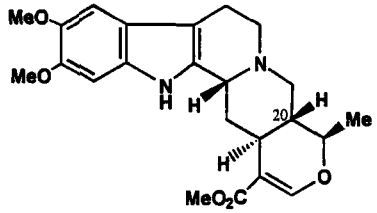


(84) Bleekerine



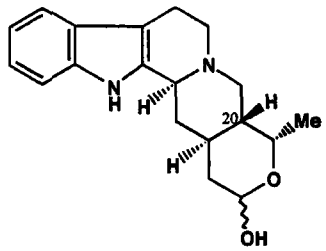
(85) Ochropposinine

for ajmalicine (**80**) had indicated the absence of this alkaloid in *Alstonia macrophylla* (leaves), *Bassia acuminata* (leaves), *Cerbera manghas* (fruits), *Ochrosia bobornica* (twigs and fruits), and *Pagiantha dichotoma* (leaves) and the occurrence of trace quantities of **80** in *Kopsia fruiticosa* (leaves), *Ochrosia bobornica* (leaves), and *Pagiantha dichotoma* (twigs) (*77*).

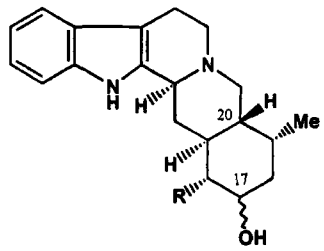


(86) 3-Epirauvanine

Hydroxy-17-decarbomethoxy-16-dihydro-epiajmalicine (**87**), $C_{19}H_{24}N_2O_2$, mp 185°C, is a new natural product encountered in the bark of *Hunteria zeylanica*, a plant endemic to Sri Lanka (*78*). Structural proof involved the semisynthesis of **87** by oxymercuration of corynantheal. Other indole alkaloids belonging to this class isolated from *H. zeylanica* included yohimbol (**88**) and the new natural product epiyohimbol (**89**), $C_{19}H_{24}N_2O$, mp 257°C, whose structures were confirmed by comparison with $NaBH_4$ reduction products of yohimbone. The fruits of *Alstonia macrophylla* have



(87) Hydroxy-17-decarbomethoxy-16-dihydro-epiajmalicine



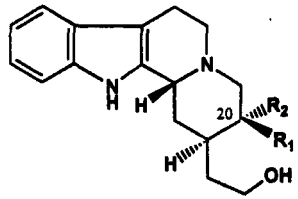
(88) **R = H, 17α-OH** Yohimbol

(89) **R = H, 17β-OH** Epiyohimbol

(90) **R = CO_2Me, 17α-OH** Yohimbine

(91) **R = CO_2Me, 17β-OH** β-Yohimbine

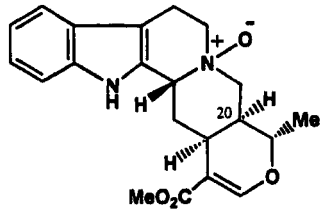
afforded yohimbine (**90**) and β-yohimbine (**91**) (*79*). Both *H. zeylanica* (*78*) and *Mitragyna parvifolia* (*80*) were found to contain dihydrocorynantheol (**92**). In addition, *M. parvifolia* afforded its isomer, corynanthediol (**93**), together with tetrahydroalstonine (**83**), dihydrocorynantheol N_4-oxide (**94**), and akuammigine N_4-oxide (**95**) (*80*).



(**92**) R_1 = H, R_2 = Et Dihydrocorynantheol

(**93**) R_1 = Et, R_2 = H Corynanthediol

(**94**) N_4-oxide of **92** Dihydrocorynantheol N_4-oxide

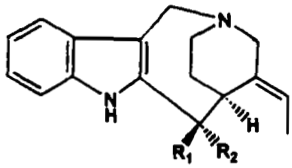


(**95**) Akuammigine N_4-oxide

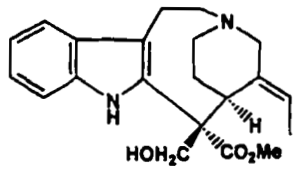
D. Apparicine–Stemmadenine Group

All the alkaloids belonging to this group in Sri Lankan plants have been isolated by Perera, Sandberg, Verpoorte, and co-workers from various parts of *Tabernaemontana dichotoma* of the family Apocynaceae. Apparicine (**96**), its derivatives vallesamine (**97**) and *O*-acetylvallesamine (**98**), and (+)-stemmadenine (**100**) have been found to occur in this plant, together with a new apparicine derivative, 16*S*-hydroxy-16,22-dihydroapparicine (**99**), $C_{18}H_{22}N_2O$, $[\alpha]_D^{20}$ +129° (*81*). The structure of this new apparicine alkaloid was elucidated by the use of UV, MS, ^1H and ^{13}C NMR spectral data and by comparison of its NMR data with those reported for vallesamine (**97**) and 16-hydroxy-16,17-dihydrouleines (*81*). For the nonindole portion of the new alkaloid two possible conformations were considered, and the conformation depicted in structure **99** was preferred based on the results

of NOE experiments, which also helped to establish the 16*S* configuration proposed for **99.**



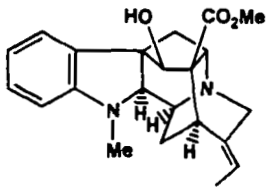
(96) $R_1+R_2 = =CH_2$ Apparicine
(97) $R_1 = CH_2OH$, $R_2 = CO_2Me$ Vallesamine
(98) $R_1 = CH_2OAc$, $R_2 = CO_2Me$ *O*-Acetylvallesamine
(99) $R_1 = Me$, $R_2 = OH$ 16*S*-Hydroxy-16,22-dihydroapparicine



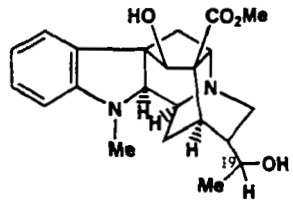
(100) (+)- Stemmadenine

E. AJMALINE–PICRALINE–SARPAGINE–INDOLOHOMOTROPANE GROUP

Of the 12 alkaloids belonging to this group occurring in Sri Lankan flora, 11 were encountered in *Alstonia macrophylla* Wall. of the family Apocynaceae, and the remaining alkaloid was isolated from *Tabernaemontana divaricata* (L.) Br. *ex* Roem et Schult. of the same family. Six of the alkaloids were found to be new. Vincamajine (**101**) and its new derivative, 19-hydroxyvincamajine (**102**), are two alkaloids of the ajmaline subgroup present in *A. macrophylla* (*82*). The structure of **102** was elucidated with the aid of IR, ^1H NMR, and low-resolution MS data. *A. macrophylla* also

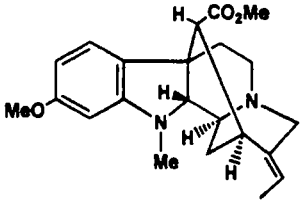


(101) Vincamajine

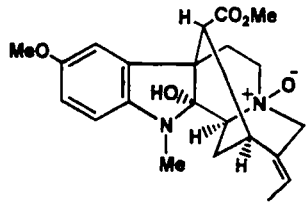


(102) 19-Hydroxyvincamajine

contained picraline-type alkaloids, cabucraline (**103**) (*82*) and alstozine *N*-oxide (**104**) (*83*), and the new alkaloids, 10-hydroxystrictamine (**105**),



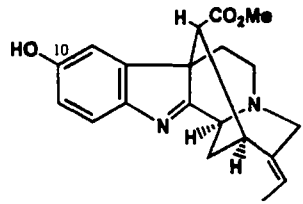
(**103**) Cabucraline



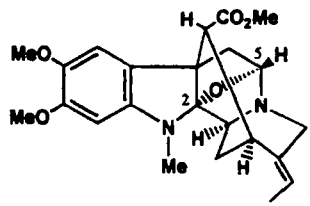
(**104**) Alstozine *N*-oxide

$C_{20}H_{22}N_2O_3$, $[\alpha]_D^{20}$ +81.6° (*84*), and alstopicralamine (**106**), $C_{23}H_{28}N_2O_5$, $[\alpha]_D^{20}$ +3.33° (*85*). The presence of a strictamine carbon skeleton in 10-hydroxystrictamine was inferred from its ^1H and ^{13}C NMR spectral data and by comparison with those reported for strictamine. The ^1H NMR coupling pattern and constants of the aromatic signals suggested the attachment of an OH group to C-10 of strictamine. Stereochemical assignments at the various asymmetric centers of **105** were made by a series of NOE experiments. Complete ^1H and ^{13}C NMR spectral assignments of 10-hydroxystrictamine (**105**) were made by comparison with reported data for related compounds and with the help of a ^1H–^1H correlated spectroscopy (COSY) spectrum.

The UV spectrum (λ_{max} 230, 245, 300, and 307 nm) of alstopicralamine (**106**) revealed the presence of a dihydroindole (indoline) system, and the



(**105**) 10-Hydroxystrictamine

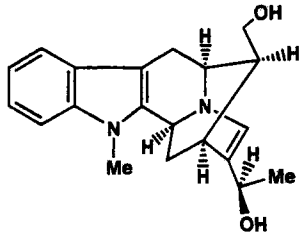


(**106**) Alstopicralamine

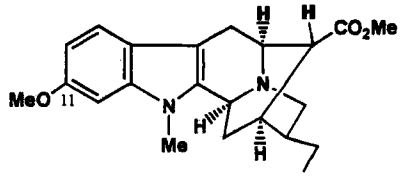
IR spectrum suggested that it had an ester function (*85*). The close similarity of the ^1H NMR spectrum with those of picraline and picralinal led to the proposal that it was a picraline-type alkaloid with a C-2–C-5 oxygen bridge. Furthermore, the ^1H NMR spectrum, although it suggested the presence of two OMe, one CO_2Me, and one *N*-Me group, helped to locate the OMe groups at C-10 and C-11. Detailed analysis of the ^1H NMR spectrum with the aid of a COSY-45 spectrum, together with UV, IR,

and high-resolution MS data, were helpful in elucidating the structure of alstopicralamine (**106**).

The sarpagine subgroup of indole alkaloids in Sri Lankan plants is represented by two new alkaloids: alstoumerine (**107**) from *Alstonia macrophylla* (*86*) and 11-methoxy-*N*-methyldihydropericyclivine (**108**) from *Tabernaemontana divaricata* (*87*). Alstoumerine, $C_{20}H_{24}N_2O_4$, mp 170°C, $[\alpha]_D$ −5.5°,



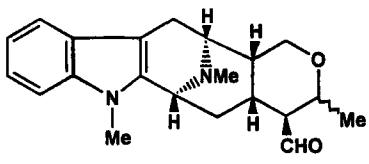
(**107**) Alstoumerine



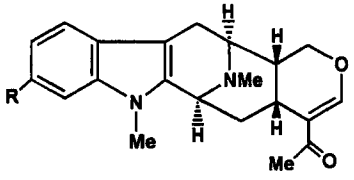
(**108**) 11-Methoxy-*N*-methyldihydropericyclivine

showed the UV λ_{max} at 225, 285, and 290 nm characteristic of the indolic chromophore and an intense IR band at 3300 cm^{-1} due to an OH group. The MS fragmentation of **107** was distinctly similar to those of other sarpagine alkaloids. The ^1H and ^{13}C NMR spectra assigned with the aid of COSY-45 and DEPT experiments were helpful in the location of the olefinic double bond and the two OH groups in alstoumerine (*86*). Structure elucidation of 11-methoxy-*N*-methyldihydropericyclivine (**108**), $C_{22}H_{28}N_2O_3$, involved application of UV, IR, MS, and ^1H NMR data and comparison of these data with those reported for pericyclivine and voacamine (*87*).

The Sri Lankan *Alstonia macrophylla* also contained a series of alkaloids belonging to the 4,21-*seco*-10-deoxysarpagine or indolohomotropane subgroup. Talcarpine (**109**) (*82,88*), alstophylline (**110**), (*82,88*), and alstonerine [demethoxyalstophylline (**111**)] (*79,82,88*) are three known alkaloids isolated from *A. macrophylla.* Alstomacrocine (**112**), $C_{21}H_{28}N_2O_2$, on the other

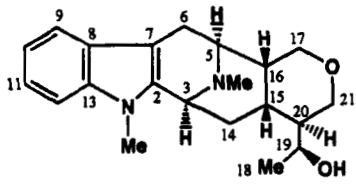


(**109**) Talcarpine



(**110**) **R** = **OMe** Alstophylline

(**111**) **R** = **H** Alstonerine



(112) Alstomacrocine

hand, is a new alkaloidreported from this plant by Atta-ur-Rahman and co-workers (*84*). The UV and IR spectra of alstomacrocine indicated the presence of an indolic chromophore and an OH group, respectively, and the MS fragmentation suggested the presence of a β-carboline system in which both N_a and N_b were substituted with methyl groups. The ^1H and ^{13}C NMR spectra were consistent with the proposed structure, and these spectral assignments were made with the help of the heteronuclear multiple quantum coherence (HMQC) technique. ^1H and ^{13}C NMR spectral assignments for alstomacrocine (**112**) are presented in Fig. 4. The relative stereochemistries of H-3, H-5, H-15, H-16, and H-20 were determined by NOE difference spectroscopy, and the configuration of the C-19–OH was established to be *R* by the application of Horeau's procedure.

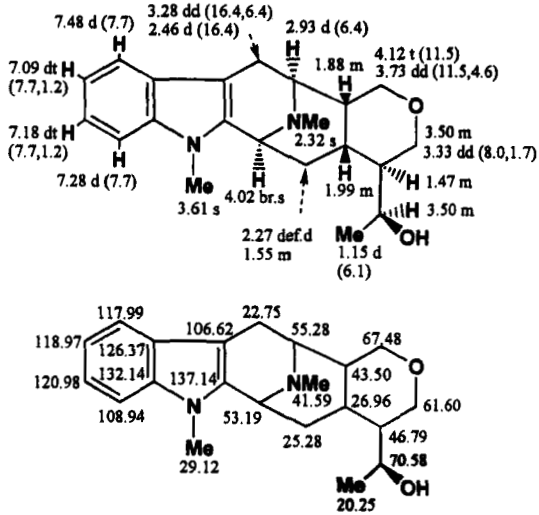
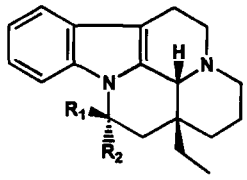


FIG. 4. ^1H and ^{13}C NMR data for alstomacrocine (**112**).

F. EBURNAMINE GROUP

Hunteria zeylanica has afforded several alkaloids of the eburnamine group (*79*). These included four previously known alkaloids, eburnamine (**113**), isoeburnamine (**114**), *O*-methyleburnamine (**115**), and



(**113**) $R_1 = OH, R_2 = H$ Eburnamine

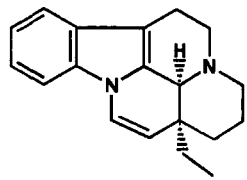
(**114**) $R_1 = H, R_2 = OH$ Isoeburnamine

(**115**) $R_1 = OMe, R_2 = H$ *O*-Methyleburnamine

(**116**) $R_1 = H, R_2 = OMe$ *O*-Methylisoeburnamine

(**117**) $R_1 = OEt, R_2 = H$ *O*-Ethyleburnamine

(+)-eburnamenine (**118**). Two new alkaloids, *O*-methylisoeburnamine (**116**) and *O*-ethyleburnamine (**117**), were also encountered in this study, and these were identified by comparison with synthetic alkaloids obtained by O-alkylation of isoeburnamine and eburnamine, respectively, with the corresponding alkyl iodide under phase transfer conditions. Possible artifactual origin of *O*-ethyleburnamine (**117**) from eburnamine (**113**) during extraction (involving EtOH) has been suggested (*78*). If this is the case, eburnamine should result in *O*-ethylisoeburnamine or an isomeric mixture of *O*-ethyleburnamine (**117**) and *O*-ethylisoeburnamine.

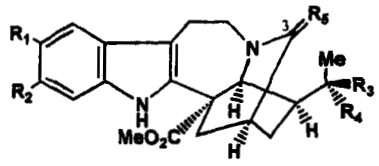


(**118**) (+)-Eburnamenine

G. CORONARIDINE GROUP

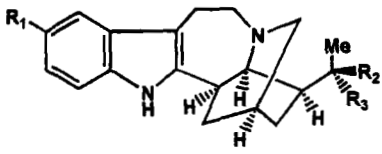
Sri Lankan plants of the genus *Tabernaemontana* have also yielded 14 coronaridine-type alkaloids. Both species investigated, namely, *T. dichotoma*

and *T. divaricata,* contained coronaridine (**119**) and voacangine (**125**) (*87, 89*), whereas 3-oxocoronaridine (**120**) (*90*), 3-ketopropylcoronaridine



(119)	$R_1 = R_2 = R_3 = R_4 = H, R_5 = H_2$	Coronaridine
(120)	$R_1 = R_2 = R_3 = R_4 = H, R_5 = O$	3-Oxocoronaridine
(121)	$R_1 = R_2 = R_3 = R_4 = H, R_5 = H,CH_2COCH_3$	3-Ketopropylcoronaridine
(122)	$R_1 = OMe, R_2 = R_4 = H, R_3 = OH, R_5 = H_2$	Voacristine
(123)	$R_1 = R_4 = H, R_2 = OMe, R_3 = OH, R_5 = H_2$	Isovoacristine
(124)	$R_1 = OMe, R_2 = R_3 = H, R_4 = OH, R_5 = H_2$	19*R*-Epivoacristine
(125)	$R_1 = OMe, R_2 = R_3 = R_4 = H, R_5 = H_2$	Voacangine
(126)	$R_1 = R_3 = R_4 = H, R_2 = OMe, R_5 = H_2$	Isovoacangine
(127)	$R_1 = R_2 = R_3 = H, R_4 = OH, R_5 = H_2$	19*R*-Epiheyneanine
(128)	$R_1 = R_2 = R_3 = H, R_4 = OH, R_5 = H,CH_2COCH_3$	3-Ketopropyl-epiheyneanine

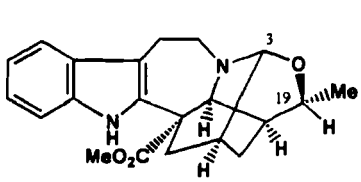
(**121**) (*91*), 19*R*-epivoacristine (**124**) (*92*), 19*R*-epiheyneanine (**127**) (*91*), 3-ketopropyl-epiheyneanine (**128**) (*93*), ibogamine (**129**) (*89*), 19*R*-epi-iboxygaine (**130**) (*92*), and voacristine hydroxyindolenine (**132**) (*93*) were



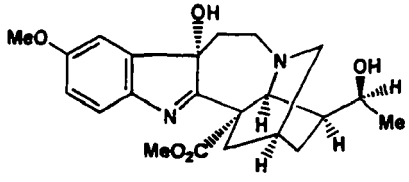
(129)	$R_1 = R_2 = R_3 = H$	Ibogamine
(130)	$R_1 = OMe, R_2 = OH, R_3 = H$	19*R*-Epi-iboxygaine

isolated only from *T. dichotoma.* Stem bark of *T. dichotoma* also yielded a new indole alkaloid, 3,19*R*-oxidocoronaridine (**131**), $C_{21}H_{24}N_2O_3$ (*93*), the structure of which was elucidated by the application of spectroscopic (UV, IR, ^{13}C NMR, and low-resolution MS) techniques and by $NaBH_4$ reduction, which afforded 19*R*-epiheyneanine (**127**) as the sole product.

The complexity of the ^{1}H and ^{13}C NMR spectra of 3,19*R*-oxidocoronaridine (**131**) was explained as due to the presence of an equilibrium mixture of **131** and its ring-opened forms, 3*R*- and 3*S*-hydroxy-19*R*-heyneanines (**133**



(131) 3,19*R*-Oxidocoronaridine

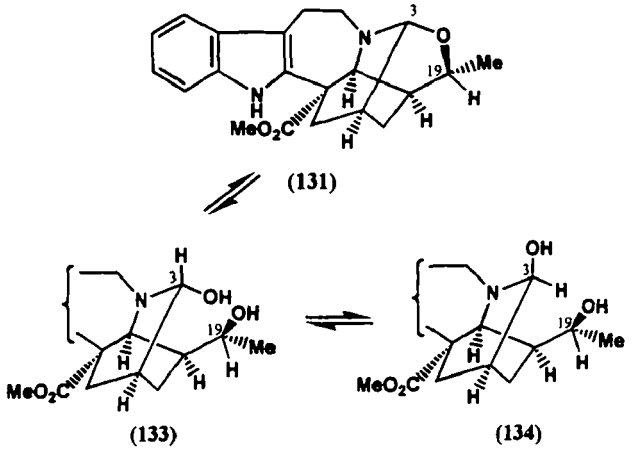


(132) Voacristine hydroxyindolenine

and **134**) (see Scheme 10). Isovoacangine (**126**), voacristine (**122**), and its isomer, isovoacristine (**123**), were isolated from *T. divaricata* (*87*).

H. Quebrachamine Group

Three alkaloids of this group, voaphylline (**135**), 12-methoxyvoaphylline (**136**), and voaphylline hydroxyindolenine (**137**), were isolated from *Tabernaemontana dichotoma*. Seeds of this plant afforded voaphylline (**135**) and voaphylline hydroxyindolenine (**137**) (*89*), whereas the fruits and leaves yielded 12-methoxyvoaphylline (**136**) and voaphylline hydroxyindolenine (**137**) (*91,92*).

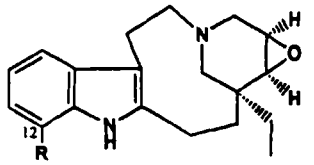


(131)

(133)

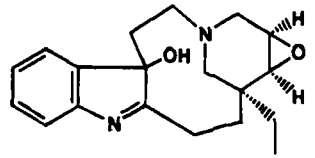
(134)

Scheme 10.



(135) R = H Voaphylline

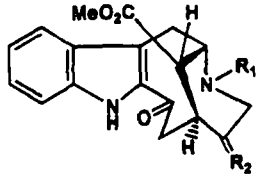
(136) R = OMe 12-Methoxyvoaphylline



(137) Voaphylline hydroxyindolenine

I. Vobasine Group

The parent alkaloid of this group, vobasine (**138**), was isolated from *Tabernaemontana dichotoma* (*91,92*), *T. divaricata* (*87*), and *Hunteria zeylanica* (*78*). Its *N*-methyl derivative, perivine (**139**), was found to occur in *T. dichotoma* (*92*), and the related alkaloid, tabernaemontanine (**140**), was found in *T. divaricata* (*87*).



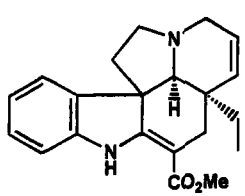
(138) R_1 = H, R_2 = CHMe Vobasine

(139) R_1 = Me, R_2 = CHMe Perivine

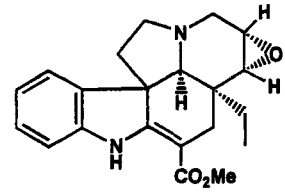
(140) R_1 = Me, R_2 = β-H, α-CH_2Me Tabernaemontanine

J. *Aspidosperma* Group

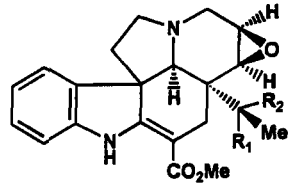
Two known alkaloids, tabersonine (**141**) and lochnericine (**142**), were encountered in *Tabernaemontana dichotoma* seeds (*89*) and *Petchia ceylanica* leaves (*74*), respectively. Almost simultaneous with the latter report, Atta-ur-Rahman, De Silva, and co-workers reported the isolation of two new *Aspidosperma* alkaloids, 19*R*-epimisiline (**143**), $C_{21}H_{24}N_2O_4$, mp 252° (decomp.), $[\alpha]_D^{27}$ −382°, and 19*S*-epimisiline (**144**), $C_{21}H_{24}N_2O_4$, mp 198° (decomp.), $[\alpha]_D^{27}$ −399°, from the leaves of *P. ceylanica* (*94*). Both 19*R*-epimisiline and 19*S*-epimisiline had identical UV, IR, and mass spectra. Their UV spectra were characteristic of an anilinoacrylate chromophore, and their IR spectra indicated the presence of OH, NH, and α,β-unsaturated



(141) Tabersonine



(142) Lochnericine



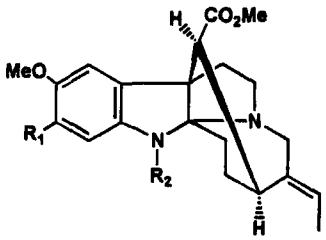
(143) R_1 = OH, R_2 = H 19*R*-Epimisiline

(144) R_1 = H, R_2 = OH 19*S*-Epimisiline

ester carbonyl functionalities. Most informative were their MS fragmentation patterns, which suggested an *Aspidosperma* skeleton. Exact mass measurements made on two of the important fragment ions helped to locate the two oxygens (other than those of the ester function) in the piperidine moiety of the *Aspidosperma* skeleton. The presence of a $-CH(OH)CH_3$ moiety at C-20 and a C-14(15)-β-epoxide was determined by extensive ^1H and ^{13}C NMR analysis, together with ^1H decoupling experiments and COSY and DEPT techniques, and by comparison with data reported for related alkaloids. Both **143** and **144** afforded the same ketone on oxidation, suggesting that the only difference in the structures of these two alkaloids was in the stereochemistry of the C-19–OH group of the $-CH(OH)CH_3$ moiety at C-20. The stereochemical disposition of the C-19–OH group in both alkaloids was determined by Horeau's procedure, which involved acylation of each with a racemic mixture of 2-phenylbutanoic anhydride in pyridine, and by measurement of the optical rotation of 2-phenylbutanoic acid by-product recovered from each reaction (*94*).

K. Vincorine Group

In addition to vincorine (**145**) (*82*), two new alkaloids belonging to this group, alstonamide (**146**), $C_{23}H_{28}N_2O_5$, $[\alpha]_D$ +82° (*86,95*), and demethoxyalstonamide (**147**), $C_{22}H_{26}N_2O_4$, $[\alpha]_D$ +74° (*86*), were reported from *Alstonia macrophylla*. UV spectra and MS fragmentation of both **146** and **147** were



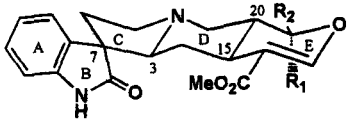
(145) $R_1 = H, R_2 = Me$ Vincorine
(146) $R_1 = OMe, R_2 = CHO$ Alstonamide
(147) $R_1 = H, R_2 = CHO$ Demethoxyalstonamide

typical of vincorine-type alkaloids. The IR spectra of both alkaloids suggested the presence of *N*-formyl and ester carbonyl functions. Furthermore, the EI MS of demethoxyalstonamide (**147**) exhibited a distinct similarity to that of (−)-norvincorine, except that in **147** the M^+ was shifted to a higher mass by 28 mu, indicating that **147** was probably a formyl derivative of (−)-norvincorine. ^1H and ^{13}C NMR data, interpreted with the help of COSY and DEPT techniques, were helpful in establishing the structures of alstonamide (**146**) and demethoxyalstonamide (**147**), whereas *J*-resolved and NOE difference ^1H NMR measurements were used in the assignment of all the protons and their relative stereochemistries.

L. Oxindole Alkaloids

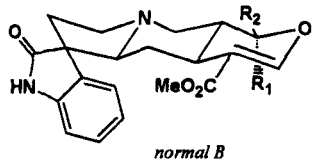
Oxindoles constitute a small and important group of monoterpene alkaloids usually found to co-occur with their corresponding ajmalicine or corynanthe analogs. Biogenetically, oxindoles are known to arise from their indole progenitors as a result of oxidation at C-7 of the indole followed by rearrangement giving rise to a spiro center at this position. Two structural classes of oxindole alkaloids are known: those with tetracyclic structures of the 17,18-secoyohimbine or corynantheidine type and those with pentacyclic structures of the heteroyohimbane or ajmalicine type. Interestingly, only the latter types of oxindole alkaloids have been encountered in Sri Lankan plants. All naturally occurring pentacyclic oxindoles differ from each other in their stereochemistry or in the pattern of substituents in the aromatic ring. Pentacyclic oxindoles have five asymmetric centers (C-3, C-7, C-15, C-19, and C-20). All naturally occurring corynane-type indoles, and therefore oxindoles possess, a 15*S* configuration. Thus, considering only the asymmetric centers in the D ring, pentacyclic oxindoles have been classified as *normal, pseudo, allo,* and *epiallo.* Of these, oxindoles with the *pseudo* con-

figuration suffer serious steric interactions and would not exist because of their instability. Each of the types can exist in A and B forms based on two possible orientations of the oxindole moiety about the C-7 spiro carbon. Six stable conformations for pentacyclic oxindoles are depicted in Fig. 5, and examples of all these are found in Sri Lankan plants.



normal A
(3*S*,7*S*,15*S*,20*R*)

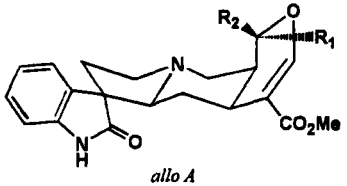
(148) R_1 = Me, R_2 = H Isomitraphylline



normal B
(3*S*,7*R*,15*S*,20*R*)

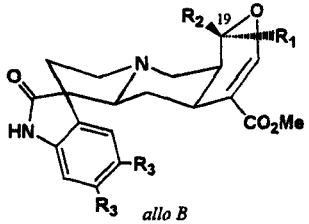
(149) R_1 = Me, R_2 = H Mitraphylline

(150) R_1 = H, R_2 = Me Formosanine (Uncarine B)



allo A
(3*S*,7*S*,15*S*,20*S*)

(151) R_1 = Me, R_2 = H Isopteropodine (Uncarine E)

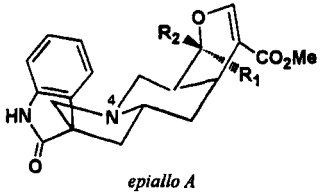


allo B
(3*S*,7*R*,15*S*,20*S*)

(152) R_1 = Me, R_2 = R_3 = H Pteropodine (Uncarine C)

(153) R_1 = Me, R_2 = H, R_3 = OMe Isocarapanaubine

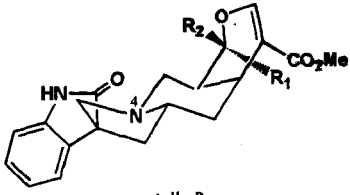
(154) R_1 = H, R_2 = Me, R_3 = OMe Neisosposinine



epiallo A

(155) R_1 = Me, R_2 = H Speciophylline (Uncarine D)

(156) 154 N_4-oxide Speciophylline N_4-oxide



epiallo B

(157) R_1 = Me, R_2 = H Uncarine F

(158) 157 N_4-oxide Uncarine F N_4-oxide

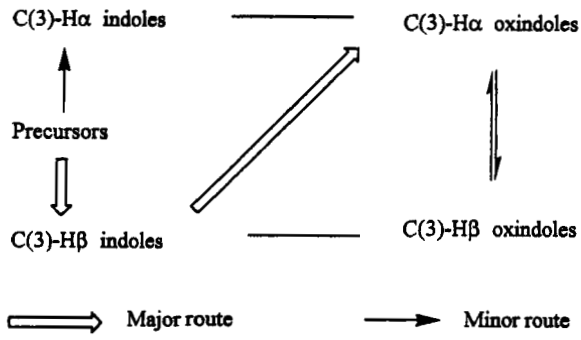
FIG. 5. Stable conformations for tetracyclic oxindole Alkaloids.

In their series of investigations of alkaloids from *Mitragyna* species collected in various geographic locations of Asia, Shellard and Houghton examined the bases present in the leaves of *M. parvifolia* collected in Kekirawa, Sri Lanka, and have reported the presence of uncarine C [pteropodine (**152**)], uncarine D [speciophylline (**155**)], uncarine E [isopteropodine (**151**)], uncarine F (**157**), uncarine D *N*-oxide (**156**), and uncarine F *N*-oxide (**158**) (*80*). These *N*-oxides were characterized from their MS and by sulfurous acid reduction to the corresponding parent tertiary alkaloids, which in turn were identified by co-TLC with authentic samples in a number of elution systems.

Investigation of *Uncaria elliptica,* a woody climber of the family Rubiaceae and endemic to Sri Lanka, afforded mitraphylline (**149**) and formosanine [uncarine B (**150**)] (*96*). The alkaloid described in this report as formosamine was recently identified as isomitraphylline (**148**) (*73*). Isocarapanaubine (**153**) was isolated from *Neisosperma oppositifolia* together with its new C-19 epimer, neisosposinine (**154**), $C_{23}H_{28}N_2O_6$, mp 228–230°C (*75*). The presence of an oxindole skeleton in neisosposinine was inferred from its nonindolic type of UV spectrum, the presence of an IR band due to an amide carbonyl, the downfield shift of the NH proton in its ^1H NMR spectrum, and its characteristic MS fragmentation. The gross ^1H and ^{13}C NMR spectral features of neisosposinine (**154**) were similar to those observed for isocarapanaubine (**153**). Differences were observed in the region of C-18 and C-19, and these were interpreted as due to the epimeric nature of the methyl group at C-19 by comparison of data reported for the isomers of epimeric pairs, runiticine/tetrahydroalstonine and rhyncophylline/isorhyncophylline. Further evidence for the stereochemical assignment of the C-19 methyl group of neiso sposinine (**154**) as β was obtained by NOE studies of both neisosposinine (**154**) and its C-19 epimer, isocarapanaubine (**153**). It is noteworthy that all of the indole and oxindole alkaloids produced by *Neisosperma oppositifolia* contained C-10 and C-11 methoxy substituents.

Biosynthesis of oxindole alkaloids in *Mitragyna* species was studied by Shellard and Houghton, who fed ajmalicine (**80**) and 3-isoajmalicine to young plants of Sri Lankan *M. parvifolia.* Both precursors were incorporated into mitraphylline (**149**) and isomitraphylline (**148**) produced by *M. parvifolia* (*97*). This and a similar series of biosynthetic experiments led to the modification of a previously postulated hypothesis for the biosynthesis of oxindole alkaloids. This modified biosynthethic pathway to oxindole alkaloids in *Mitragyna* species is presented in Scheme 11.

The Chelsea group also examined the distribution of alkaloids in young plants of *M. parvifolia* grown from seeds obtained from Sri Lanka (*97*). During this study these authors were able to resolve one of the major problems, namely, the role of mitraphylline (**149**) in the biosynthesis of *Mitragyna* alkaloids. Mitraphylline was found only in the lower part of the



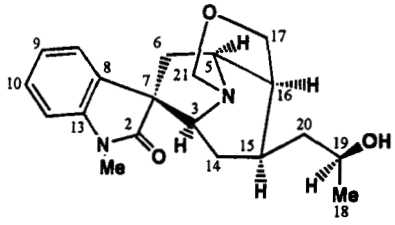
SCHEME 11. Biosynthetic pathways to oxindole alkaloids in *Mitragyna* species.

stem (hypocotylar region) and was absent in the leaves or roots. The results of these isolation studies and experiments with labeled precursors using plants grown from seeds collected in Sri Lanka were compared with results obtained using plants grown from seeds obtained from Uttar Pradesh (India). The alkaloid distribution in mature trees also supported the biosynthetic pathway outlined in Scheme 11.

M. MISCELLANEOUS MONOMERIC INDOLE AND OXINDOLE ALKALOIDS

1. Macroxine-A

The unusual oxindole alkaloid macroxine-A (**159**), $C_{20}H_{26}N_2O_3$, $[\alpha]_D$ +72.2°, from *Alstonia macrophylla* was reported by Atta-ur-Rahman and co-workers (*98*). Although UV and IR spectra of macroxine-A showed some characteristics of an oxindole alkaloid, the MS had an important fragment ion at *m/z* 152 (40%) not usually found in the MS of oxindole



(159) Macroxine-A

alkaloids. Lack of any additional substituents in the benzene ring of the indole moiety was apparent from its ^{1}H NMR spectrum, which also showed the presence of signals due to *N*-Me and CH_3CHOH groups. Evidence for the presence of the latter group was sought by Horeau's procedure, which was also used to establish its configuration as *S*. The spin systems in macroxine-A were investigated with homonuclear Hartmann-Hahn (HOHAHA) and COSY-45 NMR experiments, which indicated the presence of three spin systems. The ^{13}C NMR, together with the DEPT spectrum, suggested the presence of two methyl, five methylene, nine methine, and four quaternary carbons in the molecule, all of which were assigned with the help of chemical shift arguments and HMQC and HMBC techniques, resulting in the structure **159** proposed for macroxine-A. The lowest energy conformation of macroxine-A was determined with the help of MM2 calculations and the ^{1}H NMR coupling constants calculated for this low-energy conformation were found to be identical with the observed coupling constants. ^{1}H and ^{13}C NMR assignments for macroxine-A are depicted in Fig. 6.

Macroxine-A (**159**) is the first oxindole alkaloid with a C-17 to C-21 linkage through an oxygen atom in which the C-20–C-21 bond has been cleaved, resulting in a propyl side chain. Biogenetically, macroxine-A may arise from voachalotine oxindole, or one of its close analogs, by a series of transformations as depicted in Scheme 12.

2. N_b-*Demethylalstophylline oxindole*

In continuing their studies on *Alstonia macrophylla* alkaloids, Atta-ur-Rahman, De Silva, and co-workers isolated a novel oxindole alkaloid, N_b-demethylalstophylline oxindole (**160**), $C_{21}H_{24}N_2O_4$, $[\alpha]_D^{27}$ +76° (*99*). It displayed UV and IR spectra characteristic of an oxindole. The MS of **160** had a base peak at *m/z* 179 due to a fragment ion formed as a result of cleavage of the spiran ring. Another prominent peak was present at *m/z* 244 due to a *retro*-Diels–Alder type of fragmentation of ring D of this alkaloid. In the ^{1}H NMR spectrum, the signal due to a *N*-Me group was shifted to low field (δ 3.17 ppm), suggesting that this nitrogen was adjacent to a lactam carbonyl. The remaining two methyl singlets at δ 2.24 and 3.35 ppm were assigned to COMe and ArOMe, respectively. The attachment of the OMe group was shown to be at C-11 from the ^{1}H NMR chemical shifts and coupling patterns of the aromatic protons and was substantiated by homonuclear decoupling and COSY-45 techniques. The unusually low chemical shift of the olefinic proton (H-21) (δ 7.62 ppm) was explained as due to the presence of a directly linked oxygen and a β-carbonyl group. The remaining signals in the ^{1}H NMR spectrum were assigned with the help of a COSY-45 spectrum and homonuclear decoupling experiments. These assignments are shown in Fig. 7. Extensive NOE difference experiments were utilized in confirming the relative ste-

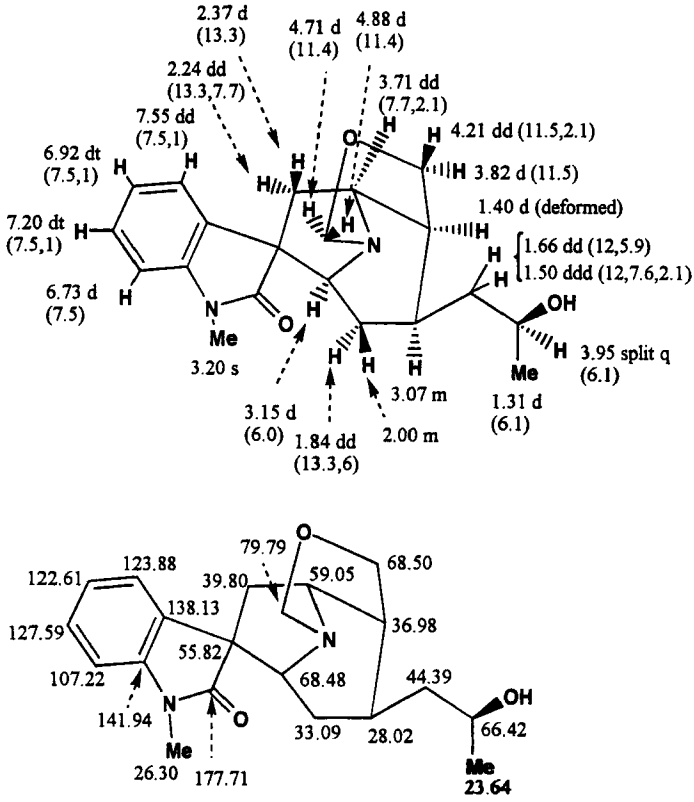
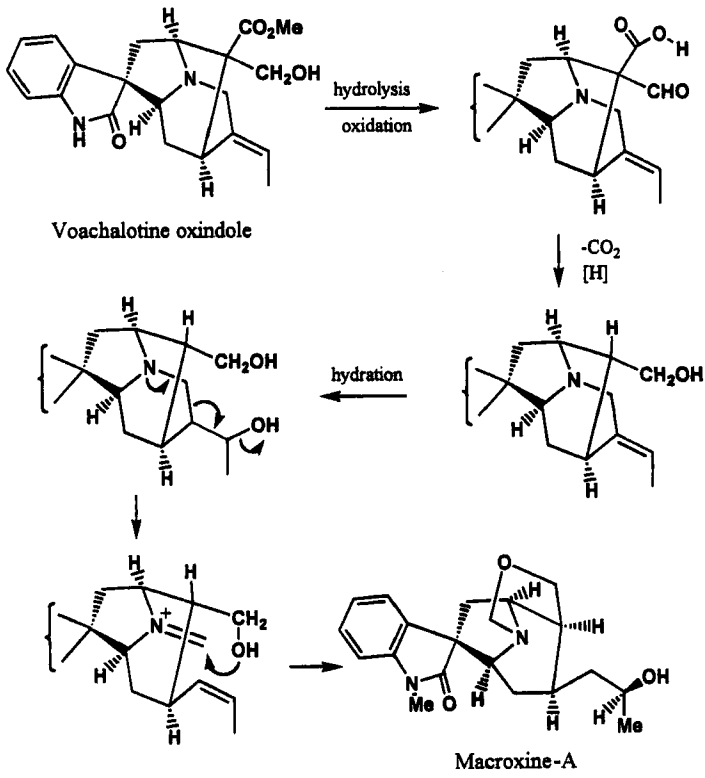


FIG. 6. ^{1}H and ^{13}C NMR data for macroxine-A (**159**).

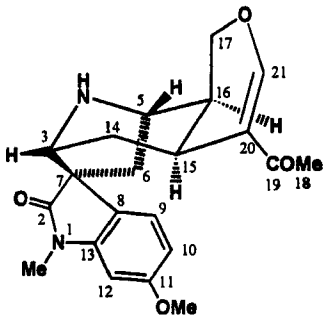
reochemistry and disposition of the protons at various centers of the molecule. The structure and stereochemistry proposed for N_b-demethylalstophylline oxindole (**160**) were further supported by its ^{13}C NMR spectral assignments (Fig. 7) and correlation of NMR data with Drieding molecular models (*99*). Biogenetically, N_b-demethylalstophylline oxindole (**160**) may arise from alstophylline (**110**), which was found to co-occur (*82,88*) with **160** in *Alstonia macrophylla.*

3. Dichomine

Dichomine (**161**) is a novel type of iboga alkaloid reported in 1983 by Perera, van Beek, and Verpoorte from the leaves of *Tabernaemontana dichotoma* (*100*). It was later found to occur in the fruits of the same species (*91*). Dichomine, $C_{19}H_{24}N_2O$, showed an unusual UV spectrum with



SCHEME 12. Proposed biogenetic route to macroxine-A.



(160) N_b-Demethylalstophylline oxindole

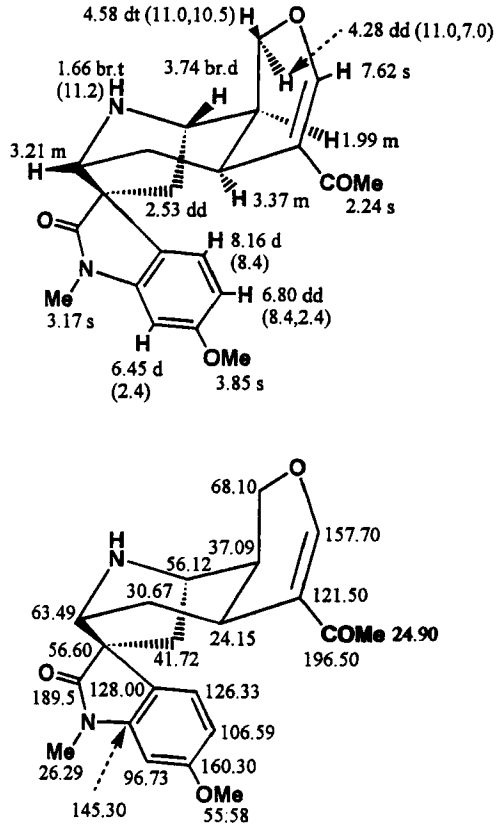
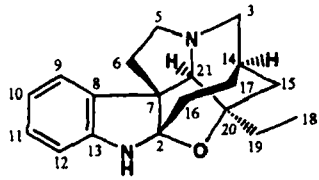


FIG. 7. ^{1}H and ^{13}C NMR data for N_b-demethylalstophylline oxindole (**160**).

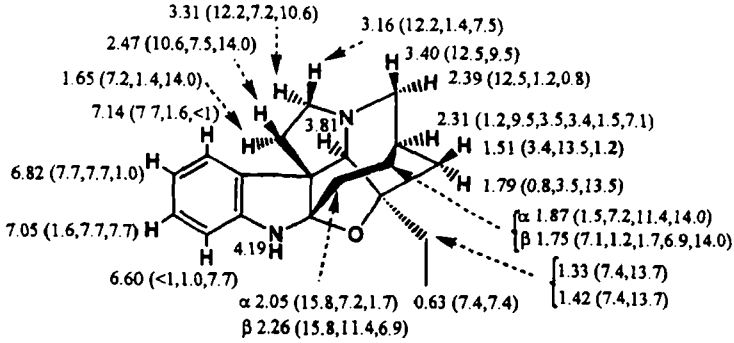
maxima at 205, 225, and 285 nm and in the MS two major fragments at *m/z* 267 (M^+–Et) and *m/z* 124. The structure of dichomine was determined by careful analysis of the ^{1}H and ^{13}C NMR spectra coupled with ^{1}H irradiation, and ^{13}C noise-decoupled and off-resonance spectroscopy, by comparison of the ^{1}H and ^{13}C NMR data (Fig. 8) with known alkaloids having related structures, and by biosynthetic arguments.

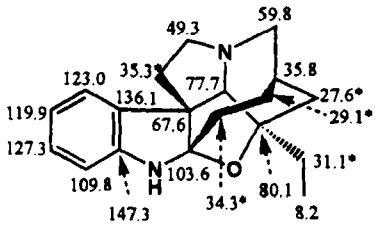
Dichomine (**161**) has five asymmetric centers, and thus 32 stereoisomers are possible. However, an examination of Drieding models indicated that for steric reasons only the structure shown in **161,** which is already highly strained and rigid, and its enantiomer, are possible. ^{1}H Coupling constants observed for various protons (H-14 with H-3α and H-17α, H-14 with H-3β and H-17β, and H-14 with H-15α and H-15β) agreed well with those



(161) Dichomine

expected by careful examination of a Drieding model of structure **161** postulated for dichomine. The relative stereochemistry at C-14 was assumed to be *S* based on biosynthetic reasoning. This was confirmed by $LiAlH_4$ reduction of dichomine (**161**), which afforded 14*S*,20*R*-velbanamine (**163**) with a C-14*S* stereochemistry, presumably via the sterically constrained

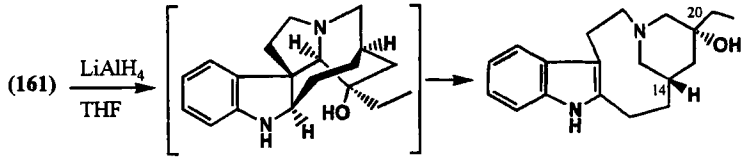




*Assignments may be interchanged.

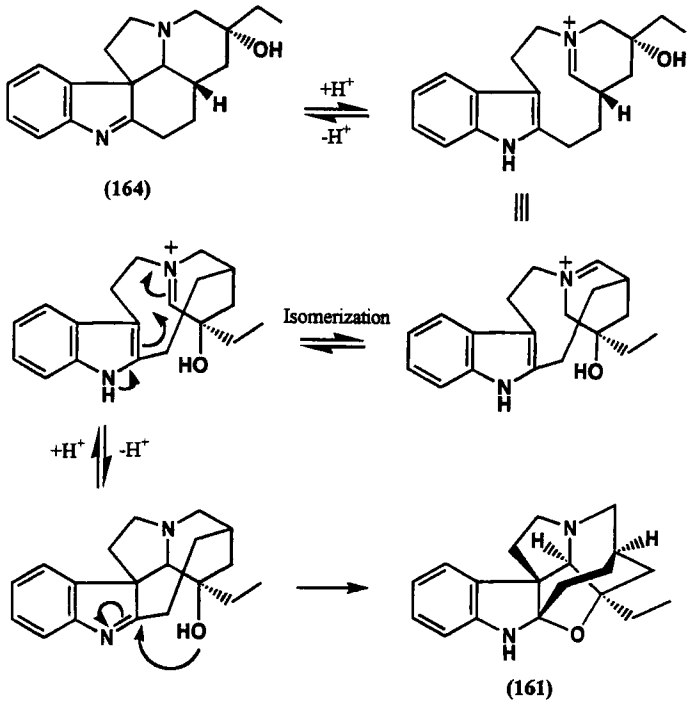
FIG. 8. ^1H and ^{13}C NMR Data for dichomine (**161**).

intermediate **162** (Scheme 13). Biogenetically, dichomine (**161**) may arise from 1,2-dehydro-20*R*-hydroxy-pseudoaspidospermidine (**164**). The authors have proposed a biogenetic pathway to **161** starting from **164** that involves a series of simple, acid-catalyzed, ring-opening, isomerization, cyclization, deprotonation, and addition reactions, as shown in Scheme 14 (*100*).



(**162**) (**163**) 14*S*,20*R*-Velbanamine

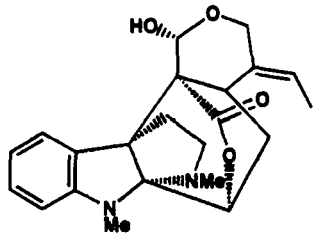
SCHEME 13.



SCHEME 14. Proposed biosynthetic conversion of 1,2-dehydro-20*R*-hydroxypseudoaspidospermidine (**164**) to dichomine (**161**).

4. Isocorymine

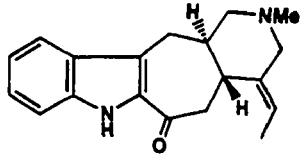
Investigation of the leaves of *Hunteria zeylanica* afforded isocorymine (**165**), mp 183°, $[\alpha]_D$ −239° (*78*).



(165) Isocorymine

5. Isomethuenine

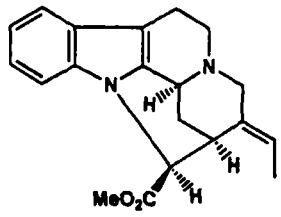
Isomethuenine (**166**) is a minor tertiary indole alkaloid occurring in *Tabernaemontana dichotoma* leaves (*92*), fruits, and stem bark (*93*).



(166) Isomethuenine

6. Pleiocarpamine

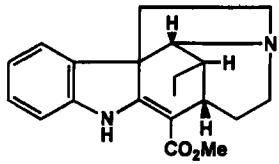
A pentacyclic indole alkaloid isolated from the leaves of *Hunteria zeylanica* was identified as pleiocarpamine (**167**) by Arambewela and Khuong-Huu (*78*).



(167) Pleiocarpamine

7. Tubotaiwine

Tubotaiwine (**168**), a condylocarpine-type indole alkaloid, obtained from *Tabernaemontana dichotoma* of Sri Lankan origin, was subjected to a stereochemical investigation with extensive NMR studies involving NOE dif-

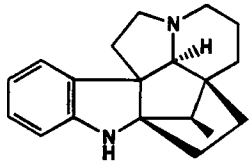


(168) Tubotaiwine

ference measurements, $^{13}C-^{1}H$ coupling constants, and protonation shifts (*101*). These studies led to the conclusion that tubotaiwine (**168**) has the C-20 *S* configuration, in contrast to several previous reports. Thus, tubotaiwine is identical to 20*S*-19,20-dihydrocondylocarpine.

8. Tuboxenine

An alkaloid isolated from the leaves of *Hunteria zeylanica* was identified as tuboxenine (**169**) (*78*).



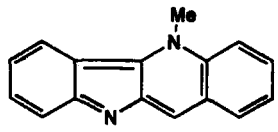
(169) Tuboxenine

9. Cryptolepine

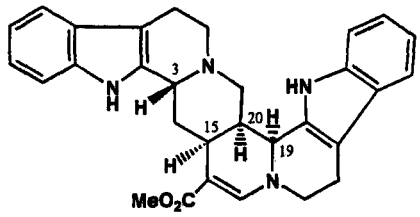
Cryptolepine (**170**), an indole alkaloid with an obscure structural relationship to tryptophan, was shown to be the major alkaloid of *Sida acuta* L. (Malvaceae) (*102*).

N. Roxburghines

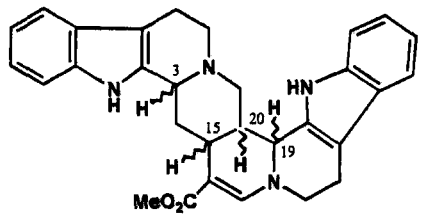
Roxburghines constitute a group of octacyclic "sesquimeric" indole alkaloids conceptually derived from two tryptamine molecules and a monoterpene moiety of the corynanthe type. Roxburghine D (**171**) and the new analog, roxburghine X (**172**), $C_{31}H_{32}N_4O_2$, mp 215°C, $[\alpha]_D^{27}$ −29°,



(170) Cryptolepine



(171) Roxburghine D



(172) Roxburghine X

were isolated from the bark of *Uncaria elliptica,* a plant endemic to Sri Lanka (*96*). The structure of roxburghine X was determined by the application of UV, IR, MS, and ^{1}H NMR techniques, all of which indicated a roxburghine-type structure. Nonagreement of the mp and $[\alpha]_D$ with those reported for known members of this series, roxburghines A–E, indicated it to be a new roxburghine. However, from the available data it was not possible to define the stereochemistries at the asymmetric centers C-3, C-15, C-19, and C-20 of roxburghine X.

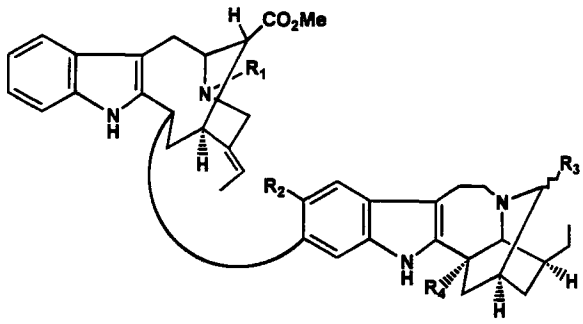
O. Bisindole Alkaloids

Bisindole alkaloids (*103*), sometimes known as dimeric indole alkaloids, are composed of two identical or different monomeric indole alkaloid units

attached to each other by a C–C, C–O–C, or C–N bond and occur mainly in plants of the families Apocynaceae, Loganiaceae, and Rubiaceae. Thus far among Sri Lankan plants, bisindole alkaloids have been encountered in *Alstonia macrophylla, Catharanthus roseus, C. pusillus, Petchia ceylanica,* and *Tabernaemontana dichotoma,* all belonging to the family Apocynaceae. The vobasine–apparicine type bisindole alkaloid monogagaine (**181**), which occurs in *Tabernaemontana dichotoma,* contains two unusual linkages, one of which involves the indolic N between the two monomeric units.

1. Vobasine–Coronaridine Group

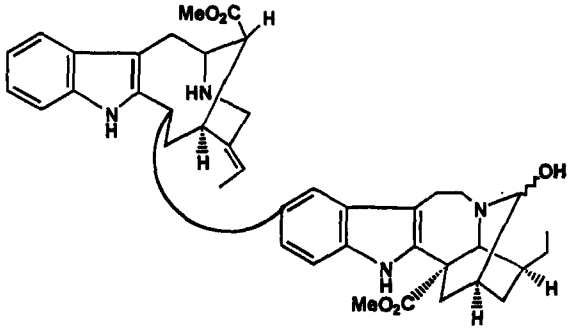
In an extensive study of indole alkaloids from *Tabernaemontana dichotoma,* Perera and co-workers reported the isolation and characterization of eight bisindole alkaloids of the vobasine–coronaridine type (*90,93*). Of these, the previously known alkaloids tabernamine (**173**), voacamine (**175**), and 3′*R/S*-hydroxyvoacamine (**178**) were identified from their spectral characteristics and co-TLC with authentic samples (*91*). UV, IR, and ^{1}H NMR data of three of the bisindole alkaloids indicated a close structural relationship to tabernamine (**173**), and the ^{1}H NMR of one of these alkaloids was identical to that of tabernamine, except that the signal at δ 2.62 ppm due to the *N*-Me group was missing. The MS and IR spectroscopic data



(173)	**R_1 = Me, R_2 = R_3 = R_4 = H**	Tabernamine
(174)	**R_1 = R_2 = R_3 = R_4 = H**	N_4-Demethyltabernamine
(175)	**R_1 = Me, R_2 = OMe, R_3 = H, R_4 = CO_2Me**	Voacamine
(176)	**R_1 = R_2 = R_4 = H, R_3 = OH**	3′*R/S*-Hydroxy-N_4-demethyltabernamine
(177)	**R_1 = Me, R_2 = R_4 = H, R_3 = OH**	3′*R/S*-Hydroxytabernamine
(178)	**R_1 = Me, R_2 = OMe, R_3 = OH, R_4 = CO_2Me**	3′*R/S*-Hydroxyvoacamine
(179)	**R_1 = R_2 = H, R_3 = OH, R_4 = CO_2Me**	3′*R/S*-Hydroxy-N_4-demethylervahanine A

together with these ^1H NMR features suggested that this alkaloid was N_4-demethyltabernamine (**174**). The other two alkaloids exhibited a MS fragmentation with fragment ions at M^+-2, M^+-16, M^+-17, and M^+-18 characteristic of the 3-hydroxy-iboga type of alkaloids. The presence of an epimeric 3-hydroxy group was also evident from their ^1H and ^{13}C NMR spectra, which had double the number of signals, thus hampering their complete assignment. $NaBH_4$ Reduction of each of these alkaloids afforded N_4-demethyltabernamine (**174**) and tabernamine (**173**), assisting the identification of these alkaloids as 3′*R/S*-hydroxy-N_4-demethyltabernamine (**176**) and 3′*R/S*-hydroxytabernamine (**177**), respectively.

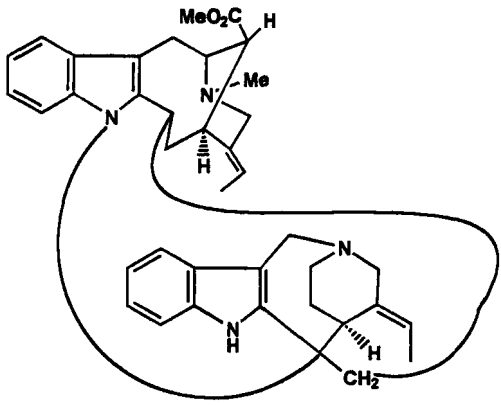
The remaining two alkaloids also had MS fragments characteristic of 3-hydroxy-iboga alkaloids, with fragment ions at M^+-2, M^+-16, M^+-17, and M^+-18. The ^1H NMR spectra, which indicated the presence of a N_4-demethylvobasinyl (perivine) moiety in both alkaloids, were identical with one another except for the signals in the aromatic region. Each of these isomeric alkaloids also had ^1H NMR signals due to two CO_2Me groups, suggesting that they belong to the ervahanine series. The aromatic region of the ^1H NMR spectrum of one of the alkaloids was identical to that of tabernamine, having a C-3–C-11′ linkage. Thus, this alkaloid was identified as 3′*R/S*-hydroxy-N_4-demethylervahanine A (**179**). Further analysis of the ^1H and ^{13}C NMR spectra, together with the above information, suggested a C-3–C-10′ linkage for the remaining isomer, which was identified as 3′*R/S*-hydroxy-N_4-demethylervahanine B (**180**).



(**180**) 3′*R/S*-Hydroxy-N_4-demethylervahanine B

2. *Vobasine–Apparicine Group*

Monogagaine (**181**), $C_{39}H_{44}N_4O_2$, is a new, minor bisindole alkaloid independently isolated from Sri Lankan *Tabernaemontana dichotoma* and *T. chippii* collected in the Ivory Coast (*104*). Structure elucidation of mono-



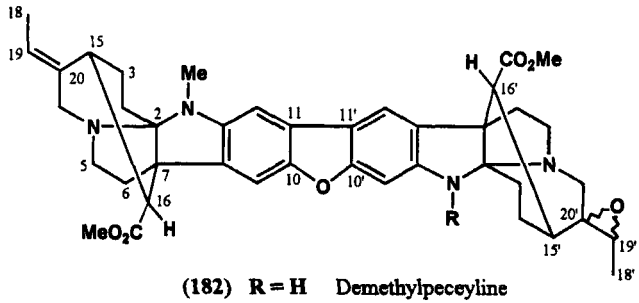
(181) Monogagaine

gagaine was carried out by van Beek and co-workers through the application of extensive spectroscopic [UV, field desorption (FD) MS, high-resolution EI MS, CD, ^{1}H NMR, ^{1}H–^{1}H COSY, NOE difference experiments, and ^{13}C NMR] techniques. The UV data indicated it to be purely indolic. The M^+ at *m/z* 600 observed in the EI MS was confirmed by FD MS. Some of the fragments observed were typical for bisindoles with a 3′-vobasinyl moiety. However, ^{1}H NMR chemical shifts and coupling constants (of *N*-Me, CO_2Me, H-14, H-16, and H-21) characteristic of many vobasinyl-type alkaloids were found shifted in monogagaine. This, together with the EI MS data, led to the conclusion that the vobasinyl half was present but in a different conformation, thus explaining the changes in the ^{1}H NMR chemical shifts and coupling constants. The ^{1}H NMR spectrum also showed the presence of two unsubstituted aromatic rings, one indolic *N*-H, two ethylidine side chains, two AB doublets (J = 17.7 Hz) at δ 4.80 and 4.45 ppm, a CO_2Me at δ 3.47 ppm, and an *N*-Me at δ 2.45 ppm. The unsubstituted nature of the aromatic ring of each monomeric half was indicative of an unusual attachment between the two halves of the dimer. Extensive analysis of the ^{1}H NMR spectrum, determination of ^{1}H–^{1}H connectivities by means of the ^{1}H–^{1}H COSY technique, application of ^{13}C NMR, and comparison of these data with the known vobasine–apparicine type of bisindole alkaloid, vobparicine, isolated from *Tabernaemontana chippii,* in which monogagaine was also found to co-occur, suggested C-16–C-1′ and C-22–C-3′ linkages for monogagaine, as shown in **181.** The relative stereochemistry of all chiral carbons (with the exception of the C-16 spiro carbon) and the conformation of most of the rings in monogagaine were determined with the help of the observed coupling constants in the ^{1}H NMR spectrum, together with an

estimation of the dihedral angles from Drieding models and application of the Karplus equation.

3. *Vincorine–Vincorine and Vincorine–Picraline Groups*

Investigation of *Petchia ceylanica,* a plant of the family Apocynaceae indigenous to Sri Lanka, afforded a series of new and unusual biphenyl type vincorine–vincorine dimers and a new vincorine–picraline type of binary indole alkaloid. Demethylpeceyline (**182**), $C_{41}H_{46}N_4O_6$, $[\alpha]_D$ −120° (*105*), had IR bands due to *N*-H and a saturated carbonyl and a UV chromophore composing an indoline system. The MS fragmentation was similar to that of corymine, which showed a *retro*-Diels–Alder type fragmentation of ring D with loss of ethylene. The MS fragmentation also showed some similarities to that of vincorine (**145**). The presence of four singlets in the aromatic region of the ^{1}H–NMR spectrum suggested that there were two aromatic protons in each monomeric portion with a *para* disposition to one another and was consistent with the presence of a dibenzofuran ring joining the two monomers. The ^{1}H NMR spectrum also indicated the presence of the olefinic proton of a $=CH-CH_3$ moiety, two methoxycarbonyl groups, two methyl doublets, an oxymethine proton as a quartet, and an *N*-Me singlet. The ^{13}C NMR spectrum, although it confirmed these structural moieties, indicated the presence of four aminomethylene carbons, six dialkylmethylenes, four methine carbons, and four nonprotonated carbons. Two of these nonprotonated carbons resonated at δ 97.87 and 95.3 ppm, indicating that each was attached to two heteroatoms. Careful analysis of the ^{1}H and ^{13}C NMR spectra suggested that demethylpeceyline (**182**) was composed of a vincorine moiety combined with vincorine oxide. NOE difference spectroscopy was used to determine which half of the dimer contained the *N*-Me group and the stereochemical disposition of the exocyclic ethylidine moiety. The alternative structure for demethylpeceyline in which the oxirane ring is at C-19–C-20 and the double bond at C-19′–C-20′ was

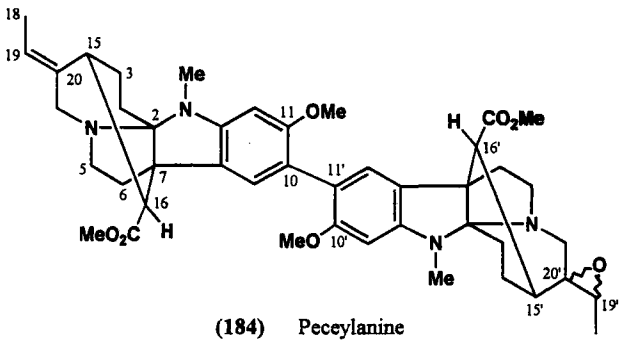


(182) R = H Demethylpeceyline

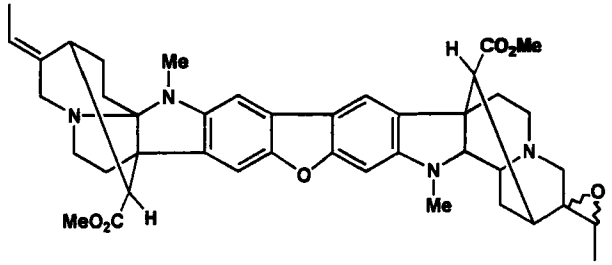
(183) R = Me Peceyline

ruled out on the basis of the MS fragmentation pattern, which had fragment ions containing the oxirane ring but no *N*-Me group, and also fragments that contained an *N*-Me together with the ethylidene moiety.

Peceyline (**183**), $C_{42}H_{48}N_4O_6$, mp 310°C (decomp.), $[\alpha]_D$ −355°, and peceylanine (**184**), $C_{44}H_{54}N_4O_7$, mp 157–158°C, $[\alpha]_D$ −237°, are two other vincorine–vincorine types of bisindole alkaloids isolated from *Petchia ceylanica* (*76,106*). Their structures were elucidated with the help of UV, IR, MS, ^1H, and ^{13}C NMR spectroscopy, and comparison of these data with those of the monomers. Pelankine (**185**), $C_{42}H_{48}N_4O_6$, $[\alpha]_D$ −214°, is a vincorine–picraline type of bisindole alkaloid isolated from the same plant, whose structure elucidation involved a similar strategy. Complete ^{13}C NMR assignments of peceyline (**183**), peceylanine (**184**), and pelankine (**185**) were also made (*106*).



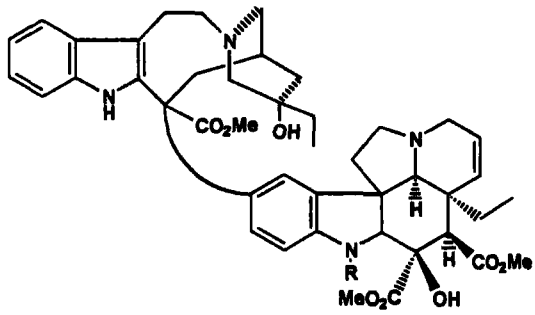
(**184**) Peceylanine



(**185**) Pelankine

4. Vindoline–Catharanthine Group

Vincaleukoblastine (**186**) and vincristine [leurocristine (**187**)] are two pharmaceutically important antitumor alkaloids of the vindoline–

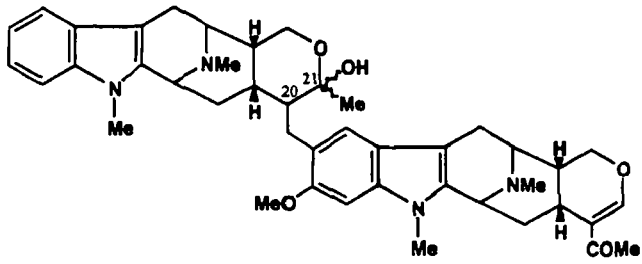


(186) R = Me Vincaleukoblastine
(187) R = CHO Vincristine

catharanthine type obtained from *Catharanthus roseus* (L.) G. Don. In Sri Lanka, the genus *Catharanthus* has two species, *C. roseus* and *C. pusillus* (Murr.) G. Don. Three different forms of *C. roseus* have also been reported (*107*). *C. pusillus* is an annual herb indigenous to Sri Lanka and India. In the mid-1970s, plants of *C. roseus* were uprooted and exported to drug manufacturers in Europe for extraction of these alkaloids. However, no organized cultivation of this plant was attempted. Realization of the disadvantages of this practice prompted an investigation into the feasibility of extracting these alkaloids from *C. roseus* and *C. pusillus* with locally available solvents and facilities with the hope of obtaining better returns to the country from this nontraditional export (*108*). This work has led to two important findings, namely, the possibility of harvesting the leaves for extraction at periodic intervals and the reduction in cost of freight by exporting the crude alkaloidal extract instead of the dried plant material. This study also showed that large-scale processing of a crude alkaloidal mixture from *C. pusillus* for **186** and **187** would prove to be easier than that from *C. roseus*. In a more recent field study it was found that foliar application of plant nutrients containing the major and minor essential elements and plant hormones produced a significant increase in alkaloid content in the leaves and roots of *C. roseus* (*109*).

5. Bis-indohomotropanes

Two bis-indohomotropane alkaloids, macralstonine (**188**) and anhydromacralstonine (**189**), were isolated from the stem bark and leaves of *Alstonia macrophylla* (*82*). Root bark of the same plant was recently reported to contain macralstonine (**188**) (*88*).

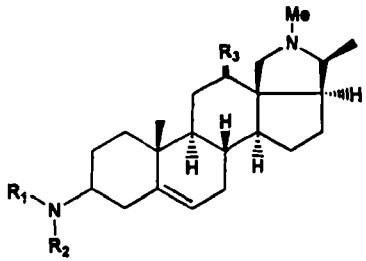


(188) Macralstonine

(189) 20,21 Anhydromacralstonine

VIII. Steroidal Alkaloids

A variety of steroidal alkaloids were isolated from the endemic medicinal plant *Holarrhena mitis* by Wannigama, Goutarel, Cavé, and their coworkers (*110–114*). The bark juice of this plant, under the name *Kalindu*, is reputed in Sri Lankan native medicine as a remedy for dysentery and fevers (*9*). In addition to the isolation of conessine (**190**) from the bark of this plant, during their early investigations Bhavanandan and Wannigama obtained evidence for the occurrence of *N*-demethylated conessines (*110*). Further investigations confirmed the occurrence of several steroidal alkaloids, namely, isoconessimine (**191**), holarrhenine (**192**), conkurchine



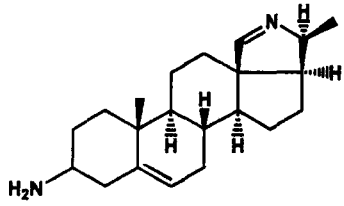
(190) $R_1 = R_2 = Me$, $R_3 = H$ Conessine

(191) $R_1 = Me$, $R_2 = R_3 = H$ Isoconessimine

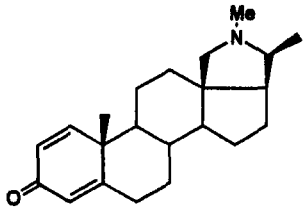
(192) $R_1 = R_2 = Me$, $R_3 = OH$ Holarrhenine

(193) $R_1 = R_2 = R_3 = H$ Conamine

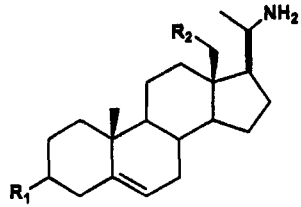
(**194**), holadienmine (**195**), holafebrine (**196**), holarrhimine (**197**), and N_3-methylholarrhimine (**198**), in the bark of this plant (*111*). The seeds of *H. mitis* were devoid of mitiphylline (**200**), but contained conessine (**190**)



(**194**) Conkurchine

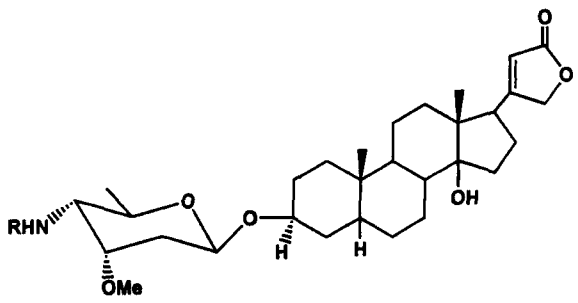


(**195**) Holadienmine



(**196**) $R_1 = OH, R_2 = H$ Holafebrine
(**197**) $R_1 = NH_2, R_2 = OH$ Holarrhimine
(**198**) $R_1 = NHMe, R_2 = OH$ *N*-Methylholarrhimine

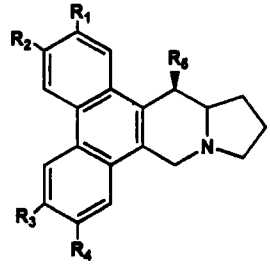
(*110,113*), isoconessimine (**191**) (*113*), and conamine (**193**) (*113*). Mitiphylline (**200**) and its *N*-demethyl analog, *N*-desmethylmitiphylline (**199**), were obtained from leaf extractives of *H. mitis* (*112,114*). Much attention has been focused on the steroidal alkaloids of *Holarrhena* species with the intention of economic exploitation of these compounds in the synthesis of valuable steroidal hormones (*115*).



(199) R = H *N*-Desmethymitiphylline
(200) R = Me Mitiphylline

IX. Phenanthroindolizidine Alkaloids

Several phenanthroindolizidine alkaloids have been isolated and/or detected in *Tylophora asthmatica* [syn. *T. indica*], *T. cordifolia,* and *T. flava,* collected in different localities of Sri Lanka. Of these species, *T. asthmatica,* known as Indian ipecacuanha, is used in indigenous medicine as an emetic, expectorant, and antidysenteric, and *T. flava* is endemic to Sri Lanka. Some phenanthroindolizidine or *Tylophora* alkaloids are known to possess antileukemic activity. Phillipson and co-workers subjected various parts of these three Sri Lankan *Tylophora* species to an alkaloid screening in which they assessed the alkaloid content by comparison of the color intensities produced by Dragendorff's reagent with the extracts and with known amounts of tylophorinine (**202**) (*116*). Their studies indicated the presence of tylophorinine, together with some unidentified alkaloids, in all the samples of *T. asthmatica, T. cordifolia,* and *T. flava* investigated. However, their results on *T. asthmatica* contrasted with those previously reported for the Indian species and indicated either that there were some variations in alkaloid content from season to season or that different strains of *T. asthmatica* existed. One similarity that did exist between the Indian and Sri Lankan materials was the very low yield of the antileukemic alkaloid tylophorinine (**202**). A detailed isolation from a large batch of *T. asthmatica* that was also carried out by Phillipson's group confirmed the presence of tylophorine (**201**), tylophorinine (**202**), and tylophorinidine (**203**) in the Sri Lankan sample.



(201) $R_1 = R_2 = R_3 = R_4 = OMe$, $R_5 = H$ Tylophorine

(202) $R_1 = H$, $R_2 = R_3 = R_4 = OMe$, $R_5 = OH$ Tylophorinine

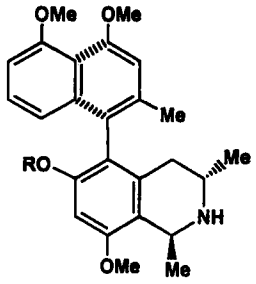
(203) $R_1 = H$, $R_2 = R_4 = OMe$, $R_3 = R_5 = OH$ Tylophorinidine

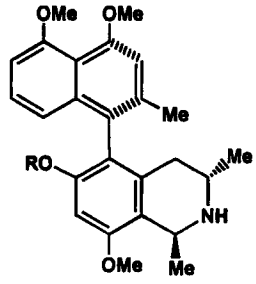
X. *Ancistrocladus* Alkaloids

This group of alkaloids is found confined mainly to plants of the genus *Ancistrocladus* of the family Ancistrocladaceae. *Ancistrocladus* alkaloids contain an isoquinoline unit linked to a naphthalene moiety. Unlike typical isoquinoline alkaloids (see Section V), which are of aromatic amino acid biogenetic origin, the isoquinoline moiety of *Ancistrocladus* alkaloids has a polyketide biogenesis. Govindachari's group, in the course of their studies on isoquinoline alkaloids, investigated the roots of *A. hamatus* (Vahl.) Gilg., which is endemic to Sri Lanka (*117*). In addition to ancistrocladine (**206**), which was previously isolated from several members of this genus, a new alkaloid, named hamatine (**204**), $C_{25}H_{29}NO_4$, mp 250–252°C, $[\alpha]_D$ +77.44°, was isolated. It was shown that the product derived from *O*-methylhamatine (**205**) by dehydrogenation is enantiomeric with the isoquinoline derived from *O*-methylancistrocladine (**207**) by the same procedure. This finding, coupled with ^1H NMR and CD data, suggested that ancistrocladine (**206**) and hamatine (**204**) were isomeric, the only difference being the relative orientation of the substituted naphthalene ring.

XI. Colchicine and Related Alkaloids

As far back as 1915 Clewer and co-workers investigated the tubers of *Gloriosa superba* L. (Liliaceae) obtained from Sri Lanka for alkaloids

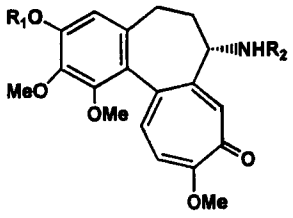


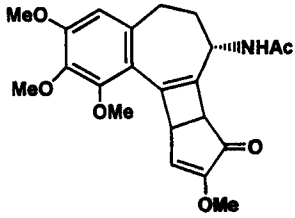


(204) R = H Hamatine
(205) R = Me *O*-Methylhamatine

(206) R = H Ancistrocladine
(207) R = Me *O*-Methylancistrocladine

(*118*). They reported the presence of colchicine (**208**) and an unidentified alkaloid, mp 177–178°C, with a probable molecular formula, $C_{33}H_{38}N_2O_9$. Subsequent examination of the mature tubers of *G. superba,* which commonly cause poisoning in some rural areas of Sri Lanka (*119,120*), revealed colchicine (**208**) to be the major alkaloid (*120*). Colchicine was also found to occur in the tender tubers, seeds, and flowers. In addition to colchicine, mature tubers contained *N*-formyl-*N*-desacetylcolchicine (**209**), 2-demethylcolchicine (**210**), lumicolchicine (**211**), and trace amounts of unidentified alkaloids (*120*). Seeds of Sri Lankan *G. superba* were also analyzed by Santávy and co-workers by paper chromatographic techniques and were shown to contain **208, 209,** and **210** (*121*). A recent analytic and phytochemical study of *G. superba* cultivated in Sri Lanka for export revealed that the seeds contain the highest amounts of total alkaloids including colchicine (*122*). Alkaloids were also present in the tubers, leaves, and pericarp of this plant.



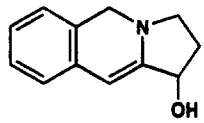


(208) R_1 = Me, R_2 = Ac Colchicine
(209) R_1 = Me, R_2 = CHO *N*-Formyl-*N*-desacetylcolchicine
(210) R_1 = H, R_2 = Ac 2-Demethylcolchicine

(211) Lumicolchicine

XII. Quinazoline and Quinazolone Alkaloids

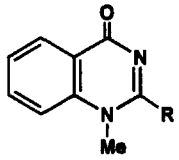
The quinazoline alkaloid vasicine (**212**) is the major alkaloid of *Adhatoda vasica* L. (Acanthaceae), a plant reputed to be used in many Ayurvedic medicinal preparations. Seasonal variation of vasicine (**212**) content in various parts of the plant (inflorescence, leaf, petiole, root, and stem bark)



(212) Vasicine

used in traditional medicine was studied by Arambewela and co-workers in an attempt to determine the best harvesting period for such use (*123*). It was found that the inflorescences contained the highest amount of vasicine throughout the year, whereas the roots contained the lowest; the highest vasicine content was observed during the months of July to September in most parts of the plant. A TLC study of medicinally useful *Sida* species for pharmacologically important alkaloids revealed the presence of vasicine (**212**) as the major alkaloid in *S. cordifolia* L. (Malvaceae) (*103*).

The quinazolone alkaloids glycorine (**213**) and arborine (**214**) were reported from the leaves of *Glycosmis bilocularis* (*26*).

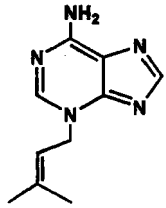


(213) R = H Glycorine

(214) R = $CH_2C_6H_5$ Arborine

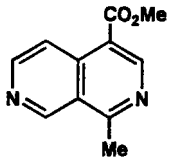
XIII. Miscellaneous Alkaloids

The purine base triacanthine (**215**) occurs in the fruit pericarp (*113*), leaves (*112,113*), and seeds (*113*) of *Holarrhena mitis.*

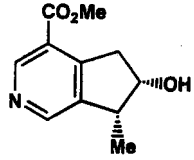


(215) Triacanthine

Neozeylanicine (**216**), $C_{11}H_{10}N_2O_2$, mp 110°C, is a new naphthyridine alkaloid isolated from the timber of *Neonauclea zeylanica* (Rubiaceae) (*124,125*), A new monoterpene alkaloid, 6*S*-hydroxy-7*R*-methyl-6,7-dihydro-2,5-pyrindene-4-carboxymethyl ester (**217**), has also been isolated from the same plant (*124*). However, details of the structure elucidation of the latter alkaloid are not yet available.



(216) Neozeylanicine



(217)

XIV. Biological Activity

Of a total of 43 Sri Lankan plants from which alkaloids have been isolated, 17 are claimed to have applications in traditional systems of medicine (Table III). As stated in the Introduction, many of these investigations were not driven by the claims of medicinal properties. Interestingly, several bioactive alkaloids have been isolated from plants with no claims of any medicinal applications.

A. Pharmacological Activity

The most comprehensive study of a Sri Lankan medicinal plant was that of *Tabernaemontana dichotoma* conducted by Perera and co-workers (*89,126*). A preliminary pharmacological assay of the crude aqueous

HOAc extract of the seeds of this plant showed a sedative effect in mice at 250 mg/kg when administered intraperitonially. At higher doses (500–1000 mg/kg), weak convulsant effects and jumping fits were observed on the isolated guinea pig ileum; 1 mg/mL of the crude seed extract exhibited a 40% decrease of the amplitude of contraction caused by 102 ng/mL histamine, and 0.4 mg/mL of the same extract inhibited 80% of the amplitude caused by electrical stimulation of the ileum (*89*). In a pharmacological screening of *T. dichotoma,* extracts from all plant parts except the seeds were found to be highly toxic, thus explaining the use of this plant in Sri Lanka only in external applications (*126*). In a subsequent study, Perera and co-workers evaluated the muscle relaxant and hypotensive activity of several indole alkaloids isolated from *T. dichotoma.* The major alkaloid of the seeds, stemmadenine (**100**), was found to have hypotensive and weak muscle relaxant activities, whereas some of the indole alkaloids isolated from the leaves, fruits, and bark, such as perivine (**139**), vobasine (**138**), coronaridine (**119**), and dichomine (**161**), exhibited hypotensive and muscle relaxant activities (*127*). It was suggested that the hypotensive effect of stemmadenine (**100**) is probably due to some interference with sympathetic transmission, although a cholinergic-like effect may also contribute to this activity. Thus, it is possible that the hypotensive effect of stemmadenine may have a central component that may in some way be associated with the reported traditional use of seeds of *T. dichotoma* as a narcotic (*128*). The hypotensive activity of an alcoholic extract of the medicinal plant *Sida carpinifolia* (syn: *S. acuta*) was related to the presence of cryptolepine (**170**) in this extract (*102*).

In a study of toxicity of Sri Lankan traditional medicinal herbs, Arseculeratne and co-workers evaluated 125 commonly used medicinal plants for the occurrence of hepatotoxic pyrrolizidine alkaloids (*129,130*). *Crotolaria juncea, C. verrucosa,* and *Holarrhena antidysenterica* were shown to contain pyrrolizidine alkaloids by TLC. When fed to rats, these plants produced hepatic lesions compatible with the action of pyrrolizidine alkaloids.

B. Antimicrobial Activity

Although the endemic species *Broussonetia zeylanica* (Thw.) has no claims of medicinal applications, when screened, some of its extracts exhibited significant antimicrobial activity against three common pathogenic organisms, *Candida albicans, Escherichia coli,* and *Staphylococcus aureus* (*15*). Bioactivity-guided fractionation led to the isolation of the major antimicrobial alkaloid, 8-hydroxyquinoline-4-carbaldehyde (**1**), active against *C. albicans* and *S. aureus* (*17,18*). 8-Hydroxyquinoline (oxine) and its derivatives are known to have an array of antimicrobial properties, and a number

of them have been used as topical antiseptics and disinfectants (*131*). The synthetic isomer of **1,** 8-hydroxyquinoline-5-carbaldehyde, was found to be effective against human type H-37 Rv strain of *Mycobacterium tuberculosis* (*132*). The possible relationship between the complex formation property and the tuberculostatic activity of this class of compounds prompted synthesis and testing of a number of 8-hydroxyquinoline carbaldehydes and their thiosemicarbazones (*133*).

In continuing their evaluation of the medicinal claims of *Tabernaemontana dichotoma,* Perera *et al.* screened the tertiary alkaloid fraction derived from the stem and root bark of this plant for antimicrobial activity. These were found to have a broad spectrum of activity against *Bacillus subtilis, S. aureus, E. coli, C. albicans,* and *Aspergillus niger* (*126*), justifying the use of aqueous extracts of this plant to heal wounds in traditional medicine (*134*). Monogagaine (**181**), a new bisindole alkaloid isolated from *T. dichotoma* stem bark, exhibited antibacterial activity against *B. subtilis* (*104*).

The aporphine alkaoid laurolitsine (**29**) obtained from the bark of *Litsea gardneri* was found to be active against *S. aureus* with a minimum inhibitory concentration (MIC) of 250 μg/mL. However, it was shown to be inactive toward *E. coli* and the fungus *Cladosporium cladosporioides* (*41*). Cryptolepine (**170**), the major alkaloid of the medicinal plant *Sida acuta,* exhibited antimicrobial activity against *Proteus vulgaris* with a MIC of 600 μg/mL (*102*). The antifungal activity of a dichloromethane extract of *Alstonia macrophylla* was shown to be due to the presence of the indole alkaloid talcarpine (**109**) (*88*). Of the three indole alkaloids, alstophylline (**110**), demethoxyalstophylline [alstonerine (**111**)], and talcarpine (**109**), and the bisindole alkaloid macralstonine (**188**), only talcarpine (**109**) exhibited moderate *in vitro* inhibitory activity against *Cercospora* species (*88*).

C. Anticancer Activity

Several alkaloids isolated from Sri Lankan plants have shown potential anticancer activity in a preliminary mechanism-based DNA-damaging assay utilizing mutant yeast strains (*135,136*) and cytotoxicity assays employing cancer cell lines. An extract of *Artabotrys zeylanicus,* which showed a positive response in the brine shrimp toxicity assay (*137*) and mechanism-based yeast assay, when fractionated using the latter assay as a guide, afforded two DNA-damaging alkaloids, artabotrine (**50**) and atherospermidine (**42**) (*49*). Artabotrine was also demonstrated to be active in a wild-type P-388 murine leukemia cell line and its camptothecin-resistant strain with IC_{50} values of 1.59 and 1.12 μM, respectively. The oxoaporphine alkaloid oxocrebanine (**46**) and two dioxoaporphines, 8-methoxyouregidione (**51**) and ouregidione (**52**) also from *A. zeylanicus,*

TABLE VI

ALPHABETICAL LIST OF THE ALKALOIDS ENCOUNTERED IN SRI LANKAN FLORA

Alkaloid Name	Class	Source	Plant Part[a]	Ref.
O-Acetylvellesamine (**98**)	Indole	*Tabernaemontana dichotoma*	Fr	*81*
Actinodaphnine (**27**)	Aporphine	*Litsea gardneri*	Bk	*41*
Ajmalicine (**80**)	Indole	*Petchia ceylanica*	Lf	*74*
		Uncaria elliptica	Pl	*72,73*
Akuammigine *N*-oxide (**95**)	Indole	*Mitragyna parvifolia*	Lf	*80*
Alstomacrocine (**112**)[b]	Indole	*Alstonia macrophylla*	Lf	*84*
(+)-Alstonamide (**146**)[b]	Indole	*Alstonia macrophylla*	Lf	*86,95*
Alstonerine (Demethoxyalstophylline) (**111**)	Indole	*Alstonia macrophylla*	Bk, Fr, Rt	*79,82,88*
Alstophylline (**110**)	Indole	*Alstonia macrophylla*	Bk, Lf, Rt	*82,88*
Alstopicralamine (**106**)[b]	Indole	*Alstonia macrophylla*	Lf	*85*
Alstoumerine (**107**)[b]	Indole	*Alstonia macrophylla*	Lf	*86*
Alstozine *N*-oxide (**104**)	Indole	*Alstonia macrophylla*	Lf	*83*
Ancistrocladine (**206**)	*Ancistrocladus*	*Ancistrocladus hamatus*	Rt	*117*
Anhydromacralstonine (**189**)	Indole	*Alstonia macrophylla*	Bk, Lf	*82*
(−)-Apparicine (**96**)	Indole	*Tabernaemontana dichotoma*	Fr, Lf	*81*
Arborine (**214**)	Quinazolone	*Glycosmis bilocularis*	Lf	*25*
Arborinine (**10**)	Acridone	*Glycosmis bilocularis*	Lf	*25*
Artabotrine (**50**)[b]	Aporphine	*Artabotrys zeylanicus*	Bk	*49*
Atalanine (**21**)[b]	Acridone	*Atalantia ceylanica*	Bk	*33*
Ataline (**22**)[b]	Acridone	*Atalantia ceylanica*	Bk	*33*
Atherospermidine (**42**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48,49*
Bleekerine (**84**)	Indole	*Neisosperma oppositifolia*	Bk	*76*
Broussonetine (**4**)[b]	Quinoline	*Broussonetia zeylanica*	Tm	*21*
Cabucraline (**103**)	Indole	*Alstonia macrophylla*	Bk, Lf	*82*
5α-Carboxystrictosidine (**78**)	Indole	*Cinchona ledgeriana*	Pl	*70,71*
		Rauvolfia serpentina	Pl	*70,71*
Cleistopholine (**6**)	Benzoquinoline	*Cananga odorata*	Bk	*24*
Colchicine (**208**)	Misc.	*Gloriosa superba*	Tu	*118,120,122*

Conamine (**193**)	Steroidal	*Holarrhena mitis*	Sd	*113*
Conessine (**190**)	Steroidal	*Holarrhena mitis*	Bk, Sd	*110,111,113*
Conkurchine (**194**)	Steroidal	*Holarrhena mitis*	Bk	*111*
Coronaridine (**119**)	Indole	*Tabernaemontana dichotoma*	Bk, Fr, Sd, Rt bk	*87,89*
		T. divaricata	Bk	*87*
Corynanthediol (**93**)	Indole	*Mitragyna parvifolia*	Pl	*80*
Cryptolepine (**170**)	Misc. indole	*Sida acuta*	Pl	*102*
Cyathocaline (**53**)[b]	Azafluorenone	*Cyathocalyx zeylanica*	Bk	*50*
		Annona reticulata	Bk	*51*
Demethoxyalstonamide (**147**)[b]	Indole	*Alstonia macrophylla*	Lf	*86*
Demethoxyalstophylline (Alstonerine) (**111**)	Indole	*Alstonia macrophylla*	Rt bk	*79,82,88*
Demethoxyerythratidinone (**59**)[b]	*Erythrina*	*Erythrina lithosperma*	Lf	*56,57*
N_b-Demethylalstophylline oxindole (**160**)[b]	Oxindole	*Alstonia macrophylla*	Lf	*99*
2-Demethylcolchicine (**210**)	Misc.	*Gloriosa superba*	Tu	*119*
Demethylpeceyline (**182**)[b]	Bisindole	*Petchia ceylanica*	Lf	*105*
N_4-Demethyltabernamine (**174**)	Bisindole	*Tabernaemontana dichotoma*	Bk	*90,93*
Des-*N*-methylacronycine (**18**)	Acridone	*Glycosmis mauritiana*	Bk	*32*
N-Desmethylmitiphylline (**199**)	Steroidal	*Holarrhena mitis*	Lf	*112,114*
Dicentrinone (**47**)	Aporphine	*Xylopia championii*	Bk	*48*
Dichomine (**160**)[b]	Indole	*Tabernaemontana dichotoma*	Fr, Lf	*91,100*
Dihydrocorynantheol (**92**)	Indole	*Hunteria zeylanica*	Bk	*78*
		Mitragyna parvifolia	Pl	*80*
Dihydrocorynantheol N_4-oxide (**94**)	Indole	*Mitragyna parvifolia*	Pl	*80*
5,6-Dihydroxyarborinine (**13**)[b]	Acridone	*Pleiospermium alatum*	Bk, Rt bk	*30*
5,6-Dimethoxyarborinine (**15**)[b]	Acridone	*Pleiospermium alatum*	Bk, Rt bk	*30*
(+)-Eburnamenine (**118**)	Indole	*Hunteria zeylanica*	Lf	*78*
Eburnamine (**113**)	Indole	*Hunteria zeylanica*	Bk, Lf	*78*
19*R*-Epiheyneanine (**127**)	Indole	*Tabernaemontana dichotoma*	Fr	*91*
19*R*-Epiiboxygaine (**130**)	Indole	*Tabernaemontana dichotoma*	Lf	*92*
19*R*-Epimisiline (**143**)[b]	Indole	*Petchia ceylanica*	Lf	*94*
19*S*-Epimisiline (**144**)[b]	Indole	*Petchia ceylanica*	Lf	*94*

(*continues*)

TABLE VI (*Continued*)

Alkaloid Name	Class	Source	Plant Part[a]	Ref.
3-Epirauvanine (**86**)[b]	Indole	*Neisosperma oppositifolia*	Bk	*76*
19-Epivoacangine (Isovoacangine) (**126**)	Indole	*Tabernaemontana divaricata*	Bk	*87*
19*R*-Epivoacristine (**124**)	Indole	*Tabernaemontana dichotoma*	Lf	*92*
Epiyohimbol (**89**)[b,c]	Indole	*Hunteria zeylanica*	Bk	*78*
Erysotrine (**56**)	*Erythrina*	*Erythrina lithosperma*	Lf	*56,57*
Erythraline (**57**)	*Erythrina*	*Erythrina lithosperma*	Lf	*56,57*
Erythratidinone (**58**)[b]	*Erythrina*	*Erythrina lithosperma*	Lf	*56,57*
O-Ethyleburnamine (**117**)[b,c]	Indole	*Hunteria zeylanica*	Bk	*78*
Eupolauridine (**55**)	Diazafluoranthene	*Cananga odorata*	Bk	*24,52*
Formosanine (Uncarine B) (**150**)	Oxindole	*Uncaria elliptica*	Bk	*73,96*
N-Formyl-*N*-deacetylcolchicine (**209**)	Misc.	*Gloriosa superba*	Tu	*120*
Girinimbilol (**66**)	Carbazole	*Murraya koenigii*	Bk	*61*
Girinimbine (**68**)	Carbazole	*Murraya koenigii*	Fr	*61,64*
Glucescine (**40**)[b]	Proaporphine	*Diploclisia glaucescens*	St	*43*
Glycomaurin (**70**)[b]	Carbazole	*Glycosmis mauritiana*	Bk	*32*
Glycomaurrol (**67**)[b]	Carbazole	*Glycosmis mauritiana*	Bk	*32*
Glycorine (**213**)	Quinazolone	*Glycosmis bilocularis*	Lf	*25*
Hamatine (**204**)[b]	*Ancistrocladus*	*Ancistrocladus hamatus*	Rt	*117*
Holadienmine (**195**)	Steroidal	*Holarrhena mitis*	Bk	*111*
Holafebrine (**196**)	Steroidal	*Holarrhena mitis*	Bk	*111*
Holarrhenine (**192**)	Steroidal	*Holarrhena mitis*	Bk	*111*
Holarrhimine (**197**)	Steroidal	*Holarrhena mitis*	Bk	*111*
5-Hydroxyacronycine (**19**)[b]	Acridone	*Atalantia ceylanica*	Wd	*33,34*
5-Hydroxyarborinine (**11**)[b]	Acridone	*Glycosmis bilocularis*	Lf	*25*
		Luvunga angustifolia	St	*23*
		Pleiospermium alatum	St	*30*
Hydroxy-17-decarbomethoxy-16-dihydro-epiajmalicine (**87**)[b,c]	Indole	*Hunteria zeylanica*	Bk	*78*
3′R/S-Hydroxy-N_4-demethyl ervahanine A (**179**)	Bisindole	*Tabernaemontana dichotoma*	Bk, Rt bk	*90,93*
3′R/S-Hydroxy-N_4-demethyl ervahanine B (**180**)	Bisindole	*Tabernaemontana dichotoma*	Bk, Rt bk	*90,93*

3′-Hydroxy-N_4-demethyl tabernamine (**176**)	Bisindole	*Tabernaemontana dichotoma*	Bk, Rt bk	*90,93*
16*S*-Hydroxy-16,22-dihydroappariceine (**99**)[b]	Indole	*Tabernaemontana dichotoma*	Lf	*81*
6-Hydroxy-5-methoxyarborinine (**14**)	Acridone	*Pleiospermium alatum*	Rt bk	*30*
6*S*-Hydroxy-7*R*-methyl-6,7-dihydro-2,5-pyrindene-4-carboxymethyl ester (**217**)[b]	Misc.	*Neonauclea zeylanica*	Un	*124*
5-Hydroxynoracronycine (**19**)[b]	Acridone	*Atalantia ceylanica*	Bk	*34*
		Pleiospermium alatum	Rt bk	*30*
5-Hydroxynoracronycine 2-(3′-methylbut-2-enyl) derivative (**20**)[b]	Acridone	*Atalantia ceylanica*	Bk	*34*
8-Hydroxyquinoline-4-carbaldehyde (**1**)[b]	Quinoline	*Broussonetia zeylanica*	Tm	*15,16*
8-Hydroxyquinoline-4-carbaldehyde oxime (**2**)[b]	Quinoline	*Broussonetia zeylanica*	Tm	*19*
10-Hydroxystrictamine (**105**)	Indole	*Alstonia macrophylla*	Lf	*84*
3′R/S-Hydroxytabernamine (**177**)	Bisindole	*Tabernaemontana dichotoma*	Bk, Rt bk	*90,93*
19-Hydroxyvincamajine (**102**)[b]	Indole	*Alstonia macrophylla*	Lf	*82*
3′R/S-Hydroxyvoacamine (**178**)	Indole	*Tabernaemontana dichotoma*	Bk, Rt bk	*90*
Ibogamine (**129**)	Indole	*Tabernaemontana dichotoma*	Bk, Sd	*89*
Integriquinolone (**5**)	Quinoline	*Limonia acidissima*	Rt bk	*23*
Isoboldine (**28**)	Aporphine	*Neolitsea fuscata*	Bk	*42*
Isocarapanaubine (**153**)	Oxindole	*Neisosperma oppositifolia*	Bk	*75*
Isoconessimine (**191**)	Steroidal	*Holarrhena mitis*	Bk, Sd	*111,113*
Isocorymine (**165**)	Indole	*Hunteria zeylanica*	Lf	*78*
Isoeburnamine (**114**)	Indole	*Hunteria zeylanica*	Bk	*78*
Isomethuenine (**166**)	Indole	*Tabernaemontana dichotoma*	Bk, Fr, Lf	*92,93*
Isomitraphylline (**148**)	Oxindole	*Mitragyna parvifolia*	Pl	*97*
		Uncaria elliptica	Bk	*73*
Isoreserpiline (**82**)	Indole	*Neisosperma oppositifolia*	Bk	*75,76*
Isovoacangine (**126**)	Indole	*Tabernaemontana divaricata*	Bk	*87*
Isovoacristine (**123**)	Indole	*Tabernaemontana divaricata*	Bk	*87*
3-Ketopropylcoronaridine (**121**)	Indole	*Tabernaemontana dichotoma*	Bk, Fr	*91*
3-Ketopropylepiheyeanine (**128**)	Indole	*Tabernaemontana dichotoma*	Bk	*93*
Koenimbine (**69**)	Carbazole	*Murraya koenigii*	Fr	*64*
Koenoline (**64**)[b,c]	Carbazole	*Murraya koenigii*	Rt bk	*60*

(*continues*)

TABLE VI (*Continued*)

Alkaloid Name	Class	Source	Plant Part[a]	Ref.
Kokusaginine (**8**)	Quinoline	*Glycosmis bilocularis*	Lf	*25*
Lanuginosine (**43**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
Laurolitsine (**29**)	Aporphine	*Litsea gardneri*	Bk	*41*
Laurotetanine (**30**)	Aporphine	*Actinodaphne speciosa*	Lf	*41*
Liriodenine (**44**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
		Cananga odorata	Bk	*24*
Lochnericine (**142**)	Indole	*Petchia ceylanica*	Lf	*74,106*
Lumicolchicine (**211**)	Misc.	*Gloriosa superba*	Tu	*120*
Macralstonine (**188**)	Bisindole	*Alstonia macrophylla*	Bk, Lf, Rt bk	*82,88*
Macroxine-A (**159**)[b]	Oxindole	*Alstonia macrophylla*	Lf	*98*
Mahanimbilol (**73**)	Carbazole	*Murraya koenigii*	Bk	*61*
Mahanimbine (**75**)	Carbazole	*Murraya koenigii*	Fr	*64*
5-Methoxyarborinine (**12**)[b]	Acridone	*Luvunga angustifolia*	St	*23*
11-Methoxy-*N*-methyldihydropericyclivine (**108**)[b]	Indole	*Tabernaemontana divaricata*	Bk	*87*
8-Methoxyouregidione (**51**)[b]	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
12-Methoxyvoaphylline (**136**)	Indole	*Tabernaemontana dichotoma*	Fr, Lf	*91,92*
O-Methyleburnamine (**115**)	Indole	*Hunteria zeylanica*	Bk	*78*
N_3-Methylholarrhimine (**198**)	Steroidal	*Holarrhena mitis*	Bk	*111*
O-Methylisoeburnamine (**116**)[b,c]	Indole	*Hunteria zeylanica*	Bk	*78*
N-Methyllaurotetanine (**31**)	Aporphine	*Actinodaphne speciosa*	Lf	*41*
Methyl 2-methyl-4-(*N*-2″β-methyl-1″,2″,3″,4″-tetrahydrocarbazol-1″α-yl-indol-3′-yl butanoate (**77**)[b]	Bisindole	*Murraya gleniei*	Rt tm	*67*
O-Methylmoschatoline (**48**)	Aporphine	*Xylopia championii*	Bk	*48*
Mitiphylline (**200**)	Steroidal	*Holarrhena mitis*	Lf	*112,114*
Mitraphylline (**149**)	Oxindole	*Mitragyna parvifolia*	Pl	*97*
		Uncaria elliptica	Bk	*73,96*

Monogagaine (**181**)[b]	Bisindole	*Tabernaemontana dichotoma*	Bk	*104*
Murrayanine (**65**)	Carbazole	*Murraya koenigii*	Bk, Rt bk	*60,61*
Neisosposinine (**154**)[b]	Oxindole	*Neisosperma oppositifolia*	Bk	*75*
Neozeylanicine (**216**)[b]	Monoterpene	*Neonauclea zeylanica*	Tm	*124,125*
Noracronycine (**17**)	Acridone	*Glycosmis mauritiana*	Bk	*32*
Ochropposinine (**85**)	Indole	*Neisosperma oppositifolia*	Bk	*75,76*
Onychine (**54**)	Azafluorenone	*Cananga odorata*	Bk	*24*
Ouregidione (**52**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
3,19*R*-Oxidocoronaridine (**131**)[b]	Indole	*Tabernaemontana dichotoma*	Bk	*93*
3-Oxocoronaridine (**120**)	Indole	*Tabernaemontana dichotoma*	Bk	*90*
Oxobuxifoline (**45**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
Oxocrebanine (**46**)	Aporphine	*Artabotrys zeylanicus*	Bk	*48*
Oxopukateine (**49**)	Oxoaporphine	*Cananga odorata*	Bk	*24*
(−)-8-Oxotetrahydropalmitine (**62**)	Protoberberine	*Anamirta cocculus*	St	*46*
Oxypalmatine (**63**)	Protoberberine	*Anamirta cocculus*	St	*46*
Peceylanine (**184**)[b]	Bisindole	*Petchia ceylanica*	Lf	*74,106*
Peceyline (**183**)[b]	Bisindole	*Petchia ceylanica*	Lf	*74,106*
Pelankine (**185**)[b]	Bisindole	*Petchia ceylanica*	Lf	*74,106*
Perivine (**139**)	Indole	*Tabernaemontana dichotoma*	Bk, Fr, Lf	*92*
Phaeanthine (**23**)	Bisbenzyl-isoquinoline	*Cyclea burmanii*	Rt	*35*
Pleiocarpamine (**167**)	Indole	*Hunteria zeylanica*	Bk	*78*
Quinine (**9**)	Quinoline	*Cinchona ledgeriana*	Bk	*28*
Reserpiline (**81**)	Indole	*Neisosperma oppositifolia*	Bk	*75,76*
Roxburghine D (**171**)	Indole	*Uncaria elliptica*	Bk	*96*
Roxburghine X (**172**)[b]	Indole	*Uncaria elliptica*	Bk	*96*
Speciophylline *N*-oxide (**156**)[e]	Oxindole	*Mitragyna parvifolia*	Pl	*80*
Srilankine (**26**)	Aporphine	*Alseodaphne semicarpifolia*	Un	*38*
(+)-Stemmadenine (**100**)	Indole	*Tabernaemontana dichotoma*	Sd	*81*
Stepharine (**41**)	Proaporphine	*Anamirta cocculus*	St	*44–46*
		Diploclisia glaucescens	St	*44*
Strictosidine (**75**)	Indole	*Rauvolfia serpentina*	Pl	*70,71*
		Strychnos nux-vomica	Pl	*70,71*

(*continues*)

TABLE VI (*Continued*)

Alkaloid Name	Class	Source	Plant Part[a]	Ref.
Tabernaemontanine (**140**)	Indole	*Tabernaemontana divaricata*	Bk	*87*
Tabernamine (**173**)	Bisindole	*Tabernaemontana dichotoma*	Rt bk, St	*90*
Tabersonine (**141**)	Indole	*Tabernaemontana dichotoma*	Sd	*89*
Talcarpine (**109**)	Indole	*Alstonia macrophylla*	Bk, Lf, Rt bk	*82,88*
Tetrahydroalstonine (**83**)	Indole	*Mitragyna parvifolia*	Lf	*80*
Tetrandrine (**24**)	Bisbenzyl-isoquinoline	*Cyclea burmanii*	Rt	*35*
Triacanthine (**215**)	Purine	*Holarrhena mitis*	Fr pc, Lf, Sd	*112–114*
Tubotaiwine (**168**)	Indole	*Tabernaemontana dichotoma*	Bk	*93,101*
Tuboxenine (**169**)	Indole	*Hunteria zeylanica*	Bk	*78*
Tylophorinidine (**203**)	Phenanthro-indolizidine	*Tylophora asthmatica*	Pl	*116*
Tylophorine (**201**)	Phenanthro-indolizidine	*Tylophora asthmatica*	Pl	*116*
Tylophorinine (**202**)	Phenanthro-indolizidine	*Tylophora asthmatica*	Pl	*116*
Uncarine C (**152**)	Oxindole	*Mitragyna parvifolia*	Pl	*80*
Uncarine D (**155**)	Oxindole	*Mitragyna parvifolia*	Pl	*80*
Uncarine E (**151**)	Oxindole	*Mitragyna parvifolia*	Fr	*80*
Uncarine F (**157**)	Oxindole	*Mitragyna parvifolia*	Pl	*80*
Uncarine F *N*-oxide (**158**)[e]	Oxindole	*Mitragyna parvifolia*	Pl	*80*
Vallesamine (**97**)	Indole	*Tabernaemontana dichotoma*	Fr	*81*
Vasicine (**212**)[d]	Quinazoline	*Adhatoda vasica*	Bk, In, Lf, Rt, Pe	*123*

Vincaleukoblastine (**186**)[d]	Bisindole	*Catharanthus pusillus*	Lf	*108*
		C. roseus	Lf	*108*
Vincamajine (**101**)	Indole	*Alstonia macrophylla*	Lf	*82*
Vincorine (**145**)	Indole	*Alstonia macrophylla*	Bk, Lf	*82*
Vincristine (**187**)[d]	Bisindole	*Catharanthus pusillus*	Lf	*108*
		C. roseus	Lf	*108*
Voacamine (**175**)	Bisindole	*Tabernaemontana dichotoma*	Rt bk, St	*90*
Voacangine (**125**)	Indole	*Tabernaemontana dichotoma*	Sd	*87,89*
Voacristine (**122**)	Indole	*Tabernaemontana divaricata*	Fl, Lf	*87*
Voacristine hydroxyindolenine (**132**)	Indole	*Tabernaemontana divaricata*	Rt bk	*93*
Voaphylline (**135**)	Indole	*Tabernaemontana dichotoma*	Fr, Sd	*89*
Voaphylline hydroxyindolenine (**137**)	Indole	*Tabernaemontana dichotoma*	Fr, Lf, Sd	*89,91,92*
Vobasine (**138**)	Indole	*Hunteria zeylanica*	Lf	*78*
		Tabernaemontana dichotoma	Fr, Lf	*91,92*
		T. divaricata	Bk	*87*
Yohimbine (**90**)	Indole	*Alstonia macrophylla*	Fr	*79*
β-Yohimbine (**91**)	Indole	*Alstonia macrophylla*	Fr	*79*
Yohimbol (**88**)	Indole	*Hunteria zeylanica*	Bk	*78*

[a] Bk, stem bark; Fr, fruits; Fr pc, fruit pericarp; In, inflorescence; Lf, leaf; Pe, petiole; Pl, whole plant; Rt, root; Rt bk, root bark; Rt tim, root timber; Sd, seed; St, stem; Tm, timber; Tu, tuber; Un, unspecified.

[b] New alkaloids.

[c] New natural products, but previously known as synthetic products.

[d] Detected by TLC, not isolated and characterized.

[e] Identified by MS and reduction into the parent alkaloid and by TLC comparison of the latter with authentic alkaloids.

have shown toxicity toward DNA-repair-deficient yeast strains compared with the wild-type DNA-repair-proficient strain (*48*). Bioactivity-guided fractionation of the bioactive MeOH extract of *Cyathocalyx zeylanica,* another plant that showed activity in the brine shrimp toxicity assay (*137*), afforded the azafluorenone alkaloid cyathocaline (**53**) (*50*). It also exhibited cytotoxicity toward the human carcinoma cell line A-549 with an IC_{50} of 8.50 μM. Of the two carbazole alkaloids occurring in the root bark of *Murraya koenigii,* koenoline (**64**), was shown to have cytotoxic activity in the KB cell-culture test system with an ED_{50} value of 4.0 μg/mL (*60*).

XV. Summary and Conclusions

Table VI summarizes the alkaloids encountered in the Sri Lankan flora, together with the classes to which they belong and the plant and its part from which each alkaloid was isolated. A total of 43 plant species, including 13 endemic species, yielded alkaloids (Table IV). From these 197 alkaloids were isolated, and 51 were found to be new (Table VI). The structures of most of the new alkaloids were elucidated by modern spectroscopic techniques, including 2D NMR methods. Except for 8-hydroxyquinoline-4-carbaldehyde (**1**), artabotrine (**50**), 8-methoxyouregidione (**51**), cyathocaline (**53**), koenoline (**64**), and monogagaine (**181**), the new bases have not been evaluated for their biological activity.

Although Sri Lanka has a rich flora and alkaloids are of medicinal significance, it is surprising that not much effort has been directed toward the isolation of this important group of metabolites from local plants. However, it is encouraging to note that since the last review on this subject in 1978 (*8*), 65 reports have described the isolation of 130 alkaloids, 40 of which are new. The importance of research in the field of plant alkaloids with potential medicinal applications need not be overemphasized. Because at least 830 flowering plants are unique to the island, and screening for alkaloids has indicated a high incidence of alkaloid-bearing plants among these, the prospects of finding novel and perhaps biologically active alkaloids from the Sri Lankan flora appear to be attractive.

Acknowledgments

The author thanks Professor Ajith Abeysekara, Dr. Lakshmi Arambewela, Professor Atta-ur-Rahman, Professor B. M. R. Bandara, Professor Lars Bohlin, Professor Geoffrey

Cordell, Dr. Ranjith Charmaratne, Dr. Lalith Jayasinghe, Dr. Veranja Karunaratne, Dr. Premila Perera, Professor G. P. Wannigama, Dr. Anura Wickremasinghe, and Dr. Kithsiri Wijeratne for providing information and/or reprints that were invaluable in the preparation of this review. Assistance rendered by Jan Taylor, Lisa Cole, and Malkanthi Gunatilaka during the preparation of the manuscript is gratefully acknowledged.

References

1. B. A. Abeywickrema, *Ceylon J. Sci.* **2,** 120 (1959).
2. B. A. Abeywickrema, M. D. Dassanayake, and R. N. de Fonseka, *Proc. Int. Symp. on Med. Plants,* Kandy, Ceylon, p. 41 (1964).
3. B. A. Abeywickrema, "Proc. Workshop on Natural Products," National Science Council, Sri Lanka, p. 11 (1975).
4. M. D. Dassanayake and F. R. Fosberg, "A Revised Handbook to the Flora of Ceylon," Vol. I–IV. Amerind Publishing Co. Pvt. Ltd., New Delhi, 1985.
5. Anon., "The Promotion and Development of Traditional Medicine," World Health Organization Technical Report, Geneva, **622,** 10 (1978).
6. R. Verpoorte, R. van der Heijden, W. M. V. Gulik, and H. J. ten Hoopen, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 40, p. 1. Academic Press, San Diego, 1991.
7. Anon., Report of a Workshop "National Products for Sri Lanka's Future," National Science Council of Sri Lanka, Colombo, Sri Lanka, 1976.
8. A. A. L. Gunatilaka, *J. Natl. Sci. Council. Sri Lanka* **6,** 39 (1978).
9. D. M. A. Jayaweera, "Medicinal Plants Used in Ceylon, Parts 1–5," National Science Council of Sri Lanka, Colombo, Sri Lanka, 1982.
10. V. Kumar, L. F. Perera, M. U. S. Sultanbawa, and G. P. Wannigama, *Proc. Ceylon Assoc. Advmt. Sci.* **29,** 138 (1973).
11. M. U. S. Sultanbawa, G. P. Wannigama, W. M. Bandaranayake, V. Kumar, A. A. L. Gunatilaka, F. A. Marikar, S. Balasubramaniam, and S. N. Arseculeratne, *Lloydia* **41,** 597 (1978).
12. A. A. L. Gunatilaka, M. U. S. Sultanbawa, and S. Balasubramaniam, *J. Natl. Sci. Council, Sri Lanka* **8,** 187 (1980).
13. A. A. L. Gunatilaka and S. Sotheeswaran, *J. Natl. Sci. Council, Sri Lanka* **8,** 11 (1980).
14. G. A. Cordell, "Introduction to Alkaloids: A Biogenetic Approach," p. 236. Wiley-Interscience, New York, 1981.
15. A. A. L. Gunatilaka, J. H. S. Q. Perera, M. U. S. Sultanbawa, R. H. Thomson, and M. Brown, "Third Asian Symposium on Medicinal Plants and Spices," Abstract 28, Colombo, Sri Lanka, 1977.
16. A. A. L. Gunatilaka, J. S. H. Q. Perera, M. U. S. Sultanbawa, M. Brown, and R. H. Thomson, *J. Chem. Res.* (S) 61; (M) 779 (1979).
17. A. A. L. Gunatilaka, *in* "Studies in Natural Products Chemistry; Structure Elucidation" (Atta-ur-Rahman, ed.), Vol. 2, Part A, p. 211. Elsevier, New York, 1988.
18. A. A. L. Gunatilaka, M. U. S. Sultanbawa, S. Surendrakumar, and R. Somanathan, *Phytochemistry* **22,** 2799 (1983).
19. E. V. Dehmlow, A. Sleegers, N. Risch, W. Trowitzsch-Kienast, V. Wray, and A. A. L. Gunatilaka, *Phytochemistry* **29,** 3993 (1990).
20. A. St. Pfau, *Helv. Chim. Acta* **22,** 382 (1939).

21. A. A. L. Gunatilaka, S. Surendrakumar, and R. H. Thomson, *Phytochemistry* **23,** 929 (1984).
22. E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron* **24,** 687 (1968).
23. E. M. K. Wijeratne, B. M. R. Bandara, A. A. L. Gunatilaka, Y. Tezuka, and T. Kikuchi, *J. Nat. Prod.* **55,** 1261 (1992).
24. L. B. de Silva, C. S. Liyanage, E. M. K. Wijeratne, W. H. M. W. Herath, V. Kumar, and M. I. Choudhary, *Proc. Sri Lanka Assoc. Advmt. Sci.* **48,** 125 (1992).
25. I. H. Bowen, K. P. W. C. Perera, and J. R. Lewis, *Phytochemistry* **17,** 2125 (1978).
26. A. C. L. Ameer-Ali, *Mod. Ceylon Studies* **5,** 93 (1974).
27. D. M. A. Jayaweera, *Trop. Agriculturist* **99,** 91 (1943).
28. R. O. B. Wijesekara, L. S. Rajapakse, and D. W. Chelvarajan, *J. Chromatogr.* **121,** 288 (1976).
29. L. A. Goonetillake, L. S. R. Arambewela, and R. De Costa, *J. Natl. Sci. Council, Sri Lanka* **12,** 141 (1984).
30. B. M. R. Bandara, A. A. L. Gunatilaka, E. M. K. Wijeratne, and J. K. MacLeod, *Phytochemistry* **29,** 297 (1990).
31. J. Attygalle, "Sinhalese Materia Medica," M. D. Gunasena & Co. Ltd., Colombo, Sri Lanka, 1917.
32. V. Kumar, J. Reisch, and A. Wickremasinghe, *Aust. J. Chem.* **42,** 1375 (1989).
33. A. W. Fraser and J. R. Lewis, *J. Chem. Soc., Chem. Commun.* 615 (1973).
34. A. W. Fraser and J. R. Lewis, *J. Chem. Soc., Perkin Trans. 1,* 1173 (1973).
35. B. M. R. Bandara, N. K. Illangasekara, U. L. B. Jayasinghe, V. Karunaratne, G. P. Wannigama, N. Bokel, W. Kraus, and S. Sotheeswaran, *Planta Med.* **56,** 245 (1990).
36. G. R. Chaudhry and M. L. Dhar, *J. Sci. Industr. Res. India* **17B,** 163 (1958).
37. B. M. R. Bandara, U. L. B. Jayasinghe, V. Karunaratne, G. P. Wannigama, and S. Sotheeswaran, *Chem. Sri Lanka* **4,** 14 (1987).
38. W. D. Smolnycki, J. L. Moniot, D. M. Hindenlang, G. A. Maina, and M. Shamma, *Tetrahedron Lett.* 4617 (1978).
39. S. Philipov, O. Petrov, and N. Mellov, *Tetrahedron* **39,** 1823 (1983).
40. H. Hara, F. Hashimito, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.* **32,** 4154 (1984).
41. B. M. R. Bandara, D. Cortes, U. L. B. Jayasinghe, V. Karunaratne, S. Sotheeswaran, and G. P. Wannigama, *Planta Med.* **55,** 393 (1989).
42. A. A. L. Gunatilaka, S. Sotheeswaran, B. Sriyani, and S. Balasubramaniam, *Planta Med.* **43,** 309 (1981).
43. U. L. B. Jayasinghe, *Chem. Sri Lanka* **9,** 23 (1992).
44. U. L. B. Jayasinghe, "Chemistry and Bioactivity of some Sri Lankan Menispermaceae and Lauraceae," Ph.D. thesis, University of Peradeniya, Sri Lanka, 1992.
45. B. M. R. Bandara, U. L. B. Jaysinghe, V. Karunaratne, G. P. Wannigama, S. Balasubramaniam, and Atta-ur-Rahman, *Chem. Sri Lanka* **6,** 14 (1989).
46. U. L. B. Jayasinghe, G. P. Wannigama, S. Balasubramaniam, Habib Nasir, and Atta-ur-Rahman, *J. Natl. Sci. Council, Sri Lanka* **20,** 187 (1992).
47. M. Shamma and R. L. Castenson, *in* "The Alkaloids" (R. H. F. Manske, ed.), Vol. 14, p. 225. Academic Press, New York, 1973.
48. E. M. K. Wijeratne, Y. Hatanaka, T. Kikuchi, Y. Tezuka, and A. A. L. Gunatilaka, *Phytochemistry* **42,** 1703 (1996).
49. E. M. K. Wijeratne, A. A. L. Gunatilaka, D. G. I. Kingston, R. C. Haltiwanger, and D. S. Eggleston, *Tetrahedron* **51,** 7877 (1995).
50. E. M. K. Wijeratne, L. B. de Silva, T. Kikuchi, Y. Tezuka, A. A. L. Gunatilaka, and D. G. I. Kingston, *J. Nat. Prod.* **58,** 459 (1995).
51. E. M. K. Wijeratne, personal communication (1996).

52. M. Leboeuf and A. Cavé, *Lloydia* **39,** 459 (1976).
53. A. M. Clark and C. D. Hufford, *in* "The Alkaloids" (G. A. Cordell, ed.), Vol. 42, p. 117. Academic Press, New York, 1992.
54. D. Tadic, B. K. Cassels, M. Leboeuf, and A. Cavé, *Phytochemistry* **26,** 537 (1987).
55. Y. Inubushi, H. Furukawa, and M. Ju-Ichi, *Chem. Pharm. Bull.* **18,** 1951 (1970).
56. D. H. R. Barton, A. A. L. Gunatilaka, and A. M. F. T. Lobo, Congresso National de Biochemica IV, Lisboa, Portugal, 25 (1972).
57. D. H. R. Barton, A. A. L. Gunatilaka, R. M. Letcher, A. M. F. T. Lobo, and D. A. Widdowson, *J. Chem. Soc Perkin Trans. 1* 874 (1973).
58. R. Verpoorte, J. J. Siwon, M. E. M. Tieken and A. B. Svendsen, *J. Nat. Prod.* **44,** 221 (1981).
59. D. P. Chakraborty and S. Roy, *in* "Progress in the Chemistry of Organic Natural Products" (W. Herz, G. W. Kirby, W. Steglich and Ch. Tamm, eds.), Vol. 57, p. 71. Springer Verlag, Wien, 1991.
60. M. Fiebig, J. M. Pezzuto, D. D. Soejarto, and A. D. Kinghorn, *Phytochemistry* **24,** 3041 (1985).
61. J. Reisch, A. C. Adebajo, V. Kumar, and A. J. Aladesanmi, *Phytochemistry* **36,** 1073 (1994).
62. C. Ito, Y. Thoyama, M. Omura, I. Kajiura, and H. Furukawa, *Chem. Pharm. Bull.* **41,** 2096 (1993).
63. J. Reisch, O. Goj, A. Wickremasinghe, H. M. T. B. Herath, and G. Henkel, *Phytochemistry* **31,** 2877 (1992).
64. J. Reisch, A. C. Adebajo, A. J. Aladesanmi, K. S. Adesina, D. Bergenthal, and U. Meve, *Planta Med.* **60,** 295 (1994).
65. J. Reisch and H. R. W. Dharmaratne, *Z. Naturforsch. Tiel B* **40,** 636 (1985).
66. A. V. Rama Rao, K. S. Bhide, and R. B. Mujumdar, *Chem. Ind.* 697 (1980).
67. V. Kumar, D. B. M. Wickremaratne, and U. Jacobson, *Tetrahedron Lett.* **31,** 5217 (1990).
68. P. Perera, T. A. van Beek, and R. Verpoorte, *J. Chromatogr.* **285,** 214 (1985).
69. P. Perera, F. Sandberg, and R. Verpoorte, *Acta Pharm. Suec.* **21,** 195 (1984).
70. K. T. D. De Silva and S. Kaluarachchi, *Proc. Ceylon Assoc. Advmt. Sci.* **28,** 128 (1972).
71. K. T. D. De Silva, *Proc. Workshop on Natural Products,* National Science Council, Colombo, Sri Lanka, p. 138 (1975).
72. T. K. K. Diyabalanage, B. M. M. Kumarihamy, A. Wickremasinghe, G. P. Wannigama, and U. L. B. Jayasinghe, *Chem. Sri Lanka* **13,** 5 (1996).
73. T. K. K. Diyabalanage, B. M. M. Kumarihamy, G. P. Wannigama, L. Jayasinghe, L. Merlini, and L. Scaglioni, *Phytochemistry* **45,** 1731 (1997).
74. A. Cavé, N. Kunesch, J. Bruneton, R. Goutarel, and G. P. Wannigama, *J. Nat. Prod.* **50,** 1178 (1987).
75. A. A. L. Gunatilaka, H. C. Fernando, Atta-ur-Rahman, M. M. Qureshi, and S. Balasubramaniam, *Heterocycles* **28,** 999 (1988).
76. A. S. Amarasekara and L. S. R. Arambewela, *Fitoterapia* **57,** 55 (1986).
77. H. Amunugama, S. Balasubramaniam, A. A. L. Gunatilaka, A. S. A. Salaam, and S. Sotheeswaran, unpublished results.
78. L. S. R. Arambewela and F. Khuong-Huu, *Phytochemistry* **20,** 349 (1981).
79. L. S. R. Arambewela, C. K. Ratnayake, and A. S. Amarasekera, *Fitoterapia* **61,** 377 (1990).
80. E. J. Shellard and P. J. Houghton, *Planta Med.* **23,** 172 (1974).
81. P. Perera, T. A. van Beek, and R. Verpoorte, *J. Nat. Prod.* **47,** 835 (1984).
82. C. K. Ratnayake, L. S. R. Arambewela, K. T. D. De Silva, Atta-ur-Rahman, and K. A. Alvi, *Phytochemistry* **26,** 868 (1987).
83. Atta-ur-Rahman, F. Nighat, G. Ahmed, M. I. Choudhary, Habib-ur-Rehman and K. T. D. De Silva, *Fitoterapia,* **90,** 230 (1990).

84. Atta-ur-Rahman, F. Nighat, A. Sultana, and K. T. D. De Silva, *Nat. Prod. Lett.* **5,** 201 (1994).
85. Atta-ur-Rahman, F. Nighat, M. I. Choudhary, and K. T. D. De Silva, *Heterocycles* **27,** 961 (1988).
86. Atta-ur-Rahman, S. A. Abbas, F. Nighat, G. Ahmed, M. I. Choudhary, K. A. Alvi, Habib-ur-Rehman, K. T. D. De Silva, and L. S. R. Arambewela, *J. Nat. Prod.* **54,** 750 (1991).
87. L. S. R. Arambewela, and T. Ranatunge, *Phytochemistry* **30,** 1740 (1991).
88. K. Vallipurum and V. Kumar, *Chem. Sri Lanka* **13,** 5 (1996).
89. P. Perera, F. Sandberg, T. A. van Beek, and R. Verpoorte, *Planta Med.* **49,** 28 (1983).
90. P. Perera, Ph.D. Thesis, University of Uppsala, Sweden, 1984 (Acta Uni. Uppsal. No. 98).
91. P. Perera, F. Sandberg, T. A. van Beek, and R. Verpoorte, *Planta Med.* **50,** 251 (1984).
92. P. Perera, G. Samuelsson, T. A. van Beek, and R. Verpoorte, *Planta Med.* **47,** 148 (1983).
93. P. Perera, F. Sandberg, T. A. van Beek, and R. Verpoorte, *Phytochemistry* **24,** 2097 (1985).
94. Atta-ur-Rahman, W. S. J. Silva, K. A. Alvi, and K. T. D. De Silva, *Phytochemistry* **26,** 543 (1987).
95. Atta-ur-Rahman and M. I. Choudhary, *in* "Phytochemistry of Plants Used in Traditional Medicine" (K. Hostettmann *et al.,* eds.), p. 279. Oxford Science Publishers, Oxford. 1995.
96. W. H. M. W. Herath, M. U. S. Sultanbawa, G. P. Wannigama, and A. Cavé, *Phytochemistry* **18,** 1385 (1979).
97. E. J. Shellard and P. J. Houghton, *Planta Med.* **23,** 80 (1974).
98. Atta-ur-Rahman, F. Nighat, A. Nelofer, K. Zaman, M. I. Choudhary, and K. T. D. De Silva, *Tetrahedron* **47,** 3129 (1991).
99. Atta-ur-Rahman, W. S. J. Silva, K. A. Alvi, and K. T. D. De Silva, *Phytochemistry* **26,** 865 (1987).
100. P. Perera, T. A. van Beek, and R. Verpoorte, *Planta Med.* **49,** 232 (1983).
101. J. Schripsema, T. A. van Beek, R. Verpoorte, C. Erkelens, P. Perera, and C. Tibell, *J. Nat. Prod.* **50,** 89 (1987).
102. A. A. L. Gunatilaka, S. Sotheeswaran, S. Balasubramaniam, I. Chandrasekara, and H. T. B. Sriyani, *Planta Med.* **39,** 66 (1980).
103. M. E. Kuehne and I. Marko, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 37, p. 77. Academic Press, New York, 1990.
104. T. A. van Beek, P. P. Lankhorst, T. Verpoorte, G. Massiot, R. Fokkens, C. Erkelens, P. Perera, and C. Tibell, *Z. Naturforsch.* **40b,** 693 (1985).
105. Atta-ur-Rahman, A. Pervin, I. Ali, A. Muzaffar, K. T. D. De Silva, and W. S. J. Silva, *Planta Med.* **54,** 37 (1988).
106. N. Kunesch, A. Cavé, E. Hagaman, and E. Wenkert, *Tetrahedron Lett.* **21,** 1727 (1980).
107. H. Huber, "A Revised Handbook of the Flora of Ceylon," Vol. 1, p. 1. Apothecaries Ltd., Colombo, 1973.
108. A. A. L. Gunatilaka, H. M. U. Siriwardane, S. Sotheeswaran, and S. Balasubramaniam, *J. Natl. Sci. Council, Sri Lanka* **4,** 163 (1976).
109. L. S. R. Arambewela, J. Ranatunge, S. Wijeratne, P. Fernando, and K. Wickramasinghe, *J. Natl. Sci. Council, Sri Lanka* **21,** 63 (1993).
110. V. P. Bhavanandan and G. P. Wannigama, *J. Chem. Soc.* 2368 (1960).
111. A. Cavé and G. P. Wannigama, *Ann. Pharm. Fr.* **30,** 535 (1972).
112. M. M. Janot, M. Leboeuf, A. Cavé, R. O. B. Wijesekara, and T. Goutarel, *Comptes Rendues* **267C,** 1050 (1968).
113. M. Leboeuf, A. Cavé, R. Goutarel, and G. P. Wannigama, *Ann. Pharm. Fr.* **30,** 837 (1972).
114. M. Leboeuf, A. Cavé, R. Goutarel, and G. P. Wannigama, *Phytochemistry* **11,** 843 (1972).
115. R. Goutarel, *Bull. Soc. Chim. Fr.* 1665 (1964).

116. J. D. Phillipson, I. Tezcan, and P. T. Hylands, *Planta Med.* **25,** 301 (1974).
117. T. R. Govindachari, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, and K. S. Ramachandran, *Ind. J. Chem.* **13,** 641 (1975).
118. H. W. B. Clewer, S. J. Green, and F. Tutin, *J. Chem. Soc.* 835 (1915).
119. B. W. M. Gooneratne, *Brit. Med. J.* **1,** 1023 (1966).
120. R. Dunuwille, K. Balasubramaniam, and S. W. Bibile, *Ceylon J. Med. Sci.* **22,** 7 (1968).
121. M. Maturova, B. Lang, T. Reichstein, and F. Santavy, *Planta Med.* **7,** 298 (1959).
122. L. S. R. Arambewela, M. A. N. Kumudini, and J. Ranatunga, *J. Natl. Sci. Council, Sri Lanka* **19,** 177 (1991).
123. L. S. R. Arambewela, C. K. Ratnayake, J. S. Jayasekara, and K. T. D. De Silva, *Fitoterapia* **59,** 151 (1988).
124. L. B. de Silva, W. H. M. W. Herath, K. M. Navaratne, Atta-ur-Rahman, I. I. Vohra, and M. I. Choudhary, *Proc. Sri Lanka Assoc. Advmt. Sci.* **43,** 201 (1987).
125. Atta-ur-Rahman, I. I. Vohra, M. I. Choudhary, L. B. de Silva, W. H. M. W. Herath, and K. M. I. Navaratne, *Planta Med.* **54,** 461 (1988).
126. P. Perera, D. Kanjanapoothi, F. Sandberg, and R. Verpoorte, *J. Ethnopharmacol.* **11,** 233 (1984).
127. P. Perera, D. Kanjanapothy, F. Sandberg, and R. Verpoorte, *J. Ethnopharmacol.* **13,** 165 (1985).
128. T. A. van Beek, R. Verpoorte, A. Baerheim Svendsen, A. J. M. Leeuwenberg, and N. G. Bissett, *J. Ethnopharmacol.* **10,** 101 (1984).
129. S. N. Aresculeratne, A. A. L. Gunatilaka, and R. G. Panabokke, *J. Ethnopharmacol.* **4,** 159 (1981).
130. S. N. Arseculeratne, A. A. L. Gunatilaka, and R. G. Panabokke, *J. Ethnopharmacol.* **13,** 323 (1985).
131. P. Courmont, A. Morel, L. Perrot, and F. Denard, *Comp. Rend. Soc. Biol.* **122,** 113, 1110 (1936).
132. S. Kikui, Y. Yajima, M. Tonomura, and K. Tago, *Kitasato Arch. Exp. Med.* **29,** 65 (1956); *Chem. Abstr.* **53,** 19128d (1957).
133. J. Büchi, A. Aebi, A. Deflorin, and H. Hurni, *Helv. Chim. Acta* **39,** 1656 (1956).
134. E. Roberts, "Native Medicines Used in Snakebites," pp. 27, 55. C. H. W. Cave and Co., Colombo, Sri Lanka, 1919.
135. A. A. L. Gunatilaka, D. G. I. Kingston, and R. K. Johnson, *Pure Appl. Chem.* **66,** 2219 (1994).
136. A. A. L. Gunatilaka and D. G. I. Kingston, *in* "Studies in Natural Products Chemistry: Structure Elucidation" (Atta-ur-Rahman, ed.), Vol. 20. Elsevier, in press.
137. A. A. L. Gunatilaka, H. C. Fernando, S. Warshamana, J. L. McLaughlin, S. Balasubramaniam, and A. H. M. Jayasuriya, *Proc. Sri Lanka Assoc. Advmt. Sci.* **42,** 164 (1986).

This Page Intentionally Left Blank

—CHAPTER 2—

THE SARPAGINE GROUP OF INDOLE ALKALOIDS

MAURI LOUNASMAA, PIRJO HANHINEN,
AND MINNA WESTERSUND (NÉE HALONEN)

Laboratory for Organic and Bioorganic Chemistry
Technical University of Helsinki
Espoo Fin-02150
Finland

I. Introduction

The sarpagine alkaloids have been reviewed only twice previously in "The Alkaloids" series (*1,2*). As both of these articles appeared in the

THE ALKALOIDS, VOL. 52
0099-9598/99 $30.00

Copyright © 1999 by Academic Press.
All rights of reproduction in any form reserved.

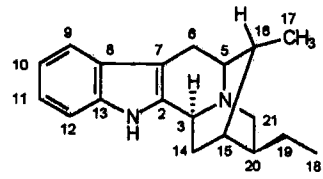


FIG. 1. Sarpagan ring system numbered according to Le Men and Taylor (*10*).

sixties, they are relatively obsolete and the need for a new review in the series is clear. A somewhat more recent review article appeared in 1983 in the series "Progress in the Chemistry of Organic Natural Products" (*3*), and that is now also out-of-date. Yearly summaries have been compiled by Saxton (*4*), and short reviews have occasionally appeared in connection with other topics (*5–9*). This chapter covers the literature up to the end of 1997. The number of known monomeric structures has grown markedly in recent years to a present count of 80. Of these, perhaps 10 may be artifacts and a few structures have not been convincingly determined (discussed later). In addition, nine bisindole alkaloids containing at least one monomeric sarpagan unit have been isolated, increasing the total number to 89.

All sarpagine alkaloids contain the polycyclic sarpagan ring system as a structural element. The "biogenetic numbering" of Le Men and Taylor (*10*) is used throughout this article (Fig. 1). The 3-oxygenated sarpagine derivatives, which exist in part in the 2-acylindole form and thus behave in a different manner, are not included in this review (Scheme 1). Readers

SCHEME 1. Equilibrium between 3-hydroxysarpagine derivatives and their 2-acylindole forms.

with a special interest in these compounds are referred to articles given in Kingston and Ekundays (*11*).

II. Occurrence

The sarpagine alkaloids occur mainly in the plant family Apocynaceae, the most important genus being *Rauvolfia,** and they are also found in the family Loganiaceae. To date, sarpagine alkaloids have been found in the following genera: *Alstonia, Amsonia, Aspidosperma, Cabucala, Catharanthus, Diplorhynchus, Ervatamia, Gabunia, Geissospermum, Gonioma, Hazunta, Hunteria, Lochnera* (*Vinca*), *Melodinus, Neisosperma, Ochrosia, Pandaca, Peschiera, Picralima, Pleiocarpa, Rauvolfia, Rhazya, Stemmadenia, Stenosolen, Tabernaemontana, Vallesia, Vinca,* and *Voacanga* (Apocynaceae), and *Gardneria, Gelsemium,* and *Strychnos* (Loganiaceae).

A detailed account of the distribution of sarpagine alkaloids among different plant species is presented in order of increasing molecular weight in Table I. The alkaloid structures, with their melting points and $[\alpha]_D$ values, where given, are presented in Table II. The CAS Registry numbers of individual compounds are indicated in both tables.

The superscripts beside several of the compounds indicate plausible artifacts or structures that, in our opinion, are questionable or in need of supplementary confirmation (discussed later). Moreover, some doubtful compounds that have persisted in earlier lists of sarpagine alkaloids have been rejected.

Six puzzling compounds, macusine C, rauvolfinine, dihydrotalpinine, alkaloid Q_3, 11-methoxy-N_a-methyldihydropericyclivine, and neosarpagine, that persistently appeared in earlier reviews as sarpagine derivatives are excluded from Tables I and II. Their history and the reasons for their rejection are noted next.

Macusine C

In the early 1960s Battersby and Yeowell (*196*) isolated two quaternary alkaloids from *Strychnos toxifera.* These they called macusine A and macusine C, which they claimed to be epimeric compounds and for which they presented structures **66** and **67,** respectively (Fig. 2). A little later Orazi *et*

* Of the two orthographies utilized in the literature, *Rauvolfia* versus *Rauwolfia,* the former is preferred in the present article because the letter *w* does not exist in the Latin alphabet.

TABLE I

SARPAGINE ALKALOIDS OF PLANT ORIGIN

MW	Formula	CAS Registry Number		Compound	Plant Source(s)	Ref.
292.4	$C_{19}H_{20}N_2O$	6874-98-2	(+)-**1**	(+)-Vellosimine	*Alstonia yunnanensis*	*12*
					Cabucala erythrocarpa var. *erythrocarpa*	*13*
					Geissospermum vellosii	*14*
					Rauvolfia caffra	*15*
					Rauvolfia cubana	*16*
					Rauvolfia macrophylla	*17*
					Rauvolfia nitida	*18*
					Rauvolfia reflexa	*19*
					Rauvolfia salicifolia	*20*
					Rauvolfia verticillata	*21*
					Rauvolfia vomitoria	*22*
					Rauvolfia yunnanensis	*23*
					Strychnos divaricans	*24*
					Vinca difformis	*25*
294.4	$C_{19}H_{22}N_2O$	604-99-9	**2**	Normacusine B	*Alstonia angustifolia*	*26*
				(Deoxysarpagine)	*Alstonia yunnanensis*	*12b*
				(Tombozine)	*Aspidosperma polyneuron*	*27*
				(Vellosiminol)	*Aspidosperma pruinosum*	*28*
					Catharanthus longifolius	*29*
					Diplorhynchus condylocarpon	*30*
					Ervatamia corymbosa	*31*
					Ervatamia hirta	*32*
					Geissospermum vellosii	*14*
					Melodinus tenuicaudatus	*33*
					Neisosperma glomerata	*34*
					Peschiera buchtieni	*35*
					Peschiera laeta	*36*
					Peschiera van heurckii	*37*
					Pleiocarpa talbotii	*38*
					Rauvolfia caffra	*39*

					Rauvolfia cumminsii	*40*
					Rauvolfia macrophylla	*41*
					Rauvolfia mombasiana	*42*
					Rauvolfia nitida	*18*
					Rauvolfia oreogiton	*43*
					Rauvolfia perakensis	*44*
					Rauvolfia suaveolens	*45*
					Rauvolfia verticillata	*46*
					Rauvolfia volkensii	*47*
					Rauvolfia vomitoria	*48*
					Strychnos dolichothyrsa	*49*
					Strychnos lucens	*50*
					Strychnos madagascariensis	*50*
					Strychnos malacoclados	*51*
					Strychnos medeola	*52*
					Strychnos mosteuoides	*53*
					Strychnos nux-vomica	*54*
					Strychnos potatorum	*55*
					Strychnos rubiginosa	*56*
					Strychnos trinervis	*57*
					Tabernaemontana brachyantha	*58*
					Tabernaemontana chippii	*59*
					Tabernaemontana pachysiphon (= *Conopharyngia pachysiphon*)	*60*
					Vinca difformis	*61*
					Vinca erecta	*62*
294.4	$C_{19}H_{22}N_2O$	1358-75-4	**3**	Koumidine (*Z*-Koumidine)	*Gelsemium elegans*	*63*
					Gelsemium sempervirens	*64*
294.4	$C_{19}H_{22}N_2O$	22226-71-7	**4**	Deoxyperaksine	*Rauvolfia vomitoria*	*65*
294.4	$C_{19}H_{22}N_2O$	126640-98-0	**5**	16-Epinormacusine B (*E*-Koumidine)	*Ervatamia hirta*	*32*
306.4	$C_{20}H_{22}N_2O$	81525-53-3	**6**	N_a-Methylvellosimine	*Rauvolfia nitida*	*18*
306.4	$C_{20}H_{22}N_2O$	138989-36-3	**7**	Dehydro-16-epiaffinisine	*Ervatamia hirta*	*32*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant Source(s)	Ref.
308.4	$C_{20}H_{24}N_2O$	2912-11-0	**8**	Affinisine	*Alstonia angustifolia*	*26*
					Alstonia macrophylla	*66*
					Ervatamia hirta	*32*
					Peschiera affinis (= *Tabernaemontana affinis*)	*67*
					Peschiera buchtieni	*35*
					Peschiera van heurckii	*37*
					Stenosolen heterophyllus	*68*
					Tabernaemontana fuchsiaefolia	*69*
					Tabernaemontana heterophylla	*70*
308.4	$C_{20}H_{24}N_2O$	68160-78-1	**9**[a]	*O*-Methylnormacusine B	*Rauvolfia cumminsii*	*71*
308.4	$C_{20}H_{24}N_2O$	139067-48-4	**10**	16-Epiaffinisine	*Ervatamia hirta*	*32*
309.4	$C_{20}H_{25}N_2O$	6792-07-0	**11**	Macusine B	*Aspidosperma polyneuron* (= *Aspidosperma peroba*)	*72*
					Pleiocarpa tubicina (= *Pleiocarpa pycnantha* var. *tubicina*)	*73*
					Strychnos amazonica	*74*
					Strychnos decussata	*75*
					Strychnos ignatii	*76*
					Strychnos toxifera	*77*
					Strychnos usambarensis	*78*
310.4	$C_{19}H_{22}N_2O_2$	482-68-8	(+)-**12**	(+)-Sarpagine (Raupine)	*Alstonia yunnanensis*	*12*
					Rauvolfia beddomei	*79*
					Rauvolfia caffra	*80*
					Rauvolfia canescens (= *Rauvolfia hirsuta*)	*81*
					Rauvolfia cubana	*82*
					Rauvolfia cumminsii	*83*
					Rauvolfia decurva	*84*
					Rauvolfia densiflora	*85*
					Rauvolfia heterophylla	*86*

					Rauvolfia indecora	*86*
					Rauvolfia ligustrina	*87*
					Rauvolfia macrophylla	*17*
					Rauvolfia mombasiana	*88*
					Rauvolfia nitida	*18*
					Rauvolfia perakensis	*89*
					Rauvolfia sellowii	*90*
					Rauvolfia serpentina	*91*
					Rauvolfia viridis	*92*
					Rauvolfia volkensii	*93*
					Rauvolfia vomitoria	*94*
					Vinca difformis	*95*
					Vinca major	*96*
310.4	$C_{19}H_{22}N_2O_2$	15527-80-7	**13**	Peraksine (Vomifoline)	*Rauvolfia caffra*	*97*
					Rauvolfia cumminsii	*40*
					Rauvolfia mombasiana	*42*
					Rauvolfia nitida	*18*
					Rauvolfia oreogiton	*43*
					Rauvolfia perakensis	*44*
					Rauvolfia sumatrana	*98*
					Rauvolfia verticillata	*21*
					Rauvolfia volkensii	*47*
					Rauvolfia vomitoria	*99*
310.4	$C_{19}H_{22}N_2O_2$	32075-02-8	**14**[b]	Ervincidine	*Vinca erecta*	*100*
310.4	$C_{19}H_{22}N_2O_2$	102490-01-7	(+)-**15**[b]	(+)-16-Episarpagine	*Alstonia yunnanensis*	*101*
310.4	$C_{19}H_{22}N_2O_2$	132242-49-0	(−)-**16**	(−)-Trinervine	*Strychnos trinervis*	*57*
312.4	$C_{19}H_{24}N_2O_2$	26263-40-1	**17**	Dihydroperaksine (Dihydrovomifoline)	*Rauvolfia caffra*	*39*
322.4	$C_{20}H_{22}N_2O_2$	975-77-9	(+)-**18**	(+)-Pericyclivine	*Alstonia undulata*	*102*
					Catharanthus lanceus	*103*
					Catharanthus longifolius	*29*
					Catharanthus ovalis	*104*
					Catharanthus roseus	*105*
					Ervatamia polyneura	*106*

(continues)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant Source(s)	Ref.
					Gabunia odoratissima	*107*
					Hazunta modesta var. *modesta* subvar. *montana*	*108*
					Rauvolfia cumminsii	*83*
					Tabernaemontana cerifera (= *Pagiantha cerifera*)	*109*
					Tabernaemontana chippii	*59*
					Tabernaemontana holstii	*110*
					Tabernaemontana divaricata (= *Ervatamia coronaria*)	*111*
					Tabernaemontana johnstonii	*112*
					Vinca rosea (= *Catharanthus roseus*) var. *albus*	*113*
					Vinca rosea var. *ocellatus*	*113*
322.4	$C_{20}H_{22}N_2O_2$	2149-40-8	**19**	10-Methoxyvellosimine	*Vinca major*	*114*
322.4	$C_{20}H_{22}N_2O_2$	23172-98-7	**20**	Gardnutine	*Gardneria nutans*	*115*
322.4	$C_{20}H_{22}N_2O_2$	119736-90-2	**21**	Panarine	*Strychnos toxifera*	*116*
322.4	$C_{20}H_{22}N_2O_2$	135355-84-9	**22**	16-Epipanarine	*Stemmadenia minima*	*117*
323.5	$C_{21}H_{27}N_2O$	55249-53-1	**23**	*O*-Methylmacusine B	*Strychnos decussata*	*75*
					Strychnos ignatii	*76*
					Strychnos nux-vomica	*118*
					Strychnos usambarensis	*78*
323.5	$C_{21}H_{27}N_2O$	83945-53-3	**24**	*O*-Methyl-16-epimacusine B	*Strychnos nux-vomica*	*118*
324.4	$C_{20}H_{24}N_2O_2$	522-47-4	(+)-**25**	(+)-Lochnerine	*Alstonia angustifolia*	*26*
					Catharanthus roseus (= *Lochnera rosea*)	*119*
					Catharanthus trichophyllus	*120*
					Lochnera (*Vinca*) *rosea* var. *alba*	*121*
					Rauvolfia biauriculata	*122*
					Rauvolfia cubana	*82*
					Rauvolfia macrophylla	*17*

				Rauvolfia nitida	*18*
				Rauvolfia sellowii	*90*
				Rauvolfia sprucei	*123*
				Rauvolfia suaveolens	*45*
324.4	$C_{20}H_{24}N_2O_2$	23172-92-1	**26** Gardnerine	*Gardneria nutans*	*115*
324.4	$C_{20}H_{24}N_2O_2$	17801-05-7	**27**[a] N_a-Methylsarpagine	*Alstonia spectabilis*	*124*
				Rauvolfia vomitoria	*65*
324.4	$C_{20}H_{24}N_2O_2$	38990-06-6	**28** Talpinine	*Pleiocarpa talbotii*	*125*
324.4	$C_{20}H_{24}N_2O_2$	54631-87-7	**29** Lochvinerine	*Rauvolfia biauriculata*	*122*
				Vinca major	*126*
324.4	$C_{20}H_{24}N_2O_2$	70319-20-9	**30**[a] *O*-Methylnormacusine B N_b-oxide	*Rauvolfia cumminsii*	*40*
324.4	$C_{20}H_{24}N_2O_2$	138989-35-2	**31** Affinisine N_b-oxide	*Ervatamia hirta*	*32*
				Peschiera buchtieni	*35*
324.4	$C_{20}H_{24}N_2O_2$	135824-73-6	(−)-**32** (−)-Alstoumerine	*Alstonia macrophylla*	*127*
324.4	$C_{20}H_{24}N_2O_2$	167696-86-8	**33** 18-Hydroxyaffinisine	*Peschiera buchtieni*	*35*
325.4	$C_{20}H_{25}N_2O_2$	47326-53-4	**34** Spegatrine	*Aspidosperma spegazzinii*	*128*
				Rauvolfia sprucei	*123*
				Rauvolfia verticillata var. *hainanensis*	*129*
				Rauvolfia verticillata var. *rubrocarpa*	*130*
325.4	$C_{20}H_{25}N_2O_2$	122908-09-2	**35** Venecurine	*Strychnos toxifera* (?)	*131*
325.5	$C_{21}H_{29}N_2O$	55249-54-2	**36**[a] 19,20-Dihydro-*O*-methylmacusine B	*Strychnos usambarensis*	*78*
332.4	$C_{22}H_{24}N_2O$	102719-87-9	**37**[c] Difforine	*Vinca difformis*	*61*
336.4	$C_{21}H_{24}N_2O_2$	63959-49-9	**38** Majvinine	*Vinca major* var. *major*	*132*
336.4	$C_{21}H_{24}N_2O_2$	3986-01-4	**39** *O*-Acetylnormacusine B	*Rauvolfia volkensii*	*47*
336.4	$C_{21}H_{24}N_2O_2$	2912-15-4	**40** N_a-Methyl-16-epipericyclivine [16-De(hydroxymethyl)voachalotine]	*Alstonia undulata*	*133*
336.4	$C_{21}H_{24}N_2O_2$	160497-66-5	**41** N_a-Methylpericyclivine	*Peschiera buchtieni*	*35*
				Peschiera van heurckii	*37*
338.4	$C_{20}H_{22}N_2O_3$	23173-00-4	**42** Hydroxygardnutine	*Gardneria nutans*	*115*
338.4	$C_{20}H_{22}N_2O_3$	132242-29-6	**43** 10-Hydroxypericyclivine	*Alstonia undulata*	*133*
339.5	$C_{21}H_{27}N_2O_2$	6901-26-4	**44** Lochneram	*Rauvolfia sprucei*	*123*
				Strychnos toxifera	*134*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant Source(s)	Ref.
339.5	$C_{21}H_{27}N_2O_2$	4849-01-8	**45**[d]	N_a-Methylsarpagine metho salt	*Pleiocarpa mutica*	*135*
					Pleiocarpa tubicina	*73*
					Rauvolfia vomitoria	*65*
339.5	$C_{21}H_{27}N_2O_2$	16103-76-7	**46**	Macrosalhine	*Alstonia macrophylla*	*136*
340.4	$C_{20}H_{24}N_2O_3$	23173-02-6	**47**[a]	18-Hydroxygardnerine	*Gardneria nutans*	*137*
340.4	$C_{20}H_{24}N_2O_3$	96688-58-3	**48**	21-Hydroxycyclolochnerine	*Rauvolfia biauriculata*	*122*
340.4	$C_{20}H_{24}N_2O_3$	107603-56-5	**49**	18-Hydroxylochnerine	*Rauvolfia biauriculata*	*122*
					Rauvolfia sprucei	*123*
341.4	$C_{20}H_{25}N_2O_3$	98243-58-4	**50**	Verticillatine	*Rauvolfia verticillata* var. *hainanensis*	*129*
					Rauvolfia verticillata var. *rubrocarpa*	*130*
350.4	$C_{21}H_{22}N_2O_3$	2520-44-7	**51**	Polyneuridine aldehyde	*Aspidosperma dasycarpon*	*138*
350.5	$C_{22}H_{26}N_2O_2$	139067-49-5	**52**[c]	*O*-Acetyl-16-epiaffinisine	*Ervatamia hirta*	*32*
352.4	$C_{21}H_{24}N_2O_3$	639-36-1	(+)-**53**[e]	(+)-*E*-Akuammidine (Rhazine)	*Alstonia boonei*	*139*
					Alstonia congensis	*140*
					Alstonia scholaris	*141*
					Amsonia angustifolia	*142*
					Amsonia brevifolia	*143*
					Amsonia tabernaemontana	*144*
					Aspidosperma quebracho-blanco	*145*
					Ervatamia daemeliana	*146*
					Catharanthus longifolius	*29*
					Gelsemium elegans	*63*
					Gonioma kamassi	*147*
					Hazunta modesta modesta var. *brevituba*	*148*
					Hunteria corymbosa	*149*
					Melodinus australis	*150*
					Melodinus celastroides	*151*
					Melodinus hemsleyanus	*152*
					Melodinus scandens	*153*
					Neisosperma glomerata	*34*

					Ochrosia nakaiana	*154*
					Pandaca ochrascens	*155*
					Peschiera laeta	*156*
					Picralima klaineana	*157*
					Picralima nitida	*158*
					Rauvolfia caffra	*39*
					Rhazya orientalis	*159*
					Rhazya stricta	*160,161*
					Strychnos angolensis	*162*
					Strychnos potatorum	*55*
					Tabernaemontana amblyocarpa	*163*
					Tabernaemontana citrifolia	*164*
					Tabernaemontana markgrafiana (= *Bonafousia longituba*)	*165*
					Tabernaemontana olivacea	*166*
					Vallesia dichotoma	*167*
					Vinca difformis	*168*
					Vinca erecta	*169*
					Voacanga chalotiana	*170*
					Voacanga grandifolia	*171*
352.4	$C_{21}H_{24}N_2O_3$	6872-44-2	(−)-**54**	(−)-Polyneuridine	*Alstonia venenata*	*172*
					Aspidosperma polyneuron	*27*
					Hazunta modesta var. *brevituba*	*148*
					Rauvolfia suaveolens	*45*
					Rauvolfia volkensii	*47*
					Strychnos potatorum	*55*
					Voacanga chalotiana	*170*
352.4	$C_{21}H_{24}N_2O_3$	73221-32-6	**55**[c]	*O*-Acetylpreperakine	*Rauvolfia volkensii*	*47*
352.4	$C_{21}H_{24}N_2O_3$	102358-21-4	**56**[c]	*O*-Acetylsarpagine	*Alstonia yunnanensis*	*101*
352.4	$C_{21}H_{24}N_2O_3$	113973-31-2	**57**	*Z*-Akuammidine	*Gelsemium elegans*	*173*
352.4	$C_{21}H_{24}N_2O_3$	132242-28-5	**58**	10-Hydroxy-N_a-methylpericyclivine	*Alstonia undulata*	*133*
352.4	$C_{21}H_{24}N_2O_3$	132242-30-9	**59**	10-Methoxypericyclivine	*Alstonia undulata*	*133*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant Source(s)	Ref.
354.4	$C_{21}H_{26}N_2O_3$	71635-29-5	**60**[b]	19,20-Dihydroakuammidine	*Rauvolfia caffra*	*15*
					Rauvolfia mombasiana	*88*
354.4	$C_{21}H_{26}N_2O_3$	85799-35-5	**61**	19,20-Dihydropolyneuridine	*Alstonia venenata*	*172*
364.4	$C_{22}H_{24}N_2O_3$	18783-45-4	**62**	Dehydrovoachalotine	*Alstonia undulata*	*133*
					Voacanga chalotiana	*174*
364.4	$C_{22}H_{24}N_2O_3$	92138-23-3	**63**	Voachalotinal	*Alstonia undulata*	*133*
366.5	$C_{22}H_{26}N_2O_3$	664-25-5	**64**	Voachalotine	*Alstonia legouixiae*	*175*
					Ervatamia yunnanensis	*176*
					Peschiera buchtieni	*35*
					Peschiera campestris	*177*
					Tabernaemontana fuchsiaefolia	*69*
					Voacanga chalotiana	*178*
366.5	$C_{22}H_{26}N_2O_3$	132242-31-0	**65**	10-Methoxy-N_a-methylpericyclivine	*Alstonia undulata*	*133*
367.5	$C_{22}H_{27}N_2O_3$	6801-39-4	**66**[a]	Macusine A	*Strychnos toxifera*	*77*
367.5	$C_{22}H_{27}N_2O_3$	2697-31-6	**67**[d]	N_b-Methylakuammidine	*Alstonia angustifolia*	*179*
					Aspidosperma spegazzinii	*128*
368.4	$C_{21}H_{24}N_2O_4$	35594-10-6	**68**	Eburnaphylline	*Hunteria eburnea*	*180*
380.4	$C_{22}H_{24}N_2O_4$	123225-55-8	**69**	17-Hydroxydehydrovoachalotine	*Alstonia undulata*	*181*
382.5	$C_{22}H_{26}N_2O_4$	5539-91-3	**70**	Voacoline	*Voacanga chalotiana*	*182*
382.5	$C_{22}H_{26}N_2O_4$	26126-83-0	**71**[b]	21-Hydroxyvoachalotine	*Voacanga chalotiana*	*170*
394.5	$C_{23}H_{26}N_2O_4$	14478-58-1	**72**[c]	Acetylakuammidine	*Aspidosperma quebracho-blanco*	*183*
395.5	$C_{24}H_{31}N_2O_3$	109269-75-2	**73**[c]	Fuchsiaefoline	*Peschiera fuchsiaefolia*	*184*
396.5	$C_{23}H_{28}N_2O_4$	56440-63-2	**74**	10-Methoxy-N_a-methylakuammidine	*Alstonia lanceolifera*	*185*
397.5	$C_{23}H_{29}N_2O_4$	163131-24-6	**75**[d]	11-Hydroxy-N_a-methylmacusine A	*Stemmadenia obovata*	*186*
397.5	$C_{23}H_{29}N_2O_4$	87340-28-1	**76**	11-Methoxymacusine A	*Strychnos angolensis*	*187*

398.5	$C_{26}H_{26}N_2O_2$	54357-60-7	**77**[c]	*O*-Benzoylnormacusine B (*O*-Benzoyltombozine)	*Vinca erecta*	*188*
410.5	$C_{24}H_{30}N_2O_4$	62404-92-6	**78**[c]	17-*O*-Acetyl-19,20-dihydrovoachalotine	*Voacanga chalotina*	*189*
411.5	$C_{24}H_{31}N_2O_4$	109304-75-8	**79**	12-Methoxy-N_b-methylvoachalotine	*Peschiera fuchsiaefolia*	*184*
					Peschiera campestris	*177*
425.6	$C_{25}H_{33}N_2O_4$	109269-78-5	**80**[c]	12-Methoxy-N_b-methylvoachalotine ethyl ester	*Peschiera fuchsiaefolia*	*184*
572.8	$C_{38}H_{44}N_4O$	7096-95-9	**81**	Geissolosimine	*Geissospermum vellosii*	*14*
584.8	$C_{38}H_{40}N_4O_2$	138683-55-3	(+)-**82**	(+)-Divaricine	*Strychnos divaricans*	*24*
629.8	$C_{40}H_{45}N_4O_3$	113728-54-4	**83**	Macrospegatrine	*Rauvolfia verticillata* var. *hainanensis*	*190*
630.8	$C_{40}H_{46}N_4O_3$	160427-83-8	**84**	*N'*-Demethylaccedinisine	*Peschiera buchtieni*	*35*
					Peschiera van heurckii	*37*
644.9	$C_{41}H_{48}N_4O_3$	17801-01-3	**85**	Macralstonidine	*Alstonia macrophylla*	*191*
					Alstonia somersetensis	*191*
					Alstonia spectabilis	*124*
644.9	$C_{41}H_{48}N_4O_3$	61551-76-6	**86**	Accedinisine	*Peschiera van heurckii*	*37*
					Tabernaemontana accedens	*192*
648.9	$C_{40}H_{48}N_4O_4$	102488-56-2	**87**	Dispegatrine	*Rauvolfia verticillata* var. *hainanensis*	*130*
702.9	$C_{43}H_{50}N_4O_5$	123901-45-1	**88**	Desformoundulatine	*Alstonia undulata*	*193*
732.9	$C_{44}H_{52}N_4O_6$	123871-90-9	**89**	Undulatine	*Alstonia sphaerocapitata*	*193*
					Alstonia undulata	*193*

The sign of the optical rotation [(+) or (−)] is indicated in conjunction with the compound name if this is given with the CAS number.

[a] In the writers' opinion, the proposed structure waits for supplementary data.

[b] Tentative structure. In the writers' opinion, the proposed structure waits for supplementary confirmation.

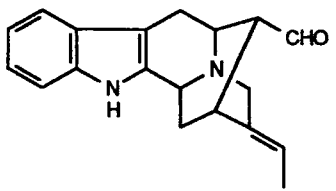
[c] In the writers' opinion, the compound in question is an artefact.

[d] CAS Registry number given for a chloride salt.

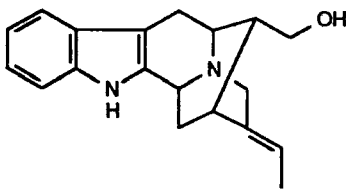
[e] In the original references 159 and 160 the isolated *E*-akuammidine was erroneously identified as polyneuridine. See Jokela and Lounasmaa (*239*).

TABLE II

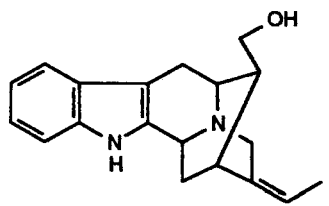
SARPAGINE ALKALOID STRUCTURES



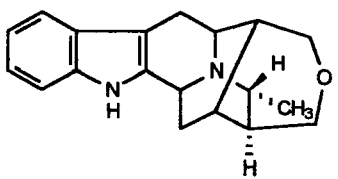
(+)-**Vellosimine**
[(+)-**1**]
[6874-98-2]
Mp. 305–306°C (MeOH)(*14*)
$[\alpha]_D^{26}$ +48° (MeOH)(*14*)



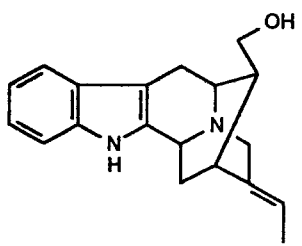
Normacusine B
[**2**]
[604-99-9]
Mp. 273–274°C (MeOH aq)(*44a*)
$[\alpha]_D^{23}$ +42° (*c* 1, EtOH)(*44a*)



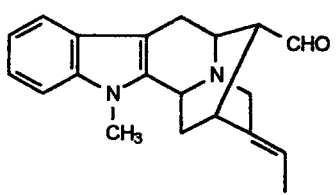
Koumidine
[**3**]
[1358-75-4]
Mp. 201–203°C (acetone)(*64*)
$[\alpha]_D$ −11° (*c* 0.07, MeOH)(*64*)



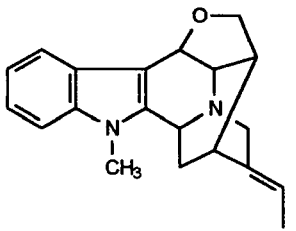
Deoxyperaksine
[**4**][a]
[22226-71-7]
Mp. 225–257°C (ether)(*44b*)
$[\alpha]_D$ n.r.



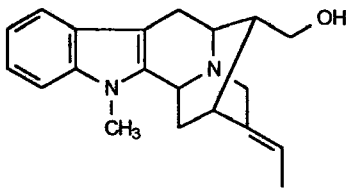
16-Epinormacusine B
[**5**]
[119241-73-5]
Mp. n.d.
$[\alpha]_D$ +3° (*c* 0.25, MeOH)(*32*)



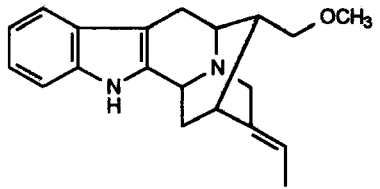
N_a-**Methylvellosimine**
[**6**]
[81525-53-3]
Mp. 255–260°C (*18*)
$[\alpha]_D^{22}$ +23° (*c* 0.01, $CHCl_3$)(*18*)



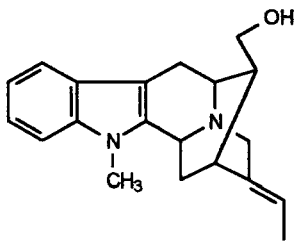
Dehydro-16-epiaffinisine
[7]
[138989-36-3]
Mp. n.d.
$[\alpha]_D$ +58.8° (*c* 0.25, MeOH)(*32*)



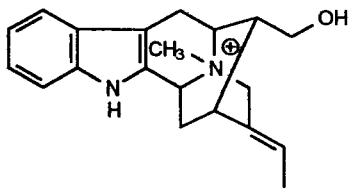
Affinisine
[8]
[2912-11-0]
Mp. 194–196°C dec. (*67b*)
$[\alpha]_D^{30}$ +19° (*c* 0.778, $CHCl_3$)(*67b*)



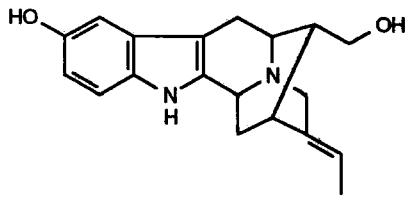
***O*-Methylnormacusine B**
[9][b]
[68160-78-1]
Amorphous (*71*)
$[\alpha]_D$ n.r.



16-Epiaffinisine
[10]
[139067-48-4]
Mp. n.d.
$[\alpha]_D$ −18° (*c* 0.5, MeOH)(*32*)



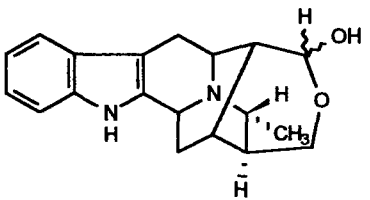
Macusine B
[11][c]
[6792-07-0]
Mp. 249–250°C dec. (MeOH)(*73*)
$[\alpha]_D^{25}$ +14° ± 6° (*c* 0.349, H_2O)(*73*)



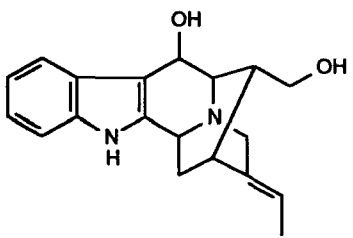
(+)-Sarpagine
[(+)-12]
[482-68-8]
Mp. 374°C (MeOH)(*89*)
$[\alpha]_D^{20}$ +55° (*c* 0.75, pyridine)(*89*)

(*continues*)

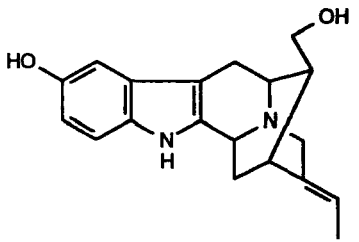
TABLE II (*Continued*)



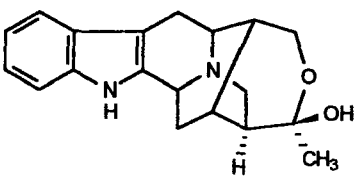
Peraksine
[13]
[15527-80-7]
Mp. 196–198°C (MeOH)(*44b*)
$[\alpha]_D$ +40.3° (*c* 1, pyridine)(*44b*)



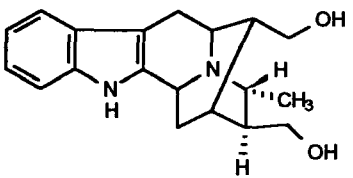
Ervincidine
[14][d]
[32075-02-8]
Mp. 279–280°C (MeOH)(*100*)
$[\alpha]_D$ +29.5° (*c* 0.6, MeOH)(*100*)



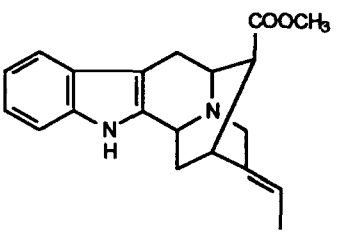
(+)-16-Episarpagine
[(+)-15][d]
[102490-01-7]
Mp. 300°C (*101*)
$[\alpha]_D^{30}$ +34.7° (*c* 0.085, EtOH)(*101*)



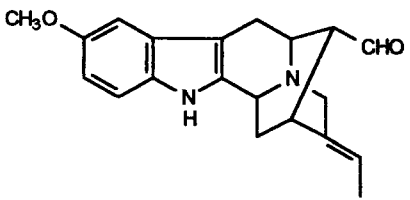
(−)-Trinervine
[(−)-16]
[132242-49-0]
Mp. 219–220°C (MeOH/EtOAc)(*57*)
$[\alpha]_D^{22}$ −7° (*c* 0.373, $CHCl_3$)(*57*)



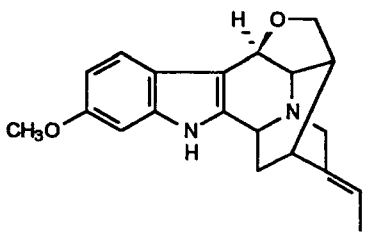
Dihydroperaksine
[17][a]
[26263-40-1]
Mp. 290–291°C (*44b*)
$[\alpha]_D$ +40.8° (*c* 1, pyridine)(*44b*)



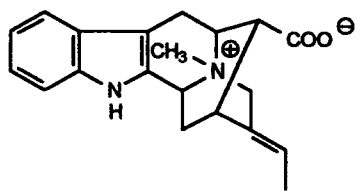
(+)-Pericyclivine
[(+)-18]
[975-77-9]
Mp. 232–233°C (EtOH)(*103*)
$[\alpha]_D^{26}$ +5.2° (*c* 1, $CHCl_3$)(*103*)



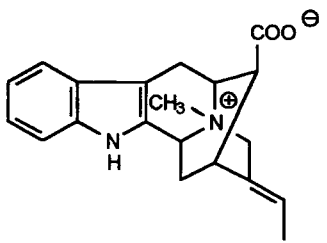
10-Methoxyvellosimine
[19]
[2149-40-8]
Mp. 226°C dec. (benzene)(*114*)
$[\alpha]_D$ +71° ($CHCl_3$)(*114*)



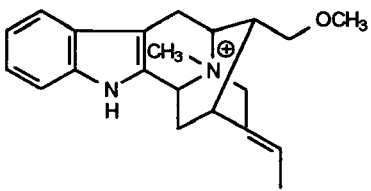
Gardnutine
[20]
[23172-98-7]
Mp. 319–320°C dec. (*115*)
$[\alpha]_D^{25}$ +30.3° (pyridine)(*115*)



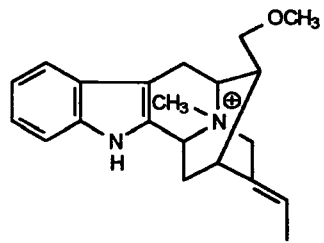
Panarine
[21]
[119736-90-2]
Mp. n.d.
$[\alpha]_D$ n.r.



16-Epipanarine
[22]
[135355-84-9]
Mp. 226°C (MeOH)(*117*)
$[\alpha]_D^{20}$ −29° (*c* 0.7, MeOH)(*117*)



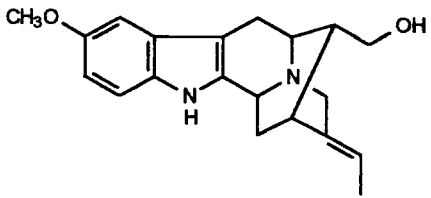
***O*-Methylmacusine B**
[23][e]
[55249-53-1]
Mp. n.d.
$[\alpha]_D$ n.r.



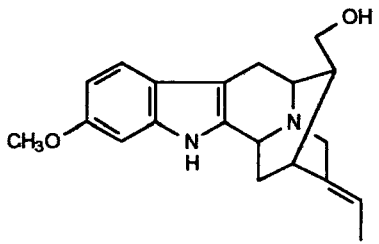
***O*-Methyl-16-epimacusine B**
[24][e]
[83945-53-3]
Mp. n.d.
$[\alpha]_D$ n.r.

(*continues*)

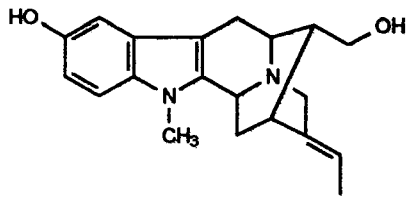
TABLE II (*Continued*)



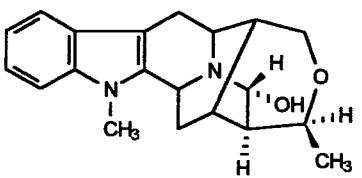
(+)-Lochnerine
[(+)-25]
[522-47-4]
Mp. 202.5–203.5°C (MeOH aq.)(*194*)
$[\alpha]_D^{25}$ +72° ± 2° (*c* 0.624, EtOH)(*194*)



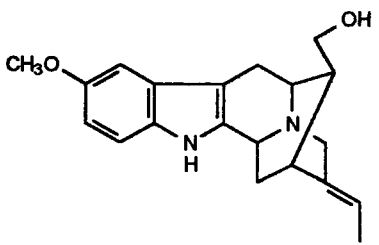
Gardnerine
[26]
[23172-92-1]
Mp. 243–244°C (*115*)
$[\alpha]_D^{25}$ −29.4°C (MeOH)(*115*)



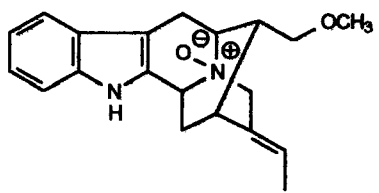
N_a-Methylsarpagine
[27][b]
[17801-05-7]
Mp. 300°C dec. (MeOH)(*124*)
$[\alpha]_D$ n.r.



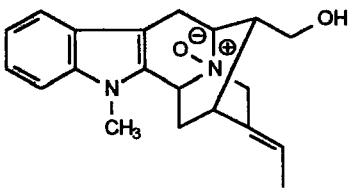
Talpinine
[28]
[38990-06-6]
Mp. 153–154°C (ether/pentane)(*125*)
$[\alpha]_D^{23}$ −30° (*c* 0.302, $CHCl_3$)(*125*)



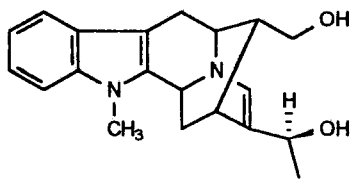
Lochvinerine
[29]
[54631-87-7]
Mp. 195–197°C dec. (EtOAc)(*126*)
$[\alpha]_D$ n.r.



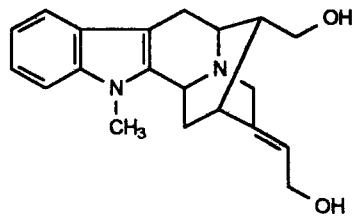
***O*-Methylnormacusine B**
N_b-oxide
[30][b]
[70319-20-9]
Amorphous (*40*)
$[\alpha]_D$ n.r.



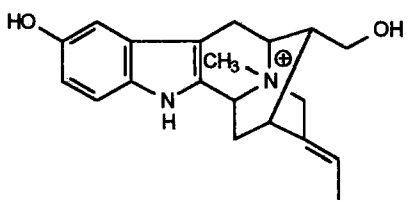
Affinisine N_b-oxide
[31]
[138989-35-2]
Mp. n.d.
$[\alpha]_D$ +3° (*c* 1, MeOH)(*32*)



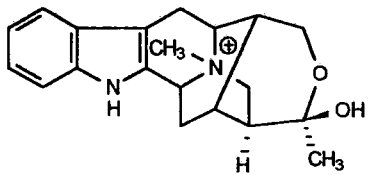
(−)-**Alstoumerine**
[(−)-32]
[135824-73-6]
Mp. 170°C (*127*)
$[\alpha]_D$ −5.5° (*c* 0.0034, $CHCl_3$)(*127*)



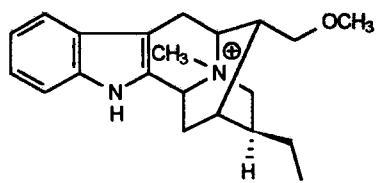
18-Hydroxyaffinisine
[33]
[167696-86-8]
Mp. n.d.
$[\alpha]_D$ n.r.



Spegatrine
[34][c]
[47326-53-4]
Mp. 294°C dec. (EtOH)(*128*)
$[\alpha]_D^{17}$ +38° (*c* 1, MeOH)(*128*)

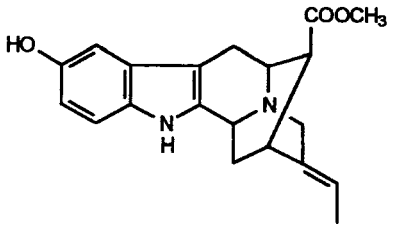


Venecurine
[35]
[122908-09-2]
Mp. n.d.
$[\alpha]_D$ n.r.

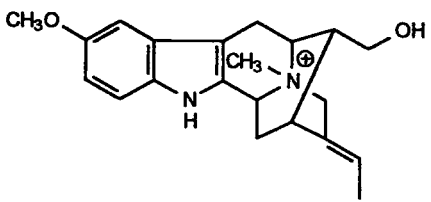


19,20-Dihydro-*O*-methylmacusine B
[36][b]
[55249-54-2]
Mp. n.d.
$[\alpha]_D$ n.r.

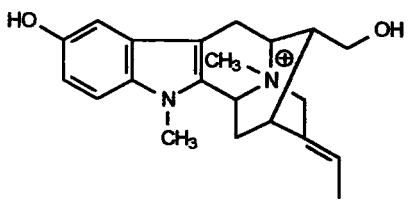
(*continues*)



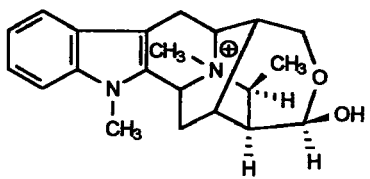
10-Hydroxypericyclivine
[43]
[132242-29-6]
Mp. n.d.
$[\alpha]_D$ n.r.



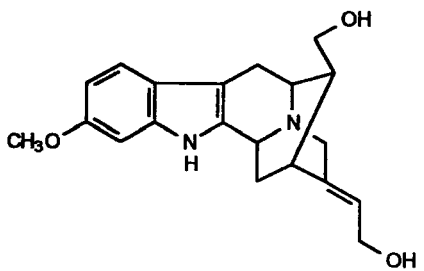
Lochneram
[44][g]
[6901-26-4]
Mp. 235–238°C (acetone)(*134*)
$[\alpha]_D^{23}$ +41° ± 2° (*c* 0.4759, EtOH)(*134*)



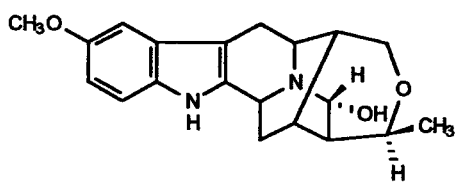
N_a-Methylsarpagine metho salt
[45][h]
[4849-01-8]
Mp. 275–280°C dec. (MeOH)(*135*)
$[\alpha]_D^{26}$ +56° ± 12° (*c* 0.174, MeOH)(*135*)



Macrosalhine
[46][c]
[16103-76-7]
Mp. 284–286°C dec. (EtOH)(*136*)
$[\alpha]_D^{24}$ +27° ± 6° (*c* 0.467, MeOH)(*136*)

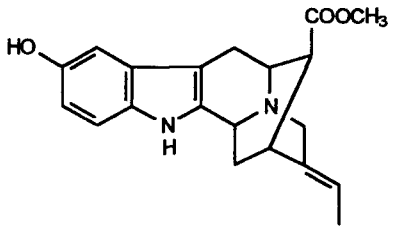


18-Hydroxygardnerine
[47][b]
[23173-02-6]
Mp. n.d.
$[\alpha]_D$ n.r.

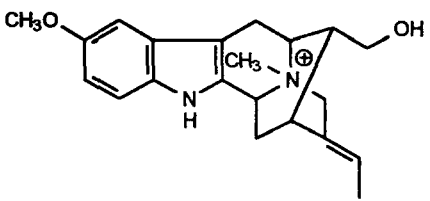


21-Hydroxycyclolochnerine
[48]
[96688-58-3]
Mp. 172°C (*195*)
$[\alpha]_D$ n.r.

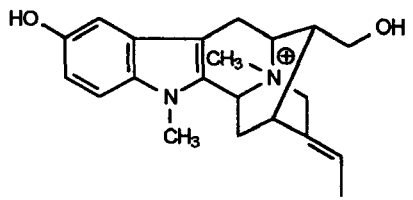
(*continues*)



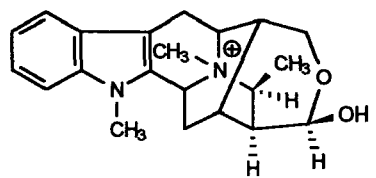
10-Hydroxypericyclivine
[43]
[132242-29-6]
Mp. n.d.
$[\alpha]_D$ n.r.



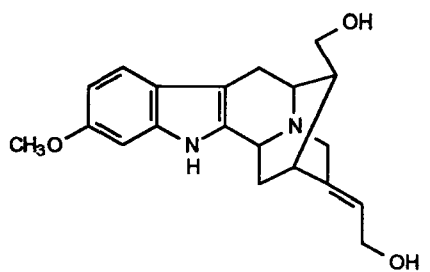
Lochneram
[44][g]
[6901-26-4]
Mp. 235–238°C (acetone)(*134*)
$[\alpha]_D^{23}$ +41° ± 2° (*c* 0.4759, EtOH)(*134*)



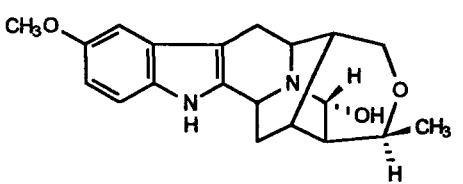
N_a-Methylsarpagine metho salt
[45][h]
[4849-01-8]
Mp. 275–280°C dec. (MeOH)(*135*)
$[\alpha]_D^{26}$ +56° ± 12° (*c* 0.174, MeOH)(*135*)



Macrosalhine
[46][c]
[16103-76-7]
Mp. 284–286°C dec. (EtOH)(*136*)
$[\alpha]_D^{24}$ +27° ± 6° (*c* 0.467, MeOH)(*136*)



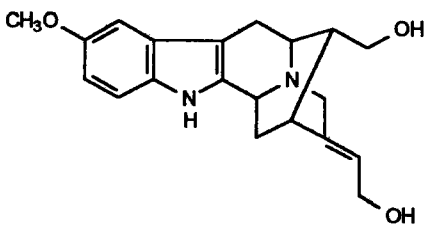
18-Hydroxygardnerine
[47][b]
[23173-02-6]
Mp. n.d.
$[\alpha]_D$ n.r.



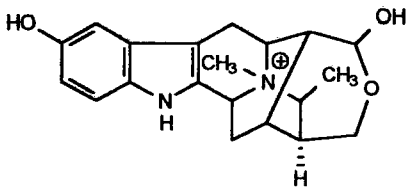
21-Hydroxycyclolochnerine
[48]
[96688-58-3]
Mp. 172°C (*195*)
$[\alpha]_D$ n.r.

(*continues*)

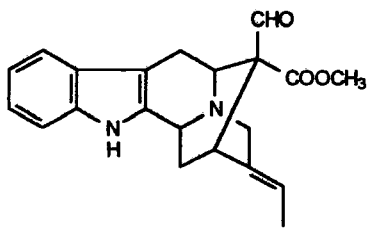
TABLE II (*Continued*)



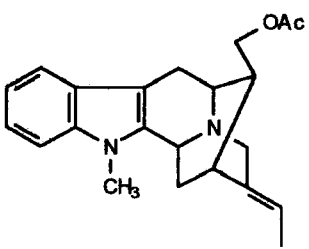
18-Hydroxylochnerine
[**49**]
[107603-56-5]
Amorphous (*122*)
$[\alpha]_D$ n.r.



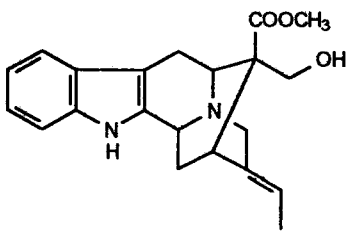
Verticillatine
[**50**][c]
[98243-58-4]
Mp. 324–326°C dec. (*129*)
$[\alpha]_D$ +11.4° (*c* 0.9, H_2O)(*129*)



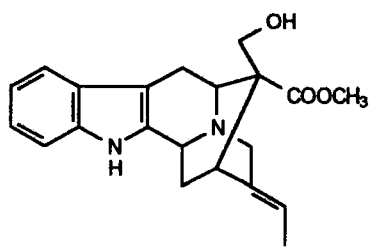
Polyneuridine aldehyde
[**51**][i]
[2520-44-7]
Mp. 231–233°C (ether)(*138*)
$[\alpha]_D$ n.r.



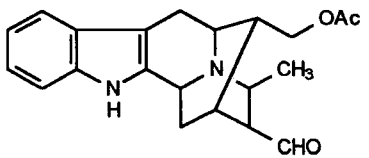
***O*-Acetyl-16-epiaffinisine**
[**52**][f]
[139067-49-5]
Mp. n.d.
$[\alpha]_D$ −14° (*c* 0.5, MeOH)(*32*)



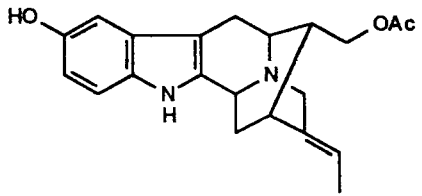
(+)-*E*-Akuammidine
[(+)-**53**]
[639-36-1]
Mp. 248.5°C (*157*)
$[\alpha]_D^{16}$ +21° (*c* 1, EtOH)(*157*)



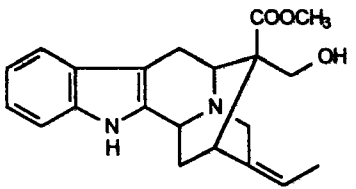
(−)-Polyneuridine
[(−)-**54**]
[6872-44-2]
Mp. 245–247.5°C (EtOH)(*27*)
$[\alpha]_D$ −68° (*c* 0.67, pyridine)(*27*)



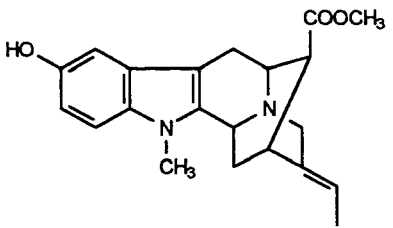
***O*-Acetylpreperakine**
[55][f]
[73221-32-6]
Amorphous (*47*)
$[\alpha]_D^{20}$ +45° (*c* 0.1, $CHCl_3$)(*47*)



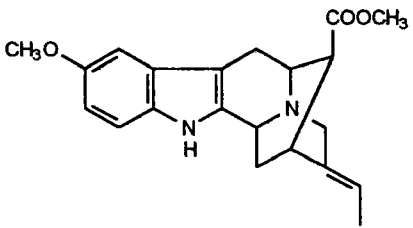
***O*-Acetylsarpagine**
[56][f]
[102358-21-4]
Mp. 303–304°C dec. (*101*)
$[\alpha]_D^{30}$ +39.6° (*c* 0.081, EtOH)(*101*)



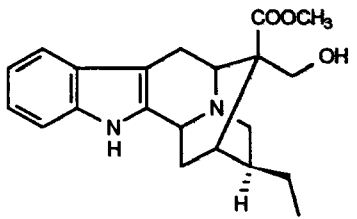
***Z*-Akuammidine**
[57]
[113973-31-2]
Mp. 240–242°C (*173*)
$[\alpha]_D^{16}$ +9° (*c* 0.16, MeOH)(*173*)



10-Hydroxy-N_a-methylpericyclivine
[58]
[132242-28-5]
Mp. n.d.
$[\alpha]_D$ 0° (*c* 0.25, $CHCl_3$)(*133*)



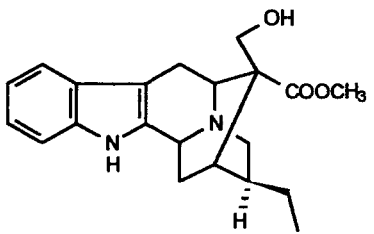
10-Methoxypericyclivine
[59]
[132242-30-9]
Mp. 235–238°C (acetone)(*133*)
$[\alpha]_D$ +1.7° (*c* 1, $CHCl_3$)(*133*)



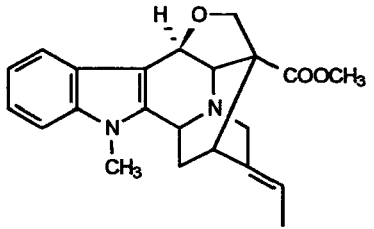
19,20-Dihydroakuammidine
[60][d,j]
[71635-29-5]
Amorphous (*88*)
$[\alpha]_D$ n.r.

(*continues*)

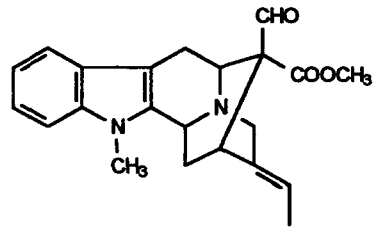
TABLE II (*Continued*)



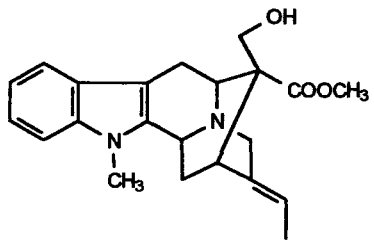
19,20-Dihydropolyneuridine
[61][j]
[85799-35-5]
Amorphous (*172*)
$[\alpha]_D$ n.r.



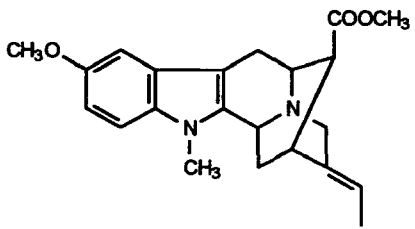
Dehydrovoachalotine
[62]
[18783-45-4]
Mp. 239–239.5°C (benzene)(*174a*)
$[\alpha]_D^{22}$ +124° ± 2° (*c* 0.9, MeOH)(*174a*)



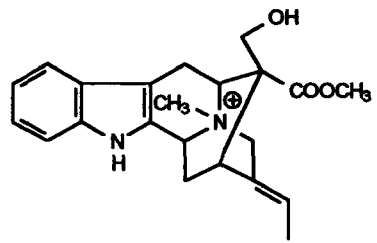
Voachalotinal
[63]
[92138-23-3]
Mp. 231°C (*133*)
$[\alpha]_D$ n.r.



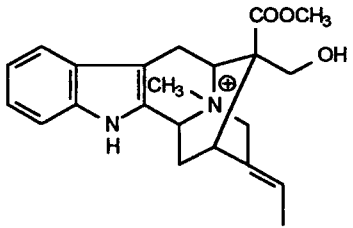
Voachalotine
[64]
[664-25-5]
Mp. 223–224°C (benzene)(*178*)
$[\alpha]_D^{22}$ −2.8° (*c* 6, $CHCl_3$)(*178*)



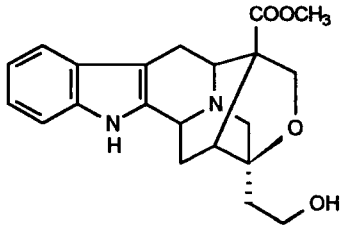
10-Methoxy-N_a-methylpericyclivine
[65]
[132242-31-0]
Mp. 230–231°C (acetone)(*133*)
$[\alpha]_D$ +23° (*c* 1, $CHCl_3$)(*133*)



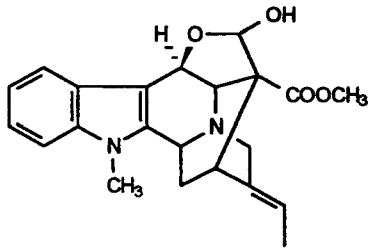
Macusine A
[66][b,c]
[6801-39-4]
Mp. 252°C (EtOH/ether)(*77*)
$[\alpha]_D^{25}$ −57.5° ± 1.5° (*c* 1.455, H_2O)(*77*)



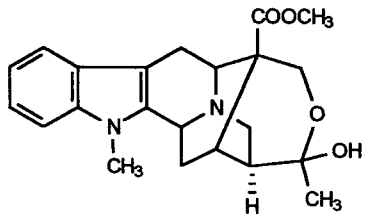
N_b-Methylakuammidine
[67][h]
[2697-31-6]
Mp. 271.0–271.7°C (*179*)
$[\alpha]_D^{24}$ +15° (*c* 0.43, H_2O)(*179*)



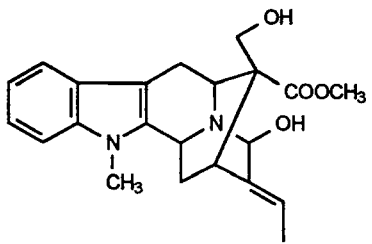
Eburnaphylline
[68]
[35594-10-6]
Mp. 237°C (acetone)(*180*)
$[\alpha]_D$ +15.4° (pyridine)(*180*)



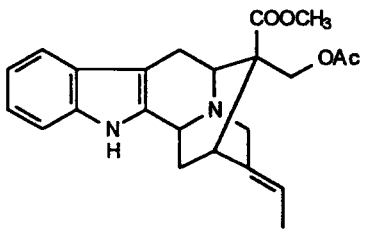
17-Hydroxydehydrovoachalotine
[69]
[123225-55-8]
Amorphous (*181*)
$[\alpha]_D$ +93° (*c* 0.5, $CHCl_3$)(*181*)



Voacoline
[70]
[5539-91-3]
Mp. 147–147.5°C (ether)(*182*)
$[\alpha]_D^{20}$ −29.8° ± 2° (*c* 0.5, $CHCl_3$)(*182*)



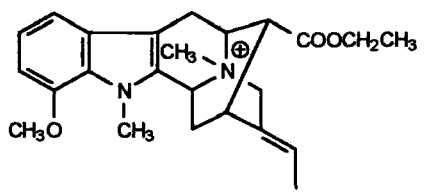
21-Hydroxyvoachalotine
[71][d]
[26126-83-0]
Mp. 218–220°C (acetone)(*170*)
$[\alpha]_D$ n.r.



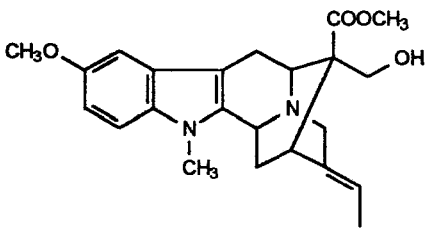
Acetylakuammidine
[72][f]
[14478-58-1]
Mp. 278–279°C dec. (MeOH)(*183*)
$[\alpha]_D^{25}$ +13° (*c* 1, $CHCl_3$)(*183*)

(*continues*)

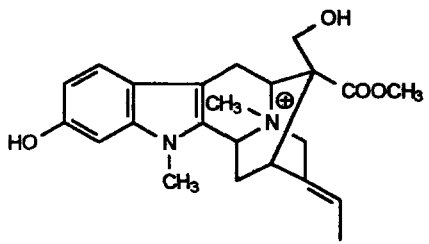
TABLE II (*Continued*)



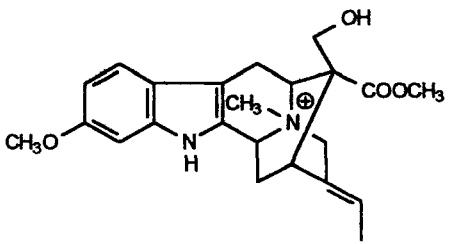
Fuchsiaefoline
[73][f]
[109269-75-2]
Oil. (*184*)
$[\alpha]_D^{25}$ −55.73° (c 0.9, MeOH)(*184*)



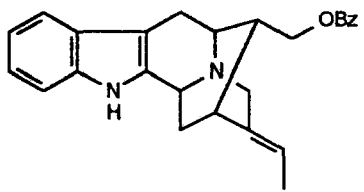
10-Methoxy-N_a-methylakuammidine
[74]
[56440-63-2]
Mp. 234–236°C (MeOH)(*185*)
$[\alpha]_D$ +52° (c 1, $CHCl_3$)(*185*)



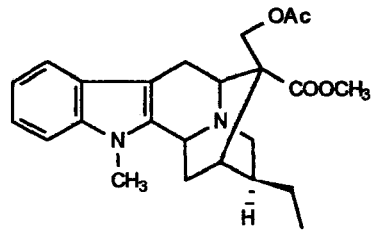
11-Hydroxy-N_a-methylmacusine A
[75][c]
[163131-24-6]
Mp. >300°C (MeOH/$CHCl_3$)(*186*)
$[\alpha]_D^{25}$ −76° (c 0.167, MeOH)(*186*)



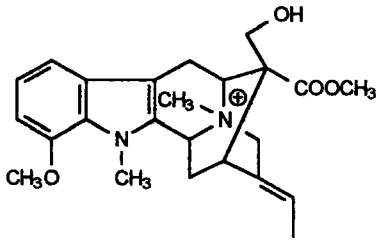
11-Methoxymacusine A
[76][c]
[87340-28-1]
Mp. 224–226°C ($CHCl_3$)(*187*)
$[\alpha]_D$ n.r.



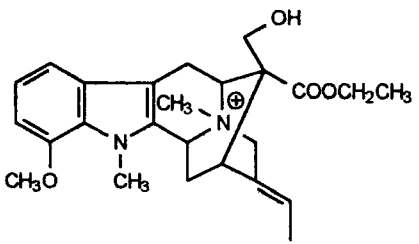
***O*-Benzoylnormacusine B**
[77][f]
[54357-60-7]
Mp. 255–256°C (ether)(*188*)
$[\alpha]_D^{20}$ +93° (c 0.3, $CHCl_3$)(*188*)



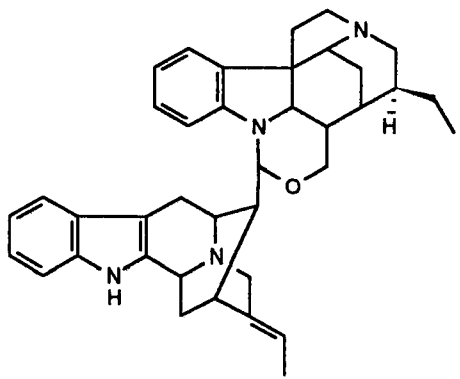
17-*O*-Acetyl-19,20-dihydrovoachalotine
[78][f]
[62404-92-6]
Mp. 201°C (EtOH)(*189*)
$[\alpha]_D^{20}$ −54° ($CHCl_3$)(*189*)



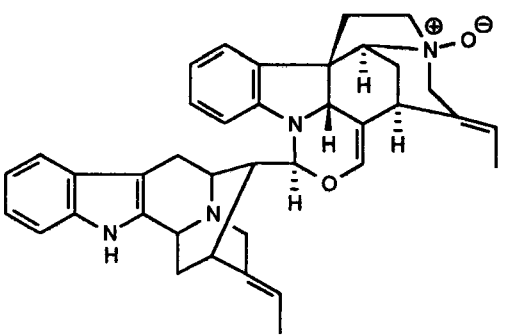
12-Methoxy-N_b-methylvoachalotine
[79]
[109304-75-8]
Mp. 221–223°C (*184*)
$[\alpha]_D^{25}$ −106.19° (*c* 1, MeOH)(*184*)



12-Methoxy-N_b-methylvoachalotine ethyl ester
[80][f]
[109269-78-5]
Mp. 211–214°C (*184*)
$[\alpha]_D^{25}$ −55.94° (*c* 1, MeOH)(*184*)



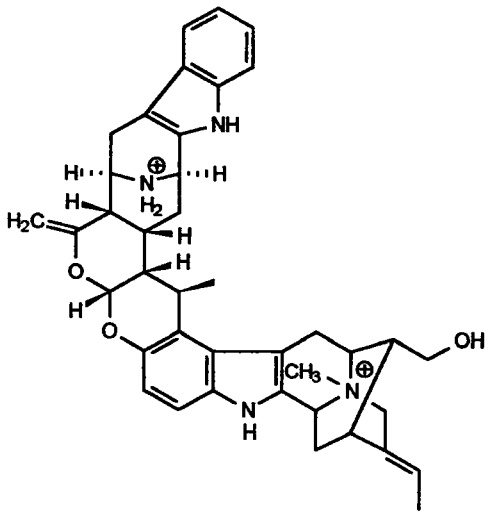
Geissolosimine
[81]
[7096-95-9]
Mp. 140°C (MeOH aq.)(*14*)
$[\alpha]_D^{22}$ +70.4° (MeOH)(*14*)



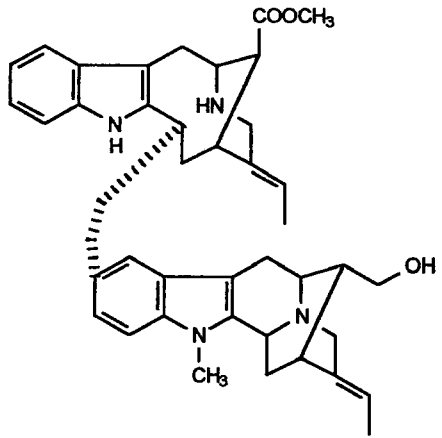
(+)-**Divaricine**
[(+)-**82**]
[138683-55-3]
Mp. 280–282°C dec. (MeOH/EtOAc)(*24*)
$[\alpha]_D^{22}$ +94° (*c* 0.1, EtOH)(*24*)

(*continues*)

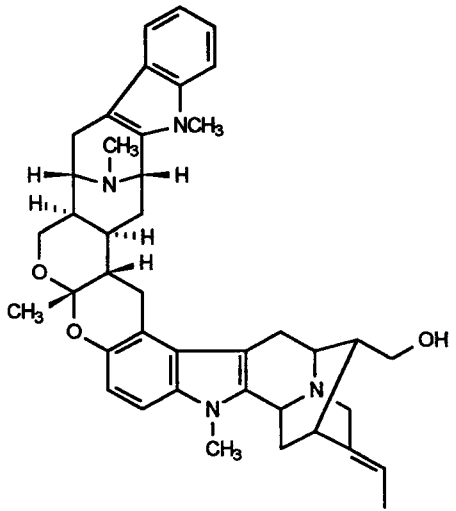
TABLE II (*Continued*)



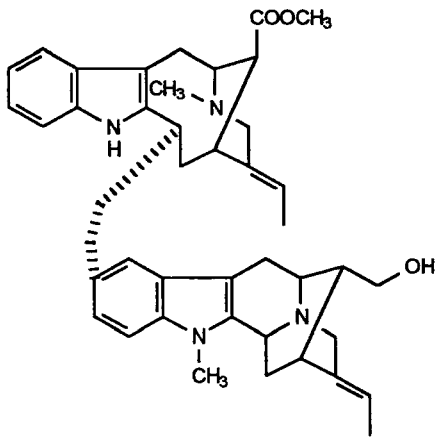
Macrospegatrine
[83][a]
[113728-54-4]
Mp. 300°C dec. (*190*)
$[\alpha]_D^{17}$ +215° (*c* 0.01, MeOH)(*190*)



***N'*-Demethylaccedinisine**
[84]
[160427-83-8]
Mp. n.d.
$[\alpha]_D$ −72° (*c* 0.5, $CHCl_3$)(*37*)



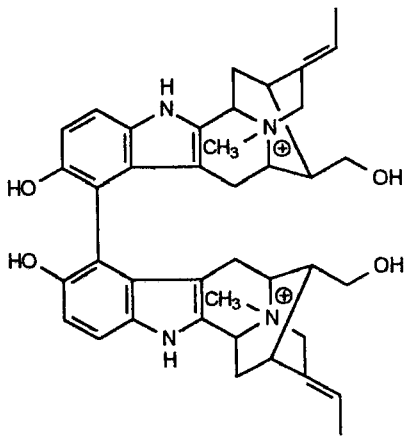
Macralstonidine
[85]
[17801-01-3]
Mp. 295–300°C (CH_2Cl_2)(*124*)
$[\alpha]_D$ +170° (*c* 0.9, $CHCl_3$)(*124*)



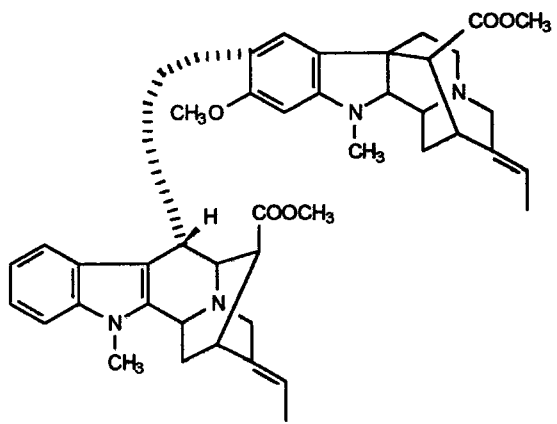
Accedinisine
[86]
[61551-76-6]
Mp. 235°C dec. (acetone)(*192*)
$[\alpha]_D^{20}$ −60° (*c* 0.4, $CHCl_3$)(*192*)

(*continues*)

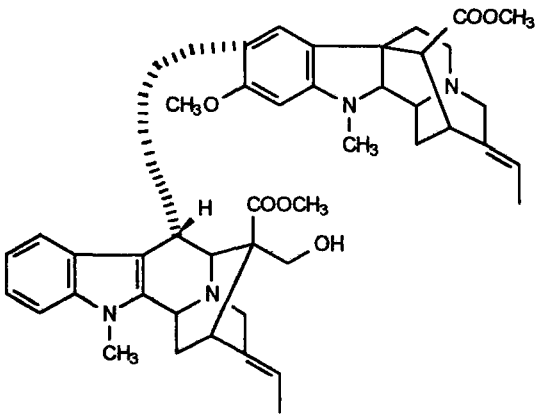
TABLE II (*Continued*)



Dispegatrine
[87][c]
[102488-56-2]
Mp. >280°C dec. (*129*)
$[\alpha]_D^{23}$ +230° (*c* 0.1, MeOH)(*129*)



Desformoundulatine
[88]
[123901-45-1]
Amorphous (*193*)
$[\alpha]_D$ n.r.



Undulatine
[89]
[123871-90-9]
Amorphous (*193*)
$[\alpha]_D$ n.r.

Abbreviations used: n.d., not determined; n.r., not recorded. The sign of the optical rotation [(+) or (−)] is indicated with the compound name if this is given with the CAS number.

[a] Physical properties given for a synthetic compound.
[b] In the writers' opinion, supplementary data is needed to confirm the proposed structure.
[c] Physical properties given for a chloride salt.
[d] Tentative structure. In the writers' opinion, the proposed structure is in need of confirmation.
[e] Counterion not indicated.
[f] In the writers' opinion, the compound in question is an artefact.
[g] Physical properties given for an iodide salt.
[h] CAS Registry number and physical properties given for a chloride salt.
[i] Stereochemistry at C-16 awaits confirmation.
[j] Stereochemistry at C-20 awaits confirmation.

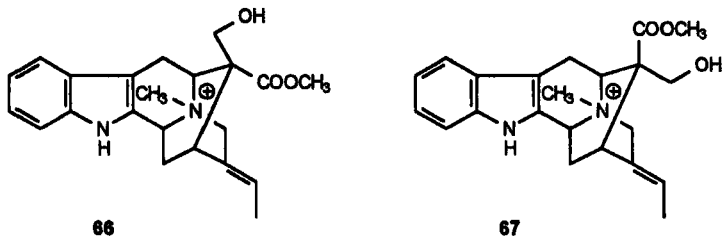


FIG. 2. The structure of macusine A (**66**) and its C-16 epimer **67**.

al. (*128*) isolated from *Aspidosperma spegazzinii* a quaternary alkaloid, which they called (+)-N_b-methylakuammidine and for which structure **67** was proposed. Recently, Hesse and co-workers (*179*) isolated the same compound from *Alstonia angustifolia* (see Tables I and II). The physical data that the Orazi and Hesse groups give for their compounds (as chloride salts) are very similar, but different from the data given by Battersby's group for their compound (also as chloride salt). In particular, the optical rotations $[\alpha]_D$, all measured in H_2O, have opposite signs: Battersby $-60.8° \pm 0.5°$ (*c* 2.13), Orazi $+12°$ (*c* 2.05), Hesse $+15°$ (*c* 0.43).

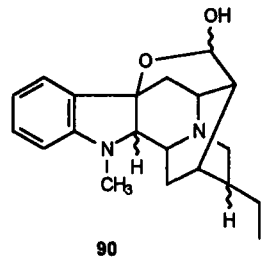
We propose that macusine C was an impure mixture of alkaloids, consisting mainly of macusine A. The optical rotation $[\alpha]_D$ given for macusine A (as a chloride salt) is $-57.5° \pm 1.5°$ (*c* 1.455, H_2O) (*77*).

RAUVOLFININE

In the mid-1950s, A. Chatterjee and co-workers (*197*) isolated, initially from *Rauvolfia serpentina* and then from *R. perakensis,* an indoline alkaloid, which they called rauvolfinine and for which they claimed the structure **90** (Fig. 3). However, the data presented for structure **90** are somewhat vague and most would apply to the indoline alkaloid structure in general. It is noteworthy that other research groups have not yet been able to reisolate rauvolfinine (*89*). In our opinion, the observations concerning the existence and structure of rauvolfinine are erroneous. Probably, as pointed out by Taylor (*1*), the isolated samples consisted of impure mixtures of alkaloids, in which isoajmaline (**91**) may have been the main component (Fig. 4).

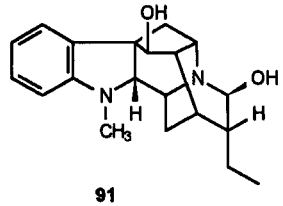
DIHYDROTALPININE

In a paper appearing in 1984, Nasser and Court describe the isolation of several indole alkaloids from *Rauvolfia caffra* (*15*). For one of these



90

FIG. 3. Proposed structure of rauvolfinine (**90**).



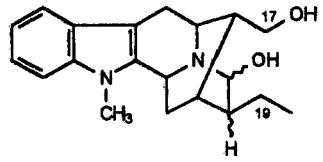
91

FIG. 4. Structure of isoajmaline (**91**).

they presented structure **92** and called it dihydrotalpinine (Fig. 5). In their paper, Nasser and Court stated that the chromogenic reactions and spectroscopic characteristics of their sample agreed with data given for the synthetic dihydrotalpinine (**93**) prepared by Schmid and co-workers (*125*) by $NaBH_4$ treatment of talpinine (**28**) (Scheme 2). Because the structures are different [*O*,19-dihydrotalpinine (**92**) versus N_b,21-dihydrotalpinine (**93**)], the claims concerning the presence of dihydrotalpinine (**92**) in *R. caffra,* are, in our opinion, premature.

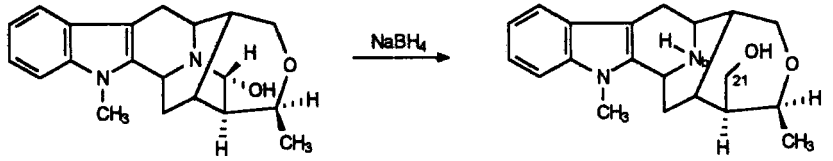
ALKALOID Q_3

In 1980 Quaisuddin isolated from *Aspidosperma peroba* a quaternary alkaloid, which he designated alkaloid Q_3 (*198*). Based on some chemical transformations, which were suggested to lead to the not yet naturally found 16-epipericyclivine (**94**), structure **95** was tentatively proposed for alkaloid Q_3 (Scheme 3). If the structure proposed for alkaloid Q_3 were correct, alkaloid Q_3 would be identical with the synthetically prepared panarine methyl ester chloride (*117*). However, because the physical properties indicated for alkaloid Q_3 and for its suggested derivative **94** (discussed



92

FIG. 5. Structure of *O*,19-dihydrotalpinine (**92**).



28 **93**

SCHEME 2. Transformation of talpinine (**28**) to N_b,21-dihydrotalpinine (**93**).

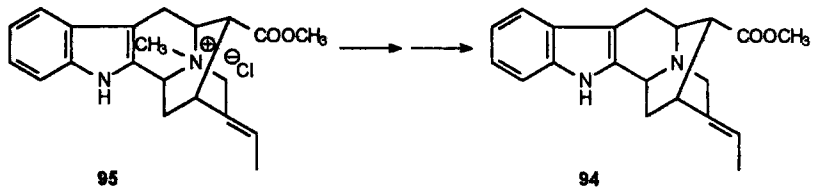
earlier) are very few, this identity cannot be established. In our opinion the structure **95,** proposed for the quaternary alkaloid called alkaloid Q_3, isolated from *A. perobe* by Quaisuddin, awaits more rigorous proof.

11-METHOXY-N_a-METHYLDIHYDROPERICYCLIVINE

In a paper published in 1991, Arambewela and Ranatunge describe the isolation of several indole alkaloids from *Tabernaemontana divaricata* (*199*). For one of them they presented structure **96** and called it 11-methoxy-N_a-methyldihydropericyclivine, although this structure represents 11-methoxy-N_a-methyldihydro-16-epipericyclivine (Fig. 6). Very few data were presented in support of the proposed structure **96** or its 16-epimer **97.** In particular, the ^{1}H NMR data δ 2.43 (3H, s) and δ 2.54 (3H, s) given for $)N-CH_3$ and $-COOCH_3$, respectively, do not support either of the epimeric structures. In the writers' opinion, the claims concerning the presence of 11-methoxy-N_a-methyldihydro-16-epipericyclivine (**96**) or 11-methoxy-N_a-methyldihydropericyclivine (**97**) in *T. divaricata* must be considered premature.

NEOSARPAGINE

In 1959 Rao and co-workers (*200*) isolated from *Rauvolfia micrantha* a minor alkaloid, which they called neosarpagine and for which they proposed



SCHEME 3. Chemical transformations presented by Quaisuddin for determination of the structure of alkaloid Q_3.

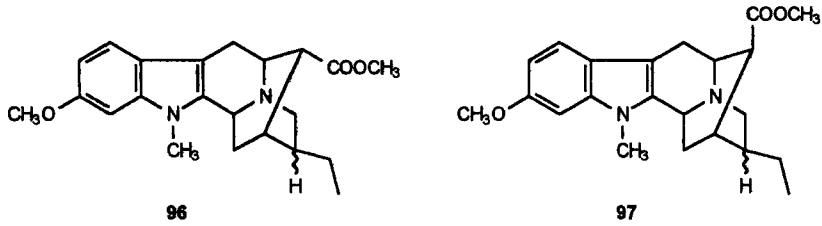


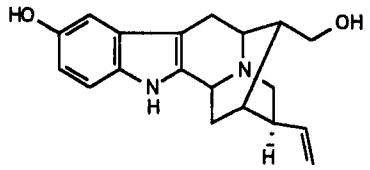
FIG. 6. Structures of 11-methoxy-N_a-methyl-dihydro-16-epipericyclivine (**96**) and 11-methoxy-N_a-methyl-dihydropericyclivine (**97**).

structure **98** [vinyl isomer of sarpagine (**12**)] (Fig. 7). There is no further mention of the occurrence of neosarpagine in the literature. Because all of the physical data presented for neosarpagine are very similar to those of sarpagine (**12**), it seems to the writers, in agreement with Taylor (*1*), that neosarpagine probably was a more or less impure sample of sarpagine.

III. Syntheses

A. VAN TAMELEN SYNTHESIS OF THE "DEOXYAJMALAL SYSTEM"; 18,19-DIHYDRO-N_a-METHYLVELLOSIMINE (**102a**) AND ITS C-16 EPIMER (**102b**)

About thirty years ago van Tamelen and Oliver (*201,202*) presented a synthetic study, based on their biosynthetic suggestions (discussed later), that they claimed to lead via a sarpagan ring system ("deoxyajmalal system") to the six-ring indole alkaloid ajmaline (**99**). The "crucial steps" in



98

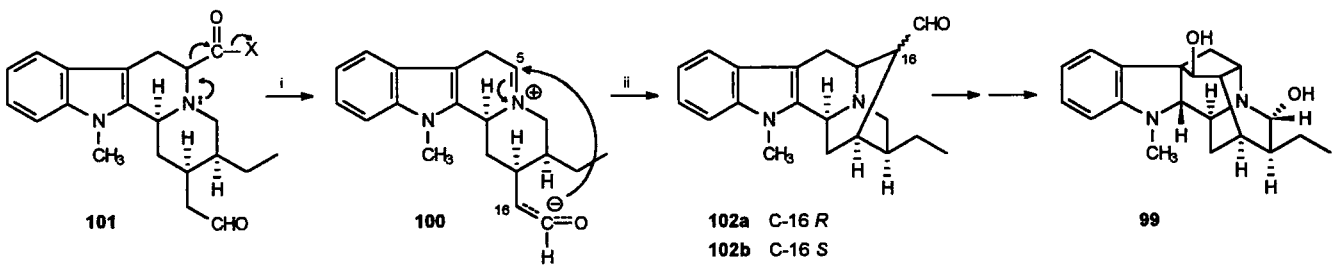
FIG. 7. Proposed structure of neosarpagine.

their approach to the sarpagan ring system were the regioselective formation of the $\Delta^{4(5)}$-iminium ion **100** (realized by decarbonylation; **101** → **100**), and subsequent spontaneous bond formation between C-5 and C-16 [spontaneous "biogenetic-type cyclization"; **100** → **102a** (→ **102b**)] (Scheme 4).

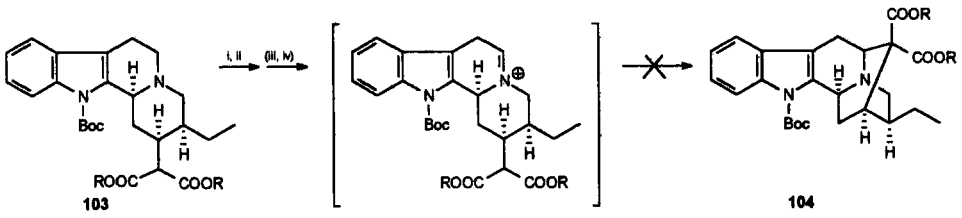
For a long time, the van Tamelen synthesis of the sarpagine ring system (discussed earlier) was authoritative in the field. However, in contrast to van Tamelen and Oliver, Lounasmaa and Hanhinen (*203*) were unable to detect any spontaneous "biogenetic-type cyclization" and were thus unable to cyclize compound **103** (or similar compounds) to the sarpagan skeleton (**103** →| **104**) (Scheme 5). This failure casts some doubt on the results of van Tamelen and Oliver. It also throws into question the proposed biogenetic formation of the sarpagine/ajmaline skeleton. In a recent paper, Lounasmaa and Hanhinen (*204*) argued that in the biogenetic formation of the sarpagine skeleton the bond between C-5 and C-16 must be formed before the closure of the D-ring (discussed later).

B. KHUONG-HUU AND CO-WORKERS' PARTIAL SYNTHESIS OF N_a-BENZENESULFONYL-2α,7α,19,20α-TETRAHYDRO-10-DESOXYSARPAGINE (**110**)

In the partial synthesis of Khuong-Huu and co-workers (*205*), corynantheidine (**105**) was reduced with $NaBH_4$ in the presence of trifluoroacetic acid (TFA) to the corresponding 2α,7α-dihydro derivative **106,** which by NaOMe/MeOH treatment was transformed to the corresponding acetal **107.** Benzenesulfonylation of compound **107** afforded compound **108.** Photosensitized oxidation of **108** in the presence of rose bengal and KCN yielded compound **109,** which, via the corresponding iminium ion, was claimed to cyclize to N_a-benzenesulfonyl-2α,7α,19,20α-tetrahydro-10-desoxysarpagine (**110**) (a dihydroindole derivative, which, however, could not be transformed to an indole derivative) (Scheme 6). It is noteworthy that



SCHEME 4. van Tamelen synthesis of the "deoxyajmalal system." Reagents: (i) DCC/TsOH; (ii) spontaneously.

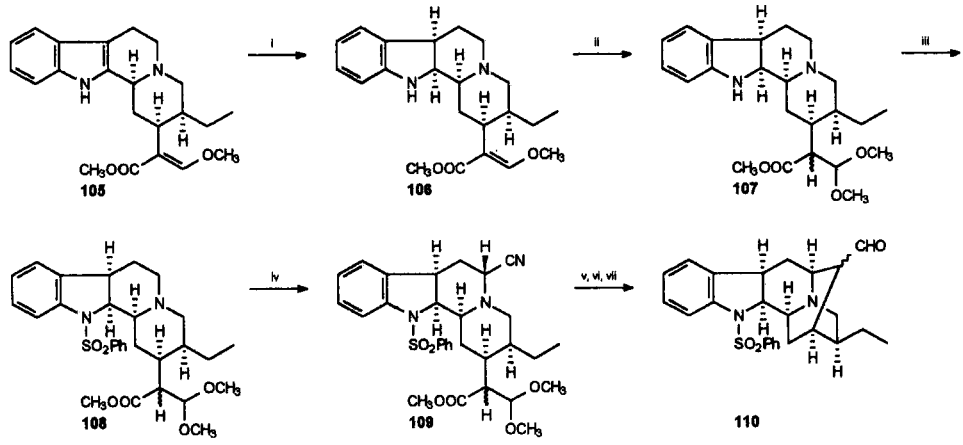


SCHEME 5. Attempts by Lounasmaa and Hanhinen to effect the spontaneous "biogenetic-type cyclization" of van Tamelen. Reagents: (i) *m*-chloroperbenzoic acid (*m*-CPBA); (ii) trifluoroacetic anhydride (TFAA); [or (i) *m*-CPBA; (ii) TFAA; (iii) KCN; (iv) $AgBF_4$].

the cyclization could be effected only in the dihydroindolic form, not the indolic form.

C. MAGNUS TOTAL SYNTHESIS OF (+)-KOUMIDINE [(+)-3] AND FORMAL SYNTHESIS OF (−)-KOUMIDINE [(−)-3]

The Magnus synthesis of (+)-koumidine [(+)-**3**] (antipode of the naturally occurring alkaloid) (*206*) begins with the condensation of **111** with 2-



SCHEME 6. Khuong-Huu and co-workers' partial synthesis of N_a-benzenesulfonyl-2α,7α,19,20α-tetrahydro-10-desoxysarpagine (**110**). Reagents: (i) $NaBH_4$/TFA; (ii) NaOMe–MeOH; (iii) $PhSO_2Cl$/py; (iv) KCN–rose bengal/CH_3–CO–COONa; (v) dioxane/NaOH/H_2O/refl.; (vi) CH_3COOH; (vii) Δ.

ketoglutaric acid and diazomethane treatment. The afforded compounds, (+)-**112** and (+)-**113** (discussed later), were separated. Epimerization at C-3 of (+)-**112** and intramolecular Dieckmann condensation of the resulting intermediate (+)-**113** led to (+)-**114**. Hydrogenolysis of (+)-**114** yielded (+)-**115**, which by $AcOH/H_2SO_4$ treatment was transformed to the ketone (+)-**116**. Treatment of (+)-**116** with propargyl bromide yielded the keto-acetylene (+)-**117**. Exposure of (+)-**117** to *t*-$BuMe_2SiOTf$ and then to *n*-BuLi/$ClCOOCH_3$ afforded (+)-**118**. Hydrolysis of (+)-**118** using $LiBF_4$–tetrahydrofuran (THF) gave (+)-**119**, which, by pyrrolidine/TFA treatment, was cyclized to (+)-**120**. Treatment of (+)-**120** with $CH_2Br_2/Zn/TiCl_2$ gave (+)-**121**, which by hydroboration and H_2O_2 oxidation was transformed to alcoholester (+)-**122**. Reduction of (+)-**122** with diisobutylaluminium hydride (DIBAL) gave the allylic alcohol (+)-**123**, which was debenzylated with Na/NH_3/THF at −30°C to yield (+)-koumidine [(+)-**3**] (Scheme 7). The preparation of intermediate (+)-**116** was inspired by the strategy earlier reported by Yoneda (*207*). For a detailed discussion of this strategy and its applications see Cook and co-workers (*208*).

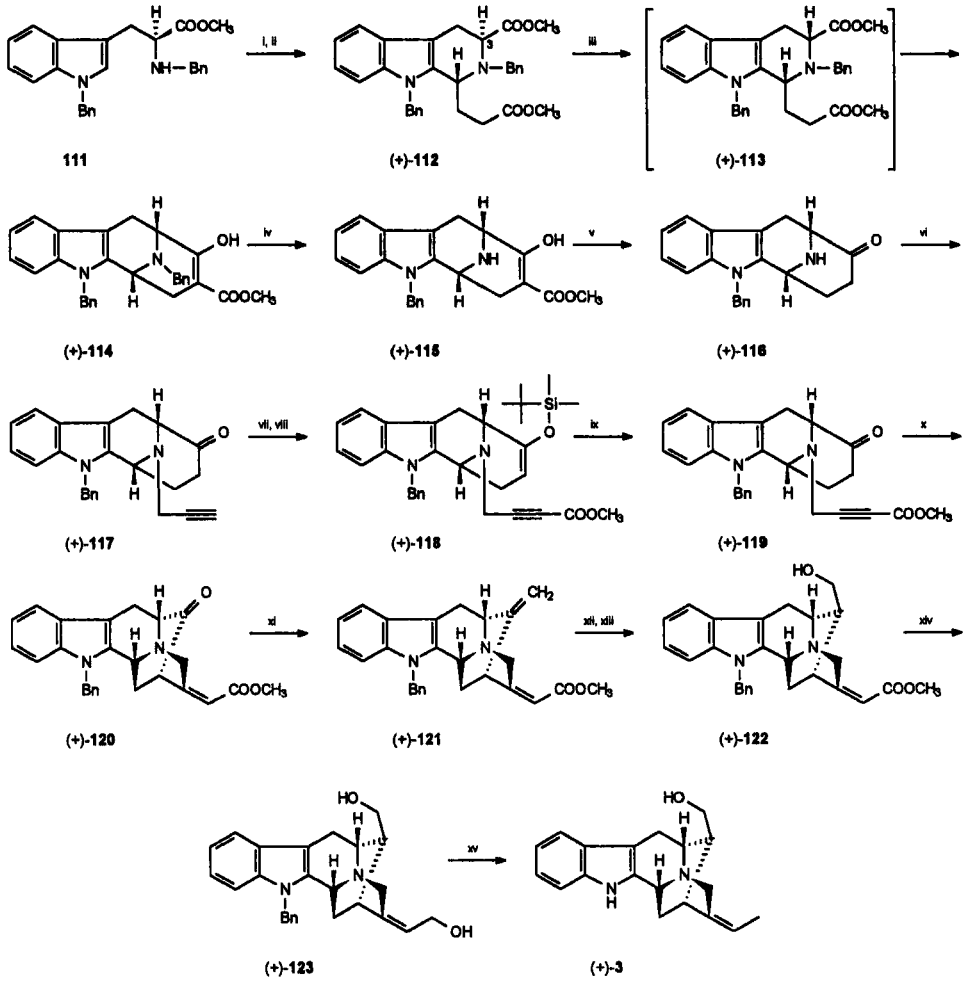
As Magnus (*206*) pointed out, the same strategy applied to compound (−)-**113** (discussed earlier) would lead to the naturally occurring antipode: (−)-koumidine [(−)-**3**][(−)-**113** → (−)-**114** → (−)-**116** → (−)-**117** → (−)-**119** → (−)-**3**] (Scheme 8).

D. Bailey *et al.* Formal Synthesis of (−)-Koumidine [(−)-3]

Bailey *et al.* (*209–211*) used a slightly modified strategy to prepare the crucial intermediate (−)-**116**. The easily accessible compound **124** was transformed in three steps to the ketone (−)-**125**, which by hydrogenolysis was deprotected to yield the aminoketone (−)-**116** (Scheme 9). Bailey *et al.* (*209*) claimed that their work constitutes a formal synthesis of (−)-koumidine [(−)-**3**].

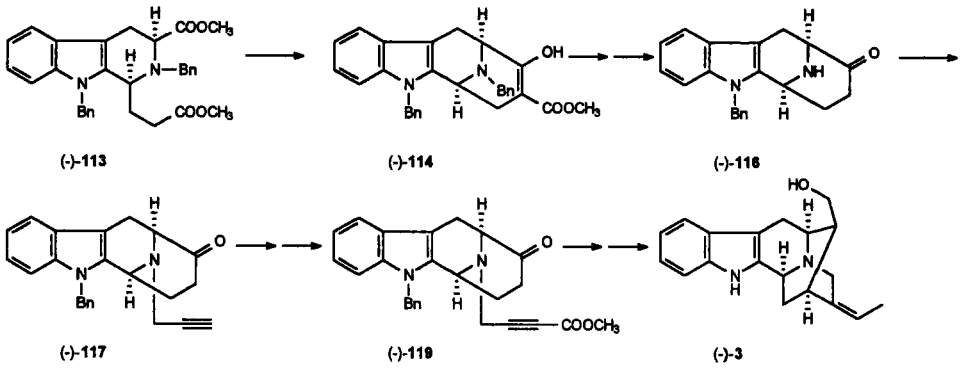
E. Cook and Co-Workers' Enantiospecific Synthesis of Compound 126, an Approach for the Preparation of Sarpagine Alkaloids

Cook and co-workers (*212*) have developed a strategy that permits an enantiospecific synthesis of compound **126**. N_b-Benzyl D-(+)-tryptophan methyl ester (**127**) was transformed with methyl 4,4-dimethoxybutyrate (or methyl γ-aldobutyrate) to the *trans* diester **128**, which, after 60 hours reflux (NaH/MeOH/toluene) led, via epimerization and Dieckmann condensation, to the β-ketoester **129** (enantiomeric purity ≥ 98%). Acid-induced decarboxylation of the β-ketoester **129** afforded the desired compound **126**



SCHEME 7. Magnus total synthesis of (+)-koumidine [(+)-**3**]. Reagents: (i) HOOC–CO–CH_2–CH_2–COOH/PhH/1,4-dioxane/80°C; (ii) CH_2N_2; (iii) MeOH/NaH/toluene/refl.; (iv) Pd/C/HCOOH; (v) $AcOH/H_2SO_4$; (vi) CH≡C-CH_2Br/K_2CO_3/EtOH; (vii) *t*-$BuMe_2SiOTf$/NEt_3/0°C/CH_2Cl_2; (viii) *n*-BuLi/THF/−78°C/ClCOOCH$_3$; (ix) $LiBF_4$/THF; (x) pyrrolidine/TFA/PhH/refl.; (xi) CH_2Br_2/Zn/$TiCl_2$/15°C; (xii) diisoamylborane/1,2-dimethoxyethane (DME)/0°C; (xiii) H_2O_2; (xiv) DIBAL/PhH/25°C; (xv) Na/NH_3/THF/−30°C.

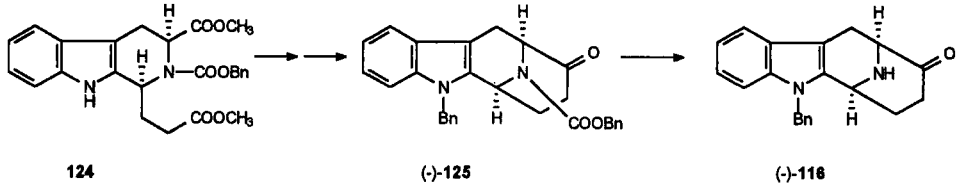
in 90% yield (Scheme 10). In their paper Cook and co-workers (*212*) present compound **126** as a potential intermediate for the preparation of numerous sarpagine-related alkaloids.



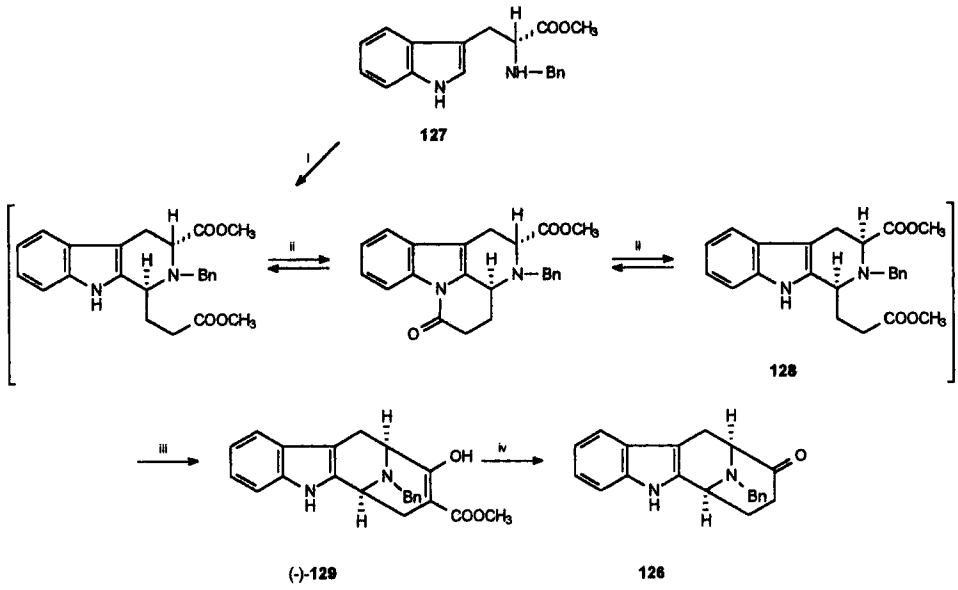
SCHEME 8. Magnus formal synthesis of (−)-koumidine [(−)-**3**].

F. SAKAI AND CO-WORKERS' PARTIAL SYNTHESIS OF (−)-KOUMIDINE [(−)-3]

In the partial synthesis of (−)-koumidine [(−)-**3**] by Sakai and co-workers (*213*), ajmaline (**99**) was converted into the hydrazone derivative, which, after hydrolysis with $CuCl_2$ in aq. THF and 2-methoxyethoxymethyl (MEM) protection at the C-17-OH group, led to compound **130.** The aldehyde was converted to its silyl enol ether, and bromine introduced with *N*-bromosuccinimide (NBS) to afford the bromoaldehyde **131.** Treatment of **131** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry *N,N*-dimethylformamide (DMF) created the double bond C-19–C-20 (mainly 19*Z* as desired) and thus afforded **132.** Reduction of **132** with $NaBH_4$ yielded the corresponding alcohol **133,** which was deprotected by alkaline hydrolysis. Ring closure using MsCl in dry pyridine followed by removal of the protecting MEM group afforded the fully cyclized alcohol **134.** Compound **134**



SCHEME 9. Bailey synthesis of intermediate (−)-**116.** Reagents: (i) $PhCH_2Br$/NaH/DMF/0°C; (ii) NaH (2.2 equiv.)/MeOH (0.1 equiv.)/DMF/r.t.; (iii) NaCl (1.2 equiv.)/H_2O (2 equiv.)/DMF/130°C; (iv) H_2/Pd/C 10%/MeOH.

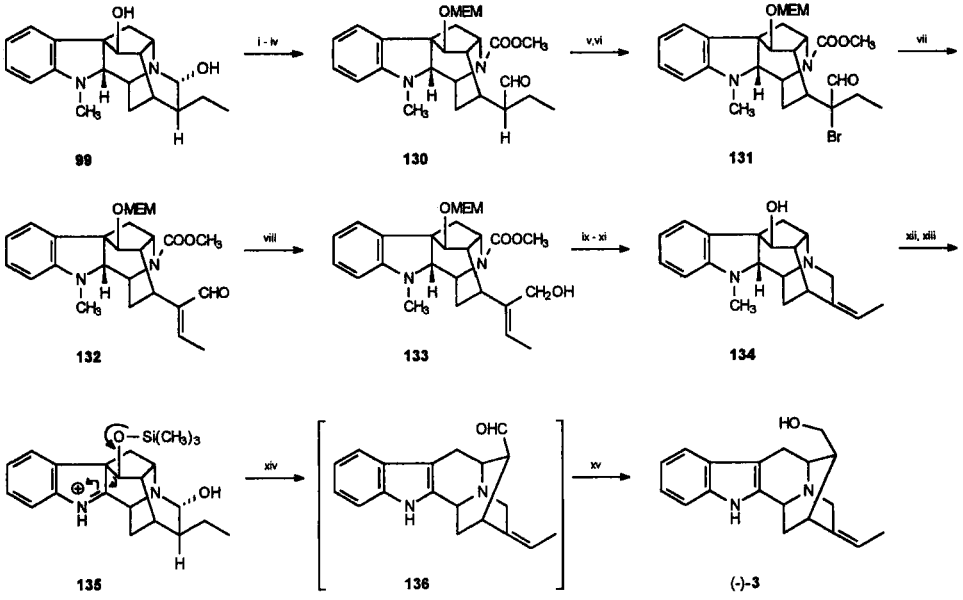


SCHEME 10. Cook and co-workers' enantiospecific synthesis of compound **126.** Reagents: (i) $(CH_3O)_2CHCH_2CH_2COOCH_3$ or $OHCCH_2CH_2COOCH_3$/TFA/CH_2Cl_2/r.t.; (ii) NaH/MeOH/toluene/refl.; (iii) refl.; (iv) HOAc/HCl/H_2O/refl.

was protected as a trimethylsilyl (TMS) ether and then oxidized with $Pb(OAc)_4$ to yield the unstable product **135.** Compound **135** was treated with aq. AcOH/THF, followed by $NaBH_3CN$, to afford, via **136,** (−)-koumidine [(−)-**3**] (Scheme 11).

G. LIU SYNTHESIS OF N_a-METHYL-Δ^{18}-ISOKOUMIDINE (137)

The Liu synthesis of N_a-methyl-Δ^{18}-isokoumidine (**137**) (*214*) starts from L-tryptophan (**138**), which was transformed to intermediate **139** in six steps. The Dieckmann condensation of **139** afforded the β-ketoester **140.** Oxidative free radical cyclization of β-ketoester **140,** initiated with $Mn(OAc)_3$,H_2O/Cu/$(OAc)_2 \cdot H_2O$, followed by the removal of the N_a-protecting group, led almost quantitatively to **141.** Hydrolysis and decarboxylation using the Barton method afforded, via compound **142,** intermediate **143.** Treatment of **143** with $(CH_3)_2S{=}CH_2$/dimethyl sulfoxide (DMSO) THF yielded the epoxy derivative **144,** which was reduced with AlH_2Cl in THF to the, not yet naturally found, N_a-methyl-Δ^{18}-isokoumidine (**137**) (Scheme 12).



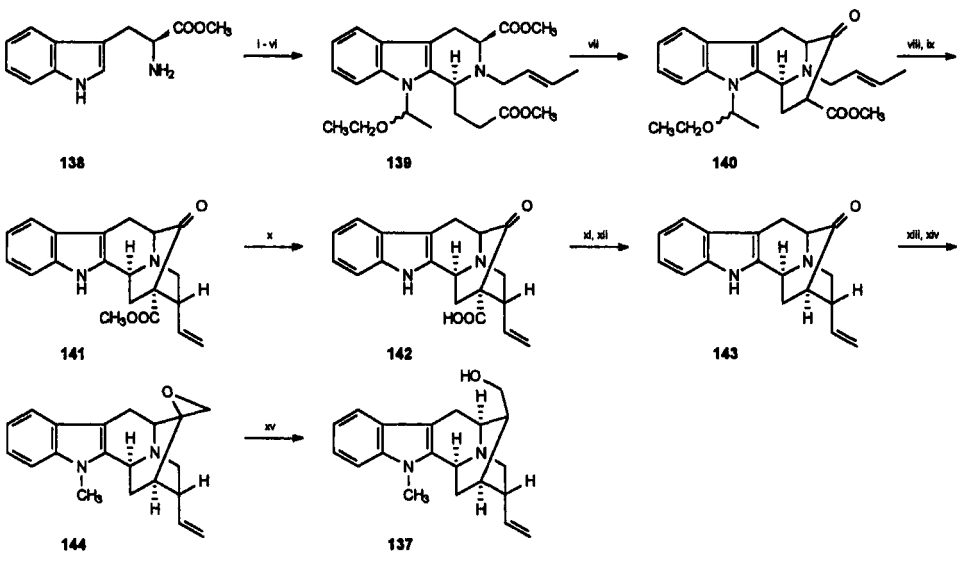
SCHEME 11. Sakai and co-workers' partial synthesis of (−)-koumidine [(−)-**3**]. Reagents: (i) $(CH_3)_2N-NH_2$/cat. H_2SO_4/3 Å mol. sieves/dry EtOH; (ii) $ClCOOCH_3$/1 M NaOH/CH_2Cl_2/0°C; (iii) $CuCl_2$/aq. THF/phosphate buffer; (iv) MEMCl/(*i*-Pr)$_2$EtN/dry CH_2Cl_2; (v) TBSOTf/Et_3N/dry CH_2Cl_2; (vi) NBS/dry THF; (vii) DBU/dry DMF; (viii) $NaBH_4$/MeOH; (ix) NaOH/HO–CH_2–CH_2–OH/H_2O; (x) MsCl/py; (xi) HCl/MeOH; (xii) TMSOTf/Et_3N/dry CH_2Cl_2; (xiii) $Pb(OAc)_4$/dry CH_2Cl_2; (xiv) AcOH/THF/H_2O; (xv) $NaBH_3CN$.

H. OTHER FORMAL SYNTHESES

The first total syntheses of (±)-ajmaline [(±)-**99**] were performed by Masamune *et al.* (*215*) and Mashimo and Sato (*216*). Because ajmaline (**99**) has been transformed to koumidine (**3**) (discussed earlier) and to other sarpagine derivatives, these syntheses can also be considered to represent formal total syntheses of (±)-koumidine [(±)-**3**] and the other sarpagine derivatives.

IV. Reactions

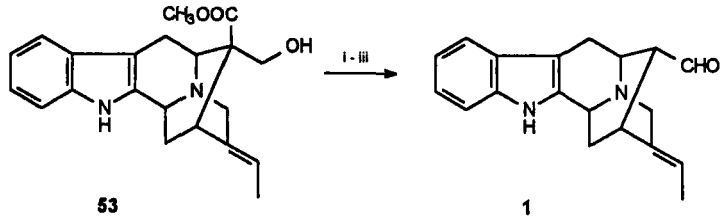
Many reactions and transformations that in earlier days played an important role in the structure determinations of the sarpagine derivatives, have



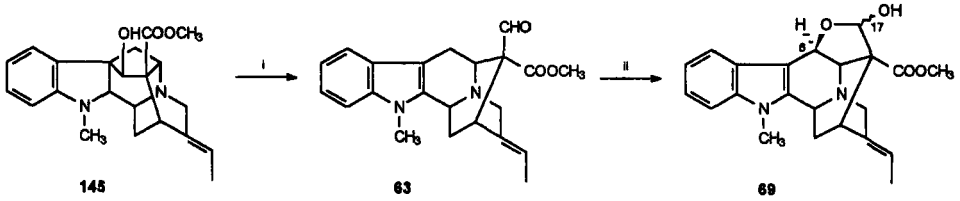
SCHEME 12. Liu synthesis of N_a-methyl-Δ^{18}-isokoumidine (**137**). Reagents: (i) $SOCl_2$/MeOH/r.t.; (ii) $MeOOCCH_2CH_2COCl$/py/r.t.; (iii) $POCl_3$/60°C; (iv) H_2/PtO_2/EtOH; (v) $BrCH_2CH{=}CHCH_3$ (*E*)/$NaHCO_3/CH_3CN$/refl.; (vi) $CH_2{=}CHOEt$/PTS (cat.)/CH_2Cl_2/30°C; (vii) $(Me_3Si)_2NNa$/DME/100°C; (viii) $Mn(OAc)_3{\cdot}H_2O/Cu(OAc)_2{\cdot}H_2O$/HOAc/r.t.; (ix) HOAc−MeOH−H_2O (2:1:1)/90°C; (x) 2N KOH/MeOH/60°C; (xi) *N*-hydroxy-2-pyridinethione/dicyclohexylcarbodiimide/(DCC)/4-*N*,*N*-dimethylsminopyridine (DMAP); (xii) *t*-BuSH/hν; (xiii) NaH/DMSO; (xiv) $(CH_3)_3SI$/THF/r.t.; (xv) $AlClH_2$/THF/refl.

been presented in previous reviews (*1,2*). These are less important today, when structural determinations are made in other ways, and interested readers are referred to Koskinen and Lounasmaa (*3*) and Saxton (*4*). A titre d'examples, here are some recent transformations.

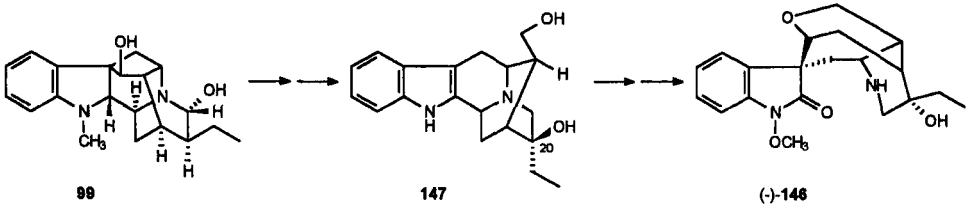
E-Akuammidine (**53**) can be transformed to vellosimine (**1**) as shown in Scheme 13 (*19*). Vincamajine (**145**) can be oxidized to voachalotinal (**63**), which, by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) treatment, is transformed to 17-hydroxy-6,17-*O*-dehydrovoachalotine (**69**) (Scheme 14) (*181*). In connection with the partial synthesis of (−)-20-hydroxydihydrorankinidine [(−)-**146**] from ajmaline (**99**), the sarpagine analog **147** is obtained as an intermediate (Scheme 15) (*217*). In a similar way, gardnerine (**26**) is transformed either directly or via *E*-koumidine (16-epinormacusine B) (**5**) to several *Gelsemium* alkaloids, for example, to gelsemicine (**148**) and gelsedine (**149**) (Scheme 16) (*218,219*). Finally, we would like to underline in this connection



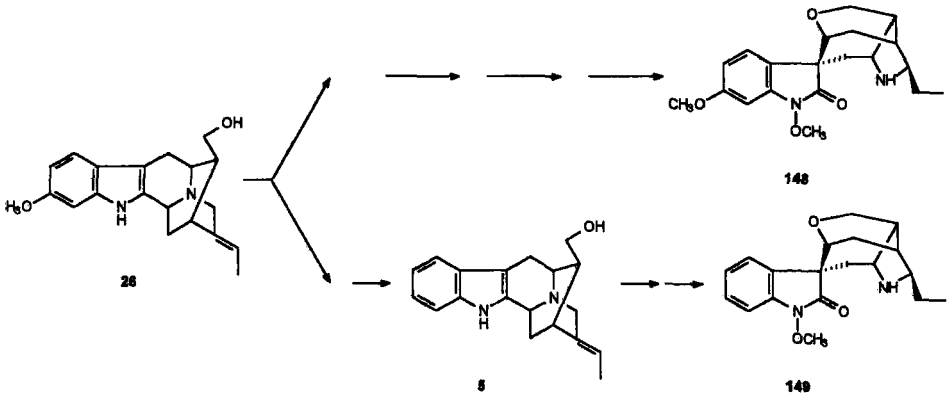
SCHEME 13. Transformation of *E*-akuammidine (**53**) to vellosimine (**1**). Reagents: (i) pyridinium chlorochromate (PCC); (ii) 2 M KOH/MeOH; (iii) 2 M HCl/heat.



SCHEME 14. Transformation of vincamajine (**145**) to voachalotinal (**63**) and 17-hydroxy-6,17-*O*-dehydrovoachalotine (**69**). Reagents: (i) CrO_3/py; (ii) DDQ/THF/H_2O.



SCHEME 15. Formation of the sarpagine analogue **147** as an intermediate in the transformation of (−)-ajmaline [(−)-**99**] to (−)-20-hydroxydihydrorankinidine [(−)-**146**].

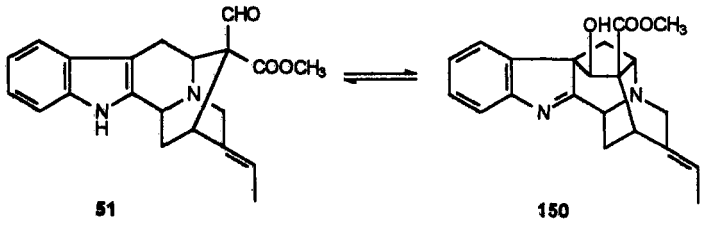


SCHEME 16. Transformation of gardnerine (**26**) to gelsemicine (**148**) and gelsedine (**149**).

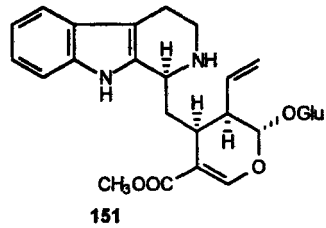
the generally easy interconversion between sarpagine and ajmaline derivatives, schematically indicated here for polyneuridine aldehyde (**51**) and the not yet naturally found 1,2-didehydroquebrachidine (**150**) (Scheme 17).

V. Biosynthesis and Biogenesis

The general role played by strictosidine (**151**) (Fig. 8) in the biosynthesis of all monoterpenoid indole alkaloids is firmly established (*220–224*). In the biogenetic formation of sarpagine (and ajmaline) alkaloids, the van Tamelen proposal (*201,202*) has been generally accepted (*213,222,223*), that is, that formation of a bond between C-5 and C-16 in the intermediate 4,5-



SCHEME 17. Interconversion between sarpagine and ajmaline derivatives.



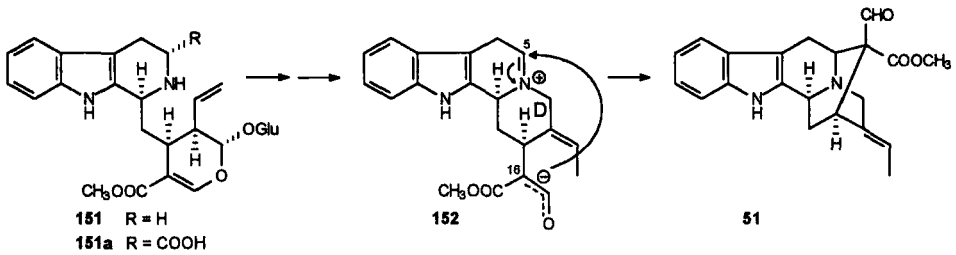
151

FIG. 8. Structure of strictosidine (**151**).

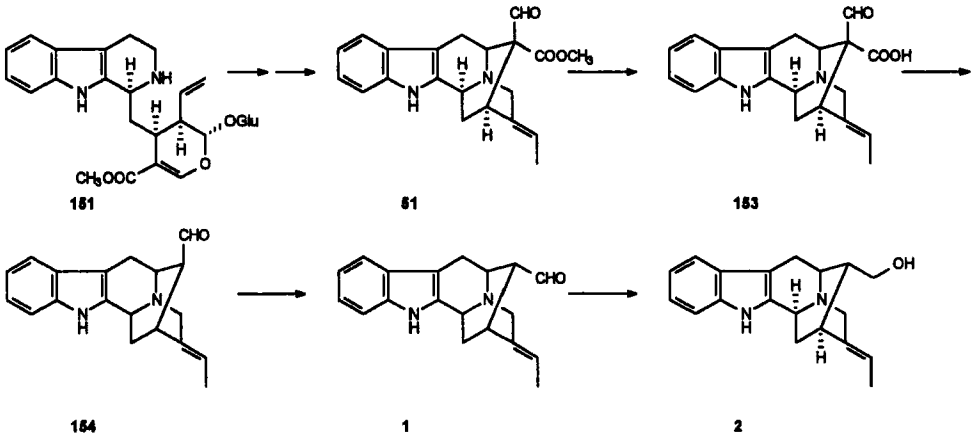
dehydrogeissoschizine ($\Delta^{4(5)}$-iminium system) (**152**) leads to the sarpagan skeleton (**152** → **51**). In explaining the formation of the $\Delta^{4(5)}$-iminium system **152,** van Tamelen suggested that 5α-carboxystrictosidine (**151a**), not strictosidine (**151**) itself, was the key intermediate. However, Stöckigt (*225*) was able to show that 5α-carboxystrictosidine (**151a**) was not involved (Scheme 18).

In several brilliant pieces of work, Stöckigt *et al.* (*8,226–229*) were able to clarify the enzymatic transformation of strictosidine (**151**) to sarpagan-type compounds (**151** → **51** → **153** → **154** → **1** → **2,** Scheme 19). However, the crucial question at which stage the bond formation between C-5 and C-16 takes place (**151** → **51**) remained open (*230*).

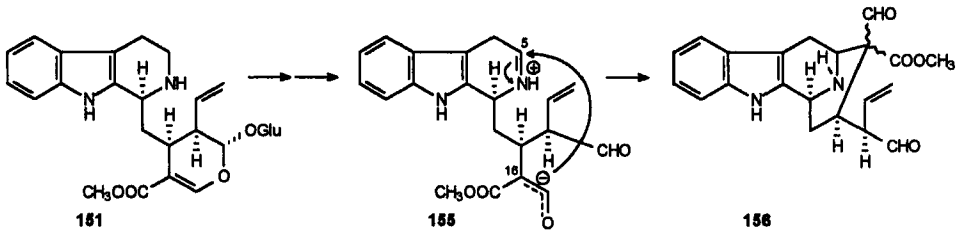
In a recent paper, Lounasmaa and Hanhinen (*204*) presented evidence to suggest that the bond formation between C-5 and C-16 takes place not *after,* as had been generally accepted (*222–224*), but *before* the D-ring formation (**151** → **155**→ **156,** Scheme 20). Once intermediate **156** is formed, transformation to sarpagine (and eventually to ajmaline) structures can take place by normal biogenetic routes (e.g., **156** → **157** → **158,** Scheme 21).



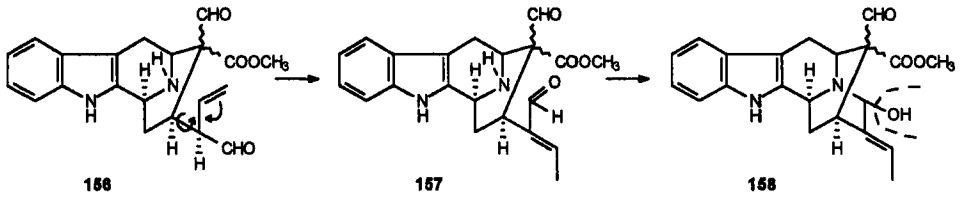
SCHEME 18. The van Tamelen proposal for the biogenetic formation of the sarpagan skeleton.



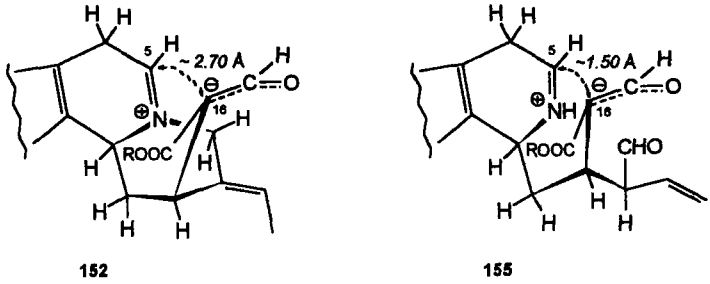
SCHEME 19. The enzymatic transformation of strictosidine (**151**) to sarpagan-type compounds according to Stöckigt *et al.*



SCHEME 20. The Lounasmaa and Hanhinen proposal for the bond formation between C-5 and C-C-16.



SCHEME 21. Transformation of intermediate **156** to sarpagine structures.



152 155

FIG. 9. The shortest possible distances between the reactive sites C-5 and C-16 in intermediates **152** and **155.**

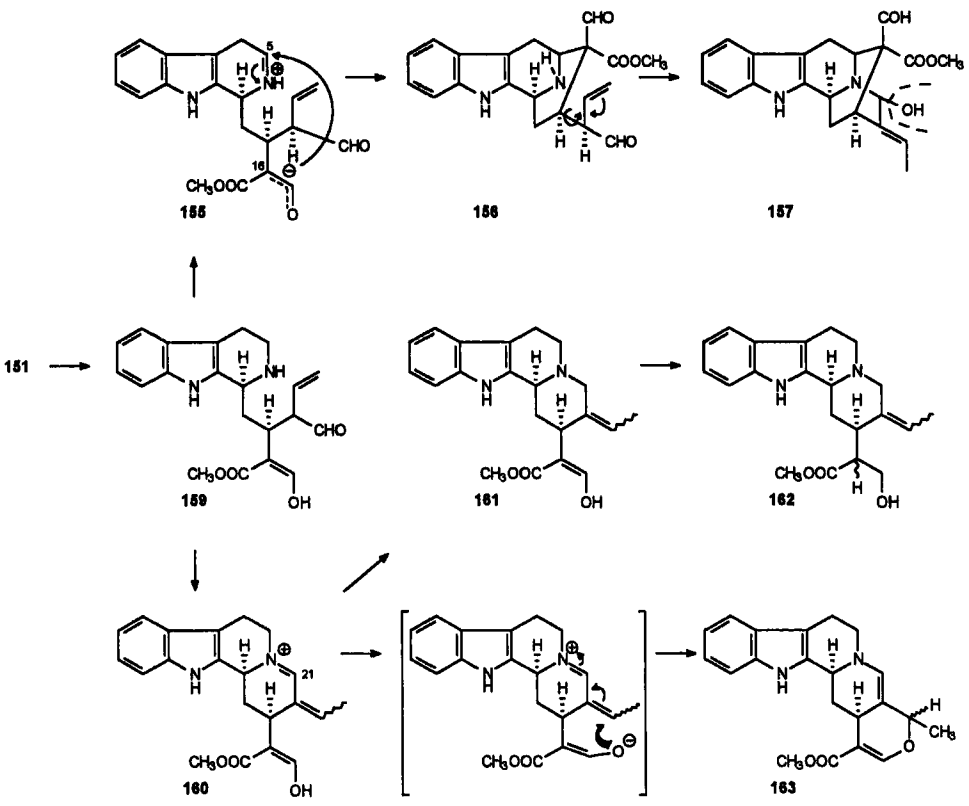
The main argument advanced by Lounasmaa and Hanhinen (*203*) in rejecting the van Tamelan proposal (*201,202*) was that the shortest possible distance between the reactive sites C-5 and C-16 in intermediate **152** is about 2.70 Å (Fig. 9), which is far too large to permit bond formation between C-5 and C-16. In the alternative proposal where the bond formation takes place before the D-ring formation, the minimal distance between the reactive sites C-5 and C-16 in intermediate **155** is about 1.50 Å, which is suitable for bond formation (Fig. 9).

Altogether this means that in the general biogenetic formation of monoterpenoid indole alkaloids possessing the unrearranged skeletal system (corynantheane skeleton) (*222–224*), the route leading to the sarpagine (and ajmaline) structures takes a course of its own (**159** → **155** → **156** → **157**) before the formation of intermediate 4,21-dehydrogeissoschizine (**160**) which can then lead to geissoschizines (**161**), isositsirikines (**162**), and cathenamines (**163**) (Scheme 22, among others).

VI. Spectroscopy

A. ^{1}H NMR Spectroscopy

Modern high-field ^{1}H NMR techniques (correlated spectroscopy (COSY), heteronuclear chemical shift correlation (HETCOR), nuclear Overhauser enhancement (NOE), etc.), which generally permit determination of the chemical shifts and coupling constants of all protons (and connectivities between certain groups), have greatly simplified the structural determination of organic natural products (e.g., *231–235*). This has certainly been the case in the field of sarpagine alkaloids.



SCHEME 22. General biogenetic formation of monoterpenoid indole alkaloids possessing the unrearranged skeletal system.

The ^{1}H NMR spectral data for sarpagine alkaloids are presented in Table III. High-field data (≥200 MHz) are reported where available, but for some compounds only older data measured by low-field techniques ("early days") were available, and these were not always complete. As these data were judged to be useful for comparison, even in the future, they are nevertheless included in Table III. It may be added that caution is needed in utilizing earlier spectral data, as they often contain errors.

There has been much confusion in the literature in assigning the ^{1}H NMR spectral data (*32,59,60,105,107,159,236–238*). For example, the structure referred to in Mukhopadhyay *et al.* (*160*) as polyneuridine (**54**) in reality represents its C-16 epimer *E*-akuammidine (**53**), and the ^{1}H NMR data given for polyneuridine are those of *E*-akuammidine. The ^{1}H NMR data

TABLE III

^{1}H NMR AND MASS SPECTRAL DATA OF INDIVIDUAL ALKALOIDS

(+)-Vellosimine [(+)-**1**]

^{1}H NMR (500 MHz, $CDCl_3$): 1.65 (3H, dt, J = 7 Hz, J = 2 Hz, H-18), 4.22 (1H, dd, J = 10 Hz, J = 2 Hz, H-3), 5.38 (1H, q, J = 7 Hz, $J \sim$ 1 Hz, H-19), 7.11 (1H, t, J = 7 Hz), 7.19 (1H, t, J = 7 Hz), 7.35 (1H, d, J = 7 Hz), 7.48 (1H, d, J = 7 Hz), 7.81 (1H, s, NH), 9.67 (1H, d, $J \leq$ 1 Hz, –CHO). (*227*)

MS: 292 (M^+), 291, 263, 249, 182, 169, 168. (*19*)

Normacusine B (**2**)

^{1}H NMR (400 MHz, $CDCl_3$): 1.63 (3H, br d, $J_{18,19}$ = 7 Hz, H-18), 1.74 (1H, ddd, $J_{14\alpha,14\beta}$ = 13 Hz, $J_{14\beta,15} \sim$ 3 Hz, $J_{3,14\beta} \sim$ 2 Hz, H-14β), 1.85 (1H, dddd, $J_{16,17}$ = 8.5 Hz, $J_{16,17'}$ = 6 Hz, $J_{15,16} \sim$ 1.5 Hz, $J_{5,16} \sim$ 1 Hz, H-16), 2.04 (1H, ddd, $J_{14\alpha,14\beta}$ = 13 Hz, $J_{3,14\alpha}$ = 11 Hz, $J_{14\alpha,15}$ = 2 Hz, H-14α), 2.64 (1H, br d, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\beta} \sim$ 1.5 Hz, H-6β), 2.8 (2H, m, H-5, H-15), 3.07 (1H, dd, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\alpha}$ = 5 Hz, H-6α), 3.52 (1H, dd, $J_{17,17'}$ = 11 Hz, $J_{16,17}$ = 8.5 Hz, H-17), 3.55 (2H, def, 2 × H-21), 3.59 (1H, dd, $J_{17,17'}$ = 11 Hz, $J_{16,17'}$ = 6 Hz, H-17′), 4.16 (1H, br d, $J_{3,14\alpha}$ = 11 Hz, $J_{3,14\beta} \sim$ 2 Hz, H-3), 5.38 (1H, br q, $J_{18,19}$ = 7 Hz, H-19), 7.09 (1H, t, H-10), 7.14 (1H, t, H-11), 7.31 (1H, d, H-12), 7.46 (1H, d, H-9), 7.91 (1H, br s, NH). (*239*), see also (*32*), (*58*), (*59*), (*60*), (*61*)

MS: 294 (M^+, 100%), 293, 279, 277, 263, 249, 182, 169 (100%), 168, 156. (*58*), see also (*27*), (*60*)

Koumidine (**3**)

^{1}H NMR (360 MHz, DMSO-d_6): 1.54 (3H, d, J = 6.7 Hz, H-18), 1.72 (2H, m, 2 × H-14), 2.04 (1H, m, H-16), 2.35 (1H, m, H-15), 2.69 (1H, dd, J = 15.7 Hz, J = 5.6 Hz, H-6α), 2.84 (1H, d, J = 15.7 Hz, H-6β), 2.92 (1H, dd, J = 15.7 Hz, J = 5.6 Hz, H-17), 3.27 (1H, dd, J = 10.4 Hz, J = 6.4 Hz, H-17), 3.42 (1H, m, J = 5.3 Hz, H-5), 3.30–3.60 (2H, 2 × H-21), 3.98 (1H, dd, J = 9.3 Hz, J = 3.6 Hz, H-3), 5.23 (1H, q, J = 6.7 Hz, H-19), 6.92 (1H, ddd, J = 7.0 Hz, J = 7.0 Hz, J = 1.4 Hz, H-10), 7.00 (1H, ddd, J = 7.0 Hz, J = 7.0 Hz, J = 1.4 Hz, H-11), 7.26 (1H, dd, J = 7.0 Hz, J = 1.4 Hz, H-12), 7.34 (1H, dd, J = 7.0 Hz, J = 1.4 Hz, H-9), 10.79 (1H, s, NH). (*64*), see also (*63*), (*248*)

MS: 294 (M^+, 100%), 293, 263, 249, 182, 169, 168. (*248*), see also (*63*)

(*continues*)

TABLE III (*Continued*)

Deoxyperaksine (**4**)
^{1}H NMR: No data available.
MS: 294 (M^+), 293 (100%), 207, 169, 168, 147. (*44b*)

16-Epinormacusine B (**5**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.55 (3H, dt, J = 6.8 Hz, J = 1.9 Hz, H-18), 1.69–1.84 (2H, m, 2 × H-14), 2.03–2.15 (1H, m, H-16), 2.81 (1H, q, J = 3.0 Hz, H-15), 2.83–2.89 (2H, m, 2 × H-6), 3.07 (1H, dd, J = 10.8 Hz, J = 8.9 Hz, H-17), 3.39 (1H, dd, J = 10.8 Hz, J = 6.3 Hz, H-17), 3.46–3.56 (3H, m, H-5, 2 × H-21), 4.04 (1H, dd, J = 9.0 Hz, J = 4.3 Hz, H-3), 5.18 (1H, br q, J = 6.8 Hz, H-19), 6.97 (1H, td, J = 7.2 Hz, J = 1.0 Hz, H-10), 7.03 (1H, td, J = 7.2 Hz, J = 1.0 Hz, H-11), 7.22 (1H, br d, J = 7.2 Hz, H-12), 7.35 (1H, br d, J = 7.2 Hz, H-9), 9.45 (1H, s, NH). (*32*)
MS: 294 (M^+, 100%), 293, 279, 277, 263, 249, 195, 182, 169, 168, 156, 144, 130. (*32*)

N_a-Methylvellosimine (**6**)
^{1}H NMR (60 MHz, DMSO-d_6): 1.65 (3H, d, H-18), 2.52 (3H, s, N–CH_3), 5.45 (1H, q, H-19), 7.01–7.65 (4H, m, H-9, H-10, H-11, H-12), 9.52 (1H, s, –CHO). (*18*)
MS: 306 (M^+), 305, 291, 278, 277 (100%), 263, 249, 235, 196, 183, 182, 181, 170, 168, 144. (*18*)

Dehydro-16-epiaffinisine (**7**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.66 (3H, dt, J = 6.8 Hz, J = 2.0 Hz, H-18), 1.81–1.98 (2H, m, 2 × H-14), 2.24–2.36 (1H, m, H-16), 2.84 (1H, q, J = 3.1 Hz, H-15), 3.43 (1H, t, J = 9.5 Hz, H-17), 3.63 (3H, s, N–CH_3), 3.72–3.87 (4H, m, H-5, H-17, 2 × H-21), 4.09 (1H, dd, J = 9.8 Hz, J = 4.0 Hz, H-3), 5.33 (1H, qt, J = 6.8 Hz, J = 2.0 Hz, H-19), 5.63 (1H, d, J = 7.6 Hz, H-6), 7.15 (1H, td, J = 7.7 Hz, J = 1.2 Hz, H-10), 7.22 (1H, td, J = 7.7 Hz, J = 1.2 Hz, H-11), 7.30 (1H, dd, J = 7.7 Hz, J = 1.2 Hz, H-12), 7.72 (1H, dd, J = 7.7 Hz, J = 1.2 Hz, H-9). (*32*)
MS: 306 (M^+, 100%), 305, 291, 289, 277, 275, 249, 196, 183, 182, 168. (*32*)

Affinisine (**8**)
^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (1H, dd(d), $J_{14\alpha,14\beta}$ = 12 Hz, $J_{14\beta,15} \sim$ 3 Hz, $J_{3,14\beta} \sim$ 2 Hz, H-14β), 1.60 (3H, d(dd), $J_{18,19}$ = 7 Hz, H-18), 1.74 (1H, br dd, $J_{16,17} = J_{16,17'} \sim$ 7 Hz, $J_{15,16} \sim$ 3 Hz, $J_{5,16} \sim$ 2 Hz, H-16), 2.03 (1H, dd(d), $J_{14\alpha,14\beta}$ = 12 Hz, $J_{3,14\alpha}$ = 10 Hz, $J_{14\alpha,15} \sim$ 3 Hz, H-14α), 2.62 (1H, d(d), $J_{6\alpha,6\beta}$ = 15 Hz, $J_{5,6\beta} \sim$ 1 Hz, H-6β), 2.74 (1H, m, H-5), 2.75 (1H, m, H-15), 3.03 (1H, dd, $J_{6\alpha,6\beta}$ = 15 Hz, $J_{5,6\alpha}$ = 5 Hz, H-6α), 3.44 (1H, dd, $J_{16,17} \sim$ 7 Hz, H-17), 3.51 (1H, dd, $J_{16,17'} \sim$ 7 Hz, H-17), 3.54 (1H, d def, H-21), 3.58 (1H, d def, H-21), 3.63 (3H, s, N–CH_3), 4.18 (1H, dd, $J_{3,14\alpha}$ = 10 Hz, $J_{3,14\beta} \sim$ 2 Hz, H-3), 5.37 (1H, br q, $J_{18,19}$ = 7 Hz, H-19), 7.09 (1H, H-10), 7.19 (1H, H-11), 7.32 (1H, H-12), 7.44 (1H, H-9). (*236*), see also (*32*), (*61*)
MS: 308 (M^+), 263. (*69*)

O-Methylnormacusine B (**9**)
^{1}H NMR: No data available.
MS: 308 (M^+), 307, 294, 293, 279, 277, 263, 185, 184, 169 (100%), 168, 167, 156, 154. (*40*), see also (*71*)

16-Epiaffinisine (**10**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.59–1.67 (1H, m, H-14), 1.63 (3H, dt, J = 6.8 Hz, J = 1.9, Hz, H-18), 1.79 (1H, br dd, J = 12.7 Hz, J = 10.3 Hz, H-14), 1.97–2.09 (1H, m, H-16), 2.75–2.84 (3H, m, 2 × H-6, H-15), 3.07 (1H, dd, J = 10.6 Hz, J = 8.8 Hz, H-17), 3.31–3.42 (1H, m, H-5), 3.36 (1H, dd, J = 10.6 Hz, J = 6.6 Hz, H-17), 3.55 (3H, s, N–CH_3), 3.56–3.62 (2H, m, 2 × H-21), 4.07 (1H, dd, J = 10.3 Hz, J = 3.1 Hz, H-3), 5.22 (1H, br q, J = 6.8 Hz, H-19), 7.08 (1H, td, J = 7.0 Hz, J = 1.2 Hz, H-10), 7.18 (1H, td, J = 7.0 Hz, J = 1.2 Hz, H-11), 7.27 (1H, br d, J = 7.0 Hz, H-12), 7.40 (1H, br d, J = 7.0 Hz, H-9). (*32*)
MS: 308 (M^+, 100%), 307, 293, 291, 277, 263, 249, 196, 183, 182, 168, 157, 154. (*32*)

Macusine B (**11**)
^{1}H NMR (400 MHz, D_2O)[a]: 1.60 (3H, d, $J_{18,19}$ = 6.5 Hz, H-18), 1.87 (1H, def, H-14b), 1.87 (1H, def, H-16), 2.37 (1H, t, $J_{14a,14b}$ = 12 Hz, $J_{3,14a}$ = 11 Hz, H-14a), 2.90 (3H, s, N^+–CH_3), 2.90 (1H, def, H-6b), 2.90 (1H, def, $J_{14b,15}$ = 3 Hz, H-15), 3.10 (1H, dd, $J_{6a,6b}$ = 17 Hz, $J_{5,6a}$ = 5 Hz, H-6a), 3.32 (1H, t, $J_{5,6a}$ = 5 Hz, H-5), 3.46 (2H, m, 2 × H-17), 4.05 (1H, d, $J_{21a,21b}$ = 15.5 Hz, H-21a), 4.25 (1H, d, $J_{21a,21b}$ = 15.5 Hz, H-21b), 4.75 (1H, def, H-3), 5.58 (1H, q, $J_{18,19}$ = 6.5 Hz, H-19), 7.14 (1H, t, $J_{9,10}$ = 8 Hz, $J_{10,11}$ = 7.5 Hz, H-10), 7.23 (1H, t, $J_{11,12}$ = 8 Hz, $J_{10,11}$ = 7.5 Hz, H-11), 7.47 (1H, d, $J_{11,12}$ = 8 Hz, H-12), 7.51 (1H, d, $J_{9,10}$ = 8 Hz, H-9). (*116*)
MS: 308 (M^+-1), 295, 294 (100%), 293, 279, 277, 263, 249, 185, 183, 169, 168, 156, 143, 130. (*74*)

(+)-Sarpagine [(+)-**12**]
^{1}H NMR (200 MHz, $CDCl_3$:DMSO-d_6 1:1): 1.55 (3H, d, J = 7 Hz, H-18), 3.96 (1H, br d, H-17), 5.27 (1H, q, J = 7 Hz, H-19), 6.48–6.96 (3H, H-9, H-11, H-12), 10.08 (1H, s, NH). (*92*)
MS: 310 (M^+), 309, 295, 293, 279, 265, 200, 198, 185 (100%), 184, 172, 155. (*246*)

Peraksine (**13**)
^{1}H NMR (100 MHz, $CDCl_3$:CD_3OD 1:1): 1.40 (3H, d, J = 6.7 Hz, H-18), 1.50 (1H, m, H-16), 3.22 (1H, H-19), 4.58, 4.98 (1H, H-17, two epimeric forms), 6.96–7.50 (4H, m, H-9, H-10, H-11, H-12). (*21*)
MS: 310 (M^+), 309 (100%), 292, 281, 209, 207, 195, 182, 169, 168, 156. (*249*)

Ervincidine (**14**)
^{1}H NMR: No data available.
MS: 310 (M^+), 309, 292, 279, 249, 182, 169 (100%), 168. (*100b*)

(*continues*)

(+)-16-Episarpagine [(+)-**15**]
^{1}H NMR (DMSO-d_6): 1.57 (3H, d, J = 7 Hz, H-18), 5.34 (1H, q, J = 7 Hz, H-19), 6.52 (1H, dd, J = 9 Hz, J = 2 Hz, H-11), 6.70 (1H, d, J = 2 Hz, H-9), 7.06 (1H, d, J = 9 Hz, H-12), 9.10 (1H, br s, NH), 10.80 (1H, s, Ar–OH). (*101*)
MS: 310 (M^+, 100%), 309, 295, 293, 279, 265, 198, 185, 184, 172, 159. (*101*)

(−)-Trinervine [(−)-**16**]
^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD 3:1): 1.38 (1H, m, H-16), 1.40 (3H, s, H-18), 1.64 (1H, m, H-14), 1.68 (1H, m, H-20), 1.89 (1H, m, H-14), 2.28 (1H, m, H-15), 2.60 (1H, d, J = 15.6 Hz, H-6), 2.96 (1H, dd, J = 13.7 Hz, J = 3.5 Hz, H-21), 3.08 (1H, dd, J = 13.7 Hz, J = 10.3 Hz, H-21), 3.12 (1H, dd, J = 15.6 Hz, J = 5.8 Hz, H-6), 3.39 (1H, t, J = 5.8 Hz, H-5), 3.47 (1H, dd, J = 10.7 Hz, J = 1.0 Hz, H-17), 4.01 (1H, dd, J = 10.3 Hz, J = 1.95 Hz, H-3), 4.06 (1H, d, J = 10.7 Hz, H-17), 7.03 (1H, t, J = 7.8 Hz, H-10), 7.10 (1H, t, J = 7.8 Hz, H-11), 7.33 (1H, d, J = 7.8 Hz, H-12), 7.43 (1H, d, J = 7.8 Hz, H-9). (*57*)
MS: 310 (M^+), 309, 292, 291, 182, 169, 168. (*57*)

Dihydroperaksine (**17**)
^{1}H NMR: No data available.
MS: 312 (M^+, 100%), 311, 295, 281, 239, 169, 168, 156. (*44b*)

(+)-Pericyclivine [(+)-**18**]
^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (3H, ddd, $J_{18,19}$ = 7 Hz, $J_{18,21\alpha}$ = $J_{18,21\beta}$ = 2 Hz, H-18), 1.76 (1H, ddd, $J_{14\alpha,14\beta}$ ~ 13 Hz, $J_{3,14\alpha}$ = 10.5 Hz, $J_{14\alpha,15}$ ~ 2 Hz, H-14α), 2.58 (1H, ddd, $J_{14\alpha,14\beta}$ ~ 13 Hz, $J_{14\beta,15}$ = 4.5 Hz, $J_{3,14\beta}$ = 2 Hz, H-14β), 2.82 (1H, dd, $J_{5,16}$ = 11 Hz, $J_{15,16}$ = 2.5 Hz, H-16), 2.91 (1H, dd, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\alpha}$ = 5 Hz, H-6α), 2.96 (1H, m, H-15), 3.07 (3H, s, –$COOCH_3$), 3.24 (1H, dd, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\beta}$ = 1.5 Hz, H-6β), 3.6 (2H, m, 2 × H-21), 3.68 (1H, ddd, $J_{5,16}$ = 11 Hz, $J_{5,6\alpha}$ = 5 Hz, $J_{5,6\beta}$ = 1.5 Hz, H-5), 4.21 (1H, br d, $J_{3,14\alpha}$ = 10.5 Hz, $J_{3,14\beta}$ = 2 Hz, H-3), 5.27 (1H, br q, $J_{18,19}$ = 7 Hz, H-19), 7.04 (1H, t, H-10), 7.10 (1H, t, H-11), 7.28 (1H, d, H-12), 7.41 (1H, d, H-9), 7.78 (1H, br s, NH). (*239*), see also (*59*)
MS: 322 (M^+), 321, 307, 263, 249, 169, (100%), 168. (*60*)

10-Methoxyvellosimine (**19**)
^{1}H NMR: 1.50 (3H, d, J = 7 Hz, H-18), 3.58 (3H, s, Ar–OCH_3), 5.0 (1H, q, J = 7.0 Hz, H-19), 9.0 (1H, s, –CHO). (*250*)
MS: 322 (M^+), 293 (100%), 279, 212, 199, 198, 182, 169, 168. (*250*)

Gardnutine (**20**)
^{1}H NMR (DMSO-d_6 + CF_3COOH): 1.69 (3H, d, J = 7 Hz, H-18), 2.17 (2H, br s, 2 × H-14), 3.10 (1H, m, H-15), 3.37 (1H, t, J = 10 Hz, H-17), 3.77 (3H, s, Ar–OCH_3), 3.81 (1H, m, H-17), 4.23 (2H, br s, 2 × H-21), 4.87 (1H, m, H-3), 4.36 (1H, d, J = 7.5 Hz, H-5), 5.50 (1H, d, J = 7 Hz, H-19), 5.65 (1H, d, J = 7.5 Hz, H-6), 11.28 (1H, s, NH). (*251*)
MS: 322 (M^+), 199, 198 (100%). (*251*)

Panarine (**21**)
^{1}H NMR (400 MHz, D_2O): 1.58 (3H, d, $J_{18,19}$ = 6.7 Hz, H-18), 2.08 (1H, dd, $J_{14a,14b}$ = 13 Hz, $J_{14b,15}$ = 4 Hz, H-14b), 2.44 (1H, t, $J_{14a,14b}$ = 13 Hz, $J_{3,14a}$ = 11 Hz, H-14a), 2.50 (1H, d, $J_{5,16}$ = 7 Hz, H-16), 2.87 (1H, d, $J_{6a,6b}$ = 17 Hz, H-6b), 3.01 (3H, s, N^+–CH_3), 3.23 (1H, dd, $J_{6a,6b}$ = 17 Hz, $J_{5,6a}$ = 5 Hz, H-6a), 3.40 (1H, br s, H-15), 4.11 (1H, d, $J_{21a,21b}$ = 15.5 Hz, H-21a), 4.21 (1H, t, $J_{5,16}$ = 7 Hz, H-5), 4.28 (1H, d, $J_{21a,21b}$ = 15.5 Hz, H-21b), 4.80 (1H, def, H-3), 5.50 (1H, q, $J_{18,19}$ = 6.7 Hz, H-19), 7.15 (1H, t, $J_{9,10}$ = 8 Hz, $J_{10,11}$ = 7.5 Hz, H-10), 7.25 (1H, t, $J_{11,12}$ = 8 Hz, $J_{10,11}$ = 7.5 Hz, H-11), 7.47 (1H, d, $J_{11,12}$ = 8 Hz, H-12), 7.52 (1H, d, $J_{9,10}$ = 8 Hz, H-9). (*116*), see also (*117*)
MS: 336 (M^+ + Me), 322 (M^+, 100%), 307, 291, 263, 249, 235, 207, 182, 169, 168, 154, 140. (*116*)

16-Epipanarine (**22**)
^{1}H NMR (400 MHz, CD_3OD): 1.72 (3H, ddd, J = 7 Hz, J = 1.5 Hz, J = 1.5 Hz, H-18), 2.26 (1H, ddm, J = 12 Hz, J = 10.5 Hz, H-14), 3.03 (1H, br dd, J = 11.5 Hz, J = 2.5 Hz, H-16), 3.06[b] (1H, H-14), 3.10 (3H, s, N^+–CH_3), 3.11[b] (1H, d, J = 5.5 Hz, H-6), 3.20 (1H, br s, H-15), 4.16 (1H, br d, J = 17.5 Hz, H-6), 4.26 (1H, dd, J = 11.5 Hz, J = 5.5 Hz, H-5), 4.31 (1H, br d, J = 16.5 Hz, H-21), 4.43 (1H, dm, J = 16.5 Hz, H-21), 4.80 (1H, br d, J = 10.5 Hz, H-3), 5.44 (1H, br q, J = 7 Hz, H-19), 7.01 (1H, ddd, J = 8 Hz, J = 8 Hz, J = 1 Hz, H-10), 7.11 (1H, ddd, J = 8 Hz, J = 8 Hz, J = 1 Hz, H-11), 7.30 (1H, dd, J = 8 Hz, J = 1 Hz, H-12), 7.47 (1H, dd, J = 8 Hz, J = 1 Hz, H-9). (*117*)
MS: 336 (M^+ + Me), 322 (M^+, 100%), 307, 291, 263, 249, 235, 207, 182, 169, 168, 154. (*117*)

O-Methylmacusine B (**23**)
^{1}H NMR (90 MHz, D_2O): 1.73 (3H, d, J = 7 Hz, H-18), 2.99 (3H, s, N–CH_3), 3.38 (3H, s, –OCH_3), 5.05 (1H, q, H-19), 7.30–7.69 (4H, m, H-9, H-10, H-11, H-12). (*75*)
MS: 323 (M^+), 322, 308, 294, 293, 279, 277, 276, 263, 185, 184, 183, 182, 180, 169, 168 (100%), 167, 156, 154. (*118*), see also (*78*)

O-Methyl-16-epimacusine B (**24**)
^{1}H NMR: No data available.
MS: 323 (M^+), 322, 308, 294, 293, 279, 277, 276, 263, 185, 183, 182, 180, 169, 168 (100%), 167, 156, 154. (*118*)

(+)-Lochnerine [(+)-**25**]
^{1}H NMR ($CDCl_3$:CD_3OD 1:1): 1.60 (3H, d, H-18), 3.85 (3H, s, Ar–OCH_3), 5.35 (1H, q, H-19), 6.7–7.3 (3H, H-9, H-11, H-12), 9.3 (1H, br s, NH). (*82*)
MS: 324 (M^+, 100%), 293, 199, 198. (*128*)

Gardnerine (**26**)
^{1}H NMR (CF_3 COOH): 1.79 (3H, d, J = 7 Hz, H-18). (*251*)
MS: 324 (M^+), 306, 293, 212, 199, 198 (100%), 184, 155. (*251*)

N_a-Methylsarpagine (**27**)
^{1}H NMR: No data available.
MS: No data available.

(*continues*)

TABLE III (*Continued*)

Talpinine (**28**)

^{1}H NMR (100 MHz, $CDCl_3$): 1.28 (3H, d, J = 7 Hz, H-18), 2.61 (1H, d, J = 15 Hz, H-6β), 3.22 (1H, dd, J = 15 Hz, J = 6 Hz, H-6α), 3.41 (1H, dd, J = 11 Hz, J = 2 Hz, H-17), 3.55 (3H, s, N–CH_3), 3.62 (1H, t, J = 11 Hz, H-17), 4.03 (1H, q, J = 7 Hz, H-19), 4.37 (1H, dd, $J_{3,14\beta}$ = 10 Hz, $J_{3,14\alpha}$ = 2 Hz, H-3), 4.67 (1H, d, J = 1.5 Hz, H-21), 6.96–7.37 (3H, m, H-10, H-11, H-12), 7.46 (1H, d, J = 7 Hz, H-9). (*125*)

MS: 324 (M^+), 323, 296, 251, 237, 225, 196, 183 (100%), 182, 181, 170, 168. (*125*)

Lochvinerine (**29**)

^{1}H NMR (60 MHz, $CDCl_3$): 1.57 (3H, d, J = 7 Hz, H-18), 2.08 (1H, s, –OH), 5.29 (1H, q, H-19), 6.75 (1H, dd, J = 8 Hz, J = 2.5 Hz, H-11), 6.89 (1H, d, J = 2.5 Hz, H-9), 7.13 (1H, d, J = 8 Hz, H-12), 8.06 (1H, s, NH). (*126*)

MS: 324 (M^+), 323, 307, 293, 279, 212, 199 (100%), 198. (*126*)

O-Methylnormacusine B N_b-oxide (**30**)

^{1}H NMR: No data available.

MS: 324 (M^+), 308, 294, 293, 279, 207, 189, 185, 168 (100%), 146, 143, 130 (*40*)

Affinisine N_b-oxide (**31**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.52 (3H, br d, J = 6.7 Hz, H-18), 1.62 (1H, br d, J = 12 Hz, H-14), 1.87 (1H, br q, J = 7 Hz, H-16), 2.19 (1H, br dd, J = 12.0 Hz, J = 10.0 Hz, H-14), 2.52 (1H, br s, H-15), 2.59 (1H, d, J = 15.6 Hz, H-6), 3.03 (1H, br dd, J = 7.0 Hz, J = 4.5 Hz, H-5), 3.13–3.28 (2H, m, 2 × H-17), 3.39 (1H, dd, J = 15.6 Hz, J = 4.5 Hz, H-6), 3.53 (3H, s, N–CH_3), 3.88 (1H, br d, J = 15.9 Hz, H-21), 4.43 (1H, br d, J = 10.0 Hz, H-3), 4.57 (1H, br d, J = 15.9 Hz, H-21), 5.26 (1H, br q, J = 6.7 Hz, H-19), 7.04 (1H, br t, J = 7.1 Hz, H-10), 7.19 (1H, br t, J = 7.1 Hz, H-11), 7.26 (1H, br d, J = 7.1 Hz, H-12), 7.29 (1H, br d, J = 7.1 Hz, H-9). (*32*)

MS: 324 (M^+), 308 (100%), 307, 293, 291, 277, 263, 249, 235, 221, 196, 183, 182, 170, 168, 154. (*32*)

(−)-Alstoumerine [(−)-**32**]

^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (3H, d, $J_{18,19}$ = 6.5 Hz, H-18), 1.63 (2H, m, H-14β, H-16α), 1.89 (1H, ddd, $J_{14\alpha,14\beta}$ = 10.8 Hz, $J_{3\alpha,14\alpha}$ = 2.6 Hz, $J_{14\alpha,15\alpha}$ = 1.2 Hz, H-14α), 2.68 (1H, d, $J_{6\alpha,6\beta}$ = 15.4 Hz, H-6β), 2.8 (1H, br s, H-15α), 3.08 (1H, t, $J_{5\alpha,16\alpha}$ = 12.8 Hz, $J_{5\alpha,6\alpha}$ = 5.6 Hz, H-5α), 3.14 (1H, dd, $J_{6\alpha,6\beta}$ = 15.4 Hz, $J_{5\alpha,6\alpha}$ = 5.6 Hz, H-6α), 3.46 (1H, dd, $J_{17a,17b}$ = 11.4 Hz, $J_{16\alpha,17a}$ = 5.0 Hz, H-17a), 3.55 (3H, s, N–CH_3), 3.64 (1H, dd, $J_{17a,17b}$ = 11.4 Hz, $J_{16\alpha,17b}$ = 5.0 Hz, H-17b), 3.93 (1H, dd, $J_{3\alpha,14\beta}$ = 10.2 Hz, $J_{3\alpha,14\alpha}$ = 2.6 Hz, H-3α), 4.55 (1H, q, $J_{18,19}$ = 6.5 Hz, H-19), 6.58 (1H, d, $J_{15\alpha,21}$ = 1.4 Hz, H-21), 7.08 (1H, m, H-10), 7.18 (1H, m, H-11), 7.30 (1H, dd, $J_{11,12}$ = 8.1 Hz, H-12), 7.50 (1H, dd, $J_{9,10}$ = 7.7 Hz, $J_{9,11}$ = 1.8 Hz, H-9). (*127*)

MS: 324 (M^+, 100%), 307, 293, 281, 182. (*127*)

18-Hydroxyaffinisine (**33**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.7 (1H, dt, J = 12 Hz, J = 3 Hz, H-14), 1.85 (1H, m, H-16), 1.9 (1H, ddd, J = 12 Hz, J = 10 Hz, J = 1.5 Hz, H-14), 2.6 (1H, d, J = 14 Hz, H-6), 2.72 (1H, t, J = 6 Hz, H-5), 3.05 (1H, br s, H-15), 3.08 (1H, dd, J = 14 Hz, J = 6 Hz, H-6), 3.45 (1H, t, J = 10.5 Hz, H-17), 3.6 (2H, m, H-17, H-21), 3.65 (3H, s, N–CH_3), 3.7 (1H, m, H-21), 4.0 (1H, dd, J = 12 Hz, J = 7 Hz, H-18), 4.2 (1H, d, J = 8 Hz, H-3), 4.25 (1H, m, H-18), 5.7 (1H, br t, J = 7 Hz, H-19), 7.1 (1H, t, J = 7 Hz, H-10), 7.2 (1H, t, J = 7 Hz, H-11), 7.3 (1H, d, J = 7 Hz, H-12), 7.45 (1H, d, J = 7 Hz, H-9). (*35*)

MS: 324 (M^+), 323, 322, 309, 307, 293, 214, 183, 182. (*35*)

Spegatrine (**34**)

^{1}H NMR (400 MHz, D_2O): 1.59 (3H, d, $J_{18,19}$ = 6 Hz, H-18), 1.83 (1H, dd, $J_{14\alpha,14\beta}$ = 14 Hz, $J_{3,14\beta}$ = 4 Hz, H-14β), 1.92 (1H, dd, $J_{14\alpha,14\beta}$ = 14 Hz, $J_{3,14\alpha}$ = 8 Hz, H-14α), 2.37 (1H, t, H-15), 2.86 (2H, t, H-6β, H-16), 2.86 (3H, s, N–CH_3), 3.10 (1H, dd, $J_{6\alpha,6\beta}$ = 17 Hz, H-6α), 3.30 (1H, t, $J_{5,6\alpha}$ = $J_{5,6\beta}$ = 6 Hz, H-5), 3.48 (2H, m, $J_{14\beta,17\alpha}$ = 11 Hz, $J_{16,17\beta}$ = 5 Hz, 2 × H-17), 4.06 (1H, d, $J_{21\alpha,21\beta}$ = 16 Hz, H-21 β), 4.27 (1H, d, $J_{21\alpha,21\beta}$ = 16 Hz, H-21α), 4.75 (1H, dd, $J_{3,14\alpha}$ = 8 Hz, $J_{3,14\beta}$ = 4 Hz, H-3), 5.59 (1H, q, $J_{18,19}$ = 6 Hz, H-19), 6.82 (1H, dd, J = 8 Hz, J = 2 Hz, H-11), 6.97 (1H, d, J = 2 Hz, H-9), 7.35 (1H, d, J = 8 Hz, H-12). (*130*)

MS: 324 (M^+-1), 310, 279, 199, 185, 184. (*129*)

Venecurine (**35**)

^{1}H NMR (400 MHz, D_2O)[a]: 1.48 (3H, s, H-18), 1.77 (1H, m, H-16), 2.02 (1H, dd, $J_{14a,14b}$ = 10.4 Hz, H-14b), 2.28 (1H, m, $J_{20,21a}$ = 10.5 Hz, H-20), 2.43 (1H, m, H-14a), 2.47 (1H, m, H-15), 3.03 (1H, d, $J_{6a,6b}$ = 17 Hz, H-6b), 3.07 (3H, s, N^+–CH_3), 3.34 (1H, dd, $J_{6a,6b}$ = 17 Hz, $J_{5,6a}$ = 5 Hz, H-6a), 3.56 (1H, m, $J_{21a,21b}$ ~ 15 Hz, H-21b), 3.60 (1H, m, H-17b), 3.86 (2H, m, H-5, H-21a), 4.04 (1H, d, $J_{17a,17b}$ = 11 Hz, H-17a), 4.79 (1H, dd, $J_{3,14a}$ = 10 Hz, H-3), 7.11 (1H, t, $J_{10,11}$ = 7.5 Hz, $J_{9,10}$ = 7.7 Hz, H-10), 7.19 (1H, t, $J_{11,12}$ = 8 Hz, $J_{10,11}$ = 7.5 Hz, H-11), 7.47 (1H, d, $J_{11,12}$ = 8 Hz, H-12), 7.51 (1H, d, $J_{9,10}$ = 7.7 Hz, H-9). (*131*)

MS: 324 (M^+-1), 309, 291 (100%), 280, 263, 249, 238, 219, 204, 194, 186, 183, 169, 159. (*131*)

19,20-Dihydro-*O*-methylmacusine B (**36**)

^{1}H NMR: No data available.

MS: 325 (M^+), 324, 310 (100%), 295, 279, 223, 183, 180, 169, 168. (*78*)

Difforine (**37**)

^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (3H, d, H-18), 1.73 (1H, dd, $J_{14\alpha,14\beta}$ = 12 Hz, $J_{14\alpha,15}$ = 2 Hz, H-14α), 2.0 (1H, t, $J_{3,14\beta}$ = $J_{14\alpha,14\beta}$ = 12 Hz, H-14β), 2.27 (3H, s, H-24), 2.45 (1H, br t, $J_{5,16}$ = $J_{16,17}$ = 7.5 Hz, $J_{15,16}$ = 1 Hz, H-16), 2.60 (1H, d, $J_{6\alpha,6\beta}$ = 15 Hz, $J_{5,6\alpha}$ = 1 Hz, H-6α), 2.70 (1H, br s, $J_{14\alpha,15}$ = 2 Hz, $J_{15,16}$ = 1 Hz, H-15), 2.98 (1H, m, H-5), 3.03 (1H, m, H-6β), 3.55 (1H, br d, H-21), 3.65 (1H, d, H-21), 4.15 (1H, d, $J_{3,14\beta}$ = 12 Hz, H-3), 5.50 (1H, q, H-19), 6.05 (1H, d, $J_{17,22}$ = 17 Hz, H-22), 6.75 (1H, dd, $J_{17,22}$ = 17 Hz, $J_{16,17}$ = 7.5 Hz, H-17), 7.07 (1H, H-10), 7.13 (1H, H-11), 7.25 (1H, H-12), 7.47 (1H, H-9), 8.55 (1H, NH). (*61*)

MS: 332 (M^+), 331, 289, 249, 235, 182, 170, 169 (100%), 168, 156. (*61*)

(*continues*)

TABLE III (*Continued*)

Majvinine (**38**)

^{1}H NMR (60 MHz, $CDCl_3$): 1.61 (3H, dt, J = 7 Hz, J = 2 Hz, H-18), 3.60 (3H, s, N–CH_3), 3.84 (3H, s, Ar–OCH_3), 5.36 (1H, q, J = 7 Hz, H-19), 6.80 (1H, dd, J = 8 Hz, J = 2.5 Hz, H-11), 6.93 (1H, d, J = 2.5 Hz, H-9), 7.17 (1H, d, J = 8 Hz, H-12), 9.73 (1H, d, J = 1.5 Hz, –CHO). (*132*)

MS: 336 (M^+), 335, 321, 307 (100%), 293, 226, 198. (*132*)

O-Acetylnormacusine B (**39**)

^{1}H NMR ($CHCl_3$): 1.54 (3H, dt, $J_{18,19}$ = 7 Hz, $J_{18,21}$ = 1 Hz, H-18), 1.80 (1H, m, H-14), 1.95 (1H, m, H-14), 1.98 (3H, s, –CO–CH_3), 2.60 (1H, q, $J_{6\alpha,6\beta}$ = 15 Hz, $J_{5,6}$ = 2 Hz, H-6), 2.70 (3H, m, H-5, H-15, H-16), 3.05 (1H, q, $J_{5,6'}$ = 2 Hz, H-6'), 3.53 (2H, m, $J_{18,21}$ = 1 Hz, 2 × H-21), 3.95 (2H, q, $J_{17a,17b}$ = 11 Hz, 2 × H-17), 4.02 (1H, m, H-3), 5.40 (1H, br q, H-19), 7.0–7.5 (4H, H-9, H-10, H-11, H-12), 8.05 (1H, NH). (*52*)

MS: 336 (M^+, 100%), 321, 293, 277, 263, 249, 183, 182, 169, 168, 156. (*47*)

N_a-Methyl-16-epipericyclivine (**40**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (3H, td, J = 7 Hz, J = 2 Hz, H-18), 1.7 (1H, ddd, J = 12 Hz, J = 3 Hz, J = 2 Hz, H-14), 2.1 (1H, ddd, J = 12 Hz, J = 10 Hz, J = 2 Hz, H-14), 2.55 (1H, dd, J = 8 Hz, J = 2 Hz, H-16), 2.7 (1H, dd, J = 12 Hz, J = 2 Hz, H-6), 3.1 (1H, d, J = 12 Hz, H-6), 3.2 (1H, m, H-15), 3.5 (3H, s, N–CH_3), 3.6 (3H, m, H-5, 2 × H-21), 3.6 (3H, s, –$COOCH_3$), 4.2 (1H, dd, J = 10, Hz, J = 2 Hz, H-3), 5.4 (1H, br q, J = 7 Hz, H-19), 7.1 (1H, t, J = 7 Hz, H-10), 7.2 (1H, t, J = 7 Hz, H-11), 7.3 (1H, d, J = 7 Hz, H-12), 7.5 (1H, d, J = 7 Hz, H-9). (*133*)

MS: 336 (M^+, 100%), 335, 321, 305, 277, 263, 196, 183, 182. (*133*), see also (*170*)

N_a-Methylpericyclivine (**41**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.7 (3H, d, J = 7 Hz, H-18), 2.15 (1H, t, J = 12 Hz, H-14), 2.75 (1H, dd, J = 12 Hz, J = 3 Hz, H-14), 2.95 (1H, dd, J = 10 Hz, J = 3 Hz, H-16), 3.1 (3H, s, –$COOCH_3$), 3.18 (1H, m, H-15), 3.4 (3H, s, N–CH_3), 3.45 (1H, dd, J = 18 Hz, J = 2 Hz, H-6), 3.75 (1H, dd, J = 18 Hz, J = 5 Hz, H-6), 4.1–4.25 (3H, m, H-5, 2 × H-21), 5.12 (1H, br d, J = 10 Hz, H-3), 5.55 (1H, q, J = 6.1 Hz, H-19), 7.05–7.3 (3H, m, H-10, H-11, H-12), 7.4 (1H, d, J = 7.6 Hz, H-9. (*35*)

MS: 366 (M^+, 100%), 321, 305, 277, 263, 196, 183, 182, 167, 154. (*35*)

Hydroxygardnutine (**42**)

^{1}H NMR: No data available.

10-Hydroxypericyclivine (**43**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (3H, dt, J = 7 Hz, J = 2 Hz, H-18), 1.8 (1H, dd, J = 12 Hz, J = 11 Hz, H-14α), 2.6 (1H, ddd, J = 12 Hz, J = 4 Hz, J = 2 Hz, H-14β), 2.82 (1H, d, J = 4 Hz, H-16), 2.85 (1H, m, H-6), 2.98 (1H, m, H-15), 3.06 (H-6), 3.1 (3H, s, $-COOCH_3$), 3.6 (m, H-21), 3.7 (1H, m, H-5), 4.2 (1H, d, J = 10 Hz, H-3), 5.6 (1H, br q, J = 7 Hz, H-19), 6.6 (1H, dd, J = 8 Hz, J = 2 Hz, H-11), 6.8 (1H, d, J = 2 Hz, H-9), 7.1 (1H, d, J = 8 Hz, H-12), 7.7 (1H, s, NH). (*133*)[c]
MS: 338 (M^+, 100%), 337, 323, 307, 279, 198, 185, 184. (*133*)

Lochneram (**44**)
^{1}H NMR[a]: 1.55 (3H, d, H-18), 2.82 (3H, s, N^+-CH_3), 3.77 (3H, s, $Ar-OCH_3$), 5.5 (1H, q, H-19), 6.7 (1H, d, J = 9 Hz, H-11), 7.0 (1H, br s, H-9), 7.35 (1H, d, J = 9 Hz, H-12). (*135*)
MS: 338 (M^+-1), 324, 323, 309, 307, 293, 212, 199 (100%). (*135*)

N_a-Methylsarpagine metho salt (**45**)
^{1}H NMR (60 MHz, D_2O)[a]. 1.67 (3H, d, J = 7 Hz, H-18), 2.92 (3H, s, N^+-CH_3), 3.35 (3H, s, $N-CH_3$), 5.60 (1H, q, J ~ 7 Hz, H-19), 6.6–7.1 (2H, m, H-9, H-11), 7.35 (1H, d, J = 9 Hz, H-12). (*135*)
MS: 338 (M^+-1), 324, 309, 307, 293, 212, 199 (100%). (*135*)

Macrosalhine (**46**)
^{1}H NMR (100 MHz, D_2O)[a]: 1.13 (1H, m, H-16), 1.64 (3H, d, J = 7 Hz, H-18), 2.0–2.5 (2H, m, 2 × H-14), 2.87 (3H, s, N^+-CH_3), 3.58 (3H, s, $N-CH_3$), 3.38–3.78 (2H, 2 × d, J ~ 11–12 Hz, 2 × H-17), 4.21 (1H, m, H-19), 4.83 (1H, br d, J ~ 10 Hz, H-3), 5.37 (1H, br s, H-21), 6.7–7.7 (4H, m, H-9, H-10, H-11, H-12). (*136*)
MS: 338 (M^+-1), 320, 251, 223, 197 (100%), 182, 181, 170. (*136*)

18-Hydroxygardnerine (**47**)
^{1}H NMR: No data available.
MS: No data available.

(*continues*)

21-Hydroxycyclolochnerine (**48**)
^{1}H NMR (400 MHz, $CDCl_3$): 1.19[d] (1H, br s, $J_{15,16} = J_{16,17} \leq 2$ Hz, H-16), 1.24 (3H, d, $J_{18,19} \leq 7$ Hz, H-18), 1.30 (1H, d, $J_{14\alpha,14\beta} = 15$ Hz, $J_{3,14\beta} = J_{14\beta,15} \leq 2$ Hz, H-14β), 1.33[d] (1H, br s, $J_{14\alpha,15} = J_{14\beta,15} = J_{15,16} = J_{15,20} \leq 2$ Hz, H-15), 1.83 (1H, dd, $J_{14\alpha,14\beta} = 15$ Hz, $J_{3,14\alpha} = 8$ Hz, $J_{14\alpha,15} \leq 2$ Hz, H-14α), 1.87 (1H, br s, $J_{15,20} = J_{19,20} = J_{20,21} \leq 2$ Hz, H-20), 2.53 (1H, d, $J_{6\alpha,6\beta} = 15$ Hz, $J_{5,6\beta} \leq 2$ Hz, H-6β), 3.13 (1H, dd, $J_{6\alpha,6\beta} = 15$ Hz, $J_{5,6\alpha} = 6$ Hz, H-6α), 3.41[d'] (1H, dd, $J_{16,17\alpha} \leq 2$ Hz, H-17α), 3.55 (1H, dd, $J_{5,6\alpha} = 6$ Hz, $J_{5,16} = 4$ Hz, $J_{5,6\beta} \leq 2$ Hz, H-5), 3.65[d'] (1H, d, $J_{16,17\beta} \leq 2$ Hz, H-17β), 3.79 (3H, s, Ar–OCH_3), 4.07 (1H, q, $J_{18,19} = 7$ Hz, $J_{19,20} \leq 2$ Hz, H-19), 4.42 (1H, d, $J_{3,14\alpha} = 8$ Hz, $J_{3,14\beta} \leq 2$ Hz, H-3), 4.81 (1H, br s, $J_{20,21} \leq 2$ Hz, H-21), 6.63 (1H, br s, H-9), 6.68 (1H, d, $J_{11,12} = 8$ Hz, H-11), 7.10 (1H, d, $J_{11,12} = 8$ Hz, H-12). (*195*), see also (*122*)
MS: 340 (M^+), 339 (100%), 338, 312, 253, 241, 240, 239, 238, 237, 227, 212, 200, 199, 198, 182, 181, 178. (*195*)

18-Hydroxylochnerine (**49**)
^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): 3.78 (3H, s, Ar–OCH_3), 5.60 (1H, t, $J = 7$ Hz, H-19), 6.82 (1H, dd, $J = 9$ Hz, $J = 3$ Hz, H-11), 6.84 (1H, d, $J = 3$ Hz, H-9), 7.15 (1H, d, $J = 9$ Hz, H-12). (*122*)
MS: 340 (M^+), 339, 323, 322, 321, 309, 267, 215, 214, 202, 201, 188, 138, 91 (100%). (*122*)

Verticillatine (**50**)
^{1}H NMR (400 MHz, D_2O)[a]: 1.62 (3H, d, $J_{18,19} = 6$ Hz, H-18), 1.74 (1H, br, H-15), 1.80 (1H, dd, $J_{14\alpha,14\beta} = 12$ Hz, $J_{3,14\beta} = 5$ Hz, H-14β), 1.90 (1H, m, H-16), 2.47 (1H, d, $J_{14\alpha,14\beta} = 12$ Hz, H-14α), 2.70 (1H, d, $J_{6\alpha,6\beta} = 17$ Hz, H-6β), 2.76 (1H, m, H-20), 2.92 (3H, s, N–CH_3), 3.11 (1H, dd, $J_{6\alpha,6\beta} = 17$ Hz, H-6α), 3.57 (1H, dd, $J_{21\alpha,21\beta} = 12$ Hz, H-21α), 4.00 (1H, t, $J_{5,6\alpha} = J_{5,6\beta} = 5$ Hz, H-5), 4.05 (1H, m, H-19), 4.10 (1H, d, $J_{21\alpha,21\beta} = 12$ Hz, H-21β), 4.74 (2H, m, H-3, H-17), 6.82 (1H, dd, $J = 8$ Hz, $J = 2$ Hz, H-11), 6.91 (1H, t, $J = 2$ Hz, H-9), 7.32 (1H, d, $J = 8$ Hz, H-12). (*130*)
MS: 340 (M^+-1), 322, 241, 199 (100%), 185, 184, 172. (*130*), see also (*129*)

Polyneuridine aldehyde (**51**)
^{1}H NMR: No data available.
MS: 350 (M^+), 349, 321, 319, 306, 291, 281, 263, 246, 223, 207, 197, 184, 183, 182, 169, 168 (100%), 143, 130, 128. (*138*)

O-Acetyl-16-epiaffinisine (**52**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.65 (3H, dt, $J = 6.8$ Hz, $J = 2.0$ Hz, H-18), 1.80 (1H, dt, $J = 13.1$ Hz, $J = 3.5$ Hz, H-14), 1.86–2.0 (1H, m, H-14), 1.97 (3H, s, –CO–CH_3), 2.25–2.36 (1H, m, H-16), 2.79 (1H, q, $J = 3.5$ Hz, H-15), 2.91 (1H, dd, $J = 16.2$ Hz, $J = 1.1$ Hz, H-6), 3.02 (1H, dd, $J = 16.2$ Hz, $J = 5.6$ Hz, H-6), 3.56–3.64 (1H, m, H-5), 3.61 (3H, s, N–CH_3), 3.68–3.73 (2H, m, 2 × H-21), 3.75 (1H, dd, $J = 11.3$ Hz, $J = 8.8$ Hz, H-17), 4.07 (1H, dd, $J = 13.3$ Hz, $J = 6.7$ Hz, H-17), 4.20 (1H, dd, $J = 10.2$ Hz, $J = 3.2$ Hz, H-3), 5.29 (1H, qt, $J = 6.8$ Hz, $J = 1.9$ Hz, H-19), 7.09 (1H, td, $J = 7.7$ Hz, $J = 1.2$ Hz, H-10), 7.18 (1H, td, $J = 7.7$ Hz, $J = 1.2$ Hz, H-11), 7.28 (1H, br d, $J = 7.7$ Hz, H-12), 7.48 (1H, br d, $J = 7.7$ Hz, H-9). (*32*)
MS: 350 (M^+), 349, 291, 277, 263, 249, 209, 196, 183 (100%), 182, 168, 157, 154. (*32*)

(+)-*E*-Akuammidine [(+)-**53**]

^{1}H NMR (400 MHz, $CDCl_3$): 1.65 (3H, ddd, $J_{18,19}$ = 7 Hz, $J_{18,21\alpha}$ = $J_{18,21\beta}$ = 2 Hz, H-18), 1.85 (1H, ddd, $J_{14\alpha,14\beta}$ = 12.5 Hz, $J_{3,14\alpha}$ = 11 Hz, $J_{14\alpha,15}$ ~ 2 Hz, H-14α), 2.67 (1H, ddd, $J_{14\alpha,14\beta}$ = 12.5 Hz, $J_{14\beta,15}$ ~ 3 Hz, $J_{3,14\beta}$ ~ 2 Hz, H-14β), 2.94 (3H, s, $-COOCH_3$), 2.94 (1H, dd, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\alpha}$ = 5 Hz, H-6α), 3.1 (2H, m, H-5, H-15), 3.30 (1H, dd, $J_{6\alpha,6\beta}$ = 16 Hz, $J_{5,6\beta}$ = 1.5 Hz, H-6β), 3.58 (2H, def, 2 × H-21), 3.67 (1H, d, $J_{17,17'}$ = 11 Hz, H-17), 3.83 (1H, d, $J_{17,17'}$ = 11 Hz, H-17'), 4.24 (1H, br d, $J_{3,14\alpha}$ = 11 Hz, $J_{3,14\beta}$ ~ 2 Hz, H-3), 5.39 (1H, br q, $J_{18,19}$ = 7 Hz, H-19), 7.05 (1H, t, H-10), 7.11 (1H, t, H-11), 7.28 (1H, d, H-12), 7.42 (1H, d, H-9), 7.90 (1H, br s, NH). (*239*), see also (*140*), (*166*)

MS: 352 (M^+), 351, 337, 321, 170, 169, 168, 154. (*140*), see also (*63*), (*154*), (*166*), (*182*)

(−)-Polyneuridine [(−)-**54**]

^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (3H, br d, $J_{18,19}$ = 6.5 Hz, H-18), 1.85 (1H, ddd, $J_{14\alpha,14\beta}$ = 13.5 Hz, $J_{3,14\beta}$ = 4 Hz, $J_{14\beta,15}$ = 3.5 Hz, H-14β), 1.91 (1H, ddd, $J_{14\alpha,14\beta}$ = 13.5 Hz, $J_{3,14\alpha}$ = 9.5 Hz, $J_{14\alpha,15}$ = 2.5 Hz, H-14α), 2.94 (1H, br d, $J_{6\alpha,6\beta}$ = 16.5 Hz, $J_{5,6\beta}$ ~ 1 Hz, H-6β), 3.10 (1H, dd, $J_{6\alpha,6\beta}$ = 16.5 Hz, $J_{5,6\alpha}$ = 6.5 Hz, H-6α), 3.21 (1H, dd, $J_{14\beta,15}$ = 3.5 Hz, $J_{14\alpha,15}$ = 2.5 Hz, H-15), 3.6 (2H, m, 2 × H-21), 3.61 (1H, d, $J_{17,17'}$ = 11.5 Hz, H-17), 3.71 (1H, d, $J_{17,17'}$ = 11.5 Hz, H-17'), 3.73 (3H, s, $-COOCH_3$), 4.06 (1H, dd, $J_{3,14\alpha}$ = 9.5 Hz, $J_{3,14\beta}$ = 4 Hz, H-3), 4.27 (1H, br d, $J_{5,6\alpha}$ = 6.5 Hz, $J_{5,6\beta}$ ~ 1 Hz, H-5), 5.28 (1H, br q, $J_{18,19}$ = 6.5 Hz, H-19), 7.10 (1H, t, H-10), 7.15 (1H, t, H-11), 7.31 (1H, d, H-12), 7.48 (1H, d, H-9), 7.81 (1H, br s, NH). (*239*)

MS: 352 (M^+, 100%), 351, 334, 321, 293, 275, 249, 182, 169, 168. (*246*), see also (*27*), (*47*), (*172*)

O-Acetylpreperakine (**55**)

^{1}H NMR ($CDCl_3$): 1.24 (3H, d), 1.56 (1H, dd), 2.14 (3H, s), 2.44 (1H, q), 2.74 (1H, dd), 3.88 (2H, s), 4.16 (1H, q), 4.92 (1H, s), 7.00–7.80 (4H, m), 9.92 (1H, d). (*47*)

MS: 352 (M^+), 351, 323, 309, 279, 265, 251, 237, 223, 209, 196, 183, 182, 169 (100%), 168, 156. (*47*)

O-Acetylsarpagine (**56**)

^{1}H NMR (DMSO-d_6): 1.53 (3H, d, J = 7 Hz, H-18), 1.98 (3H, s, $-CO-CH_3$), 3.94 (2H, d, J = 10 Hz, 2 × H-17), 5.36 (1H, q, J = 7 Hz, H-19), 6.51 (1H, dd, J = 9 Hz, J = 2 Hz, H-11), 6.67 (1H, d, J = 2 Hz, H-9), 7.06 (1H, d, J = 9 Hz, H-12), 8.52 (1H, s, NH), 10.46 (1H, s, Ar–OH). (*101*)

MS: 352 (M^+), 351, 337, 293, 279, 198, 185 (100%), 184, 172, 159. (*101*)

Z-Akuammidine (**57**)

^{1}H NMR (300 MHz, DMSO-d_6): 1.54 (3H, d, J = 6.7 Hz, H-18), 1.75 (1H, m, H-14), 1.80 (1H, m, H-14), 2.61 (1H, dd, J = 15.8 Hz, J = 4.5 Hz, H-6), 2.65 (1H, br d, J = 5.5 Hz, H-5), 2.65 (1H, m, H-15), 2.88 (3H, s, $-COOCH_3$), 3.22 (1H, dd, J = 15.8 Hz, J = 4.5 Hz, H-6), 3.30 (1H, m, H-21), 3.49 (1H, br d, J = 11.7 Hz, H-17), 3.51 (1H, m, H-21), 3.70 (1H, br d, J = 11.7 Hz, H-17), 4.05 (1H, d, J = 8.7 Hz, H-3), 4.68 (1H, s, –OH), 5.32 (1H, q, J = 6.7 Hz, H-19), 6.92 (1H, dt, J = 7.8 Hz, J = 1.4 Hz, H-10), 6.98 (1H, dt, J = 7.8 Hz, J = 1.4 Hz, H-11), 7.22 (1H, d, J = 7.8 Hz, H-12), 7.31 (1H, d, J = 7.8 Hz, H-9), 10.69 (1H, s, NH). (*159*), see also (*248*)

MS: 352 (M^+, 100%), 351, 321, 293, 249, 169, 168. (*248*)

(*continues*)

10-Hydroxy-N_a-methylpericyclivine (**58**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (3H, td, J = 7 Hz, J = 2 Hz, H-18), 1.75 (1H, dd, J = 12 Hz, J = 11 Hz, H-14α), 2.55 (1H, m, J = 11 Hz, H-14β), 2.8 (1H, d, J = 13 Hz, H-16), 2.9 (1H, dd, J = 13 Hz, J = 3 Hz, H-6), 3.0 (1H, m, H-15), 3.05 (3H, s, $-COOCH_3$), 3.5 (3H, s, $N-CH_3$), 3.6 (m, H-21), 3.7 (1H, dd, J = 10 Hz, J = 4 Hz, H-5), 4.2 (1H, dd, J = 10 Hz, J = 2 Hz, H-3), 5.3 (1H, q, J = 7 Hz, H-19), 6.8 (1H, dd, J = 8 Hz, J = 2 Hz, H-11), 6.9 (1H, d, J = 2 Hz, H-9), 7.2 (1H, d, J = 8 Hz, H-12). (*133*)
MS: 352 (M^+), 351, 337, 321, 279, 212, 199, 198 (100%). (*133*)

10-Methoxypericyclivine (**59**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (3H, br d, J = 7 Hz, H-18), 1.7 (1H, br t, J = 12 Hz, H-14α), 2.6 (1H, br d, J = 12 Hz, H-14β), 2.85 (1H, d, J = 11 Hz, H-16), 2.9 (1H, dd, J = 16 Hz, J = 5 Hz, H-6), 3.0 (1H, m, H-15), 3.1 (3H, s, $-COOCH_3$), 3.2 (1H, d, J = 16 Hz, H-6), 3.6 (2H, br s, 2 × H-21), 3.7 (1H, dd, J = 11 Hz, J = 5 Hz, H-5), 3.8 (3H, s, $Ar-OCH_3$), 4.2 (1H, d, J = 11 Hz, H-3), 5.3 (1H, q, J = 7 Hz, H-19), 6.8 (1H, dd, J = 9 Hz, J = 2 Hz, H-11), 6.9 (1H, d, J = 2 Hz, H-9), 7.2 (1H, d, J = 9 Hz, H-12), 7.7 (1H, br s, NH). (*133*)
MS: 352 (M^+, 100%), 351, 337, 321, 279, 199, 198. (*133*)

19,20-Dihydroakuammidine (**60**)
^{1}H NMR: No data available.
MS: 354 (M^+), 353 (100%), 339, 323, 310, 309, 295, 251, 225, 223, 182, 170, 169, 168, 156. (*88*)

19,20-Dihydropolyneuridine (**61**)
^{1}H NMR (80 MHz, $CDCl_3$): 0.82 (3H, t, J = 7 Hz, H-18), 3.34 (2H, 2 × H-17), 3.78 (3H, s, $-COOCH_3$), 4.23 (1H, br s, H-3), 7.03–7.49 (4H, m, H-9, H-10, H-11, H-12), 7.73 (1H, br s, NH). (*172*)
MS: 354 (M^+), 353 (100%), 249, 184, 170, 169, 168. (*172*)

Dehydrovoachalotine (**62**)
^{1}H NMR (60 MHz, $CDCl_3$): 1.58 (3H, d, J = 7 Hz, H-18), 2.00 (2H, m, 2 × H-14), 3.27 (1H, t, H-15), 3.61 (3H, s, $N-CH_3$), 3.70 (2H, def., 2 × H-21), 3.70 (3H, s, $-COOCH_3$), 3.80 (2H, 2 × H-17), 4.05 (1H, m, H-3), 4.49 (1H, d, J = 8 Hz, H-5), 5.34 (1H, q, J = 7 Hz, H-19), 5.77 (1H d, J = 8 Hz, H-6), 7.0–7.8 (3H + 1H, 2 × m, H-9, H-10, H-11, H-12). (*174*), see also (*182*)
MS: 364 (M^+), 349, 347, 333, 305, 275, 196, 183, 182 (100%). (*174*), see also (*246*)

Voachalotinal (**63**)
^{1}H NMR (300 MHz, $CDCl_3$): 1.65 (3H, br d, J = 6 Hz, H-18), 1.9 (1H, dd, J = 12 Hz, J = 11 Hz, H-14), 2.1 (1H, dd, J = 12 Hz, J = 2 Hz, H-14), 3.15 (2H, br s, 2 × H-6), 3.5 (1H, br d, J = 2 Hz, H-15), 3.59 (3H, s, $N-CH_3$), 3.6 (2H, br s, 2 × H-21), 3.7 (3H, s, $-COOCH_3$), 4.19 (1H, br s, H-5), 4.25 (1H, br d, J = 11 Hz, H-3), 5.3 (1H, q, J = 6 Hz, H-19), 7.1 (1H, t, J = 7 Hz, H-10), 7.2 (1H, t, J = 7 Hz, H-11), 7.3 (1H, d, J = 7 Hz, H-12), 7.4 (1H, d, J = 7 Hz, H-9), 9.1 (1H, s, –CHO). (*133*)
MS: 364 (M^+), 363, 336, 335, 263, 261 (100%), 247, 183, 182. (*133*)

Voachalotine (**64**)

^{1}H NMR (400 MHz, $CDCl_3$): 1.61 (3H, ddd, $J_{18,19}$ = 6.5 Hz, $J_{18,21\alpha}$ = $J_{18,21\beta}$ ~ 2 Hz, H-18), 1.79 (1H, ddd, $J_{14\alpha,14\beta}$ = 13.5 Hz, $J_{3,14\beta}$ ~ 3.5 Hz, $J_{14\beta,15}$ ~ 3 Hz, H-14β), 1.98 (1H, ddd, $J_{14\alpha,14\beta}$ = 13.5 Hz, $J_{3,14\alpha}$ = 10.5 Hz, $J_{14\alpha,15}$ = 2.5 Hz, H-14α), 2.94 (1H, br d, $J_{6\alpha,6\beta}$ = 16.5 Hz, $J_{5,6\beta}$ ~ 1 Hz, H-6β), 3.11 (1H, dd, $J_{6\alpha,6\beta}$ = 16.5 Hz, $J_{5,6\alpha}$ = 6.5 Hz, H-6α), 3.22 (1H, dd, $J_{14\beta,15}$ ~ 3 Hz, $J_{14\alpha,15}$ = 2.5 Hz, H-15), 3.57 (1H, d, $J_{17,17'}$ = 11 Hz, H-17), 3.61 (3 H, s, N–CH_3), 3.68 (1H, d, $J_{17,17'}$ = 11 Hz, H-17′), 3.7 (2H, m, 2 × H-21), 3.73 (3H, s, –$COOCH_3$), 4.16 (1H, dd, $J_{3,14\alpha}$ = 10.5 Hz, $J_{3,14\beta}$ ~ 3.5 Hz, H-3), 4.28 (1H, br d, $J_{5,6\alpha}$ = 6.5 Hz, $J_{5,6\beta}$ ~ 1 Hz, H-5), 5.30 (1H, br q, $J_{18,19}$ = 6.5 Hz, H-19), 7.09 (1H, t, H-10), 7.19 (1H, t, H-11), 7.28 (1H, d, H-12), 7.47 (1H, d, H-9), (*239*)

MS: 366 (M^+), 365, 349, 348, 335, 263, 183 (100%). (*182*)

10-Methoxy-N_a-methylpericyclivine (**65**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (3H, td, J = 7 Hz, J = 2 Hz, H-18), 1.87 (1H, ddd, J = 12 Hz, J = 10 Hz, J = 3 Hz, H-14α), 2.6 (1H, ddd, J = 12 Hz, J = 4 Hz, J = 2 Hz, H-14β), 2.85 (1H, dd, J = 11 Hz, J = 2 Hz, H-16), 2.95 (1H, dd, J = 15 Hz, J = 4 Hz, H-6), 3.0 (1H, m, H-15), 3.1 (3H, s, –$COOCH_3$), 3.2 (1H, dd, J = 15 Hz, J = 2 Hz, H-6), 3.5 (3H, s, N–CH_3), 3.7 (3H, m, H-5, 2 × H-21), 3.84 (3H, s, Ar–OCH_3), 4.4 (1H, br d, J = 9 Hz, H-3), 5.3 (1H, br q, J = 7 Hz, H-19), 6.8 (1H, dd, J = 9 Hz, J = 2 Hz, H-11), 6.9 (1H, d, J = 2 Hz, H-9), 7.1 (1H, d, J = 9 Hz, H-12). (*133*)

MS: 366 (M^+, 100%), 365, 351, 335, 307, 213, 212. (*133*)

Macusine A (**66**)

^{1}H NMR: No data available.

MS: No data available.

N_b-Methylakuammidine (**67**)

^{1}H NMR (400 MHz, CD_3OD)[a]: 1.76 (1H, d, J = 6.7 Hz, H-18), 2.42 (1H, dt, J = 13.2 Hz, J = 10.4 Hz), 2.97 (3H, s, N^+–CH_3), 3.18 (3H, s, –$COOCH_3$), 3.70 (1H, d, J = 9.9 Hz), 3.85 (1H, d, J = 9.9 Hz), 4.26 (1H, br d, J = 14.0 Hz), 4.51 (1H, br d, J = 14.0 Hz), 4.96 (1H, m), 5.65 (1H, br q, J = 6.7 Hz, H-19), 7.08 (1H, t, J = 7.9 Hz), 7.18 (1H, t, J = 7.9 Hz), 7.37 (1H, d, J = 7.9 Hz), 7.48 (1H, d, J = 7.9 Hz), 7.89 (1H, s). (*179*)

MS: 366 (M^+-1), 337, 336, 335, 322 (100%), 321, 308, 307, 293, 291, 276, 275, 263, 261, 249, 247, 235, 182, 169, 168, 156, 154. (*179*)

Eburnaphylline (**68**)

^{1}H NMR: No data available.

MS: 368 (M^+), 323, 309, 169, 168. (*252*)

17-Hydroxydehydrovoachalotine (**69**)

^{1}H NMR (300 MHz, $CDCl_3$): 1.65 (3H, dt, J = 7 Hz, H-18), 1.85 (m, H-14), 3.40 (1H, t, J = 3 Hz, H-15), 3.60 (m, H-21), 3.61 (3H, s, N–CH_3), 3.70 (3H, s, –$COOCH_3$), 3.9 (1H, dd, J = 11 Hz, J = 5 Hz, H-3), 4.55 (1H, dd, J = 8.3 Hz, J = 1 Hz, H-5), 5.25 (1H, br s, J = 1 Hz, H-17), 5.35 (1H, qq, J = 7 Hz, H-19), 5.85 (1H, d, J = 8.3 Hz, H-6), 7.10–7.60 (4 H, m, H-9, H-10, H-11, H-12). (*181*)

MS: 380 (M^+), 336, 335, 183 (100%), 182 (100%). (*181*)

(*continues*)

Voacoline (**70**)
^{1}H NMR (60 MHz, $CDCl_3$): 1.3 (3H, s, H-18), 2.8 (1H, s, –OH), 3.0 (3H, s, $-COOCH_3$), 3.6 (3H, s, $N-CH_3$), 3.7 (2H, br s, 2 × H-17). (*182*)
MS: 382 (M^+), 381, 365, 364, 351, 279, 183 (100%). (*182*), see also (*253*)

21-Hydroxyvoachalotine (**71**)
^{1}H NMR (60 MHz, $CDCl_3$): 3.55 (3H, s, $N-CH_3$), 3.68 (3H, s, $-COOCH_3$), 6.9–7.65 (4H, H-9, H-10, H-11, H-12). (*170*)
MS: 382 (M^+), 351, 323, 279, 183 (100%), 168. (*170*)

Acetylakuammidine (**72**)
^{1}H NMR: No data available.
MS: 394 (M^+), 335 (100%), 321, 249, 182, 169, 168. (*183*)

Fuchsiaefoline (**73**)
^{1}H NMR (60/100 MHz, $CDCl_3$): 1.26 (3H, t, J = 6 Hz, $-CH_2CH_3$), 1.65 (3H, d, J = 6 Hz, H-18), 3.47 (3H, s, N^+-CH_3), 3.95 (3H, s, $N-CH_3$), 4.07 (3H, s, $Ar-OCH_3$). (*184*)
MS: 394 (M^+-1), 349, 381, 380 (100%), 379, 366, 351, 335, 307, 293, 280, 279, 226, 213, 212, 197. (*184*)

10-Methoxy-N_a-methylakuammidine (**74**)
^{1}H NMR (60 MHz, $CDCl_3$): 1.65 (3H, d, J = 7 Hz, H-18), 2.97 (3H, s, $-COOCH_3$), 3.54 (3H, s, $N-CH_3$), 3.81 (3H, s, $Ar-OCH_3$), 5.4 (1H, m, H-19), 6.77 (1H, dd, J = 8.5 Hz, J = 2.5 Hz, H-11), 6.88 (1H, dd, J = 2.5 Hz, J = 1 Hz, H-9), 7.12 (1H, dd, J = 8 Hz, J = 1 Hz, H-12). (*185*)
MS: 396 (M^+, 100%), 381, 365, 337, 293, 213, 212, 187, 174. (*185*)

11-Hydroxy-N_a-methylmacusine A (**75**)
^{1}H NMR (400 MHz, $CDCl_3$)[a]: 1.65 (3H, d, J = 6.9 Hz, H-18), 2.03 (1H, dt, J = 13.7 Hz, J = 1.0 Hz, H-14β), 2.43 (1H, br dd, J = 13.8 Hz, J = 11.5 Hz, H-14α), 3.17 (3H, s, N^+-CH_3), 3.26 (2H, br s, 2 × H-6), 3.33 (1H, br s, H-15), 3.56 (3H, s, $N-CH_3$), 3.60 (1H, d, J = 9.2 Hz, H-17), 3.67 (1H, d, J = 9.2 Hz, H-17), 3.71 (3H, s, $-COOCH_3$), 4.26 (1H, br d, J = 16.1 Hz, H-21), 4.37 (1H, br d, J = 16.1 Hz, H-21), 4.93 (1H, d, J = 6.1 Hz, H-5), 5.02 (1H, br d, J = 9.7 Hz, H-3), 5.45 (1H, q, J = 6.9 Hz, H-19), 6.64 (1H, dd, J = 8.0 Hz, J = 2.0 Hz, H-10), 6.75 (1H, d, J = 1.9 Hz, H-12), 7.31 (1H, d, J = 8.0 Hz, H-9). (*186*)
MS: 396 (M^+-1), 382, 367, 366, 352, 351, 338, 337, 307, 279, 199 (100%), 198, 186, 184, 168, 167. (*186*)

11-Methoxymacusine A (**76**)
^{1}H NMR (100 MHz, pyridine-d_5)[a]: 1.70 (3H, d, H-18), 3.02 (3H, s, $N-CH_3$), 3.70 (6H, $-COOCH_3$, $Ar-OCH_3$), 6.97 (1H, dd, J = 8 Hz, J = 2 Hz, H-10), 7.32 (1H, d, J = 2 Hz, H-12), 7.45 (1H, d, J = 8 Hz, H-9), 8.55 (1H, s, NH). (*187*)
MS: 397 (M^+), 396, 383, 382, 381, 367, 366, 365, 353, 352, 351 (100%), 337, 336, 323, 322, 292, 279, 269, 268, 259, 205, 200, 199, 198, 197, 186, 184, 174, 173, 161, 160. (*187*)

O-Benzoylnormacusine B (**77**)
^{1}H NMR ($CDCl_3$): 1.51 (3H, d, H-18), 5.40 (1H, q, H-19), 7.01–8.02 (9H, H-9, H-10, H-11, H-12, 5 × H–Bz), 8.39 (1H, s, NH). (*188*)
MS: 398 (M^+), 397, 293, 277, 276, 275, 263, 169, 168, 105. (*188*)

17-*O*-Acetyl-19,20-dihydrovoachalotine (**78**)
^{1}H NMR (60 MHz, $CDCl_3$): 0.88 (3H, t, H-18), 1.88 (3H, s, $-CO-CH_3$), 3.55 (3H, s, $N-CH_3$), 3.6 (3H, s, $-COOCH_3$), 4.12 (2H, s, 2 × H-17), 6.8–7.4 (4H, H-9, H-10, H-11, H-12). (*189*)
MS: 410 (M^+), 351, 265, 237, 196, 183, 182. (*189*)

12-Methoxy-N_b-methylvoachalotine (**79**)
^{1}H NMR (60/100 MHz, $CDCl_3$): 1.55 (3H, d, J = 6 Hz, H-18), 3.13 (3H, s, N^+-CH_3), 3.75 (3H, s, $-COOCH_3$), 3.92 (6H, s, $N-CH_3$, $Ar-OCH_3$) 4.69 (1H, d), 5.14–5.41 (2H, m), 5.4 (1H, m, H-19), 6.2–7.1 (3H, m, H-9, H-10, H-11). (*184*)
MS: 410 (M^+-1), 396 (100%), 395, 381, 379, 365, 337, 293, 213, 212. (*184*)

12-Methoxy-N_b-methylvoachalotine ethyl ester (**80**)
^{1}H NMR (60/100 MHz, $CDCl_3$): 1.32 (3H, t, J = 6 Hz, $-CH_2CH_3$), 1.57 (3H, d, J = 6 Hz), 3.10 (3H, s), 4.00 (6H, s). (*184*)
MS: 424 (M^+-1), 410 (100%), 409, 379, 365, 337, 293, 280, 213, 212. (*184*)

Geissolosimine (**81**)
^{1}H NMR (60/100 MHz, $CDCl_3$): 1.71 (3H, d, J = 7 Hz, H-18), 5.21 (1H, d, J = 10 Hz, H-17), 5.55 (1H, q, J = 7 Hz, H-19), 9.42 (1H, br s, NH). (*14*)
MS: No data available.

(+)-Divaricine [(+)-**82**]
^{1}H NMR (500 MHz, CD_3OD)[e]: 0.80 (3H, dt, J = 7 Hz, J = 1.8 Hz, H-18′), 1.47 (1H, dt, J = 15 Hz, J = 2.5 Hz, H-14′), 1.70 (3H, dt, J = 7 Hz, J = 1.8 Hz, H-18), 1.73 (1H, ddd, J = 13.2 Hz, J = 4.5 Hz, J = 2 Hz, H-14), 2.12 (1H, ddd, J = 13.2 Hz, J = 9.5 Hz, J = 2 Hz, H-14), 2.28 (1H, m, H-6′), 2.42 (1H, m, H-6′), 2.45 (1H, m, H-16), 2.50 (1H, dt, J = 15 Hz, J = 2.5 Hz, H-14′), 2.77 (1H, dd, J = 15 Hz, J = 2 Hz, H-6), 2.91 (1H, br s, H-15′), 2.98 (1H, m, H-15), 3.00 (1H, br s, H-5), 3.04 (1H, ddd, J = 15 Hz, J = 4.5 Hz, J = 1.6 Hz, H-6), 3.45 (1H, d, J = 14 Hz, H-21′), 3.62 (t, J = 2 Hz, H-21), 3.76 (1H, m, H-5′), 3.77 (1H, br s, H-2′), 3.87 (1H, d, J = 14 Hz, H-21′), 4.00 (1H, m, H-5′), 4.18 (1H, br s, H-3′), 4.28 (1H, br d, J = 9.5 Hz, H-3), 4.51 (1H, q, J = 7 Hz, H-19′), 5.18 (1H, d, J = 10.2 Hz, H-17), 5.56 (1H, q, J = 7 Hz, H-19), 6.28 (1H, d, J = 1.4 Hz, H-17′), 6.86 (1H, d, J = 8.5 Hz, H-12′), 6.91 (1H, t, J = 8.5 Hz, H-10′), 7.09 (1H, t, J = 8.5 Hz, H-10), 7.17 (1H, t, J = 8.5 Hz, H-11), 7.25 (1H, d, J = 8.5 Hz, H-9′), 7.25 (1H, t, J = 8.5 Hz, H-11′), 7.32 (1H, d, J = 8.5 Hz, H-12), 7.39 (1H, d, J = 8.5 H-9). (*24*)
MS: 584 (M^+), 249, 248, 247, 169, 144, 143, 130. (*24*)

(*continues*)

TABLE III (*Continued*)

Macrospegatrine (**83**)
^{1}H NMR (D_2O)[a,e]: 1.31 (3H, J = 6 Hz, H-18′), 1.70 (3H, d, J = 6 Hz, H-8), 1.86–2.24 (6H, m, 2 × H-14, 2 × H-14′, H-16, H-16′), 2.54 (1H, t, J = 12 Hz, H-6β), 2.87–3.21, 3.42 (6H, m, H-6α, 2 × H-6′, H-15, H-15′, H-20′), 3.32 (3H, s, N^+–CH_3), 3.60 (2H, m, 2 × H-17), 4.26 (2H, m, H-21β, H-19′), 4.46 (1H, d, J = 16 Hz, H-21α), 5.30 (1H, d, J = 8 Hz, H-21′), 5.42 (1H, q, J = 6 Hz, H-19), 5.88 (1H, d, J = 3 Hz, H-22′), 4.92 (1H, d, J = 3 Hz, H-22′), 6.24 (1H, d, J = 9 Hz, H-11), 6.72 (1H, d, J = 9 Hz, H-12), 6.90 (1H, d, J = 8 Hz, H-9′), 7.15 (2H, m, H-10′, H-11′), 7.38 (1H, d, J = 8 Hz, H-12′). (*190*)
MS: (FAB: $C_{40}H_{46}N_4O_3Cl_2$): 723 [(M + Na)$^+$], 700 (M^+), 685, 664, 651, 633. (*190*)

N′-Demethylaccedinisine (**84**)
^{1}H NMR (300 MHz, CD_3OD)[e]: 1.6 (3H, d, J = 7 Hz, H-18), 1.7 (3H, d, J = 7 Hz, H-18′), 1.85 (1H, q, J = 7 Hz, H-16), 2.1 (1H, m, H-14′), 2.2 (t, J = 14 Hz, H-14), 2.5 (3H, s, –$COOCH_3$), 2.7 (3H, m, H-6, H-14′, H-16′), 2.8 (2H, m, H-5, H-15), 3.1 (1H, dd, J = 14 Hz, J = 6 Hz, H-6), 3.45 (1H, d, J = 15 Hz, H-21′), 3.5 (2H, m, 2 × H-17), 3.6 (6H, m, H-6′, N–CH_3, 2 × H-21), 3.7 (1H, m, H-6′), 3.8 (1H, m, H-15′), 4.1 (1H, d, J = 15 Hz, H-21′), 4.2 (1H, d, J = 8 Hz, H-3), 4.35 (1H, br t, J = 8 Hz, H-5′), 4.65 (1H, dd, J = 13 Hz, J = 3 Hz, H-3′), 5.4 (1H, q, J = 7 Hz, H-19), 5.5 (1H, q, J = 7 Hz, H-19′), 7.0–7.1 (5H, m), 7.2 (1H, d, J = 8 Hz), 7.25 (1H, s, H-9), 7.6 (1H, m, H-9′). (*35*)
MS: No data available.

Macralstonidine (**85**)
^{1}H NMR (100 MHz, $CDCl_3$)[e]: 1.36 (3H, s, H-18′), 1.65 (3H, d, J = 7.5 Hz, H-18), 2.27 (3H, s, N^+–CH_3), 3.43 (3H, s, N′–CH_3), 3.55 (3H, s, N′–CH_3), 4.13 (1H, d, J = 8–10 Hz), 4.60 (1H, t, $J_{16,17\alpha} = J_{17\alpha,17\beta} \sim 12$ Hz, H-17′α), 5.39 (1H, q, J = 7.5 Hz, H-19), 6.70 (1H, d, J = 8.5 Hz, H-11), 6.9–7.4 (3H, m, H-9′, H-10′, H-11′), 7.12 (1H, d, J = 8.5 Hz, H-12), 7.5 (1H, dm, H-12′). (*191b*)
MS: 644 (M^+, 100%), 629, 613, 574, 519, 447, 444, 375, 336, 322 (M^{++}), 308, 305, 251, 239, 211, 197, 182, 170. (*191b*)

Accedinisine (**86**)
^{1}H NMR (300 MHz, $CDCl_3$)[e]: 1.70 (6H, m, H-18, H-18′), 2.50 (3H, s, $-COOCH_3$), 2.60 (3H, s, N^+-CH_3), 3.30 (m, H-6′), 3.57 (3H, s, $N-CH_3$), 4.05 (1H, m, H-5′), 4.15 (1H, d, J = 8 Hz, H-3), 4.68 (1H, J = 10 Hz, H-3′), 5.35–5.40 (2H, m, H-19, H-19′), 6.95 (1H, d, J = 8 Hz, H-11), 7.00–7.20 (4H, m, H-10′, H-11′, H-12, H-12′), 7.35 (1H, d, J = 8 Hz, H-9), 7.54 (1H, m, H-9′). (*37*), see also (*192*)
MS: 644 (M^+), 613, 612, 611, 514, 465, 464, 462, 451, 450, 333, 322, 308, 307, 183, 182, 181 (100%), 180, 122. (*192*)

Dispegatrine (**87**)
^{1}H NMR[a,e]: 1.61 (2H, J = 6 Hz, H-18, H-18′), 2.05–2.21 (6H, 2 × H-14, 2 × H-14′, H-16, H-16′), 2.50 (2H, J = 12 Hz, H-15, H-15′), 3.07 (4H, 2 × H-6, 2 × H-6′), 3.41 (4H, 2 × H-17, 2 × H-17′), 4.02 (2H, d, J = 16 Hz, H-21, H-21′), 4.32 (2H, d, J = 16 Hz, H-21, H-21′), 5.48 (2H, d, J = 6 Hz, H-19, H-19′), 6.98 (2H, d, J = 8 Hz, H-11, H-11′), 7.48 (2H, d, J = 8 Hz, H-12, H-12′). (*129*)
MS (FAB; $C_{40}H_{48}N_4O_4Cl_2$): 648 [$(M-2\ Cl)^+$], 634, 618, 616, 193, 189, 188, 173, 169, 156, 154, 151, 139, 135, 124 (100%). (*129*)

Desformoundulatine (**88**)
^{1}H NMR[e]: 3.1 (3H, $Ar-OCH_3$), 3.62 (1H, $J_{5',6'}$ = 1 Hz, H-5′), 4.77 (1H, s, $J_{5',6'}$ = 1 Hz, H-6′), 6.23 (1H, s, H-12), 6.4 (1H, s, H-9). (*193*)
MS: 702 (M^+, 100%), 687, 643, 335, 194, 183, 182, 139, 122. (*193*)

Undulatine (**89**)
^{1}H NMR: 3.0 (3H, $Ar-OCH_3$). (*193*)
MS: 732 (M^+), 365 (100%). (*193*)

---

^{1}H NMR signals reassigned by the writers are marked with underlining.

[a] Spectral data given for a chloride salt.

[b] Partly overlapped.

[c] In the writers' opinion there is some confusion in the given signals: e.g., the signal at δ 2.82 assigned to H-16 seems to represent the upper part of a doublet of doublets partly masked by the signal at δ 2.85 reassigned to H-6.

[d,d′] Signals may be reversed.

[e] The non-sarpagan moities of the bisindoles are marked with primes.

given for polyneuridine in Lin and Cordell (*159*) also seem to be erroneous. In a recent paper, Jokela and Lounasmaa (*239*) reexamined and corrected the ^{1}H NMR spectral data of five basic sarpagine-type alkaloids: normacusine B (**2**), pericyclivine (**18**), *E*-akuammidine (**53**), polyneuridine (**54**), and voachalotine (**64**) (Fig. 10). The corrected data, confirmed by homonuclear COSY and NOE measurements, are reproduced in Table III.

The chemical shift of the $-COOCH_3$ group at C-16 ($\delta \approx 3.6$ ppm versus $\delta \approx 3.1$ ppm) is diagnostic for the C-16 stereochemistry of sarpagine alkaloids containing a $-COOCH_3$ group at C-16, as shown for N_a-methyl-16-epipericyclivine (**40**) and N_a-methylpericyclivine (**41**) (Fig. 11) (e.g., *133*). References for the ^{1}H NMR spectral data of individual compounds, when available, are given in Table III.

B. ^{13}C NMR Spectroscopy

^{13}C NMR spectroscopy has allowed several stereochemical problems of sarpagine alkaloids to be solved (e.g., *231–233,240,241*). Moreover, identical ^{13}C NMR spectral data of two compounds, together with identical optical rotations, would appear to provide the best and most rapid way to establish the identity of two compounds. ^{13}C NMR spectral data for 44 monomeric and 8 bisindolic alkaloids are presented in Table IV.

As with the ^{1}H NMR spectra (discussed earlier), there has been much confusion in the literature over the ^{13}C NMR spectra of sarpagine alkaloids.

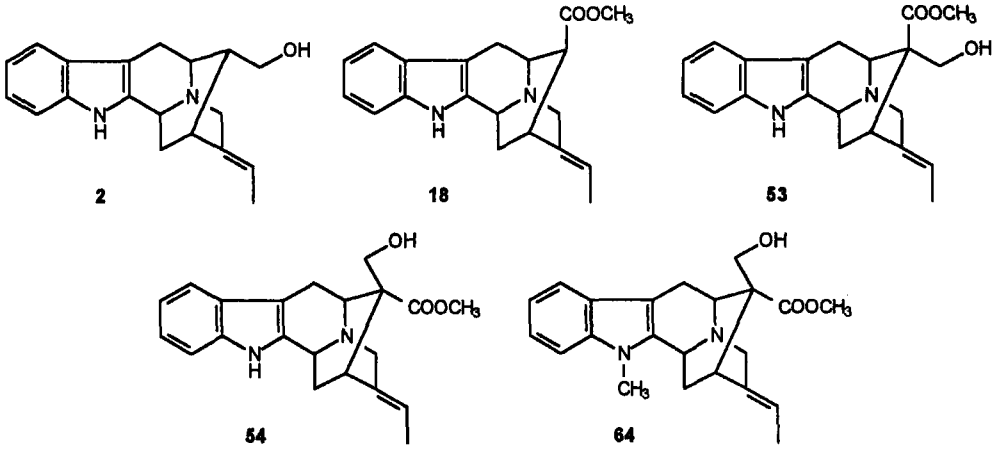
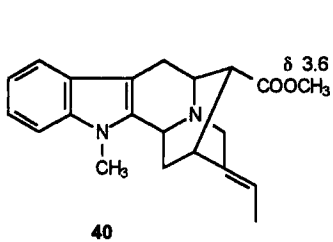
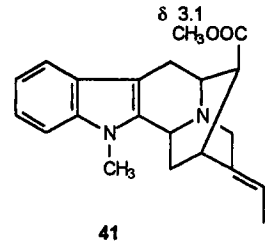


FIG. 10. Normacusine B (**2**), pericyclivine (**18**), *E*-akuammidine (**53**), polyneuridine (**54**), and voachalotine (**64**).



40



41

FIG. 11. The ^1H NMR chemical shifts of the $-COOCH_3$ group in N_a-methyl-16-epipericyclivine (**40**) (C-16 *R*) and N_a-methylpericyclivine (**41**) (C-16 *S*).

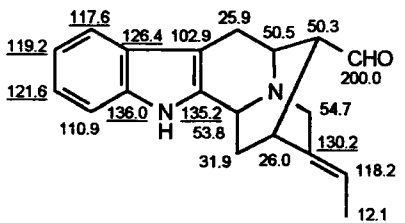
For example, the chemical shifts presented for *E*-akuammidine (**53**) (*242*) are those of an unknown compound that definitely is not *E*-akuammidine. Several of the ^{13}C NMR values given for pericyclivine (**18**) (*105*) need to be interchanged. As in the case of the ^1H NMR spectra, Jokela and Lounasmaa (*239*) reexamined and corrected the ^{13}C NMR spectral data of the five basic sarpagine alkaloids: normacusine B (**2**), pericyclivine (**18**), *E*-akuammidine (**53**), polyneuridine (**54**), and voachalotine (**64**). The corrected data, confirmed by HETCOR measurements, are reproduced in Table IV. References for the ^{13}C NMR spectral data of individual compounds, when available, are given in Table IV.

C. MASS SPECTROMETRY

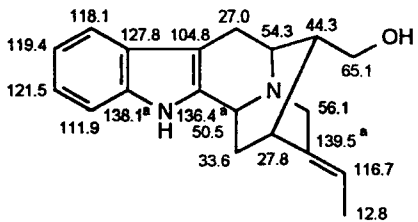
The mass spectral fragmentation of sarpagine alkaloids by electron impact ionization (EI) has been thoroughly treated in earlier papers (*243–246*). Only the main features are noted here. Cleavage of the C-5–C-16 bond, followed by a rearrangement of one of the C-6 hydrogens and cleavage of the C-3 hydrogen, gives rise to the M^+-1 ion (Scheme 23). For steric reasons the direct cleavage of the C-3 hydrogen from the molecular ion is not plausible. Alternatively, cleavage of the C-5–C-16 bond, followed by transfer of one of the C-18 hydrogens and cleavage of the C-15–C-16 bond under a six-membered transition state, leads to the indoloquinolizidine unit **164,** corresponding to *m/z* 265 for sarpagine derivatives and *m/z* 249 for desoxysarpagine derivatives (Scheme 24). Intense peaks at *m/z* 184 and 185 for sarpagine derivatives (corresponding to *m/z* 168 and 169 for desoxysarpagine derivatives) are due to ions **165** and **166** (Fig. 12). Alkaloids possessing a hydroxyl group at C-17 generally show relatively intense (M^+-17) and (M^+-31) peaks. The presence of a methoxycarbonyl (CH_3COO-) group is indicated by a (M^+-59) peak.

TABLE IV

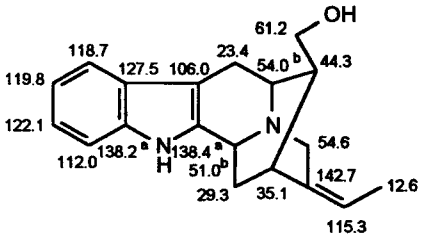
^{13}C-NMR Spectral Data of Individual Alkaloids



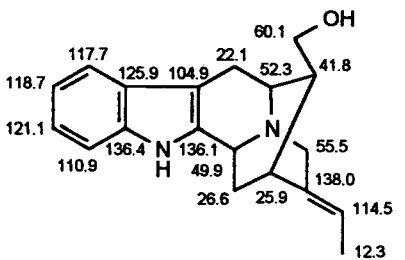
1 (+)-Vellosimine
(*19*) 100 MHz, $CDCl_3$



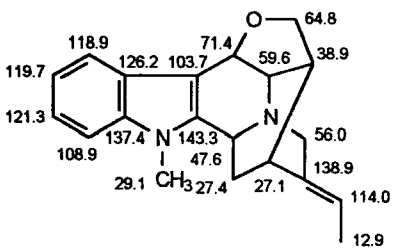
2 Normacusine B
(*239*) 100.577 MHz, $CDCl_3$
see also (*32*), (*184*)



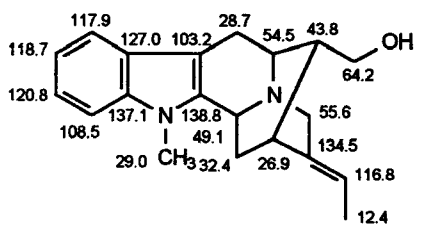
3 Koumidine
(*248*) 67.8 MHz, CD_3OD
see also (*9b*), (*64*)



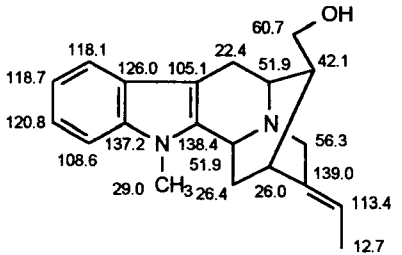
5 16-Epinormacusine B
(*32*) 75 MHz, $CDCl_3$



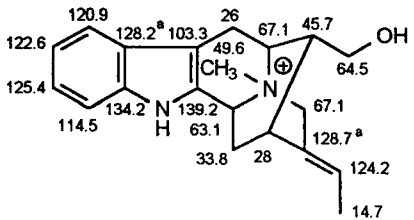
7 Dehydro-16-epiaffinisine
(*32*) 75 MHz, $CDCl_3$



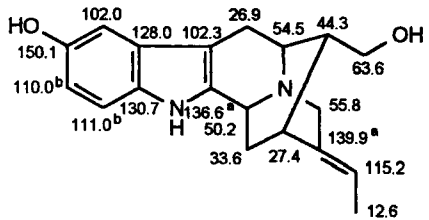
8 Affinisine
(*32*) 75 MHz, $CDCl_3$
see also (*61*), (*184*)



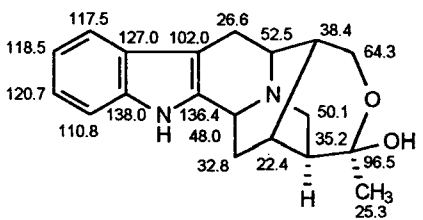
10 16-Epiaffinisine
(*32*) 75 MHz, $CDCl_3$



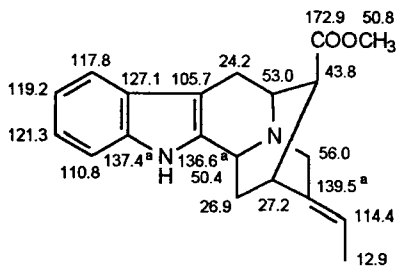
11 Macusine B*
(*116*) 100.8 MHz, D_2O



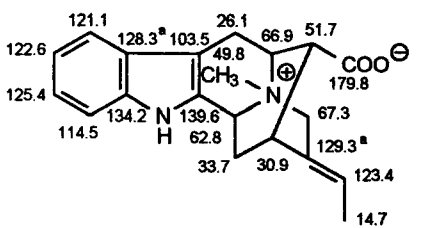
12 (+)-Sarpagine
(*92*) 50 MHz, $CDCl_3$:DMSO-d_6 1:1



16 (−)-Trinervine
(*57*) 100.61 MHz,
$CDCl_3$:CD_3OH 3:1



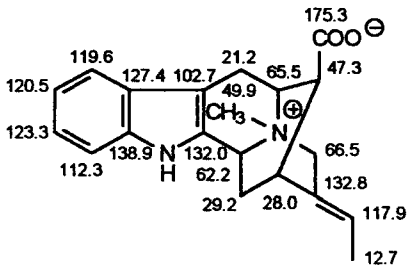
18 (+)-Pericyclivine
(*239*) 100.577 MHz, $CDCl_3$



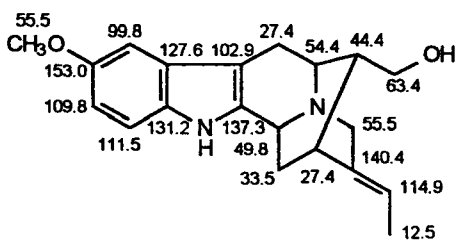
21 Panarine
(*116*) 100.8 MHz, D_2O

(*continues*)

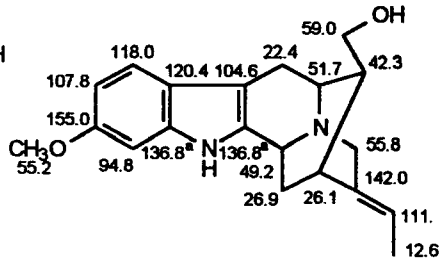
TABLE IV (*Continued*)



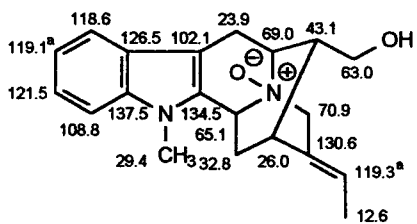
22 16-Epipanarine
(*117*) 100 MHz, CD_3OD



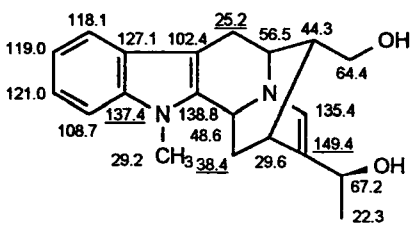
25 (+)-Lochnerine
(*122*) 22.63 MHz/15.08 MHz, DMSO-d_6



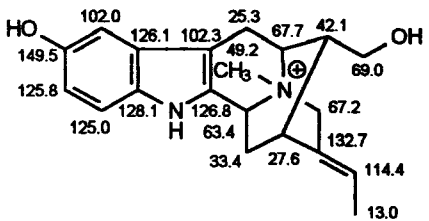
28 Gardnerine
(*254*) 125 MHz, DMSO-d_6
see also (*137*)



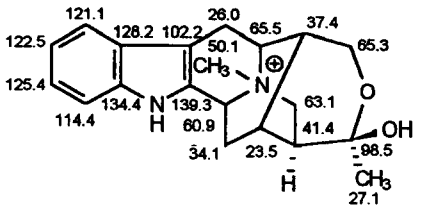
31 Affinisine N_b-oxide
(*32*) 75 MHz, $CDCl_3$



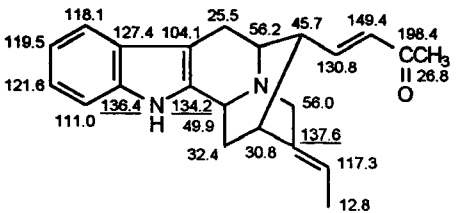
32 (−)-Alstoumerine
(*127*) 100 MHz, $CDCl_3$



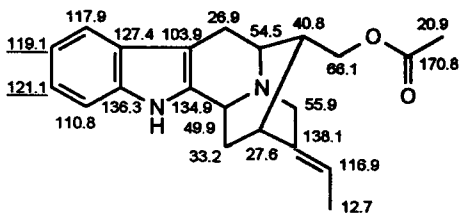
34 Spegatrine
(*129*) 90 MHz, CF_3COOD



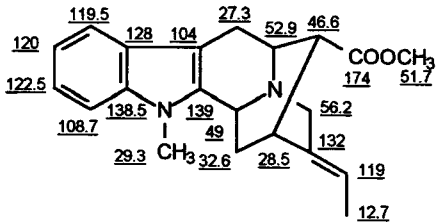
35 Venecurine*
(*131*) 100 MHz, D_2O



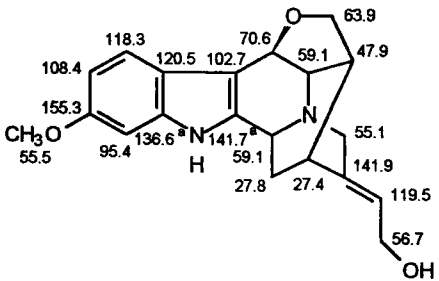
37 Difforine
(*61*) 20 MHz, $CDCl_3$



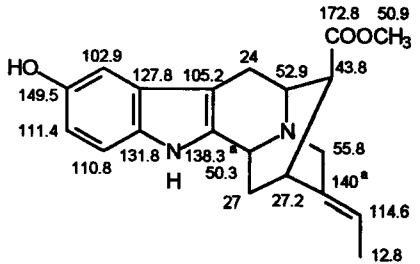
39 *O*-Acetylnormacusine B
(56) 100 MHz, $CDCl_3$



40 N_a-Methyl-16-epipericyclivine
(*133*) $CDCl_3$



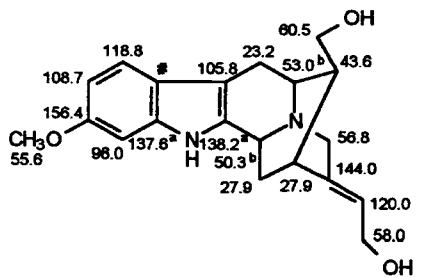
42 Hydroxygardnutine
(*137*) DMSO-d_6



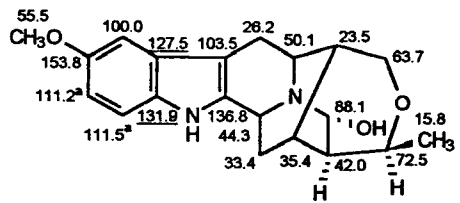
43 10-Hydroxypericyclivine
(*133*) $CDCl_3$

(*continues*)

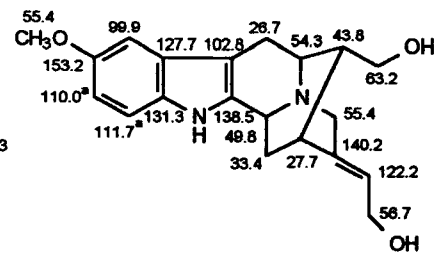
TABLE IV (*Continued*)



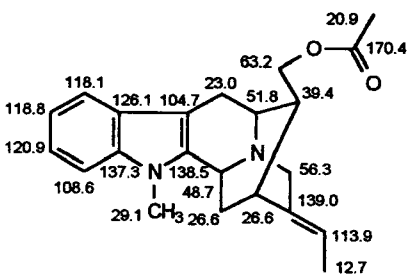
47 18-Hydroxygardnerine
(*137*) pyridine-d_5



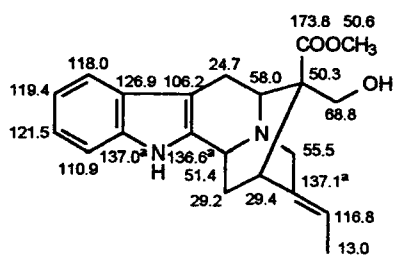
48 21-Hydroxycyclolochnerine
(*195*) $CDCl_3$



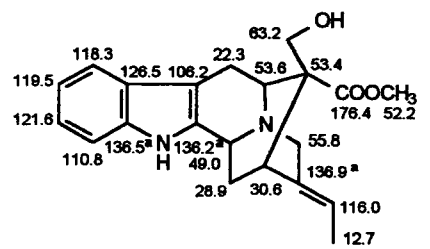
49 18-Hydroxylochnerine
(*122*) 22.63/15.08 MHz, DMSO-d_6



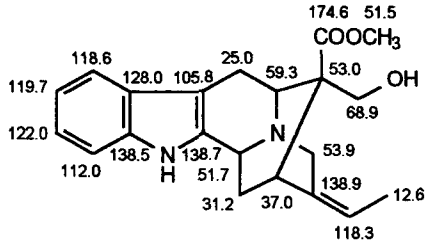
52 *O*-Acetyl-16-epiaffinisine
(*32*) 75 MHz, $CDCl_3$



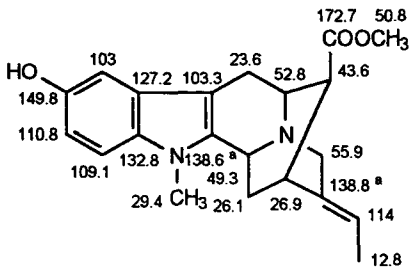
53 (+)-***E*-Akuammidine**
(*239*) 100.577 MHz, $CDCl_3$
see also (*9b*), (*161b*), (*236*), (*248*)



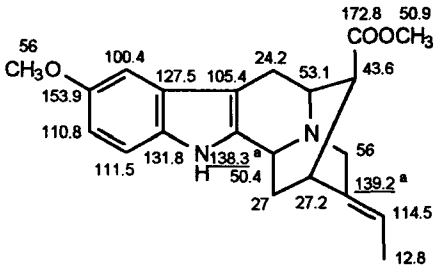
54 (−)-**Polyneuridine**
(*239*) 100.577 MHz, $CDCl_3$



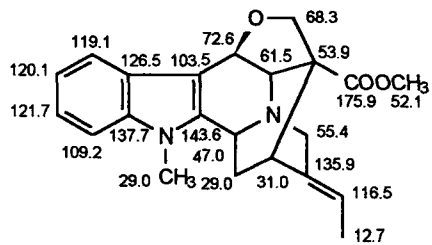
57 *Z*-Akuammidine
(*9b*) CD_3OD



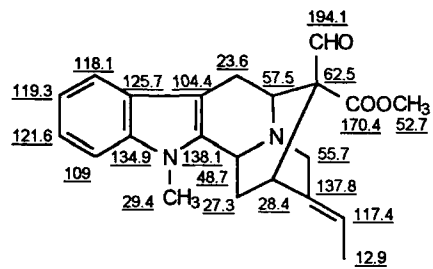
58 10-Hydroxy-N_a-methylpericyclivine
(*133*) $CDCl_3$



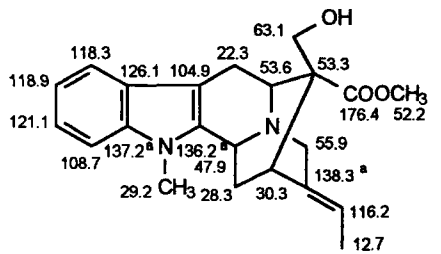
59 10-Methoxypericyclivine
(*133*) $CDCl_3$



62 Dehydrovoachalotine
(*189*) 25.6 MHz, $CDCl_3$



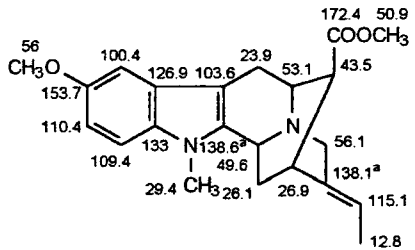
63 Voachalotinal
(*133*) $CDCl_3$



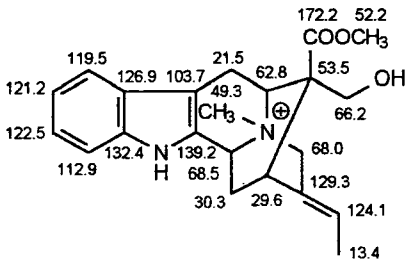
64 Voachalotine
(*239*) 100.577 MHz, $CDCl_3$
see also (*184*), (*189*)

(*continues*)

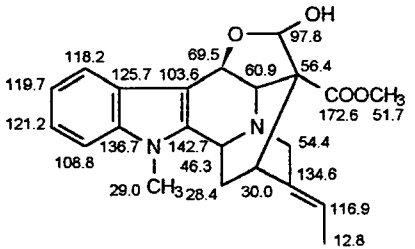
TABLE IV (*Continued*)



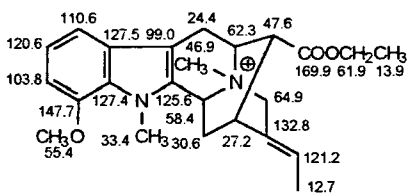
65 10-Methoxy-N_a-methylpericyclivine
(*133*) $CDCl_3$
see also (*193*)



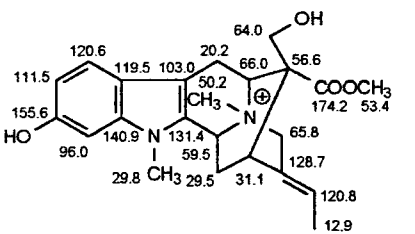
67 N_b-Methylakuammidine*
(*179*) 50.4 MHz, CD_3OD



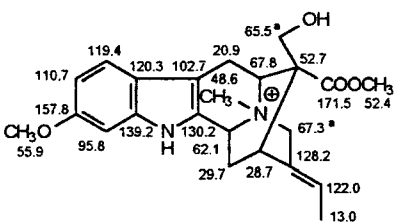
69 17-Hydroxydehydrovoachalotine
(*181*) 75 MHz, $CDCl_3$



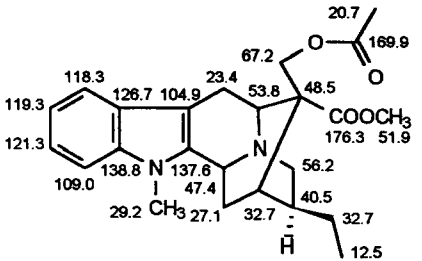
73 Fuchsiaefoline
(*184*) 25.2 MHz, $CDCl_3$



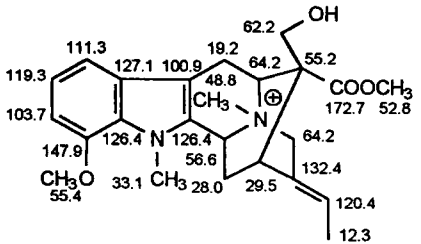
75 11-Hydroxy-N_a-methylmacusine A*
(*186*) 50.32 MHz, CD_3OD



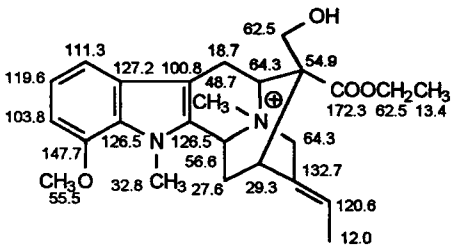
76 11-Methoxymacusine A*
(*187*) 25.2 MHz, CD_3OD



78 17-*O*-Acetyl-19,20-dihydrovoachalotine
(*189*) 25.6 MHz, $CDCl_3$



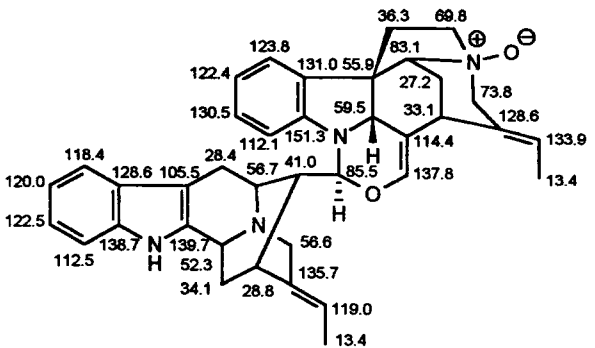
79 12-Methoxy-N_b-methylvoachalotine
(*184*) 25.2 MHz, $CDCl_3$



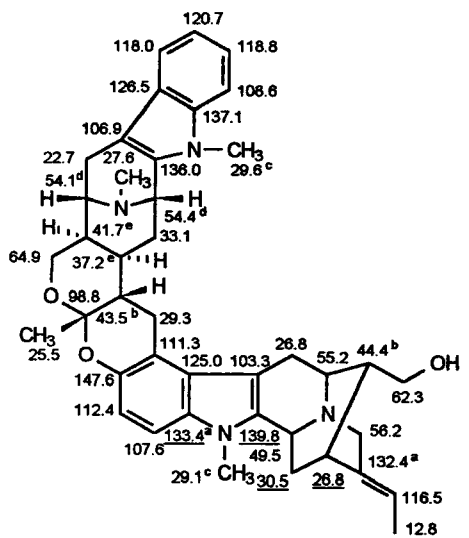
80 12-Methoxy-N_b-methylvoachalotine ethyl ester
(*184*) 25.2 MHz, $CDCl_3$

(*continues*)

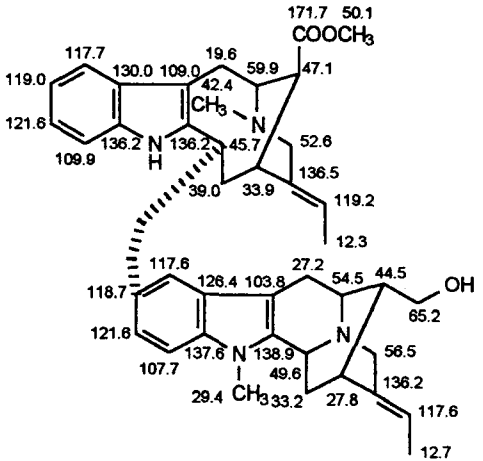
TABLE IV (*Continued*)



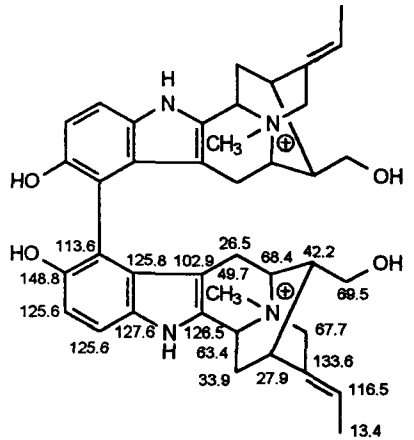
82 (+)-**Divaricine**
(*24*) CD_3OD



85 Macralstonidine
(*255*) 22.63 MHz, $CDCl_3$



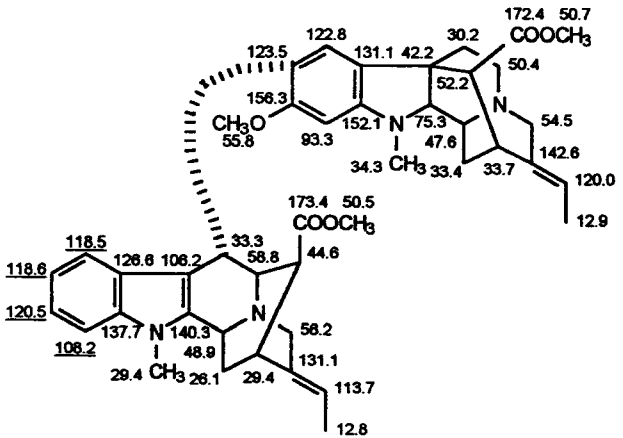
86 Accedinisine
(*37*) 75 MHz, $CDCl_3$



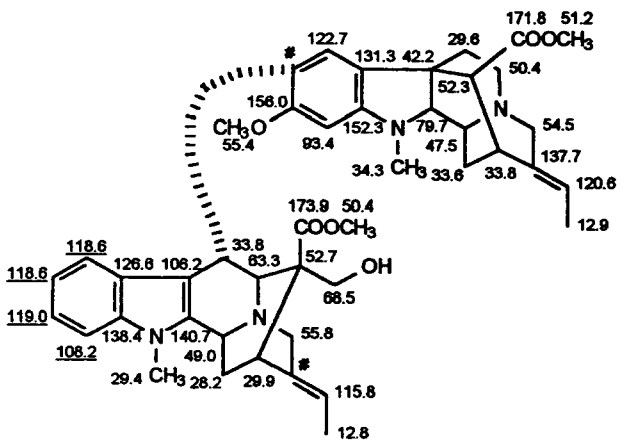
87 Dispegatrine*
(*129*) 90 MHz, CF_3COOD

(*continues*)

TABLE IV (*Continued*)

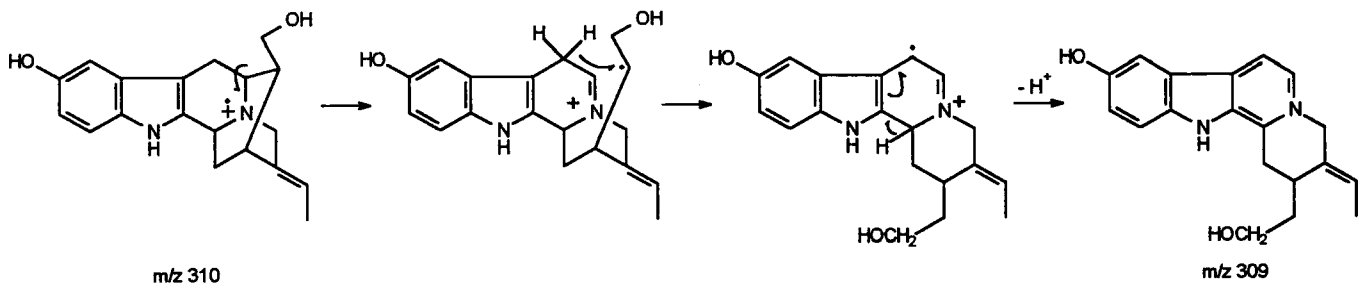


88 Desformoundulatine
(*193*) 75 MHz, $CDCl_3$

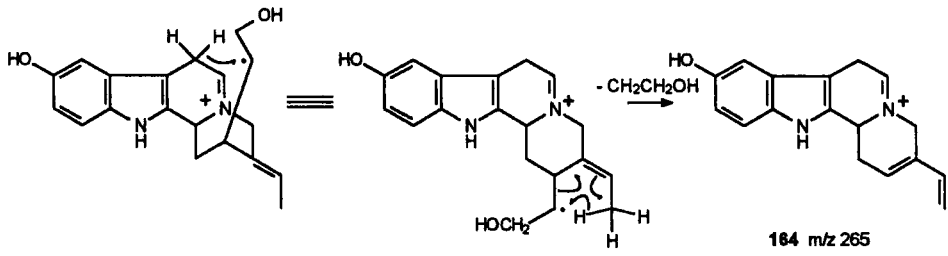


89 Undulatine
(*193*) 75 MHz, $CDCl_3$

^{13}C NMR signals reassigned by the writers are marked with underlining.
$^{a-e}$, Assignments may be reversed.
#, Value not mentioned.
*, Spectral data given for a chloride salt.



SCHEME 23. Formation of the M^+-1 ion.



SCHEME 24. The fragmentation of sarpagine derivatives.

Thermal loss of water, present for polyneuridine (**54**) and similar compounds and absent for akuammidine (**53**) and similar compounds, is characteristic for the stereochemistry at C-16. The difference in the behaviour of compounds of type **54** and **53** has been explained by the involvement of the N_a-hydrogen during the elimination process (Scheme 25) (*244*). References for the mass spectral data of individual compounds, when available, are given in Table III.

The FAB-CAB (Fast Atom Bombardment–Collision Activated Dissociation) linked scan (constant *B/E*) mass spectra of trinervine (**16**) and venecurine (**35**) have been examined by Das *et al.* (*247*). In contrast to the EI mass spectra, the FAB-CAD linked scan (constant *B/E*) spectra exhibited prominent fragment ion peaks at *m/z* 293 and *m/z* 251 for **16** and at *m/z* 307 and *m/z* 265 for **35** (Figs. 13 and 14). The fragments giving structurally useful information are due to losses of H_2O (18 mass units) and CH_3COOH (60 mass units) from **16**H^+ (*m/z* 311) and **35** (*m/z* 325) (Scheme 26).

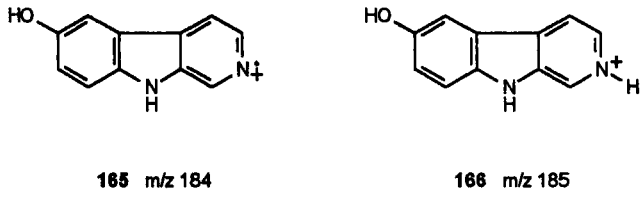
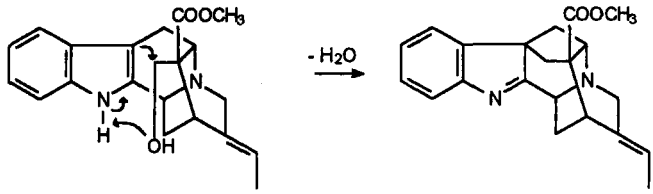


FIG. 12. Structures corresponding to peaks at *m/z* 184 and 185.



SCHEME 25. Thermal loss of water in polyneuridine (**54**) and similar compounds.

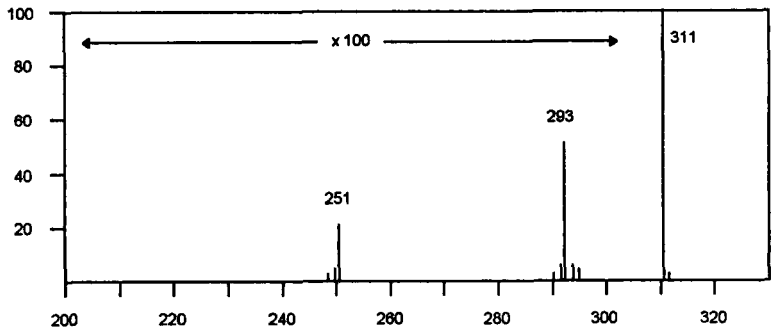


FIG. 13. Linked scan spectrum of protonated trinervine (**16**H$^+$).

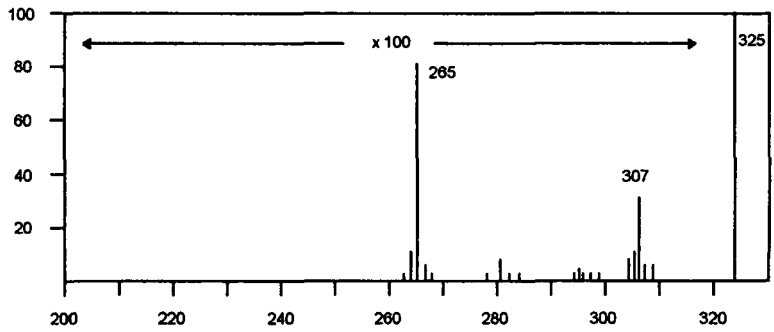
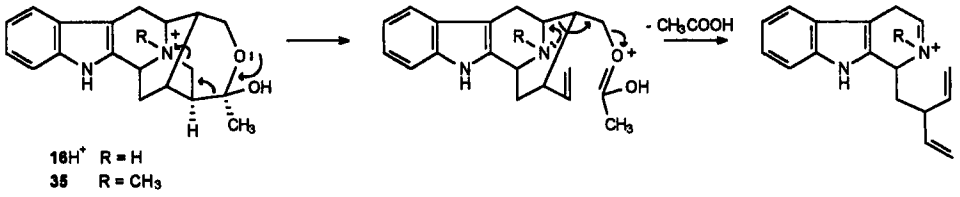


FIG. 14. Linked scan spectrum of venecurine (**35**).



SCHEME 26. Elimination process of CH_3COOH from protonated trinervine (**16H**$^+$) and venecurine (**35**).

VII. Pharmacology

Very few pharmacological effects have been indicated for the alkaloids of the sarpagine group. Normacusine B (**2**) has sedative and ganglion blocking activity (*256*). Lochnerine (**25**) shows hypoglycemic activity (*257*), and pericyclivine (**18**) has been indicated to have weak cytotoxic activity against leukemia P-388 (*112*). Gardnutine (**20**), gardnerine (**26**), and hydroxygardnutine (**42**) have been shown to have ganglion blocking effects (*258*).

The mixture of constituents [e.g., normacusine B (**2**), affinisine (**8**), N_a-methylpericyclivine (**41**), voachalotine (**64**)] present in *Peschiera van heurckii* from the tropical rain forest in Bolivia is known for its alleged leishmanicidal and bactericidal activity (*37*). Like many quaternary alkaloids, the major quaternary alkaloid from *Strychnos angolensis,* 11-methoxymacusine A (**76**), shows muscle-relaxant activity (*187*). The crude mixture of nine alkaloids present in *Ervatamia yunnanensis* is used in Chinese folk medicine for the treatment of hypertension (*176*). One of these alkaloids is a sarpagine derivative [voachalotine (**64**)].

VIII. Perspectives

Altogether 89 alkaloids belonging to the sarpagine group (*sensu stricto*) have been isolated from plant sources. It can be expected that the intensity of the search for new alkaloids of the sarpagine type will continue. Recently, considerable effort has been concentrated on the biogenetic formation of sarpagine alkaloids. Although considerable progress has been made (*vide supra*), several crucial problems still remain. The research on cell culture methods towards the preparation of sarpagine alkaloids can be expected

to continue (*259–263*). So far, unfortunately, the alkaloid content in cultured cells has tended to be low. Finally, methods for the preparation of sarpagine (and other) alkaloids based on gene transfer systems can be expected to be competitive in the future.

References

1. W. I. Taylor, *in* "The Alkaloids" (R. H. F. Manske, ed.), Vol. 8, p. 785. Academic Press, New York, 1965.
2. W. I. Taylor, *in* "The Alkaloids" (R. H. F. Manske, ed.), Vol. 11, p. 41. Academic Press, New York, 1968.
3. A. Koskinen and M. Lounasmaa, *in* "Progress in the Chemistry of Organic Natural Products" (W. Herz, H. Grisebach, and G. W. Kirby, eds.), Vol. 43, p. 267. Springer, Wien, 1983.
4. J. E. Saxton, *Nat. Prod. Rep.* **1,** 21 (1984); **2,** 49 (1985); **3,** 353 (1986); **4,** 591 (1987); **6,** 1 (1989); **6,** 433 (1989); **7,** 191 (1990); **8,** 251 (1991); **9,** 393 (1992); **10,** 349 (1993); **11,** 493 (1994); **12,** 385 (1995); **13,** 327 (1996).
5. M. Alvarez and J. A. Joule, *in* "Monoterpenoid Indole Alkaloids" (J. E. Saxton, ed.), Supplement, p. 217. Wiley, Chichester, 1994.
6. Z. Liu and R. Lu, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 33, p. 83. Academic Press, San Diego, 1988.
7. L. K. Hamaker and J. M. Cook, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 9, p. 23. Pergamon (Elsevier), Oxford, 1995. See also Y. Bi, L. K. Hamaker, and J. M. Cook, *in* "Studies in Natural Products Chemistry" (Atta-ur-Rahman, ed.), Vol. 13, p. 383. Elsevier, Amsterdam, 1993.
8. J. Stöckigt, *in* "The Alkaloids" (G. A. Cordell, ed.), Vol. 47, p. 115. Academic Press, San Diego, 1995.
9. (a) H. Takayama and S. Sakai, *in* "The Alkaloids" (G. A. Cordell, ed.), Vol. 49, p. 1, Academic Press, San Diego, 1997; (b) H. Takayama and S. Sakai, *in* "Studies in Natural Products Chemistry" (Atta-ur-Rahman, ed.), Vol. 15, p. 465. Elsevier, Amsterdam, 1995.
10. J. Le Men and W. I. Taylor, *Experientia* **21,** 508 (1965).
11. D. G. I. Kingston and O. Ekundays, *J. Nat. Prod.* **44,** 509 (1981). See also J. P. Kutney, *Heterocycles* **8,** 813 (1977); J. A. Martinez, C. Gomez, T. Santana, and H. Velez, *Planta Med.* **55,** 283 (1989); and J. A. Martinez, H. Velez, and T. Santana, *Phytochemistry* **28,** 961 (1989).
12. (a) W. Chen, Y. Yan, and Z. Xie, *Yaoxue Tongbao* **16,** 630 (1981); *Chem. Abstr.* **96,** 214278c (1982); (b) W. Chen, Y. Yan, and X. Liang, *Planta Med.* **49,** 62 (1983).
13. L. Douzoua, M. Mansour, M.-M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry* **13,** 1994 (1974).
14. H. Rapoport and R. E. Moore, *J. Org. Chem.* **27,** 2981 (1962). See also H. Rappoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Am. Chem. Soc.* **80,** 1601 (1958).
15. A. M. A. G. Nasser and W. E. Court, *J. Ethnopharmacol.* **11,** 99 (1984).
16. H. A. Lastra, M. Palacios, R. Menendez, M. Larionova, F. Rodriquez, and V. Fuste, *Rev. Cubana Farm.* **16,** 316 (1982); *Chem. Abstr.* **98,** 176193c (1983).
17. M. M. A. Amer and W. E. Court, *Planta Med. Suppl., 8* (1980).

18. M. A. Amer and W. E. Court, *Phytochemistry* **20,** 2569 (1981).
19. J. Banerji, B. Das, R. Chakrabarti, and J. N. Shoolery, *Indian J. Chem.* **26B,** 709 (1987).
20. P. Sierra and L. Novotný, *Planta Med.* **42,** 108 (1981). See also P. Sierra, L. Novotný, Z. Samek, M. Buděšínský, L. Dolejš, and K. Bláha, *Collect. Czech. Chem. Commun.* **47,** 2912 (1982).
21. H. R. Arthur, S. R. Johns, J. A. Lamberton, and S. N. Loo, *Aust. J. Chem.* **21,** 1399 (1968). See also Lin *et al.* (*129*).
22. A. Chatterjee and S. Bandyopadhyay, *Indian J. Chem.* **18B,** 87 (1979).
23. X. Feng and F. Fu, *Yaoxue Xuebao* **16,** 510 (1981); *Chem. Abstr.* **97,** 3593j (1982).
24. R. Mukherjee, B. A. da Silva, B. C. Das, P. A. Keifer, and J. N. Shoolery, *Heterocycles* **32,** 985 (1991).
25. M. Ohashi, H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Lévy, J. Gosset, J. Le Men, and M.-M. Janot, *Tetrahedron* **19,** 2241 (1963).
26. K. Ghedira, M. Zèches-Hanrot, B. Richard, G. Massiot, L. Le Men-Olivier, T. Sévenet, and S. H. Goh, *Phytochemistry* **27,** 3955 (1988).
27. L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Am. Chem. Soc.* **84,** 2161 (1962).
28. D. S. Nunes, L. Koike, J. J. Taveira, and F. de A. M. Reis, *Phytochemistry* **31,** 2507 (1992).
29. P. Rasoanaivo, N. Langlois, and P. Potier, *Phytochemistry* **11,** 2616 (1972).
30. D. Stauffacher, *Helv. Chim. Acta* **44,** 2006 (1961).
31. M. Zèches, K. Mesbah, A. Loukaci, B. Richard, H. Schaller, T. Sévenet, and L. Le Men-Olivier, *Planta Med.* **61,** 97 (1995).
32. P. Clivio, B. Richard, J.-R. Deverre, T. Sévenet, M. Zéches, and L. Le Men-Olivier, *Phytochemistry* **30,** 3785 (1991).
33. Y. L. Zhou, J. H. Ye, Z. M. Li, and Z. H. Huang, *Planta Med.* **54,** 315 (1988).
34. E. Séguin, F. Hôtellier, M. Koch, and T. Sévenet, *J. Nat. Prod.* **47,** 687 (1984).
35. M. Azoug, A. Loukaci, B. Richard, J.-M. Nuzillard, C. Moretti, M. Zèches-Hanrot, and L. Le Men-Olivier, *Phytochemistry* **39,** 1223 (1995).
36. L. Jahodář, Z. Votický, and M. P. Cava, *Phytochemistry* **13,** 2880 (1974).
37. V. Muñoz, C. Moretti, M. Sauvain, C. Caron, A. Porzel, G. Massiot, B. Richard, and L. Le Men-Olivier, *Planta Med.* **60,** 455 (1994).
38. M. Pinar, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **56,** 2719 (1973).
39. A. M. A. G. Nasser and W. E. Court, *Phytochemistry* **22,** 2297 (1983). See also A. M. A. G. Nasser and W. E. Court, *Planta Med.* **47,** 242 (1983).
40. M. M. Iwu and W. E. Court, *Phytochemistry* **17,** 1651 (1978).
41. M. M. A. Amer and W. E. Court, *Planta Med.* **43,** 94 (1981).
42. M. M. Iwu and W. E. Court, *Planta Med.* **33,** 232 (1978).
43. B. A. Akinloye and W. E. Court, *Phytochemistry* **19,** 2741 (1980).
44. (a) A. K. Kiang, H. Lee, J. Goh, and A. S. C. Wan, *Lloydia* **27,** 220 (1964); (b) A. K. Kiang, S. K. Loh, M. Demanczyk, C. W. Gemenden, G. J. Papariello, and W. I. Taylor, *Tetrahedron* **22,** 3293 (1966).
45. S. P. Majumdar, J. Poisson, and P. Potier, *Phytochemistry* **12,** 1167 (1973).
46. D. Yu and M. Lin, *Yaoxue Xuebao* **17,** 309 (1982); *Chem. Abstr.* **97,** 3591g (1982).
47. B. A. Akinloye and W. E. Court, *Planta Med.* **37,** 361 (1979).
48. N. N. Sabri and W. E. Court, *Phytochemistry* **17,** 2023 (1978).
49. R. Verpoorte, M. J. Verzijl, and A. Baerheim Svendsen, *Planta Med.* **44,** 21 (1982).
50. C. Delaude, P. Thépenier, M.-J. Jacquier, G. Massiot, and L. Le Men-Olivier, *Bull. Soc. R. Sci. Liege* **61,** 429 (1992).
51. R. Verpoorte, *Pharm. Weekbl.* **113,** 1249 (1978); *Chem. Abstr.* **90,** 109840h (1979).

52. G. B. Marini-Bettòlo, S. E. Giuffra, C. Galeffi, and E. M. Delle Monache, *Gazz. Chim. Ital.* **103,** 591 (1973).
53. P. Rasoanaivo, G. Galeffi, Y. de Vicente, and M. Nicoletti, *Rev. Latinoamer. Quim.* **22,** 32 (1991).
54. K. H. C. Baser, N. G. Bisset, and P. J. Hylands, *Phytochemistry* **18,** 512 (1979).
55. G. Massiot, P. Thépenier, M.-J. Jacquier, L. Le Men-Olivier, and C. Delaude, *Phytochemistry* **31,** 2873 (1992).
56. G. B. Marini-Bettòlo, C. Galeffi, M. Nicoletti, and I. Messana, *Phytochemistry* **19,** 992 (1980).
57. R. Mukherjee, M. de F. F. Melo, C. A. de M. Santos, E. Guittet, and B. C. Das, *Heterocycles* **31,** 1819 (1990).
58. M. B. Patel, L. Thompson, C. Miet, and J. Poisson, *Phytochemistry* **12,** 451 (1973).
59. T. A. van Beek, R. Verpoorte, A. Baerheim Svendsen, and R. Fokkens, *J. Nat. Prod.* **48,** 400 (1985).
60. T. A. van Beek, F. L. C. Kuijlaars, P. H. A. M. Thomassen, R. Verpoorte, and A. Baerheim Svendsen, *Phytochemistry* **23,** 1771 (1984).
61. J. Garnier and J. Mahuteau, *Planta Med.* **52,** 66 (1986).
62. M. B. Sultanov and T. Saidkasymov, *Dokl. Akad. Nauk. Uz. SSR* **22,** 41 (1965); *Chem. Abstr.* **63,** 13853g (1965).
63. H. Jin and R. Xu, *Acta Chim. Sinica* **40,** 1129 (1982); *Chem. Abstr.* **98,** 104296r (1983). See also Schun and Cordell (*64*).
64. Y. Schun and G. A. Cordell, *Phytochemistry* **26,** 2875 (1987).
65. M. M. Iwu and W. E. Court, *Planta Med.* **45,** 105 (1982).
66. A. Banerji, M. Chakrabarty, and B. Mukherjee, *Phytochemistry* **11,** 2605 (1972).
67. (a) J. A. Weisbach, R. F. Raffauf, O. Ribeiro, E. Macko, and B. Douglas, *J. Pharm. Sci.* **52,** 350 (1963); (b) M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, R. F. Raffauf, and O. Ribeiro, *Chem. Ind. (London)*, 1193 (1964).
68. C. Kan, A. Henriquès, Y. Jasor, C. Moretti, and H.-P. Husson, *J. Nat. Prod.* **47,** 478 (1984).
69. H. Achenbach, *Tetrahedron Lett.*, 4405 (1966).
70. W. W. Filho, M. L. B. Pinheiro, and A. I. da Rocha, *Acta Amazonica* **13,** 409 (1983); *Chem. Abstr.* **102,** 3271z (1985).
71. M. M. Iwu and W. E. Court, *Planta Med.* **33,** 360 (1978).
72. F. Fish, M. Qaisuddin, and J. B. Stenlake, *Chem. Ind. (London)*, 319 (1964).
73. Z. M. Khan, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **50,** 625 (1967).
74. C. Galeffi, E. M. Delle Monache, and G. B. Marini-Bettòlo, *Ann. Chim. (Rome)* **63,** 849 (1973); *Chem. Abstr.* **82,** 152144f (1975).
75. A. A. Olaniyi, W. N. A. Rolfsen, and R. Verpoorte, *Planta Med.* **43,** 353 (1981).
76. B. de Datta and N. G. Bisset, *Planta Med.* **56,** 133 (1990).
77. A. R. Battersby, R. Binks, H. F. Hodson, and D. A. Yeowell, *J. Chem. Soc.*, 1848 (1960). See also A. T. McPhail, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 1832 (1963).
78. L. Angenot, *Planta Med.* **27,** 24 (1975).
79. S. Bose, S. K. Talapatra, and A. Chatterjee, *J. Indian Chem. Soc.* **33,** 379 (1956).
80. M. S. Habib and W. E. Court, *Phytochemistry* **12,** 1821 (1973).
81. B. U. Vergara, *J. Am. Chem. Soc.* **77,** 1864 (1955). See also J. Keck, *Naturwiss.* **42,** 391 (1955).
82. J. A. Martínez, R. Valero, M. E. Sosa, and M. Manchúa, *Rev. Cubana Quim.* **6,** 48 (1992); *Chem. Abstr.* **120,** 73468q (1994).
83. M. M. Iwu and W. E. Court, *Planta Med.* **34,** 390 (1978).
84. C. K. Atal, *J. Am. Pharm. Assoc.* **48,** 37 (1959).
85. S. Bhattacharji, M. M. Dhar, and M. L. Dhar, *J. Sci. Ind. Res. (India)* **21B,** 454 (1962).

86. M. Ishidate, M. Okada, and K. Saito, *Pharm. Bull.* **3,** 319 (1955).
87. J. M. Müller, *Experientia* **13,** 479 (1957).
88. M. M. Iwu and W. E. Court, *Planta Med.* **36,** 208 (1979).
89. A. K. Kiang and A. S. C. Wan, *J. Chem. Soc.,* 1394 (1960).
90. M. L. Belem-Pinheiro, A. F. Imbiriba da Rocha, J. Quetin-Leclercq, J. N. Wauters, and L. Angenot, *Fitoterapia* **59,** 429 (1988). See also M. L. Belem-Pinheiro, A. F. Imbiriba da Rocha, J. Quetin-Leclercq, J. N. Wauters, and L. Angenot, *J. Pharm. Belg.* **43,** 379 (1988).
91. A. Stoll and A. Hofmann, *Helv. Chim. Acta* **36,** 1143 (1953).
92. J. A. Martinez, M. R. Rodriguez, M. Dehesa, and M. Machua, *Rev. Cubana Quim.* **4,** 43 (1988); *Chem. Abstr.* **111,** 229015s (1989).
93. B. A. Akinloye and W. E. Court, *J. Ethnopharmacol.* **4,** 99 (1981).
94. J. Poisson and R. Goutarel, *Bull. Soc. Chim. Fr.,* 1703 (1956).
95. M.-M. Janot, J. Le Men, and C. Fan, *Ann. Pharm. Fr.* **15,** 513 (1957).
96. N. R. Farnsworth, H. H. S. Fong, R. N. Blomster, and F. J. Draus, *J. Pharm. Sci.* **51,** 217 (1962).
97. M. S. Habib and W. E. Court, *Phytochemistry* **13,** 661 (1974).
98. S. Subhadhirasakul, H. Takayama, N. Aimi, D. Ponglux, and S. Sakai, *Chem. Pharm. Bull.* **42,** 1427 (1994).
99. J.-L. Pousset, and J. Poisson, *Ann. Pharm. Fr.* **23,** 733 (1965).
100. (a) D. A. Rakhimov, M. R. Sharipov, K. N. Aripov, V. M. Malikov, T. T. Shakirov, and S. Yu Yunusov, *Chem. Nat. Comp.* **6,** 724 (1970); (b) V. M. Malikov, M. R. Sharipov, and S. Yu Yunusov, *Chem. Nat. Comp.* **8,** 741 (1972).
101. W. Chen, Y. Yan, Y. Wang, and X. Liang, *Yaoxue Xuebao* **20,** 906 (1985); *Chem. Abstr.* **105,** 3520s (1986).
102. D. Guillaume, A. M. Morfaux, B. Richard, G. Massiot, L. Le Men-Olivier, J. Pusset, and T. Sévenet, *Phytochemistry* **23,** 2407 (1984).
103. N. R. Farnsworth, W. D. Loub, R. N. Blomster, and M. Gorman, *J. Pharm. Sci.* **53,** 1558 (1964).
104. N. Langlois, L. Diatta, and R. Z. Andriamialisoa, *Phytochemistry* **18,** 467 (1979).
105. S. Mukhopadhyay and G. A. Cordell, *J. Nat. Prod.* **44,** 335 (1981).
106. P. Clivio, B. Richard, H. A. Hadi, B. David, T. Sévenet, M. Zèches, and L. Le Men-Olivier, *Phytochemistry* **29,** 3007 (1990).
107. M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, R. F. Raffauf, and J. L. Beal, *Tetrahedron Lett.,* 931 (1965).
108. A.-M. Bui, B. C. Das, and P. Potier, *Phytochemistry* **19,** 1473 (1980).
109. M. Bert, F. Tillequin, G. Baudouin, M. Koch, and T. Sévenet, *Fitoterapia* **60,** 141 (1989).
110. D. G. I. Kingston, B. T. Li, and F. Ionescu, *J. Pharm. Sci.* **66,** 1135 (1977).
111. R. van der Heijden, A. Hermans-Lokkerbol, L. P. J. de Kool, P. J. Lamping, P. A. A. Harkes, and R. Verpoorte, *Planta Med.* **54,** 393 (1988).
112. D. G. I. Kingston, B. B. Gerhart, F. Ionescu, M. M. Mangino, and S. M. Sami, *J. Pharm. Sci.* **67,** 249 (1978).
113. V. Y. Vachnadze and K. S. Mudzhiri, *in* "Khromatogr. Metody Farm." (B. I. Chumburidze, ed.), p. 156, Tbilis. Gos. Med. Inst., Tiflis USSR, 1977; *Chem. Abstr.* **90,** 164704s (1979).
114. P. Potier, R. Beugelmans, J. Le Men, and M.-M. Janot, *Ann. Pharm. Fr.* **23,** 61 (1965).
115. J. Haginiwa, S. Sakai, A. Kubo, and T. Hamamoto, *Yakugaku Zasshi* **87,** 1484 (1967); *Chem. Abstr.* **69,** 19365u (1968). See also S. Sakai, A. Kubo, and J. Haginiwa, *Tetrahedron Lett.,* 1485 (1969).

116. J. Quetin-Leclercq, L. Angenot, L. Dupont, and N. G. Bisset, *Phytochemistry* **27,** 4002 (1988). See also L. Dupont, O. Dideberg, M. Sbit, J. Quetin-Leclercq, and L. Angenot, *Acta Cryst. C* **44,** 2156 (1988).
117. H. Achenbach, M. Löwel, R. Waibel, M. P. Gupta, and P. Solis, *J. Nat. Prod.* **54,** 473 (1991).
118. K. H. C. Baser and N. G. Bisset, *Phytochemistry* **21,** 1423 (1982).
119. M.-M. Janot and J. Le Men, *C. R. Acad. Sci. Ser. C* **243,** 1789 (1956).
120. S. Mukhopadhyay, G. A. Cordell, G. A. Sim, and P. J. Cox, *Tetrahedron* **39,** 3639 (1983).
121. W. B. Mors, P. Zaltzman, J. J. Beereboom, S. C. Pakrashi, and C. Djerassi, *Chem. Ind.,* 173 (1956).
122. J. Abaul, E. Philogène, P. Bourgeois, G. Mérault, C. Poupat, A. Ahond, and P. Potier, *J. Nat. Prod.* **49,** 829 (1986).
123. A. Madinaveitia, E. Valencia, J. Bermejo, and A. G. Gonzalez, *Biochem. Syst. Ecol.* **23,** 877 (1995).
124. N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.* **25,** 2739 (1972).
125. J. Naranjo, M. Pinar, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **55,** 752 (1972).
126. A. Banerji and M. Chakrabarty, *Phytochemistry* **13,** 2309 (1974).
127. Atta-ur-Rahman, S. A. Abbas, F. Nighat, G. Ahmed, M. I. Choudhary, K. A. Alvi, Habib-ur-Rehman, K. T. D. De Silva, and L. S. R. Arambewela, *J. Nat. Prod.* **54,** 750 (1991). **Note!** The structure, originally given for alstoumerine by Atta-ur-Rahman *et al.,* has been corrected to structure (-)-**32** by M. Lounasmaa and P. Hanhinen: Symposium *"Synthesis in Bioorganic Chemistry,"* Hannover, Germany, February 26–28, 1998.
128. O. O. Orazi, R. A. Corral, and M. E. Stoichevich, *Can. J. Chem.* **44,** 1523 (1966).
129. M. Lin, B. Yang, and D. Yu, *Yaoxue Xuebao* **21,** 114 (1986); *Chem. Abstr.* **104,** 221983r (1986).
130. M. Lin, D. Yu, X. Liu, F. Fu, Q. Zheng, C. He, G. Bao, and C. Yu, *Yaoxue Xuebao* **20,** 198 (1985); *Chem. Abstr.* **103,** 138514x (1985).
131. J. Quentin-Leclercq, R. Warin, N. G. Bisset, and L. Angenot, *Phytochemistry* **28,** 2221 (1989).
132. A. Banerji and M. Chakrabarty. *Phytochemistry* **16,** 1124 (1977).
133. T.-M. Pinchon, J.-M. Nuzillard, B. Richard, G. Massiot, L. Le Men-Olivier, and T. Sévenet, *Phytochemistry* **29,** 3341 (1990).
134. W. Arnold, F. Berlage, K. Bernauer, H. Schmid, and P. Karrer, *Helv. Chim. Acta* **41,** 1505 (1958). See also P. Karrer and H. Schmid, *Helv. Chim. Acta* **29,** 1853 (1946) and H. Wieland, W. Konz, and R. Sonderhoff, *Liebigs Ann. Chem.* **527,** 160 (1937).
135. Z. M. Khan, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **48,** 1957 (1965).
136. Z. M. Khan, M. Hesse, and H. Schmid, *Helv. Chim. Acta* **50,** 1002 (1967).
137. N. Aimi, K. Yamaguchi, S. Sakai, J. Haginiwa, and A. Kubo, *Chem. Pharm. Bull.* **26,** 3444 (1978).
138. J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron* **21,** 1717 (1965).
139. G. Croquelois, N. Kunesch, M. Debray, and J. Poisson, *Plant. Med. Phytother.* **6,** 122 (1972).
140. A. Banerji and S. Jana, *J. Indian Chem. Soc.* **63,** 449 (1986).
141. A. Chatterjee, B. Mukherjee, S. Ghosal, and P. K. Banerjee, *J. Indian Chem. Soc.* **46,** 635 (1969).
142. K. Bojthe-Horvath, A. Kocsis, I. Mathe, J. Tamas, and O. Clauder, *Acta Pharm. Hung.* **44** (Suppl.), 66 (1974); *Chem. Abstr.* **81,** 136347y (1974).
143. P. Sharma, Y. Shirataki, and G. A. Cordell, *Phytochemistry* **27,** 3649 (1988).
144. J.-M. Panas, A.-M. Morfaux, L. Olivier, and J. Le Men, *Ann. Pharm. Fr.* **30,** 273 (1972).
145. S. Markey, K. Biemann, and B. Witkop, *Tetrahedron Lett.,* 157 (1967).
146. L. Allorge, P. Boiteau, J. Bruneton, T. Sévenet, and A. Cavé, *J. Nat. Prod.* **43,** 514 (1980).

147. R. Kaschnitz and G. Spiteller, *Monatsh. Chem.* **96,** 909 (1965).
148. A.-M. Bui, P. Potier, M. Urrea, A. Clastres, D. Laurent, and M.-M. Debray, *Phytochemistry* **18,** 1329 (1979).
149. P. L. Majumder, *J. Indian Chem. Soc.* **45,** 853 (1968).
150. H. H. A. Linde, *Helv. Chim. Acta* **48,** 1822 (1965).
151. A. Rabaron, M. H. Mehri, T. Sévenet, and M. M. Plat, *Phytochemistry* **17,** 1452 (1978).
152. L.-W. Guo and Y.-L. Zhou, *Phytochemistry* **34,** 563 (1993).
153. H. Mehri, M. Plat, and P. Potier, *Ann. Pharm. Fr.* **29,** 291 (1971).
154. S. Sakai, N. Aimi, K. Takahashi, M. Kitagawa, K. Yamaguichi, and J. Haginiwa, *Yakugaku Zasshi* **94,** 1274 (1974); *Chem. Abstr.* **82,** 43633u (1975).
155. J. M. Panas, B. Richard, C. Sigaut, M.-M. Debray, L. Le-Men-Olivier, and J. Le Men, *Phytochemistry* **13,** 1969 (1974).
156. Z. Votický, L. Jahodář, and M. P. Cava, *Coll. Czech. Chem. Commun.* **42,** 1403 (1977).
157. T. A. Henry, *J. Chem. Soc.,* 2759 (1932).
158. J. Lévy, J. Le Men, and M.-M. Janot, *C. R. Acad. Sci., Ser. C* **253,** 131 (1961).
159. L.-Z. Lin and G. A. Cordell, *Phytochem. Anal.* **1,** 26 (1990). See also Jokela and Lounasmaa (*239*).
160. S. Mukhopadhyay, G. A. Handy, S. Funayama, and G. A. Cordell, *J. Nat. Prod.* **44,** 696 (1981). See also Jokela and Lounasmaa (*239*).
161. (a) A. Chatterjee, C. R. Ghosal, N. Adityachaudhury, and S. Ghosal, *Chem. Ind.* (*London*), 1034 (1961); (b) E. A. Abdel Sattar, M. M. El Olemy, and J. S. Mossa, *Saudi Pharm. J.* **2,** 135 (1994).
162. C. Delaude, P. Thépenier, M.-J. Jacquier, J.-M. Nuzillard, G. Massiot, and L. Le Men-Olivier, *Bull. Soc. R. Sci. Liege* **64,** 243 (1995).
163. I. Perez and P. Sierra, *Rev. Latinoamer. Quim.* **11,** 132 (1980).
164. J. P. Kutney and I. Perez, *Helv. Chim. Acta* **65,** 2242 (1982).
165. H. B. Nielsen, A. Hazell, R. Hazell, F. Ghia, and K. B. G. Torssell, *Phytochemistry* **37,** 1729 (1994).
166. H. Achenbach and B. Raffelsberger, *Z. Naturforsch* **35B,** 885 (1980).
167. A. Walser and C. Djerassi, *Helv. Chim. Acta* **48,** 391 (1965).
168. J. Gosset, J. Le Men, and M.-M. Janot, *Ann. Pharm. Fr.* **20,** 448 (1962).
169. V. M. Malikov, P. K. Yuldashev, and S. Yu Yunusov, *Chem. Nat. Comp.* **2,** 276 (1966).
170. J.-C. Braekman, M. Tirions-Lampe, and J. Pecher, *Bull. Soc. Chim. Belg.* **78,** 523 (1969).
171. P. L. Majumder and B. N. Dinda, *J. Indian Chem. Soc.* **51,** 370 (1974).
172. P. Majumder and A. Basu, *Phytochemistry* **21,** 2389 (1982).
173. S. Sakai, S. Wongseripipatana, D. Ponglux, M. Yokota, K. Ogata, H. Takayama, and N. Aimi, *Chem. Pharm. Bull.* **35,** 4668 (1987).
174. G. Tirions, M. Kaisin, J. C. Braekman, J. Pecher, and R. H. Martin, *Chimia* **22,** 87 (1968).
175. G. Lewin, O. Tamini, P. Cabalion, and J. Poisson, *Ann. Pharm. Fr.* **39,** 273 (1981).
176. G. Liu, Z. Liu, and X. Feng, *Planta Med.* **54,** 519 (1988).
177. A. E. Gower, B. da S. Pereira, and A. J. Marsaioli, *Phytochemistry* **25,** 2908 (1986).
178. J. Pecher, N. Defay, M. Gauthier, J. Peeters, R. H. Martin, and A. Vandermeers, *Chem. Ind.* (*London*), 1481 (1960).
179. W. Hu, J. Zhu, and M. Hesse, *Planta Med.* **55,** 463 (1989).
180. A.-M. Morfaux, L. Olivier, J. Lévy and J. Le Men, *Ann. Pharm. Fr.* **27,** 679 (1969).
181. A.-M. Morfaux, D. Guillaume, G. Massiot, and L. Le Men-Olivier, *C. R. Acad. Sci., Ser. II* **309,** 33 (1989).
182. G. Lhoest, R. de Neys, N. Defay, J. Seibl, J. Pecher, and R. H. Martin, *Bull. Soc. Chim. Belg.* **74,** 534 (1965).
183. R. L. Lyon, H. H. S. Fong, and N. R. Farnsworth, *J. Pharm. Sci.* **62,** 833 (1973).

184. R. M. Braga and F. de A. M. Reis, *Phytochemistry* **26,** 833 (1987).
185. G. Lewin, N. Kunesch, A. Cavé, T. Sévenet, and J. Poisson, *Phytochemistry* **14,** 2067 (1975).
186. A. Madinaveitia, E. Valencia, J. Bermejo, A. G. Gonzalez, and M. P. Gupta, *J. Nat. Prod.* **58,** 250 (1995).
187. R. Verpoorte, L. Bohlin, D. Dwuma-Badu, W. Rolfsen, and J. Strömbom, *J. Nat. Prod.* **46,** 572 (1983).
188. M. R. Sharipov, M. Khalmirzaev, V. M. Malikov, and S. Yu Yunusov, *Chem. Nat. Comp.* **10,** 422 (1974).
189. E. Bombardelli, A. Bonati, B. Gabetta, E. Martinelli, G. Mustich, and B. Danieli, *Phytochemistry* **15,** 2021 (1976).
190. M. Lin, B. Yang, D. Yu, X. Lin, and Y. Zhang, *Yaoxue Xuebao* **22,** 833 (1987); *Chem. Abstr.* **108,** 164701d (1988).
191. (a) T. M. Sharp, *J. Chem. Soc.,* 1227 (1934); (b) E. E. Waldner, M. Hesse, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta* **50,** 1926 (1967).
192. H. Achenbach and E. Schaller, *Chem. Ber.* **109,** 3527 (1976).
193. J.-M. Nuzillard, T.-M. Pinchon, C. Caron, G. Massiot and L. Le Men-Olivier, *C. R. Acad. Sci., Ser, II* **309,** 195 (1989).
194. W. Arnold, W. von Philipsborn, H. Schmid, and P. Karrer, *Helv. Chim. Acta* **40,** 705 (1957).
195. W. Kohl, B. Witte, W. S. Sheldrick, and G. Höfle, *Planta Med.* **50,** 242 (1984).
196. A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.,* 4419 (1964).
197. A. Chatterjee and S. Bose, *Science and Culture* **17,** 139 (1951); *Chem. Abstr.* **46,** 9264a (1952); A. Chatterjee and S. Talapatra, *Naturwiss.* **42,** 182 (1955); A. Chatterjee, S. C. Pakrashi, and G. Werner, *in* "Progress in the Chemistry of Organic Natural Products" (L. Zechmeister, ed.), Vol. 13, p. 346. Springer, Wien, 1956.
198. M. Quaisuddin, *Bangladesh J. Sci. Ind. Res.* **15,** 35 (1980); *Chem. Abstr.* **96,** 3651f (1982).
199. L. S. R. Arambewela and T. Ranatunge, *Phytochemistry* **30,** 1740 (1991).
200. P. P. Pillay, D. S. Rao, and S. B. Rao, *J. Sci. Ind. Res.* **19B,** 135 (1960).
201. E. E. van Tamelen and L. K. Olivier, *J. Am. Chem. Soc.* **92,** 2136 (1970). See also E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron* **24,** 687 (1968).
202. E. E. van Tamelan and L. K. Olivier, *Bioorg. Chem.* **5,** 309 (1976). See also E. E. van Tamelan, J. P. Yardley, M. Miyano, and W. B. Hinshaw Jr., *J. Am. Chem. Soc.* **91,** 7349 (1969).
203. M. Lounasmaa and P. Hanhinen, *Tetrahedron* **52,** 15225 (1996).
204. M. Lounasmaa and P. Hanhinen, *Planta Med.,* in press.
205. D. Herlem, A. Florès-Parra, F. Khuong-Huu, A. Chiaroni, and C. Riche, *Tetrahedron* **38,** 271 (1982). See also Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron* **31,** 3049 (1975).
206. P. Magnus, B. Mugrage, M. DeLuca, and G. A. Cain, *J. Am. Chem. Soc.* **111,** 786 (1989). See also P. Magnus, B. Mugrage, M. R. DeLuca, and G. A. Cain, *J. Am. Chem. Soc.* **112,** 5220 (1990).
207. Y. Yoneda, *Chem. Pharm. Bull.* **13,** 1231 (1965).
208. Y. Bi, L.-H. Zhang, L. K. Hamaker, and J. M. Cook, *J. Am. Chem. Soc.* **116,** 9027 (1994) and references therein.
209. P. D. Bailey and N. R. McLay, *J. Chem. Soc., Perkin Trans. 1,* 441 (1993). See also P. D. Bailey and N. R. McLay, *Tetrahedron Lett.* **32,** 3895 (1991).
210. P. D. Bailey, S. P. Hollinshead, M. H. Moore, K. M. Morgan, D. I. Smith, and J. M. Vernon, *Tetrahedron Lett.* **35,** 3585 (1994). See also P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith, and J. M. Vernon, *Tetrahedron Lett.* **35,** 3587 (1994).

211. P. D. Bailey, I. D. Collier, S. P. Hollinshead, M. H. Moore, K. M. Morgan, D. I. Smith, and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1,* 1209 (1997).
212. P. Yu, T Wang, E. Yu, and J. M. Cook, *Tetrahedron Lett.* **38,** 6819 (1997). See also E. D. Cox, L. K. Hamaker, J. Li, P. Yu, K. M. Czerwinski, L. Deng, D. W. Bennett, and J. M. Cook, *J. Org. Chem.* **62,** 44 (1997) and X. Fu and J. M. Cook, *J. Am. Chem. Soc.* **114,** 6910 (1992).
213. M. Kitajima, H. Takayama, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1,* 1773 (1991); H. Takayama, M. Kitajima, S. Wongseripipatana, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1,* 1075 (1989); H. Takayama, M. Kitajima, and S. Sakai, *Tetrahedron* **50,** 11813 (1994).
214. Z. Liu and F. Xu, *Tetrahedron Lett.* **30,** 3457 (1989). See also F. Xu and Z. Liu, *Huaxue Xuebao* **49,** 290 (1991); *Chem. Abstr.* **115,** 92663n (1991).
215. S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar, and Y. Yasunari, *J. Am. Chem. Soc.* **89,** 2506 (1967).
216. K. Mashimo and Y. Sato, *Tetrahedron Lett.,* 905 (1969). See also K. Mashimo and Y. Sato, *Tetrahedron Lett.,* 901 (1969) and K. Mashimo and Y. Sato, *Tetrahedron* **26,** 803 (1970).
217. C. Phisalaphong, H. Takayama, and S. Sakai, *Tetrahedron Lett.* **34,** 4035 (1993).
218. M. Kitajima, H. Takayama, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1,* 1573 (1994).
219. H. Takayama, Y. Tominaga, M. Kitajima, N. Aimi, and S. Sakai, *J. Org. Chem.* **59,** 4381 (1994).
220. J. Stöckigt and M. Zenk, *J. Chem. Soc., Chem. Comm.,* 646 (1977). See also M. Rueffer, N. Nagakura, and M. H. Zenk, *Tetrahedron Lett.,* 1593 (1978).
221. A. I. Scott, S. L. Lee, P. de Capite, M. G. Culver, and C. R. Hutchinson, *Heterocycles* **7,** 979 (1977).
222. Atta-ur-Rahman and A. Basha, "Biosynthesis of Indole Alkaloids," p. 68. Clarendon Press, Oxford, 1983.
223. M. Luckner, "Secondary Metabolism in Microorganisms, Plants, and Animals," 3rd ed., p. 353. Springer Verlag, Berlin, 1990.
224. J. Bruneton, "Pharmacognosie, Phytochimie, Plantes Médicinales," 2nd ed., p. 821. Technique et Documentation—Lavoisier, Paris, 1993.
225. J. Stöckigt, *Tetrahedron Lett.,* 2615 (1979).
226. A Pfitzner and J. Stöckigt, *Tetrahedron Lett.* **24,** 1695 (1983).
227. A. Pfitzner and J. Stöckigt, *Planta Med.* **48,** 221 (1983).
228. A. Pfitzner and J. Stöckigt, *J. Chem. Soc., Chem. Comm.,* 459 (1983).
229. A. Pfitzner, B. Krausch, and J. Stöckigt, *Tetrahedron* **40,** 1691 (1984).
230. D. Schmidt and J. Stöckigt, *Planta Med.* **61,** 254 (1995).
231. Atta-ur-Rahman, "One and Two Dimensional NMR Spectroscopy," Elsevier, Amsterdam, 1989.
232. G. E. Martin and A. S. Zektzer, "Two-Dimensional NMR Methods for Establishing Molecular Connectivity," VHC-Publishers, Weinheim, 1988.
233. H. Günther, "La Spectroscopie de RMN," Masson, Paris, 1993.
234. M. Lounasmaa and A. Tolvanen, *Heterocycles* **24,** 3229 (1986).
235. D. Neuhaus and M. P. Williamson, "The Nuclear Overhauser Effect in Structural and Conformational Analysis," VCH, New York, 1989.
236. M. Lounasmaa, R. Jokela, A. Tolvanen, and S.-K. Kan, *Planta Med.* **51,** 519 (1985).
237. A. K. Bashir, A. A. Abdalla, E. S. Hassan, I. A. Wasfi, M. A. Amiri, and T. A. Crabb, *Arab Gulf J. Scient. Res.* **12,** 119 (1994); *Chem. Abstr.* **121,** 200861k (1994).
238. Atta-ur-Rahman, M. M. Qureshi, K. Zaman, S. Malik, and S. S. Ali, *Fitoterapia* **60,** 291 (1989).

239. R. Jokela and M. Lounasmaa, *Heterocycles* **43,** 1015 (1996).
240. M. S. Morales-Ríos, J. Espiñeira, and P. Joseph-Nathan, *Magn. Reson. Chem.* **25,** 377 (1987).
241. R. Verpoorte, T. A. van Beek, R. L. M. Riegman, P. J. Hylands, and N. G. Bisset, *Org. Magn. Reson.* **22,** 328 (1984).
242. K. Jewers, D. F. G. Pusey, S. R. Sharma, and Y. Ahmad, *Planta Med.* **38,** 359 (1980).
243. K. Biemann, "Mass Spectrometry. Organic Chemical Applications," McGraw-Hill, New York, 1962.
244. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Alkaloids, Holden-Day, San Francisco, 1964. See also H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, 1967.
245. G. Spiteller, "Massenspektrometrische Strukturanalyse organischer Verbindungen," Verlag Chemie, Weinheim, 1966.
246. M. Hesse, *in* "Progress in Mass Spectrometry" (H. Budzikiewicz, ed.), Vol. 1 (Teil 1), Verlag Chemie, Weinheim, 1974. See also E. de Hoffmann, J. Charette, and V. Stroobant, "Spectrométrie de Masse," Masson, Paris, 1994.
247. O. Laprévote, C. Girard, B. C. Das, and R. Mukherjee, *Rapid Commun. Mass Spectrom.* **6,** 318 (1992). See also O. Laprévote, A.-M. Bui, B. C. Das, B. Charles, and J.-C. Tabet, *Org. Mass Spectrom,* **26,** 622 (1991).
248. D. Ponglux, S. Wongseripipatana, S. Subhadhirasakul, H. Takayama, M. Yokota, K. Ogata, C. Phisalaphong, N. Aimi, and S. Sakai, *Tetradehron* **44,** 5075 (1988).
249. J.-L. Pousset, M. Debray, and J. Poisson, *Phytochemistry* **16,** 153 (1977).
250. M. Plat, R. Lemay, J. Le Men, M.-M. Janot, C. Djerassi, and H. Budzikiewicz, *Bull. Soc. Chim. Fr.,* 2497 (1965).
251. S. Sakai, A. Kubo, T. Hamamoto, M. Wakabayashi, K. Takahashi, H. Ohtani, and J. Haginiwa, *Chem. Pharm. Bull.* **21,** 1783 (1973).
252. G. Lhoest and A. Frigerio, *Adv. Mass Spectrom. Biochem. Med.* **2,** 339 (1976); *Chem. Abstr.* **87,** 4876j (1977).
253. A.-M. Morfaux, L. Olivier, and J. Le Men, *Bull. Soc. Chim. Fr.,* 3967 (1971).
254. H. Takayama, W. Nitta, M. Kitajima, N. Aimi, and S. Sakai, *J. Nat. Prod.* **57,** 521 (1994).
255. B. C. Das, J. P. Cosson, G. Lukacs, and P. Potier, *Tetrahedron Lett.,* 4299 (1974).
256. M. Hava, *in* "The *Vinca* Alkaloids" (W. I. Taylor and N. R. Farnsworth, eds.), p. 305. Marcel Dekker, New York, 1973.
257. G. H. Svoboda and D. A. Blake, *in* "The *Catharanthus* Alkaloids" (W. I. Taylor and N. R. Farnsworth, eds.), p. 45. Marcel Dekker, New York, 1974.
258. M. Harada, Y. Ozaki, and H. Ohno, *Chem. Pharm. Bull.* **27,** 1069 (1979); M. Harada and Y. Ozaki, *Chem. Pharm. Bull.* **26,** 48 (1978); M. Harada and Y. Ozaki, *Chem. Pharm. Bull.* **24,** 211 (1976).
259. R. Verpoorte, R. van der Heijden, W. M. van Gulik, and H. J. G. ten Hoopen, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 40, p. 1. Academic Press, San Diego, 1991. See also R. Verpoorte, R. van der Heijden, and P. R. H. Moreno, *in* "The Alkaloids" (G. A. Cordell, ed.), Vol. 49, p. 221. Academic Press, San Diego, 1997.
260. M. Lounasmaa and J. Galambos, *in* "Progress in the Chemistry of Organic Natural Products" (W. Herz, H. Grisebach, G. W. Kirby, and Ch. Tamm, eds.), Vol. 55, p. 89. Springer, Wien, 1989.
261. R. Verpoorte, R. van der Heijden, and H. J. G. ten Hoopen, *Plant Cell Tissue Org. Cult.* **18,** 231 (1989).
262. G. Ganapathi and F. Kargi, *J. Exp. Bot.* **41,** 259 (1990).
263. P. R. H. Moreno, R. van der Heijden, and R. Verpoorte, *Plant Cell Tissue Org. Cult.* **42,** 1 (1995).

This Page Intentionally Left Blank

——CHAPTER 3——

PHARMACOLOGY OF IBOGAINE AND IBOGAINE-RELATED ALKALOIDS

PIOTR POPIK

Institute of Pharmacology
Polish Academy of Sciences
31-343 Kraków, Poland

PHIL SKOLNICK

Neuroscience Discovery
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

I. Introduction

Ibogaine (12-methoxyibogamine, NIH 10567, Endabuse) is one of the psychoactive indole alkaloids found in the West African shrub,

THE ALKALOIDS, VOL. 52
0099-9598/99 $30.00

Copyright © 1999 by Academic Press.
All rights of reproduction in any form reserved.

Tabernanthe iboga. For over a century, both extracts of *T. iboga* and its constituent alkaloids, including ibogaine, have been used as medicinals (*1*). What makes this alkaloid of particular interest to contemporary pharmacology are anecdotal observations indicating that ibogaine possesses "antiaddictive" properties. Thus, ibogaine (6–25 mg/kg, in humans) has been claimed to attenuate both dependence and withdrawal symptoms to a variety of abused drugs including opiates, alcohol, nicotine, and psychostimulants (*2–9*). Preclinical studies demonstrating that ibogaine reduces self-administration of both cocaine and morphine, and attenuates the symptoms of morphine withdrawal, are consistent with these claims [reviewed in Popick and Glick (*10*)]. This chapter reviews the pharmacological properties of ibogaine and related alkaloids. Since our last comprehensive review (*11*), more than a hundred new reports on the pharmacological actions of ibogaine and ibogaine-like alkaloids have appeared. The chemistry of ibogaine has been reviewed by Taylor in this series (*12,13*).

II. Historical Overview

Ibogaine is derived from *Tabernanthe iboga,* a shrub indigenous to Central-West Africa. The iboga shrub, a member of the family Apocynaceae (order Contortae), is typically found in the undergrowth of tropical forests (*14*). The roots of *T. iboga* were used in tribal initiation rites (*15,16*). Although the details of such ceremonies vary, it was believed that iboga root enabled initiates to make contact with ancestors in the spirit world. Ibogaine has also been found in *T. crassa* (*17*). Nineteenth-century reports from French and Belgian explorers first described the stimulant and aphrodisiac effects of eating iboga root (*1,16*). The first botanical description of the plant was made by Baillon in 1889 (*18*).

Dybovsky and Landrin (*19*), as well as Haller and Heckel (*20*), were the first to isolate a crystalline alkaloid from iboga root, which they called "ibogaine" or "ibogine." In 1901, French pharmacologists found ibogaine to have an unusual type of excitatory effect in animals (*21–23*). Phisalix (*23*) suggested that ibogaine could produce hallucinations, based on observations of unusual behavior in dogs. The alkaloid was subsequently tested in Western clinical settings and was recommended as a stimulant for the treatment of convalescence and neurasthenia (*24*). Despite such recommendations, ibogaine never enjoyed wide clinical use and was neglected by researchers for almost 30 years. In the 1940s Raymond-Hamet and coworkers published a series of papers describing the pharmacological properties of ibogaine on isolated tissues and the cardiovascular system (*25–32*).

Lambarene, an extract of the roots of the iboga relative *T. manii,* was sold in France during the 1930s. It contained about 8 mg of ibogaine and was described as a stimulant. Iperton, another ibogaine extract, was also used as a tonic or stimulant (*33*). Ibogaine has been used by athletes as a performance-enhancing drug (*34*). In many countries, including the United States, ibogaine use is prohibited, perhaps because of its purported hallucinogenic effects (widely publicized in the late 1960s) and its appearance on the illicit drug market. In 1970, the United States Food and Drug Administration classified ibogaine as a Schedule I substance (all non-research use forbidden).

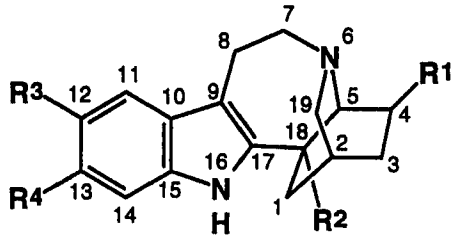
Beginning in 1985, a series of patents was issued for the use of ibogaine as a rapid means of interrupting addiction to narcotics (morphine and heroin) (*3*), cocaine and amphetamine (*4*), alcohol (*5*), nicotine (*6*) and polydrug dependency syndrome (*35*). These patents claim that an oral or rectal dose of ibogaine (4–25 mg/kg) interrupts the dependence syndrome, allowing patients to maintain a drug-free lifestyle for at least 6 months.

Based on open clinical studies, it has been claimed (*36*) that ibogaine therapy resulted in 25% of patients remaining drug-free without craving for 6 months. This group included those who were both highly motivated to quit and had relatively stable home environments. Another 40–50% of patients had their addictions interrupted successfully and required psychotherapy. Twenty to 30% of patients had returned to drug use within a month following treatment. Somewhat lower success rates (10–15%) are cited by Touchette (*37*).

In the absence of appropriately controlled clinical studies, the efficacy of ibogaine as an antiaddictive agent cannot be rigorously assessed at the present time. Nonetheless, interest in ibogaine as a treatment for addiction has increased. In 1985 NDA International, Inc. (Staten Island, NY) began a campaign to persuade the U.S. government to initiate controlled clinical trials with ibogaine (*38*). At the same time, the use of ibogaine for treating opioid dependence has increased in Europe (*39*). At present, clinical trials to evaluate the safety of ibogaine are under way at the University of Miami and are planned in New York. Clinical trials to test the antiaddictive efficacy of ibogaine are under way in The Netherlands and Panama (*38,40–44*). According to Ali *et al.* (*45*), the U.S. Food and Drug Administration and the National Institute for Drug Abuse has approved the use of ibogaine on a limited basis to treat cocaine addiction.

III. Chemical Structure and Properties

Although ibogaine was first isolated and identified in 1901 (*19–21,46*), the structure of this and related alkaloids (Fig. 1) were first established by



Compound	R^1	R^2	R^3	R^4
Ibogaine	CH_2CH_3	H	OCH_3	H
O-Desmethylibogaine	CH_2CH_3	H	OH	H
(±)-Ibogamine	CH_2CH_3	H	H	H
(±)-Coronaridine	CH_2CH_3	CO_2CH_3	H	H
Tabernanthine	CH_2CH_3	H	H	OCH_3
O-*t*-Butyl-*O*-desmethylibogaine	CH_2CH_3	H	$OC(CH_3)_3$	H

FIG. 1.

Taylor in 1957 (*47*) [see also Taylor (*12,13*)]. Total synthesis from nicotinamide was reported using a 13- (*48*) or 14-step (*49*) sequence. The ^{13}C NMR spectra of several iboga alkaloids were published in 1976 (*50*). The synthesis of tritiated ibogaine was recently reported (*51,52*).

Ibogaine (mol. wt. 310.44) has a melting point of 153° at 0.01 mm Hg and a pK_a of 8.1 in 80% methylcellosolve. The absorption maxima in methanol are 226 (log ε 4.39) and 296 (log ε 3.93) nm. Ibogaine crystallizes from alcoholic solutions into small, reddish prismatic needles; it is levorotatory $[\alpha]_D$ −53° (in 95% ethanol) and is soluble in ethanol, methanol, chloroform, and acetone, but insoluble in water. Ibogaine hydrochloride decomposes at 299°, is also levorotatory $[\alpha]_D$ −63° (ethanol), $[\alpha]_D$ −49° (H_2O) and is soluble in water, ethanol, and methanol, is slightly soluble in acetone and chloroform, and is practically insoluble in ether (*53*). Ibogaine is heat and light sensitive (*54*), and can spontaneously oxidize in solution, giving iboluteine and ibochine (*16,34*). Alkaloids structurally related to ibogaine include tabernanthine, ibogamine, iboxigaine, gabonine, iboquine, kisantine, and ibolutenine. Structural similarities between ibogaine and other indole alkaloid hallucinogens have also been reported (*55*). The synthesis of several ibogaine derivatives has recently been published by Repke and coworkers (*56*).

IV. Pharmacokinetics

After parenteral administration, ibogaine has been identified in various biological materials, including blood and urine (humans), and in the liver, kidney, and brain of laboratory animals (*54,57–59*). One hour after intraperitoneal administration, high concentrations of ibogaine were present in rat liver and kidneys (*60*). After intravenous injection of 10 mg/kg to mice, maximal brain concentrations [48 μg/g wet weight (~133 μM)] were achieved in 105 (*61*).

Recently, Gallagher *et al.* (*62*) have developed a highly sensitive and specific method to quantify ibogaine in plasma and tissues. This method uses organic extraction, derivatization with trifluroacetic anhydride, and detection by gas chromatography-mass spectrometry (GC/MS). Similar methods were developed by Hearn *et al.* (*63*), Alburges *et al.* (*64*) and Ley *et al.* (*65*). Using a GC/MS method, Pearl and colleagues (*66*) reported that 1, 5, and 19 h after intraperitoneal administration of 40 mg/kg of ibogaine, the whole brain levels of ibogaine were 10, 1, and 0.7 μM in female rats and 6, 0.9, and 0.2 μM in male rats, respectively. Hough *et al.* (*67*) studied the tissue distribution of ibogaine after i.p. and s.c. administration in rats. One hour after i.p. dosing (40 mg/kg), drug levels ranged from 106 ng/mL (~0.3 μM) in plasma to 11,308 ng/g (~36 μM) in fat, with significantly higher values after s.c. administration of the same dose. Drug levels were 10 to 20-fold lower 12 h later. These data indicate that ibogaine is subject to a significant "first-pass" effect after i.p. dosing and that there is a marked propensity for ibogaine to be deposited in adipose tissue, reflecting its lipophilicity. Consistent with its lipophilicity, ibogaine levels in adipose tissue were very high for at least 12 h after administration. Based on these data, it was suggested that a single dose of ibogaine may provide a long-acting, depot-like time course of action (*67*).

The reported long-term effects of ibogaine [e.g., (*68–70*)], have led to the hypothesis that this alkaloid may be metabolized to an active principle with a long half-life (*71*). At present, there is no *direct* evidence to support this hypothesis. Ibogaine was reported to disappear from the rat at a rate of ~4% of the administered dose per hour, with ~5% of the injected dose eliminated unchanged in urine. Elimination kinetics from brain yielded a half-life of 60 min in rodents (*60,61*) and suggest a one-compartment model. After administration of ibogaine (10 mg/kg, p.o.) to rabbits, urine concentrations reached a maximum 4–5 h later, then decreased rapidly and disappeared after 6 h (*54,60*). Taken together, these data suggest that ibogaine is extensively metabolized. Inspection of ibogaine's structure (Fig. 1) led us to hypothesize that a likely degradation pathway is *O*-demethylation at

C12. Based on this hypothesis, *O*-desmethylibogaine (also known as noribogaine or 12-hydroxyibogamine), was synthesized by Dr. C. Bertha at the National Institutes of Health in 1994. At the same time, *O-tert*-butyl-*O*-desmethylibogaine was synthesized in an attempt to make an ibogaine derivative resistant to *O*-demethylation (Fig. 1). Thus, the first compound was synthesized to investigate the potential pharmacological actions of a likely ibogaine metabolite. The second compound permitted examination of the pharmacological effects of an ibogaine derivative that would not be degraded by *O*-demethylation. The synthesis of these compounds was described by Layer *et al.* (*72*).

Recent studies have indeed demonstrated that ibogaine is metabolized and that *O*-desmethylibogaine can be detected in human plasma (*73*), as well as in the plasma and brains of ibogaine-treated rats (*66*). Behavioral and neurochemical studies in rodents have established that *O*-desmethylibogaine is pharmacologically active (discussed later).

Following an i.p. dose of ibogaine (40 mg/kg), Pearl *et al.* (*66*) reported brain *O*-desmethylibogaine concentrations of 20, 10, and 0.8 μM in female rats and 13, 7, and 0.1 μM in male rats, respectively, at 1, 5, and 19 h after administration. These data suggest that gender differences in pharmacological responses to ibogaine may be attributed to pharmacokinetic rather than pharmacodynamic, factors. Although a report of one human subject (*73*) indicated that *O*-desmethylibogaine persisted in plasma at high levels for at least 24 h after oral ibogaine administration, it is not clear if this pattern will be representative.

There is evidence indicating that the various pharmacological effects of ibogaine may be attributable, at least in part, to its metabolite(s). For example, the tremorigenic effects of ibogaine dissipate much more rapidly than its ability to attenuate the morphine withdrawal syndrome in rats (*74*). This finding suggests that an active principle(s) responsible for one action may be more rapidly metabolized than compound(s) involved in other actions. Alternatively, the various pharmacological effects of ibogaine may involve different neurotransmitter pathways (discussed later).

V. General Pharmacological Actions

A. Animal Studies

1. Locomotor Activity

Ibogaine produces complex effects on locomotor activity in rodents. A dose of 20 mg/kg (i.p.) slightly increased locomotor activity in mice (*75*),

while Sershen *et al.* (*76*) reported that 40 mg/kg (i.p.) decreased locomotor activity in male mice at 1, but not 24, h after injection. The same dose inhibited locomotion in female rats during the first hour after injection, whereas 1 week later, locomotor activity was increased (*69*).

Recently, Pearl and colleagues (*66*) noted gender differences in the effects of ibogaine on locomotor activity (40 mg/kg, i.p., 5 or 19 h before test). In control males and females the locomotor activity decreased during the second hour of observation. Ibogaine treatment in females prevented this decrease in locomotor activity. In females, but not males, ibogaine decreased locomotor activity when given 19 h before the test (*66*). Another study revealed that in male rats, a single dose of 40 mg/kg inhibited locomotor activity 4 h after injection; a dose of 80 mg/kg decreased motor activity 24 h after injection (*77*).

Rats injected with doses of 20–60 mg/kg of ibogaine displayed slower response times on sensory and sensory-motor tests and were also impaired in performing specific motor reflexes at doses of 40–60 mg/kg. Furthermore, these rats exhibited a marked reduction in locomotor activity as well as in emotionality at doses ranging from 10–40 mg/kg. At higher doses ($\geq$ 40 mg/kg), rats appeared virtually inactive (*78*). In other studies, at doses above 25 mg/kg, ibogaine produced ataxia, splayed hind limbs, outstretched forelimbs, Straub tail, and hyperexcitability (*79*).

One hour after *O*-desmethylibogaine or 18-methoxy-coronaridine injection (40 mg/kg), locomotor activity was increased during the second hour of observation (*66, 80*). In our studies, high doses (120 mg/kg) of *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine produced profound ataxia and convulsions (*72*). Ibogaine, *O*-desmethylibogaine, and *O*-*t*-butyl-*O*-desmethylibogaine (80 mg/kg) did not significantly influence rotorod performance in mice (*72*).

a. Effects on Locomotor Activity Induced by Other Drugs

Ibogaine has been found to affect the motor stimulant properties of amphetamine, cocaine, and morphine in rodents (hyperlocomotion induced by these drugs is believed to reflect their "psychotomimetic" qualities in man). Although the results of these studies are not uniform, in general, it has been found that in female rats this alkaloid potentiates the locomotor response to amphetamine and cocaine, whereas opposite effects were reported in male rats and mice.

Sershen *et al.* (*81*) found that ibogaine (40 mg/kg, i.p., 2 or 18 h before amphetamine) enhanced amphetamine (1 mg/kg)-induced hypermotility in female rats. In other studies, an amphetamine-induced increase in locomotor activity was potentiated in female rats pretreated with ibogaine (40 mg/kg, i.p.) 19 h earlier (*82*). Cocaine-induced hypermotility in female rats was

also potentiated by ibogaine (*83,84*). Broderick *et al.* (*85,86*) reported that ibogaine (20–40 mg/kg, i.p.) administration to male rats for 4 days reduced cocaine (20 mg/kg)-induced hypermotility. Ibogaine (40 mg/kg, i.p.) administration also reduced cocaine (25 mg/kg, s.c.)-induced hypermotility in male mice (*76*), a finding in agreement with the amphetamine (1 mg/kg)–ibogaine interaction (*81*) in this gender and species. Recent data demonstrate that the effects of ibogaine on cocaine (20 mg/kg)-induced hyperactivity in female rats are time dependent. Thus, given 1 h before cocaine, ibogaine and *O*-desmethylibogaine (40 mg/kg) inhibited cocaine-induced hyperactivity, but when given 19 h before cocaine they produced the opposite effect (*80*).

Ibogaine pretreatment (40 mg/kg, i.p., 19 h before measurement) decreased or blocked the locomotor stimulation induced by morphine (0.5–20 mg/kg) in rats (*69,71*). Ibogaine administered 1 week (but not 1 month) before morphine (5 mg/kg), reduced the motor stimulant effects of this opiate (*69*). Pearl *et al.* (*87*) found that ibogaine (5–60 mg/kg) is more potent in inhibiting morphine-induced hyperlocomotion in rats pretreated with morphine for several (1–4) days compared to nonpretreated rats. Doses of ibogaine (5–10 mg/kg) that alone were inactive in drug-naive animals attenuated morphine-induced hyperactivity in the morphine-pretreated rats. The inhibitory effects of ibogaine on morphine-induced hyperlocomotion appear gender related because ibogaine is more potent in female rats (*66*). Ibogaine-induced inhibition of morphine-induced hyperlocomotion can be reversed by coadministration of a kappa antagonist (norbinaltorphine, 10 mg/kg) and an N-methyl-D-aspartate (NMDA) agonist (NMDA, 20 mg/kg). However, neither norbinaltorphine nor NMDA alone blocked this action of ibogaine (*88*).

O-Desmethylibogaine (10–40 mg/kg) also inhibited morphine-induced hyperlocomotion in female rats. However, in male rats, the dose of 10 mg/kg potentiated and 40 mg/kg inhibited morphine-induced hyperlocomotion (*66,89*).

2. *Tremor*

Like the somewhat structurally related alkaloid harmaline, ibogaine produces tremors. In mice, ibogaine is tremorigenic both when given intracerebrally (ED_{50} 127 nmol/g brain, ~46 μg/g with a latency to tremor of about 1 min) (*90*), and systemically (ED_{50} 12 mg/kg, s.c.) (*61*). In rats, ibogaine produced fine tremors, flattening of body posture, and flaccid hind limbs up to 2 h after administration of 40 mg/kg (i.p.) (*91*). Low-amplitude whole-body tremors appearing within 10 min after administration of as little as 10 mg/kg of ibogaine have also been reported (*92*). O'Hearn and Molliver (*93*) reported that a high dose of ibogaine (100 mg/kg) produced ataxia

and high-frequency tremor of the head and trunk in rats. Ibogaine-induced tremor preferentially involves the head and upper extremity in rats and mice (*94*). Ibogaine (20 mg/kg)-induced tremors in mice were blocked more potently by CCK-8 and ceruletide compared to other reference compounds, including prolyl-leucylglycine amide (MIF), atropine, haloperidol, biperiden, ethopropazine, trihexyphenidyl, methixene, and clonazepam (*95*).

Zetler *et al.* (*61*) established the tremorigenic structure–activity relationship of several ibogaine-like compounds in descending order of potency: tabernanthine > ibogaline > ibogaine > iboxygaine > *O*-desmethylibogaine. Glick *et al.* (*96*) found that at behaviorally effective doses (2–80 mg/kg), ibogaine, desethylcoronaridine, harmaline, and tabernanthine produced tremors for at least 2–3 h. Both the *R*- and *S*-enantiomers of ibogamine and coronaridine were devoid of this action. The ibogaine-like alkaloids 18-methoxycoronaridine and *O*-desmethylibogaine were also found to lack tremorigenic effects (*89,97*).

The tremorigenic properties of ibogaine and related compounds have been attributed to an action on GABAergic pathways (*98–100*) and to the blockade of voltage-dependent sodium channels.

3. Anxiety and Fear

Schneider and Sigg (*101*) described the behavioral effects of ibogaine in cats. The authors concluded that after intravenous administration of 2–10 mg/kg, ibogaine produced fearlike reactions that persisted for 10–20 min with a normal appearance observed 1–2 h after injection. The electroencephalographic pattern obtained after ibogaine administration (2–5 mg/kg) showed a typical arousal syndrome, resembling that observed after direct stimulation of the reticular formation. This arousal syndrome was inhibited by atropine (2 mg/kg) (*101*). Gershon and Lang (*102*) described the effects of ibogaine in dogs, which become more tense and alert, interpreted as the appearance of anxiety. Moreover, they observed that the dogs exhibited a lack of recognition of both their regular handlers and environment.

Recently, Benwell *et al.* (*103*) reported reductions in open-arm entries in the elevated plus-maze test when rats were tested 22 h after pretreatment with ibogaine (40 mg/kg, i.p.). In mice, ibogaine (2.5 mg/kg) exhibited anxiogenic actions, whereas a dose of 1 mg/kg had anxiolytic effects (*104*). These are perhaps the most compelling preclinical data that ibogaine may influence anxiety levels, because anxiolytic agents (e.g., benzodiazepines) increase open-arm entries in this test.

4. Effects on Self-Administration of Other Drugs

Ibogaine (40 mg/kg, i.p.) inhibits the self-administration of cocaine in rodents. Cappendijk and Dzoljic (*105*) trained male Wistar rats to intra-

venously self-administer cocaine; a single dose of ibogaine (40 mg/kg) decreased cocaine intake by 40–60% for several days, and repeated treatment with ibogaine at 1-week intervals decreased cocaine self-administration by 60–80%. This decrease was maintained for several weeks. Similar effects were found in mice that developed a preference for cocaine in the drinking water. Thus, ibogaine administration (2 weeks after the beginning of a choice period, 2 doses of 40 mg/kg, 6 h apart) diminished cocaine preference for 5 days (70). According to Vocci and London (*106*), some investigators have failed to replicate ibogaine's effect on cocaine self-administration in the rat (*107*) and rhesus monkey (*108*). Also, Dorkin *et al.* (*109*) reported that neither 40 mg/kg of ibogaine given 60 min before the session nor 80 mg/kg given 24 h before the session suppressed responding maintained by intravenous cocaine infusions. In this study, cocaine self-administration was inhibited by pretreatment with ibogaine (80 mg/kg) either 60 or 90 min prior to the session (*109*). However, because this dose of ibogaine reduced scheduled food intake, these latter effects of ibogaine on cocaine self-administration appear to be unspecific.

Glick *et al.* (*96*) demonstrated that ibogaine and several *iboga* alkaloids (tabernanthine, *R*- and *S*-coronaridine, *R*- and *S*-ibogamine, desethylcoronaridine, and harmaline) reduced cocaine self-administration in rats in a dose-related fashion (2.5–80 mg/kg). For some alkaloids, these effects were seen the day after injection. *O*-Desmethylibogaine (40 mg/kg) (*89*) and 18-methoxycoronaridine (*97*) were also reported to inhibit cocaine self-administration.

Ibogaine dose-dependently (2.5–40 mg/kg) reduced intravenous morphine self-administration in female Sprague–Dawley rats immediately after injection, as well as on the next day (*68*). In some animals, a reduced morphine intake was observed for several days; other rats required several doses of ibogaine to achieve a prolonged reduction. Similar effects were demonstrated for other ibogaine-like alkaloids including *O*-desmethylibogaine (*89*), tabernanthine, *R*- and *S*-coronaridine, *R*- and *S*-ibogamine, desethylcoronaridine, harmaline (*96*), and 18-methoxycoronaridine (*97*). However, data from another study revealed somewhat different results. Thus, Dworkin *et al.* (*109*) found that ibogaine (40 or 80 mg/kg) diminished heroin self-administration in male Fisher rats only on the day it was administered. Moreover, the same study revealed that ibogaine treatment resulted in a 97% decrease in responding for a food reinforcement schedule, suggesting that its effects on heroin self-administration were unspecific.

Ibogaine-induced inhibition of morphine self-administration has been found to be reversed by sequential administration of a kappa antagonist (norbinaltorphine, 10 mg/kg) and an NMDA agonist (NMDA, 20 mg/kg). Neither norbinaltorphine nor NMDA alone were effective in this respect (88).

Ibogaine (10–60 mg/kg) reduced alcohol intake in alcohol-preferring Fawn Hooded rats, without affecting either blood alcohol concentrations or food intake (*110,111*). The authors concluded that a metabolite could be involved, because ibogaine was effective in this measure when administered intraperitoneally and intragastrically, but not subcutaneously (*112*). A recent study demonstrated an attenuation of alcohol consumption by the ibogaine congener 18-methoxycoronaridine in rats (*113*).

5. *Effects on Drug Dependence*

Repeated administration of ibogaine (10 or 40 mg/kg) did not produce dependence in rats as measured using the Primary Physical Dependence test (*114*).

In morphine-dependent rats, the opioid antagonist naloxone induces a withdrawal syndrome, characterized (in rats) by increased rearing, digging, jumping, salivation, and "wet-dog" head shaking. Ibogaine dose-dependently reduced the frequency of some of these withdrawal symptoms (jumping, rearing, digging, head hiding, chewing, teeth chattering, writhing, penile licking) after both intracerebroventricular (4–16 μg) (*115*) and i.p. administration (40 and 80 mg/kg) (*74,116*). However, these effects could not be replicated in other studies in either rats (*39,117*) or mice (*118*). At least the second failure to replicate can be attributed to the fact that in the Frances *et al.* (*118*) study, ibogaine was administered to animals that developed a full withdrawal syndrome. In morphine-dependent monkeys, ibogaine (2 and 8 mg/kg, s.c.) partially suppressed the total number of withdrawal signs (*114*). Our studies (*72,119*) demonstrated that ibogaine inhibits the morphine withdrawal syndrome in mice in a dose-related fashion. This effect was reversed by combining ibogaine treatment with glycine. Structure-activity studies revealed that among various ibogaine-like compounds (including *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine), only ibogaine inhibited the intensity of morphine withdrawal (*72*). Both the ability of glycine to inhibit this effect of ibogaine and the failure of other ibogaine derivatives to potently inhibit the binding of noncompetitive NMDA antagonists (e.g., [^{3}H] N-[1-(2-thienyl)cyclo-hexyl]-3,4-pipenoline (TCP) and [^{3}H] MK-801) suggest that the NMDA antagonist actions of ibogaine are responsible for its antiwithdrawal effects. This hypothesis is supported by the observation that although *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine had much higher affinities for kappa opioid receptors than ibogaine did, only ibogaine exhibited a significant affinity for NMDA receptors.

6. *Pain and Analgesia*

Ibogaine did not mimic the analgesic action of morphine in either the tail flick (1–40 mg/kg, i.p.) or hot plate (up to 20 mg/kg, i.p.) tests, although it exhibited analgesic activity in the phenylquinone writhing test (ED_{50} 9.7 mg/

kg) (*114,120,121*). Ibogaine did not exhibit antinociceptive activity when given twice a day for 4 days (*122*). Ibogaine either increased (*120,123*) or did not affect (*114,121*) morphine analgesia in the tail flick test. Similarly, it did not influence analgesia produced by either a kappa-opioid agonist (U-50,488H) or a delta-opioid agonist [D-Pen^2,D-Pen^5]enkepholin (DPDPE) (*121*). Ibogaine has been reported to decrease analgesia in rats when given 19 h prior to morphine (*123*), but another report indicates ibogaine is not effective when given 4-24 h prior to morphine administration in mice (*121*). In addition, Cao an Bhargava (*122*) demonstrated that ibogaine (40–80 mg/kg) inhibited the development of analgesia to mu, but not kappa or delta, agonists in mice.

O-Desmethylibogaine (40 mg/kg) potentiated morphine-induced analgesia in rats (*123*) and mice (*121*). This effect was no longer apparent 19 hours after its administration (*123*). The potentiation of morphine-induced analgesia may be attributed to the relatively high affinity of *O*-desmethylibogaine at opioid mu (K_i 2.66 ± 0.62 μM) and kappa (K_i 0.96 ± 0.08 μM) receptors (*124*). However, this interpretation appears unlikely because *O*-desmethylibogaine pretreatment did not influence either kappa- or delta-opioid-agonist-induced antinociception (*121*).

Ibogaine (10–40 mg/kg) completely blocked the antinociceptive effect of (−)-epibatidine in rodents but was ineffective when given at a dose of 40 mg/kg 24 h before epibatidine. These data suggest that this was an effect of ibogaine and not of its putative, long-lasting metabolite (*125*). This blockade of the antinociceptive effect of epibatidine is not surprising, because epibatidine-induced analgesia is mediated by a mechanism fundamentally different from that of the opioids.

7. Aggression

Compared to other psychoactive compounds (e.g., psilocybin, JB-336, and bufotenine), ibogaine (10 mg/kg) had a negligible effect on the aggressiveness of isolated mice and muricidal behavior in rats (*126*).

8. Interoceptive Properties

Animals can be trained to "recognize" similarities among drugs. Such discriminative (interoceptive) properties may suggest a similar mechanism of action not necessarily related to the structure of a compound.

No generalization between ibogaine and serotonergic ligands [e.g., fenfluramine, *N*-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), methylenedioxymethamphetamine (MDMA), quipazine, or LSD] was found in drug-discrimination paradigms (*127,128*). However, Palumbo and Winter (*129*) did observe a generalization between ibogaine (15–20 mg/kg) and dimethoxymethylamphetamine (DOM) (0.6 mg/kg) as well as between ibogaine and LSD

(0.1 mg/kg) in a two-lever discrimination task. Because pizotyline (BC-105) blocked DOM-appropriate and LSD-appropriate responses, an involvement of 5-HT_2 or 5-HT_1 receptors in the stimulus properties of ibogaine was suggested. Similarly, no generalization between ibogaine and CGS 10476B (a dopamine-release-inhibiting agent) was found in a drug-discrimination paradigm (*127*).

In contrast, ibogaine substituted as an interoceptive cue in mice trained to recognize MK-801 (dizocilpine) (*119*), but not to [(+)-HA-966] (a low-efficacy partial agonist of the glycine site at the NMDA receptor) (*130*) in a T-maze drug discrimination paradigm.

Helsley and colleagues (*131*) studied the interoceptive cue produced by ibogaine in male Fisher rats. The time course of the ibogaine (10 mg/kg) cue revealed that a maximum of ibogaine-appropriate responses were observed at a 60-min pretreatment time and that at the pretreatment time of 8 h, no ibogaine-like responses were observed. These findings, together with the observation that *O*-desmethylibogaine substituted only partially to the ibogaine cue, suggest that the subjective effects of ibogaine are not due to this putative metabolite. The same study however, revealed that harmaline completely substituted as an ibogaine cue (*131*). This later finding indicates that animals may recognize the tremorigenic effects of ibogaine.

9. Reinforcing Effects

Ibogaine does not appear to possess rewarding or aversive effects as measured in the conditioned place-preference/aversion test (*132*), a preclinical procedure that can predict abuse potential in humans. Nonetheless, the same authors reported that ibogaine (40 mg/kg) may attenuate the acquisition, but not the expression, of morphine and amphetamine place preference in male rats (*77,132,133*). This dose of ibogaine did not interfere with the acquisition of conditioned place aversion induced by either naloxone or lithium chloride (*132*). Ibogaine (40 mg/kg, 22 h before the test) attenuated the establishment of lithium- and morphine-induced conditioned taste aversion (*134*). These results suggest a specific action of ibogaine on the neurochemical and behavioral (both reinforcing and aversive) actions of morphine rather than on opioid system(s) because the reinforcing effects of naloxone were unaffected. In support of these findings, it has been reported that ibogaine (20 or 40 mg/kg, 24 h before the test) neither decreased the preference for a sweet solution nor attenuated conditioned preference for a flavor previously associated with sweet taste (*135*).

10. Effects on Learning and Memory

At a dose used in the majority of contemporary behavioral studies in rodents (40 mg/kg), ibogaine has been found to attenuate the acquisition

of spatial memory, perhaps due to reductions in locomotor activity and in detection of sensory information (*78*). However, at much lower doses (0.25–2.5 mg/kg), ibogaine as well as *O*-desmethylibogaine (but not *O*-*t*-butyl-*O*-desmethylibogaine) facilitated spatial memory retrieval (*136*). Using a spatial memory task, Helsley *et al.* (*92*) found that (i) two doses of ibogaine (50 mg/kg, spaced by 8 h) decreased the response rate but did not affect acquisition rate, (ii) ibogaine, even at the highest doses of 30 and 46 mg/kg, given 20 min before the learning trial did not affect task acquisition, and (iii) 30 mg/kg of ibogaine administered just after the learning trial facilitated the consolidation of memory trace.

11. Cardiovascular Actions

Gershon and Lang (*102*) found that ibogaine produced a rise in blood pressure and increased heart rate in conscious dogs. These effects were blocked by atropine (*137*). However, in anesthetized dogs, ibogaine produced a fall in blood pressure and reduced heart rate reduction, leading the authors to propose an interaction between anaesthesia and the cardiovascular effects of ibogaine (*102*). Schneider and Rinehart (*137*) postulated a centrally mediated stimulatory effect of ibogaine. Ibogaine also potentiated the pressor response to both adrenaline and noradrenaline. More recently, Hajo-Tello *et al.* (*138*) found that tabernanthine (an alkaloid closely related to ibogaine) induced a negative inotropic effect in electrically stimulated myocardial tissue and a negative chronotropic effect in the perfused rat heart. Tabernanthine also produced bradycardia and hypotension in anesthetized rats and dogs (*139*). Binienda *et al.* (*140*) reported that ibogaine (50 mg/kg) reduced heart rate in rats immediately after injection; this reduction persisted up to 90 min after injection.

B. Human Studies

Numerous psychotropic actions of ibogaine have been reported. These actions seem to depend on both dose and setting. In addition, the psychoactive effects of iboga extracts (which are likely to contain additional alkaloids and are usually taken in a ritualistic setting) may be different from those of ibogaine. Thus, users of the crude extract of *Tabernanthe iboga* taken in sufficiently high doses have reported fantastic visions, feelings of excitement, drunkenness, mental confusion, and hallucinations (*101*). The total extract of iboga shrub is certainly a central stimulant and in higher doses may lead to convulsions, paralysis, and finally respiratory arrest. The psychotropic actions of the plant extract include visual sensations; objects are seen to be surrounded by specters or rainbows. In high doses it may produce auditory, olfactory, and taste synesthesias. The state of mind has been reported to vary from profound fear to frank euphoria (*141*).

When given orally, both ibogaine and the total iboga extract elicit subjective reactions that last for approximately 6 h. Fifty percent of subjects are reported to experience dizziness, incoordination, nausea, and vomiting (*7,33,142*). Typically, the drug produced a state of drowsiness in which subjects did not want to move, open their eyes, or attend to the environment. Many subjects were light sensitive and covered their eyes or asked that the lights be turned off. Sounds or noises were disturbing. Ibogalin (0.1–1.2 mg/kg, p.o.), an alkaloid closely related to ibogaine and a constituent of the total iboga extract, did not produce psychotomimetic effects in humans (*143*). Ibogalin also differs from ibogaine in pharmacokinetics and tremorigenic activity (*90*).

The psychoactive properties of ibogaine and related compounds were studied by Naranjo (*33,142*), who reported that patients described the psychic state produced by ibogaine (~300 mg) as similar to a dream state without loss of consciousness. Ibogaine-induced fantasies [often described as a "movie run at high speed" or "slide show" (*7*)] were reported as rich in archetypal contents, involving animals and/or the subject with or without other individuals. These fantasies were easy to manipulate by both the subjects and the psychotherapist (*33,142*). At higher doses, ibogaine appears to produce visual and other hallucinations associated with severe anxiety and apprehension (*101,144,145*).

VI. Lethality and Neurotoxic Effects

The LD_{50} of ibogaine has been determined in guinea pigs (82 mg/kg, i.p.) and rats (327 mg/kg, intragastrically, and 145 mg/kg, i.p.) (*60,146*).

No significant pathological changes in rat liver, kidney, heart, and brain following chronic ibogaine treatment (10 mg/kg for 30 days or 40 mg/kg for 12 days, i.p.) were reported (*60*). Sanchez-Ramos and Mash (*42*) found no evidence of gross pathology in African green monkeys given ibogaine in doses of 5–25 mg/kg, p.o. for 4 consecutive days.

However, O'Hearn *et al.* (*147,148*) and O'Hearn and Molliver, (*93*) reported that repeated administration of ibogaine (100 mg/kg, i.p.) to rats caused the degeneration of a subset of Purkinje cells in the cerebellar vermis. This degeneration was accompanied by a loss of microtubule-associated protein 2 (MAP-2) and calbindin. Argyrophilic degeneration, astrocytosis, and microgliosis were also observed. The damage seemed to be dependent on the presence of an intact inferior olivary nucleus (*149*). Ibogaine-induced cerebellar toxicity seems to be independent in its action at NMDA receptors because neither MK-801 nor phencyclidine produce

the same pattern of degeneration (*150*). The neurotoxic effects of high doses of ibogaine were confirmed in rats, but not mice, by Scallet *et al.* (*151,152*) and Molinari *et al.* (*153*), who also found that the "typical" dose of 40 mg/kg did not produce significant damage to female rat cerebellum. The lack of neurotoxicity after lower, behaviorally active doses of ibogaine was also demonstrated by showing that chronic administration (60 days) of 10 mg/kg of ibogaine produced no change in the number of Purkinje cerebellar cells (*154*).

In spite of these findings, examination of cellular markers that are more sensitive to neurotoxic agents than gross histology indicates that ibogaine administration may produce significant changes in many other brain structures. Thus, O'Callaghan *et al.* (*155,156*) examined the effects of acute and chronic administration of ibogaine on glial fibrillary acidic protein (GFAP) levels. Acutely, ibogaine increased GFAP in both sexes, whereas chronic administration (14 days) produced increases only in females. Ibogaine-induced changes in GFAP were dose related and, contrary to other studies, observed in other brain structures including hippocampus, olfactory bulb, brain stem, and striatum. In addition, these authors reported that in females treated chronically with ibogaine, severe hippocampal damage was present as measured by increases in the cytoskeletal proteins neurofilament 68 (NF-68) and beta-tubulin. These latter markers indicate a damage-induced sprouting response (*156*). Ibogaine administration also produced an increase in c-Fos immunostaining in several brain regions of mice and rats; the effects in rats were observed in all cortical layers, whereas in mice the response was limited to cortical layer 2 (*152*). Human SK-N-SH neuroblastoma cells cultured in the presence of 3–30 μM ibogaine (but not *O*-desmethylibogaine or 18-methoxycoronaridine) demonstrated concentration- and time-dependent morphological changes characterized by the loss of processes, cell rounding, detachment, and ultimately cell death (*157*). Similar results were observed with primary cultures of rat cerebellar granular cells. Because in this study only alkaloids that had marked affinity at $sigma_2$ sites were neurotoxic, Vilner *et al.* (*157*) proposed that $sigma_2$ sites may be implicated in the neurotoxicity of ibogaine. The neurotoxic effects of ibogaine have recently been reviewed by Vocci and London (*106*).

Acute treatment with the ibogaine-like alkaloid 18-methoxycoronaridine (100 mg/kg) did not produce gross pathological changes in the cerebellum (*97*). In contrast, another indole alkaloid, harmaline, produced ibogaine-like degeneration of Purkinje cells in the cerebellar vermis (*93*).

It has been reported that multiple doses of a non-NMDA agonist (GYKI 52466) resulted in a substantially greater loss of Purkinje cells and microglial activation compared to ibogaine (50–100 mg/kg) alone (*158*). On the other hand, the noncompetitive NMDA antagonist MK-801 (1 mg/kg) markedly

attenuated the degree of Purkinje cell loss caused by ibogaine (*158*). This latter finding strongly supports the notion that the loss of cerebellar Purkinje cells produced by ibogaine is unrelated to its NMDA antagonist properties (*159*). In fact, ibogaine can also exhibit neuroprotective properties, reducing glutamate-induced neurotoxicity in primary cultures of cerebellar granule cell neurons with an EC_{50} of 4–5 μM (*119*). These neuroprotective effects of ibogaine have recently been patented by Olney (*160*). Consistent with its properties as an NMDA antagonist, ibogaine inhibited NMDA-induced lethality in mice in a dose-dependent manner (*161*) and also protected mice from maximal electroshock seizures (ED_{50} ~31 mg/kg) (*162*).

Phase I toxicity studies in drug-addicted individuals are in progress at the University of Miami (*42,163*).

VII. Effects on Specific Neurotransmitter Systems

A. Ibogaine Effects on Dopaminergic Systems

Ibogaine (at concentrations $\leq$100 μM) does not affect radioligand binding to dopamine receptors (D_1, D_2, D_3, D_4) (*164–166*). The affinity of ibogaine for dopamine transporters as measured by inhibition of [^{3}H]WIN 35,248, [^{125}I]RTI-121 or [^{125}I]RTI-55 binding was ~1.5–4 μM (*73,76,166,167*). However, in another study, ibogaine did not affect binding of [^{3}H]GBR-12935, a ligand that also appears to label dopamine transporters (*85*). Ibogaine inhibited [^{3}H]dopamine uptake in porcine kidney cells transfected with dopamine transporter with a K_i ~86 μM (*168*).

The *in vivo* and *ex vivo* effects of ibogaine on dopamine metabolism in mesolimbic areas of the rodent brain (striatum, nucleus accumbens) are controversial and highly inconsistent. In an attempt to reconcile several contradictory findings, one may note the following.

Dopamine concentrations are reduced and dopamine metabolites dihydroxyphenyl-acetic acid (DOPAC), homovanillic acid (HVA) are increased by ibogaine under certain experimental conditions, for example, when measurements are taken shortly (within 2 h) after ibogaine administration or when relatively high concentrations ($\leq$ 100 μM) are used (*69,71,76,81,169–173*). Reductions in extracellular dopamine concentrations were also observed after administration of a number of ibogaine derivatives, including *O*-desmethylibogaine (*89*) and 18-methoxycoronaridine (*97*).

When dopamine is measured at longer periods after ibogaine administration (e.g., up to a week) or low concentrations (e.g., 10 μM) are applied,

TABLE I

INTERACTIONS OF IBOGAINE WITH NEUROTRANSMITTER SYSTEMS: RADIOLIGAND BINDING STUDIES

Receptor System	Ligand	K_i or IC_{50}† [μM]	Reference
Alpha-adrenergic$_1$	prazosin	7.2 ± 3.0†	*166*
Dopamine transporter	WIN 35,248	1.5†	*76*
Dopamine transporter	WIN 35,248	3.5 ± 0.6†	*166*
Dopamine transporter	RTI-121	2.0	*73*
Dopamine transporter	RTI-55	4.11 ± 0.45†[a]	*167*
Monoamine transporter (vesicular)	tetrabenazine	2.23 ± 0.22†[b]	*167*
Muscarinic M_1	pirenzepine	7.6 ± 0.7†	*166*
Muscarinic M_2	AF-DX384	5.9 ± 1.4†	*166*
Nicotinic	nicotine	4.0 ± 0.6	*125*
Nicotinic noncompetitive	carbamylcholine-induced ^{22}NaCl influx	0.02 ± 0.007†[c]	*125*
NMDA ion channel	MK-801	1.0 ± 0.1	*159*
NMDA ion channel	MK-801	1.1 ± 0.03[d]	*72*
NMDA ion channel	MK-801	5.6 ± 0.8†	*166*
NMDA ion channel	MK-801	4–10	*191*
NMDA ion channel	MK-801 or TCP	0.01–0.05 and 2–4	*202*
NMDA ion channel	TCP	1.5 ± 0.3	*119*
Opioid	naloxone	0.13 ± 0.03	*183*
Opioid (kappa)	U69,593	2.1 ± 0.2	*165*
Opioid (kappa)	U69,593	29.8 ± 8.3†[e] (rat) 13.8 ± 0.6†[f] (mouse) 21.0 ± 1.1†[g] (guinea-pig)	*72*
Opioid (kappa)	U69,593	5.5	*56*

Opioid (kappa)	U69,593	3.77 ± 0.81[h]	*124*
$Serotonin_2$	ketanserin	4.8 ± 1.4†	*166*
$Serotonin_3$	GR-75558	3.9 ± 1.1†	*166*
Serotonin transporter	RTI-55	0.55 ± 0.03	*73*
Serotonin transporter	RTI-55	10	*168*
Serotonin transporter	RTI-55	0.59 ± 0.09†[i]	*167*
Serotonin transporter	paroxetine	9.30 ± 1.70†[j]	*167*
Sigma	haloperidol	0.003†	*164*
Sigma	pentazocine	0.086†	*11*
$Sigma_1$	pentazocine	9.3 ± 0.63	*194*
$Sigma_1$	pentazocine	8.6 ± 1.1	*193*
$Sigma_1$	pentazocine	1.5–3	*202*
$Simga_2$	DTG	0.0904 ± 0.0101	*194*
$Sigma_2$	DTG	0.201 ± 0.023[k]	*193*
$Sigma_2$	DTG	1.5–3	*202*
Voltage-dependent sodium channels	batrachotoxin A 20-α-benzoate	8.1 ± 1.3	*165*

Presented are K_i or IC_{50} (†) values for various neurotransmitter systems affected by ibogaine with affinities higher than 10 μM. The affinities of *O*-desmethylibogaine for the corresponding receptors are presented in the footnotes.

[a] 3.35 ± 0.5† μM.
[b] 4.99 ± 0.48† μM.
[c] 1.5 μM.
[d] 5.48 ± 0.17 μM.
[e] 0.28 ± 0.11† μM.
[f] 1.2 ± 0.1† μM.
[g] 2.6 ± 0.5† μM.
[h] 0.96 ± 0.08 μM.
[i] 0.04 ± 0.01† μM.
[j] 0.90 ± 0.06† μM.
[k] 5.22 μM.

brain concentrations appear unchanged and metabolite concentrations are decreased (*69,71,76,81,82,169,170,172*).

The increased levels of extracellular dopamine metabolites together with decreased or unchanged levels of dopamine suggest that ibogaine increases dopamine turnover shortly after administration. This may be followed by a decrease in turnover that may persist for some time after ibogaine administration. French *et al.* (*91*) demonstrated that doses of ibogaine (~1.5 mg/kg, i.v.) much lower than a "typical" dose of 40–80 mg/kg markedly excited dopaminergic neurons in the ventral tegmental area of the rat.

1. Dopaminergic Effects: Pharmacological Specificity

Administration of a kappa antagonist (norbinaltorphimine, 10 mg/kg) and NMDA (10 mg/kg) (either jointly or individually) reversed ibogaine (40 mg/kg)-induced decreases in striatal dopamine and increases in dopamine metabolites (*88*). Similarly, Reid *et al.* (*172*) observed that the decrease in dopamine levels produced by ibogaine (100 μM) was reversed by either naloxone (1 μM) or norbinaltorphimine (1–10 μM). However, functionally opposite effects were observed by Sershen *et al.* (*174,175*), who reported that the ability of the kappa opioid agonist (U-62066) to inhibit electrical- or cocaine-induced [^{3}H]dopamine release from mouse striatum was attenuated by pretreatment of mice with ibogaine (40 mg/kg, i.p., 2 h prior; or 2 × 40 mg/kg, 6 h apart, killed 18 h later) (*174,175*).

Ibogaine-induced dopamine release from the isolated mouse striatum has been studied by Harsing *et al.* (*176*). Ibogaine increased basal tritium outflow ([^{3}H] dopamine (DA) and [^{3}H]DOPAC), but was without effect on electrically stimulated tritium overflow. This dopamine-releasing effect was (i) reduced by the dopamine uptake inhibitors cocaine and nomifensine, (ii) unaltered by omission of Ca^{++} from the perfusion buffer, (iii) tetrodotoxin insensitive, (iv) unaffected by an agonist (quinpirole) or an antagonist (sulpiride) of the D_2 dopamine receptor, and (v) unaffected by pretreatment with reserpine. In this study, ibogaine did not affect dopamine uptake, whereas Reid *et al.* (*172*) found that both ibogaine and harmaline (10 μM–1 mM) inhibited it. As mentioned earlier, ibogaine has been reported to inhibit radioligand binding to the dopamine transporter with relatively high affinity.

Sershen *et al.* (*177*) reported an involvement of serotonin receptors in the regulation of dopamine release by ibogaine. Thus, administration of ibogaine blocked the ability of a $5HT_{1B}$ agonist (CGS-12066A [10 μM]) to increase [^{3}H]dopamine increase in striatal slices. In other studies, a concentration of ibogaine (1 μM) that was without effect on dopamine efflux inhibited both NMDA (25 μM)- and (±)pentazocine (100 nM)-induced dopamine release in striatal slices (*178*).

There are few reports of the effects of ibogaine-like alkaloids on dopamine metabolism. Like ibogaine, *O*-desmethylibogaine acutely decreases dopa-

mine release in the rat nucleus accumbens and striatum (*89*). Administration of the *R* enantiomers of coronaridine and ibogamine decreased dopamine levels in both nucleus accumbens and striatum, whereas the *S* enantiomers produced no significant changes in dopamine levels in either region (*96*).

In an attempt to reconcile several conflicting findings, Staley *et al.* (*167*) proposed that ibogaine might promote redistribution of intraneuronal dopamine from vesicular to cytoplasmic pools. Ibogaine displays micromolar affinity for vesicular monoamine transporters labeled with [^{125}I]-tetrabenazine (*167*); these sites are crucial for the translocation of dopamine into synaptic vesicles. The inhibitory effect of ibogaine on vesicular monoamine transporters could result in redistribution of dopamine in the cytoplasm. Under such conditions, rapid metabolism of dopamine by monoamine oxidase would account for the decrease in tissue dopamine content and the parallel increase in its metabolites.

Multiple transmitter systems have been shown to modulate dopaminergic function in the central nervous system. Because ibogaine can interact with many of these systems, including kappa-opioid receptors, NMDA receptors, serotonin receptors, and dopamine transporters, it is not surprising that this alkaloid can produce complex (and sometimes apparently opposite) effects on dopaminergic function. Thus, the effects of ibogaine on dopaminergic function described in this section likely reflect the dose (or concentration) of alkaloid preparation employed (e.g., slice vs. intact animal), and brain region studied.

2. *Ibogaine Alters the Effects of Abused Drugs on Dopaminergic Systems*

In general, ibogaine attenuates the increases in mesolimbic dopamine produced by drugs (e.g., nicotine, morphine) that appear to act preferentially at dopaminergic cell bodies. In the case of drugs that act at terminal regions (e.g., cocaine and amphetamine), a gender difference has been observed. In female rats, ibogaine enhances stimulant-induced increases in dopamine concentrations, whereas it decreases the effects of these stimulants in male rats and mice.

Neurochemical studies were performed in male mice given two doses of ibogaine (40 mg/kg, i.p., 18 h apart) followed by amphetamine (5 mg/kg) administered 2 h after the second dose of ibogaine (*81*). Striatal levels of dopamine and dopamine metabolites [DOPAC, HVA, and 3-methoxytyramine (MT)] measured 1 h after amphetamine were decreased in mice that received ibogaine relative to saline-pretreated, amphetamine-treated controls. Compared to controls, levels of DOPAC and HVA were decreased in the amphetamine and ibogaine groups, and further decreased in the group that received ibogaine and amphetamine. However, in female rats, amphetamine-induced increases in extracellular dopamine concentrations

in both the striatum and the nucleus accumbens were further potentiated by ibogaine (40 mg/kg, i.p., 19 h preceding amphetamine) (*82*). Similarly, Glick *et al.* (*169*) found that ibogaine potentiated amphetamine-induced increases in extracellular dopamine concentrations in female rat nucleus accumbens and striatum. In this study, however, no effect of ibogaine was seen on amphetamine-induced decreases in extracellular concentrations of dopamine metabolites. Similarly, ibogaine potentiated cocaine-induced increases in extracellular dopamine levels in striatum and nucleus accumbens of female rats (*84*). However, quite opposite data were obtained by Broderick *et al.* (*85,86*), who examined dopamine release in male rats using semiderivative *in vivo* voltametry. In these experiments, ibogaine (40 mg/kg, i.p., given for 4 days) reduced the increase in dopamine release from nucleus accumbens induced by cocaine (20–40 mg/kg, s.c.). A presynaptic mechanism for these actions was suggested. An inhibitory effect of ibogaine on amphetamine metabolism has been proposed (*179*), because amphetamine levels were higher after ibogaine administration in female rats. However, ibogaine administration had no effect on brain cocaine levels (*169*).

Ibogaine (40 mg/kg, i.p. in rats) given 19 h before morphine (5 mg/kg) prevented the increase in extracellular dopamine concentration in the striatum, prefrontal cortex, and nucleus accumbens typically observed in rats (*71,83*). However, in the ibogaine plus morphine group, the levels of dopamine *metabolites* were increased (as was observed in the morphine group), suggesting that ibogaine did not prevent morphine from activating dopamine neurons. The authors suggest that ibogaine treatment may change the properties of dopaminergic neurons in such a way that dopamine release is unaffected under normal conditions, but altered when stimulated (in this case, by morphine). Nineteen hours after placebo or ibogaine (10 mg/kg, i.p.), female rats responded similarly with increased dopamine release in nucleus accumbens following a morphine challenge (*180*). However, in rats that received two doses of morphine during 2 days preceding the experiment, ibogaine pretreatment had inhibitory effects on dopamine response to a morphine challenge. A pharmacokinetic explanation for the effects of ibogaine on morphine-induced actions is unlikely, because ibogaine (40 mg/kg, i.p., 19 h before measurement) did not modify brain levels of morphine (10 mg/kg) in rats (*71*).

Benwell *et al.* (*103*) reported that ibogaine (given 22 h before nicotine) attenuated the increase in dopamine overflow in the nucleus accumbens evoked by nicotine administration. Similar effects were demonstrated when ibogaine was administered 19 h prior to nicotine infusion (*181*).

B. Opioid Systems

At concentrations of up to 100 μM, ibogaine was reported not to affect [^{3}H]carfentanil or [^{3}H]enkephalin binding, indicating that this alkaloid does

not affect mu- or delta-opioid receptors (*124,165*). In contrast, Pearl *et al.* (*124*) and Sweetnam *et al.* (*166*) demonstrated that ibogaine inhibited radioligand binding to mu-opioid receptors with K_i values of ~11–20 μM. *Ex vivo* studies demonstrated that ibogaine and *O*-desmethylibogaine enhanced the inhibition of adenylyl cyclase activity by a maximally effective concentration of morphine in the rat frontal cortex, midbrain, and striatum (*182*). This latter effect is not likely mediated via a direct action at opioid receptors because it was observed at a maximally effective concentration of morphine.

Ibogaine inhibits (K_i ~2–4 μM) [^{3}H]U-69593 binding to kappa-opioid receptors (*56,72,124,165*). This binding is reversible, suggesting that the long-term effects of ibogaine cannot be attributed to an irreversible effect at this site. Recently, Codd (*183*) demonstrated that ibogaine inhibits binding to sites labeled by [^{3}H]naloxone characterized by a two-site model, with K_i values of 130 nM and 4 μM.

O-Desmethylibogaine had a higher affinity than ibogaine for all of the opioid receptors studied: kappa, K_i ~1 μM; mu, K_i ~2.7 μM, and delta, K_i ~24.7 μM (124) [a recent study showed much higher affinity of *O*-desmethylibogaine at the mu receptor; K_i ~160 nM (*184*)]. Our work (*72*) demonstrated that *O*-desmethylibogaine had a 10- to 100-fold higher affinity for kappa receptors compared to ibogaine. The magnitude of this potency difference was species specific (e.g., in rats: IC_{50} ~0.3 μM for *O*-desmethylibogaine and IC_{50} ~30 μM for ibogaine). The same study demonstrated a moderate affinity of *O*-*t*-butyl-*O*-desmethylibogaine for kappa receptors (IC_{50} ~17 μM in rat forebrain) suggesting that if any of ibogaine's *in vivo* actions are produced at kappa receptors, then *O*-*t*-butyl-*O*-desmethylibogaine would be active. In this respect, *O*-*t*-butyl-*O*-desmethylibogaine did not influence the morphine withdrawal syndrome (*72*) at doses comparable to ibogaine.

C. Serotonergic Systems

Ibogaine (at concentrations up to 1 μM) had no effect on [^{3}H]serotonin binding (*185*), and concentrations of up to 3.5 μM had no effect on [^{3}H]LSD binding (*186*). More recent studies using serotonin-subtype-selective ligands are discrepant. Deecher *et al.* (*165*) reported that ibogaine did not displace ligands acting at 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c}, 5-HT_{1d}, 5-HT_2, or 5-HT_3 receptors. However, Repke *et al.* (*56*) reported that ibogaine inhibited binding of 5-HT_{1a}, 5-HT_{2a}, or 5-HT_3 ligands with low affinity (K_i values: >100, 12.5, and >100 μM, respectively) and Sweetnam *et al.* (*166*) reported IC_{50} values of ~4 μM to inhibit radioligand binding to both 5-HT_2, and 5-HT_3 receptors.

Despite these discrepancies, both *ex vivo* and *in vivo* studies suggest that ibogaine can affect serotonergic transmission. *Ex vivo* studies indicate that

ibogaine and *O*-desmethylibogaine enhance the inhibitory effects of serotonin on adenylyl cyclase activity in rat hippocampus (*182*). Broderick *et al.* (*86*) reported that ibogaine (40 mg/kg, i.p., for 4 days) increased 5-HT concentrations in rat nucleus accumbens. Consistent with this finding, Ali *et al.* (*171*) demonstrated that ibogaine increased 5-HT levels in striatum. Sershen *et al.* (*76*) reported that ibogaine (40–50 mg/kg) decreased levels of the serotonin metabolite 5-hydroxyindoleacetic acid [5-HIAA] in mouse frontal cortex, hippocampus, and olfactory tubercle 2 and 24 h after injection. Ibogaine also decreased 5-HIAA levels in rat nucleus accumbens and striatum (*103,71*), but increased 5-HIAA and decreased 5-HT levels (lasting at least 7 days) in medial prefrontal cortex (*103*). Long and Lerrin (*187*) demonstrated that ibogaine is a reversible inhibitor of the active transport of serotonin into blood platelets, a finding supported by a recent observation that ibogaine inhibited serotonin transporters (in a porcine kidney cell line) with a K_i ~10 μM (*168*).

Sershen *et al.* (*177*) demonstrated that ibogaine inhibited the ability of a 5-HT_{1b} agonist (CGS-12066A) to increase stimulation-evoked [^{3}H]-dopamine release from both rat and mouse striatal slices. Additionally, ibogaine increased the ability of a 5-HT_3 agonist (phenylbiguanide) to enhance stimulation-evoked [^{3}H]dopamine release from the mouse striatal slice (*174*). In these studies, ibogaine (40 mg/kg, i.p.) was administered 2 h prior to slice preparation. In other studies, ibogaine (20 mg/kg) enhanced cocaine-induced reductions in serotonin concentration in the nucleus accumbens (rat), an action attributed to a presynaptic release mechanism (*85,86*). However, Sershen *et al.* (*175*) reported that cocaine increased [^{3}H] serotonin efflux in striatal slices and this efflux was absent in mice pretreated with either ibogaine or a 5-HT_{1b} agonist. These later findings led Sershen to suggest an action of ibogaine at the HT_{1b} receptor that is likely unrelated to the ability of cocaine to inhibit serotonin reuptake blockade (*188*). The inhibitory effect of the kappa-opioid agonist U-62066 (1 μM) on [^{3}H]serotonin release in striatal slices could be blocked by *in vivo* ibogaine administration (*175*).

D. Calcium Regulation

Ibogaine (80 μM) noncompetitively antagonized calcium-induced contraction of rat aorta and mesenteric artery (*138*), which was interpreted as an action on intracellular calcium metabolism. Tabernanthine, an alkaloid related to ibogaine, inhibited depolarization-stimulated ^{45}Ca influx and contractions in the rat aorta (*189*). Ibogaine inhibited the binding of [^{3}H]isradipine (an L-type calcium channel blocker) in the mouse cerebral cortex with an IC_{50} of ~28 μM (*11*).

E. Cholinergic Systems

Ibogaine (at concentrations of up to 100 μM) was reported not to inhibit the binding of ligands acting at nicotinic or muscarinic receptors (*165*). However, subsequent studies demonstrated that ibogaine inhibited the binding of muscarinic M_1, M_2, and M_3 ligands at concentrations of ~31, 50, and 12.5 μM, respectively (*56*). Sweetnam *et al.* (*166*) showed that ibogaine inhibited radioligand binding to M_1 and M_2 receptors with IC_{50} values of 5–7 μM. These authors also reported that ibogaine did not inhibit the binding of [^{3}H]NMCI, a nonselective ligand at nicotinic receptors. *Ex vivo* studies have shown that neither ibogaine nor *O*-desmethylibogaine affect the inhibitory action of the muscarinic acetylcholine agonist carbachol on adenylyl cyclase activity in the rat (*182*).

In a recent study, Badio *et al.* (*125*) demonstrated that ibogaine potently (IC_{50} ~20 nM) blocked ^{22}NaCl influx through nicotinic receptor channels in rat pheochromocytoma cells. This effect was seen in the cells expressing ganglionic, but not neuromuscular, nicotinic receptor subtypes. This inhibition was noncompetitive because it was not overcome by increasing concentrations of agonist. Moreover, the blockade was not completely reversible, suggesting that ibogaine may have a long-lasting effect. *O*-Desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine were 75- and 20-fold less potent, respectively, than ibogaine in blocking nicotinic-receptor-mediated responses. The same study demonstrated that ibogaine, as expected for a noncompetitive blocker, had a relatively low affinity (K_i ~4 μM) as an inhibitor of the binding of an agonist, [^{3}H]nicotine. In support of these findings, Schneider *et al.* (*190*) reported recently that ibogaine ($\leq$10 μM) had an inhibitory action on nicotinic-receptor-mediated catecholamine release in bovine adrenal chromaffin cells. Consistent with the Badio *et al.* (*125*) study, these inhibitory effects appeared to be long-lasting.

F. Gamma-Aminobutyric Acidergic (GABAergic) Systems

Two independent studies (*165,166*) did not find any effect of ibogaine (at concentrations of up to 100 μM) on radioreceptor binding to $GABA_A$ receptors. In addition, ibogaine did not influence $^{36}Cl^-$ uptake through GABA-gated channels (*165*) or GABA-evoked currents in rat cultured hippocampal neurons (*162*).

G. Voltage-Dependent Sodium Channels

Ibogaine inhibited (K_i ~8.1 μM) [^{3}H]batrachotoxin A 20-α-benzoate binding to voltage-dependent sodium channels in depolarized mouse neu-

ronal preparations (*165*). Ibogaine analogs, including ibogamine, tabernanthine, and coronaridine, exhibited potencies similar to ibogaine in this assay.

H. Glutamatergic Systems

Our studies (*159*) indicate that ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding (K_i ~1 μM) to NMDA-receptor-coupled ion channels. In contrast, ibogaine did not affect [^{3}H](±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid ([^{3}H]AMPA), [^{3}H]kainate, or [^{3}H]glutamate to either the NMDA or metabotropic receptor sites binding. These findings are consistent with a specificity of ibogaine for NMDA-receptor-coupled cation channels (*159,162,166*) The potency of ibogaine to inhibit [^{3}H]MK-801 binding was also examined in eight distinct brain regions of Sprague–Dawley male rats and compared with the dissociation constants for [^{3}H]MK-801 estimated using saturation analyses. A high correlation (r = 0.976, P = 0.0004) was obtained between the K_i of ibogaine and K_d of [^{3}H]MK-801 in these brain regions (*119*), consistent with the notion that these compounds share a common binding site. The ability of ibogaine to act as a noncompetitive NMDA antagonist can also be demonstrated using [^{3}H]1-[1-(2-thienyl)cyclohexyl]piperidine ([^{3}H]TCP), a thienyl derivative of phencyclidine, resulting in a K_i of ~1.5 μM in rat forebrain (*119*).

Structure–activity studies were performed using a series of ibogaine analogs, including the putative ibogaine metabolite *O*-desmethylibogaine, its metabolism-resistant analog *O*-*t*-butyl-*O*-desmethylibogaine, the iboga alkaloids [(±)-ibogamine, (±)-coronaridine, tabernanthine], harmaline, and indolotropanes. Ibogaine was the most potent inhibitor of [^{3}H]MK-801 binding (K_i ~1.2 μM); the compounds with the greatest structural similarity to ibogaine, *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine, were much less potent (K_i ~5.5 and 179.0 μM respectively) (*72*). A ~5-fold lower affinity of *O*-desmethylibogaine compared to ibogaine at [^{3}H]MK-801 binding sites was also reported by Mash *et al.* (*191*).

Consistent with these neurochemical studies, ibogaine produced a voltage-dependent block of NMDA-evoked currents in hippocampal cultures (*119,162*). In addition, ibogaine (100 μM) and *O*-desmethylibogaine (1 mM) blocked the ability of NMDA (100 μM, 5 s) to depolarize frog motoneurons in a noncompetitive and use-dependent manner (*192*).

I. Sigma Receptors

In our studies, ibogaine inhibited [^{3}H]pentazocine (a sigma$_1$-receptor ligand) binding to high (IC_{50} ~86 nM)-(*11*) and low (IC_{50} ~5.6 μM)-affinity

sites in mouse cerebellum. Bowen *et al.* (193) demonstrated that ibogaine had high affinity for $sigma_2$ sites (K_i ~200 nM), low affinity for $sigma_1$ sites (K_i ~8.5 μM), and an ~43-fold selectivity for $sigma_2$ sites. The affinities of tabernanthine (13-methoxyibogamine) and (±)-ibogamine for $sigma_2$ sites were similar to that of ibogaine. *O*-Desmethylibogaine had a markedly reduced affinity for $sigma_2$ sites (K_i ~5 μM) and also lacked affinity for $sigma_1$ sites. The related alkaloids, (±)-coronaridine [(±)-18-carbomethoxyibogamine), and harmaline lacked affinity for both sigma receptor subtypes. *O-t*-Butyl-*O*-desmethylibogaine inhibited radioligand binding to $sigma_1$ sites with a K_i of ~3.5 μM and $sigma_2$ sites with a K_i of ~346 nM [cf. Bowen *et al.* (*72*)]. The much higher affinity of ibogaine for $sigma_2$ sites compared to $sigma_1$ sites was also reported by Mach *et al.* (*194*). Bowen *et al.* (*195*) examined the ability of ibogaine and related compounds to modulate calcium release from intracellular stores in indo-1-loaded human SK-N-SH neuroblastoma cells. Consistent with its affinity at $sigma_2$ sites, ibogaine produced a concentration-dependent increase (13–45%) in intracellular calcium levels. *O*-Desmethylibogaine was ineffective in this measure at concentrations up to 100 μM. These data suggest that the shared *in vivo* effects of ibogaine and *O*-desmethylibogaine are probably not mediated by sigma sites.

J. Miscellaneous Actions of Ibogaine

Deecher *et al.* (*165*) reported that ibogaine (up to 100 μM) did not inhibit radioligand binding to cannabinoid receptors. Ibogaine and *O*-desmethylibogaine had no influence on basal or forskolin-stimulated adenylyl cyclase in the rat frontal cortex, midbrain, or striatum (*182*). *O*-Desmethylibogaine, but not ibogaine, produced concentration-dependent increases in the generation of [^{3}H]inositol phosphates that were not altered by inclusion of tetrodotoxin, cadmium, or omega-conotoxin (*196*). These results suggest that the effect of *O*-desmethylibogaine on phosphoinositide hydrolysis was not secondary to the release of one or more neurotransmitters. Ali *et al.* (*45*) reported that ibogaine (0.5–250 μM) reduced nitric oxide synthase activity in mouse brain; similar effects were noted in the striatum, hippocampus, and cerebellum of mice treated parenterally with ibogaine (50 mg/kg). In radioligand binding studies, no effect of ibogaine has been found on $alpha_1$-, $alpha_2$-, or $beta_1$-adrenergic receptors (*165*). Moreover, ibogaine (20 mg/kg) did not modify cerebral noradrenaline levels in rats (*197*). Binienda *et al.* (*140,198*) reported that although ibogaine (50 mg/kg) challenge in rats was associated with a decrease in delta, theta, alpha, and beta power spectra of cortical EEGs during the first 30 min and subsequent recovery of all except delta bands in the next 15 min, MK-801 (1 mg/kg)

treatment was followed by a decrease in power of all four frequency bands for the entire time of recording. The selective power decrease in delta EEG frequency band of the cortical EEG may suggest the activation of dopamine receptors.

In the anesthetized rat, ibogaine produced a slight hypoglycemia (*60*). After administration of 50 mg/kg of ibogaine, elevations of corticosterone levels were noted 15–120 min, but not 24 h later (*170,171,173*). The same dose of ibogaine rapidly and transiently increased plasma prolactin levels (*171,173*). Bunag and Walaszek (*199*) reported that ibogaine antagonized the contractile responses produced in guinea pig ileum by substance P and angiotensin. Alburges and Hanson (*200*) reported that ibogaine administration produced increases of neurotensin-like immunoreactivity in striatum, nucleus accumbens, and substantia nigra, and substance P–like immunoreactivity in striatum and substantia nigra. Ibogaine or harmaline suppressed several (T-cell regulatory and effector, B-cell, and natural killer cell) immune functions *in vitro* (*201*). Van Beek *et al.* (*17*) reported that ibogaine showed activity against the Gram-positive *Bacillus subtilis.* Ibogaine did not alter colonic temperature in mice, nor did it affect morphine- or kappa [U-50,488H]-opioid-induced hypothermia (*121*).

VIII. Conclusions

The renewed interest in ibogaine during the past decade stems from anecdotal clinical observations that ibogaine offers a novel means of treating drug addictions. Preclinical studies are in general consistent with these claims. Thus, ibogaine reduces self-administration of cocaine and morphine, attenuates morphine withdrawal, and blocks conditioned place preference produced by morphine and amphetamine. Preclinical studies also suggest that there is no abuse liability associated with ibogaine. At doses that interfere with tolerance and dependence phenomena, brain concentrations of ibogaine are at levels that can affect a variety of neurotransmitter systems. Many of these effects (e.g., use-dependent block of NMDA-receptor-coupled cation channels, interactions with dopamine transporters and kappa-opioid receptors) have previously been implicated in drug-seeking phenomena. However, at the present time, the only mechanism that can be invoked to explain ibogaine's effects on drug-seeking phenomena with some certainty is its ability to inhibit naloxone-precipitated jumping through blockade of NMDA receptors. Nonetheless, it is still uncertain whether the anti-addictive properties of ibogaine result from a single mechanism or are produced at multiple loci.

The involvement of dopaminergic pathways in drug-seeking phenomena can be considered dogma, and ibogaine undoubtedly affects these pathways. Nonetheless, based on available data, no clear picture has emerged about how this interaction contributes to the anti-addictive properties of ibogaine, or any other anti-addictive medications. Additional systematic studies are obviously needed. Anecdotal reports claim long-term effects of ibogaine on drug seeking following a single administration or short course of therapy. This claim has been borne out, at least in part, by preclinical studies. Based on these observations, it is unlikely that ibogaine serves simply as substitution therapy. It has been hypothesized that a long-lived metabolite is responsible for ibogaine's putative antiaddictive properties, but additional studies are required in this area.

One of the central issues regarding the molecular mechanisms responsible for the anti-addictive actions of ibogaine is whether its NMDA antagonist action is sufficient to explain these effects. Thus, there is an established body of preclinical data (and an emerging body of clinical data) demonstrating that NMDA antagonists interrupt drug-seeking phenomena for a variety of addictive substances. Although it is now well established that ibogaine is a noncompetitive NMDA antagonist (albeit 1000-fold less potent than the prototype compound, dizocilpine), with the exception of its ability to block naloxone-precipitated jumping in morphine-dependent mice, it is uncertain if these effects can be attributed to other mechanisms.

Recent structure activity studies demonstrate that *O*-desmethylibogaine, which is less potent than ibogaine at NMDA receptors, appears as active as ibogaine in acutely blocking morphine and cocaine self-administration. This observation strongly suggests that other mechanisms may be operative. A similar argument can be made for harmaline, which is somewhat structurally related to ibogaine and shares some of its pharmacological actions (e.g., tremor and neurotoxic effects, reductions in cocaine and morphine self-administration), but is not an NMDA antagonist. Although inhibition of drug self-administration by harmaline may be due to unspecific effects (e.g., general malaise), these findings nonetheless raise the possibility that ibogaine's anti-addictive properties may be produced through multiple mechanisms. The involvement of sigma sites in these phenomena appears to be even more obscure because in contrast to ibogaine, harmaline has no appreciable affinity at sigma sites whereas *O*-desmethylibogaine lacks affinity at a $sigma_2$ site, yet all three block cocaine and morphine self-administration.

Ibogaine can affect several aspects of serotonergic transmission at concentrations that are readily achieved in the brain following pharmacologically relevant doses [reviewed by Sershen *et al.* (*188*)]. Because multiple serotonin receptor subtypes, as well as serotonin re-uptake, are modulated by ibogaine, it is not surprising that the effects of this alkaloid on steady-

state levels of serotonin and its metabolites (whether measured *in situ* or *ex vivo*) are complex. Clearly, additional clinical studies are necessary to examine the efficacy of ibogaine as an anti-addictive agent. Similarly, additional preclinical studies will be required to elucidate the molecular mechanism(s) responsible for these pharmacological actions.

Acknowledgment

The authors thank Dr. H. Sershen for helpful discussions on the effects of ibogaine on dopaminergic and serotonergic transmission.

References

1. A. Lecomte, *Arch. Med. Navale* **2,** 264 (1864).
2. R. Goutarel, O. Gollnhofer, and R. Sillans, *Psyched. Mono. Essays* **6,** 71 (1993).
3. H. S. Lotsof, *U S Patent* **4,499,096,** (1985).
4. H. S. Lotsof, *U S Patent* **4,587,243,** (1986).
5. H. S. Lotsof, *U S Patent* **4,857,523,** (1989).
6. H. S. Lotsof, *U S Patent* **5,026,697,** (1991).
7. H. S. Lotsof, *Bull. MAPS* **5,** 16 (1995).
8. C. D. Kaplan, E. Ketzer, J. de Jong, and M. de Vries, *Soc. Neurosc. Bull.* **6,** 6 (1993).
9. B. Sisko, *Bull. MAPS* **IV,** 15 (1993).
10. P. Popik and S. D. Glick, *Drugs Future* **21,** 1109 (1996).
11. P. Popik, R. T. Layer, and P. Skolnick, *Pharmacol. Rev.* **47,** 235 (1995).
12. W. I. Taylor, in "The Alkaloids: Chemistry and Physiology" (R. H. F. Manske, ed.), Vol. 8, p. 203. Academic Press, New York, London, 1965.
13. W. I. Taylor, in "The Alkaloids: Chemistry and Physiology" (R. H. F. Manske, ed.), Vol. 9, p. 79. Academic Press, New York, London, 1968.
14. R. E. Schultes and A. Hofmann, *in* "The Botany and Chemistry of Hallucinogens" (R. E. Schultes and A. Hofmann, eds.), p. 235. Charles C Thomas, Springfield, 1980.
15. J. W. Fernandez, "Bwiti - an ethnography of religious imagination in Africa." Princeton Press, Princeton, NJ, 1982.
16. H. G. Pope, Jr., *Econ. Bot.* **23,** 174 (1969).
17. T. A. Van Beek, C. de Smidt, and R. Verpoorte, *J. Ethnopharmacol.* **14,** 315 (1985).
18. H. Baillon, *Bull. Mens. Soc. Lin. de Paris* **1,** 782 (1889).
19. J. Dybovsky and E. Landrin, *C. R. Acad. Sci.* **133,** 748 (1901).
20. A. Haller and E. Heckel *C. R. Acad. Sci.* **133,** 850 (1901).
21. M. Lambert and E. Heckel, *C. R. Acad. Sci.* **133,** 1236 (1901).
22. M. Lambert, *Arch. Int. Pharmacodyn.* **10,** 101 (1902).
23. M. C. Phisalix, *C. R. Soc. Biol.* **53,** 1077 (1901).

24. G. Pouchet and J. Chevalier, *Bull. Gen. Ther.* **149,** 211 (1905).
25. E. Rothlin and M. Raymond-Hamet, *C. R. Soc. Biol.* **127,** 592 (1938).
26. M. Raymond-Hamet and E. Rothlin, *Arch. Int. Pharmacodyn. Ther.* **63,** 27 (1939).
27. M. Raymond-Hamet, *C. R. Soc. Biol.* **134,** 541 (1940).
28. M. Raymond-Hamet, *C. R. Soc. Biol.* **133,** 426 (1940).
29. M. Raymond-Hamet, *C. R. Acad. Sci.* **211,** 285 (1940).
30. M. Raymond-Hamet, *C. R. Soc. Biol.* . **135,** 176 (1941).
31. M. Raymond-Hamet, *C. R. Acad. Sci.* **212,** 768 (1941).
32. M. Raymond-Hamet and D. Vincent, *C. R. Soc. Biol.* **154,** 2223 (1960).
33. C. Naranjo, *Clin. Toxicol.* **2,** 209 (1969).
34. F. De Sio, *Med. Sport* **23,** 362 (1970).
35. H. S. Lotsof, *U S Patent* **5,152,994,** (1992).
36. L. R. Regan, *Justicia* **September,** 1 (1992).
37. N. Touchette, *Nature Med.* **1,** 288 (1995).
38. FDA Advisory CMTE, *in* "The NDA Pipeline." (E. Clarke, C. Frederick, and K. Balog, eds.), p. V-76. F-D-C Reports, Inc., Chevy Chase, MD, 1993.
39. L. G. Sharpe and J. H. Jaffe, *NeuroReport* **1,** 17 (1990).
40. N. Touchette, *J. NIH Res.* **5** (November), 50 (1993).
41. J. Buie, *Psych. Times* **XI** (7), 44 (1994).
42. J. Sanchez-Ramos and D. Mash, *Bull. MAPS* **4,** 11 (1994).
43. S. G. Sheppard, *J. Subst. Abuse Treat.* **11,** 379 (1994).
44. B. E. Judd, Ibogaine, Psychotherapy, and the Treatment of Substance-related Disorders. The Eighth International Conference on Drug-Related Harm. (1994).
45. S. F. Ali, S. C. Chetty, X. M. Meng, G. D. Newport, and W. Slikker, *J. Neurochem.* **65,** S172 (1995).
46. A. Landrin, *Bull. Sci. Pharmacol.* **11,** 319 (1905).
47. W. I. Taylor, *J. Am. Chem. Soc.* **79,** 3298 (1957).
48. G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.* **88,** 3099 (1966).
49. P. Rosenmund, W. H. Haase, J. Bauer, and R. Frische, *Chem. Ber.* **180,** 1871 (1975).
50. E. Wenkert, D. W. Cochran, H. E. Gottlieb, and E. W. Hagaman, *Helv. Chim. Acta* **59,** 2437 (1976).
51. H. H. Seltzman, D. F. Odear, F. I. Carroll, and D. Wyrick, *J. Chem. Soc., Chem. Commun.* 1757 (1992).
52. H. H. Seltzman, D. F. Odear, and C. P. Lauderman, *J. Labeled Compd. Radiopharm.* **34,** 367 (1994).
53. S. Budavari, M. O'Neil, A. Smith, P. E. Heckelman, and J. F. Kinneary, "The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals," 12th Ed., Merck & Co., Inc., Whitehouse Station, NJ, 1996.
54. G. P. Cartoni and A. Giarusso, *J. Chromatogr.* **71,** 154 (1972).
55. J. M. Kelley and R. H. Adamson, *Pharmacology* **10,** 28 (1973).
56. D. B. Repke, D. R. Artis, J. T. Nelson, and E. H. Wong, *J. Org. Chem.* **59,** 2164 (1994).
57. H. I. Dhahir, N. C. Jain, and R. B. Forney, *J. Forensic Sci.* **16,** 103 (1971).
58. H. I. Dhahir, N. C. Jain, and J. I. Thornton, *J. Forensic Sci.* **12,** 309 (1972).
59. E. Bertol, F. Mari, and R. Froldi, *J. Chromatogr.* **117,** 239 (1976).
60. H. I. Dhahir, *Diss. Abstr. Int.* **32/04-B,** 2311 (1971).
61. G. Zetler, G. Singbarth, and L. Schlosser, *Pharmacology* **7,** 237 (1972).
62. C. A. Gallagher, L. B. Hough, S. M. Keefner, A. Seyed Mozaffari, S. Archer, and S. D. Glick, *Biochem. Pharmacol.* **49,** 73 (1995).
63. W. L. Hearn, J. Pablo, G. W. Hime, and D. C. Mash, *J. Anal. Toxicol.* **19,** 427 (1995).

64. M. E. Alburges, R. L. Foltz, and D. E. Moody, *J. Anal. Toxicol.* **19,** 381 (1995).
65. F. R. Ley, A. R. Jeffcoat, and B. Thomas, *J. Chromatogr. A* **723,** 101 (1996).
66. S. M. Pearl, L. B. Hough, D. L. Boyd, and S. D. Glick, *Pharmacol. Biochem. Behav.* **57,** 809 (1997).
67. L. B. Hough, S. M. Pearl, and S. D. Glick, *Life Sci.* **58,** PL119 (1996).
68. S. D. Glick, K. Rossman, S. Steindorf, I. M. Maisonneuve, and J. N. Carlson, *Eur. J. Pharmacol.* **195,** 341 (1991).
69. I. M. Maisonneuve, K. L. Rossman, R. W. Keller, Jr., and S. D. Glick, *Brain Res.* **575,** 69 (1992).
70. H. Sershen, A. Hashim, and A. Lajtha, *Pharmacol. Biochem. Behav.* **47,** 13 (1994).
71. I. M. Maisonneuve, R. W. Keller, and S. D. Glick, *Eur. J. Pharmacol.* **199,** 35 (1991).
72. R. T. Layer, P. Skolnick, C. M. Bertha, M. E. Kuehne, and P. Popik, *Eur. J. Pharmacol.* **309,** 159 (1996).
73. D. Mash, J. K. Staley, M. H. Baumann, R. B. Rothman, and W. L. Hearn, *Life Sci.* **57,** PL45 (1995).
74. S. D. Glick, K. Rossman, N. C. Rao, I. M. Maisonneuve, and J. N. Carlson, *Neuropharmacology* **31,** 497 (1992).
75. G. Chen and B. Bohner, *J. Pharmacol. Exp. Ther.* **123,** 212 (1958).
76. H. Sershen, A. Hashim, L. Harsing, and A. Lajtha, *Life Sci.* **50,** 1079 (1992).
77. T. Luxton, L. A. Parker, and S. Siegel, *Prog. Neuro-Psych. Biol. Psych.* **20,** 857 (1996).
78. R. P. Kesner, P. Jackson-Smith, C. Henry, and K. Amann, *Pharmacol. Biochem. Behav.* **51,** 103 (1995).
79. J. G. Page, L. E. Rodan, D. R. Franell, and J. F. Martin, *NIDA Contract Report* **SRI-CBE-94-002-7486,** (1994).
80. I. M. Maisonneuve, K. E. Visker, G. L. Mann, U. K. Bandarage, M. E. Kuehne, and S. D. Glick, *Eur. J. Pharmacol.* **336,** 123 (1997).
81. H. Sershen, L. G. Harsing, Jr., A. Hashim, and A. Lajtha, *Life Sci.* **51,** 1003 (1992).
82. I. M. Maisonneuve, R. W. Keller, Jr., and S. D. Glick, *Brain Res.* **579,** 87 (1992).
83. I. M. Maisonneuve, *Diss. Abst. Int.* 1 (1992).
84. I. M. Maisonneuve and S. D. Glick, *Eur. J. Pharmacol.* **212,** 263 (1992).
85. P. A. Broderick, F. T. Phelan, and S. P. Berger, *in* "NIDA Research Monograph No. 119. Problems of Drug Dependence" (L. S. Harris, ed.), p. 285. U.S. Government Printing Office, Washington, DC, 1992.
86. P. A. Broderick, F. T. Phelan, F. Eng, and R. T. Wechsler, *Pharmacol. Biochem. Behav.* **49,** 711 (1994).
87. S. M. Pearl, D. W. Johnson, and S. D. Glick, *Psychopharmacology* **121,** 470 (1995).
88. S. D. Glick, I. M. Maisonneuve, and S. M. Pearl, *Brain Res.* **749,** 340 (1997).
89. S. D. Glick, S. M. Pearl, J. Cai, and I. M. Maisonneuve, *Brain Res.* **713,** 294 (1996).
90. G. Singbarth, G. Zetler, and L. Schlosser, *Neuropharmacology* **12,** 239 (1973).
91. E. D. French, K. Dillon, and S. F. Ali, *Life Sci.* **59,** PL199 (1996).
92. S. Helsley, D. Fiorella, R. A. Rabin, and J. C. Winter, *Pharmacol. Biochem. Behav.* **58,** 37 (1997).
93. E. O'Hearn and M. E. Molliver, *Neuroscience* **55,** 303 (1993).
94. S. L. Costache "Pharmacological attenuation of the tremorigenic effects of ibogaine." Unpublished M.S. thesis. Albany Medical College, Albany, NY, 1995.
95. G. Zetler, *Neuropharmacology* **22,** 757 (1983).
96. S. D. Glick, M. E. Kuehne, J. Raucci, T. E. Wilson, D. Larson, R. W. Keller, and J. N. Carlson, *Brain Res.* **657,** 14 (1994).
97. S. D. Glick, M. E. Kuehne, I. M. Maisonneuve, U. K. Bandarage, and H. H. Molinari, *Brain Res.* **719,** 29 (1996).

98. S. M. King and G. Tunnicliff, *Biochem. Int.* **20,** 821 (1990).
99. E. Roberts, E. Wong, G. Svenneby, and P. Degener, *Brain Res.* **152,** 614 (1978).
100. J. H. Trouvin, P. Jacqmin, C. Rouch, M. Lesne, and C. Jacquot, *Eur. J. Pharmacol.* **140,** 303 (1987).
101. J. A. Schneider and E. B. Sigg, *Ann. NY Acad. Sci.* **66,** 765 (1957).
102. S. Gershon and W. J. Lang, *Arch. Int. Pharmacodyn. Ther.* **135,** 31 (1962).
103. M. E. M. Benwell, P. E. Holtom, R. J. Moran, and D. J. K. Balfour, *Br. J. Pharmacol.* **117,** 743 (1996).
104. E. S. Onaivi, S. F. Ali, and A. Chakrabarti, *Ann. N. Y. Acad. Sci.* **844,** 227 (1998).
105. S. L. T. Cappendijk and M. R. Dzoljic, *Eur. J. Pharmacol.* **241,** 261 (1993).
106. F. J. Vocci and E. D. London, *Ann. N. Y. Acad. Sci.* **820,** 29 (1996).
107. Presented to the Food and Drug Administration's Drug Advisory Committee, **#26,** (1993).
108. R. S. Mansbach, R. L. Balster, M. Gregory, and E. Soenghen, "NIDA Contract Report" **SA92.16,** (1992).
109. S. I. Dworkin, S. Gleeson, D. Meloni, T. R. Koves, and T. J. Martin, *Psychopharmacology* **117,** 257 (1995).
110. Y. W. Lee, A. H. Rezvani, and D. H. Overstreet, *Soc. Neurosci. Abstr.* **20,** 1608 (1994).
111. A. H. Rezvani, D. H. Overstreet, and Y. W. Leef, *Pharmacol. Biochem. Behav.* **52,** 615 (1995).
112. A. H. Rezvani, D. Mash, D. H. Overstreet, W. L. Hearn, and Y. W. Lee, *Alcohol. Clin. Exp. Res.* **19,** 15A (1995).
113. A. H. Rezvani, D. H. Overstreet, Y. Yang, I. M. Maisonneuve, U. K. Bandarage, M. E. Kuehne, and S. D. Glick, *Pharmacol. Biochem. Behav.* **58,** 615 (1997).
114. M. D. Aceto, E. R. Bowman, and L. S. Harris, *NIDA Res. Monogr.* **95,** 578 (1990).
115. E. D. Dzoljic, C. D. Kaplan, and M. R. Dzoljic, *Arch. Int. Pharmacodyn.* **294,** 64 (1988).
116. S. L. T. Cappendijk, D. Fekkes, and M. R. Dzoljic, *Behav. Brain Res.* **65,** 117 (1994).
117. L. G. Sharpe and J. H. Jaffe, *NIDA Res. Monogr.* **105,** 477 (1991).
118. B. Frances, R. Gout, J. Cros, and J. M. Zajac, *Fundam. Clin. Pharmacol.* **6,** 327 (1992).
119. P. Popik, R. T. Layer, L. Fossom, M. Benveniste, B. Getter-Douglas, J. M. Witkin, and P. Skolnick, *J. Pharmacol. Exp. Ther.* **275,** 753 (1995).
120. J. A. Schneider and M. McArthur, *Experientia* **12,** 323 (1956).
121. H. N. Bhargava, Y. J. Cao, and G. M. Zhao, *Brain. Res.* **752,** 234 (1997).
122. Y. J. Cao and H. N. Bhargava, *Brain Res.* **752,** 250 (1997).
123. A. A. Bagal, L. B. Hough, J. W. Nalwalk, and S. D. Glick, *Brain Res.* **741,** 258 (1996).
124. S. M. Pearl, K. Herrickdavis, M. Teitler, and S. D. Glick, *Brain Res.* **675,** 342 (1995).
125. B. Badio, W. L. Padgett, and J. W. Daly, *Mol. Pharmacol.* **51,** 1 (1997).
126. W. Kostowski, W. Rewerski, and T. Piechocki, *Pharmacology* **7,** 259 (1972).
127. M. D. Schechter and T. L. Gordon, *Eur. J. Pharmacol.* **249,** 79 (1993).
128. M. D. Schechter, *Life Sci.* **60,** PL83 (1997).
129. P. A. Palumbo and J. C. Winter, *Pharmacol. Biochem. Behav.* **43,** 1221 (1992).
130. J. M. Witkin, S. Brave, D. French, and B. Geterdouglass, *J. Pharmacol. Exp. Ther.* **275,** 1267 (1995).
131. S. Helsley, R. A. Rabin, and J. C. Winter, *Life Sci.* **60,** PL147 (1997).
132. L. A. Parker, S. Siegel, and T. Luxton, *Exp. Clin, Psychopharm.* **3,** 344 (1995).
133. I. Moroz, L. A. Parker, and S. Siegel, *Exp. Clin. Psychopharm.* **5,** 119 (1997).
134. L. A. Parker and S. Siegel, *Learn. Motiv.* **27,** 170 (1996).
135. J. R. Blackburn and K. K. Szumlinski, *Soc. Neurosci. Abstr.* **21,** 1467 (1995).
136. P. Popik, *Life Sci.* **59,** PL379 (1996).
137. J. A. Schneider and R. K. Rinehart, *Arch. Int. Pharmacodyn. Ther.* **CX,** 92 (1957).

138. N. Hajo-Tello, C. Dupont, J. Wepierre, Y. Cohen, R. Miller, and T. Godfraind, *Arch. Int. Pharmacodyn. Ther.* **276,** 35 (1985).
139. N. Hajo, C. Dupont, and J. Wepierre, *J. Pharmacol.* **12,** 441 (1981).
140. Z. Binienda, M. A. Beaudoin, B. T. Thorn, D. R. Prapurna, J. R. Johnson, C. M. Fogle, W. Slikker, and S. F. Ali, *Ann. N. Y. Acad. Sci.* **844,** 265 (1998).
141. E. L. Mandrile and G. M. Bongiorno de Pfirter, *Acta. Farm. Bonaerense* **4,** 49 (1985).
142. C. Naranjo, "The Healing Journey. New Approaches to Consciousness." Pantheon, New York, 1973.
143. P. B. Von Schmid, *Arzneim.-Forsch.* **17,** 485 (1967).
144. R. S. Sloviter, E. G. Drust, B. P. Damiano, and J. D. Connor, *J. Pharmacol. Exp. Ther.* **214,** 231 (1980).
145. N. R. Farnsworth, *Science* **162,** 1086 (1968).
146. J. Delourme-Houde, *Ann. Pharm. Fr.* **4,** 30 (1946).
147. E. O'Hearn, D. B. Long, and M. E. Molliver, *Neuroreport* **4,** 299 (1993).
148. E. O'Hearn, P. Zhang, and M. E. Molliver, *Neuroreport* **6,** 1611 (1995).
149. E. O'Hearn and M. E. Molliver, *J. Neurosci.* **1,** 8828 (1997).
150. E. O'Hearn and M. E. Molliver, *Soc. Neurosci. Abstr.* **23,** 2308 (1997).
151. A. C. Scallet, X. Ye, R. Rountree, P. Nony, and S. F. Ali, *Ann. NY Acad. Sci.* **801,** 217 (1996).
152. A. C. Scallet, X. Ye, and S. F. Ali, *Ann. N. Y. Acad. Sci.* **801,** 227 (1996).
153. H. H. Molinari, I. M. Maisonneuve, and S. D. Glick, *Brain Res.* **737,** 255 (1996).
154. S. Helsley, C. A. Dlugos, R. J. Pentney, R. A. Rabin, and J. C. Winter, *Brain Res.* **759,** 306 (1997).
155. J. P. O'Callaghan, L. E. Rodman, T. S. Rogers, J. B. Terril, and J. G. Page, *Soc. Neurosci. Abstr.* **20,** 1650 (1994).
156. J. P. O'Callaghan, T. S. Rogers, L. E. Rodman, and J. G. Page, *Ann. N. Y. Acad. Sci.* **801,** 205 (1996).
157. B. J. Vilner, U. K. Bandarage, M. E. Kuehne, C. M. Bertha, and W. D. Bowen, *in* "Problems of Drug Dependence. Proceedings of the 59th Annual Scientific Meeting, NIDA Res. Monograph." (L. S. Harris, ed.). U.S. Government Printing Office, Washington, DC, 1997.
158. E. O'Hearn and M. E. Molliver, *Soc. Neurosci. Abstr.* **21,** 1340 (1995).
159. P. Popik, R. T. Layer, and P. Skolnick, *Psychopharmacology* **114,** 672 (1994).
160. J. W. Olney, *U S Patent* **5,629,307,** (1997).
161. K. Chen, T. G. Kokate, S. Yamagishi, F. I. Carroll, and M. A. Rogawski, *Soc. Neurosci. Abstr.* **21,** 1105 (1995).
162. K. Chen, T. G. Kokate, S. D. Donevan, F. I. Carroll, and M. A. Rogawski, *Neuropharmacology* **35,** 423 (1996).
163. D. C. Mash, R. Douyon, W. L. Hearn, N. C. Sambol, and J. Sanchezramos, *Biol. Psychiat.* **37,** 652 (1995).
164. P. M. Whitaker and P. Seeman, *J. Pharm. Pharmacol.* **29,** 506 (1977).
165. D. C. Deecher, M. Teitler, D. M. Soderlund, W. G. Bornmann, M. E. Kuehne, and S. D. Glick, *Brain Res.* **571,** 242 (1992).
166. P. M. Sweetnam, J. Lancaster, A. Snowman, J. Collins, S. Perschke, C. Bauer, and J. Ferkany, *Psychopharmacology* **118,** 369 (1995).
167. J. K. Staley, Q. Ouyang, J. Pablo, W. L. Hearn, D. D. Flynn, R. B. Rothman, K. C. Rice, and D. C. Mash, *Psychopharmacology* **127,** 10 (1996).
168. C. Messer and G. Rudnick, *Soc. Neurosci. Abstr.* **21,** 1383 (1995).
169. S. D. Glick, K. Rossman, S. Wang, N. Dong, and R. W. Keller, Jr., *Brain Res.* **628,** 201 (1993).

170. S. F. Ali, G. D. Newport, W. Slikker, R. B. Rothman, and M. H. Baumann, *Soc. Neurosci. Abstr.* **21,** 2107 (1995).
171. S. F. Ali, G. D. Newport, W. Slikker, Jr., R. B. Rothman, and M. H. Baumann, *Brain Res.* **737,** 215 (1996).
172. M. S. Reid, K. Hsu, K. H. Souza, P. A. Broderick, and S. P. Berger, *J. Neural. Transm.* **103,** 967 (1996).
173. M. H. Baumann, R. B. Rothman, and S. F. Ali, *Ann. N. Y. Acad. Sci.* **844,** 252 (1998).
174. H. Sershen, A. Hashim, and A. Lajtha, *Brain Res. Bull.* **36,** 587 (1995).
175. H. Sershen, A. Hashim, and A. Lajtha, *Pharmacol. Biochem. Behav.* **53,** 863 (1996).
176. L. G. Harsing, H. Sershen, and A. Lajtha, *J. Neur. Trans.* **96(3),** 215 (1994).
177. H. Sershen, A. Hashim, and A. Lajtha, *Neurochem. Res.* **19,** 1463 (1994).
178. H. Sershen, A. Hashim, and A. Lajtha, *Brain Res. Bull.* **40,** 63 (1996).
179. S. D. Glick, C. A. Gallagher, L. B. Hough, K. L. Rossman, and I. M. Maisonneuve, *Brain Res.* **588,** 173 (1992).
180. S. M. Pearl, I. M. Maisonneuve, and S. D. Glick, *Neuropharmacology* **35,** 1779 (1996).
181. I. M. Maisonneuve, G. L. Mann, C. R. Deibel, and S. D. Glick, *Psychopharmacology* **129,** 249 (1997).
182. R. A. Rabin and J. C. Winter, *Eur. J. Pharmacol.* **316,** 343 (1996).
183. E. E. Codd, *Life Sci.* **57,** PL315 (1995).
184. J. P. Pablo and D. C. Mash, *Neuroreport* **9,** 109 (1998).
185. P. M. Whitaker and P. Seeman, *Psychopharmacology* **59,** 1 (1978).
186. P. M. Whitaker and P. Seeman, *Proc. Natl. Acad. Sci. USA* **75,** 5783 (1978).
187. R. F. Long and A. W. Lessin, *Biochem. J.* **82,** 4P (1962).
188. H. Sershen, A. Hashim, and A. Lajtha, *Brain Res. Bull.* **42,** 161 (1997).
189. R. C. Miller and T. Godfraind, *Eur. J. Pharmacol.* **96,** 251 (1983).
190. A. S. Schneider, J. E. Nagel, and S. J. Mah, *Eur. J. Pharmacol.* **317,** R1 (1996).
191. D. Mash, J. K. Staley, J. P. Pablo, A. M. Holohean, J. C. Hackman, and R. A. Davidoff, *Neurosci. Lett.* **192,** 53 (1995).
192. J. Pablo, J. K. Staley, A. M. Holohean, J. C. Hackman, R. A. Davidoff, and D. C. Mash, *Soc. Neurosci. Abstr.* **21,** 1264 (1995).
193. W. D. Bowen, B. J. Vilner, W. Williams, C. M. Bertha, M. E. Kuehne, and A. E. Jacobson, *Eur. J. Pharmacol.* **279,** R1 (1995).
194. R. H. Mach, C. R. Smith, and S. R. Childers, *Life Sci.* **57,** PL57 (1995).
195. W. D. Bowen, B. J. Vilner, U. K. Bandarage, and M. E. Kuehne, *Soc. Neurosci. Abstr.* **22,** 2006 (1996).
196. R. A. Rabin and J. C. Winter, *Brain Res.* **731,** 226 (1996).
197. E. Cretet, M. Prioux-Guyonneau, C. Jacquot, H. Sentenac, and J. Wepierre, *Arch. Pharmacol.* **313,** 119 (1980).
198. Z. Binienda, J. Johnson, B. Thorn, and S. F. Ali, *Soc. Neurosci. Abstr.* **23,** 1227 (1997).
199. R. D. Bunag and E. J. Walaszek, *Ann. N. Y. Acad. Sci.* **104,** 437 (1968).
200. M. E. Alburges and G. R. Hanson, *Soc. Neurosci. Abstr.* **23,** 2408 (1997).
201. R. V. House, P. T. Thomas, and H. N. Bhargava, *Pharmacology* **51,** 56 (1995).
202. Y. Itzhak and S. F. Ali, *Soc. Neurosci. Abstr.* **21,** 2108 (1995).

This Page Intentionally Left Blank

—CHAPTER 4—

CHEMISTRY AND BIOLOGY OF STEROIDAL ALKALOIDS FROM MARINE ORGANISMS

ATTA-UR-RAHMAN AND M. IQBAL CHOUDHARY

International Center for Chemical Sciences
H. E. J. Research Institute of Chemistry
University of Karachi
Karachi-75270, Pakistan

I. Introduction

Steroids are ubiquitous members of a large class of carbon compounds of marine and terrestrial origin, having a perhydro-1,2-cyclopentanophenanthrene ring system. Steroidal alkaloids have been the subject of

THE ALKALOIDS, VOL. 52
0099-9598/99 $30.00

Copyright © 1999 by Academic Press.
All rights of reproduction in any form reserved.

vigorous investigations during the last fifty years, mainly due to their pharmacological properties and their importance as raw materials for the synthesis of diosgenin, contraceptive drugs, corticoids, sex hormones, vitamins, metabolic steroids, and so on.

Until a few decades ago, terrestrial plants were the only source of steroidal alkaloids with a few exceptions (amphibians: *Phyllobates, Salamandra,* etc.). In 1976, triterpenoidal alkaloids of unknown biosynthetic origin were isolated from a marine zoanthid, followed by the isolation of a large number of dimeric steroidal alkaloids from a Western Indian Ocean worm, *Cephalodiscus gilchristi,* and the tunicate *Ritterella tokioka.* A few more organisms, such as the sponges of *Plakina* and *Corticum* spp., have also yielded steroidal alkaloids. Steroidal amines isolated from the starfish *Styracaster caroli,* 6-hydroximino steroids from sponges *Cinachyrella* spp., and rearranged triterpenoid-type alkaloids from colonial zoanthids have also been included in this chapter. Many of these compounds possess novel chemical structures and also exhibit pronounced antitumor, cytotoxic, and other biological activities.

Marine natural products have been extensively reviewed in many monographs and journals (*1–17*). Kobayashi and Ishibashi have reviewed marine alkaloids in general in this series (*16*), and our recent review (*17*) provides an account of toxic alkaloids of marine origin. This chapter is intended to provide the reader a brief description of the isolation, structure elucidation, synthetic studies, and biological screening of important classes of steroidal alkaloids and amines of marine origin.

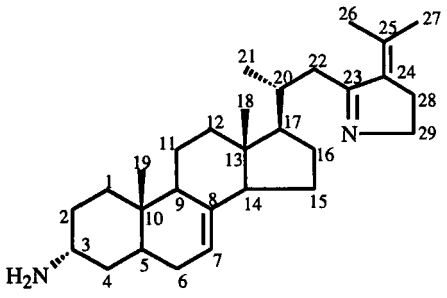
II. Monomeric Steroidal Alkaloids

A. Alkaloids from the Marine Sponge, *Plakina* Spp.

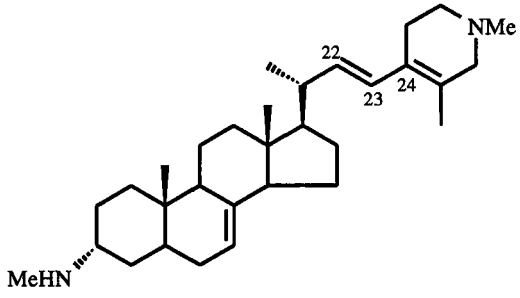
Sponges of the genus *Plakina* were collected from shallow waters of Mant Island, Ponape, where they were found to grow widely and kill corals. The crude extract of the sponge showed antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* (*18*).

The major metabolite, plankinamine A (**1**), $C_{29}H_{46}N_2$, $[\alpha]_D$ +16° ($CHCl_3$)(0.3% dry weight), was separated from the crude extracts of the sponge by solvent-solvent extraction. Compound **1** showed ^1H NMR signals at δ 0.59 and 0.77, and in the ^{13}C NMR spectrum two methyl singlets appeared at δ 12.0, which could be assigned to the C-18 and C-19 methyl groups of a steroid skeleton. A striking feature of the ^{13}C NMR spectrum

was the presence of five signals at $\delta > 100$; the signals at δ 117.7 (d) and 139.2 (s) were in agreement with the literature values for C-7 and C-8 of a Δ^7-sterol; the signals at δ 173.2 (s), 137.1 (s), and 129.0 (s) were assigned to the fully substituted double bond (C-24–C-25) and an imine group. The UV absorption at 246 nm indicated the presence of an α,β-unsaturated imine. The mass spectrum of **1** showed peaks at *m/z* 123.1052 ($C_8H_{13}N$, 100%) and 300.2721 ($C_{21}H_{34}N$).



(**1**) Plakinamine A



(**2**) Plakinamine B

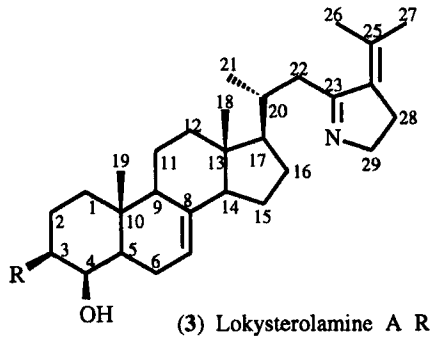
The nature of the C-17 side chain was determined from the ^{1}H NMR data. Irradiation at δ 2.04 resulted in decoupling of two mutually coupled signals at δ 2.73 (dd, 1H, J_1 = 15 Hz, J_2 = 2 Hz) and 2.28 (dd, 1H, J_1 = 15 Hz, J_2 = 11 Hz) and also of the methyl doublet at δ 0.95. These signals were assigned to the C-20, C-22, and C-21 protons, respectively. The methyl singlets at δ 1.79 and 1.99 were assigned to the C-26 and C-27 vinyl methyl groups (*18*).

The hydrochloride salt of plakinamine B (**2**), $C_{31}H_{50}N_2$, $[\alpha]_D$ −29° (CH_3OH)(0.1% dry weight) was isolated as a minor metabolite by fractional crystallization from methanol. The structure of the steroidal nucleus of plakinamine B (**2**) was established by comparing its ^{13}C NMR data with those of 3α-(*N*-methylamino)-ergosta-7,22-diene. The chemical shifts for the carbons C-1–C-20 were almost identical in both spectra. The structure of the side chain was established from the ^{1}H NMR data. Irradiation of the C-20 proton multiplet at δ 2.13 resulted in decoupling of the C-21 methyl signal resonating at δ 1.05 (J = 7 Hz) and of the C-22 olefinic proton at δ 5.42 (dd, 1H, J = 15 Hz, J = 9 Hz). The ^{13}C NMR spectrum indicated the presence of an additional tetrasubstituted olefinic bond. The UV absorption at 241 nm (ε 2700) and the chemical shift of the C-23 olefinic proton signal required the presence of a conjugated diene system between C-22 and C-25. A vinyl methyl resonating at δ 1.71 was assigned to the C-26 methyl group, and the presence

of a broad singlet at δ 2.86 suggested a nitrogen substituent at C-27. Mutually coupled signals at δ 2.54 (dt, 1H, J = 12.6 Hz) and 2.51 (dt, 1H, J = 12.6 Hz), which were also coupled to a signal at δ 2.25 (m, 2H), were assigned to two methylene groups in a six-membered ring. Plakinamine B (**2**) and plakinamine A (**1**) were found to have the same carbon skeleton. The ^{13}C NMR signals assigned to the carbons C-24–C-29 in compound **2** compare well with the signals of *N*-methyl-Δ^3-piperideine, which is the closest simple model (*18*).

B. Alkaloids from the Marine Sponge *Corticium* Spp.

Sponges of the genus *Corticium* (Homosclerophorida, Plakinidae) collected from Bunaken Island, Sulawesi, Indonesia, showed antimicrobial activity against *Bacillus subtilis*. Through a bioassay-directed isolation procedure, two new steroidal alkaloids, lokysterolamines A (**3**) and B (**4**), were isolated (*19*). Alkaloids **3** and **4** were found to be structurally related to plakinamine-A (**1**)(*18*).



(**3**) Lokysterolamine A R = Me_2N
(**4**) Lokysterolamine B R = AcNH

Lokysterolamine A (**3**), $C_{31}H_5N_2O$, 0.13%, $[\alpha]_D$ −12.6° ($CHCl_3$), (M^+) *m/z* 466.3934, was found to have a steroidal skeleton on the basis of its spectrum, the methyl singlets at δ 1.04 and 0.60 and a methyl doublet at δ 0.88 being particularly diagnostic. An IR absorption at 3400 cm^{-1} and a carbon signal at δ 70.4 attached to a proton resonating at δ 3.92 (triplet) indicated the presence of a hydroxy substituent at C-4 as confirmed by the heteronuclear multiple bond connectivity (HMBC) spectrum. The presence of an $N(CH_3)_2$ group at C-3 was deduced on recording the ^1H NMR spectrum in CD_3OD acidified with deuterotrifluoroacetic acid (TFA), which resulted in downfield shifts of the 6H singlet and of the C-3 proton. The downfield shift of C-3 at δ 69.2 and the

coupling constant of the H-3 signal ($J_{2,3}$ = 12.5 Hz) indicated a β-orientation (equatorial) of the $N(CH_3)_2$ group. Comparison of the ^{13}C NMR data with plakinamine A (**1**) helped to establish the nature of the side chain and the stereochemistry at C-20. The spectroscopic evidence indicated that lokysterolamine A (**3**) is *N,N*-dimethyl-4β-hydroxy-3-epi-plakinamine A.

Lokysterolamine B (**4**), $C_{31}H_{48}N_2O_2$, *m/z* 480.3722, 0.02, $[\alpha]_D$ −31° ($CHCl_3$), was found to be an *N*-acetyl derivative of compound **3.** The spectrum of **4** showed a 3H singlet at δ 1.94. The ^{13}C NMR spectrum exhibited a downfield quaternary carbon signal at δ 172.3. This suggested the presence of an acetamido moiety at C-3 instead of an $N(CH_3)_2$ group. This was further confirmed by the appearance of an NH doublet at δ 5.48 coupled to the C-3 proton (J = 8.3 Hz) (*19*).

C. Alkaloids of Unknown Biosynthetic Origin from a Colonial Zoanthid

Chemical investigations on a new species of a colonial zoanthid of the genus *Zoanthus* collected in the Bay of Bengal and from the Karachi coast of the Arabian Ocean have resulted in the isolation of a new class of alkaloids of unknown biosynthetic origin. The colonial zoanthids occur as dense mats on intertidal rocks along the coast of the Indian subcontinent. The animals can eject jets of water when they are disturbed. If the spray comes in contact with a victim's eyes, it causes tears followed by prolonged redness and pain.

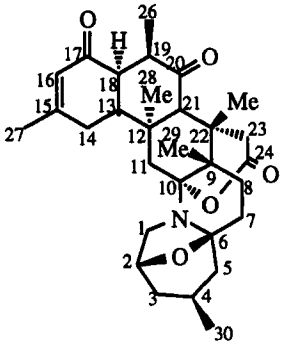
Rao *et al.* in 1984 isolated the first member of the new class of alkaloids, zoanthamine (**5**), $C_{30}H_{41}NO_5$, $[\alpha]_D$ 18° ($CHCl_3$), which was obtained as a white crystalline solid. The molecular formula required that compound **5** be heptacyclic and have both a fully substituted nitrogen atom and an ether linkage. Analysis of the ^{13}C NMR data revealed the presence of a ketone [δ 212.0 (s)], an α,β-unsaturated ketone [δ 197.2 (s), 159.9 (s), and 126.8 (d)], and an ester [δ 172.5 (s)]. The structure was unambiguously assigned by single X-ray diffraction analysis (*20*).

Zoanthenamine (**6**), $C_{30}H_{39}NO_6$, (M^+) *m/z* 509.2782, was obtained as a white powder. The presence of the β-methyl enone functionality in ring A was deduced from the characteristic signals in the ^{13}C NMR spectrum [δ 199.3 (s), 127.0 (d), 159.8 (s), 23.4 (q)] and ^1H NMR signals at δ 5.88 (s, 1H) and 1.98 (s, 3H). The carbon skeleton of **6** retains the stereochemistry of zoanthamine (**5**) (*21*).

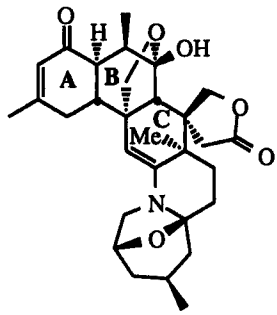
Zoanthamine (**7**), $C_{30}H_{37}NO_7$, $[\alpha]_D$ 133° ($CHCl_3$), (M^+) *m/z* 523.2549, was found to be an oxidation product of zoanthamine (**5**). Comparison of the spectral data suggested that the C-12–C-21 portions of **5** and **7** were identi-

cal. The olefinic carbon signals at δ 140.1 (s) and 110.9 (d) suggested an enamide in ring C (*21*).

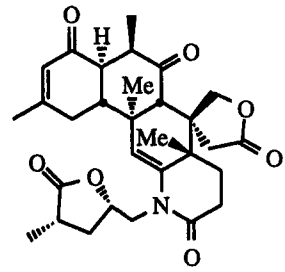
The isomeric alkaloids 28-deoxyzoanthenamine (**8**) and 22-epi-28-deoxyzoanthenamine (**9**), have the same molecular formula $C_{30}H_{39}NO_5$, which corresponds to one less oxygen atom than is present in zoanthenamine (**6**). Comparison of the spectral data of **8** and **9** revealed no major difference, except for the chemical shifts of proton and carbon signals associated with the lactone ring. Further studies suggested that the compounds were isomeric at C-22 (*22*).



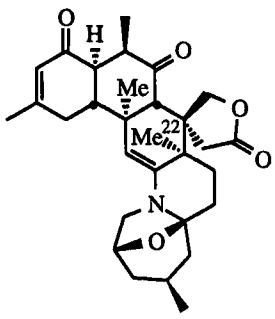
(**5**) Zoanthamine



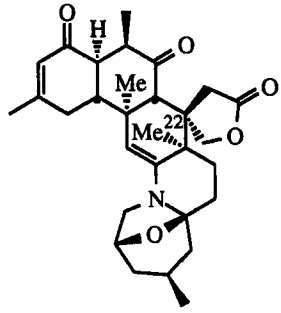
(**6**) Zoanthenamine



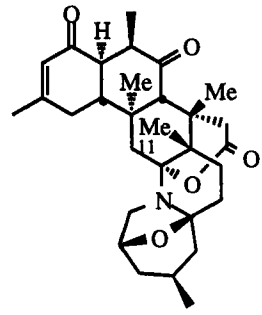
(**7**) Zoanthamide



(**8**) 28-Deoxyzoanthenamine



(**9**) 22-*epi*-28-deoxyzoanthenamine



(**10**) Zoanthaminone

Our group in Pakistan has also isolated an alkaloid zoanthaminone (**10**) $C_{30}H_{39}NO_6$, $[\alpha]_D$ 30° ($CHCl_3$), (M^+) *m/z* 509.2882, by extensive solvent–solvent fractionation of the ethanolic extract of a colonial zoanthid collected from the intertidal rocks of the Karachi coast. The structure of the alkaloid was solved by single-crystal X-ray diffraction analysis and was found to be a C-11 keto analog of zoanthamine (**5**) (*23*).

III. Dimeric Steroidal Alkaloids

A. Alkaloids from *Cephalodiscus gilchristi*

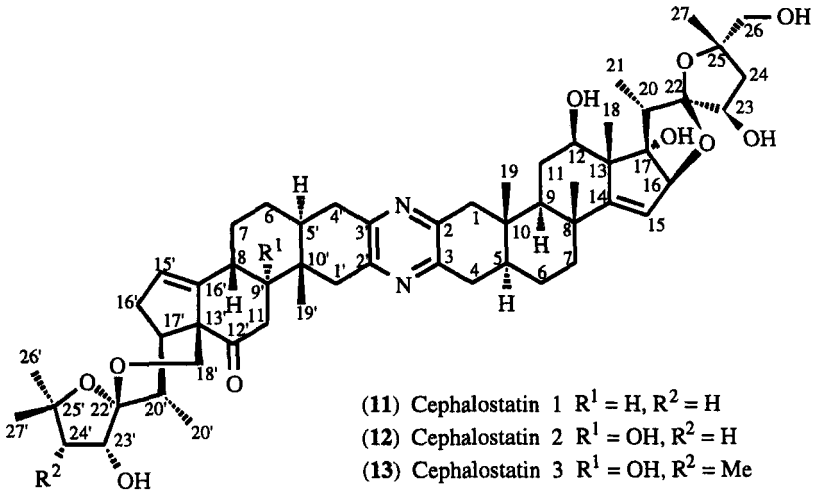
Pettit *et al.* (*24*), working on the marine worm *Cephalodiscus gilchristi* (order Cephalodisicida, phyla Hemichordata, class Pterobranchia) collected from the Indian Ocean off Southeast Africa, have isolated a number of bioactive bis-steroidal pyrazine alkaloids, the cephalostatins 1–15 (**11–25**).

Cephalostatin 1 (**11**), $C_{54}H_{74}N_2O_{10}$, $[\alpha]_D$ 112° (CH_3OH), was isolated from the active methylene chloride fraction of *C. gilchristii* using a detailed bioassay-guided (P-388 murine lymphocytic leukemia cell lines) series of chromatographic separations. The alkaloid has $(M + H)^+$ *m/z* 1079 as determined by SP-HRSIMS (high-resolution secondary ion mass spectrometry). The UV absorption at 289 nm indicated the presence of a pyrazine ring. The structure of cephalostatin 1 was solved by spectroscopic and X-ray diffraction analysis and found to be quite unusual, consisting of nine fused rings formed by the coupling of two steroid nuclei at C-2 (C-2′) and C-3 (C-3′). In addition, two spiroketal rings terminate each end of the fused ring system, generating a total of 13 rings and 23 asymmetric centers (*24*).

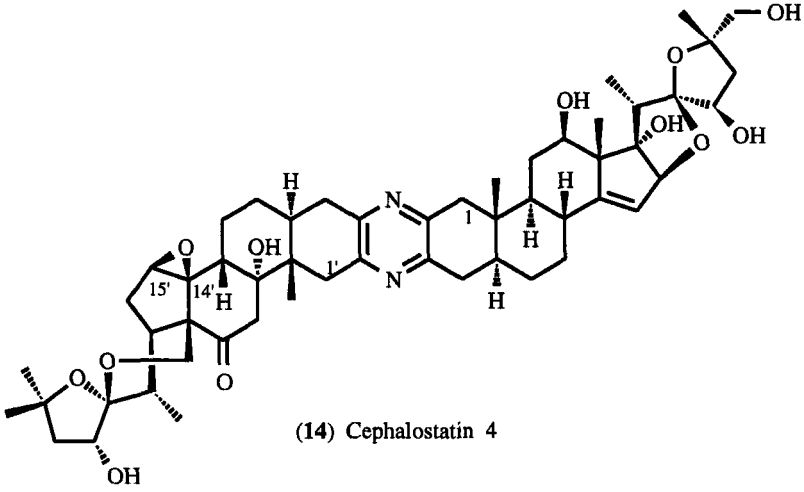
With the complete X-ray structural assignment and completely interpreted NMR spectra of compound **11**, it became easier to determine the structures of other members of this interesting series. Cephalostatin 2 (**12**), $C_{54}H_{74}N_2O_{11}$, $[\alpha]_D$ 111° (CH_3OH), $(M + H)^+$ *m/z* 927.5372, was crystallized from ethyl acetate–methanol. Compound **12** exhibited ^1H and ^{13}C NMR spectra very similar to those of cephalostatin 1 (**11**). The structure was found to have one extra hydroxyl group at C-9′. Cephalostatin 3 (**13**), $C_{55}H_{76}N_2O_{11}$, $[\alpha]_D$ 99° (CH_3OH), $(M + H)^+$, *m/z* 941.5546 was found to be a C-24′ methyl derivative of cephalostatin 2 (**12**) as evidenced by a new 3H doublet in the ^1H NMR spectrum of **13** (*25*).

Cephalostatin 4 (**14**), $C_{54}H_{74}N_2O_{12}$, $[\alpha]_D$ 89° (CH_3OH), $(M + H)^+$ *m/z* 943.5343, was found to contain an epoxy group between C-14′ and C-15′. Such 14,15-epoxides are not very common in nature (*25*).

Cephalostatin 5 (**15**), $C_{54}H_{72}N_2O_{10}$, $[\alpha]_D$ 100° (CH_3OH), *m/z* 908.5187 $(M)^+$, and cephalostatin 6 (**16**), $C_{53}H_{70}N_2O_{10}$, $[\alpha]_D$ 100° (CH_3OH), $(M)^+$ *m/z* 894.4985, were also isolated from the active methylene chloride fraction of the animal through column chromatography and HPLC. The NMR signals attributed to the "left side" steroidal unit in cephalostatins 5 and 6 (**15–16**) were identical to cephalostatins 1–4 (**11–14**). The right side of the molecules was found to contain 10 degrees of unsaturation, which



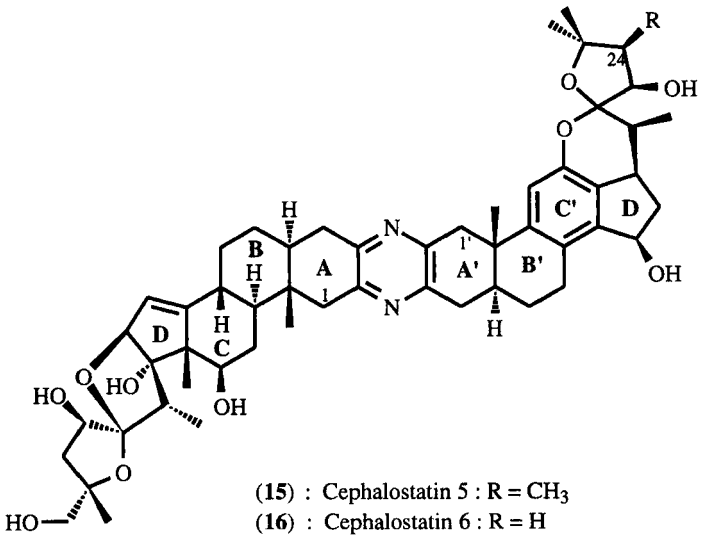
(**11**) Cephalostatin 1 $R^1 = H, R^2 = H$
(**12**) Cephalostatin 2 $R^1 = OH, R^2 = H$
(**13**) Cephalostatin 3 $R^1 = OH, R^2 = Me$



(**14**) Cephalostatin 4

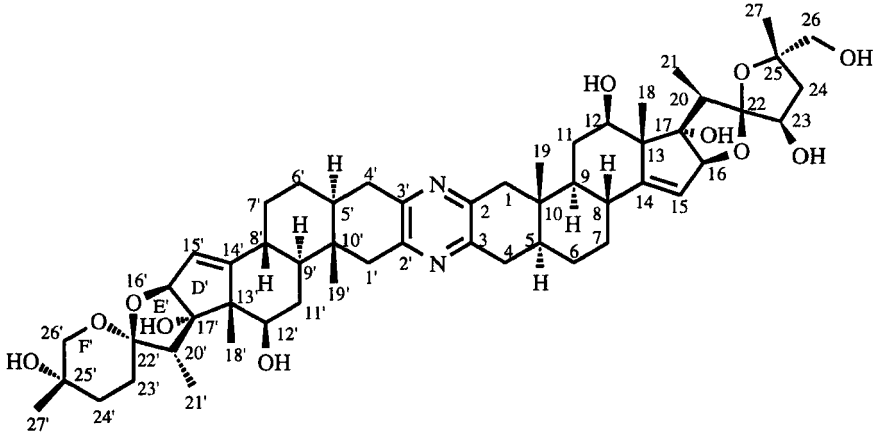
indicated an aromatic ring in this half. Location of the aromatic ring C′ was determined by NOE effects between the aromatic proton at δ 6.93 (C-11′; δ_C 111.4) and one of the C-1′ methylene protons. Cephalostatin 6 (**16**) was found to be a demethyl derivative of cephalostatin 5 (**15**).

The right-side subunits of cephalostatins 5 and 6 (**15** and **16**) contain an aromatic ring C′. Naturally occurring and synthetic steroids with ring A aromatized are well known, but steroids bearing an aromatic ring C are quite rare and examples of biosynthetic origin are essentially unknown (*26*).

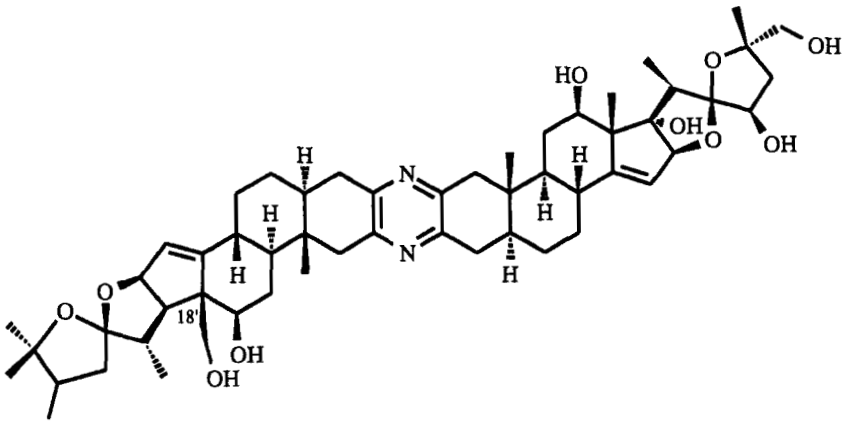


(**15**) : Cephalostatin 5 : R = CH_3
(**16**) : Cephalostatin 6 : R = H

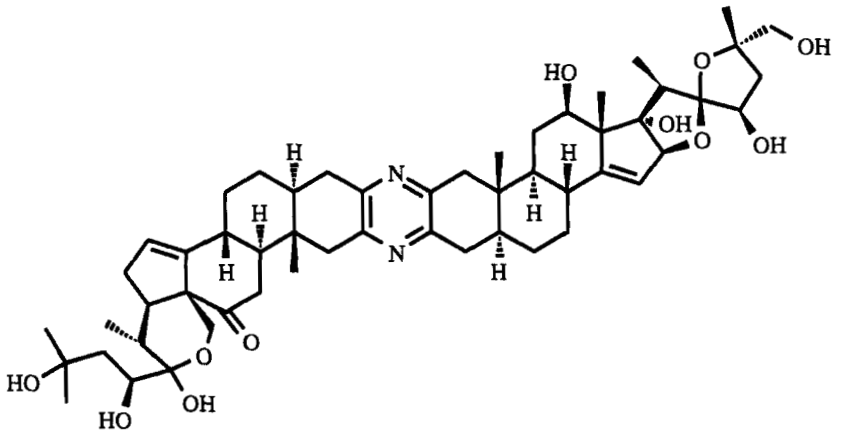
Cephalostatin 7 (**17**), $C_{54}H_{76}N_2O_{11}$, $[\alpha]_D$ 106° (CH_3OH), $(M + K)^+$ *m/z* 967.5067, cephalostatin 8 (**18**), $C_{55}H_{78}N_2O_{10}$, $[\alpha]_D$ 110° (CH_3OH), $(M + K)^+$ *m/z* 965.5261, and cephalostatin 9 (**19**), $C_{54}H_{76}N_2O_{11}$, $[\alpha]_D$ 105° (CH_3OH), $(M + H)^+$ *m/z* 929.5529, were found to contain a right-side moiety identical with that of cephalostatin 1 (**11**), but beyond the left-side ring C, each compound was found to have substantial differences (*27*).



(**17**) Cephalostatin 7



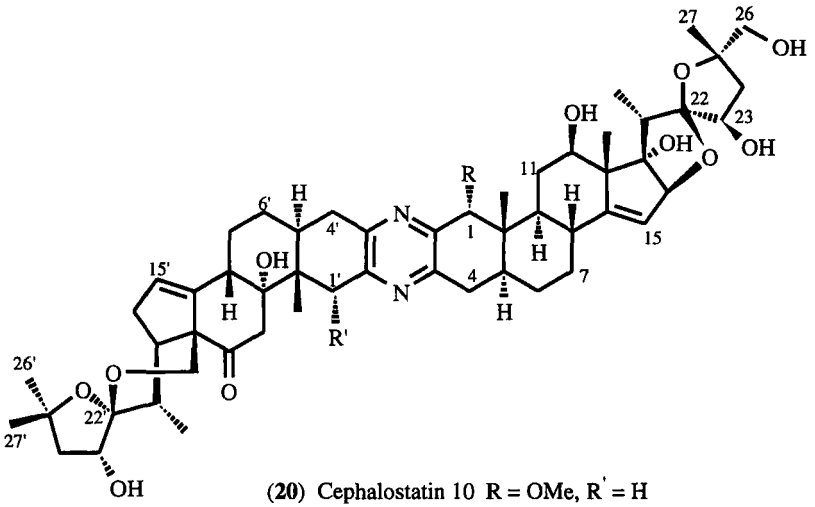
(**18**) Cephalostatin 8



(**19**) Cephalostatin 9

Cephalostatins 10 (**20**) and 11 (**21**) were found to be structural isomers [$C_{55}H_{77}N_2O_{12}$, $(M + H)^+$ *m/z* 957.5492] containing an OMe substituent on either C-1 or C-1′, respectively (*28*).

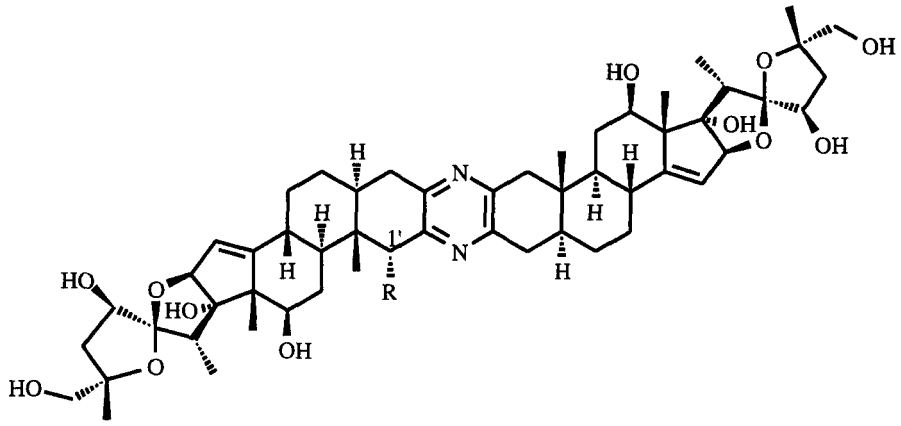
A sequence (using P-388 guided bioassay) of steric exclusion and partition-type chromatographic separations of the active butanolic fraction by reversed-phase semipreparative HPLC led to the isolation of cephalostatin 12 (**22**), $C_{54}H_{76}N_2O_{12}$, $[\alpha]_D$ 157° (CH_3OH), $(M + H)^+$ *m/z* 945.5444, and cephalostatin 13 (**23**), $C_{54}H_{76}N_2O_{13}$, $[\alpha]_D$ 108° (CH_3OH), $(M + H)^+$ *m/z* 961.5451. The ^{13}C NMR spectrum of cephalostatin 12 (**21**) exhibited only 27 signals, suggesting a twofold symmetrical axis. Comparison of the NMR data with those of steroidal subunits of the other known cephalostatins indicated that the right-side subunit of cephalostatin 12 (**22**) is identical to the right-side subunit of cephalostatin 1 (**11**). All of the right-side



(**20**) Cephalostatin 10 R = OMe, R' = H
(**21**) Cephalostatin 11 R = H, R' = OMe

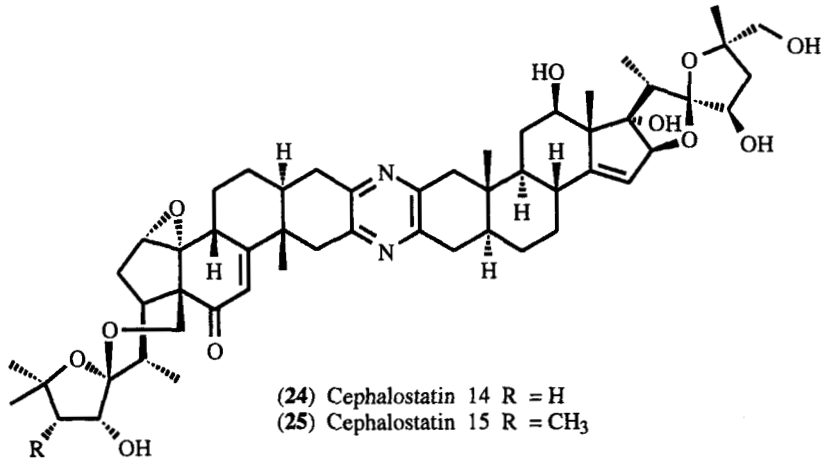
steroidal subunit and rings D′, E′, and F′ of the left-side subunits of cephalostatin 13 (**23**) were identical to those of **22.** However, NMR and mass spectrometric data indicated an additional secondary hydroxyl group at C-1′ of cephalostatin 13 (**23**) (29).

Cephalostatin 14 (**24**), $C_{54}H_{72}N_2O_{12}$, $[\alpha]_D$ 80.9° (CH_3OH), $(M + Na)^+$ *m/z* 963.4983, was found to have an identical right-side subunit, as in cephalostatin 1 (**11**), as inferred from 1D and 2D NMR data. Furthermore, it was found that the rings A′, E′, and F′ in the left-side subunit corresponded to those of cephalostatin 1 (**11**). However, two downfield olefinic signals and the upfield



(**22**) Cephalostatin 12 R = H
(**23**) Cephalostatin 13 R = OH

shift of the C-12′ carbonyl signal in the ^{13}C NMR spectrum indicated that the C-12′ carbonyl group is conjugated with a double bond. Cephalostatin 15 (**25**), $C_{55}H_{74}N_2O_{12}$, $[\alpha]_D$ 71° (CH_3OH), $(M + H)^+$ *m/z* 955.5320, was found to be a naturally occurring C-24′ methyl derivative of **24** (30).



(**24**) Cephalostatin 14 R = H
(**25**) Cephalostatin 15 R = CH_3

B. Steroidal Alkaloids from *Ritterella tokioka*

Ritterella tokioka Kott, a tunicate of the family Polyclinidae, collected from the Izu Peninsula 100 km southwest of Tokyo, on extraction and partitioning between a number of solvent systems followed by repeated chromatography, afforded another series of bis-steroidal pyrazine alkaloids, ritterazines A–M (**26–38**). Structures of these alkaloids were found to be related to the cephalostatins isolated from the hemichordate *Cephalodiscus gilchristii.*

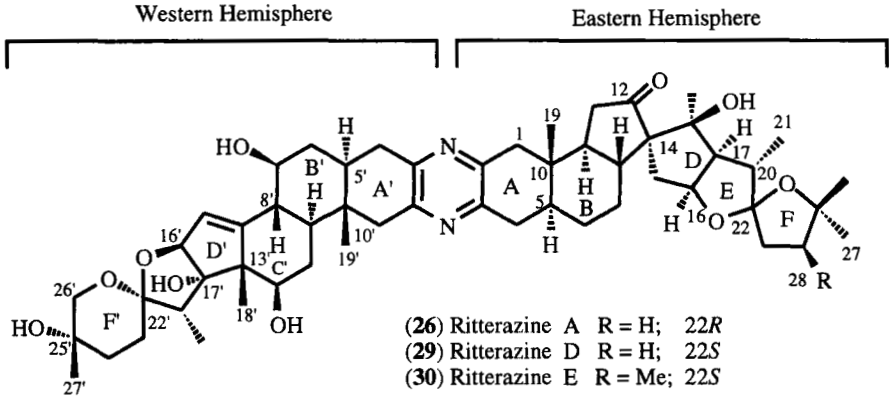
Ritterazine A (**26**), $[\alpha]_D$ 112° (CH_3OH), was found to have the molecular formula $C_{54}H_{76}N_2O_{10}$, as determined by HR-FABMS, $(M + H)^+$ *m/z* 913.5576. The UV absorption at 287 nm indicated the presence of a pyrazine ring, which was supported by four ^{13}C NMR signals in the range δ 145–150.

The ^1H NMR spectrum of **26** showed well-dispersed signals of 76 protons, which included seven methyl singlets and two methyl doublets. The ^{13}C NMR spectrum revealed a ketonic carbonyl carbon (δ 221.2), two acetal/hemiacetal carbons (δ 108.9, 119.8), four oxygenated quaternary carbons, four oxygenated methines, and an oxygenated methylene carbon. In addition to the pyrazine carbons, two sp^2 carbon signals resonating at δ 121.2

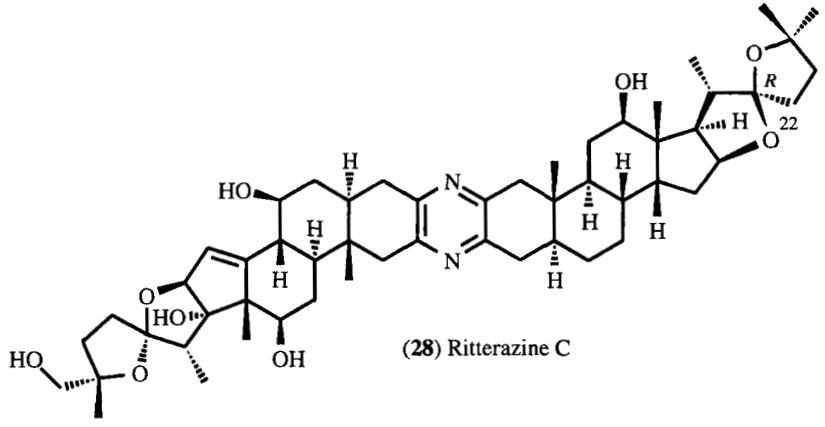
and 152.0 also appeared in the spectrum. To satisfy the molecular formula, two steroid units were connected through a tetrasubstituted pyrazine ring. Relative stereochemistry of each steroidal subunit in ritterazine A (**26**) was determined by coupling constants and NOESY data (*31*).

Ritterazine B (**27**), $[\alpha]_D$ 43° (CH_3OH), showed the $(M + H)^+$ ion at *m/z* 899.5873 in the high-resolution FAB+ve, which agreed with the pseudomolecular formula $C_{54}H_{79}N_2O_9$. The eastern hemisphere of ritterazine B (**27**) was found to contain a saturated ring D, a 5/5 spiroketal system, and an OH group at C-12. The western hemisphere of **27** was identical to that of ritterazine A (**26**).

Ritterazine C (**28**), $C_{54}H_{78}N_2O_9$, $[\alpha]_D$ 72° (CH_3OH), is a structural isomer of **27**. The ^1H NMR spectrum of **28** displayed the same sets of signals observed for the eastern hemisphere of ritterazine B (**27**), whereas the



(**26**) Ritterazine A R = H; 22*R*
(**29**) Ritterazine D R = H; 22*S*
(**30**) Ritterazine E R = Me; 22*S*



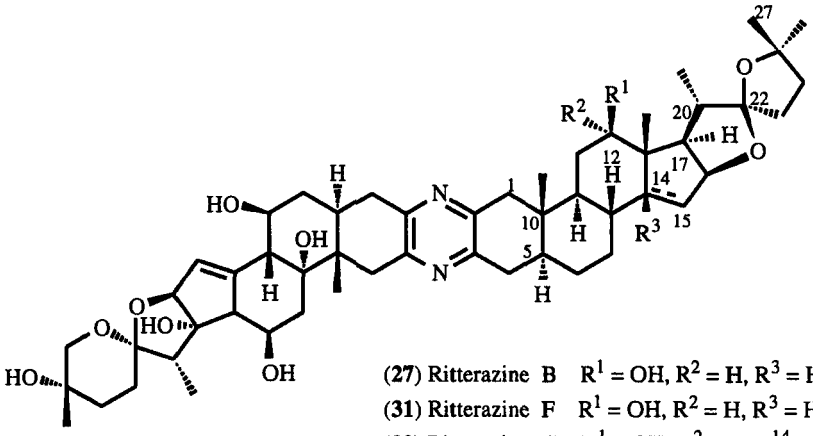
(**28**) Ritterazine C

spectrum of the western hemisphere was distinctly different. Interpretation of COSY, heteronuclear multiple quantum coherence (HMQC), and HMBC spectra, as well as the chemical shift of C-22 (δ 118.1), suggested the presence of a 5/5 spiroketal in the western hemisphere of **28.** Ritterazine B (**27**) can be converted into ritterazine C (**28**) when kept in $CDCl_3$, presumably due to the presence of trace amounts of DCl in $CDCl_3$ (*32*).

Ritterazine D (**29**), $[\alpha]_D$ 81° (CH_3OH), had the same molecular formula, $C_{54}H_{76}N_2O_{10}$, as ritterazine A (**26**). The gross structure of **29** was also found to be identical with that of ritterazine A (**26**). However, the ^1H and ^{13}C NMR chemical shifts of the nuclei around C-20 (eastern hemisphere) were significantly different in the two compounds. NOESY data suggest that the ritterazine D (**29**) has a 22*S* configuration, unlike **26,** which has a 22*R* configuration (33).

Ritterazine E (**30**), $C_{55}H_{78}N_2O_{10}$, $[\alpha]_D$ 71° (CH_3OH), $(M + H)^+$ *m/z* 927.5724, was found to be very similar to ritterazine D (**39**), with one additional CH_3 doublet in the ^1H NMR spectrum. Interpretation of 2D NMR data showed that ritterazine E was 24-methylritterazine D.

Ritterazine F (**31**), $[\alpha]_D$ 59° (CH_3OH), showed an $(M + H)^+$ ion at *m/z* 899.5764 in the high resolution positive fast atom bombardment mass (HR-FAB)+ve spectrum, which agreed with the molecular formula $C_{54}H_{79}N_2O_9$. The gross structure of **31** was similar to that of ritterazine B (**27**). However, the NMR data of the compounds were different in the chemical shift region of C-22. The stereochemistry C-22*S* was assigned on the basis of the ROESY data.



(**27**) Ritterazine B R^1 = OH, R^2 = H, R^3 = H; 22*R*
(**31**) Ritterazine F R^1 = OH, R^2 = H, R^3 = H; 22*S*
(**32**) Ritterazine G R^1 = OH, R^2 = H; Δ^{14}; 22*S*
(**33**) Ritterazine H R^1, R^2 = O, R^3 = H; 22*R*
(**34**) Ritterazine I R^1, R^2 = O, R^3 = OH; 22*S*

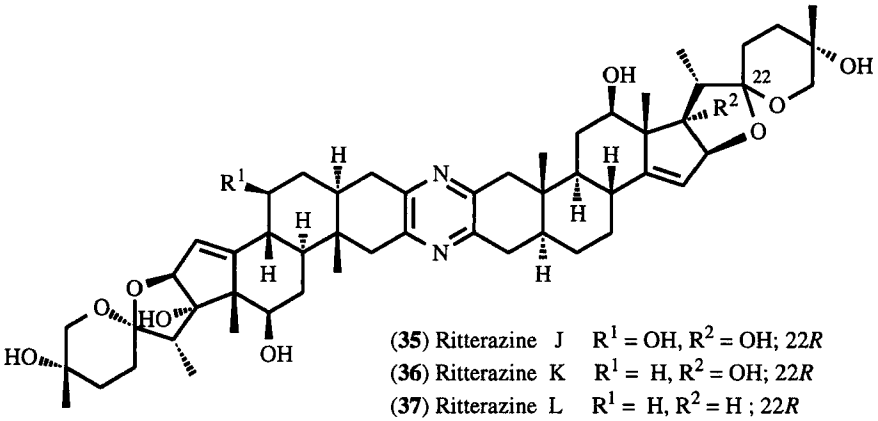
Ritterazine G (**32**), $C_{54}H_{76}N_2O_9$, $[\alpha]_D$ 91° $(M + H)^+$, *m/z* 897.5598, has one more double bond than ritterazine F (**31**). Spectroscopic studies indicate an additional double bond in the eastern hemisphere between C-14 and C-15. The compound has a 22*S* stereochemistry as determined by the rotating overhauser enhancement spectroscopy (ROESY) technique.

Ritterazine H (**33**), $C_{54}H_{76}N_2O_9$, $[\alpha]_D$ 96° (CH_3OH), was found to have a ketonic function at C-12 of the eastern hemisphere as inferred from the ^{13}C NMR spectrum. The stereochemistry of **33** was found to be identical to that of ritterazine B (**27**). Ritterazine I (**34**), $C_{54}H_{76}N_2O_{10}$, $[\alpha]_D$ 74° (CH_3OH), is found to possess one more oxygen atom than ritterazine H (**33**). The gross structure of ritterazine I was identical with that of **33** except for the presence of a C-14 hydroxyl group at the junction of rings E and F.

Ritterazine J (**35**), $[\alpha]_D$ 66° (CH_3OH), was the most highly oxygenated isolate, as revealed by the molecular formula $C_{54}H_{76}N_2O_{11}$. The eastern hemisphere had an identical structure to that of the western hemisphere, except for C-7, which bore no hydroxyl group.

Ritterazine K (**36**), $C_{54}H_{76}N_2O_{10}$, $[\alpha]_D$ 74° (CH_3OH), has a symmetrical nature and the mass and ^1H NMR data are consistent with its dimeric structure. Interestingly, the structure of the steroidal unit of ritterazine K (**36**) was the same as that of the western hemisphere of cephalostatin 7 (**17**) (*33*).

Ritterazine L (**37**), $C_{54}H_{76}N_2O_9$, $[\alpha]_D$ 85° (CH_3OH), was determined to be 17-deoxyritterazine K on the basis of the 2D NMR data. Ritterazine M (**38**), $C_{54}H_{76}N_2O_9$, $[\alpha]_D$ 95° (CH_3OH), was an isomer of ritterazine L with a different stereochemistry at C-22 (i.e., *S*) (*33*).



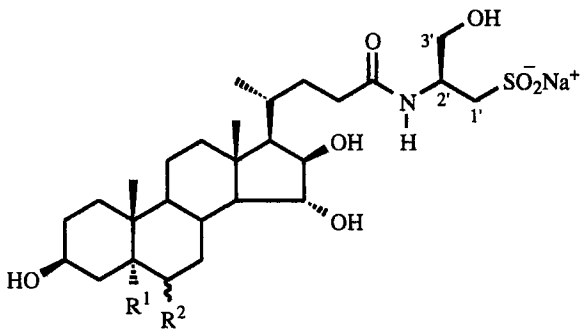
(**35**) Ritterazine J R^1 = OH, R^2 = OH; 22*R*
(**36**) Ritterazine K R^1 = H, R^2 = OH; 22*R*
(**37**) Ritterazine L R^1 = H, R^2 = H ; 22*R*
(**38**) Ritterazine M R^1 = H, R^2= H; 22*S*

IV. Steroidal Amines from Marine Animals

A. Steroidal Amines from the Starfish *Styracaster caroli*

Starfish (*Styracaster caroli*) were collected at a depth of 2000 m between the islands of Thio and Lifou (New Caledonia). Polar (aqueous and acetone) extracts of the starfish yielded three unique polyhydroxylated steroidal amines with an unusual 20-epicholanic skeleton, carolisterols A and B (**39–41**). The separation was achieved by column chromatography (Sephadex LH-20), droplet counter current chromatography, and reversed-phase HPLC (*34*).

Carolisterol A (**39**) ($C_{27}H_{46}NO_{19}S$) Na^+, exhibited the pseudo-molecular ion at (M−) *m/z* 576 in the negative fast atom bombardment (FAB-ve) mass spectrum. This indicated the presence of a nitrogen atom. The IR spectrum indicated the presence of an amide function (1,653 cm^{-1}) and sulfonate salt (1,200 and 1,044 cm^{-1}). The ^1H NMR spectrum of **39** suggested the presence of a 3β,5α,6β,15α,16β-pentahydroxy cholestane tetracyclic nucleus. The presence of cysteinolic acid residue linked to the steroidal moiety through an amide functionality was inferred from the HETCOR and HMBC spectra. The D configuration in the cyteinolic residue was inferred by analogy with other compounds containing the same substituents.



(**39**) Carolisterol A $R^1 = OH$; $R^2 = \beta\text{-}OH$
(**40**) Carolisterol B $R^1 = OH$; $R^2 = =O$
(**41**) Carolisterol C $R^1 = H$; $R^2 = \alpha\text{-}OH$

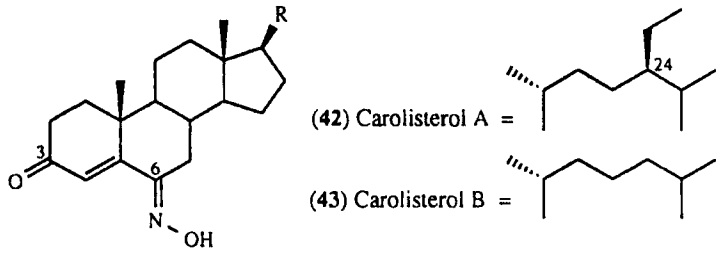
Carolisterol B (**40**), $(C_{27}H_{44}NO_{10}S)^-$ Na^+, (M^-) *m/z* 574, was found to be a 6-keto analog of **39.** The keto function was localized at C-6 with the assistance of ^1H–^1H COSY experiments.

Carolisterol C (**41**), $(C_{27}H_{46}NO_9S)^-$ Na^+, M^- *m/z* 560), was found to be a minor constituent with a tetrahydroxylated saturated cholanic acid skeleton linked with a cysteinolic residue (*34*).

B. Alkamines from the Sponge *Cinachyrella* Spp.

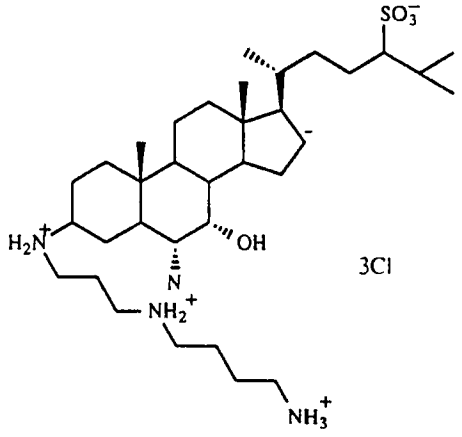
Two new 6-hydroxyimino-4-en-3-one steroids were isolated from a mixture of two morphospecies of the sponge *Cinachyrella* (*C. alloclada* and *C. apion*). The sponges of the *Cinachyrella* genus belong to the family Tetillidae (sublcass Tetractinomorpha, order Spirohorida). The methanolic extract of a mixture of the two morphospecies collected at Pituba Beach in Salvador de Bahia, Brazil, yielded two new compounds, (24*R*,6*E*)-24-ethylcholest-6-hydroxyimino-4-en-3-one (**42**) and (6*E*)-cholest-6-hydroxyimino-4-en-3-one (**43**) (*35*).

Compound **42**, $C_{29}H_{47}NO_2$, (M^+) *m/z* 441.3604, was found to contain an oxime moiety as inferred from IR absorption bands at 3340 (N—OH) and 1647 (C=N—O) cm^{-1}. Compound **43** was identified as (6*E*)-cholest-6-hydroxyimino-4-en-3-one (*35*).



C. Alkamines from Dogfish Shark *Squalus acanthias*

A novel unsaturated polyaminosteroidal sulfate, squalamine (**44**), was isolated from tissues of the dogfish shark *Squalus acanthias*. Squalamine (**49**) is found to be a 3β-*N*-1-*N*[3-(4-aminobutyl)] 1,3-diaminopropane-7α,24(*R*)-



dihydroxy-5α-cholestane-24-sulfate trihydrochloride as determined by spectroscopic and X-ray diffraction methods (*36,37*).

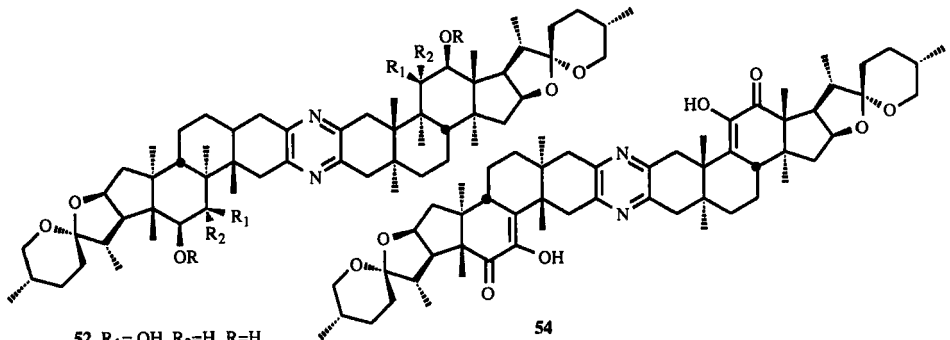
V. Synthetic Studies

A. Synthesis of Nonacyclic and Trisdecacyclic Pyrazines Related to Cephalostatins

Four years after the isolation of cephalostatin A, the first synthetic studies in this area were reported. Fuchs *et al.* (*38*) reported the conversion of steroidal α-azidoketones **48** to the C-2 symmetrical nonacyclic and trisdecacyclic pyrazines **49** through catalytic reduction (Scheme 1). In the process they also observed an unusual azide-mediated formation of an unsymmetrical heterobenzyl azide (Scheme 2). Use of excess azide served as a base to generate the α-aminoenone **50.** Dimerization of **50,** followed by $SN^{2'}$ reaction with the hydrazoic acid coproduct yielded the unsymmetrical azidopyrazine **51.**

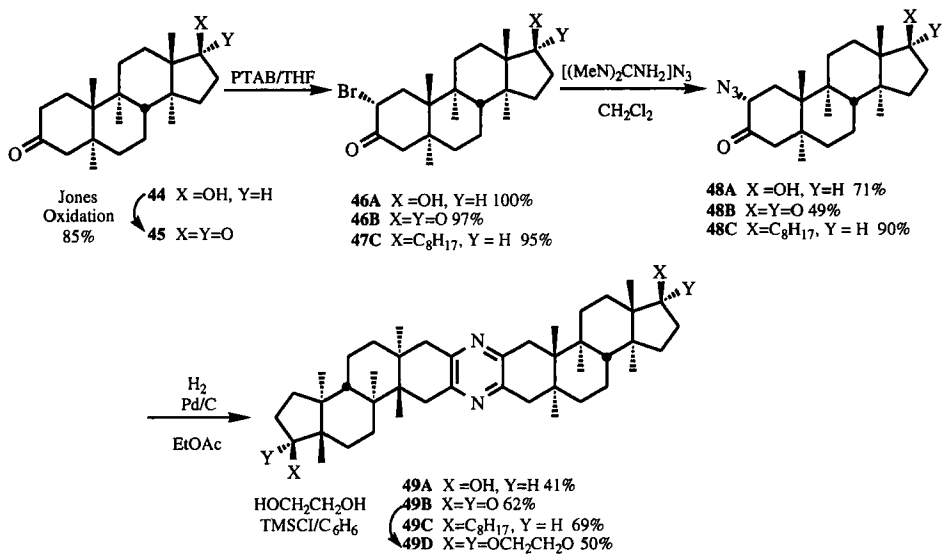
Investigators observed that the azidopyrazine **51** was about 100-fold more cytotoxic than the symmetrical pyrazines **49** in *in vitro* testing against human cancer cell lines (*38*).

Fuchs *et al.* have also synthesized the trisdecacyclic pyrazines (**52–54**) from commercially available 3β,12β-diacetoxy-5α-spirostan-11-one in 13–24% overall yields (*38*). It is important to remember that all cephalostatins and ritterazines have a trisdecacyclic dimeric steroidal skeleton. The efforts of Fuchs *et al.* represent the first studies directed at the total synthesis of this bissteroidal skeleton (*38*).

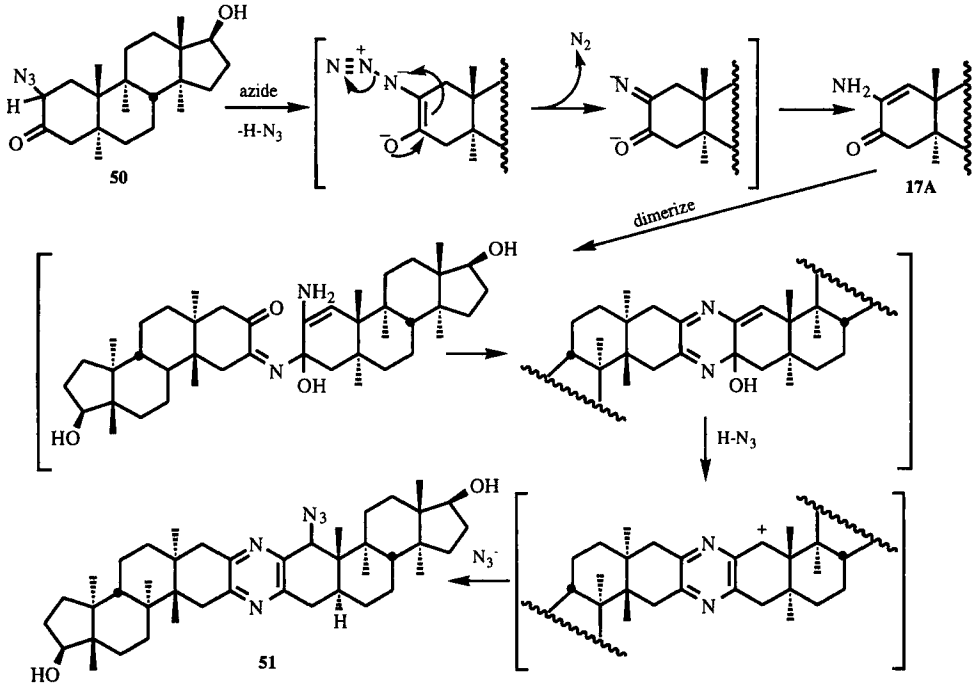


52 R_1= OH, R_2=H, R=H
53 R_1=O, R_2=O, R=H

54



SCHEME 1. Synthesis of symmetrical nonacyclic pyrazines through the catalytic reduction of steroidal azidoketones (**48**).



SCHEME 2. Unusual azide-mediated formation of unsymmetrical azidopyrazine **53**.

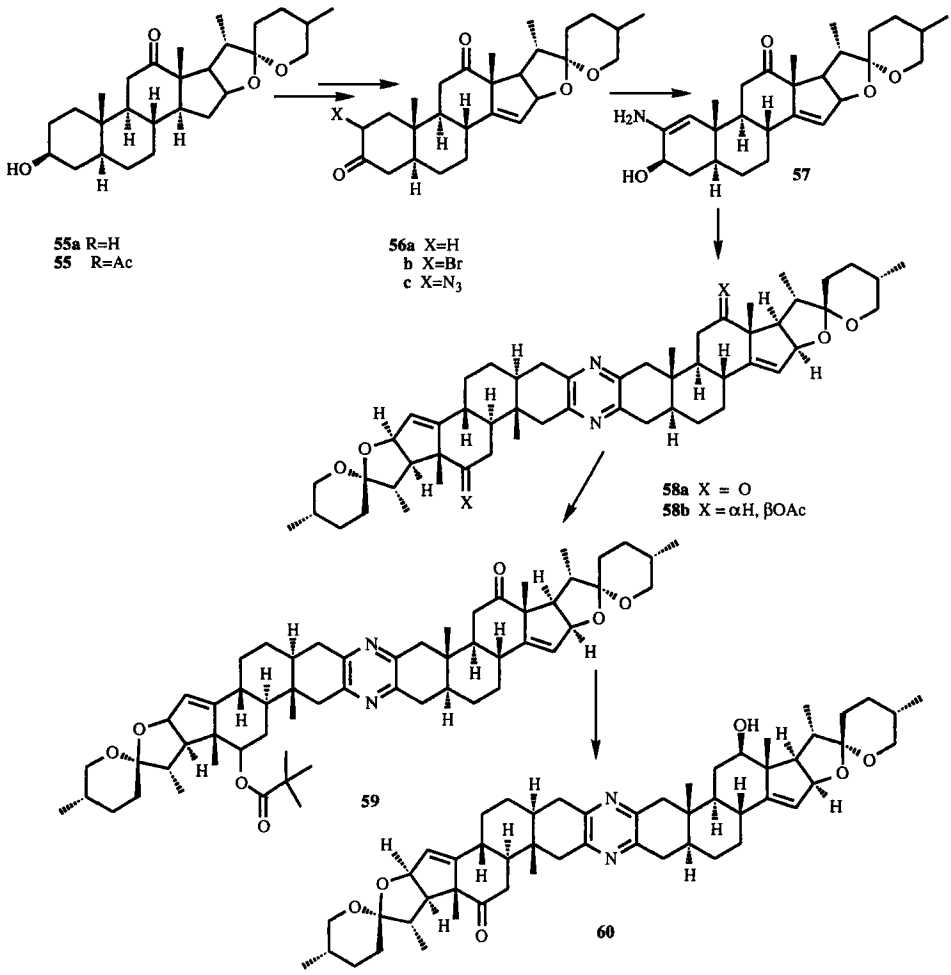
B. Synthesis of Cephalostatin Analogs

In 1993, Winterfeldt *et al.* reported a short route to cephalostatin analogs. This route led to both the nonsymmetrical compounds and a compound containing a $\Delta^{14,15}$-double bond. The route started with a diketone, **56a,** which is a $\Delta^{14,15}$-hecogenin derivative. Compound **56a** can be readily prepared from hecogenin (**55a**) by a photoprocess followed by an oxidation. Compound **55a** can be converted into the α-ketoazide **56c** through standard bromination and subsequent nucleophilic substitution by sodium azide. The α-ketoazide **56c** was converted slowly to yield the enamino ketone **57** in 90% yield. Compound **57** showed the tendency of pyrazine formation. Hydrogenation of the resulting pyrazine gave the cephalostatin analog **58a** in good yield (54%). Sodium borohydride–MeOH reduction and subsequent acetylation yielded the corresponding 12,12′β-diacetate **58b** (60%). The pyrazine dione **58a,** when treated with pivaloyl chloride in the presence of potassium hexamethyl disilazanide, yielded the desired monopivalate **59.** Borohydride reduction of **59** followed by hydrolysis of the enol pivalate yielded the hydroxy ketone **60,** which bears a steroidal ring system as in cephalostatin 1 (Scheme 3) (*39*).

C. Synthesis of Unsymmetrical Bis-Steroidal Pyrazines Related to Cephalostatin 1 (**11**)

In 1992 Heathcock and Smith developed efficient routes for the synthesis of symmetrical and unsymmetrical bis-steroidal pyrazines from readily available precursors such as 3-cholestanone and androstanone (*40*). In a later publication they synthesized the unsymmetrical bis-steroidal pyrazines by the reaction of appropriate α-acetoxy ketones with α-amino oximes. Heating either 2β,17β-dihydroxyandrostan-3-one diacetate or 2β-17β-dihydroxyhecogenin-3-one diacetate with 2-amino-3-methoxyiminocholestane in toluene at 145°C gave the corresponding symmetrical pyrazine in moderate yields.

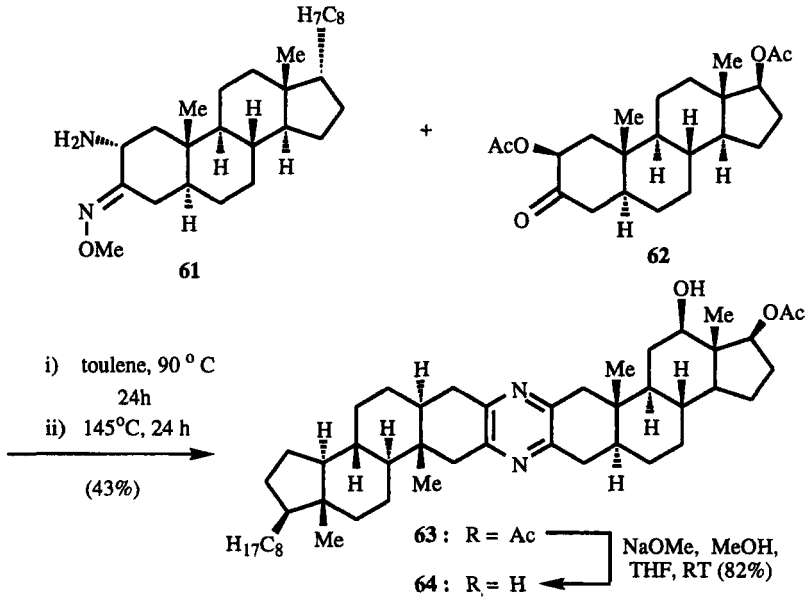
O-Methyloxime **61** was coupled with the acetoxy steroidal ketone **62** by heating a degassed toluene solution of the two in a sealed tube at high temperature for two days to yield the unsymmetrical bis-steroidal pyrazine **63,** which on saponification yielded **64** (Scheme 4). The aminoxime **61** also reacted with the keto acetate **71** under the usual conditions to yield the unsymmetrical bis-steroidal pyrazine **72.** The acetate **72** on saponification provided crystalline **73** (Scheme 5). *In vitro* disease-oriented cytotoxic screening of **63, 64, 72,** and **73** showed no significant activity, which indicated that the double bonds in ring D are essential for the cytotoxic activity (*41*).



SCHEME 3. Synthesis of cephalostatin analogs.

D. BIOMIMETIC TOTAL SYNTHESIS OF (+)-CEPHALOSTATIN 7 (**17**), (−)-CEPHALOSTATIN 12 (**22**), AND (+)-RITTERAZINE K (**36**).

Fuchs *et al.* in 1995 reported the first biomimetic synthesis of cephalostatins 7 (**17**) and 12 (**22**) and ritterazine K (**36**) (*42*). This synthesis is based



SCHEME 4. Synthesis of the unsymmetrical bis-steroidal pyrazines **63** and **64.**

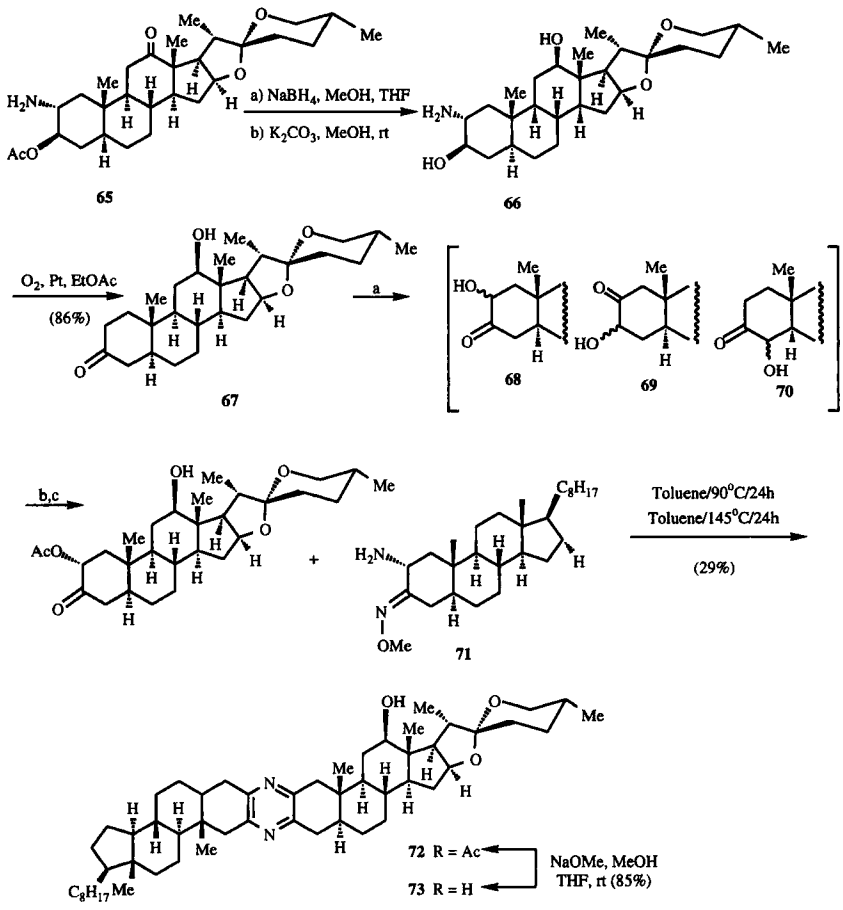
on a biogenetic scheme proposed by Pettit in which he hypothesized that the pyrazine core is assembled via dimerization and oxidation of steroidal α-amino ketones (*24*).

VI. Biogenesis

Alkaloids from colonial zoanthids such as zoanthamine, zoanthamide, 28-deoxyzoanthenamine, and others form a new class of alkaloids of unknown biosynthetic origin, although some structural features suggest a triterpenoid origin (*20–23*).

Pettit *et al.*, have proposed a biogenetic pathway for the dimeric pyrazine-containing steroidal alkaloids, the cephalostatins isolated from the marine worm *Cephalodiscus gilchristi* and the tunicate *Ritterella tokioka.* These alkaloids contain at least 13 fused rings, which constitutes the largest such system known in marine animals.

The biogenesis of the eastern hemisphere of the molecule is derivable from a 12-hydroxy-Δ^{14}-steroid skeleton as shown in Scheme 7. The isolation of closely related dimeric alkaloids from two different phyla (Hemichordata

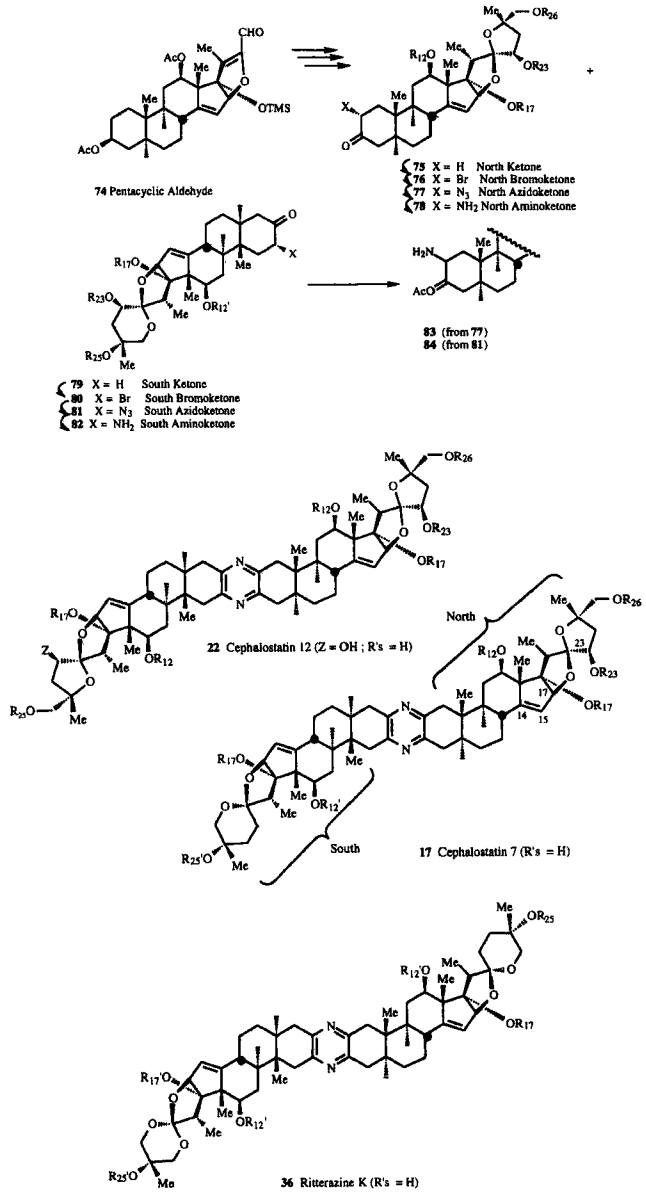


SCHEME 5. Synthesis of the unsymmetrical bis-steroidal pyrazines **72** and **73.**

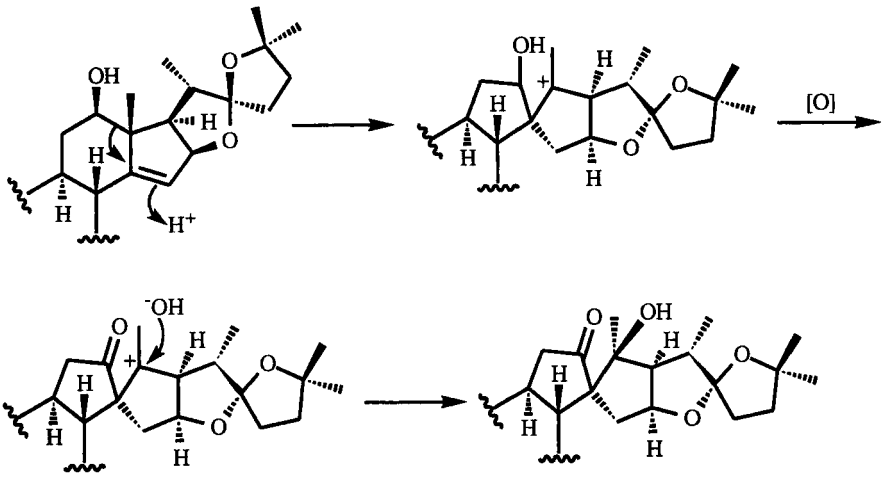
and tunicate) poses a problem of their true origin. Apparently these alkaloids (i.e., cephalostatins and ritterazines) result in part from a biosynthetic condensation of 2-amino-3-oxo steroid units (*24,31*).

VII. Pharmacology

Plakinamine A (**1**), an alkaloid isolated from an unidentified species of *Plakina,* was found to inhibit the growth of *Staphylococcus aureus* and



SCHEME 6. Synthesis of cephalostatins 7 (**17**) and 12 (**22**), and ritterazine K (**36**).



SCHEME 7. Proposed biosynthesis of ritterazine A (**26**).

Candida albicans at concentrations of 25 μg/disk and 10 μg/disk, respectively. The hydrochloride salt of plakinamine B (**2**) also exhibited antibacterial activity at a level of 10 μg/disk and 2 μg/disk against *S. aureus* and *C. albicans,* respectively (*18*).

Lokysterolamine A (**3**) exhibited *in vitro* cytotoxic activity against the mouse lymphoid leukemia (P-388), human lung carcinoma (A-549), human melanoma (MEL-28), and human colon adenocarcinoma (HT-29) cell lines. Owing to its structural similarity with plakinamines A and B, the alkaloid also exhibited antibacterial activity against *Bacillus subtilis* and *C. albicans.* In addition, it showed moderate immunomodulatory activity (LcV/MLR > 187) (*19*).

Alkaloids isolated from an unidentified colonial zoanthid have also exhibited interesting biological activities. Zoanthamine (**5**), zoanthenamine (**6**), zoanthamide (**7**), and 28-deoxyzoanthenamine (**8**) possess inhibitory activity in the phorbol myristate acetate (PMA)-induced mouse ear inflammation assay, as well as analgesic activity (*22*). Zoanthamine (**5**) also exhibited strong nematicidal activity against the root-knot nematode (*Meloidogyne javanica*) and antibacterial activity (*41*).

The bis-steroidal alkaloids cephalostatins 1–15 (**11–25**) (*24–30*) and ritterazines A–M (**26–38**) (*31–33*) isolated from the marine worm *Cephalodiscus gilchristi* and the tunicate *Ritterella tokioka,* respectively, also exhibit powerful cell growth inhibitory activity against a number of cell lines.

Cephalostatin 1 (**11**) is a powerful cell growth inhibitory substance with the P-388 cell line, showing ED_{50} 10^{-7}–10^{-9} μg/mL (*24*). Cephalostatins 2–4 (**12–14**) were also found to exhibit potent cell growth inhibition (P-388 ED_{50} 10^{-7}–10^{-9} μg/mL) (**25**). In cephalostations 5 and 6 (**15,16**), the introduction of aromatization in ring C′ was found to greatly reduce the cytotoxic activity (P-388 ED_{50} $\sim 10^{-2}$ μg/mL). Perhaps cephalostatins 5 and 6 represent a biosynthetic misadventure in the long evolutionary history of *Cephalodiscus* (**26**). Cephalostatins 7–9 (**17–19**) also exhibit potent cytotoxicity against certain human cancer cell lines. This suggests that the pyridazine right-side subunit is essential for such biological activity. They displayed potent activity [TI_{50} (molar) values of 10^{-9}–10^{-10})] against a number of cell lines, such as the non-small-cell lung HOP-62, small-cell lung DMS-273, renal RXF-393, brain U-251 and SF-295, and leukemia CCRF-CEM, HL-60, and RPMI-8226, and values of 10^{-8}–10^{-9} for the breast MCF-7 cell line (*27*). Comparative antitumor evaluations of cephalostatins 1 (**11**), 10 (**20**), and 11 (**21**) in the NCI's *in vitro* disease-oriented, primary screen revealed an overall potency of cephalostatins 10 (**20**) and 11 (**21**) approaching that of cephalostatin 1 (**11**) (*28*). Cephalostatins 12 (**22**) and 13 (**23**) were found to be considerably less potent (GI_{50} ~ 400–1000 nmolar) than most other members of the cephalostatin series (*30*). Results of the study of human cancer cell growth inhibition by different cephalostatins indicate that modification of the "left-side" subunit moiety, by introduction of the 8β-hydroxy-11-en-12-one and/or the 14,15α-epoxy system, served to reduce *in vitro* activity. Presumably, the α-orientation of the epoxide is responsible for this effect (*30*).

Ritterazine A (**26**) exhibited cytotoxicity against P-388 marine leukemia cells with an IC_{50} value of 3.8×10^{-3} μg/mL (*31*). Ritterazines B and C (**27,28**) also showed potent cytotoxicity against the P388 cells, with IC_{50} values of 0.018 and 8.4 μg/mL, respectively (*32*). Ritterazines D–M (**29–38**) showed potent cytotoxicity against P-388 cells, with IC_{50} values of 16, 3.5, 0.73, 0.73, 16, 14, 13, 9.5, 10, and 15 μg/mL, respectively (*32, 33*).

Unlike other sulfated sterols of marine origin, the AB and carolisterols (**42,43**) isolated from *Styracaster caroli* spp. have not shown any protection against the cytopathic effects of HIV-1 in NCI's primary anti-HIV screen (*34*).

Squalamine (**49**) isolated from the dogfish shark *Squalus acanthias,* was found to have broad-spectrum antibiotic activity, and it is also extremely active against both Gram-negative and Gram-positive bacteria. This host-defense agent is also active *in vitro* against various sexually transmitted disease organisms such as *Nesseria gonorrhoeae,* herpes simplex virus, and human immunodeficiency virus (*36,37*).

VIII. Spectroscopy

^{15}N NMR spectroscopic techniques such as ^{15}N HMBC can be used to determine the orientation of two steroidal units about the pyrazine ring in ritterazine A (**26**). Cross peaks were observed between H_2-1 and H_2-1′ and the nitrogen atoms having different ^{15}N chemical shifts, which was consistent with the previously determined orientation. The ^{15}N HMBC spectrum of ritterazine A (**26**) provided virtually identical results, indicating that the orientation of the steroidal units in ritterazine A was the same as that in ritterazine B (**37**) (*44*).

References

1. D. J. Faulkner, *Nat. Prod. Rep.* **1,** 251 (1984).
2. D. J. Faulkner, *Nat. Prod. Rep.* **1,** 551 (1984).
3. D. J. Faulkner, *Nat. Prod. Rep.* **3,** 1 (1986).
4. D. J. Faulkner, *Nat. Prod. Rep.* **4,** 539 (1987).
5. D. J. Faulkner, *Nat. Prod. Rep.* **5,** 613 (1988).
6. D. J. Faulkner, *Nat. Prod. Rep.* **7,** 269 (1990).
7. R. G. Kerr and B. G. Baker, *Nat. Prod. Rep.* **8,** 465 (1991).
8. D. J. Faulkner, *Nat. Prod. Rep.* **8,** 97 (1991).
9. D. J. Faulkner, *Nat. Prod. Rep.* **9,** 323 (1992).
10. D. J. Faulkner, *Nat. Prod. Rep.* **10,** 497 (1993).
11. D. J. Faulkner, *Nat. Prod. Rep.* **11,** 355 (1994).
12. D. J. Faulkner, *Nat. Prod. Rep.* **12,** 223 (1995).
13. D. J. Faulkner, *Nat. Prod. Rep.* **13,** 75 (1996).
14. D. J. Faulkner, *Nat. Prod. Rep.* **14,** 259 (1997).
15. K. L. Rinehart and K. Tachibana, *J. Nat. Prod.* **58,** 344 (1995).
16. J. Kobayashi and M. Ishibashi, *in* "The Alkaloids." (A. Brossi, ed.), Vol. 41, p. 41. Academic Press, San Diego, 1992.
17. Atta-ur-Rahman and M. I. Choudhary, *in* "Chemistry and Toxicology of Diverse Classes of Alkaloids" (M. S. Blum, ed.), Vol. 1, p. 11. Alakan, Inc., Fort Collins, CO, 1996.
18. R. M. Rosser and D. J. Faulkner, *J. Org. Chem.* **49,** 5157 (1984).
19. J. Jurek, P. J. Scheuer, and M. Kelly-Borges, *J. Nat. Prod.* **57,** 1004 (1994).
20. C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkataeswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen, and J. Clardy, *J. Am. Chem. Soc.* **106,** 7983 (1984).
21. C. B. Rao, A. S. R. Anjaneyulu, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser, and D. J. Faulkner, *J. Org. Chem.* **50,** 3757 (1985).
22. C. B. Rao, D. V. Rao, V. S. N. Raju, B. W. Sullivan, and D. J. Faulkner, *Heterocycles* **28,** 103 (1989).
23. Atta-ur-Rahman, K. A. Alvi, S. A. Abbas, M. I. Choudhary, and J. Clardy, *Tetrahedron Lett.* **30,** 6825 (1989).

24. G. R. Pettit, M. Inoue, Y. Kamano, D. L. Herald, C. Arm, C. Dufresne, N. D. Christie, J. M. Schmidt, D. L. Doubek and T. S. Krupa, *J. Am. Chem. Soc.* **110,** 2006 (1988).
25. G. R. Pettit, M. Inoue, Y. Kamano, C. Dufresne, N. Christie, M. L. Niven, and D. L. Herald, *J. Chem. Soc., Chem. Commun.* 865 (1988).
26. G. R. Pettit, Y. Kamano, C. Dufresne, M. Inoue, N. Christie, J. M. Schmidt, and D. L. Doubek, *Can. J. Chem.* **67,** 1509 (1989).
27. G. R. Pettit, Y. Kamano, M. Inoue, C. Dufresne, M. R. Boyd, C. L. Herald, J. M. Schmidt, D. L. Doubek, and N. Christie, *J. Org. Chem.* **57,** 429 (1992).
28. G. R. Pettit, J.-P. Xu, M. D. Williams, N. S. Christie, D. L. Doubek, J. M. Schmidt, and M. R. Boyd, *J. Nat. Prod.* **57,** 52 (1994).
29. G. R. Pettit, Y. Ichihara, J. Xu, M. R. Boyd, and M. D. Williams, *Bioorg. Med. Chem. Lett.* **4,** 1507 (1994).
30. G. R. Pettit, J. Xu, Y. Ichihara, M. D. Williams, and M. R. Boyd, *Can. J. Chem.* **72,** 2260 (1994).
31. S. Fukuzawa, S. Matsunaga, and N. Fusetani, *J. Org. Chem.* **59,** 6164 (1994).
32. S. Fukuzawa, S. Matsunaga, and N. Fusetani, *J. Org. Chem.* **60,** 608 (1995).
33. S. Fukuzawa, S. Matsunaga, and N. Fusetani, *Tetrahedron* **51,** 6707 (1995).
34. F. D. Riccardis, L. Minale, R. Riccio, M. Iorizzi, C. Debitus, D. Duhet, and C. Monniot, *Tetrahedron Lett.* **34,** 4381 (1993).
35. J. Rodriguez, L. Nunez, S. Peixinho, and C. Jimenez, *Tetrahedron Lett.* **38,** 1833 (1997).
36. S. L. Wehrli, K. S. Moore, H. Eroder, S. Durell, M. Zasloff, *Steroids,* **58,** 370 (1993); K. S. Moore, S. Wehrli, H. Roder, M. Rogers, J. N. Forrest, Jr., D. McCrimmon, and M. Zasloff, *Proc. Natl. Acad. Sci. USA* **90,** 1354 (1993).
37. R. M. Moriarty, L. A. Enache, W. A. Kinney, C. S. Allen, J. W. Canary, S. M. Tuladhar, and L. Guo, *Tetrahedron Lett.* **36,** 5139 (1995).
38. Y. Pan, R. L. Merriman, L. R. Tanzer, and P. L. Fuchs, *Bioorg. Med. Chem. Lett.* **2,** 967 (1992).
39. A. Kramer, U. Ullmann, and E. Winterfeldt, *J. Chem. Soc., Perkin Trans I* 2865 (1993).
40. S. C. Smith and C. H. Heathcock, *J. Org. Chem.* **57,** 6379 (1992).
41. C. H. Heathcock and S. C. Smith, *J. Org. Chem.* **59,** 6829 (1994).
42. U. Jeong, S. C. Sutton, S. Kim, and P. L. Fuchs, *J. Am. Chem. Soc.* **117,** 10157 (1995).
43. Atta-ur-Rahman, A. M. Khan, M. Abid, M. Shabbir, M. I. Choudhary, A. Nasreen, M. A. Maqbool, M. Shameel, and R. Swaleh, *Pak. J. Nematol.* **115,** 95 (1997).
44. S. Fukuzawa, S. Matsunaga, and N. Fusetani, *Tetrahedron Lett.,* **37,** 1447 (1996).

——CHAPTER 5——

THE MONOTERPENE ALKALOIDS

GEOFFREY A. CORDELL

College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

I. Introduction

The last review of the monoterpene alkaloids was published in this series in 1977 (*1*) and was based on the literature to the end of 1974. Since that time a substantial number of new monoterpene alkaloids have been isolated, new sources of established alkaloids have been identified, and several innovative syntheses of alkaloids in this series have been described. In addition, the *in vitro* formation of monoterpene alkaloids from iridoids has been pursued, including studies with human fecal flora, and some work

THE ALKALOIDS, VOL. 52
0099-9598/99 $30.00

Copyright © 1999 by Academic Press.
All rights of reproduction in any form reserved.

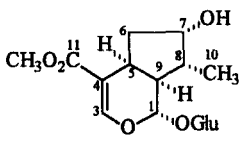
discussing the biological properties of alkaloids in this series has appeared. Very little work has been described on the biosynthesis of these alkaloids, although there has been some progress in delineating the pathway for the formation of the parent monoterpenes. This chapter therefore aims to bring the previous chapter up-to-date and is comprised of information available to late 1997. Some earlier work that was inadvertently omitted from the previous review is also included.

A very brief review of selected aspects of the monoterpenoid alkaloids was published in Volume 26 of this series in a chapter dealing with pyridine and piperidine alkaloids (*2*). A partial review has appeared in a textbook on alkaloids (*3*), and they are briefly discussed in the various reviews published by The Royal Society of Chemistry in the "Specialist Periodical Reports: The Alkaloids" (*4–12*) and subsequently in "Natural Product Reports" (*13–23*).

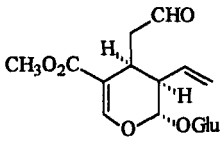
II. Isolation and Structure Elucidation

A. Isolation and Structure Elucidation of New Alkaloids

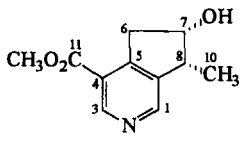
A summary of the new alkaloids isolated since early 1975 is presented in Table I (*24–78*). As in the previous review (*1*), these alkaloids are typically organized by their degree of complexity and biogenetic location relative to loganin (**1**) and secologanin (**2**). At least three numbering systems have been used for the monoterpene pyridine alkaloids. The one used here corresponds to that used for the iridoid precursors and is shown for cantleyine (**3**) and in subsequent structures. As a result of using this numbering system, the names of some alkaloids have been changed compared with the original literature. For example, 7,8-dehydro-coelobillardierine has been renamed as 8,10-dehydro-coelobillardierine.



1 Loganin



2 Secologanin



3 Cantleyine

1. Leptorhabine (4)

The initial structure elucidation of leptorhabine (**4**) from *Leptorhabdos parviflora* (Scrophulariaceae) (*79*) was discussed in the previous review (*1*).

TABLE I
ISOLATION OF NEW MONOTERPENE ALKALOIDS

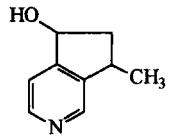
Alkaloid	Plant	Reference
Acanthicifoline (**103**)	*Acanthus ilicifolia*	*24*
3-Acetyl-2,7-naphthyridine (**108**)	*Valeriana officinalis*	*25*
Altemicidin (**78**)	*Streptomyces sioyaensis*	*26*
Austrodimerine (**102**)	*Osmanthus austrocaledonica*	*27*
4,4′-Bis-methyl-5,5′-[(1-methyltrimethylene)di] methylnicotinoate) (**99**)	*Ligustrum vulgare*	*28*
	Osmanthus austrocaledonica	*27*
3-Carbomethoxy-5-ethyl-4-methyl pyridine (**115**)	*Ligustrum vulgare*	*29*
3-Carbomethoxy-5-ethyl-pyridine (**114**)	*Ligustrum vulgare*	*29*
Carbomethoxy-pedicularine (**30**)	*Penstemon whippleanus*	*30*
3-Carbomethoxy-5-vinyl-pyridine (**113**)	*Pauridiantha lyallii*	*31*
Centaurium alkaloid I (**83**)	*Centaurium spicatum*	*32,33*
Centaurium alkaloid II (**84**)	*Centaurium spicatum*	*32,33*
10-*cis*-(4-Hydroxycinnamoyloxy) cantleyine (**18**)	*Coelospermum billardieri*	*34*
10-*O-trans*-(4-Hydroxycinnamoyloxy) cantleyine (**19**)	*Coelospermum billardieri*	*34*
Coelobillardierine (**5**)	*Coelospermum billardieri*	*34*
Coelosperminone (**6**)	*Coelospermum billardieri*	*34*
8,10-Dehydro-coelobillardierine (**7**)	*Coelospermum billardieri*	*34*
Deoxyrhexifoline (**24**)	*Castilleja rhexifolia*	*35*
Dihydrojasminine (**101**)	*Osmanthus austrocaledonica*	*27*
Dihydrotecomanines	*Tecoma arequipensis*	*36*
Dinklageine (**65**)	*Strychnos dinklagei*	*37,38*
7,8-Epoxyracemigerine (**21**)	*Scaevola racemigera*	*39*
Euphrosine (**25**)	*Orthocarpus luteus*	*40*
Gentiananine (**93**)	*Pedicularis macrochila*	*41*
7-Hydroxy-5,6-dehydroskytanthine (**58**)	*Tecoma stans*	*42*
5β-Hydroxy-incarvilline (**43**)	*Incarvillea sinensis*	*43*
4-Hydroxy-β-phenethyl-3-carbomethoxy-5-ethyl-4-pyridinyl acetate (**100**)	*Ligustrum vulgare*	*29*
	Osmanthus austrocaledonica	*27*
5β-Hydroxy-skytanthine (**44**)	*Tecoma stans*	*45–47*
4-Hydroxy-tecomanine (**59**)	*Tecoma stans*	*42*
Hydroxytecomanines	*Tecoma arequipensis*	*36*
Incarvillateine (**34**)	*Incarvillea sinensis*	*48*
Incarvilline (**35**)	*Incarvillea sinensis*	*43,49*
Incarvine A (**38**)	*Incarvillea sinensis*	*50*
Incarvine B (**41**)	*Incarvillea sinensis*	*51*
Incarvine C (**42**)	*Incarvillea sinensis*	*51*
Isocantleyine (**17**)	*Siphonostegia chinensis*	*52*
Isoplectrodorine (**27**)	*Plectronia odorata*	*53*
Jasminidine (**96**)	*Syringa vulgaris*	*54*
Kinabalurine A (**46**)	*Kopsia pauciflora*	*55,56*
Kinabalurine B (**47**)	*Kopsia pauciflora*	*56*
Kinabalurine C (**48**)	*Kopsia pauciflora*	*56*
Kinabalurine D (**49**)	*Kopsia pauciflora*	*56*
Kinabalurine E (**50**)	*Kopsia pauciflora*	*56*
Kinabalurine F (**51**)	*Kopsia pauciflora*	*56*

(*continues*)

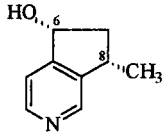
TABLE I (*continued*)

Alkaloid	Plant	Reference
Kopsilactone (**53**)	at*Kopsia macrophylla*	*57*
Kopsirachine (**77**)	*Kopsia dasyrachis*	*58*
Kopsone (**54**)	*Kopsia macrophylla*	*57*
Lindenialine (**60**)	*Lindenia austro-caledonica*	*59*
Lindeniamine (**61**)	*Lindenia austro-caledonica*	*59*
Loxylostosidine A (**91**)	*Lonicera xylosteum*	*60*
Loxylostosidine B (**92**)	*Lonicera xylosteum*	*60*
Methyl boschniakinate (**24**)	*Plantago arenaria*	*61*
	P. psyllium	*61*
4-Methyl-5,5′-[(1-methyltrimethylene) di] (methylnicotinoate)(**98**)	*Ligustrum vulgare*	*28*
	Osmanthus austrocaledonica	*27*
4-Methyl-2,6-naphthyridine (**104**)	*Antirrhinum majus*	*62,63*
Neozeylanicine (**70**)	*Neonauclea zeylanica*	*64*
7-*O*-Nicotinoyl-strychnovoline (**66**)	*Scaevola racemigera*	*39*
7-*O*-Nicotinoyl-tetrahydrocantleyine (**67**)	*Scaevola racemigera*	*39*
δ-*N*-Nor-methylskytanthine (**32**)	*Tecoma arequipensis*	*36*
Oxerine (**8**)	*Oxera morieri*	*65*
Plectrodorine (**26**)	*Plectronia odorata*	*53*
(3-Pyridyl)-1-ethanol (**111**)	*Melodinus celastroides*	*66,67*
Racemigerine (**20**)	*Scaevola racemigera*	*39*
Rhexifoline (**23**)	*Castilleja occidentalis*	*68*
	C. rhexifolia	*35*
	C. rhexifolia aff. *miniata*	*35*
	C. sulphurea	*68*
	Platyptillia pica	*35,68*
Scaevodimerine A (**71**)	*Scaevola racemigera*	*69*
Scaevodimerine B (**72**)	*Scaevola racemigera*	*69*
Scaevodimerine C (**73**)	*Scaevola racemigera*	*69*
Scaevodimerine D (**74**)	*Scaevola racemigera*	*69*
Scaevoline (**22**)	*Plectronia odorata*	*53*
	Scaevola racemigera	*39*
Schultesia guianensis alkaloid (**87**)	*Schultesia guianensis*	*70*
Spicatine (**85**)	*Centaurium spicatum*	*32,33*
Strychnovoline (**64**)	*Scaveola racemigera*	*38,39*
	Strychnos dinklagei	*38*
	Strychnos longicaudata	*71*
	S. variabilis	*71*
Tetrahydrocantleyine (**16**)	*Alstonia angustifolia*	*72*
	A. undulifolia	*73*
	Lasianthera austrocaledonica	*74*
	Scavevola racemigera	*39*
	Strychnos longicaudata	*71*
	S. variabilis	*71*
Valerianine (**13**)	*Valeriana officinalis*	*75*
Venoterpine-related glucoside (**11**)	*Alstonia scholaris*	*76*
7-*O*-(5-Vinylnicotinoyl)tetrahydrocantleyine (**68**)	*Scaevola racemigera*	*39*
Xylostosidine (**88**)	*Lonicera xylosteum*	*77,78*

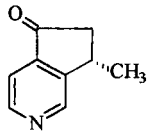
Subsequent work resulted in the isolation of a base, $C_9H_{11}ON$, that was isomeric with leptorhabine and was presented as "a racemate of leptorhabine" (*80*). The NMR data were slightly different for the two samples, with the aliphatic protons shifted upfield and the aromatic protons shifted downfield, suggesting different solvents (not specified). No coupling constant data that would assist in assigning the stereochemistry were offered.



4 Leptorhabine



5 Coelobillardierine



6 Coelosperminone

2. Coelobillardierine (5)

From the leaves and stems of the New Caledonian liana *Coelospermum billardieri* (Rubiaceae), after treatment with ammonia or Na_2CO_3, Pusset and co-workers isolated six alkaloids (*34*). One of the isolates was cantleyine (**3**), the other five alkaloids were new.

Coelobillardierine, $[\alpha]_D$ −9°, showed hydroxyl group absorption (3,575 cm^{-1}) and no carbonyl group. The molecular ion appeared at *m/z* 149, and the proton NMR spectrum established a 3,4-substituted pyridine (s, 8.29 ppm, H-1; d, 8.29 ppm, J = 6.8 Hz H-3; d, 7.29 ppm, J = 6.8 Hz, H-4), together with an oxymethine (dd, 5.10, J = 7.5, 8.0 Hz; δ_C 74.2 ppm), and a methylene showing doublets of triplets at 1.48 (J = 12.5, 8.0 Hz) and 2.70 ppm (J = 12.5, 7.5 Hz). Also noted was a benzylic methine (δ_H 3.05 ppm; δ_C 35.1 ppm) with an attached methyl group (d, δ_H 1.29, J = 7.0 Hz; δ_C 19.7 ppm). The relative stereochemistry was supported by an NOE observed between H-6 and H-8 (*34*). The relationship between leptorhabine (*79,80*) and coelobillardierine is unclear, as the proton data for **5** (*34*) do not correspond with either of the sets of data for leptorhabine.

3. Coelosperminone (6)

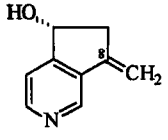
Coelosperminone (**6**), $[\alpha]_D$ +19°, showed a molecular ion at *m/z* 147 and a ketone carbonyl (1,725 cm^{-1}, δ_C 204.2 ppm). Although the methyl group was still present (d, δ_H 1.48 ppm; δ_C 20.9 ppm), the oxymethine signal was absent from the ^{1}HNMR spectrum and the three aromatic protons were shifted downfield (s, 8.96 ppm, H-1; d, 8.89 ppm, J = 6.8 Hz, H-3, and d, 7.55 ppm, J = 6.8 Hz, H-4). Reduction with $NaBH_4$ afforded **5**, and thus the structure of coelosperminone was established as **6** (*34*).

4. 8,10-Dehydro-coelobillardierine (7)

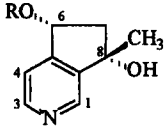
The third isolate characterized from *Coelospermum billardieri,* 10-dehydro-coelobillardierine (**7**), $[\alpha]_D$ +41°, also showed a molecular ion at *m/z* 147, two mass units less than **5**. In this alkaloid, the oxymethine signal was still present (dd, δ_H 5.27 ppm, J = 4.5, 8.0 Hz, δ_C 72.7 ppm), and the methyl doublet was replaced by geminal olefinic protons at 5.20 and 5.60 ppm. Additional olefinic carbons were seen at 106.4 and 144.1 ppm. Reduction with Adam's catalyst in ethanol afforded **5,** indicating that **8,** 10-dehydro-coelobillardieriene has the structure **7** (*34*).

5. Oxerine (8)

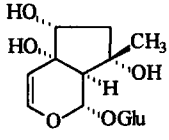
From the aerial parts of *Oxera morieri* (Verbenaceae), a new monoterpene alkaloid was isolated without treatment with ammonia (*65*). Oxerine (**8**), $[\alpha]_D$ −11°, showed a molecular ion at *m/z* 165 analyzing for $C_9H_{11}NO_2$, and displaying hydroxyl (3,400 cm^{-1}), but no carbonyl absorption in the IR spectrum. Fragment ions were observed at *m/z* 150 (M^+-CH_3), 147 (M^+-H_2O) and 132 ($M^+-CH_3-H_2O$). Characteristic pyridine UV absorption bands were observed at λ_{max} 259, 267 (sh) and 285 nm. Two α- and one β-pyridine ring protons resonated at 8.56 (H-1), 8.47 (d, J = 5 Hz, H-3) and 7.47 (d, J = 5 Hz, H-4), respectively, and an AMX system of three protons was observed at 2.13 (J = 13 and 7 Hz), 2.73 (J = 13 and 6.5 Hz), and 5.09 ppm (J = 7 and 6.5 Hz, H-6) together with a singlet methyl group at 1.53 ppm. Acetylation afforded a monoacetyl derivative **9,** in which the methine proton had shifted to 5.98 ppm. Although these data suggested a planar structure for oxerine, the configurations at C-6 and C-8 were determined through semisynthesis from harpagide (**10**) (see Section III.A.2). Thus, oxerine has the structure **8** (*65*).



7 8,10-Dehydro-Coelobillardierine



8 Oxerine, R = H
9 R = $COCH_3$

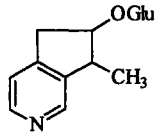


10 Harpagide

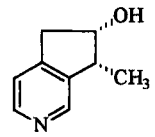
6. Venoterpine-Related Glucoside (11)

From the bark of *Alstonia scholaris* (Apocynaceae) Biswas and Saharia isolated and partially characterized an alkaloidal glycoside (*76*). The compound was very hygroscopic and readily formed a tetraacetate, as shown by the ^1H NMR spectrum. The ^1H NMR spectrum also showed three

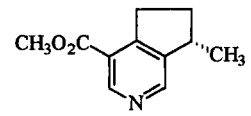
aromatic protons in the region 8.4–7.5 ppm and a three-proton doublet at 0.98 ppm for the methyl group. Acid hydrolysis of the parent compound afforded a product identical (TLC and IR) with venoterpine (**12**), and a Kiliani hydrolysis identified the sugar as D-glucose. Substantial confirmation of the structure was derived from the mass spectrum, which showed a molecular ion at *m/z* 311 and major fragment ions at *m/z* 163 (sugar) and *m/z* 169 (alkaloid moiety). Thus the suggestion was made that the alkaloid was venoterpine glucoside (**11**) (*76*). No further details of this alkaloid have been published, so the stereochemistry (relative and absolute) remains unknown, hence the designation as a venoterpine-related glucoside. Ammonia was used in the basification step during alkaloid processing.



11



12 Venoterpine



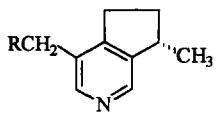
13 (-)-Valerianine

7. Valerianine (13)

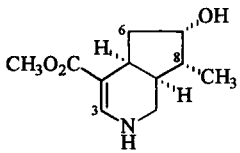
Chromatography of the tertiary base fraction of the roots of *Valeriana officinalis* gave an optically active alkaloid ($[\alpha]_D$ −10.5°) having a molecular formula $C_{11}H_{15}NO$ (*75*). The proton NMR spectrum indicated a pyridine derivative unsubstituted at C-2 and C-6, together with the presence of a doublet methyl (1.32 ppm), a methoxy group (3.40 ppm), and a benzylic methylene (4.46 ppm). In this way, the structure of valerianine was proposed as **13,** in which the *S* stereochemistry at C-8 was deduced through relationship with actinidine (**14**) and tecostidine (**15**) (*75*).

8. Tetrahydrocantleyine (16)

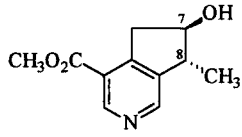
Tetrahydrocantleyine (**16**) was isolated, together with the known alkaloid cantleyine (**3**), from an ammonia-treated sample of the trunk bark of *Lasianthera austrocaledonica* (Icacinaceae) (*74*). Subsequently, **16** was also isolated from the leaves, but not the stem bark, of *Alstonia angustifolia*



14 (-)-Actinidine, R = H
15 (-)-Tecostidine, R=OH



16 Tetrahydrocantleyine



17 Isocantleyine

(Apocynaceae) (*72*), from the stem bark of *A. undulifolia* (*73*), from the aerial parts of *Scaevola racemigera* (Goodeniaceae) (*39*) and from the seeds of *Strychnos longicaudata* and *S. variabilis* (Loganiaceae) (*71*). Ammonia was used in the work-up of the plant material for alkaloids in each of these cases.

The structure of the alkaloid was deduced through interpretation of spectral data (*39*). The carbomethoxy group was noted at 3.68 ppm (δ_C 50.5, 169.2 ppm), with the olefinic proton appearing at 7.42 ppm (δ_C 143.1 ppm). A methyl group (δ_H 1.00, J = 7 Hz, H_3-10; δ_C 13.0 ppm) was coupled to a methine multiplet (δ_H 1.71, J = 8,7,4 Hz, H-8; δ_C 41.4 ppm), itself coupled to a hydroxymethine (δ_H 4.06, J = 5,4,2 Hz, H-7; δ_C 74.2 ppm) and a ring junction proton (δ_H 1.88, J = 9,8,7,5 Hz, H-9; δ_C 41.7 ppm). The magnitude of the coupling with the second ring junction proton (δ_H 3.05, J = 9,7 Hz, H-5; δ_C 32.7 ppm) indicated the *cis* relationship between H-5 and H-9, and similarly a *cis* relationship was deduced for H-7 and H-8. The methylene groups were observed at 1.47 and 2.17 ppm (H_2-6) (δ_C 41.4 ppm) and 2.74 and 3.18 ppm (H_2-1) (δ_C 43.0 ppm). Consequently, the structure of tetrahydrocantleyine was deduced to be **16** (*39*).

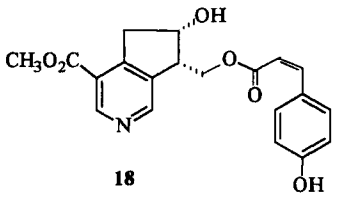
*9. Isocantleyine (**17**)*

From the aerial parts of the traditional Chinese medicinal herb *liu-jinu, Siphonostegia chinensis* (Scrophulariaceae), the monoterpene lactone loliolide and a new isomer of cantleyine were isolated (*52*). Isocantleyine, $[\alpha]_D$ +18.2°, showed a molecular ion at *m/z* 207 and both hydroxyl (3224 cm^{-1}) and carbomethoxy (1725 cm^{-1}) absorptions in the IR spectrum. The ^1H and ^{13}C NMR spectra were similar to those of cantleyine (**3**), although H-7 was shifted upfield by 0.33 ppm and the methyl doublet was shifted upfield by 0.09 ppm. In the ^{13}C NMR spectrum the ring methyl (C-10), C-7, and C-8 were shifted downfield (by 5.53, 5.39, and 4.14 ppm, respectively). These data suggested that the stereochemistry at C-7 and/or C-8 was different from that of cantleyine. NOE studies served to establish the correct stereochemistry at these two centers. When H-7 at 4.29 ppm was irradiated, enhancement was observed in the H_2-5 protons and the methyl doublet to the extent of 8.8, 3.7, and 3.5%, respectively. When the 7-OH was irradiated, enhancement was only seen in the 6α-H. These data indicated that in isocantleyine H-8 and the 7-OH are *cis* to each other. Thus isocantleyine is the C-7 epimer of cantleyine and has the structure **17** (*52*).

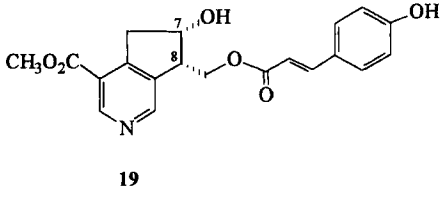
*10. 10-O-Cis-(**18**) and 10-O-Trans-(4-hydroxycinnamoyloxy)cantleyline (**19**)*

The two remaining new alkaloids isolated from the leaves and stems of *Coelospermun billardieri* (Rubiaceae) were the isomers 10-*O*-*cis*- (**18**) and

10-*O-trans*-(4-hydroxycinnamoyloxy)cantleyline (**19**) (*34*). The *trans* isomer, $[\alpha]_D$ −121°, was the major alkaloid constituent of the extract. Two α-pyridine protons were observed at 8.82 and 9.01 ppm, as well as a carbomethoxy group (δ_H 4.00 ppm; δ_C 51.8, 165.4 ppm), an oxymethine (δ_H 4.78 ppm; δ_C 71.3 ppm), and an acylated hydroxymethyl (δ_H 4.59, 4.68 ppm; δ_C 62.3 ppm). The compound formed a diacetate, in which the oxymethine carbon was shifted downfield (δ_H 5.75 ppm; δ_C 74.1 ppm). Complete proton and carbon assignments were made through a combination of two-dimensional NMR techniques. From the mass spectrum of the isolate, which showed a molecular ion at *m/z* 369 and fragment ions at *m/z* 206, 164, and 147, and the NMR spectrum, which showed a *para*-disubstituted coumaroyl group (d, 6.94 and 7.71 ppm, J = 8 Hz, and 6.94 and 7.72 ppm, J = 16.0 Hz), the isolate was identified as **19.** In **18,** the *cis* stereochemistry for the 7-OH and the 8-acylated hydroxymethyl groups was established through the coupling, J = 6 Hz, between H-7 and H-8. For the second isolate, which was a minor constituent, the only major difference was the coupling constant (J = 12.5 Hz) of the olefinic protons. Thus, the isolate has the structure 10-*cis*-(4-hydroxycinnamoyloxy)cantleyline (**18**) (*34*).



18



19

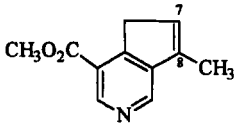
*11. Racemigerine (**20**)*

A further three new monoterpene alkaloids, all pyridine derivatives, were isolated from *Scaevola racemigera* (*39*). Racemigerine (**20**) showed a molecular ion at *m/z* 189 and fragment ions at *m/z* 158 (M^+–OCH_3) and 130 (M^+–$COOCH_3$). The IR spectrum showed an absorption band at 1720 cm^{-1} for a conjugated ester carbonyl, which was traced to a methyl ester (3.87 ppm). Two α-pyridine protons were observed at 8.79 and 8.40 ppm, together with an olefinic proton at 6.15 ppm, an olefinic methyl group at 2.15 ppm, and a methylene at 3.15 ppm. These data suggested the structure **20** for racemigerine, and this was confirmed through chemical correlation. Treatment of cantleyine (**3**) with methane sulfonyl chloride in the presence of triethylamine for 2 h afforded **20** in 50% yield (*39*).

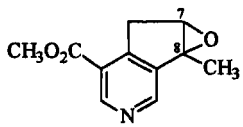
*12. 7,8-Epoxyracemigerine (**21**)*

From mass spectrometry, the molecular weight of 7,8-epoxyracemigerine (**21**) was 205, with prominent fragment ions at *m/z* 190 (M^+–CH_3) and 174

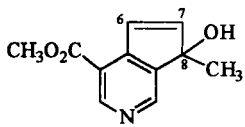
(M^+-OCH_3) (*39*). The proton NMR spectrum was very similar to that of **20** in that two α-pyridine protons were observed (8.75 and 9.08 ppm), along with a carbomethoxy group (3.94 ppm) and a methylene group (3.36 ppm, J = 19, 5 Hz; 3.58 ppm, J = 19, 3 Hz). The olefinic proton of **20** was replaced by a methine proton (3.77 ppm, J = 5, 3 Hz), and the methyl group was shifted from 2.15 ppm to 1.52 ppm, suggesting attachment to a carbon-bearing oxygen. The accumulated data indicated the structure **21** for the isolate, which, somewhat surprisingly, was racemic (*39*).



20 Racemigerine



21 7,8-Epoxy-racemigerine



22 Scaevoline

13. Scaevoline (22)

The third monomeric alkaloid characterized from *Scaevola racemigera* was scaevoline (**22**), which showed a molecular ion at *m/z* 205 and was therefore isomeric with **21** (*39*). Spectroscopically, the IR spectrum showed the presence of a hydroxyl group (3270 cm^{-1}; δ_H 3.80 ppm), and the pyridine α-protons were present (8.77 and 8.46 ppm), as were the carbomethoxy group (3.93 ppm) and a singlet methyl (1.62 ppm). The C-5 methylene group was missing, replaced by two olefinic protons at 7.16 and 6.65 ppm as coupled doublets (J = 6 Hz). The structure **22** was therefore proposed for scaevoline, which was also isolated in racemic form (*39*).

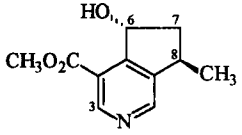
14. Rhexifoline (23)

The stems and leaves of *Castilleja rhexifolia* (Scrophulariaceae) afforded the pyrrolizidine alkaloids senecionine and its *N*-oxide, and, as the main alkaloid, rhexifoline (**23**), $[\alpha]_D$ +18°, a new monoterpene alkaloid (*35*). High-resolution mass spectrometry established the molecular formula as $C_{11}H_{13}NO_3$, which was followed by a major fragment ion at *m/z* 174, reflecting losses of H_2O and a methyl radical. Two pyridine α-protons were observed at 9.04 and 8.67 ppm, and the NMR spectrum also showed a methyl doublet at 1.34 ppm and a carbomethoxy methyl singlet at 4.00 ppm. A methine doublet of doublets (J = 3.7, 7.4 Hz) was found at 5.61 ppm, and the methine coupling with the methyl doublet (J = 7 Hz) was located at 3.59 ppm. By comparison with leptorhabine (**3**) (*77*), it was suggested that the hydroxy group was located at C-5 rather than C-7. These groups were supported also by the ^{13}C NMR spectrum, which displayed a

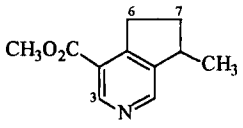
carbomethoxy group (52.6, 166.8 ppm), a methyl group (20.6 ppm) and attached methine (35.6 ppm), an oxymethine carbon (73.7 ppm), a methylene (41.6 ppm), and five pyridine carbons (*35*).

The stereochemistry of rhexifoline was deduced from NOE studies, in which irradiation of H-5 enhanced H-6β at 2.03 ppm, but not H-6α at 2.43 ppm. Irradiation of this latter proton enhanced H-7 (3.59 ppm) but not H-5. Therefore the methine protons were deduced to be *anti* to each other, and rhexifoline has the stereochemistry shown in **23** (*35*). The stereochemistry was confirmed by semisynthesis (see Section III.G) (*81*). The yield of **23** was not altered depending on whether NH_3 or NaOH was used for basification. A related taxon, *C. rhexifolia* aff. *miniata,* also yielded **23** as the major alkaloid, concentrated in the seeds and flowers (*35*).

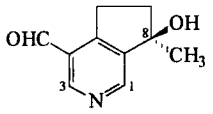
C. rhexifolia serves as the host for the plume moth, *Pletyptilia pica,* and the larvae, moth frass, and adults were analyzed for alkaloids. An alkaloid fraction derived from an extract of the adult moths was found to contain rhexifoline (**23**) by gas chromatography–mass spectrometry (GC-MS), but no alkaloids were detected in the frass or larvae, and no pyrrolizidine alkaloids were detected in the adults (*35*). Expanded studies by Stermitz and co-workers (*68*) demonstrated the presence of rhexifoline (**23**) in specimens of the aerial parts of *C. sulphurea, C. occidentalis,* and *C. rhexifolia,* but not *C. hispida* var. *acuta.* Analyses of the moths of *P. pica* predating on these species indicated the presence of **23** from samples hosted by *C. sulphurea* as well as *C. rhexifolia.* The moths do not sequester the iridoids of the host plants, and analysis of various body parts of the moths indicated the presence of **23** in all insect parts examined. Thus, the alkaloid was presumed not to be a pheromone or allomone. The origin of **23** remains a question, recognizing that **23** is at its highest concentration in the primary larval food, the seeds of the *Castilleja* species in question. It was proposed that **23** is either a kairomone feeding stimulant or results from incomplete metabolism and excretion (*68*).



23 Rhexifoline



24
Methyl boschniakinate/
Deoxyrhexifoline



25 Euphrosine

15. Methyl Boschniakinate and Deoxyrhexifoline

A new alkaloid, methyl boschniakinate (**24**), was isolated from the two *Plantago* species, *P. arenaria* and *P. psyllium* (*61*). The alkaloid was charac-

terized by its IR spectrum, which showed a great similarity with those of boschniakine, except for an ester carbonyl group at 1730 cm^{-1}, and also by its mass spectrum, which displayed an M^+ at *m/z* 191 and fragment ions at *m/z* 176 and 160. No NMR data were reported.

From the seeds of *Castilleja rhexifolia* deoxyrhexifoline (**24**) was isolated (*35*). The molecular ion was observed at *m/z* 191, 16 amu less than **23**, and the difference of one oxygen atom was confirmed by high-resolution measurement. The base peak was observed at *m/z* 176 due to loss of a methyl radical. No hydroxyl absorption was seen in the IR spectrum, and the NMR spectrum showed no downfield oxymethine proton. Rather, two sets of methylene protons (3.38, 3.13 ppm; 2.38, 1.67 ppm) were seen. Thus, the alkaloid was deduced to be the 5-deoxy derivative and was named deoxyrhexifoline (**24**) (*35*). The relationship between methyl boschniakinate and deoxyrhexifoline has not been established, but the available data would appear to indicate that they are the same alkaloid. Neither group reported an $[\alpha]_D$ for the respective isolates.

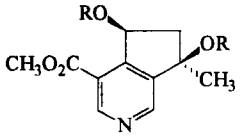
16. Euphrosine (25)

During the course of examining the iridoid content of a number of *Orthocarpus* species, Stermitz and co-workers (*40*) isolated a new monoterpene pyridine alkaloid, euphrosine (**25**) from *Orthocarpus luteus* (Scrophulariaceae). The mass spectrum showed a molecular ion at *m/z* 177 and a major fragment ion at *m/z* 159 for the loss of H_2O. Two pyridine α-protons were observed at 8.76 and 8.89 ppm for H-1 and H-3, respectively, and a singlet at 10.2 ppm indicated the presence of an aromatic aldehyde. A three-proton singlet at 1.65 ppm suggested proximity to the aromatic system and an attached hydroxy group, and this was confirmed in the ^{13}C NMR spectrum with a quaternary carbon for C-8 at 79.8 ppm. Two sets of methylene protons (3.19 and 3.42 ppm for H_2-6, and 2.30 and 2.28 ppm for H_2-7) were noted, and the latter of these sets showed an NOE effect on irradiation of the methyl group. When the aldehyde proton was irradiated, the proton at 8.89 ppm was enhanced. Euphrosine therefore has the structure **25** (*40*). The alkaloid was isolated in the absence of the use of ammonia for extraction purposes, and in greater yield when ammonia was used. The structure was confirmed through semisynthesis (see Section III.G).

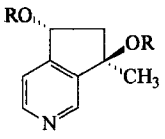
17. Plectrodorine (26) and Isoplectrodorine (27)

When the aerial parts of *Plectronia odorata* (Rubiaceae) were treated with ammonia, two new racemic, isomeric alkaloids, plectrodorine (**26**) and isoplectrodorine (**27**), were isolated by Koch and co-workers (*53*). The molecular ion appeared at *m/z* 223 and corresponded to the formula

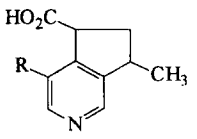
$C_{11}H_{13}NO_4$ by high-resolution measurement. Fragmentation ions were observed indicating successive losses of H_2O and methyl radical. Although their ^1H NMR spectra were very similar, showing two α-pyridine protons, a carbomethoxy group, and a methylene group, some differences were observed in the chemical shifts of the singlet methyl groups (1.60 ppm for **26** and 1.80 ppm for **27**) and in the oxymethine protons (5.42 ppm for **26** and 5.67 ppm for **27**). Thus, the compounds were isomeric at C-6. A distinction between the two was made when their acetate and diacetate derivatives were prepared. Additional evidence came when the dibenzoate derivatives **28** and **29** were reduced with tributyl tin hydride to each afford deoxyrhexifoline (**24**) (*53*).



26 Plectrodorine, R = H
28 R = COC_6H_5



27 Isoplectrodorine, R = H
29 R = COC_6H_5



30 Carbomethoxy-pedicularine, R = CO_2CH_3
31 Pedicularine, R = H

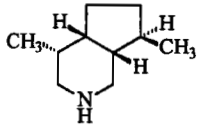
18. Carbomethoxy-pedicularine (30)

Carbomethoxy-pedicularine (**30**) was proposed as the structure for an alkaloid of mass 235 amu from a NH_3 chemical ionization gc/ms analysis of the alkaloid extract of the flowers of *Penstemon whippleanus* (Scrophulariacaeae) (*30*). No molecular ion was observed in the electron impact mass spectrum, only an $(M-45)^+$ ion at *m/z* 190. The further fragmentation of this ion (*m/z* 162, 146, and 117) compared well with the mass spectrum of pedicularine (**31**) (*1,82,83*), so the alkaloid was tentatively suggested to be a carbomethoxypedicularine (*30*). Isomeric structures for this alkaloid cannot excluded, particularly given biogenetic considerations. The isolate may even be the methyl ester of pedicularine.

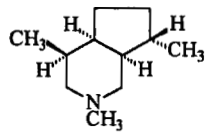
19. (−)-δ-N-Nor-methylskytanthine (32)

The bark of *Tecoma arequipensis* (Bignoniaceae) yielded a major alkaloid, (−)-δ-*N*-nor-methylskytanthine (**32**), $[\alpha]_D$ −21.5°, whose structure was established through X-ray crystallographic analysis of the *N*-(4-bromophenylthiourea) derivative (*36*). Other alkaloids detected by GC-MS analysis included 5,6-dehydroskytanthine, skytanthine, actinidine, 5-hydroxy-skytanthine and tecomanine. Additional components were partially characterized (MS data only) as two hydroxytecomanines and four

dihydrotecomanines. The optical rotation of the isolate was opposite to that of (+)-δ-skytanthine (**33**), $[\alpha]_D$ +10°, from *T. stans* (*84*).



32 (-)-δ-*N*-Normethyl-skytathine



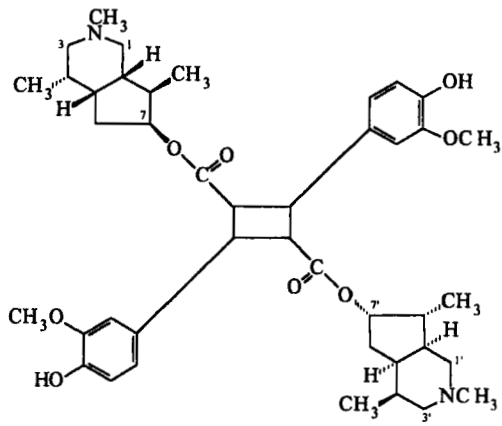
33 (+)-δ-Skytanthine

The EIMS data for the isolate displayed a molecular ion at *m/z* 153, together with prominent ions at *m/z* 138, 122, 96, and 44. The ^{1}H NMR spectrum showed two doublet methyl groups at 0.83 and 0.94 ppm, together with a series of aliphatic protons. The ^{13}C NMR spectrum provided evidence for only two methyl groups (17.4 and 22.4 ppm) and the absence of any *N*-methyl group, so the data substantiate the structure derived from the crystallographic analysis (*36*).

*20. Incarvillateine (**34**)*

Incarvillateine was isolated from the aerial parts of the Chinese plant known as *jiao-hao, Incarvillea sinensis,* in the family Bignoniaceae (*48*). This plant had not been studied previously, and indeed the genus of 11 species has been afforded scant attention.

The structure of incarvillateine (**34**) was elucidated through X-ray crystallographic analysis as a dimer of a 7-hydroxyskytanthine derivative that has been esterified by 4-hydroxy-3-methoxycinnamic acid (*48*). No spectral data

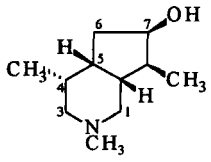


34 Incarvillateine

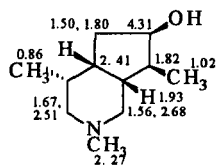
were reported for the isolate. Subsequent work on the species revealed a series of new skytanthine-related alkaloids.

21. Incarvilline (35)

The aerial parts of *Incarvillea sinensis* also yielded a simple monoterpene alkaloid, incarvilline, $[\alpha]_D$ −8.0°, as colorless crystals (*49*). The alkaloid displayed a molecular ion at *m/z* 183 and a hydroxyl absorption in the IR spectrum (3160 cm^{-1}). Two 3-proton doublets (0.86 and 1.02 ppm), together with an *N*-methyl group (2.27 ppm) and the absence of double bonds in the ^{13}C NMR spectrum, indicated that the alkaloid was a skytanthine derivative. Three methylene [57.97 (2C), 32.68 ppm], four methine (45.78, 42.29, 37.49, and 30.48 ppm), and three methyl (46.23, 17.40, and 14.15 ppm) carbons were shown in the ^{13}C NMR spectrum, together with a methine carbon at 73.42 ppm, indicating the presence of a hydroxy group. Correlations between carbons and protons were deduced from the HETCOR spectrum, and, together with the COSY spectrum, permitted unambiguous proton assignments to be made (see structure **36**). The *cis* stereochemistry of the ring junction was deduced from X-ray crystallographic analysis. Thus incarvilline has the structure **35** (*49*).

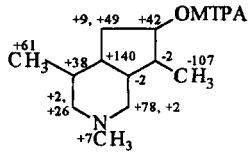


35 Incarvilline



36

More recently, the absolute stereochemistry of incarvilline has been deduced through two independent routes (*43*). With the assignment of the protons of **35** established, the Mosher method (*85,86*) was used to derive $\Delta\delta$ ($\delta S - \delta R$) values (see **37**) for the MTPA esters and allowed the configuration



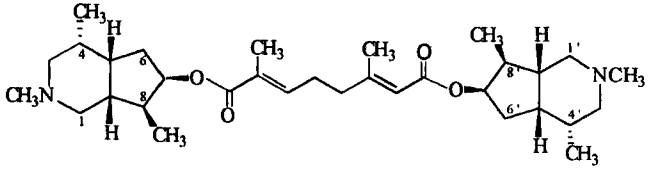
37 $\Delta\delta$ values (x 1000) for MTPA Esters of **36**

4*R*,5*S*,7*R*,8*S*,9*S* to be deduced. For crystallographic purposes, the methiodide of incarvilline was prepared and showed quaternary *N*-methyl

resonances at 3.05 and 3.13 ppm. The absolute configuration determined was the same as that found from the NMR studies of the Mosher esters. Thus, the absolute structure of incarvilline is represented by **35** (*43*).

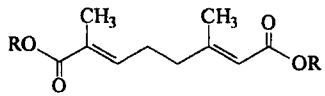
22. Incarvilline Derivatives

Several derivatives related to incarvilline (**35**) were also isolated from *Incarvillea sinensis.* Incarvine A (**38**), $[\alpha]_D$ −0.9° (*50*), showed a molecular



38 Incarvine A

ion at *m/z* 529 and a molecular formula of $C_{32}H_{52}N_2O_4$. When the ^1H and ^{13}C NMR spectra were examined, it became apparent that the molecule contained two units of incarvilline linked by a monoterpene diacid composed of two methyl groups, two trisubstituted double bonds, and two methylene groups. The ^1H NMR spectrum confirmed the nature of the monoterpene alkaloid unit and established that the monoterpene diacid was Hildebrandt's acid (**39**), previously obtained as a metabolite of monoterpenes in animals (*87*). The linkages between the diacid and the two identical alkaloid units were established through long-range proton–carbon correlation experiments. Base hydrolysis and methylation afforded a dimethyl ester of the acid, **40,** which was characterized, and incarvilline (**35**), identical to the natural alkaloid (*50*).

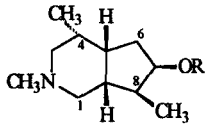


39 Hildebrandt's acid, R = H

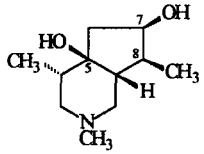
40 R = CH_3

Further work (*51*) led to the isolation of incarvines B and C. Incarvine B (**36**), $[\alpha]_D$ +14.0°, showed a molecular ion at *m/z* 363, which lost a unit to afford a fragment ion at *m/z* 183, corresponding to incarvilline (**35**). The ^{13}C NMR spectrum confirmed a unit of incarvilline and suggested that the second unit in the molecule was the monoterpene diacid, Hildebrandt's acid. A long-range COSY experiment established the linkage of C-10′ of the diacid with H-7 of incarvilline (**35**), and this was supported by the ^1H

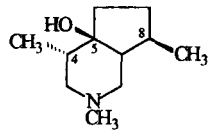
NMR spectrum, which showed a downfield shift of H-7 to 5.27 ppm in **41,** from 4.31 ppm in **35.** Base hydrolysis afforded Hildebrandt's acid (**39**), which was characterized as its dimethyl ester, and incarvilline (**35**), identical to the natural product (*51*).



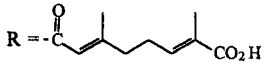
41 Incarvine B



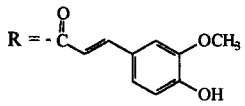
43 5β-Hydroxy incarvilline

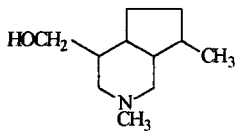


44 5β-Hydroxy skytanthine



42 Incarvine C





45 Tecostanine

Incarvine C (**42**), $[\alpha]_D$ −20.8°, displayed a molecular ion at *m/z* 359, which also showed a direct loss to yield a fragment ion corresponding to incarvilline (**35**) (*51*). The carbon-13 signals of **35** were again discerned, and the residual carbons were identified as belonging to ferulic acid. The locations of the methoxy and hydroxy groups on the phenyl ring were established through NOE experiments, and the chemical shift of H-7 (5.38 ppm) again suggested that the ester was located at the C-7 hydroxy group in **42.** The authors suggest that incarvine C is the biosynthetic precursor of incarvillateine (**34**) (*51*).

A simple hydroxy derivative of incarvilline, $[\alpha]_D$ −6.1°, has also been isolated (*43*). The molecular ion in the mass spectrum was 16 amu higher than that of **35,** and the ^1H NMR spectrum displayed the characteristic signals for the 4-, 8-, and *N*-methyl groups and the 7-H. The ^{12}C NMR spectrum, however, showed downfield shifts for C-4 (+8.7 ppm), C-6 (+6.5 ppm), and C-9 (+8.7 ppm), implying that a hydroxy group was located at C-5. The HMBC spectrum established correlations between the 4-methyl protons and C-5 (83.5 ppm), and between the 8-methyl and C-7 (74.1 ppm) and C-9 (54.5 ppm). NOE effects were observed between H-6α and H-1α and the 4-methyl group, thereby suggesting that the stereochemistry at the ring junction had remained *cis* and that the derivative was 5β-hydroxyincarvilline (**43**) (*43*). The studies on the *Incarvillea* alkaloids have been summarized (*88*).

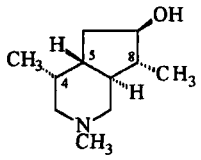
23. 5β-Hydroxy-skytanthine (44)

Originally isolated as "Alkaloid C" by Jones and Dickinson (*45*), the structure was deduced to be that of a 5- or 9-hydroxy-skytanthine derivative, with the former structure preferred. To clarify this ambiguity the methiodide salt was subjected to X-ray crystallographic analysis (*46,47*), which showed that the isolate was 5β-hydroxy-skytanthine (**44**). The same compound was also isolated from the fruits of *Tecoma stans,* and the proton and ^{13}C NMR data were established (*42*).

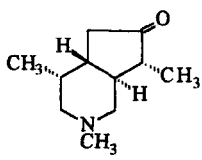
The leaves of *T. stans* revealed two polar skytanthine derivatives, which were partially characterized as δ-skytanthine (**33**), 5-hydroxy-skytanthine (**44**) (R_f 0.14), *N*-nor-methylskytanthine (**32**), or tecostanine (**45**) (R_f 0.06) by TLC (*89*).

24. Kinabalurines A (46)–F (51)

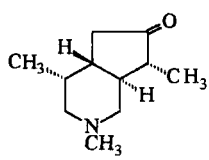
Kinabalurine A (**46**), $[\alpha]_D$ +26°, was the first member of a new group of alkaloids isolated from the leaf extract of *Kopsia pauciflora* (Apocynaceae) from North Borneo (*55*). The mass spectrum showed a molecular ion at *m/z* 183 with fragments corresponding to losses of H, CH_3, and OH, as well as characteristic ions at *m/z* 84, 58, and 44. The IR spectrum (3357 cm^{-1}) and the disappearance of a signal in the ^1H NMR spectrum at 3.27 ppm indicated the presence of a hydroxy group, and this was confirmed by the presence of an oxymethine carbon at 80.0 ppm. Two doublet methyl groups (0.97 and 1.06 ppm) and an *N*-methyl group (2.25 ppm) were also noted. The stereochemical assignments of the centers C-9 (Hα) and C-5 (Hβ) were deduced through *J* values ($J_{1\beta,9}$ = 10 Hz), and the remaining centers were assigned following X-ray crystallographic analysis. Thus, kinabalurine A has the structure **46** (*55*) and differs in stereochemistry from incarvilline (**35**) at C-4, C-5, and C-7. A full paper describing this work was published subsequently (*56*), and at the same time the structures of several other kinabalurine derivatives were presented.



46 Kinabalurine A



47 Kinabalurine B



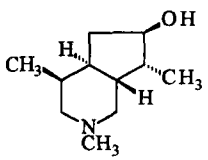
48 Kinabalurine C

Kinabalurine B (**47**), $[\alpha]_D$ −100°, showed a molecular ion at *m/z* 181 ($C_{11}H_{19}NO$), two units less than that of **46** (*56*). The hydroxyl absorption was missing in the IR spectrum, replaced by a ketone carbonyl (1741 cm^{-1}),

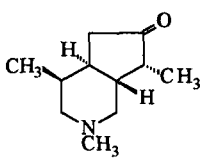
and a carbonyl was also observed in the ^{13}C NMR spectrum at 219.1 ppm in place of the oxymethine (80.0 ppm) in **46.** These data suggested that kinabalurine B had the structure **47,** and this was confirmed by pyridinium chlorochromate (PCC) oxidation of **46** to afford **47** (*56*).

Kinabalurine C (**48**), $[\alpha]_D$ +25°, showed a molecular ion at *m/z* 167 ($C_{10}H_{17}NO$), a ketonic carbonyl (1741 cm^{-1}, δ_c 218.6 ppm), but no *N*-methyl group (*56*). The stereochemistry was established through the multiplicity and coupling constants of H-9 as a quartet of doublets (J = 12, 4 Hz). Such an observation requires that H-9 be *trans* diaxial with H-1, H-5, and H-8, which is possible only when there is a *trans*-ring junction and H-8 and the methyl group at C-8 are both α. NOE enhancement of the 4-methyl signal on irradiation of H-9α established the stereochemistry at C-4; kinabalurine C therefore has the structure **48** (*56*).

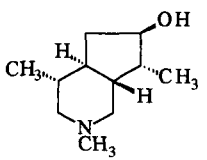
The mass spectrum of kinabalurine D (**49**), $[\alpha]_D$ −13°, was similar to that of kinabalurine A (**46**), and the IR spectrum also displayed a hydroxyl group (3355 cm^{-1}) (*56*). The ^{13}C NMR spectrum, although showing some slight chemical shift changes, was also quite similar to that of **46.** However, the ^1H NMR spectrum showed different chemical shifts and multiplicities, and the stereochemistry could not be assigned. The methiodide salt of kinabalurine D was therefore subjected to X-ray crystallographic analysis, indicating that the structure was **49,** in which the stereochemistry at H-5, H-9, and of the 4-methyl group are reversed compared with those centers in **46** (*56*). Kinabalurine E (**50**) was deduced to be the 7-oxo derivative of **49** from comparison of its molecular ion (*m/z* 181) and similar ^1H and ^{13}C NMR spectra, except for the loss of an oxymethine (δ_H 3.84 ppm; δ_C 81.1 ppm), which was replaced by a ketonic carbonyl (1742 cm^{-1}, δ_C 220.3 ppm). PCC oxidation of **49** afforded **50** (*56*).



49 Kinabalurine D



50 Kinabalurine E



51 Kinabalurine F

Kinabalurine F (**51**), $[\alpha]_D$ +56°, was isolated in trace quantities, and the mass spectrum displayed a molecular ion at *m/z* 183. The IR and ^1H and ^{13}C NMR data indicated that the isolate was an isomer of **46** and **49.** From carbon-13 data it was inferred that the 7-OH stereochemistry was β (δ_C 80.7 ppm), compared with incarvilline, which has the 7α-OH stereochemistry (*49*). The assignment of H-8 was assisted by an NOE effect between H-7α and the C-8 methyl group, and the NOE effects observed

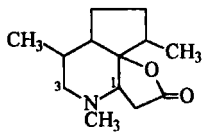
between H-7 and H-6 and between H-5 and H-6 indicated that the latter protons were also α. H-1α was assigned as a triplet based on the NOE between H-8β and H-1β, so H-9 and H-1α are *trans* diaxial and H-9 is β. The H_2-3 resonances were distinguished by their coupling (H_α-3, J = 11,11 Hz; H_β-3, J = 2,11 Hz), which allowed the 4-methyl group to be assigned the α-stereochemistry. Kinabalurine F therefore has the structure **51** (*56*).

25. Kopsilactone (53)

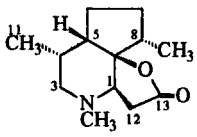
From a *Kopsia* species, *K. macrophylla,* native to Malaysia, Husson and co-workers isolated two new monoterpene alkaloids (*57*). Kopsilactone (**53**), $[\alpha]_D$ +43°, showed a molecular ion at *m/z* 223 ($C_{13}H_{21}NO_2$) and fragment ions at *m/z* 208, 180, 165, 164 (base peak), 150, and 126, and the IR spectrum showed an absorption for a γ-lactone (1770 cm^{-1}). The carbon spectrum confirmed this group (δ_C 176.3 ppm), and displayed a second quaternary carbon at 92.7 ppm. Two methyl doublets (0.88 and 0.97 ppm), together with an *N*-methyl group (2.29 ppm), and two methylene protons (J = 18.2 Hz), one of which was coupled (J = 5.7 Hz) to a methine proton at 2.63 ppm (δ_C 59.3 ppm), were observed. These data suggested the gross structure **52,** which was stereochemically refined through evaluation of the coupling constants between H_{ax}-3 and H-5 and between H-4 and H-5. The NOESY spectrum showed a weak correlation between the *N*-methyl and H-1, which suggests that kopsilactone has the stereochemistry shown in **53** (*57*).

26. Kopsone (54)

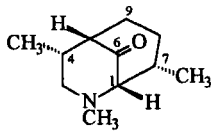
The second monoterpene alkaloid isolated from *Kopsia macrophylla* was kopsone (**52**), $[\alpha]_D$ +132°, which had a molecular formula of $C_{11}H_{19}NO$ and showed a ketone carbonyl signal in both the IR (1720 cm^{-1}) and ^{13}C NMR spectra (218.3 ppm) (*57*). Two methyl doublets (0.96 and 1.14 ppm)



52



53 Kopsilactone



54 Kopsone

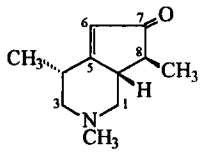
and an *N*-methyl group (2.49 ppm) were observed. The carbon spectrum showed a deshielded (δ_C 72.0 ppm) methine and only one deshielded methylene (δ_C 55.9 ppm). Long-range proton–carbon correlations permitted the rearranged structure **54** to be proposed for kopsone. The relative stereochemistry was deduced from the proton coupling constants. H_{ax}-3

(3.19 ppm) appeared as a doublet of doublets (J = 13.9, 11.8 Hz), indicating that the C-4 methyl was equatorial. Given the sum of the couplings for H-7, it was deduced that H-7 is axial and that kopsone has the structure **54** (*57*).

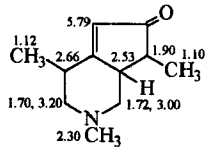
*27. Tecomanine (Tecomine) (**55**)*

Tecomine was originally isolated from *Tecoma stans* in 1959 by Hammouda and Motawi (90) and subsequently by Jones and co-workers (*45,91*), who named the alkaloid tecomanine. Direct comparison of the alkaloids and their picrates established their identity (*92*). Therefore the former name, tecomine, should take precedence. However, current nomenclature in usage for the alkaloid and for its derivatives has favored the name tecomanine, and this name will be used here.

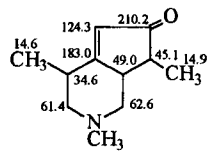
The initial studies were unable to deduce the stereochemistry of tecomanine, so a derivative, the methoperchlorate, was prepared from the iodide through anion exchange and subjected to X-ray crystallography (*46,47*). In this way, the absolute configuration of tecomanine was established as **55.** Subsequent isolation work on the fruits of *T. stans* (*42*) afforded a sample of tecomanine for which complete ^{1}H and ^{13}C NMR data were obtained and are shown in **56** and **57,** respectively.



55 Tecomanine



56



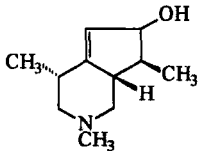
57

*28. 7-Hydroxy-5,6-dehydroskytanthine (**58**)*

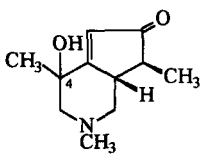
The leaves of *Tecoma stans* (Bignoniaceae) were studied previously (*1*) because of their reputed antidiabetic properties, which appear to have been traced to the monoterpene alkaloid fraction. Further studies of this plant by Lins and D'arc Felicio (*42*) have now revealed the presence of two new alkaloids, 7-hydroxy-5,6-dehydroskytanthine (**58**) and 4-hydroxy-tecomanine (**59**), in the fruits of *T. stans.* In addition, two known alkaloids, 5β-hydroxy-skytanthine (**44**) and tecomanine (**55**) were obtained. ^{1}H and ^{13}C NMR data for these known alkaloids were reported for the first time.

7-Hydroxy-5,6-dehydroskytanthine (**58**), the principal alkaloid, showed a molecular ion at *m/z* 181 for a molecular formula of $C_{11}H_{19}NO$, and displayed hydroxyl (3650 cm^{-1}) and olefinic bond (1616 cm^{-1}) absorptions

in the IR spectrum. One olefinic proton was observed at 5.29 ppm and was correlated with an oxymethine proton at 4.32 ppm. Three methyl groups were observed, including one *N*-methyl group at 2.22 ppm and two methyl doublets (J = 8 Hz) at 0.99 and 1.10 ppm. Establishment of the structural framework was achieved through HETCOR experiments. In the long-range HETCOR spectrum, the methyl doublet at 0.99 ppm was correlated with the carbons at 32.2 ppm (C-4) and at 149.7 ppm (C-5). The other doublet, at 1.10 ppm, showed correlations with the carbons at 48.1 (C-8), 50.1 (C-9), and 84.1 ppm (C-7). The stereochemistry of **58** was assigned through analysis of the coupling constants (*42*). The alkaloid was previously only known, tentatively, as a reduction product of tecomanine (**55**) (*45*).



58 7-Hydroxy-5,6-dehydro-skytanthine



59 4-Hydroxy tecomanine

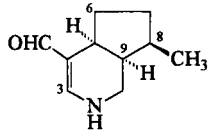
*29. 4-Hydroxy-tecomanine (**59**)*

A second new alkaloid isolated from the fruits of *Tecoma stans* was deduced to be 4-hydroxy-tecomanine (**59**) (*42*). A molecular ion was observed at *m/z* 195 ($C_{11}H_{17}NO_2$), and from the IR spectrum both hydroxy (3660 cm^{-1}) and double-bond (1605 cm^{-1}), as well as carbonyl (1720 cm^{-1}), groups were noted. These inferences were supported by the ^{13}C NMR spectrum, which displayed resonances for a carbonyl carbon at 209.7 ppm, a double bond (175.4 and 122.9 ppm), and a quaternary carbonilic carbon (71.3 ppm). Only one methyl doublet (1.25 ppm, J = 8 Hz) was observed, and this was correlated with a doublet of quartets at 2.27 ppm (H-8), the second methyl group being a singlet at 1.50 ppm. Comparison with the ^{13}C NMR data for tecomanine (**57**) indicated the location of the additional hydroxy group to be at C-4, because this carbon was shifted from 34.6 ppm in **55** to 71.3 ppm in **59.** Adjacent carbons (C-3, C-5, C-9, and C-10) were also shifted. The relative stereochemistry at C-8 and C-9 was deduced from the coupling constants to be *cis*. However, the stereochemistry of the methyl and hydroxy groups at C-4 remains unknown (*42*).

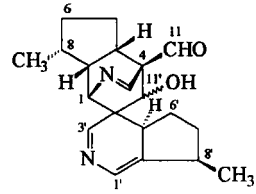
*30. Lindenialine (**60**) and Lindeniamine (**61**)*

From the leaves of *Lindenia austro-caledonica* (Rubiaceae), two new monoterpene alkaloids were isolated, lindenialine (**60**), a monomer, and

lindeniamine (**61**), a dimer (*59*). Lindenialine, $[\alpha]_D$ +20°, showed a molecular ion at *m/z* 165 analyzing for $C_{10}H_{15}NO$, and IR absorptions for NH (3450 cm^{-1}) and carbonyl (1740 and 1720 cm^{-1}). The latter was traced to an aldehyde group (δ_H 8.95 ppm; δ_c 187.8 ppm), and the ^{13}C NMR spectrum also showed two olefinic carbons (151.7 and 117.6 ppm) and three methine, three methylene, and one methyl carbon. The location of the methyl group at C-9 was on biogenetic grounds and the absence of an NOE effect with the aldehyde proton, and from their coupling constants (J = 9 Hz), the H-4 and H-5 protons were *cis*-related. The assignment of the stereochemistry of the methyl group was inferred from the carbon-13 chemical shifts of related compounds (*39*). On this basis, the structure was deduced to be **60** (*59*).

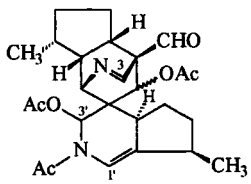


60 Lindenialine

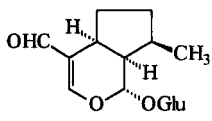


61 Lindeniamine

Lindeniamine, $[\alpha]_D$ −26°, also showed absorption maxima at 3450, 1740, and 1720 cm^{-1}, and a molecular ion at 327 amu in the CI mass spectrum corresponding to a molecular formula of $C_{20}H_{26}N_2O_2$ (*59*). Similarities in the spectra of the isolates suggested that lindeniamine was a dimer of **55.** However, only one signal (δ_H 9.9 ppm; δ_C 205.1 ppm) for a saturated aldehyde was observed, together with three olefinic protons at 8.82, 8.51, and 7.0 ppm. Two secondary methyl groups (1.11 and 1.01 ppm) and two, one-proton singlets at 4.25 and 4.05 ppm were noted. Quaternary carbons were also observed at 114.8, 60.8, and 50.2 ppm. Acetylation afforded a triacetate derivative **62** (singlets at 2.04, 2.05, and 2.11 ppm), and reduction with $NaBH_4$ gave a diol in which the aldehyde and the imine had been reduced. In the spectrum of **61,** singlets were observed at 6.53 and



62



63 Boshnaloside

7.01 ppm for H-3′ and H-1′, respectively, with the imine proton (H-3) appearing at 8.31 ppm (*59*).

Neither lindenialine (**60**) nor lindeniamine (**61**) are true natural products; rather, they were produced through reaction of the powdered leaves with the ammonia used during the isolation process. Although the precursor for lindenialine (**60**) is probably boschnaloside (**63**) (*93*), the origin of lindeniamine (**61**) remains less apparent (see Section IV).

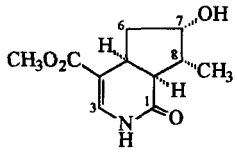
31. Strychnovoline (64) and Dinklageine (65)

Strychnovoline (**64**) (*38*) and dinklageine (**65**) (*37,38*) were isolated by Koch and co-workers from the leaves of *Strychnos dinklagei* (Loganiaceae) collected in the Ivory Coast. Dinklageine (**65**), $[\alpha]_D$ +60°, gave a molecular ion at *m/z* 345, analyzing for $C_{19}H_{23}NO_5$, and showed prominent losses to afford ions at *m/z* 314, 238, 226, and 130. The formulas for these ions suggested that dinklageine was a monoterpene alkaloid with a hydroxyphenethyl group. The ^1H NMR spectrum supported a *para*-substituted phenyl group (A_2B_2 system at 6.95 and 6.64 ppm), a deshielded olefinic proton at 7.15 ppm, a carbomethoxy group (3.60 ppm), an oxymethine as a triplet of doublets at 3.78 ppm (J = 2, 4, 4 Hz), and a methyl doublet (J = 7 Hz) at 1.05 ppm. These deductions were also supported by the ^{13}C NMR spectrum. Coupling constant analysis ($J_{5,9}$ = 11 Hz, $J_{8,9}$ = 8 Hz and $J_{7,8}$ = 4 Hz) and comparison with loganin (**1**) afforded suggestions regarding the stereochemistry of the cyclopentane ring. On this basis, the structure **65** was proposed for dinklageine (*37*), and this was confirmed, and the absolute configuration established, through semisynthesis from loganin (**1**) (see Section III.G).

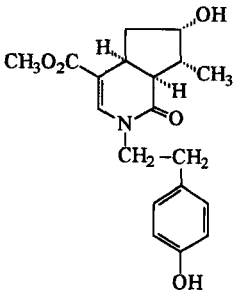
Strychnovoline (**64**) was isolated from the leaves of *S. dinklagei* after treatment with ammonia (*38*). It was indicated that **64** also occurred in the aerial parts of *Scaevola racemigera* (Goodenaceae) (*38,39*). Like **65,** it was optically active ($[\alpha]_D$ +98°), and the IR spectrum showed a hydroxyl group (3500–3300 cm^{-1}) and a complex carbonyl region (1685, 1670, 1660 cm^{-1}). The mass spectrum displayed a molecular ion at *m/z* 225 ($C_{11}H_{15}NO_4$). The ^1H and ^{13}C NMR data corresponded to those of dinklageine (**65**), except for the absence of the 4-hydroxyphenethyl moiety, and thus strychnovoline was suggested to have the structure **64** (*38*). Verification of this structure was obtained by semisynthesis from loganin (**1**) (see Section III.G) (*38*).

32. 7-O-Nicotinoyl-strychnovoline (66)

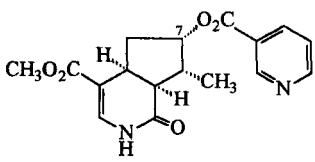
Among the six new monoterpene alkaloids isolated from the aerial parts of *Scaevola racemigera* (*39*) was 7-*O*-nicotinoyl-strychnovoline (**66**). The molecular ion was observed at *m/z* 330, with a major fragment ion at *m/z*



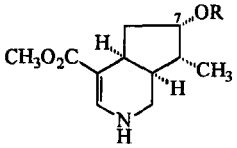
64 Strychnovoline



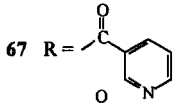
65 Dinklageine



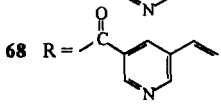
66 7-*O*-Nicotinoyl-strychnovoline



67 R=



68 R=



207 ($M^+-C_6H_5NO$), and the IR spectrum showed carbonyl bands at 1710 and 1680 cm^{-1} for unsaturated ester and lactam moieties. The ^1H NMR spectrum showed the signals that corresponded to strychnovoline (**64**), except that the signal for H-6 was shifted downfield from 4.06 ppm to 5.46 ppm, suggesting that it was esterified, and this unit was identified from the ^1H NMR spectrum as a nicotinoyl moiety. The structure **66** for the isolate, and its absolute configuration, were confirmed through semi-synthesis (see Section III.G) (*39*).

33. 7-O-Nicotinoyl-tetrahydrocantleyine (67)

Another of the new alkaloids isolated from *Scaevola racemigera* was 7-*O*-nicotinoyl-tetrahydrocantleyine (**67**) (*39*), whose structure was elucidated in a manner similar to that described for **66.** A molecular ion was observed at *m/z* 316, with major fragment ions at *m/z* 193 ($M^+-C_6H_5NO_2$) and *m/z* 192. Two carboxylic ester bands were observed at 1710 and 1680 cm^{-1}, and the ^1H NMR spectrum confirmed the presence of a nicotinoate unit. The remaining signals in the spectrum indicated the presence of a tetrahydrocantleyine (**16**) unit, and the site of acylation was again determined to be C-7. Thus, compared with **16,** H-7 was deshielded from 4.06 to 5.51 ppm and C-7 was shifted from 74.2 to 78.6 ppm. Once again the structure was confirmed as **67,** and the absolute configuration determined, through semi-synthesis (see Section III.G) (*39*).

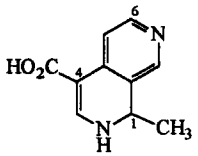
34. 7-O-(5-Vinylnicotinoyl)tetrahydrocantleyine (68)

7-*O*-(5-Vinylnicotinoyl)tetrahydrocantleyine (**68**) was characterized spectroscopically (*39*). The molecular ion at *m/z* 342 was accompanied by fragment ions at *m/z* 192 ($M^+-C_8H_7NO_2$) and *m/z* 192 ($M^+-C_8H_8NO_2$). The ^1H NMR spectrum revealed that the 26-amu difference between the isolate and **67** was due to a vinyl group (δ_H 6.73 ppm, J = 12, 18 Hz; 5.91 ppm, J = 18 Hz; 5.47 ppm, J = 12 Hz). Establishment of the location of this functionality was made through the presence of three pyridinyl protons at 9.08 ppm (J = 1 Hz), 8.74 ppm (J = 1 Hz), and 8.29 ppm (J = 1, 1 Hz). The remaining signals were very similar to those of tetrahydrocantleyine (**16**). Methanolysis afforded **16** (*39*).

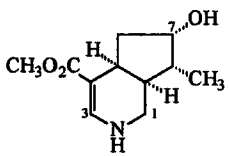
35. Scaevodimerines A (71)–D (74)

Besides a number of alkaloids described previously in this chapter (see Section II.A.*11–13*), the aerial parts of *Scaevola racemigera* have also yielded four novel bis-monoterpene alkaloids (*69*). Scaevodimerine A, $[\alpha]_D$ +31°, was analyzed as $C_{21}H_{25}N_3O_4$ by high-resolution mass spectrometry, and the UV spectrum (237, 269, and 335 nm) showed both pyridine and vinylogous urethane chromophores. Saturated and conjugated esters (1715 and 1665 cm^{-1}) were observed in the IR spectrum, and one set of signals in the ^1H NMR spectrum indicated the presence of a tetrahydrocantleyine (**16**) unit, with the shift of the H-7 proton (from 4.06 ppm in **16** to 5.38 ppm) indicating esterification at this site.

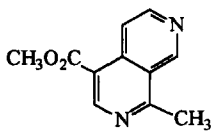
The additional signals in the ^1H NMR spectrum indicated that the esterifying unit was 1,2-dihydro-1-methyl-2,7-naphthyridine-4-carboxylic acid (**69**), and this was confirmed by methanolysis to afford the methyl ester of **69** and tetrahydrocantleyine (**16**). The absolute configuration of the methyl group at 1′ on the 1,2-dihydronaphthyridine unit could not be determined due to rapid aerial oxidation to **70.** Hence the structure of scaevodimerine A was deduced to be **71** (*69*).



69



16 Tetrahydrocantleyine

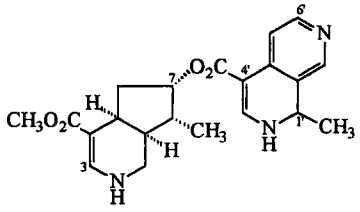


70

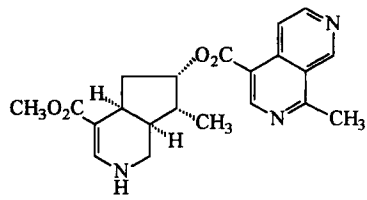
The general features of scaevodimerine B were very similar to those of **71** ($[\alpha]_D$ +39°, $C_{21}H_{23}N_3O_4$), but the UV spectrum (222, 283 nm) indicated that only pyridine chromophores were present. The NMR spectrum dis-

played the characteristic 7-*O*-esterified cantleyine unit, and methanolysis of scaevodimerine B afforded **16** and 4-carbomethoxy-1-methyl-2,7-naphthyridine (**70**) in almost quantitative yield. Thus, the structure of scaevodimerine B was deduced to be **72** (*69*).

Scaevodimerine C, $[\alpha]_D$ −18°, $C_{21}H_{21}N_3O_4$, showed in the ^1H NMR spectrum the signals for a 6-*O*-esterified cantleyine unit coupled with the same 1,2-dihydro-1-methyl-2,7-naphthyridine-4-carboxylic acid moiety as in **71** and therefore had the structure **73** (*69*).

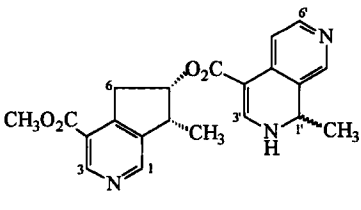


71 Scaevodimerine A

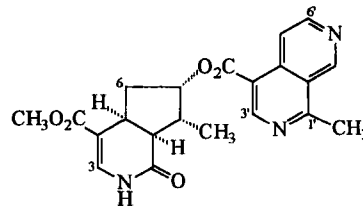


72 Scaevodimerine B

Scaevodimerine D (**74**), $[\alpha]_D$ +48°, $C_{21}H_{21}N_3O_5$, on the other hand, showed a 2,7-naphthyridine unit identical to that in **72,** attached to strychnovoline (**64**). Complete ^1H NMR spectral details were presented in support of these structures (*69*). It should be noted that all of these isolates were isolated after the plant material was extracted in the presence of ammonia and that the possible artifactual nature of these compounds was suggested by the authors.



73 Scaevodimerine C

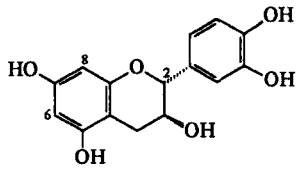


74 Scaevodimerine D

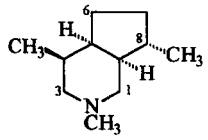
36. Kopsirachine (77)

The leaves of *Kopsia dasyrachis* (Apocynaceae) afforded an alkaloid, kopsirachine, derived from units of catechin (**75**) and two units of skytanthine (*58*). By mass spectrometry, the molecular weight was established as 620 amu, and the UV spectrum (256 and 281 nm) indicated a relationship to catechin. The major fragment in the mass spectrum appeared at *m/z*

166, analyzing as $C_{11}H_{20}N$, with further ions at *m/z* 165, 84, 58, and 44 suggesting a skytanthine type of alkaloid (*1*). Methylation afforded a dimethyl ether derivative, acetylation of which afforded a triacetate. Thermolysis of the parent compound followed by zinc/acid reduction afforded δ-skytanthine (**33**), $[\alpha]_D$ +7.6°, and permanganate oxidation of the dimethyl ether indicated the catechol nature of the B ring. The ^1H NMR spectrum

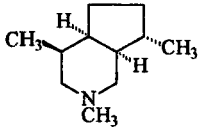


75 (+) - Catechin

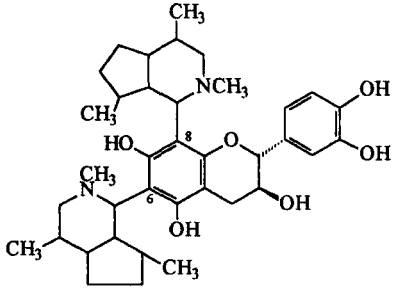


33 δ - Skytanthine

showed a 1,3,4-trisubstituted aromatic nucleus and two *N*-methyl groups (2.29 and 2.08 ppm). The carbon spectrum of kopsirachine showed a doubling of many of the monoterpene alkaloid resonances, and comparison with the data for catechin (**75**) and β- (**76**) and δ-skytanthines (**33**) indicated that substitution by two skytanthine units had occurred at C-6 (shifted from 95.5 to 106.3 ppm) and C-8 (94.3 to 104.4 ppm) of catechin. The data for the skytanthine unit did not permit the unambiguous assignment of the stereochemistry of the monoterpene alkaloid units, and thus the structure of kopsirachine was proposed as **77** (*58*).



76 β - Skytanthine

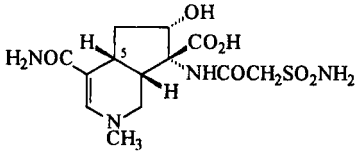


77 Kopsirachine

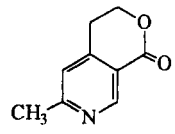
37. Altemicidin (78)

Extracts of a strain of *Streptomyces sioyaensis* SA-1758 isolated from sea mud collected in Gamo, Japan were found to possess strong acaricidal and antitumor activity, which was traced to a novel isolate, altemicidin (**78**).

The molecular formula was established as $C_{13}H_{20}N_4O_7S$, and was supported by the ^1H and ^{13}C NMR spectra (*26*). The structure of the highly water-soluble compound was deduced through spectral analysis. Amide (1650 cm^{-1}) and sulfonyl (1345 and 1165 cm^{-1}) groups were observed in the IR spectrum. An olefinic proton (7.39 ppm) and an *N*-methyl group were observed in the NMR spectrum, together with a pair of exchangeable methylene protons (4.29 and 4.82 ppm). Methylation afforded a methyl ester, which permitted solubility in pyridine and clarification of some of the NMR resonances. The structure of altemicidin as **78** was deduced



78 Altemicidin

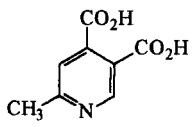


79 Gentianidine

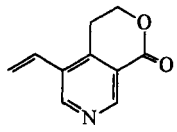
through extensive correlations observed in the HMBC experiment, and the absolute configuration was established on the 9-*N*-(9-xanthenyl) derivative of the methyl ester by X-ray crystallography (*94*). This is the first monoterpene alkaloid derived from a fungal source and has the opposite absolute configuration at C-5 as alkaloids in the skytanthine series.

*38. Gentianidine (**79**)*

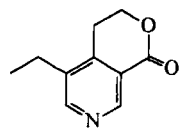
The structure elucidation of gentianidine (**79**) was described by Chinese (*95*) and Japanese (*96*) over 30 years ago. However, details were not available for the previous review (*1*). The Chinese group (*95*) found that the alkaloid gave a positive test for a pyridine ring (cyanogen bromide followed by benzidine to give an orange-red precipitate), and the presence of a lactone was demonstrated by hydroxylamine/ferric chloride. Permanganate degradation gave berberonic acid (**80**). The ^1H NMR spectrum showed



80 Berberonic acid



81 Gentianine



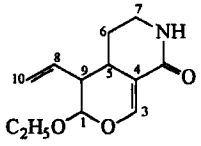
82 Dihydrogentianine

singlets for the pyridine protons at 8.98 and 7.00 ppm, triplets for the methylene groups at 4.50 and 3.00 ppm, and a three-proton singlet at 2.58 ppm. Through comparison with the data for gentianine (**81**) it was concluded that gentianidine had the structure **79.**

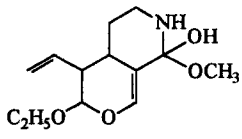
The Japanese group (*96*) showed that the UV spectrum of gentianidine (263 nm) was very similar to that of methyl nicotinoate (264 nm) rather than methyl isonicotinoate (275 nm), which fixed the orientation of the lactone group. Comparison of the ^{1}H NMR spectrum with dihydrogentianine (**82**) also indicated that rather than two pyridine α-protons, gentianidine had only one. The artifactual nature of both gentianidine (**79**) and gentianine (**81**) in *Swertia japonica* was established (*93*).

*39. Spicatine (**85**) and Related Alkaloids from* Centaurium spicatum

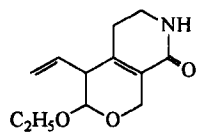
Previous studies on the aerial parts of *Centaurium spicatum* (Gentianaceae) had shown that the major alkaloid is gentianine (*97*). Follow-up studies, not using ammonia in the extraction procedure, afforded five alkaloids, of which two were known, gentianine (**81**) and gentianidine (**79**), and three were new (*32,33*). The most abundant of the new alkaloids showed the presence of a vinyl function in the ^{1}H NMR spectrum (2H, 5.26 ppm; 1H, 5.12 ppm), and two 2H-coupled multiplets at 4.34 and 1.70 ppm characteristic of a $-CH_2CH_2N-$ group. The IR spectrum confirmed the presence of an amide function (1640, 3200 cm^{-1}). An ethyl group was also observed (3H, 1.23 ppm; 2H, 3.67 ppm), the latter chemical shift and the mass spectrum suggesting attachment to an oxygen atom. Given the unsaturated nature of the amide group (λ_{max} 285 nm) and the presence of an olefinic proton at 5.37 ppm, the only possible structure was **83.** In the ^{1}H NMR



83



84



85 Spicatine

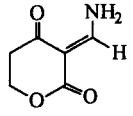
spectrum of the second new alkaloid essentially all of the signals of **77** were observed, together with a singlet (3H) at 3.38 ppm. No carbonyl group was observed in the IR spectrum and therefore the compound was regarded as having the structure **84,** a hemiacetal derivative of **77** (*32,33*).

The third new alkaloid, spicatine, was an isomer of **83,** (M^+) 223, showing λ_{max} 290 nm, but missing the olefinic proton at 5.37 ppm. Given the presence of all of the other NMR signals of **83,** the structure **83** was suggested for spicatine (*32,33*).

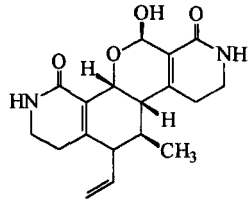
40. Schultesia guianensis *Alkaloid (**87**)*

Together with gentianine (**81**), gentiocrucine (**86**), and gentianidine (**79**), an alcoholic extract of the whole plant of *Schultesia guianensis* (Gentiana-

ceae) yielded a new alkaloid whose mass spectrum showed a molecular ion at *m/z* 330 (*70*). The IR spectrum showed bands for hydroxyl (3550 cm^{-1}), vinyl (930 cm^{-1}), and lactam (1680 cm^{-1}) groups. The structure was solved by X-ray crystallographic analysis and shown to be **87;** no additional spectral data have been reported.



86 Gentiocrucine



87

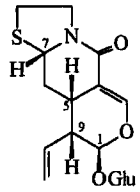
41. Xylostosidine (88)

Xylostosidine (**88**) is the first member of a new series of monoterpene alkaloids containing sulfur (*77,78*). The alkaloid was isolated from *Lonicera xylosteum* and represents the first alkaloid isolated from the Caprifoliaceae. Xylostosidine showed a molecular ion at *m/z* 415 analyzing as $C_{18}H_{25}O_8NS$, a UV spectrum (λ_{max} 238 nm) similar to that of bakankoside (**89**), and an IR spectrum that indicated the presence of an α,β-unsaturated lactam (υ_{max} 1658 cm^{-1}). Losses of $C_6H_{11}O_5$ and $C_6H_{11}O_6$ from the molecular ion indicated the presence of a glycoside moiety, and acetylation afforded a tetraacetate derivative. The ^{13}C NMR spectrum was highly informative, with 15 of the 18 resonances being very close to those of sweroside (**90**). The signals at 49.83 and 28.63 ppm were assigned, respectively, to NCH_2- and SCH_2- groups and the doublet at 62.29 ppm to C-7. On this basis, and with biogenetic considerations, the stereochemical configurations at C-1, C-5, and C-9 were suggested. The ^1H NMR spectrum showed that H-5 and H-7 were *cis* to each other because both show a large coupling (J = 13 Hz and J = 11 Hz, respectively) with H-6_{ax}. The coupling constants of H-9 with H-1 (J = 2 Hz) and H-5 (J = 5.5 Hz) were very similar to the data for sweroside (**90**), whose configuration is known (*98*), and which, together with loganin (**1**), co-occurred with **88** in *L. xylosteum,* and therefore the structure was proposed as **88** (*77,78*). The biogenesis of **88** was suggested to occur from secologanin (**2**) and cysteine.

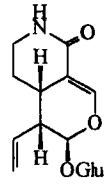
42. Loxylostosidines A (91) and B (92)

Further isolation work on extracts of *L. xylosteum* led to the isolation of two closely related derivatives of **88,** namely, loxylostosidines A (**91**)

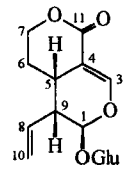
and B (**92**) (*60*). In the case of loxylostosidine A, a molecular ion was observed at *m/z* 431, 16 amu higher than that of **88,** that analyzed for $C_{18}H_{25}O_9NS$. The UV and IR spectra also supported the presence of a β-alkoxyacrylamide function. A tetraacetate derivative was formed on acetyl-



88 Xylostosidine

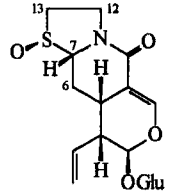


89 Bakankoside

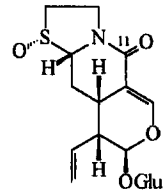


90 Sweroside

ation. Fourteen of the 18 ^{13}C NMR signals of **91** were the same as those in **88,** with shifts appearing for C-6 (−4.64 ppm), C-12 (−5.83 ppm), C-13 (+20.92 ppm), and C-7 (+21.11 ppm). The shifts for C-7 and C-13 suggested the presence of a sulfoxide group, and the small γ-effect for C-6 indicated a *trans* arrangement of C-6 and the sulfoxide oxygen atom (*99*). The ^1H NMR spectrum, like that of **88,** established the stereochemistry of C-1, C-5, and C-9 to be the same as that of **88** and sweroside (**90**). In addition, the downfield shift of 0.33 ppm in H-6_{eq} indicated that this proton was quasi *syn* axial to the sulfoxide oxygen (*100*). Thus, loxylostosidine A was assigned the structure **91** (*60*).



91 Loxylostosidine A



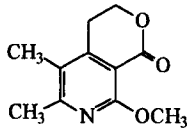
92 Loxylostosidine B

The second isolate, loxylostosidine B, was isomeric with **91** on the basis of its mass spectral, IR, and UV data (*60*). The ^1H and ^{13}C NMR data indicated that the only difference between the two isolates was the configuration of the sulfoxide oxygen atom. The chemical shift of C-6 in **92** was at 24.35 ppm, indicating a difference of −8.12 ppm (syn γ-effect) compared with **88,** and H-6_{ax} was shifted downfield by 0.23 ppm, whereas H-6_{eq} was unchanged. A 1.98-ppm downfield shift for the lactam carbonyl group (C-11) was also observed, and this shift was thought to be due to an axial

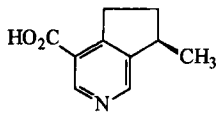
orientation for the sulfoxide oxygen atom. Loxylostosidine B was therefore assigned the structure **92** (*60*).

43. Gentiananine (93)

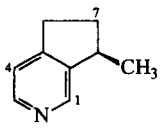
Gentiananine was originally isolated from the aerial parts of *Gentiana olivieri* and *G. turkestanorum* (*101*); no physical or spectral data were presented. The alkaloid was subsequently isolated from *Pedicularis macrochila* (Scrophulariaceae) (*41*), together with boschniakinic acid (plantagonine) (**94**) and 4-noractinidine (**95**). The very high melting point (380–382°C) alkaloid had a molecular formula of $C_{11}H_{13}NO_3$ and a UV spectrum that indicated a pyridine nucleus. The IR spectrum confirmed the aromatic unit (1600 cm^{-1}) and also a lactone carbonyl group (1735 cm^{-1}). Two aromatic methyl groups (2.25 and 1.78 ppm) and one methoxy group (3.38 ppm) were observed in the NMR spectrum, but no downfield aromatic protons. Two structures were proposed for gentiananine on this basis, of which **93** was favored on biogenetic grounds (*41*).



93 Gentiananine



94 Boshniakinic acid

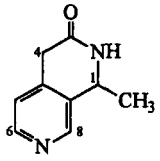


95 4-Nor-actinidine

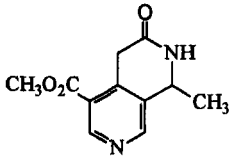
44. Jasminidine (96)

Jasminidine (**96**), $[\alpha]_D$ −3.2°, was isolated from the leaves of *Syringa vulgaris* (Oleaceae) (*54*), together with jasminine (**97**), $[\alpha]_D$ −37.5°, isolated previously from *Jasminum* species (*102*), and from *Ligustrum novoguineense* (*102*) and *Olea paniculata* (*103*). Jasminidine displayed a molecular ion at *m/z* 162, which analyzed as $C_9H_{10}N_2O$, and showed a single carbonyl adsorption at 1682 cm^{-1}. The UV spectrum (259 nm) suggested a 3,4-disubstituted pyridine and in the ^1H NMR spectrum aromatic protons were observed as a complex at 8.45 ppm (2H) and a doublet (J = 4.9 Hz) at 7.07 ppm. Also noted were a methylene group at 4.05 ppm, an NH signal at 7.70 ppm, and a secondary methyl (q, 4.72 ppm; d, 1.58 ppm). By comparison, jasminine (**97**) showed an additional resonance for the carbomethoxy group at 3.95 ppm, a loss of the doublet aromatic signal, and a downfield shift of H-6 to 9.04 ppm and of H-8 to 8.59 ppm. Thus, jasminidine was proposed to have the structure **96.** The stereochemistry of these isolates was deduced to be *S* at C-1, the same as in (−)-actinidine (**14**), from their negative Cotton effects in the region of 255–267 nm (*54*).

It was demonstrated that neither of these alkaloids was an artifact of isolation.



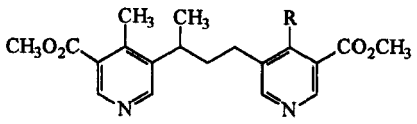
96 Jasminidine



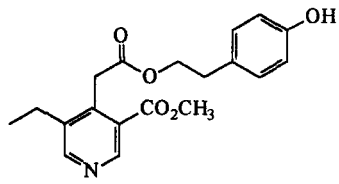
97 Jasminine

*45. Dihydrojasminine (**101**) and Austrodimerine (**102**)*

Skaltsounis and co-workers have recently reported (*27*) on the isolation of several monoterpene alkaloids from the New Caledonian plant *Osmanthus austrocaledonica* in the family Oleaceae. Four of the alkaloids were known and two were new. All of the alkaloids were produced when either ammonia or Na_2CO_3 was used in the extraction process. The known alkaloids were 4-methyl-5,5′-[(1-methyltrimethylene)di](methylnicotinoate) (**98**) (*28*), 4,4′-bis-methyl-5,5′-[(1-methyltrimethylene)di](methylnicotinoate) (**99**) (*28*) and 4-hydroxy-β-phenethyl-5-ethyl-3-methoxycarbonyl-4-pyridinyl acetate (**100**) (*29*) (see Section II.A.52), and the new alkaloids were 2,5-dihydrojasminine (**101**) and austrodimerine (**102**) (*27*).



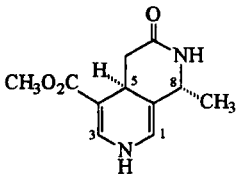
98 R = H
99 R = CH_3



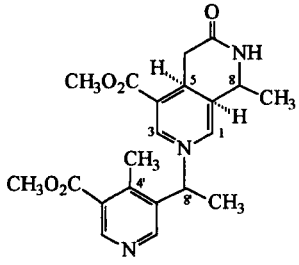
100

2,5-Dihydrojasminine (**101**), $[\alpha]_D$ +300°, afforded a molecular formula of $C_{11}H_{14}N_2O_3$ by high resolution mass spectrometry, and the UV spectrum showed absorptions corresponding to a 1,4-dihydropyridine system (*27*). In support of this, the ^1H NMR spectrum showed two doublets at 7.22 ppm (J = 5 Hz, H-3) and 5.93 ppm (J = 3.5 Hz, H-1), which collapsed to singlets on the addition of D_2O. The remaining signals were very similar to, but upfield of, those of jasminine (**97**), including a methyl doublet at 1.29 ppm, a methine doublet (J = 6 Hz), a carbomethoxy group at 3.70 ppm, and a methylene group at 2.29 and 2.92 ppm. A one-proton doublet of doublets (J = 5,11 Hz) was observed at 3.80 ppm and was assigned to H-5. The relative configuration between H-5 and H-8 was deduced from the NOE

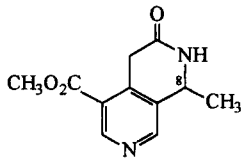
cross-peak observed between H-5 and the C-8 methyl group. Dihydrojasminine therefore has the structure **101** (*27*).



101 Dihydrojasminine



102 Austrodimerine



103 Acanthicifoline

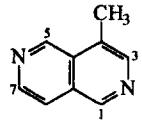
Austrodimerine (**102**), $[\alpha]_D$ +75°, showed a molecular ion at *m/z* 401, corresponding to the molecular formula $C_{21}H_{27}N_3O_4$, with two major fragment ions at *m/z* 223 and 178, suggesting a bimolecular structure comprised of a tetrahydrojasminine moiety and a carbomethoxy-methyl-ethyl-pyridine unit (*27*). The ^1H and ^{13}C NMR confirmed the presence of these units, and the points of attachment, N-2 and C-8′, were established through the NOESY spectrum, which showed correlations between H-3 and H-8′ and H-3 and the 9′-CH_3. In addition, long-range ^1H–^{13}C correlations were observed between H-8′ at 4.77 ppm and the carbon resonances at 142.0 and 39.4 ppm (C-3 and C-1, respectively). The relative configurations at C-5 and C-9 were established through a NOESY cross-peak between H-5 and H-9, and the configuration at C-8 was determined through molecular modeling considerations. Austrodimerine therefore has the structure **102** (*27*).

*46. Acanthicifoline (**103**)*

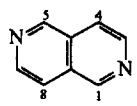
From an ethanolic extract of *Acanthus ilicifolius* (Acanthaceae), was isolated another alkaloid related to jasminine (**97**) and jasminidine (**96**), namely, acanthicifoline (**103**), $[\alpha]_D$ −31.6° (*24*). The base peak in the mass spectrum was observed at *m/z* 191 as an M^+–H peak, and IR absorptions were noted at 3182 and 1680 cm^{-1}. The ^1H NMR spectrum showed resonances for a methylene group at 4.02 ppm, a methoxyl singlet at 3.65 ppm, a methyl doublet at 1.65 ppm coupled to a methine at 4.65 ppm, and two pyridine α-protons at 8.54 and 8.66 ppm. On the basis of this evidence the structure **103** was assigned to acanthicifoline (*24*).

*47. 4-Methyl-2,6-naphthyridine (**104**)*

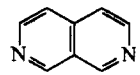
The first 2,6-naphthyridine alkaloid isolated was the 4-methyl derivative **104,** which was obtained by Harkiss and Swift from the dried plant of



104 4-Methyl-2,6-naphthyridine



105 2,6-Naphthyridine



106 2,7-Naphthyridine

Antirrhinum majus (*62*) in 1970. Other bases were also obtained, but remain uncharacterized. The isolate showed a molecular ion at *m/z* 144 for $C_9H_8N_2$ and a UV spectrum showing absorptions at 260 and 338 nm. Three singlets were observed in the ^1H NMR spectrum at 8.55, 9.20, and 9.51 ppm, a pair of doublets (J = 5.5 Hz) at 8.74 and 7.77 ppm, and a three-proton singlet at 2.75 ppm.

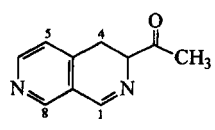
Comparison of the ^1H NMR data with those of both 2,6- and 2,7-naphthyridine was not possible, although 2,6-naphthyridine (**106**) shows resonances at 9.39 (H-1 and H-5), 8.77 (H-3 and H-7), and 7.80 ppm (H-4 and H-6) (*104,105*). In addition, in the UV spectra of the two systems absorption beyond 330 nm is only observed for the 2,6-naphthyridine (**105**) system (*104*); 2,7-naphthyridine (**105**) shows a long-range maximum at 305 nm (*106*). On this basis, the compound was assigned the structure 4-methyl-2,6-naphthyridine (**104**) (*57*). However, the structure drawn in the paper is of 4-methyl-2,7-naphthyridine (**107**). Additional details of the isolation and spectroscopic properties were published subsequently (*63*); although no structures were presented in this paper. Further work by Taurins and Li (*107*) established the structure through synthesis (see Section III.D.1).

107 4-Methyl-2,7-naphthyridine

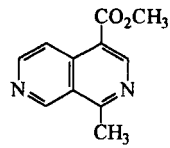
*48. 3-Acetyl-2,7-Naphthyridine (**108**)*

In addition, to actinidine (**14**), Janot and co-workers also isolated a new monoterpene alkaloid from the roots of *Valeriana officinalis* following treatment with ammonia (*25*). The isolate was analyzed for the formula $C_{10}H_8N_2O$, and the UV spectrum showed maxima at 261, 314, and 324 nm, and the IR spectrum a band at 1680 cm^{-1} for an aryl ketone. The mass spectrum displayed a molecular ion at *m/z* 172 with fragment ions at *m/z* 157 (M^+-15) and 129 (M^+-43), suggesting the presence of a methyl ketone. A methyl singlet was observed at 2.65 ppm, and a complex pattern of five

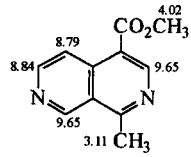
aromatic protons was seen. The structure of 3-acetyl-2,7-naphthyridine (**108**) was deduced from X-ray crystallographic analysis (*25*).



108 3-Acetyl-2,7-naphthyridine



70 Neozeylanicine



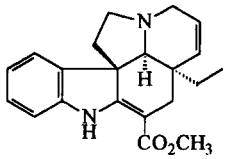
109

*49. Neozeylanicine (**70**)*

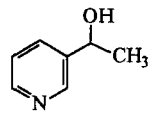
The timber of the Sri Lankan tree *Neonauclea zeylanica* (Hook. f.) Merr. in the family Rubiaceae has yielded an interesting monoterpene alkaloid possessing two nitrogen atoms in a 2,7-naphthyridine ring system (*64*). The UV spectrum showed maxima at 214, 287, and 308 nm, and the IR spectrum displayed an unsaturated ester carbonyl absorption at 1710 cm^{-1}. The molecular ion at *m/z* 202 was accurately measured for $C_{11}H_{10}N_2O_2$, and an ion at *m/z* 143 ($C_9H_7N_2$) gave evidence for the loss of a carbomethoxy group. The ^1H NMR spectrum was almost deceptively simple, showing four downfield aromatic protons (doublets at 8.84 and 8.79 ppm; singlets at 9.25 and 9.65 ppm), an aromatic methyl singlet at 3.11 ppm, and the carbomethoxymethyl singlet at 4.02 ppm. The strong aromatic field currents were clearly displaying a profound effect on the chemical shifts of the planar molecule. Two-dimensional NMR experiments (COSY and NOESY) established the relationships between the substituents. Thus, NOE effects were observed between the aromatic proton at 9.65 ppm and the aromatic methyl, and the proton at 9.25 ppm showed an NOE with the carbomethoxymethyl singlet at 4.02 ppm. On this basis, the structure of neozeylanicine was proposed as **70**; the proton assignments are shown on **109** (*64*). The structure is the same as that deduced for the degradation product scaevodimerine B (**72**) (see Section II.A.35) (*69*). Cantleyine (**16**) was also isolated (*44*).

*50. (3-Pyridyl)-1-ethanol (**111**)*

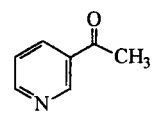
The aerial parts of *Melodinus celastroides* (Apocynaceae), as well as yielding several monoterpene indole alkaloids, including tabersonine (**110**),



110 Tabersonine



111

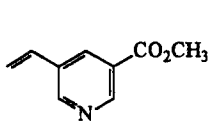


112

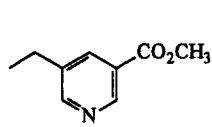
and the monoterpene alkaloid, venoterpine (**12**), afforded the simple pyridine alkaloid, (±)-(3-pyridyl)-1-ethanol (**111**) (*66,67*), which, biogenetically, is probably a member of the monoterpene alkaloid series, particularly given the nature of the co-occurring alkaloids. The mass spectrum displayed a molecular ion at *m/z* 123 and fragment ions at *m/z* 108 and 80 ($M^+-C_2H_3O$). The ^1H NMR spectrum showed a methine quadruplet at 4.90 ppm coupled with a methyl doublet (J = 7.5 Hz) at 1.50 ppm. Four aromatic protons were noted [8.50 (2H), 7.80, and 7.30 ppm] and were not assigned. Consequently, the structure was assigned as (±)-(3-pyridyl)-1-ethanol (**111**) (*66*). The structure was confirmed by synthesis when reduction of 3-acetyl pyridine (**112**) with sodium borohydride afforded material identical with the natural product (*66*).

*51. 3-Carbomethoxy-5-vinyl-pyridine (**113**)*

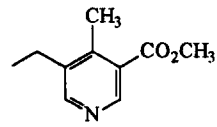
3-Carbomethoxy-5-vinyl-pyridine (**113**) was first isolated from *Nauclea diderrichii* (Rubiaceae) by McLean and Murray (*108*), and was subsequently reisolated from *Pauridiantha lyallii* (Rubiaceae) by French workers (*31*). Strictly speaking it is not a monoterpene alkaloid; however, its relationship to gentianine (**81**) is apparent. It is a low molecular weight alkaloid (M^+ 163) displaying a rather simple ^1H NMR spectrum with resonances for the vinyl group at 5.40 (J = 11 Hz), 5.85 (J = 17 Hz), and 6.70 ppm (J = 11, 17 Hz), three pyridine ring protons at 8.25, 8.70, and 9.00 ppm. and a carbomethoxy group at 3.90 ppm (*31*).



113



114



115

*52. 3-Carbomethoxy-5-ethyl-pyridine (**114**) and Related Derivatives*

When the crude secoiridoid glucoside mixture derived from the fruits of *Ligustrum vulgare* (Oleaceae) was treated with 5% sulfuric acid and then with ammonia, TLC analysis revealed the presence of 12 alkaloid-positive spots (*29*). No alkaloids were detected in the absence of ammonia. Four of these "alkaloids" were characterized. One was identical with jasminine (**97**); the other three isolates were new.

3-Carbomethoxy-5-ethyl-pyridine (**114**) was characterized spectroscopically. The mass spectrum showed a molecular ion at *m/z* 165 ($C_9H_{11}NO_2$) and resonances for an ethyl group (q, 2.7 ppm; t, 1.2 ppm) and a carbomethoxy group (s, δ_H 3.9 ppm; δ_c 52.5, 166.0 ppm). Three coupled aromatic protons were observed, two doublets at 8.9 and 8.7 ppm and a triplet (J =

2.1 Hz) at 8.1 ppm, thereby identifying the isolate as 3-carbomethoxy-5-ethyl-pyridine (**114**) (*29*).

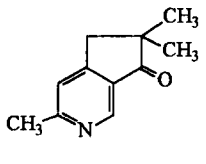
The second compound had a molecular ion at *m/z* 179 ($C_{10}H_{13}NO_2$). The triplet for H-4 was missing in the ^1H NMR spectrum, replaced by a methyl singlet at 2.5 ppm. Thus, the compound was identified as 3-carbomethoxy-5-ethyl-4-methyl pyridine (**115**) (*29*).

A third new isolate was identified as 4-hydroxy-β-phenethyl-3-carbomethoxy-5-ethyl-4-pyridinyl acetate (**100**). This structure was supported by a molecular ion at *m/z* 343 ($C_{19}H_{21}NO_5$) and the presence of an AB system (6.92 and 6.73 ppm) in the ^1H NMR spectrum, together with two methylene triplets at 2.8 and 4.26 ppm and a singlet methylene at 4.0 ppm. A second ester carbonyl was observed at 169.7 ppm (*29*).

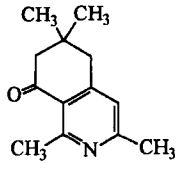
In subsequent studies (*28*), two additional alkaloidal isolates (artifacts) were characterized. The ^1H and ^{13}C NMR data for each compound were quite similar, showing resonances for carbomethoxy groups, a three-proton doublet at 1.3 ppm coupled with a sextet at 3.1 ppm, a three-proton singlet at 2.5 ppm for a C-4 methyl group, and singlet pyridine α-protons at 8.83 and 8.58 ppm. In one of the compounds, signals for a second pyridine ring were observed as doublets at 8.54 and 9.05 ppm and a triplet at 8.05 ppm. A molecular ion for this alkaloid was displayed at *m/z* 342. NOE studies indicated the proximity between the aromatic methyl and the methine sextet, and between an aliphatic methylene group and two of the coupled aromatic protons. Thus, this isolate was deduced to be 4-methyl-5,5′-[(1-methyltrimethylene)di](methylnicotinoate) (**98**) (*28*). The second isolate differed from the first through the absence of the aromatic triplet at 8.05 ppm, replaced by a methyl singlet at 2.5 ppm. Correspondingly, the aromatic proton doublets were simplified to singlets at 8.35 and 8.84 ppm. The mass spectrum showed a molecular ion at *m/z* 356, and thus the structure was concluded to be 4,4′-bis-methyl-5,5′-[(1-methyltrimethylene)di](methylnicotinoate) (**99**) (*28*).

53. Terpenoid Alkaloids from Nicotiana tabacum *Condensate*

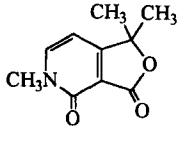
Fractions from the condensate of Burley tobacco afforded two terpenoid alkaloids, 1,3,6,6-tetramethyl-5,6,7,8-tetrahydro-isoquinolin-8-one (**116**)



116



117



118 Cerpegin

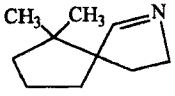
and 3,6,6-trimethyl-5,6-dihydro-7*H*-2-pyridin-7-one (**117**) (*109*). The structures were determined by spectroscopic analysis and verified by synthesis. The compounds are not regarded as derivatives of monterpene units, but rather as degradation products from a xanthophyll-type precursor (*109*).

*54. Cerpegin (**118**)*

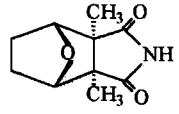
A pyridine alkaloid that has attracted a lot of synthetic attention since its isolation and characterization is cerpegin (**118**) (*110*). There is no evidence that cerpegin is derived from a monoterpene precursor; however, it may be derived in part from an isoprene unit, and thus it is included here. The plant *Ceropegia juncea* (Asclepiadaceae) is reported to be the source of the Ayurvedic medicine *soma,* extracts of which have been reported to have a broad range of biological activities, including antipyretic, local anesthetic, antiulcer, analgesic, hepatoprotective, hypertensive, and tranquilizing activities (*110*). Phytochemical investigation afforded lupeol and a new pyridine alkaloid, which was named cerpegin. Analysis indicated a molecular formula of $C_{10}H_{11}NO_3$, and IR bands were observed at 1675 and 1750 cm^{-1} for the α-pyridone and α,β-unsaturated-γ-lactone systems. A molecular ion was observed at *m/z* 193, with intense fragments at *m/z* 178 and 150. One *N*-methyl group (3.50 ppm) was observed in the ^1H NMR spectrum together with two tertiary methyl groups (1.54 ppm), and two coupled (J = 5 Hz) pyridone ring protons (at 7.43 and 6.10 ppm). The ^{13}C NMR spectrum showed carbonyl resonances at 166.2 (pyridone) and 171.9 ppm (lactone), an oxycarbon at 82.1 ppm, methyl resonances at 25.4 (2C) and 36.8 ppm, and protonated pyridone carbons at 147.7 and 98.2 ppm. Hence, the structure of cerpegin was deduced as **118** (*110*).

*55. Polyzonimine (**119**)*

Polyzonimine (**119**) was isolated as the principal constituent of the defensive secretion of the milliped *Polyzonium rosalbum* by squeezing or pinching the animals and removing the whitish secretion with filter paper, followed by preparative gas chromatography (*111*). High-resolution mass spectral analysis established a molecular formula of $C_{10}H_{17}N$, and the IR spectrum displayed a strong imine band at 1626 cm^{-1}. Two methyl singlets



119 Polyzonimine



120 Cantharidinimide

were observed at 0.90 and 0.93 ppm, together with a doublet of triplets at 3.80 ppm and a triplet for the imine proton at 7.40 ppm. The structure **119** was deduced through X-ray crystallographic analysis of the perchlorate (*111*).

*56. Cantharidinimide (**120**)*

The powdered bodies of *Mylabris mongolica,* when extracted under alkali (not NH_3) conditions afforded cantharidinimide (**120**), and the same substance was also isolated from cantharis (*Lytta vesicatoria*) (*112*). The IR spectrum showed bands at 1760, 1710, and 1698 cm^{-1}, the mass spectrum displayed an M^+ at *m/z* 195, and the ^1H NMR spectrum indicated the high symmetry of the isolate, showing a six-proton singlet at 1.25 ppm and a two-proton multiplet at 4.65 ppm for the oxymethine protons.

B. Isolation and Characterization of Known Alkaloids

The reisolations of the known monoterpene alkaloids are given in Table II (*113–165*). Some comments are worthy of mention with respect to certain of these isolations, particularly the frequent use of ammonia in the isolation process.

Actinidine (**14**) has been isolated from the roots and rhizomes of *Valeriana officinalis* (Valerianaceae) (*116–119*) and is a constituent of the volatile fraction of the voodoo lily, *Sauromatum guttatum* (Araceae) (*115*), the essential oil of *Nepeta clarkei* (Labiatae) (*114*), the leaves of *Tecoma stans* (Bignoniaceae) (*86*), and the rhizomes of *Nardostachys jatamansi* (Valerianaceae) (*113*). Several isolations from "insects" have also been reported. The insect ant, *Iridomyrmex nitidiceps,* collected on *Eucalyptus* and *Angophora* species, afforded actinidine (**14**) as a minor constituent (*166*), subsequent to its isolation as a major constituent of two species of dolichderine ants of the genus *Cnomyrma* (*167*). Two iridodials were among the major constituents (*168*). The defensive secretions of the beetle *Ontholestes murinus* (Staphylinidae) also yielded **14,** together with iridodial as the major constituent (*168*). A study of the biosynthesis of the iridodials in the defensive glands of beetle larvae indicated the presence of actinidine (**14**) in the volatile compounds from *Phaedon cochleariae* (*169*).

The seeds of *Plantago sempervirens* (Plantaginaceae) have yielded the alkaloid boschniakine (indicaine) (**121**). During the course of this work, the absolute configuration of boschniakine was determined through optical rotatory dispersion methods in comparison with other monoterpene alkaloids, including cantleyine (**3**), actinidine (**14**), and venoterpine (**12**), which have the same C-8 configuration (*120*).

TABLE II
ISOLATION OF KNOWN MONOTERPENE ALKALOIDS

Alkaloid	Plant	Reference
Actinidine (**14**)	*Nardostachys jatamansi*	*113*
	Nepeta clarkei	*114*
	Sauromatum guttatum	*115*
	Tecoma arequipensis	*36*
	T. stans	*89*
	Valeriana officinalis	*27,116–119*
Boschniakine (**121**)	*Camsis chinensis*	*120*
	Penstemon rydbergii var. *rydbergii*	*121*
	Penstemon whippleamus	*30*
	Plantago albicans	*122,123*
	P. arenaria	*61*
	P. coronopus	*122*
	P. crypsoides	*122*
	P. cylindrica	*122*
	P. major	*122*
	P. notata	*122,123*
	P. ovata	*122*
	P. psyllium	*61,122*
	P. sempervirens	*124*
	Orthocarpus luteus	*40*
	Tecoma stans	*89*
Boschniakinic Acid (**94**)	*Pedicularis macrochila*	*41*
	Plantago albicans	*122,123*
	P. coronopus	*122*
	P. crypsoides	*122*
	P. cylindrica	*122*
	P. major	*122*
	P. notata	*122,123*
	P. ovata	*122*
	P. psyllium	*122*
	Verbascum songoricum	*125*
Cantleyine (**3**)	*Alstonia angustiloba*	*126*
	A. pneumatophora	*126*
	A. patulata	*126*
	A. undulifolia	*73*
	Aspidosperma oblongum	*127*
	Castilleja miniata	*30*
	Coelospermum billardieri	*34*
	Dipsacus sylvestris	*128*
	Lasianthera austrocaledonica	*74*
	Neisosperma glomerata	*129*
	Neonauclea zeylanica	*44*
	Scaevola racemigera	*39*
	Strychnos dinklagei	*38*
	S. longicaudata	*71*
	S. potatorum	*130*
	S. variabilis	*71*

TABLE II (*continued*)

Alkaloid	Plant	Reference
3-Carbomethoxy-5-(1′-hydroxyethyl)pyridine (**122**)	*Isertia haenkeana*	*131*
5,6-Dehydroskytanthine (**123**)	*Tecoma arequipensis*	*36*
6,7-Dihydro-4-(hydroxymethyl)-2-(4-hydroxyphenethyl)-7-methyl-5*H*-2-pyridinium (**124**)	*Valeriana wallichii*	*132*
Enicoflavine (**125**)	*Swertia chirata*	*133*
	S. purpurascens	*134*
Gentianadine (**126**)	*Cephalaria gigantea*	*135*
	C. kotschyi	*135*
	C. nachiczevanica	*135*
	Gentiana olgae	*136*
Gentianamine (**127**)	*Gentiana olgae*	*136*
	G. tianshanica	*136*
	G. vvedenskyi	*136*
	Swertia connata	*136*
Gentianaine (**128**)	*Cephalaria gigantea*	*135*
	C. kotschyi	*135,137*
	C. nachiczevanica	*135,137*
Gentianidine (**79**)	*Centaurium spicatum*	*32,33*
	Gentiana regescens	*138*
	Schultesia guianensis	*70*
Gentianine (**81**)	*Alstonia lanceolata*	*139*
	A. lenormandii var. *lenormandii*	*140*
	A. lenormandii var. *minutifolia*	*140*
	Centaurium spicatum	*32,33*
	Cephalaria gigantea	*135*
	C. kotschyi	*135*
	C. nachiczevanica	*135*
	Erythraea centaurium	*141*
	Fagraea fragrans	*142*
	Faroa chalcophylla	*143*
	F. graveolens	*144*
	Gentiana caucasica var. *cardescens*	*145*
	G. pedicellata	*146*
	G. regescens	*138*
	G. scabra	*147*
	G. schistocalyx	*145*
	G. tianshanica	*136*
	G. vvedenskyi	*136*
	Schultesia guianensis	*70*
	Strychnos dinklagei	*38,148*
	S. ligustrina	*149*
	Swertia chirata	*133,150*
	S. connata	*136*
	S. davida	*151*
	S. purpurascens	*134*
	S. randaiensis	*152*

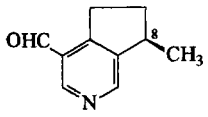
(*continues*)

TABLE II (*continued*)

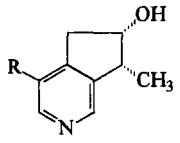
Alkaloid	Plant	Reference
Gentiocrucine (**86**)	*Schultesia guianensis*	*70*
	Swertia chirata	*133*
	S. purpurascens	*134*
Gentioflavine (**129**)	*Gentiana olgae*	*136*
	G. tianshanica	*136*
	Swertia connata	*136*
N-(4-Hydroxyphenethyl)-actinidine (**130**)	*Valeriana officinalis*	*117*
	V. wallichii	*132*
Indicamine[a]	*Plantago albicans*	*122,123*
	P. coronopus	*122*
	P. crypsoides	*122*
	P. cylindrica	*122*
	P. major	*122*
	P. notata	*122,123*
	P. ovata	*122*
	P. psyllium	*122*
Jasminine (**97**)	*Ligustrum vulgare*	*29*
	Syringa vulgaris	*54*
Leptorhabine (**4**)	*Leptorhabdos parviflora*	*80*
4-Noractinidine (**95**)	*Pedicularis macrochila*	*41*
	Penstemon whippleanus	*30*
	Tecoma stans	*89*
β-Skytanthine (**76**)	*Tecoma arequipensis*	*36*
Tecomanine (**55**)	*Tecoma arequipensis*	*36*
	T. stans	*42,89*
Venoterpine (**12**)	*Alangium chinense*	*153*
	A. handelii	*153*
	A. lamarckii	*154*
	A. platanifolium	*153*
	A. salviifolium	*153,155*
	Alstonia angustiloba	*126*
	A. pneumatophora	*126*
	A. patulata	*126*
	Alstonia vitiensis var. *vitiensis*	*156,157*
	Camptotheca acuminata	*158,159*
	Dipsacus asperoides	*160*
	Lonicera japonica	*161*
	Melodinus aenus	*162*
	M. celastroides	*66,67*
	Neisosperma glomerata	*129*
	Ochrosia nakaiana	*163*
	Striga hermonteca	*164*
	Strychnos dinklagei	*148*
	Vinca major	*165*

[a] In spite of numerous isolations, this reviewer is unable to find a definitive structure proposal for this alkaloid [see also Cordell (*1*)].

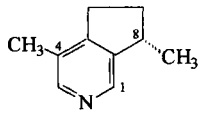
Boschniakine (**121**), indicamine (no structure reported), and boschniakinic acid (plantagonine) (**94**) were isolated from several *Plantago* species, including *P. coronopus* (*122*), *P. crypsoides* (*122*), *P. cylindrica* (122), *P. major* (*122*), *P. psyllium* (*122*), *P. ovata* (*122*), *P. notata* (*122,123*), and *P. albicans* (*122,123*). *Plantago arenaria* and *P. psyllium* also yielded boschniakine (**121**) (*61*). Boschniakinic acid (**94**) is a constituent of *Pedicularis macrochila* (Scrophulariaceae) (*41*) and *Verbascum songoricum* (Scrophulariaceae) (*125*). A *Penstemon* species, *P. whippleanus,* also yielded boschniakine (**121**), and the carbon-13 data for this alkaloid were reported for the first time (*30*). Using a new HPLC method, **121** was subsequently isolated



121 (+)-Boschniakine

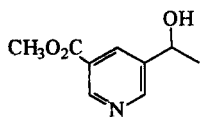


3 Cantleyine, R = CO_2CH_3
12 Venoterpine, R = H

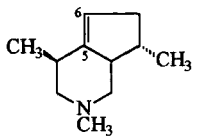


14 (-)-Actinidine

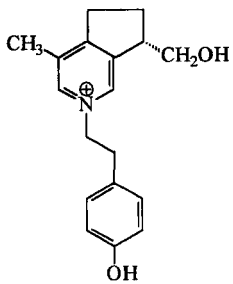
from *Penstemon rydbergii* var. *rydbergii,* but could not be detected in a sample of *P. rydbergii* var. *aggregatus* (*121*). Boschniakine (**121**) is a natural constituent of *Orthocarpus luteus* (Scrophulariaceae) (*40*), the roots of *Campsis chinensis* (Bignoniaceae) (*120*), and the leaves of *Tecoma stans* (*89*).



122

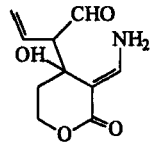


123 5,6-Dehydroskytanthine

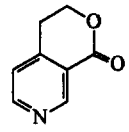


124

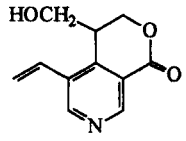
The occurrence of venoterpine (**12**) in the Apocynaceae (*1*) has substantially broadened, although the artifactual nature in certain instances is clear. Venoterpine (**12**) was isolated from *Striga hermonteca,* its first isolation from the family Scrophulariaceae (*164*), and also from the aerial parts of *Vinca major* (Apocynaceae) together with several monoterpene indole alkaloids (*165*). The same alkaloid ($[\alpha]_D$ +25°) was obtained from an



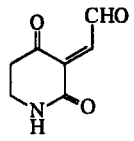
125 Enicoflavine



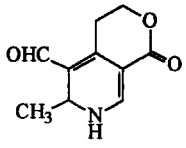
126 Gentianadine



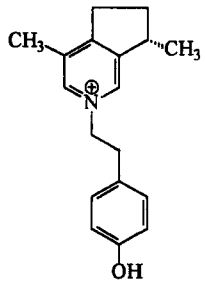
127 Gentianamine



128 Gentianaine

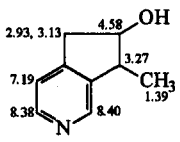


129 Gentioflavine

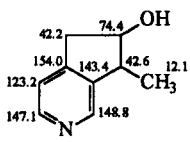


130

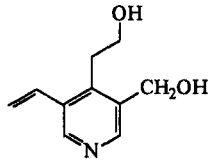
ammonia-treated extract of the seeds of *Alangium lamarckii* (Alangiaceae) (*154*), and subsequently from several other *Alangium* species, including *A. salviifolium* (*153,155*), *A. handelii, A. platanifolium,* and *A. chinense* (*153*), as well as from an ammonia-treated sample of the bark of *Neisosperma glomerata* (Apocynaceae) (*129*). ^{1}H NMR data were reported for a sample of venoterpine isolated from *Lonicera japonica* (Caprifoliaceae) (*161*), and these data, together with the ^{13}C NMR assignments (*126*) are shown in structures **131** and **132,** respectively. The $[\alpha]_D$ of this material was somewhat lower (+13°) than that (+27°) reported previously (*170*). From an ammonia-treated sample of the leaves of *Melodinus aenus* (Apocynaceae), venoter-



131



132



133

pine (**12**) and a range of indole alkaloids was isolated (*162*), and the aerial parts of *M. celastroides* have also yielded **12** (*66,67*), although in this case the $[\alpha]_D$ was a little higher (+36°) (*66*). The fruits of *Camptotheca acuminata* (Nyssaceae), an important source of camptothecin and derivatives, also yielded **12** (*159*), and the same alkaloid was also isolated from the roots of *C. acuminata,* where the $[\alpha]_D$ was 21.3° with no sign of rotation recorded

(*158*). The stem bark and twigs of *Alstonia vitiensis* var. *vitiensis* (Apocynaceae) (*156,157*), the roots of *Dipsacus asperoides* (Dipsacaceae) (*160*), the bark of *Ochrosia nakaiana* (Apocynaceae) (*163*), and the stem bark of *Strychnos dinklagei* (*133*) have also yielded **12.**

Specific attention has been paid to the absolute configuration of venoterpine (*126*). The absolute configuration previously deduced, **12,** rested on a CD study (*171*), with the result that the configuration was the opposite to that of cantleyine (**3**), which was chemically correlated with loganin (**1**) (*172*). When venoterpine and cantleyine were isolated from the same plants, namely, *Alstonia angustiloba, A. pneumatophora,* and *A. patulata* (*126*), the opportunity arose to reinvestigate this anomalous situation through chemical correlation.

Cantleyine (**3**) ($[\alpha]_D$ −40°) was hydrolyzed with barium hydroxide, and the resulting acid was subjected to flash pyrolysis at 460°C (*126*). The product ($[\alpha]_D$ +40°) was identical to natural venoterpine ($[\alpha]_D$ +32°). On this basis, it was concluded that venoterpine has the same absolute configuration at C-8 as that of loganin (**1**) and therefore has the structure **12** (*126*).

Cantleyine (**3**) was isolated from the trunk bark of *Lasianthera australocaledonica* (*74*), from the stem bark and leaves of *Alstonia undulfolia* (Apocynaceae) (*73*), from the seeds of *Aspidosperma oblongum* (Apocynaceae) (*127*), from the bark of *Neiosperma glomerata* (Apocynaceae) (*129*), from the leaves of *Dipsacus sylvestris* (Dipsacaeae) (*128*), from the aerial parts of *Coelospermum billardieri* (Rubiaceae) (*34*) and *Scaevola racemigera* (Goodeniaceae) (*39*), and also, in 0.1% yield, from the powdered root bark of *Strychnos potatorum* (Loganiaceae) (*130*). Ammonia was used in the processing phase of each of these extraction procedures. When extracts of the flower heads, bracts, stems, and leaves of *Castilleja miniata* (Scrophulariaceae) were treated with ammonia (not with NaOH) during work-up for an alkaloid fraction, cantleyine (**3**) was detected by NH_3-chemical ionization GC-MS (*173*) and subsequently isolated (*30*).

Gentianine (**81**) is the major alkaloid of the aboveground parts of *Centaurium spicatum* (Compositae) (*32,33*). Gentianidine (**79**) co-occurs (*32,33*) and is also the dominant alkaloid in *Erythraea centaurium* (Gentianaceae) (*141*), *Fagraea fragrans* (Loganiaceae) (*142*), *Gentiana pedicellata* (*147*), *G. scabra* (*146*), and *G. caucasica* va. *cardescens,* and *G. schistocalyx* (*145*). Gentianine (**81**) and gentianidine (**79**) were isolated from an alcoholic extract of the aerial parts of *Gentiana regescens* (*138*). Gentianine (**81**) co-occurs with gentianadine (**126**) and gentianaine (**128**) in the roots of three species of *Cephalaria* (Dipsacaeae), *C. kotchyi* (*135,137*), *C. nachiczevanica* (*135,137*), and *C. giganteae* (*135*). Gentianine (**81**), gentiocrucine (**86**), and gentianidine (**79**) were isolated from an alcoholic extract of *Schultesia guianensis* (*70*). Gentianine (**81**) and gentianamine (**93**) were isolated from

the aerial parts of *Gentiana vvedenskyi, G. tianshanica,* and *Swertia connata* (*136*). Gentianamine (**93**), gentianadine (**79**), and gentioflavine (**129**) co-occurred in *Gentiana olgae* (*136*), and gentioflavine was also present in *G. tianshanica* and *S. connata* (*136*). Ammonia treatment was not employed in these isolations (*136*).

Gentianine (**81**) was isolated from the petroleum ether extract of the whole plant of *Swertia chirata;* however, enicoflavine (**125**) and gentiocrucine (**86**) were isolated from the ethanol extract only after treatment with ammonia (*133*). Gentianine (**81**) was isolated from ammonia-treated samples of the leaves and stem bark of two varieties of *Alstonia lenormandii* (Apocynaceae) (*140*), the stem bark of *A. lanceolata* (*139*), the stem bark of *Strychnos dinklagei* (*133*) , the trunk of *S. ligustrina* (*147*), and the whole plant of *Faroa chalcophila* (Gentianaceae) (*143*), *F. graveolens* (*144*), *Swertia chirata* (Gentianaceae) (*150*), *S. davidii* (*151*), and *S. randaiensis* (*152*). In addition to gentianine, *S. purpurascens* also yielded the known alkaloids gentiocrucine (**86**) and enicoflavine (**125**) (*134*). As part of a study on the ^{13}C NMR parameters of iridoids, the ^{13}C NMR data for gentianine (**81**) and gentiadiol (**133**) were obtained (*174*).

4-Noractinidine (**95**) was tentatively identified (UV, MS) as being present in the flowers of *Penstemon whippleanus* (*30*), although other isomers could not be excluded. It was also detected in the leaves of *Tecoma stans* (*89*) and the aerial parts of *Pedicularis macrochila* (Scrophulariaceae) (*41*).

Two quaternary alkaloids, derivatives of actinidine and 8-hydroxyactinidine, previously isolated from *Valeriana officinalis* (1), *N*-(4-hydroxyphenethyl)-actinidine (**130**) and 6,7-dihydro-4-(hydroxymethyl)-2-(4-hydroxyphenethyl)-7-methyl-5*H*-2-pyridinium (**124**), were isolated from *Valeriana wallichii* (*132*).

3-Carbomethoxy-5-(1′-hydroxyethyl)pyridine (**122**), originally isolated from *Nauclea diderrichii* (Rubiaceae) (*175*), was reisolated from *Isertia haenkeana* (Rubiaceae) (*131*) and the ^{13}C NMR data reported. Although the isolate was optically active ($[\alpha]_D$ +23°), no absolute configuration was deduced (see Section III.E).

Jasminine (**97**) has been isolated from two new sources in the Oleaceae, *Ligustrum vulgare* (*29*) and *Syringa vulgaris* (*54*).

III. Synthesis and Semisynthesis

There has been substantial progress in the synthesis of the monoterpene pyridine alkaloids in the past 23 years. Particularly, this progress has oc-

curred in three areas: the chiral synthesis of the natural and unnatural alkaloids, the development of versatile intermediates that can act as synthons for several closely related alkaloids, and investigations of the controlled reactions of iridoids with bacterial preparations and with glucosidase and/or ammonia.

A. Actinidine and Derivatives

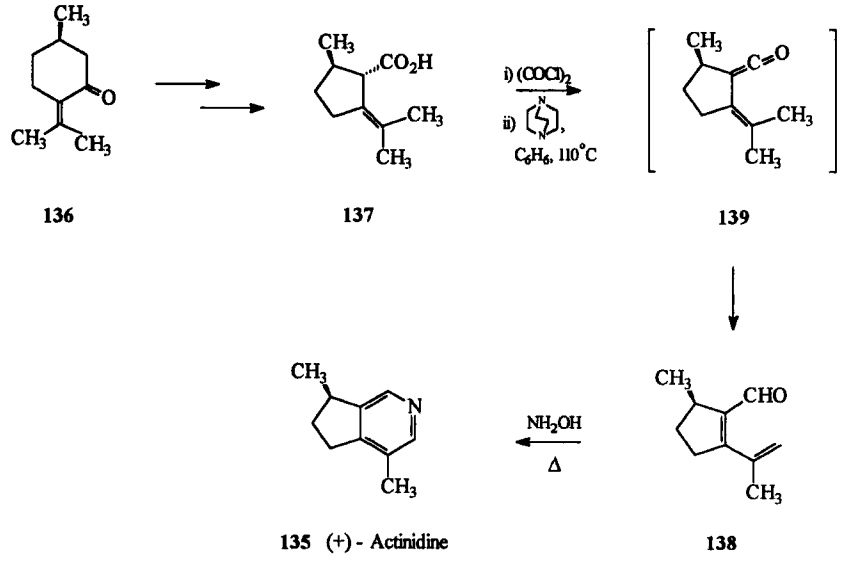
1. Actinidine (14)

As noted previously (1), actinidine (**14**) was first synthesized by Sakan and colleagues (*176*) in racemic form. Interest in this area has continued, and several syntheses of racemic (**134**) and chiral actinidine (**14**) have appeared (*177–183*).

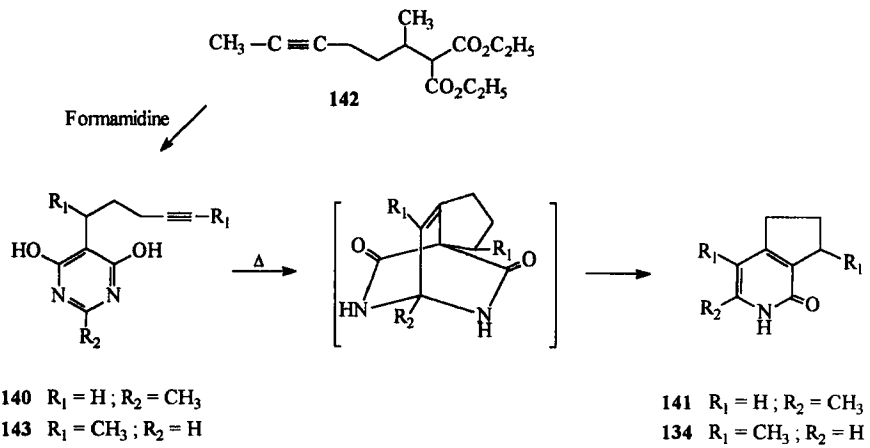
The first chiral synthesis of actinidine, albeit of the antipode **135,** was described by Wuest and colleagues (*177*), and resulted from a program aimed at examining the chemistry of vinylketenes. (+)-Pulegone (**136**) was used as the starting material and was converted, through a known procedure (*184*), to (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid (**137**). Treatment of **137** with oxalyl chloride followed by heating at 110°C with 1,4-diazabicyclo[2.2.2]octane afforded the aldehyde **138** in 40% yield. This reaction presumably occurs through a [1,5] sigmatropic shift in the intermediate ketene **139.** Treatment with hydroxylamine at reflux gave (+)-actinidine (**135**) in 90% yield (Scheme 1) (*177*). The isolate showed $[\alpha]_D$ +10.8° and was the optical antipode of natural actinidine (**14**).

(±)-Actinidine (**134**) was synthesized by Sammes and co-workers (*178*) using as a key step a thermal intramolecular cycloaddition of a substituted pyrimidine by an acetylene moiety. In the *nor* series, thermolysis of the pyrimidine **140** at 200°C gave the substituted pyridone **141** directly. Condensation of the acetylene **142** with formamidine proceeded in high yield to afford the pyrimidine **143,** which, on treatment with phosphoryl chloride and catalytic hydrogenation, afforded (±)-actinidine (**134**) (Scheme 2) (*178*).

Another intramolecular approach to the formation of actinidine was developed by Nitta and co-workers (*179*). Recognizing the thermal rearrangement of 2,6-dimethylphenyl propargyl ether (**144**) to 3,7-dimethylindan-2-one (**145**) (*185*), a similar rearrangement was envisaged for the corresponding pyridine derivative **146.** This compound was synthesized in two steps, in very high yield, from 3,5-dimethyl-4-nitro-pyridine-*N*-oxide (**147**) on reaction with propargyl alcohol in the presence of K_2CO_3 in refluxing acetonitrile, followed by deoxygenation with phosphorous trichloride. Thermolysis at 450°C and distillation afforded 3,7-dimethyl-5-aza-indan-2-one (**148**) in



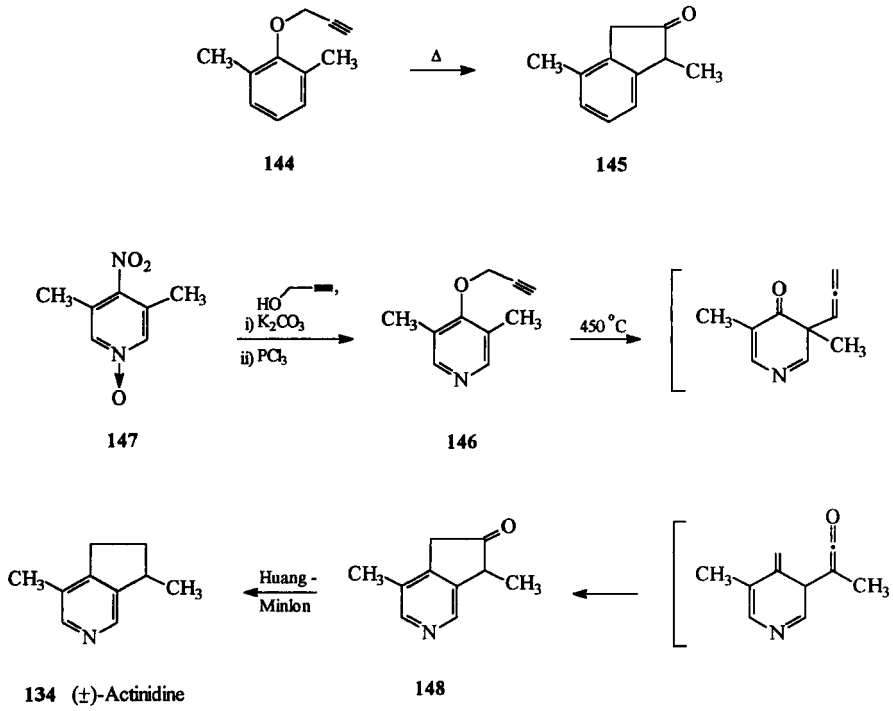
SCHEME 1. Wuest *et al.* synthesis of (+)-actinidine (**135**) (*177*).



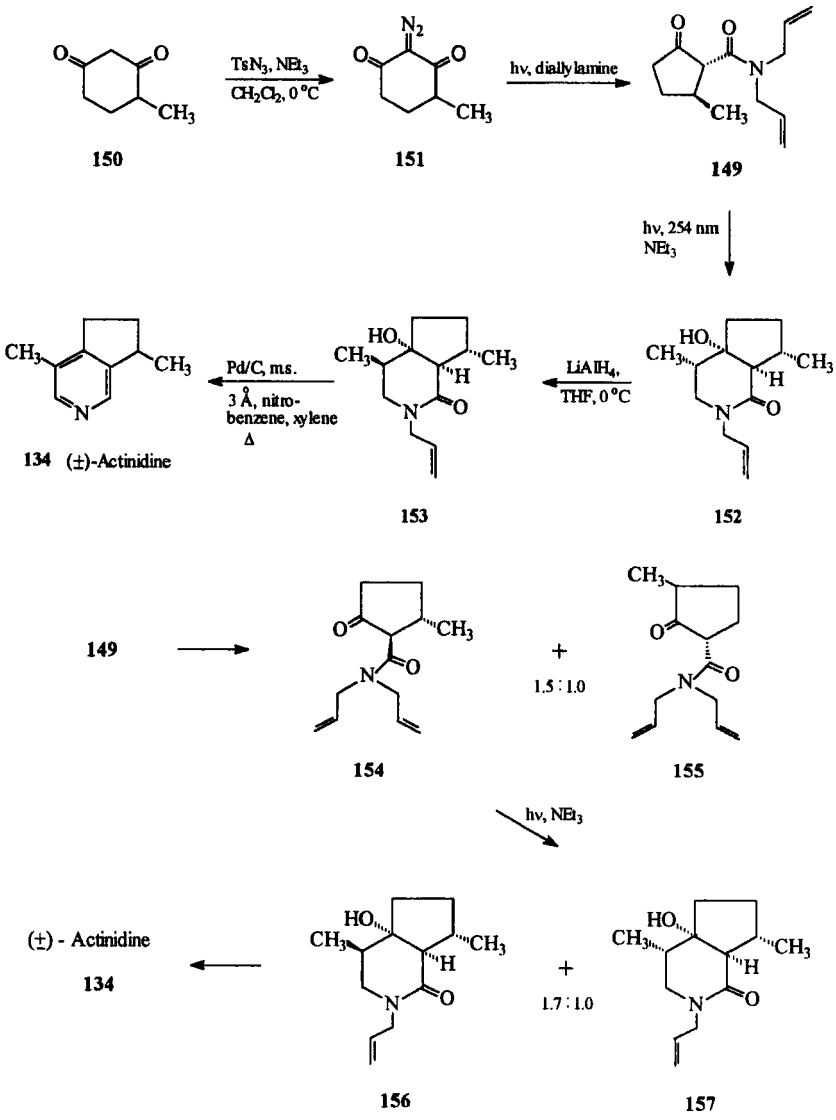
SCHEME 2. Sammes *et al.* synthesis of (±)-actinidine (**134**) (*178*).

55% yield. Huang–Minlon reduction afforded (±)-actinidine (**134**) in 63% yield (Scheme 3) (*179*).

A further intramolecular approach to actinidine, this time a photoreductive cyclization, was described by Cossy and Belotti (*180*). Six-membered lactams can be formed by irradiation of 2-oxo-cycloalkanecarboxamides (*186*). Retrosynthetic analysis suggested that such a reaction on **149** would lead to an intermediate convertible to actinidine. Treatment of 6-methylcyclohexane-1,3-dione (**150**) with tosylazide in the presence of triethylamine gave the azidodiketone **151,** and Wolff rearrangement in the presence of diallylamine gave the desired *N,N*-diallyl-2-oxocyclopentanecarboxamide (**149**). Irradiation in the presence of triethylamine for 4 h gave the lactam **152** in 50% yield, which was reduced with $LiAlH_4$ to afford the *N*-allylpiperidine **153** in 70% yield. Deprotection, dehydration, and dehydrogenation in the presence of nitrobenzene afforded (±)-actinidine (**134**) in 35% yield (Scheme 4) (*180*). Further investigation of this reaction sequence



SCHEME 3. Nitta and co-workers synthesis of (±)-actinidine (**134**) (*179*).



SCHEME 4. Cossy and Belotti synthesis of (±)-actinidine (**134**) (*180*).

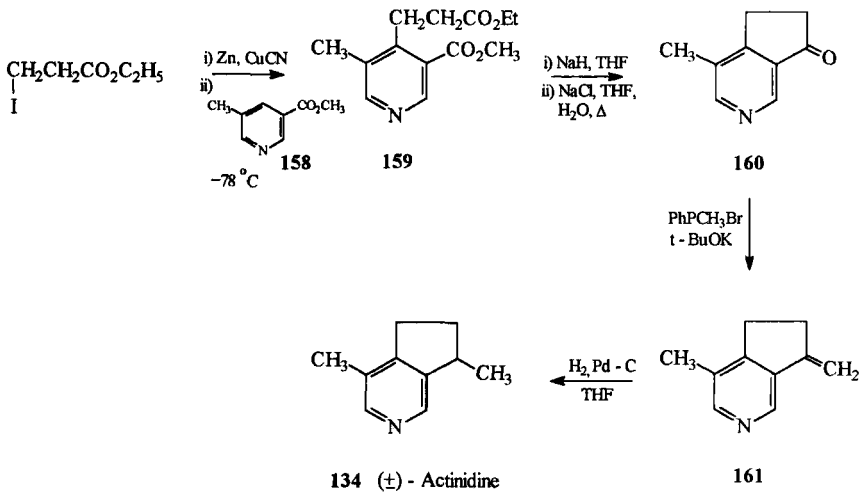
(*182*) revealed that the lactam **152** was a mixture of regioisomers (1.5 : 1.0) in which the separated compounds **154** and **155** were the isomers having a *trans* relative configuration at C-1 and C-5. Irradiation of **154** gave a mixture

of the lactam isomers **156** and **157** in the ratio of 1.7 : 1.0, which was separated for the purposes of characterization or carried through as a mixture to (±)-**134** by dehydrogenation with Pd/C in nitrobenzene (*182*).

Using functionalized 3,4-dialkyl pyridines, Shiao and co-workers have described an alternative synthesis of actinidine (*183*) based on mixed metal reactions with 1-(alkoxycarbonyl)pyridinium salts. Thus, ethyl 3-iodopropionate was successively treated with zinc and cuprous cyanide, and after being cooled to −78°C the resulting solution was reacted with 5-methylmethylnicotinoate (**158**) and the mixture warmed to room temperature to afford **159.** Cyclization and decarboxylation was effected with sodium hydride followed by heating in aqueous solution to afford **160.** A Wittig reaction on **160** gave the olefin **161,** and catalytic hydrogenation (Pd–C) afforded (±)-actinidine (**134**) (Scheme 5) (*183*).

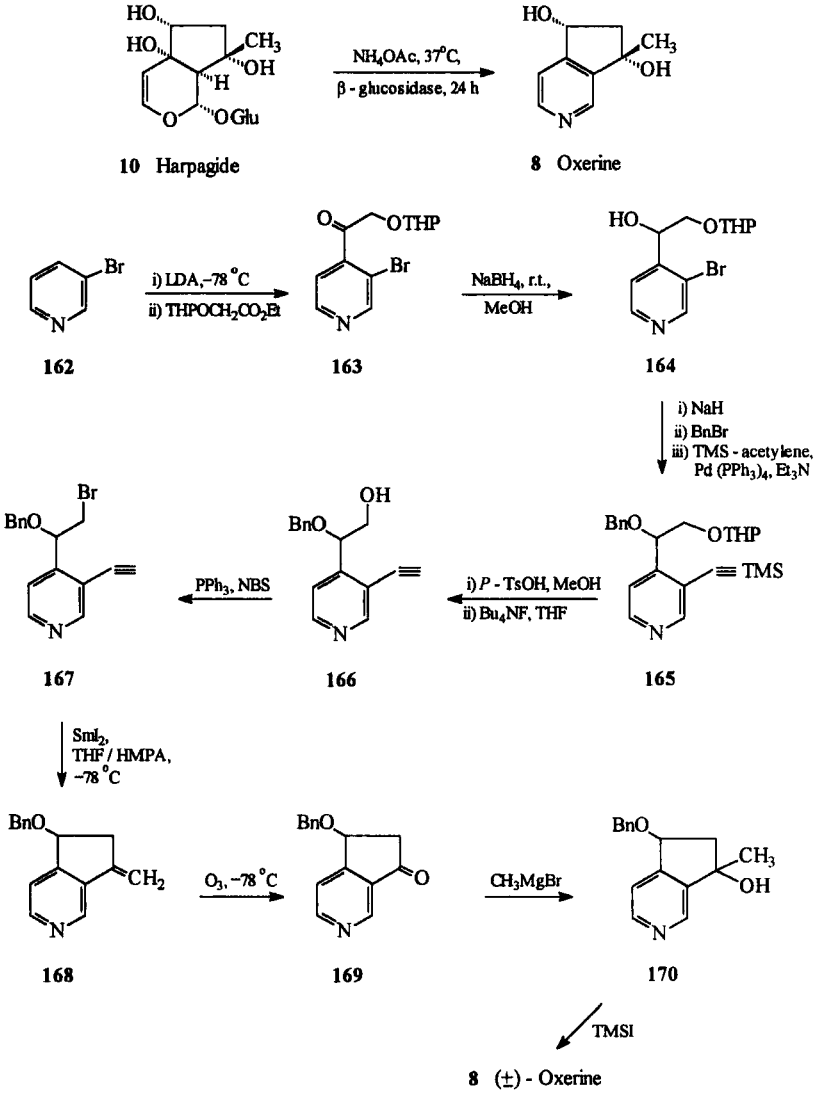
2. Oxerine (8)

As described in Section II,A.5, the spectroscopic data for oxerine could not define the configurations at the two stereocenters. These were determined, and the structure confirmed, through semisynthesis from the co-occurring iridoid harpagide (**10**) (*65*). A solution of **10** in 30% aqueous ammonium acetate was treated with β-glucosidase at 37°C for 24 h to afford oxerine, identical to the natural material, in very low yield. Thus, the relative and absolute configuration of oxerine was deduced to be **8** (*65*).



SCHEME 5. Shiao and co-workers synthesis of (±)-actinidine (**134**) (*183*).

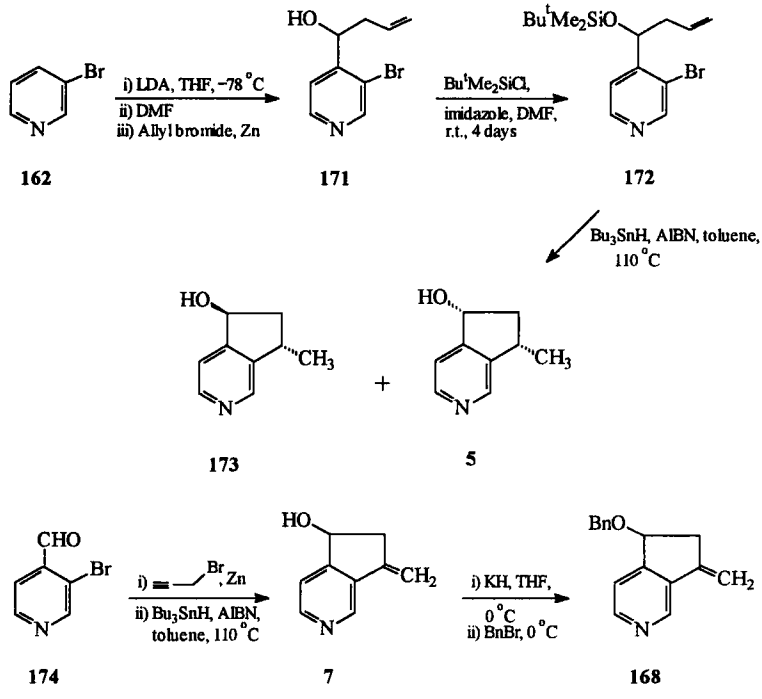
The first total synthesis of (±)-oxerine (**8**) was performed by Aoyagi and co-workers (*187*), and is shown in Scheme 6. The route is based on the use of a samarium iodide–mediated intramolecular cyclization as the key



SCHEME 6. Aoyagi and co-workers synthesis of oxerine (**8**) (*187*).

reaction. Alkylation of the lithium salt of 3-bromopyridine (**162**) with ethyl 2-tetrahydropyranyloxyacetate gave **163,** which was reduced in quantitative yield to **164.** Protection as the benzyl ether, followed by coupling with trimethylsilyl acetylene in the presence of palladium, gave **165.** Removal of the THP ether with *para*-toluene sulfonic acid and of the trimethylsilyl group with tetrabutyl ammonium fluoride gave the acetylenic alcohol **166,** which was converted to the bromide **167** with *N*-bromosuccinimide-triphenylphosphine. When the bromide **167** was treated with samarium iodide in the presence of HMPA, the cyclopentano[2,3-*c*]pyridine **168** was produced in 86% yield. Ozonolysis afforded a ketone, **169,** which was reacted with methyl magnesium bromide to afford the protected alcohol **170.** The relative configurations were established through a NOESY experiment. Debenzylation to afford (±)-oxerine (**8**) was accomplished with trimethylsilyl iodide (Scheme 6) (*187*).

Recently, a second synthesis has appeared in which a 3-pyridyl radical cyclization was used as a key step (Scheme 7) (*188*). Formylation of 3-

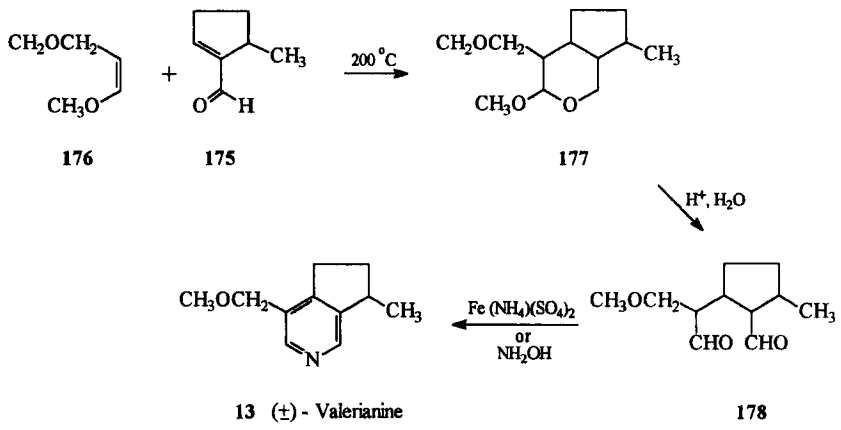


SCHEME 7. Jones and Fiumana formal total synthesis of oxerine (**8**) (*188*).

bromopyridine (**162**) at the 4-position was followed by treatment with activated zinc powder and allyl bromide at room temperature to afford the bromoalcohol **171,** which was protected as the *t*-butyldimethylsilyl derivative **172.** Reaction with tributyltin hydride/AIBN in toluene at 110°C gave an inseparable mixture of the isomers **5** and **173** in 88% yield with the *cis* isomer predominating. These compounds may be regarded as deoxyoxirenes, and one should be (±)-coelobillardierine, isolated previously (*34*). For the synthesis of oxerine itself, a dehydro derivative **7** (*34*) was required. Reaction of 3-bromo-pyridine-4-carboxaldehyde (**174**) with propargyl bromide and zinc followed by reaction with *t*-butyl tin hydride under the same conditions afforded **7.** Attempts to convert this compound directly to **8** failed, as did an ozonolysis/methylation sequence. Consequently, **7** was converted into its benzyl ether **168,** which had previously (*187*) been converted to **8.** Thus a formal synthesis of **8** was completed (*188*).

3. Valerianine (13)

Valerianine (**13**) was synthesized in racemic form by Franck and co-workers (*75*) in 1970. Diene condensation of 5-methyl-1-cyclopentene carboxaldehyde (**175**) with 1,3-dimethoxy propene (**176**) afforded the tetrahydropyranyl ether **177,** which, on acid hydrolysis, afforded 9-methoxy-iridodial (**178**). This compound was not isolated, but was converted directly to (±)-valerianine **13**) with either $Fe(NH_4)_2SO_4$ or NH_2OH (Scheme 8)



SCHEME 8. Franck and co-workers synthesis of (±)-valerianine (**13**) (*75*).

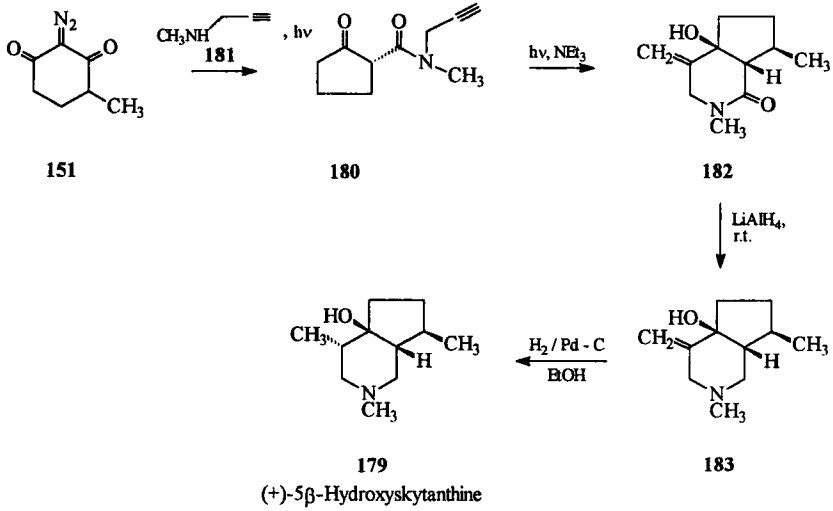
(*75*). (±)-Actinidine (**134**) could also be prepared from **178** by steam distillation in the presence of base after treatment with $Fe(NH_4)_2SO_4$ (*75*).

B. Skytanthines

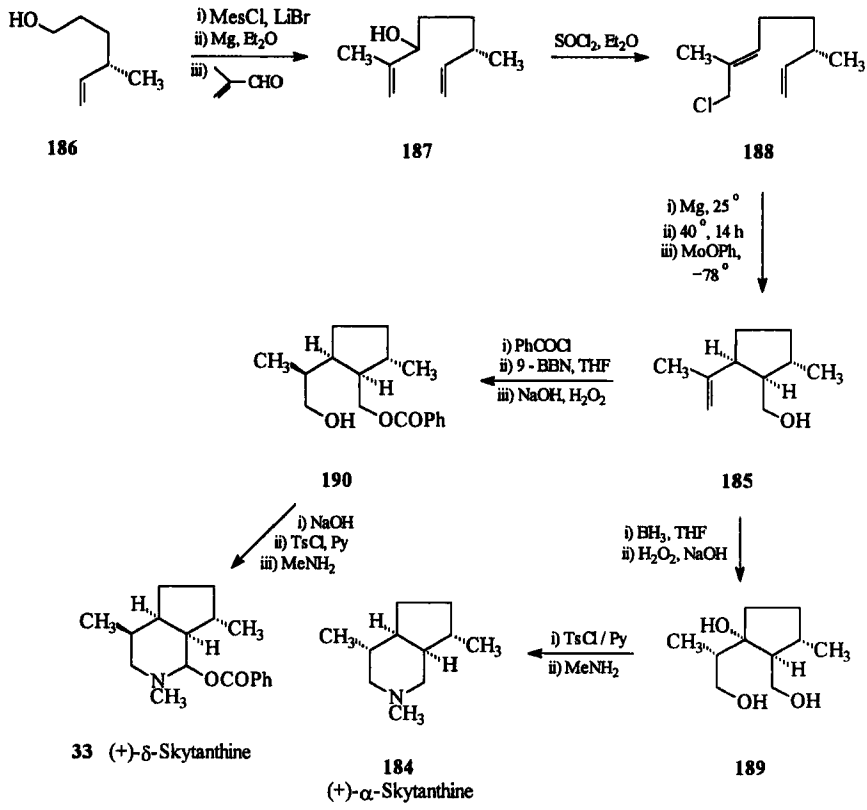
The reaction sequence used for (±)-actinidine (**134**) by Cossy and Belotti (*182*) was elaborated to afford the first synthesis of (±)-5β-hydroxy-skytanthine (iso-oxyskytanthine) (**179**) (*182,189*). Irradiation of **180,** derived from irradiating **151** in the presence of *N*-methylpropargylamine (**181**), led to only a single isomer **182.** Reduction of **182** with $LiAlH_4$ at room temperature afforded the olefin **183,** which on catalytic hydrogenation (Pd–C) gave (±)-5β-hydroxy-skytanthine (iso-oxyskytanthine) (**179**) in 87% yield (Scheme 9) (*182,189*).

The concept of Mg-ene reactions (*190*) was extended by Oppolzer and co-workers to the chiral synthesis of (+)-α-skytanthine (**184**) and (±)-δ-skytanthine (**33**) through a route in which the en-ol **185** is a key intermediate (Scheme 10) (*191*).

The synthesis begins with the alcohol **186,** which was converted into its bromide, metallated with Mg and the resulting Grignard reacted with acrolein to afford the dienol **187** as a 1 : 1 diastereomeric mixture. Heating with



Scheme 9. Cossy and Belotti synthesis of (±)-5β-hydroxy-skytanthine (**179**) (*182*).



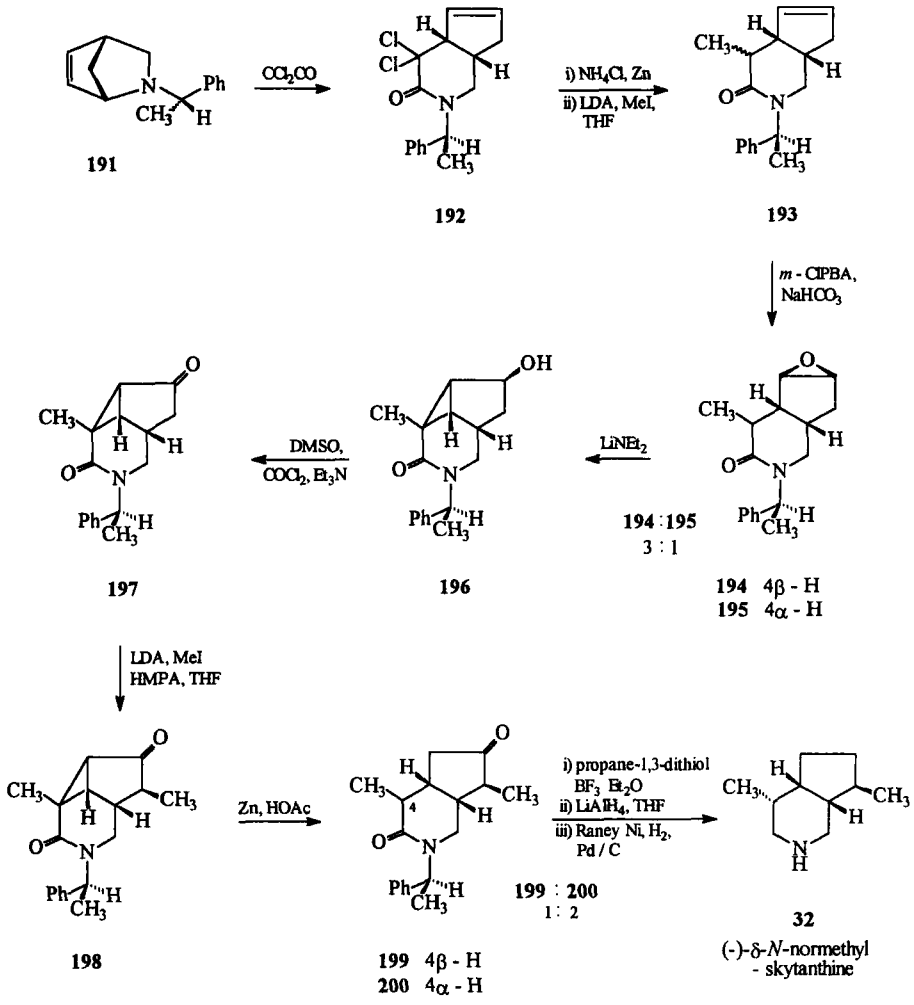
SCHEME 10. Oppolzer and co-workers synthesis of (+)-α-skytanthine (**184**) and (+)-δ-skytanthine (**33**) (*191*).

thionyl chloride gave the allyl chloride **188,** which was added to Mg powder in ether, and the resulting solution was refluxed for 14 h. Oxidative trapping with MoOPh at −78°C gave a mixture of cyclized alcohols in 58% yield. The major isomer (49% yield from **188**) was **185.** Hydroboration/oxidation gave a mixture of epimers from which (+)-iridodiol (**189**) was isolated as the major compound. Using a previous procedure (*192*), treatment of **189** with tosyl chloride/pyridine and methylamine afforded (+)-α-skytanthine (**184**) in 67% yield (Scheme 10) (*191*).

On the other hand, benzoylation of **185** followed by hydroboration with 9-BBN and oxidation afforded the opposite C-4 epimer **190,** which, after

hydrolysis and the tosyl chloride/pyridine and methylamine sequence, afforded (+)-δ-skytanthine (**33**) (Scheme 10) (*191*).

Following the isolation of (−)-δ-*N*-nor-methylskytanthine (**32**) (*36*), Pombo-Villar and co-workers described a synthesis of the alkaloid in chiral form (Scheme 11) (*193*). A ketene amino-Claisen rearrangement (*194*) was



191 192 193 194 195 196 197 198

SCHEME 11. Pombo-Villar and co-workers synthesis of (−)-δ-*N*-nor-methylskytanthine (**32**) (*193,195*).

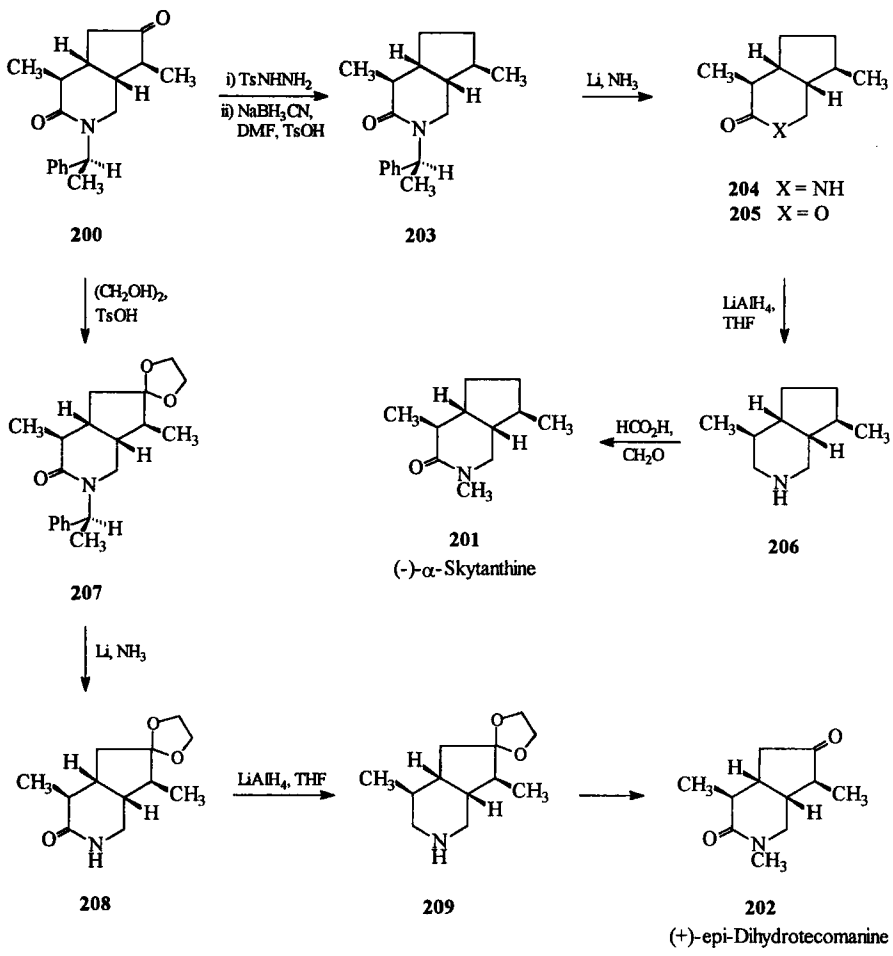
a key reaction step in producing the azabicyclo[4.3.0]nonane skeleton. Thus, treatment of the (*S*)-phenethylamine derivative **191** with dichloroketene at 2°C gave the lactam **192.** Reductive dehalogenation with zinc and ammonium chloride followed by monomethylation of the lithium salt led to a mixture of epimers at C-5 (**193**), which was treated with *meta*-chloroperbenzoic acid (*m*-CPBA) in the presence of $NaHCO_3$ to give the epoxides **194** and **195** in the ratio 3:1.

The mixture was treated with lithium diethylamide to afford the same alcohol **196,** which was subjected to Swern oxidation and the resulting ketone **197** monomethylated to afford a versatile intermediate **198.** Zinc in acetic acid resulted in reductive ring opening of the cyclopropane to give a 1:2 mixture of the two diastereomeric bicycloketoamides **199** and **200** in the ratio 1:2. The ketone of **199** was protected as the dithiane and the amide reduced with $LiAlH_4$ in refluxing THF. Raney nickel treatment, followed by Pd–C reduction under pressure, removed the benzylic group and afforded (−)-δ-*N*-normethylskytanthine (**32**) identical ($[\alpha]_D$ −22.7°) with the natural product ($[\alpha]_D$ −21.5°) (Scheme 11) (*193*). This work was published subsequently with full experimental detail and the strategy extended to other related compounds (*195*).

Thus, Cid and Pombo-Villar have also described the synthesis of (−)-α-skytanthine (**201**) and (+)-epi-dihydrotecomanine (**202**) from the common intermediate **200** (*195*). Treatment of **200** with (4-toluenesulfonyl)hydrazide and *in situ* reduction with sodium cyanoborohydride afforded the piperidone **203** in 44% yield. Debenzylation with Li–NH_3 followed by reduction of the lactam **204** [which is formally an *aza*-analog of (+)-isoiridomyrmecin (**205**)] with $LiAlH_4$ gave **206,** and *N*-methylation under Eschweiler–Clarke conditions afforded (−)-α-skytanthine (**201**) (Scheme 12) (*195*).

Alternatively, protection of the carbonyl group of **200** as a dioxolane, **207,** through treatment with ethylene glycol (74% yield), was followed by debenzylation (Li–NH_3) in 90% yield. The resulting lactam **208** was reduced with $LiAlH_4$ to **209** which afforded (+)-epi-dihydrotecomanine (**202**) in 61% yield by treatment with formaldehyde in HCOOH and acid hydrolysis of the ketal (Scheme 12) (*195*).

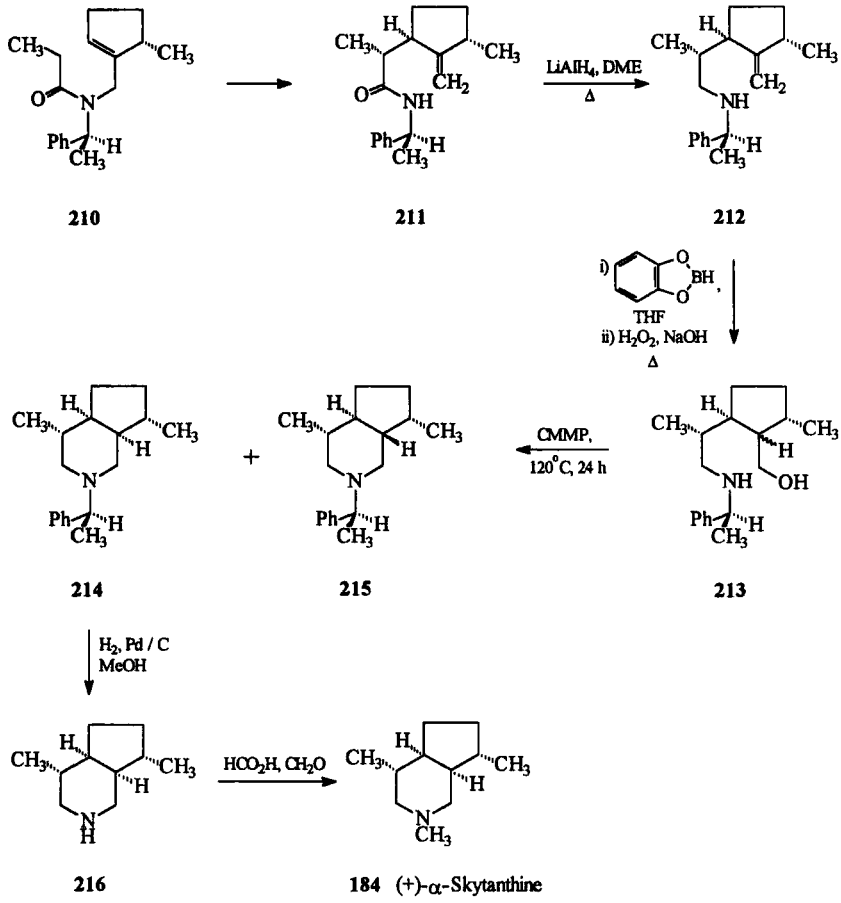
The Mitsunobu reaction has been used by Itô and co-workers as a key step in the synthesis of unnatural (+)-α-skytanthine (**184**) (*196*). The chiral amide **210** (*197*) was subjected to an aza-Claisen rearrangement, and the resulting amide **211** was reduced with $LiAlH_4$ to afford the amine **212** in 80% yield. A hydroboration–oxidation sequence led to a mixture of amino alcohols **213,** which was heated at 100°C for 24 h in the presence of cyanomethylene–trimethylphosphorane (CMMP) to yield a 92:8 mixture of *cis*- and *trans*-fused isomers **214** and **215** in 81% yield from **212.**



SCHEME 12. Pombo-Villar and co-workers synthesis of (−)-α-skytanthine (**201**) and (+)-epi-dihydrotecomanine (**202**) (*195*).

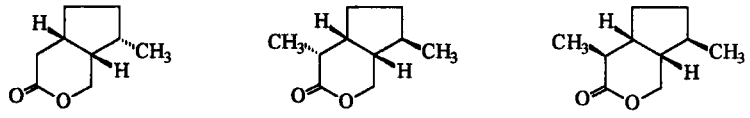
Debenzylation afforded (+)-nor-α-skytanthine (**216**), which was methylated (CH_2O,HCOOH) in 82% yield to afford (+)-α-skytanthine (**184**), $[\alpha]_D$ +70°, antipodal to the natural product, $[\alpha]_D$ −75° (Scheme 13) (*196*).

It should also be mentioned that substantial synthetic effort has been directed towards the formation of monoterpene lactone derivatives such as boschnialactone (**217**), iridomyrmecin (**218**), and isoiridomyrmecin (**205**)



210 211 212 214 215 213 216 184 (+)-α-Skytanthine

SCHEME 13. Itô and co-workers synthesis of (+)-α-skytanthine (**184**) (*196*).



217 (+)-Boschnialactone 218 (+)-Iridomyrmecin 205 (+)-Isoiridomyrmecin

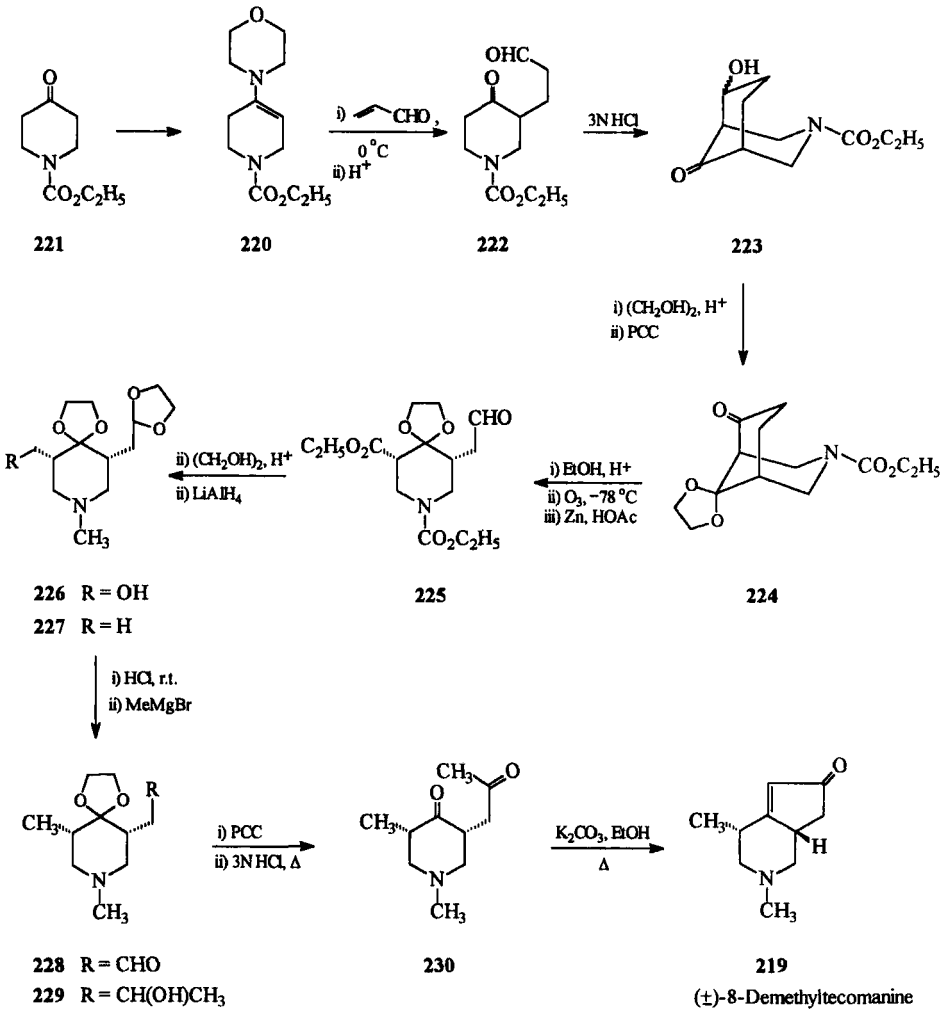
(see, for example, references *197* and *198* and references therein). These compounds are very closely related structurally to a number of monoterpene pyridine alkaloids.

C. Tecomanine and Derivatives

The hypoglycemic effects reported for tecomanine (**55**) (*199*) have resulted in several attempts to synthesize the parent alkaloid and/or related derivatives. The earliest of these attempts was published in 1979 and is a stereoselective synthesis of racemic 8-demethyltecomanine (**219**) (*200*) by Imanishi and co-workers. The synthesis (Scheme 14) takes advantage of the *cis* relationship of the C-4 methyl group and C-8 to convert the 3-azabicyclo[3.3.1]nonane system into the hydroactinidine skeleton. The morpholine enamine **220** of 1-ethoxycarbonyl-4-piperidone (**221**) was treated with acrolein at 0–5°C. Hydrolysis afforded the ketoaldehyde **22,** which was cyclized under acidic conditions (3 N HCl) to afford a diastereomeric mixture of **223.** Ketalization and oxidation of the alcohol with pyridine chlorochromate (PCC) afforded a ketone, **224,** whose enol ether was treated with ozone at −78°C and reduced to the aldehyde **225.** The amino alcohol **226** was formed when the acetal of **225** was treated with $LiAlH_4$, and the hydroxy group of **226** was replaced by hydrogen through a mesylation/NaI–zinc procedure. The doubly protected **227** was selectively hydrolyzed to the aldehyde **228,** which, on treatment with methyl Grignard, afforded the methyl carbinol **229.** Oxidation with PCC followed by hydrolysis (3 N HCl, reflux) gave a diketone (**230**), previously prepared by Jones and coworkers (*201*). An aldol condensation on this material was effected with K_2CO_3 in refluxing EtOH to afford the desired 8-demethyltecomanine (**219**) (Scheme 14) (*200*).

Attempts to extend this route to tecomanine (**55**) apparently were not successful (*200*), but in spite of this, the first synthesis of tecomanine (**55**) was also reported by Imanishi and coworkers (*202,203*), beginning with ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**231**) (Scheme 15). Reaction of **231** with methyl Grignard gave predominantly the 1,2-adduct **232,** which was heated with ethyl propenyl ether in the presence of mercuric acetate at 200° C for 3 days. The resulting alcohol was oxidized with PCC to a ketone, **233,** which was then protected. Hydroboration of the ketal **234** fortuitously gave only two secondary alcohols, **235** and **236.** Treatment with acid, oxidation with PCC, and aldol condensation (K_2CO_3/EtOH, 45°C) afforded, regioselectively and stereoselectively, the anticipated hexahydropyrindinone **237** in 88% yield. $LiAlH_4$ reduction to **238** and oxidation of the alcohol (PCC–NaOAc) afforded (±)-tecomanine (**55**) (Scheme 15) (*202*). A full paper describing the details of the synthesis has also appeared (*203*).

The first chiral synthesis of (+)-tecomanine (**55**) was described by Kametani and co-workers (Scheme 16) (*204*) and began with (−)-carvone (**239**) as the chiral starting material. Favorskii-type rearrangement of (+)-carvone



221 **220** **222** **223**

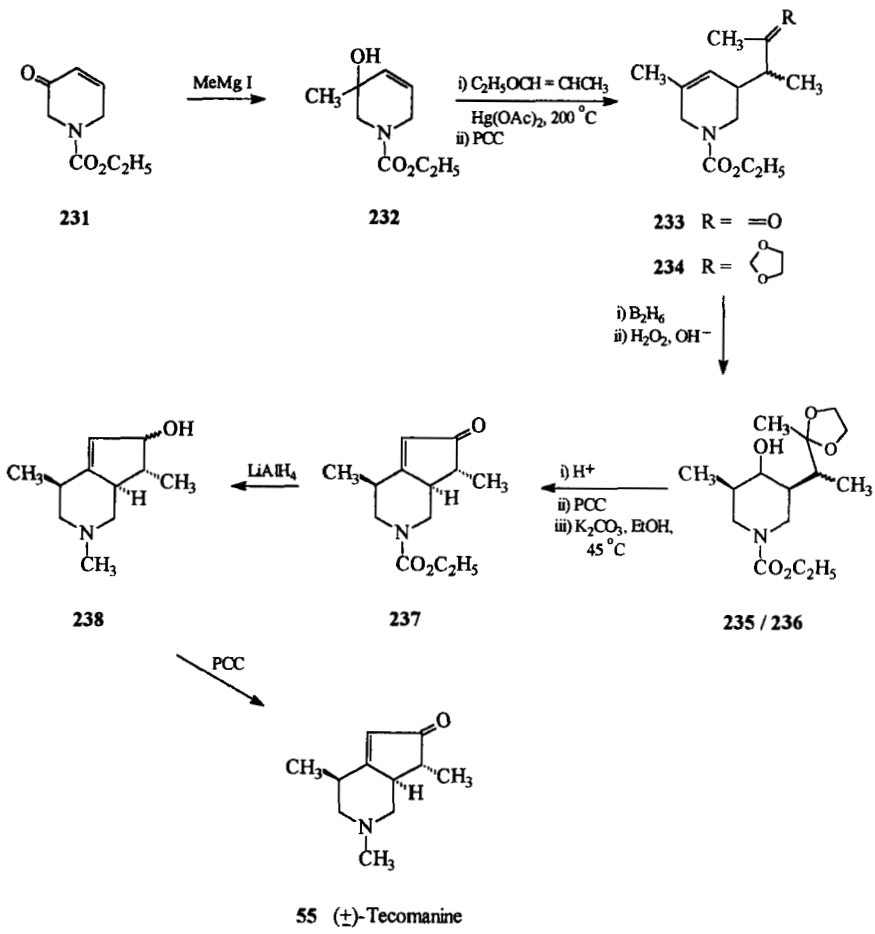
224 **225** **226** R = OH
227 R = H

228 R = CHO
229 R = $CH(OH)CH_3$

230 **219**
(±)-8-Demethyltecomanine

SCHEME 14. Imanishi and co-workers synthesis of (±)-8-demethyltecomanine (**220**) (*200*).

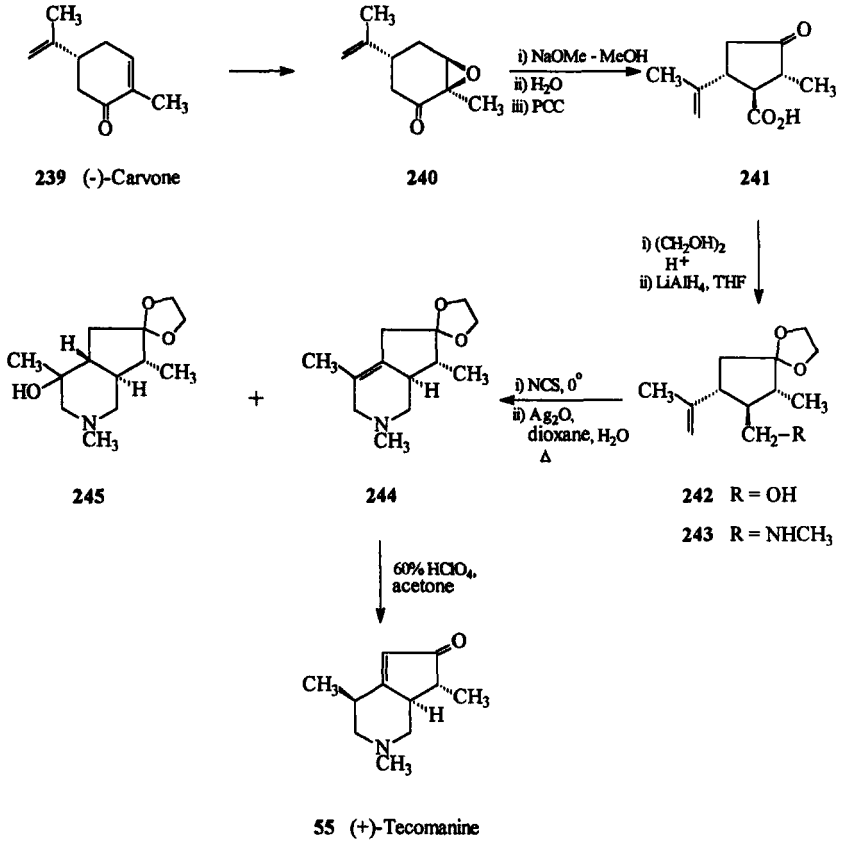
monoepoxide (**240**) with sodium methoxide followed by hydrolysis and oxidation gave the chiral cyclopentanone **241.** Protection of the ketone and $LiAlH_4$ reduction gave the alcohol **242,** whose mesylate, on reaction with methylamine in the presence of sodium methoxide, afforded the amine **243** in 83% yield. *N*-Chlorination and cyclization of the chloride in the presence of Ag_2O gave the bicyclic olefin **244** (21% yield) and the alcohol **243** (59%



SCHEME 15. Imanishi and co-workers synthesis of (±)-tecomanine (**55**) (*202,203*).

yield). Deprotection of the ketal of **244** with 60% $HClO_4$ led to migration of the double bond and the formation of (+)-tecomanine (**55**) $[\alpha]_D$ +146° (Scheme 16) (*204*).

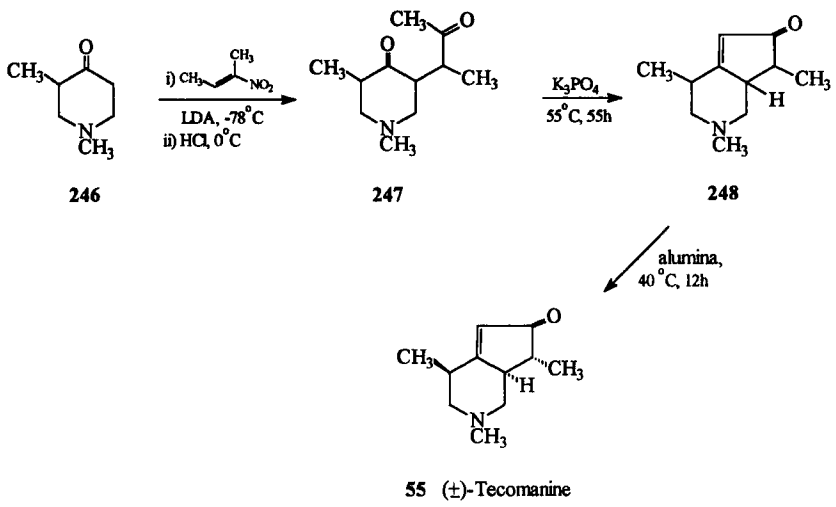
Irie and co-workers have reported a synthesis of (±)-tecomanine (**55**) based on a cyclopentenone annulation of 1,4-diketones (Scheme 17) (*205*). Treatment of 1,3-dimethylpiperidone (**246**) with lithium diisopropylamide (LDA) and 2-nitro-2-butene, and reaction with 10% hydrochloric acid (Nef reaction) afforded the substituted piperidine 1,4-diketone **247** (a homolog of **230** in Scheme 14) in 87% yield. Reaction of the mixture of isomers with K_3PO_4 at 55°C for 55 h gave a single cyclized product **248,** whose



SCHEME 16. Kametani and co-workers synthesis of (+)-tecomanine (**55**) (*204*).

stereochemistry was not deduced. Treatment with basic alumina at 40°C overnight gave (±)-tecomanine (**55**) in 50% yield identical (IR, NMR) with the natural product (Scheme 17) (*205*).

An interesting new approach to monoterpene pyridine alkaloids has been described recently by Vidari and co-workers (*206*), based on the ability of a Schmidt reaction to desymmetrize bicyclo[3.3.0]octane-3,7-dione (**249**). This was achieved through reaction with sodium azide and boron trifluoride in CH_2Cl_2:H_2O (1:1) at 25°C for 3 h, which gave the lactam **250** in 25% yield. This could be increased to 50% yield by reacting **249** with sodium azide and conc. HCl. Ketalization followed by *N*-methylation with a phase transfer catalyst gave the lactam **251.** Monomethylation of **251** afforded



246 247 248

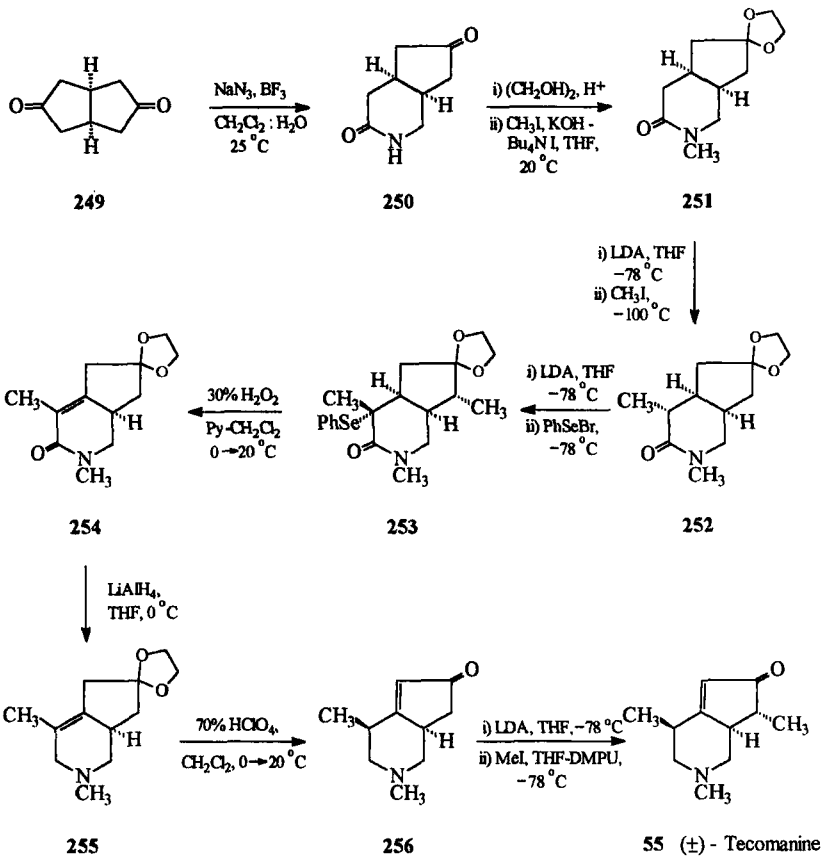
55 (±)-Tecomanine

SCHEME 17. Irie and co-workers synthesis of (±)-tecomanine (**55**) (*205*).

stereospecifically **252** in which the *exo* product dominated 28 : 1 (60% yield), and reaction with phenylselenyl bromide gave **253.** Oxidative elimination afforded a mixture of isomers in 92% yield in which the *endo*-olefin **254** predominated 3.6 : 1. Lithium aluminum hydride reduction gave the amine **255,** and reaction with 70% perchloric acid effected cleavage of the ketal, conjugation of the double bond, and equilibration at C-4 to give a single isomer **256** in 70% yield. Formation of the kinetic enolate followed by alkylation with methyl iodide at −78°C gave diastereomerically pure (±)-tecomanine (**55**) (Scheme 18) (*206*).

Thal's group has synthesized an isomer of tecomanine, 8,9-dehydro-5α*H*-isotecomanine (**257**) (*204*), following the development of a synthesis of the aminodiene **258** (*206,207*). As a model reaction, treatment of the dimethyl acetal of DMF with *N*-methyl cyclopentadienylpropylamine (**259**) afforded the cyclopenta[*c*]tetrahydropyridine **260.** In the homologous series, reaction of the formamide derivative **261** with the dimethyl acetal of DMF gave a quantitative yield of the aminofulvene **262.** Reaction with phosphorus oxychloride at −70°C gave, regiospecifically, after hydrolysis, the formyl cyclopenta[*c*]tetrahydropyridine **263** (*208*). Reduction of this intermediate gave the aminodiene **258** (Scheme 19) (*206*).

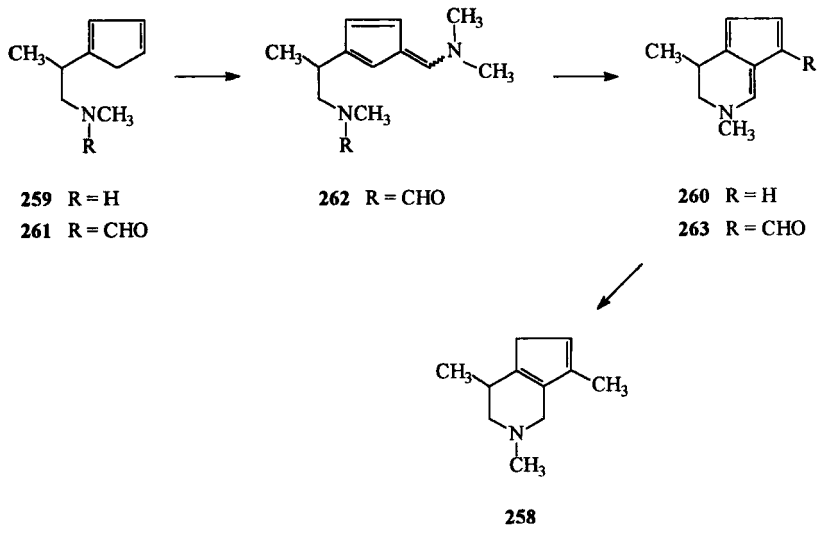
A stepwise, double hydroboration followed by oxidation on **258** gave a mixture of hydroxy aminoboranes **264** in 90% yield, which was oxidized with PCC to the keto-aminoborane **265.** Isomerization with *N-tert*-butyl-



SCHEME 18.

N,N',N'',N'''-tetramethylguanidine (TMTBG) at −20°C gave the two isomeric boranes **266.** Deboronation in refluxing ethanol afforded 8,9-dehydro-5α*H*-isotecomanine (**257**) in 85% yield (Scheme 20) (*207*). Full details of this reaction sequence, including the stereospecific considerations of various stages, were published subsequently (*210*). Also described at this time was a synthesis of the isomer 8,9-dehydro-5β*H*-isotecomanine (**267**). Thus, when the enone *N*-borane **265** was treated with ethanol under reflux, **267** was produced in 24% yield, together with three more polar isomers, **268, 269,** and **270,** in the ratio 3:1:1, in 61% yield (Scheme 21) (*210*).

Further studies led to the synthesis of (±)-epi-8,9-tecomanine (**271**) (Scheme 22) (*211*). Photo-oxidation of the dominant amino borane **272** from the BH_3–DMS reaction of the aminodiene **248** afforded regio- and



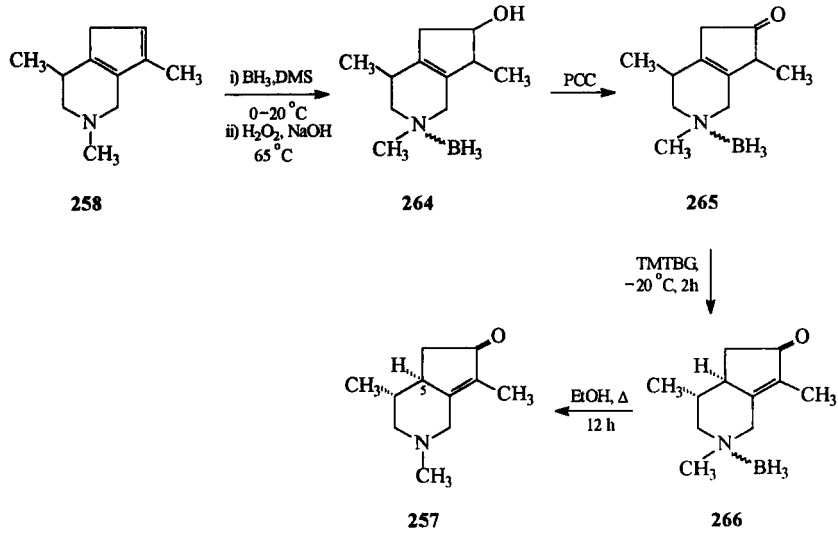
259 R = H
261 R = CHO

262 R = CHO

260 R = H
263 R = CHO

258

SCHEME 19. Synthesis of the aminodiene **258** (*208,209*).



258

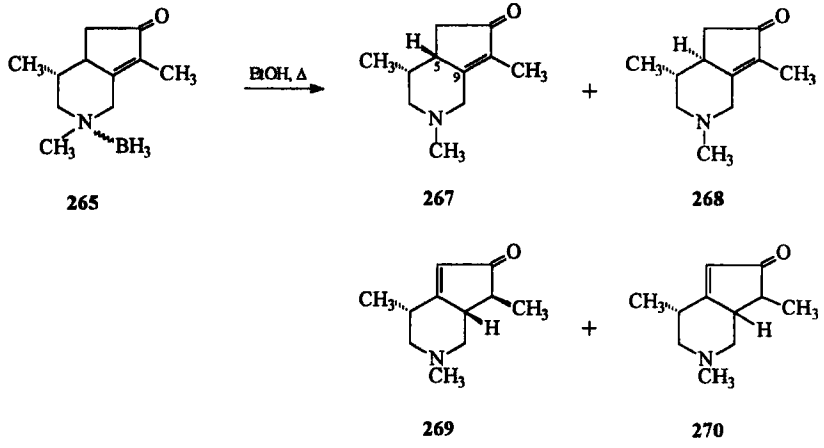
264

265

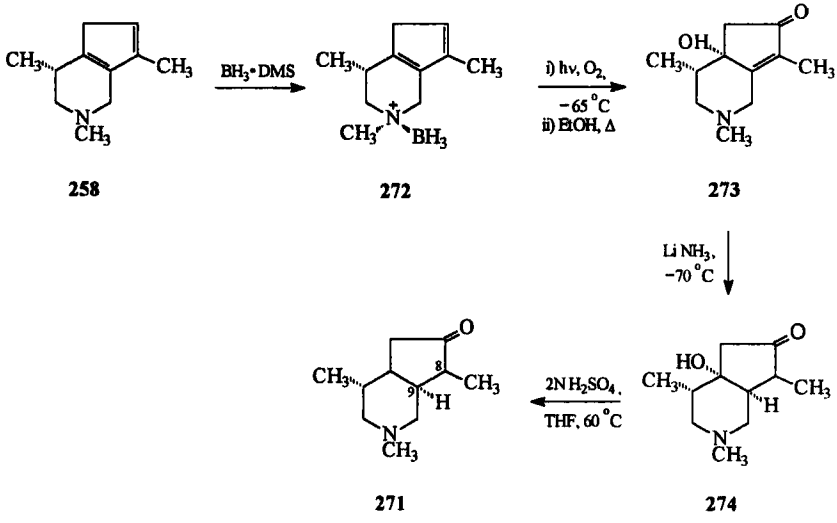
257

266

SCHEME 20. Thal and co-workers synthesis of (±)-8,9-5α*H*-dehydroisotecomanine (**257**) (*207*).



SCHEME 21. Thal and co-workers synthesis of (±)-8,9-5βH-dehydroisotecomanine (**267**) (*210*).



SCHEME 22. Thal and co-workers synthesis of (±)-8,9-epi-tecomanine (**271**) (*210*).

stereoselectively the enone **273** in 61% yield after deboronation with refluxing ethanol. Reduction with Li/NH_3 at $-70°C$ gave exclusively the ketone **274** (94% yield), which could be dehydrated with 2 N sulfuric acid in THF at 60°C to give, in 52% yield, 8,9-epi-tecomanine (**271**) (Scheme 22) (*211*).

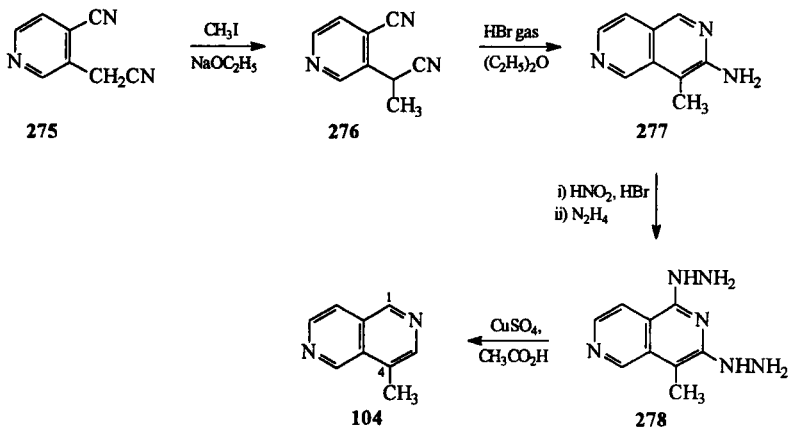
D. Naphthyridine Derivatives

*1. 4-Methyl-2,6-naphthyridine (**104**)*

Following their work on the synthesis of the parent compound 2,6-naphthyridine (**105**) (*105*). Taurins and Li reported their work in full (*107*) and at the same time reported a synthesis of the 4-methyl derivative **104,** isolated by Harkiss and Swift (*62*). 4-Cyano-3-pyridyl-acetonitrile (**275**) was methylated (CH_3I–$NaOC_2H_5$) in the side chain to afford 2-(4-cyano-3-pyridyl)propionitrile (**276**), which was treated with hydrogen bromide in ether to afford 3-amino-1-bromo-4-methyl-2,6-naphthyridine (**277**). Diazotization/bromination and replacement of the bromine groups with hydrazine gave **278,** and reaction with $CuSO_4$ in acetic acid afforded 4-methyl-2,6-naphthyridine (**98**) (Scheme 23) (*107*), whose spectroscopic properties were identical with those reported previously (*62,63*).

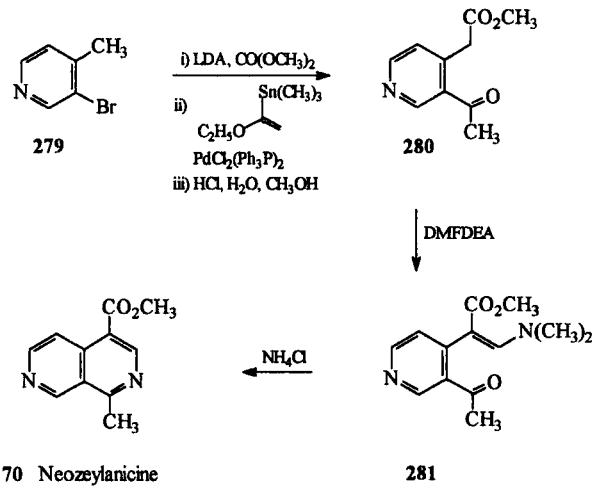
*2. Neozeylanicine (**70**)*

Recently, Bracher and Mink have reported a synthesis of neozeylanicine (**70**) (*212*). Treatment of the lithium salt of 3-bromo-4-methyl pyridine (**279**) with dimethyl carbonate followed by a palladium-catalyzed cross



275 276 277 104 278

Scheme 23. Taurins and Li synthesis of 4-methyl-2,6-naphthyridine (**104**) (*107*).

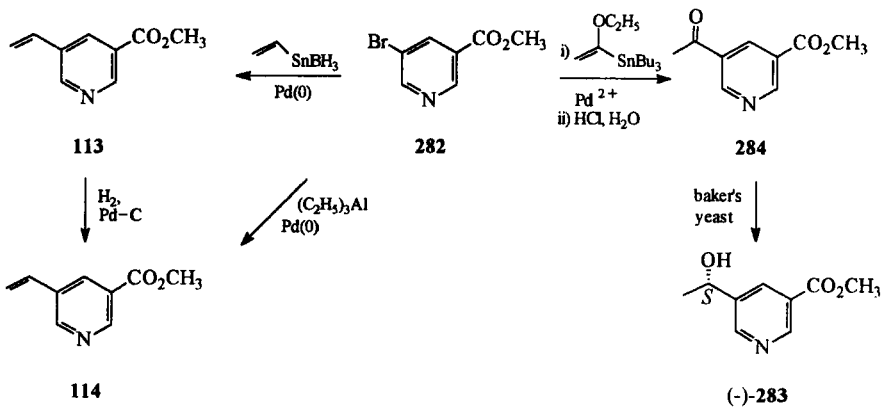


SCHEME 24. Bracher and co-workers synthesis of neozeylanicine (**70**) (*212*).

coupling reaction with trimethyl(1-ethoxyvinyl)stannane and hydrolysis of the intermediate enol ether gave the methyl ketone **280** in 45% yield. Condensation of **280** with the diethyl acetal of DMF afforded the vinylogous urethane **281** which was ring closed with ammonium chloride in refluxing ethanol to give neozeylanicine (**70**) (Scheme 24) (*212*).

E. 3-CARBOMETHOXY PYRIDINE DERIVATIVES

Several derivatives of 3-carbomethoxy-pyridine have been isolated following the original work of McLean and Murray (*108,175*). Recently, Bracher and Papke (*213*) have examined the synthesis and antimicrobial activities of several of these closely related alkaloids. Treatment of 5-bromo-3-carbomethoxy-pyridine (**282**) with various organometallic reagents in a series of Pd-catalyzed cross-coupling reactions gave rise to 5-substituted derivatives exclusively (Scheme 25). Thus reaction of **282** with vinyl tri-*n*-butylstannane gave the vinyl derivative **113** in 92% yield, which could be catalytically reduced to **114.** Alternatively, treatment of **282** with triethylaluminum in the presence of Pd(0) gave **114** directly in 24% yield. For the preparation of the alcohol **283,** the methyl ketone **284** was selected as a target molecule. Reaction of **282** with 1-ethoxyvinyl tributylstannane in a Pd^{2+}-catalyzed cross-coupling reaction, followed by mild acid hydrolysis, gave **284** in 63% yield. Reduction with *Saccharomyces cerevisiae* gave (−)-**283** with enantiomeric excesses in the range 84 to 95%. The Mosher method



SCHEME 25. Bracher and Papke synthesis of 3-carbomethoxy-pyridine derivatives (*213*).

(*85,86*) was used to determine the absolute configuration to be *S*. Thus, the natural alkaloid, which is dextrorotatory, has the *R* configuration at the 1′-position (*213*).

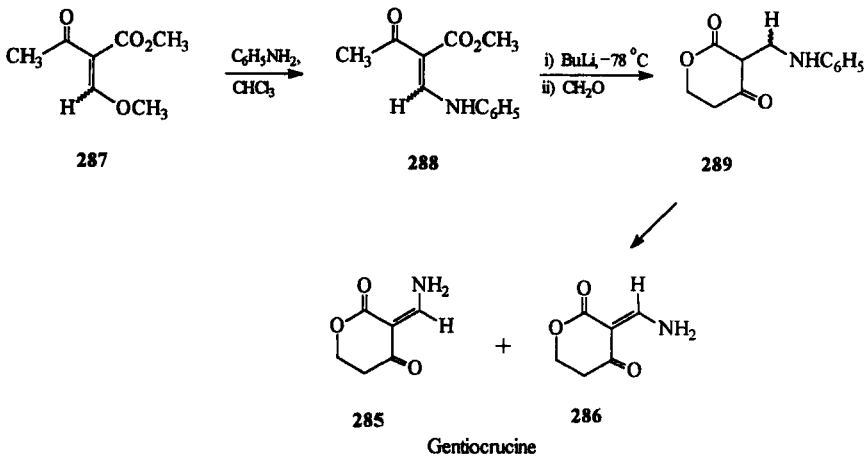
F. GENTIOCRUCINE (GENTIANAINE) (285/286)

Following the establishment that gentiocrucine and gentianaine were identical (*214*), and the revision of the structure of gentiocrucine to a mixture of isomeric enamides (**285** and **286**) (*215*), Ganem recognized a need to confirm the structure proposed for this unusual primary enamide through synthesis (*216*).

Treatment of methyl 2-(methoxymethylene)acetoacetate (**287**) with aniline produced the corresponding enaminoketoester **288** in 97% yield. Formation of the orange Li salt followed by passage of dry gaseous formaldehyde at −78°C and warming gave the oxo-δ-lactone **289.** Facile conversion to the natural alkaloid was achieved in 66% yield through dissolution of **289** in liquid ammonia. The spectral data of the product confirmed that it was a mixture of the two isomers **285/286.** Thus, for example, the methylene protons adjacent to the carbonyl appeared as two triplets at 2.45 and 2.50 ppm in the ratio of 1.5:2.5 (Scheme 26) (*216*).

G. *IN VITRO* CONVERSION OF IRIDOIDS AND SECOIRIDOIDS TO MONOTERPENE ALKALOIDS

As discussed in the previous review (*1*), it is well established that under certain circumstances monoterpenoid alkaloids are produced from their

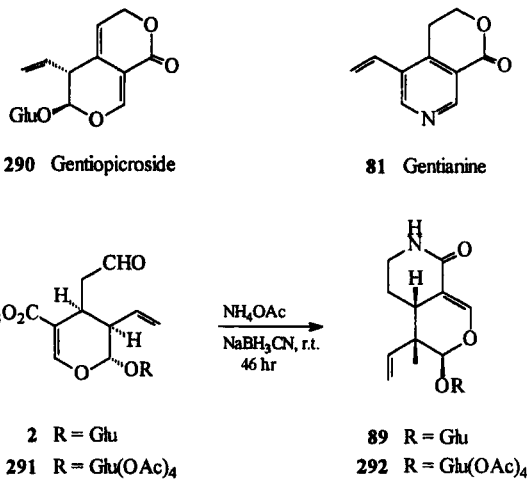


287 288 289

285 286

Gentiocrucine

SCHEME 26. Ganem synthesis of gentiocrucine (**285/286**) (*216*).



290 Gentiopicroside

81 Gentianine

2 R = Glu
291 R = Glu(OAc)$_4$

89 R = Glu
292 R = Glu(OAc)$_4$

iridoid precursors during the processing of the plant material with ammonia. This area has expanded in recent years to a more structured approach in which iridoid glucosides are hydrolyzed under defined conditions and the products reacted with an ammonia source, either oxidatively or reductively, to afford pyridine or piperidine alkaloids, respectively.

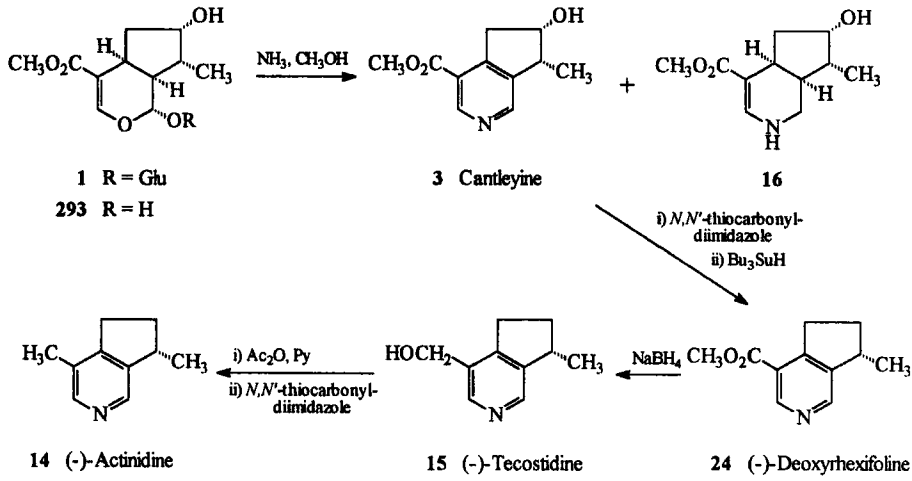
Hayashi and Higashino (*217*) examined the gentiopicroside (**290**) content of commercial samples of *qinjão,* which is the root of either *Gentiana*

macrophylla or *G. dahurica* (Gentianaceae). The content of **290** varied in the range of about 0.2 to 1.4% in both samples when the roots were worked up in the absence of ammonia. Gentianine (**81**), which had previously (*218*) been isolated as the major alkaloid, was not detected. A more detailed investigation of this traditional medicinal drug was conducted by Zhong and Lin (*219*). Gentianine (**81**) and gentianal were analyzed in *G. crassicaulis* and *G. macrophylla* each from two different provinces, and *G. dahurica* from one province. Levels of gentianine (**81**) were highest in *G. crassicaulis* from Sichuan Province (1.373%) and *G. macrophylla* from Gansu Province (1.496%), and in the latter case alkaloid content was highest in the roots (*219*).

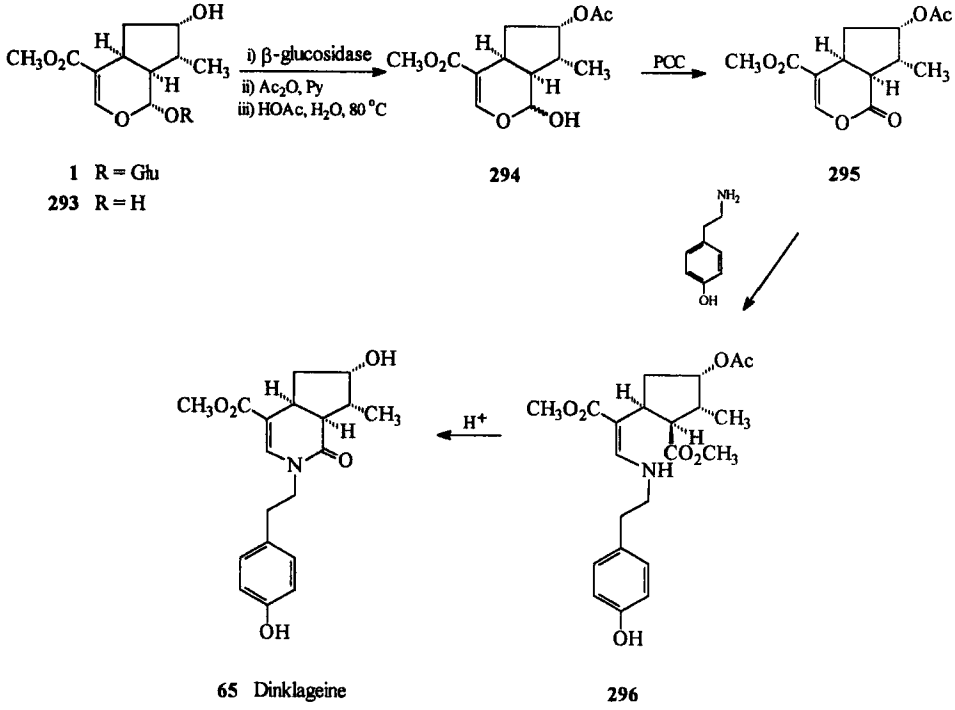
Although the early work of Büchi and Manning (*220*) had suggested a structure for bakankoside, there was no stereochemistry proposed. In the last review (*1*), it was suggested that the stereochemistry was probably derived from that of a secoiridoid precursor and therefore that bakankoside should have the structure **89.** In order to investigate this point, Inouye and co-workers converted secologanin (**2**) to bakankoside (**89**) through reductive amination (*221*). When secologanin tetraacetate (**291**) was allowed to stand with ammonium acetate in methanol in the presence of sodium cyanoborohydride at room temperature for 46 h and the product hydrolyzed with alkali, bakankoside tetraacetate (**292**) was isolated in low yield.

Several transformations of loganin (**1**) have been reported by Tillequin and co-workers (*39,181*). Reaction of loganin (**1**) with β-glucosidase afforded the acetal **293,** which could be treated with ammonia-saturated methanol and worked up with acid to afford a 1:1 mixture of cantleyine (**3**) and tetrahydrocantleyine (**16**) (*39*). Following this work, Tillequin and co-workers have described the semisynthesis of three additional monoterpene alkaloids from loganin (**1**) (*179*). Treatment of cantleyine (**3**) with *N,N'*-thiocarbonyldiimidazole followed by radical deoxygenation with tributyltin hydride gave (−)-deoxyrhexifoline (**24**) in 78% yield. Sodium borohydride reduction then afforded (−)-tecostidine (**15**). Acetylation of tecostidine (**15**) and catalytic hydrogenolysis produced (−)-actinidine (**14**) in 65% yield (Scheme 27) (*181*).

Dinklageine (**65**) was also synthesized from loganin (**1**) (Scheme 28) (*37*). Treatment of **1** with β-glucosidase to afford the acetal **293** was followed by acetylation and mild hydrolysis to give the monoacetate **294** in 12% overall yield. Oxidation with PCC at 20°C gave the lactone **295,** which, in methanolic solution, was treated with tyramine to give the vinylogous urethane **296** in quantitative yield. Acid hydrolysis gave dinklageine (**65**) identical with the natural product (*37*).



SCHEME 27. Transformation of loganin (**1**) to (−)-tecostidine (**15**) and (−)-actinidine (**14**) (*181*).

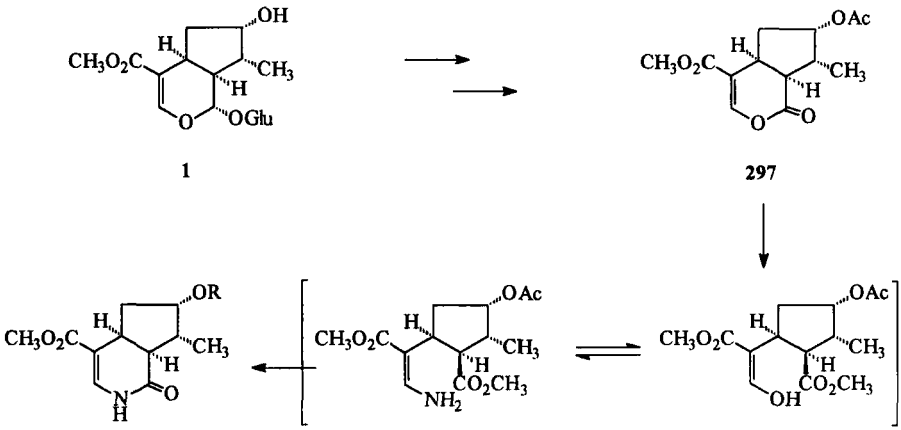


SCHEME 28. Transformation of loganin (**1**) to dinklageine (**65**) (*37*).

An exactly analogous strategy was used for the synthesis of strychnovoline (**64**) from loganin (**1**) (Scheme 29) (*38*). Thus, treatment of the unsaturated lactone **297** with ammonia-saturated methanol followed by gaseous HCl gave 7-*O*-acetyl-strychnovoline (**298**), which on reaction with methanolic HCl gave **64**, identical with the natural product.

The structure and absolute configuration of 7-*O*-nicotinoyl-strychnovoline (**66**) were also established through semisynthesis. Treatment of strychnovoline (**64**) with nicotinic acid anhydride in the presence of 4-dimethylaminopyridine gave **66,** identical with the natural product (*39*). Similarly, when tetrahydrocantleyine (**16**) was treated with nicotinic anhydride, 7-*O*-nicotinoyl-tetrahydrocantleyine (**67**) was produced, identical with the natural product (*39*).

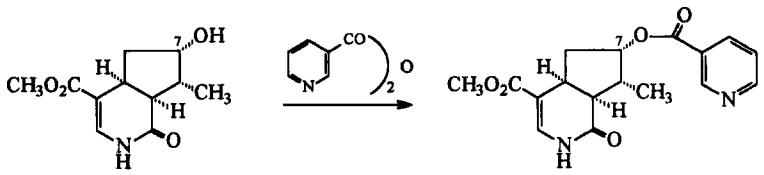
Popov and co-workers have investigated the *in vitro* transformations of gentiopicroside (**290**) and swertiamarin (**299**) (*222*). Treatment of gentiopicroside (**290**) with ammonia-saturated ethanol overnight followed by evaporation, reflux with acid, and basification with ammonia afforded three basic products: gentianine (**81**), gentianidine (**79**), and an unidentified polar product. When the reaction was analyzed prior to acidifcation, gentianine (**81**) and the polar alkaloid were present, but gentianidine (**73**) was absent, replaced by gentioflavine (**129**). The relationship between gentioflavine (**129**) and gentianidine (**79**) was confirmed when the former was separately treated with aqueous hydrochloric acid. On the other hand, when swertia-



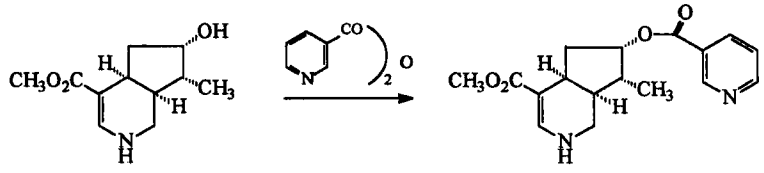
298 R = $COCH_3$

64 R = H

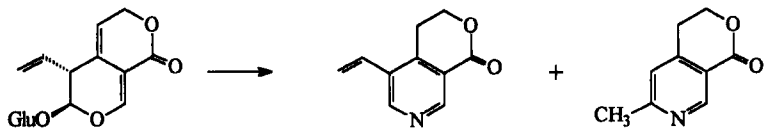
SCHEME 29. Transformation of loganin (**1**) to strychnovoline (**64**) (*38*).



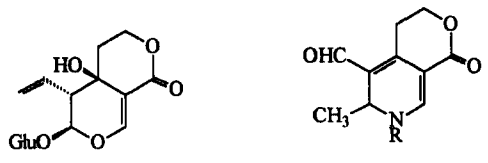
64 Strychnovoline 66



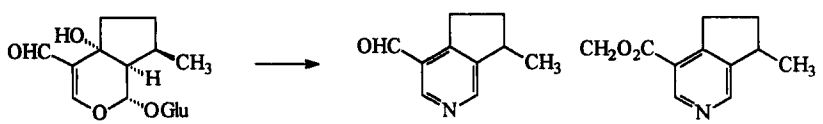
16 Tetrahydrocantleyine 67



290 Gentiopicroside 81 Gentianine 79 Gentianidine



299 Swertiamarin 129 Gentioflavine, R = H
300 R = C_2H_5



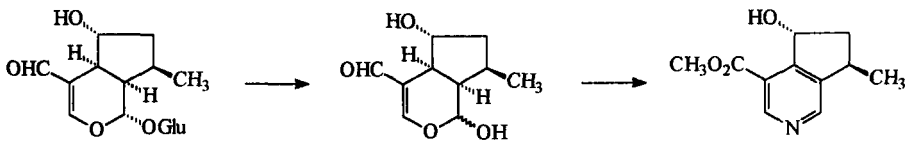
301 Plantarenaloside 121 Boschniakine 24 Methyl boschniakinate

marin (**299**) was treated with ammonia, either with or without acid treatment, only gentianine (**81**) was isolated. Oxidation to the pyridine could also be blocked in the case of gentiopicroside (**290**) by reacting with an alkyl amine. Thus reaction of **290** with ethylamine afforded *N*-ethylgentioflavine (**300**). The ^1H NMR spectrum of the product displayed all of the signals of gentioflavine and an additional *N*-ethyl group (1.35 and 3.50 ppm) (*222*).

The same group (*61*) has also investigated the formation of boschniakine (**121**) in *Plantago arenaria.* Alkalinization of the plant extract with ammonia increased the alkaloid level compared with the use of $NaHCO_3$, and the content of both boschniakine (**121**) and methyl boschniakinate (**24**) were increased. In the former case this was traced to the iridoid plantarenaloside (**301**). When **301** was treated with 1 : 1 ethanolic ammonia at room temperature for 24 hr, boschniakine (**121**) was isolated in low yield (*61*). It was also suggested that a corresponding iridoid was responsible for the formation of **24.**

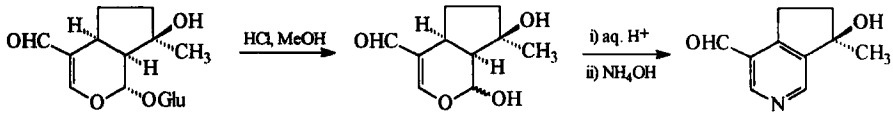
Following the isolation and structure elucidation of rhexifoline (**23**) from *Castilleja rhexifolia* (*35*), further work on the flower heads yielded three iridoid glucosides, one of which was penstemonoside (**302**). Recognizing the potential relationship between **23** and **302,** Roby and Stermitz carried out the synthetic transformation of **302** to **23** (*81*). Treatment of penstemonoside (**302**) with β-glucosidase afforded a 2:1 epimeric mixture of the lactol **303.** Reaction with methanolic HCl followed by ammonia afforded rhexifoline (**23**) in 31% overall yield (Scheme 30) (*81*). Euphroside (**304**), the principal iridoid of *Orthocarpus* spp., was used for the structure confirmation of euphrosine (**25**) (*40*). Acid hydrolysis of **304** in methanol afforded **305,** which was treated with aqueous acid followed by basification with ammonia to afford a low yield of euphrosine (**25**), identical with the natural product (Scheme 31) (*40*).

The basic extract of *Coelospermum billardieri* had yielded six monoterpene alkaloids (*34*). When the neutral fraction was examined, one of



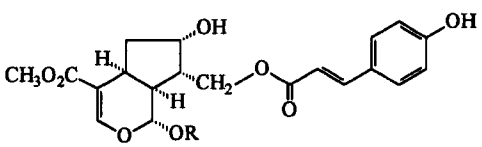
302 Penstemonoside **303** **23** Rhexifoline

SCHEME 30. Roby and Stermitz semisynthesis of rhexifoline (**23**) (*81*).

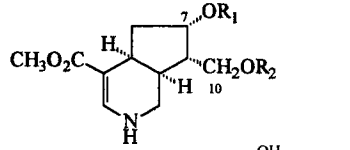


304 Euphroside **305** **25** Euphrosine

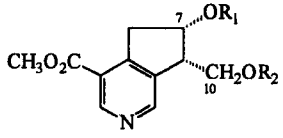
SCHEME 31. Transformation of euphoside (**304**) to euphosine (**25**) (*40*).



306 R = H
307 R = Glu

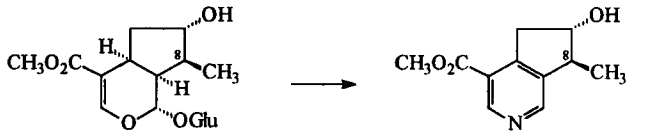


308 R_1 = , R_2 = H
309 R_1 = H, R_2 =
311 R_1 = R_2 = H

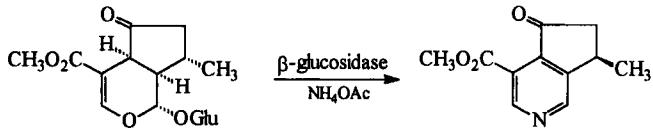


19 R_1 = H, R_2 =
310 R_1 = , R_2 = H
312 R_1 = R_2 = H

the isolates was characterized as 10-*O-trans*-(4-hydroxycinnamoyloxy) loganigenin (**306**) (*223*). This same compound could also be produced through enzymatic synthesis from the corresponding glucoside **307,** which co-occurred. Treatment of **306** with ammonia, followed by HCl gas, gave a mixture containing seven components: methyl 4-hydroxycinnamate, 10-hydroxy-7-*O-trans*-(4-hydroxycinnamoyl)tetrahydrocantleyine (**308**), 10-*O-trans*-(4-hydroxycinnamoyloxy)tetrahydrocantleyine (**309**), 10-hydroxy-7-*O-trans*-(4-hydroxycinnamoyl)cantleyine (**310**), 10-*O-trans*-(4-hydroxycinnamoyloxy)cantleyine (**19**), 10-hydroxy-tetrahydrocantleyine (**311**), and 10-hydroxycantleyine (**312**) (*223*). The absolute configuration of the previously isolated alkaloid 10-*O-trans*-(4-hydroxycinnamoyloxy)-cantleyine (**19**) was determined.

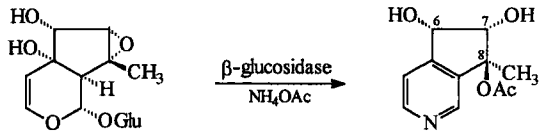


313 8-Epi-loganin 314 8-Epi-cantleyine



315 Cornin 316

317 Aucubinine A 6 Coelosperminone



318 Antirrhinoside 319

H. Unnatural Alkaloid Derivatives from Iridoid Glucosides

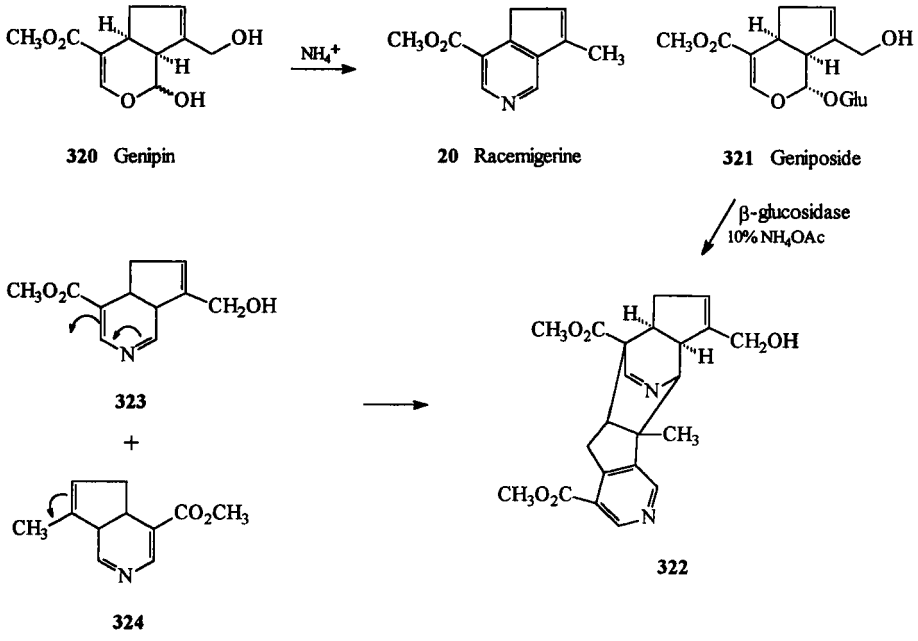
Fredericksen and Stermitz (*224*) described the reaction of a number of iridoid glucosides under standard conditions in which the glucoside is treated with β-glucosidase in 10% NH_4OAc at 37°C for 4 h and the resulting product extracted into organic solvent. When these reaction conditions were applied to 8-epi-loganin (**313**), 8-epi-cantleyine (**314**) was produced in 20% yield. Reaction of cornin (**315**) under these conditions afforded the pyridine **316,** which proved difficult to purify. The relationship to aucubinin B (**317**) or to coelosperminone (**6**) (*34*) is not known.

When antirrhinoside (**318**) was reacted under the standard conditions, the dihydroxy acetate monoterpene pyridine alkaloid derivative **319** was produced cleanly in about 10% yield (*224*). The structure was deduced spectroscopically. An acetate group was apparent (δ_H 2.1; δ_C 21.9, 172.6) and doublets (J = 5.6 Hz) at 4.31 and 5.11 ppm. The latter showed an NOE with H-4 and was therefore assigned to H-6. X-ray crystallography affirmed the acetate group to be located at C-8 and defined the stereochemistry of C-6 and C-7 to be as shown in **319.**

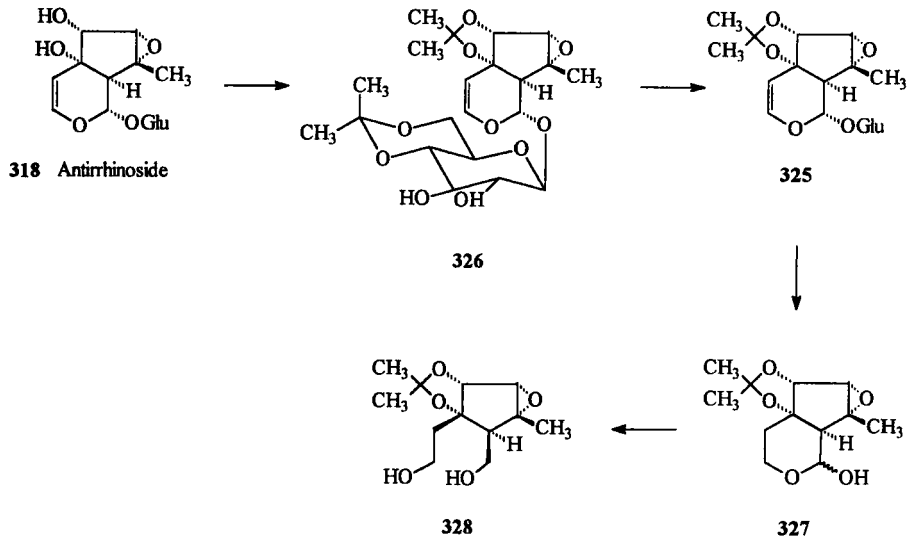
Reaction of genipin (**320**) with ammonia followed by acidification yielded the natural alkaloid racemigerine (**20**), which also proved to be unstable (*224*). However, when the parent glycoside geniposide (**321**) was treated with β-glucosidase in 10% NH_4OAc, a single product, in 9% isolated yield, was established to be a bis-monoterpene pyridine derivative. The FABMS indicated a molecular formula $C_{22}H_{24}N_2O_5$ and the ^1H NMR spectrum showed two carbomethoxy groups at 3.86 and 3.92 ppm. Two α-pyridine protons were observed at 8.52 and 8.98 ppm, and a similarly shifted singlet at 8.54 ppm was correlated with a carbon at 169.6 ppm, suggesting the presence of an imine group. One olefinic proton (5.34 ppm), one methyl group (1.28 ppm), and one hydroxymethyl group (4.06 ppm) were observed, and the structure **322** was proposed on the basis of NOE and HMBC experiments. It was considered that the bis-alkaloid **322** was the result of a Diels–Alder addition between a dihydropyridine **323** and the olefin of a second (dihydro)pyridine **324** (Scheme 32) (*224*).

Additional studies using antirrhinoside (**318**) as a template for modification have also been reported (*226*). The first challenge was to develop a divergently useful synthon, and for this purpose the doubly protected dialdehyde **325** was chosen. Reaction of **318** with 2,2-dimethoxypropane gave a diisopropylidene derivative **326** from which the sugar protecting group could be selectively removed with dilute acetic acid at 60°C to afford **325** in 72% overall yield. Hydrogenation followed by treatment with β-glucosidase afforded a hemiacetal, **327,** in 85% yield, which could be reduced, in variable yield, to the potentially versatile **328** (Scheme 33) (*226*). This compound proved too labile under weakly basic conditions, and the approach was abandoned.

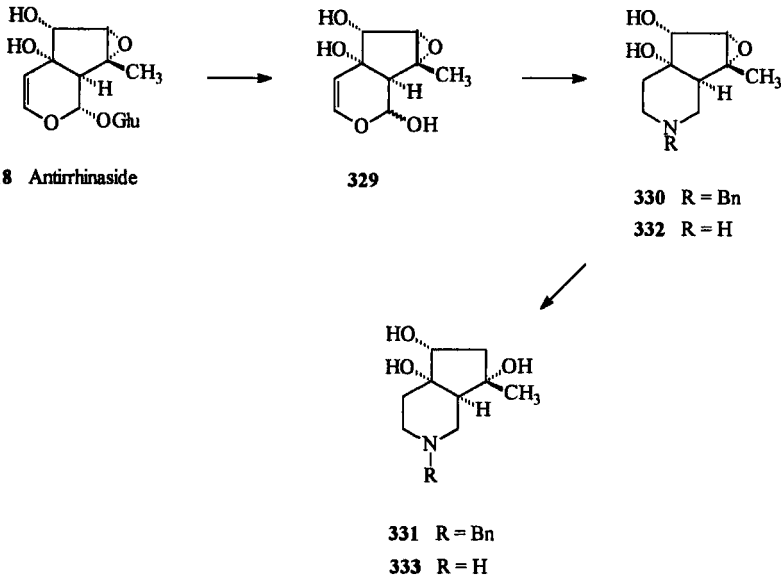
The alternative strategy was to cleave the glucose unit of **318** first with β-glucosidase to afford **329,** which was reacted with benzylamine in the presence of sodium cyanoborohydride to afford **330** in about 37% yield. Reduction with $LiAlH_4$ gave the tertiary alcohol **331,** and both **330** and **331** could be converted to their debenzyl derivatives **332** and **333,** respectively, under conditions of catalytic (Pd/C) hydrogenation (Scheme 34) (*226*). Although these products do not represent the synthesis of natural



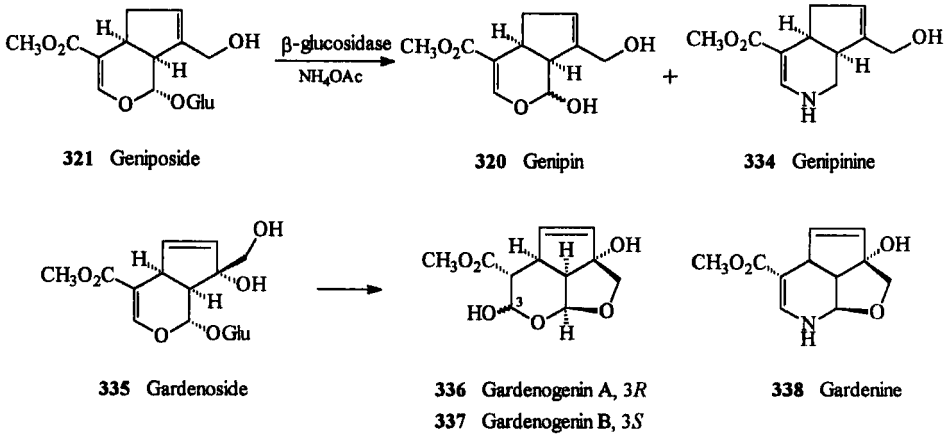
SCHEME 32.



SCHEME 33. Transformations of antirrhinoside (**318**) (*226*).



SCHEME 34. Further transformations of antirrhinoside (**318**) (*226*).



alkaloids, they do offer approaches for the preparation of derivatives related to the skytanthines and tecomanines for biological evaluation.

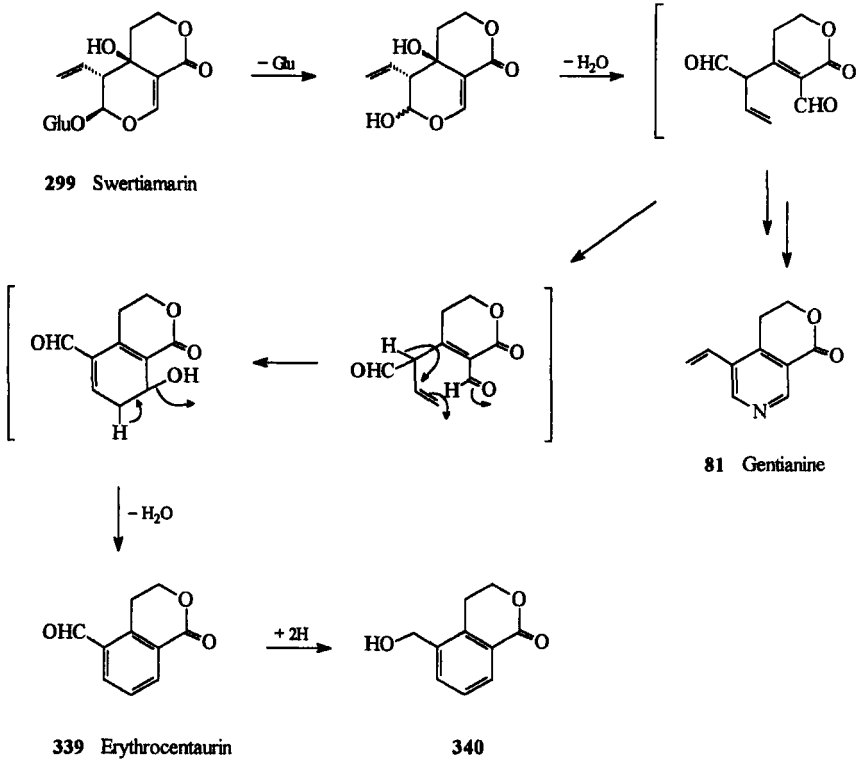
Similar experiments were also reported by Hattori and co-workers with geniposide (**321**) isolated from the fruit of *Gardenia jasminoides* (Rubiaceae) (*227*). *G. jasmonoides* is widely used in traditional Chinese medicine

as an antiphlogistic and cholagogue, and thus the metabolism of the iridoids is of interest. Treatment of geniposide (**321**) with β-glucosidase and ammonium ion for 4 h at 37°C gave genipin (**320**) and a new monoterpene alkaloid derivative, genipinine, characterized as **334.** The isolate showed a molecular ion analyzing by HRMS for $C_{11}H_{15}NO_3$ and showed two methylene protons, two olefinic protons, two methine protons, and hydroxymethyl and methoxycarbonyl groups. Selective irradiation experiments established the relationships of H-9 with H-1a, H-5, and H-1b, and of H-5 with H-6a, H-6b, and H-9, and therefore the structure **334** (*227*). Reaction of gardenoside (**335**) under similar conditions gave a mixture of the gardenogenins A and B (**336/337**) and another new monoterpene alkaloid, gardenine (**338**). The molecular formula was established as $C_{11}H_{13}NO_4$, and the ^1H NMR spectrum displayed two *cis* olefinic protons (6.16 and 5.69 ppm), a β-proton on a vinylogous urethane system (7.43 ppm) and one methylene and three methine protons. One of these methine protons appeared at 5.18 ppm as a doublet coupled with H-9. Thus, gardenine was assigned the structure **338** (*227*).

I. Human Fecal Flora and Intestinal Bacteria for the Transformation of Iridoid Glucosides

When swertiamarin (**299**) was metabolized under anaerobic conditions with a preparation of human fecal flora, three metabolites were produced, erythrocentaurin (**339**), gentianine (**81**), and 5-hydroxymethylisochroman-1-one (**340**) (*228*). A series of 26 individual human intestinal bacteria strains were also incubated with swertiamarin (**299**) and the products examined. The same three metabolites were observed in varying amounts from the various preparations. Gentianine (**81**) was detected from the preparations of 14 different bacteria, and the alkaloid yield optimized with *Proteus mirabilis* after about 6–12 h. A mechanistic explanation for the formation of the three primary metabolites was presented (Scheme 35) (*228*).

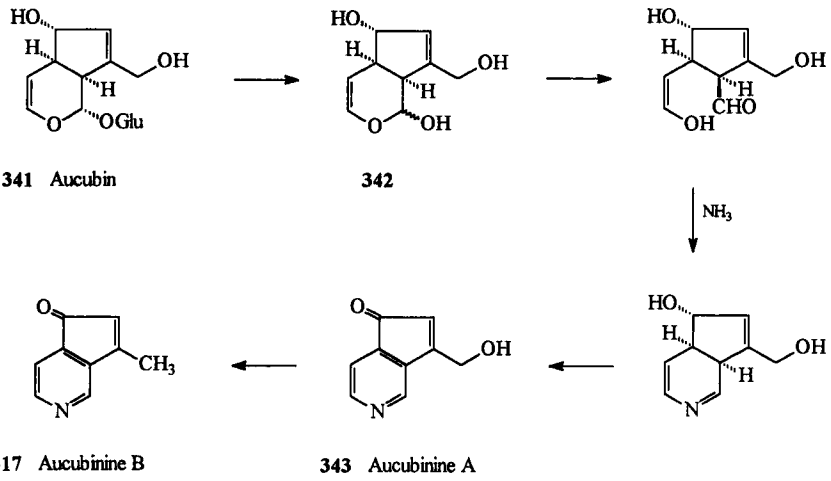
The success of these experiments led Hattori and co-workers to carry out a similar investigation with aucubin (**341**) (*225*). One of the dominant bacterial species in the human intestinal tract is *Bacteroides fragilis,* and when aucubin (**341**) was cultured with this organism, three metabolites, aucubigenin (**342**) and two new alkaloidal metabolites, aucubinine A (**343**) and aucubinine B (**317**), were produced. Aucubinine A had a molecular formula $C_9H_9NO_2$, and the IR spectrum indicated hydroxy (3400 cm^{-1}) and ketonic carbonyl (1720 cm^{-1}) groups. In the ^1H NMR spectrum a methylene (2.60 and 2.89 ppm), a methine (3.71 ppm), and a hydroxymethyl group (3.90 and 4.00 ppm) were observed, together with three downfield aromatic protons (7.58, 8.71, and 9.06 ppm). Irradiation of the resonance at 3.71 ppm



SCHEME 35. Metabolic transformation of swertiamarin (**299**) (*227*).

(H-8) collapsed the methylene and hydroxymethyl group resonances, and thus the structure of aucubinine A was suggested to be **343** (*225*).

Aucubinine B differed from **343** in that the hydroxymethyl group resonance was replaced by a doublet methyl group (1.48 ppm, $J = 7.1$ Hz), and thus the structure **317** was proposed for this metabolite. These metabolites were also produced when aucubin (**341**) was incubated with a bacterial mixture derived from human fecal flora, and by a series of individual strains of human intestinal flora. Thus, when **341** was incubated with 25 species of bacteria, 21 of the species produced aucubinine A (**343**) and a trace of aucubinine B (**317**) (*225*). One of the more potent organisms for the transformation of aucubin (**341**) was *Klebsiella pneumoniae,* where production of **343** maximized after 18 h. Finally, when aucubin (**341**) was treated with ammonium ion directly, almost no **343** was produced. However, in the presence of β-glucosidase and ammonium ion for 7 h at 37°C, **343** was



SCHEME 36. Metabolic transformation of aucubin (**341**) (*225*).

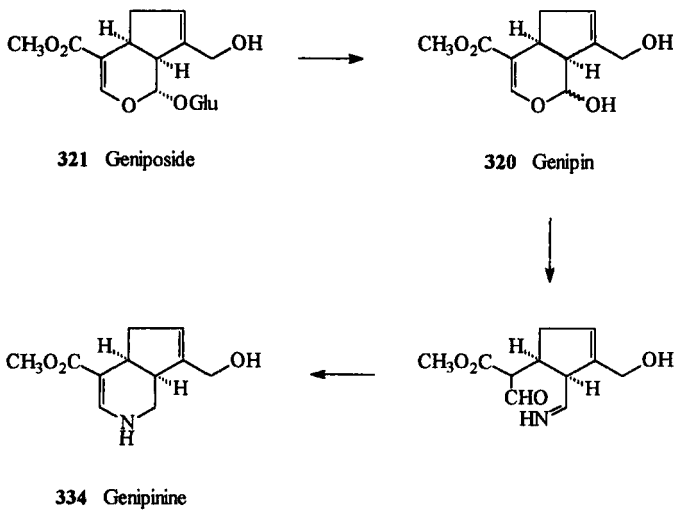
produced in good yield with an optimum concentration of 100 mM NH_4Cl (*225*). Again, a mechanistic pathway was presented for the formation of these metabolites from aucubin (**343**) (Scheme 36) (*225*).

Using various strains of human intestinal bacteria the metabolism of geniposide (**321**) was also examined, and of the 25 strains, 15 afforded the alkaloid genipinine (**334**) as one of the products. *Klebsiella pneumoniae* was again a significant producer of **321** and maximum concentrations were reached after about 24 h. *Peptostreptococcus anaerobius* was the most productive organism for the metabolism of **321** to **334** (*227*). When geniposide (**308**) was incubated with human fecal flora under anaerobic conditions, formation of genipine (**334**) was 10-fold that produced with the individual bacteria. The proposed mechanism for the formation of **334** from **321** is shown in Scheme 37, and that of **338** from **335** is shown in Scheme 38 (*227*).

J. Synthesis of Miscellaneous Terpene Alkaloids

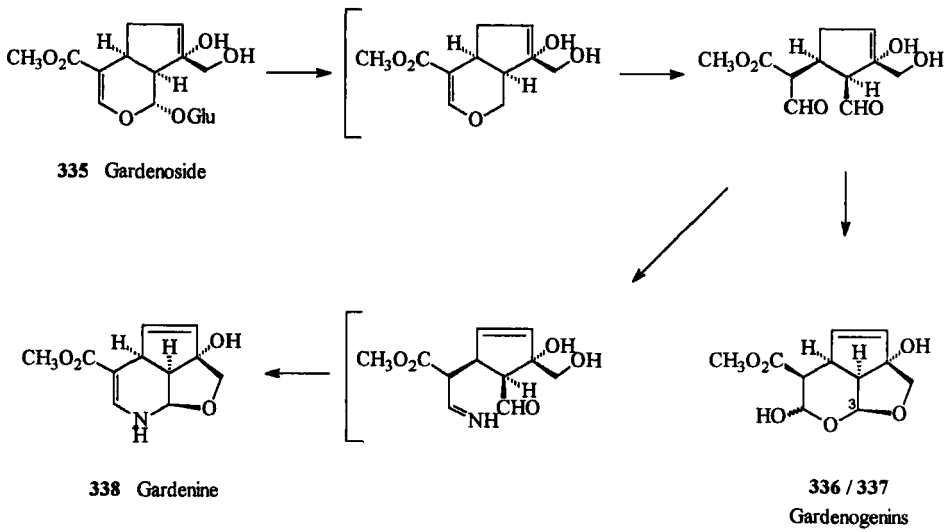
1. Cerpegin (118)

The simple structure of the alkaloid cerpegin (**118**) has attracted a lot of synthetic attention. The first synthesis (*229*) was completed in six steps beginning with 3-*N*,*N*-diisopropylcarbamoyl-2-methoxypyridine (**344**), itself prepared from 2-chloronicotinic acid. Treatment of **344** with TMPLi



321 Geniposide **320** Genipin **334** Genipinine

SCHEME 37. Metabolic transformation of geniposide (**321**) (*227*).



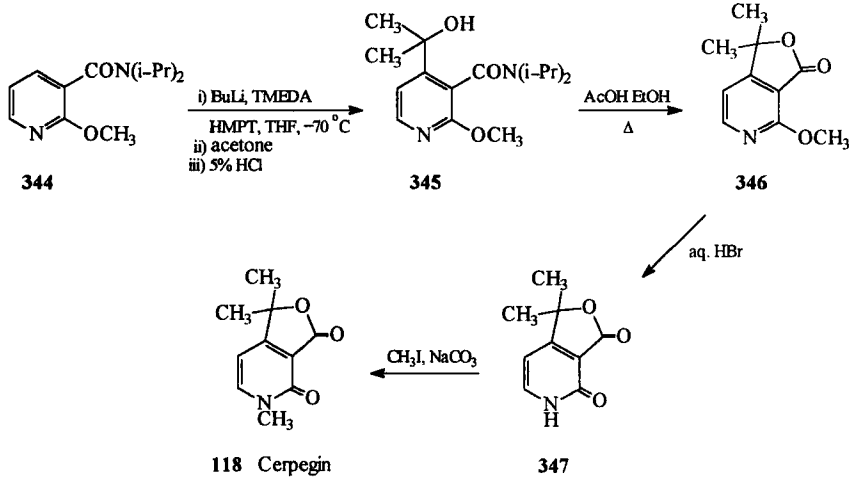
335 Gardenoside **338** Gardenine **336 / 337** Gardenogenins

SCHEME 38. Metabolic transformation of gardenoside (**335**) (*227*).

in the presence of TMEDA at −70°C and reaction of the lithiated species with acetone and acidification gave the alcohol **345.** Reflux in ethanol–HOAc afforded the lactone **346** in 91% yield, and when followed by demethylation with 48% HBr and *N*-methylation of the derived pyridine **347** with methyl iodide in the presence of Na_2CO_3, gave cerpegin (**118**) in overall yield of 28% from **344** (Scheme 39) (*229*).

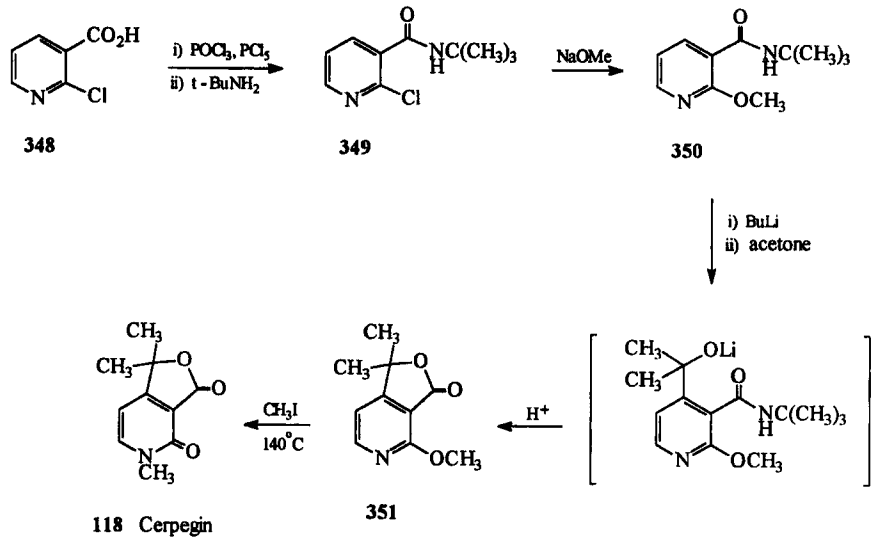
In an alternative synthesis (*230*), 2-chloronicotinic acid (**348**) was converted to its *tert*-butyl amide **349,** which was readily converted to its methoxy derivative **350.** Treatment with butyl lithium, then acetone and acidification afforded **351,** and the methyl group was effectively transposed from oxygen to nitrogen by heating with methyl iodide at 140°C to afford **118** (Scheme 40).

Matsuo and co-workers have described two syntheses of cerpegin (**118**) (*231–233*). In the first synthesis, reaction of the lithium salt of phenylthioacetonitrile (**352**) with treated with 2-methoxycarbonyl-5,5-dimethyl-2-buten-4-olide (**353**) at −78°C and then warmed to room temperature and treated with acid afforded a stereoisomeric mixture of **354** in 93% yield. Oxidation of **354** with *meta*-chloroperbenzoic acid followed by reflux in benzene gave **355.** Catalytic reduction (Pd–C–HCl) and treatment with base gave **356** in 44% yield. Various methylation procedures were unsuccessful, but reaction with methyl 4-toluene sulfonate in the presence of NaH gave **118** in 81% yield (Scheme 41) (*231,232*).

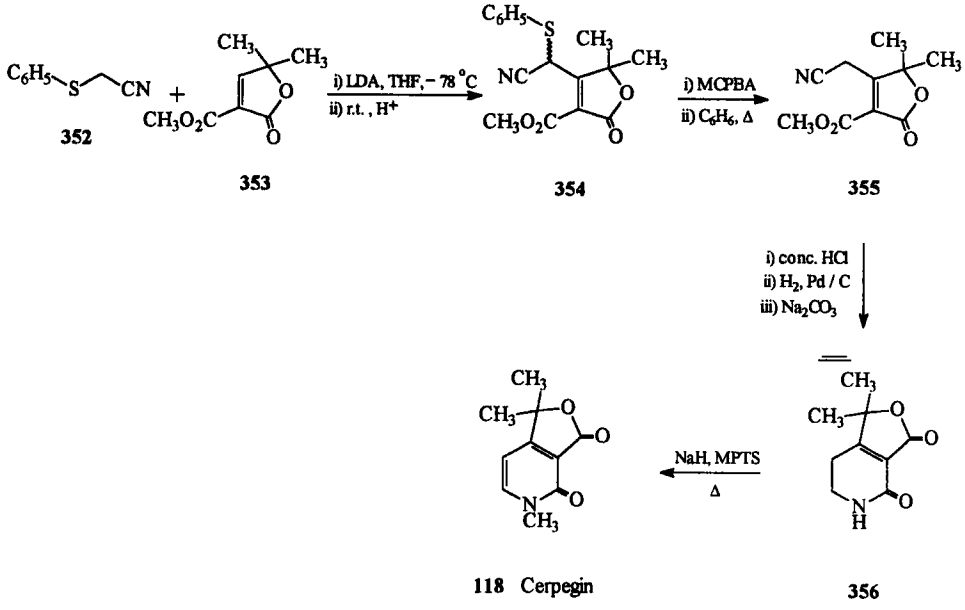


344 345 346 347 118 Cerpegin

SCHEME 39. Synthesis of cerpegin (**118**) (*229*).



SCHEME 40. Synthesis of cerpegin (**118**) (*230*).

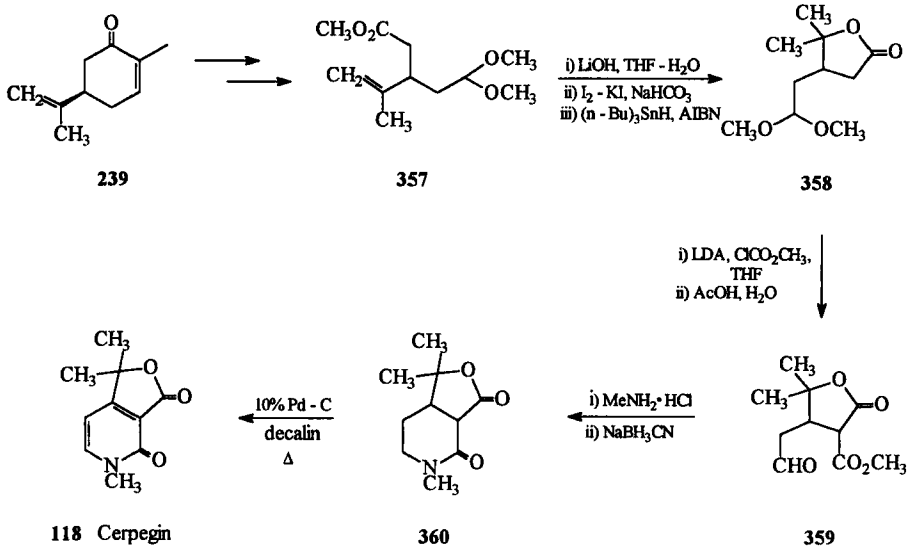


SCHEME 41. Matsuo synthesis of cerpegin (**118**) (*231,232*).

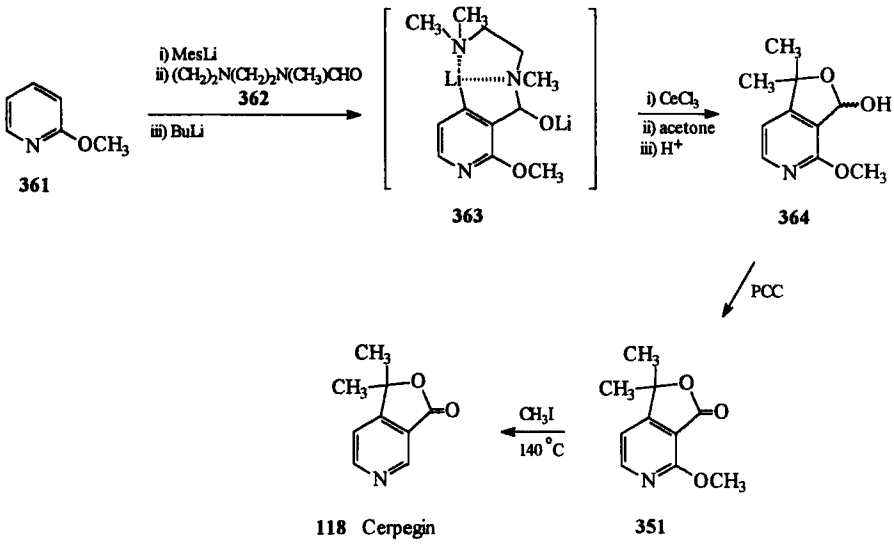
The second Matsuo synthesis (*233*) was initiated with methyl 3-(2,2-dimethoxyethyl)-4-methyl-4-pentenoate (**357**) prepared (*234*) from carvone (**239**). Hydrolysis with lithium hydroxide followed by iodolactonization (I_2–KI–$NaHCO_3$) and reduction with tri-*n*-butyl tin hydride in the presence of azobisisobutyronitrile in benzene under reflux afforded **358.** The carbomethoxy group was introduced with methyl chloroformate and LDA in quantitative yield, and reductive amination of **359** with methylamine and sodium cyanoborohydride gave the lactone **360.** Heating of **360** with 10% Pd/C in decalin gave cerpegin (**118**) in 81% yield (Scheme 42) (*233*).

A three-step synthesis of cerpegin (**118**) was described by Hong and Comina (*235*). Lithiation of 2-methoxypyridine (**361**) with mesityllithium followed by the addition of *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine (**362**) gave an α-amino alkoxide which was treated with *n*-butyl lithium. The resulting dianion **363** was reacted with cerium chloride followed by acetone to yield, after acidification, the lactol **364.** Oxidation with PCC gave **365,** which was treated with methyl iodide at 145°C to afford **118** (Scheme 43) (*235*). The overall yield was 34%.

Another three-step synthesis of cerpegin (**118**) was described by Villemin and Liao (*236*). Condensation of 3-hydroxy-3-methyl-2-butanone (**365**) with diethyl malonate in the presence of cesium carbonate, and with Aliquat as



SCHEME 42. Second Matsuo synthesis of cerpegin (**118**) (*233*).



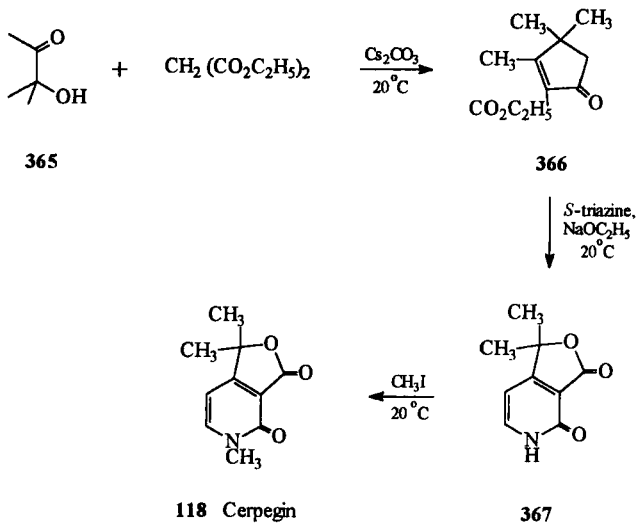
SCHEME 43. Hong and Comina synthesis of cerpegin (**118**) (*235*).

a phase transfer catalyst, gave the butenolide **366** in 85% yield. Reaction of **366** with *s*-triazine under basic conditions (NaOEt) gave the pyridone **367** in 90% yield, which gave cerpegin (**118**) on treatment with methyl iodide. All of the reactions were achieved in a one-pot reaction sequence in 75% overall yield (Scheme 44) (*236*).

2. *Polyzonimine (119)*

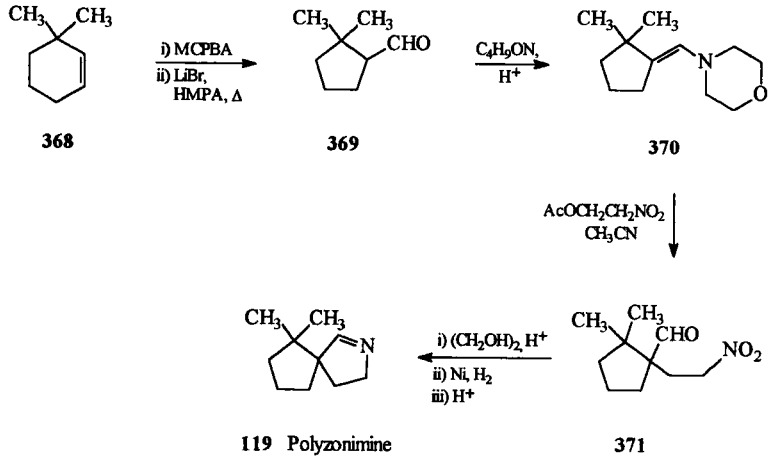
The first synthesis of polyzonimine (**119**) was a synthesis of the racemate carried out by Smolanoff and co-workers in 1975 at the time of its isolation and structure elucidation (*111*). Oxidation of 3,3-dimethylcyclohexene (**368**) with *meta*-perchlorobenzoic acid followed by treatment of the epoxide with lithium bromide and HMPA in refluxing benzene gave the carboxaldehyde **369.** The morpholino enamine **370** was then subjected to Michael addition with nitro-ethylene, generated from 2-acetoxy-nitroethane, to afford a nitro aldehyde **371.** Ketalization and reduction with Raney nickel then afforded (±)-**119** in overall yield for the five steps of 22% (Scheme 45) (*111*).

Takano and co-workers have described the synthesis of the (+)-isomer of **119** through a [2,3] sigmatropic rearrangement of an ammonium ylide (*237*). From 2,2-dimethyl-cyclopentanone (**372**) through condensation with



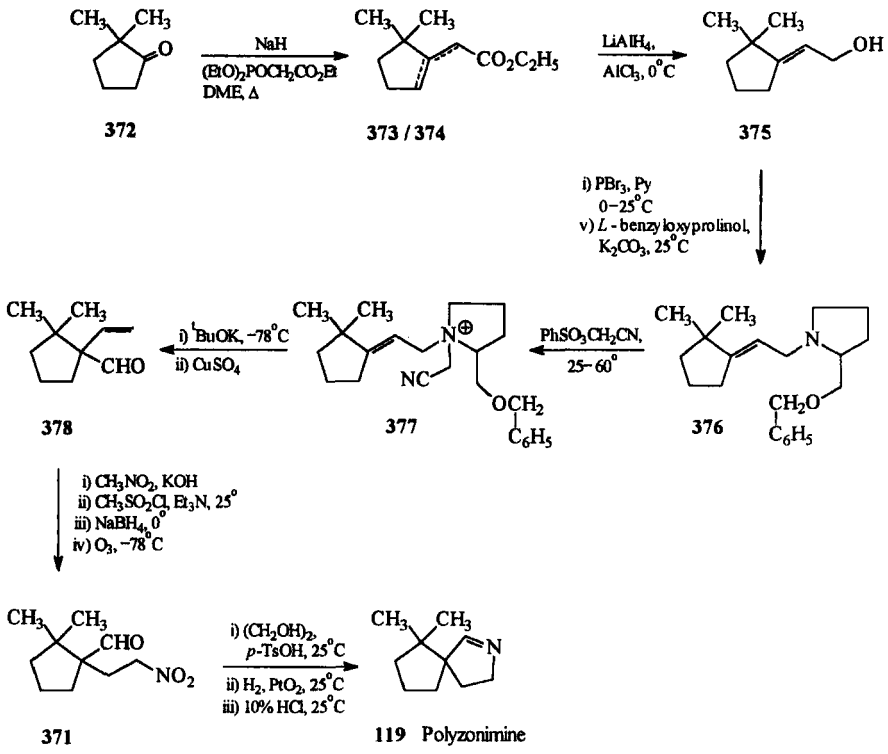
SCHEME 44. Villemin and Liao synthesis of cerpegin (**118**) (*236*).

triethylphosphonoacetate under basic conditions, a mixture of unsaturated esters was generated, and two of these isomers, **373** and **374,** on treatment with PPA followed by $LiAlH_4$–$AlCl_3$ reduction at 0°C gave the allylic alco-

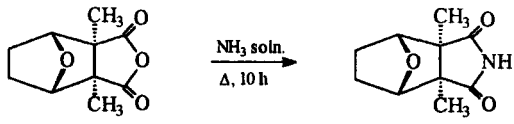


SCHEME 45. Sinolanoff and co-workers synthesis of polyzonimine (**119**) (*111*).

hol **375** exclusively. Bromination and amination with L-benzyloxyprolinolafforded **376,** which could be converted with cyanomethylbenzene sulfonate to **377.** Base treatment (KOtBu/THF at −78°C) and hydrolysis with $CuSO_4$ then afforded the olefin-aldehyde **378.** Condensation with nitromethane followed by $NaBH_4$ reduction and ozonolysis yielded the nitro-aldehyde **371.** Protection as the acetal, catalytic reduction, and deprotection then afforded (+)-polyzonimine (**119**) (Scheme 46) (*237*).



SCHEME 46. Takano and co-workers synthesis of polyzonimine (**119**) (*237*).



379 Cantharidin **120** Cantharidinimide

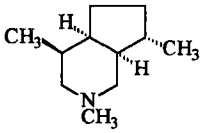
*3. Cantharidinimide (**120**)*

When cantharidine (**379**) was treated with 25% ammonia solution for 10 h under reflux, cantharidinimide (**120**) was formed in about 95% yield (*112*).

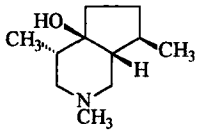
IV. Physical and Spectral Properties

In the previous summary of the monoterpene alkaloids (*1*), many of the properties of the alkaloids then known were presented. In this chapter, some references to and examples of the various physical data for the monoterpene alkaloids were discussed as the information for the various newly isolated alkaloids was examined. Table III summarizes the more recently available information for the known alkaloids, as well as those alkaloids discussed for the first time in this review.

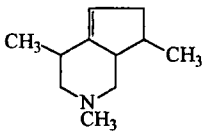
A detailed study of the mass spectra of seven of the main alkaloids isolated from *Tecoma stans* has been described (*238*). As a result, the important fragmentation pathways for these alkaloids can be discussed. δ-Skytanthine (**33**), 5β-hydroxyskytanthine (**44**), 5,6-dehydroskytanthine (**123**), δ-*N*-normethylskytanthine (**32**), tecostanine (**45**), tecomanine (**55**),



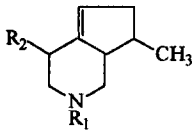
33 δ-Skytanthine



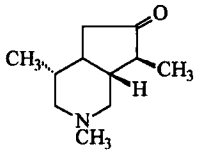
44 5β-Hydroxyskytanthine



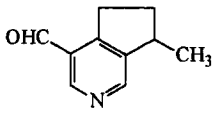
123 5,6-Dehydro-skytanthine



32 $R_1 = H$; $R_2 = CH_3$
45 $R_1 = CH_3$; $R_2 = CH_2OH$



33 Tecomanine



121 Boschniakine

TABLE III
PHYSICAL AND SPECTROSCOPIC DATA OF MONOTERPENE PYRIDINE ALKALOIDS AND DERIVATIVES[a]

Alkaloid	Optical Rotation	^{1}H NMR	^{13}C NMR	X-ray
Acanthicifoline (**103**)	−31.6° (*24*)	*24*		
3-Acetyl-2,7-naphthyridine (**108**)		*25*		*25*
Actinidine (**14**)	*124*	*117*		
Altemicidin (**78**)	−7.6° (*26,92*)	*26,92*	*26,92*	*92*
Austrodimerine (**102**)	+35° (*27*)	*27*		
Bakankoside (**89**)			*174*	
4,4′-Bis-methyl-5,5′-[(1-methyltrimethylene)di] (methylnicotinoate) (**99**)		*28*		
Boschniakine (**121**)	*124*	*30,120*	*30*	
Cantleyine (**3**)	+31.4° (*124*), −35.8° (*128*), −40° (*126*), *124*	*52,128*	*52,126*	
3-Carbomethoxy-5-ethyl-4-methyl pyridine (**115**)		*29*	*29*	
3-Carbomethoxy-5-ethyl-pyridine (**114**)		*29*	*29*	
3-Carbomethoxy-5-(1′-hydroxy ethyl)pyridine (**122**)	+23° (*131*)	*131*	*131*	
3-Carbomethoxy-5-vinyl-pyridine (**113**)		*31*		
Centaurium alkaloid I (**83**)		*33*		
Centaurium alkaloid II (**84**)		*33*		
Coelobillardierine (**5**)	−9° (*34*)	*34*	*34*	
Coelosperminone (**6**)	+19° (*34*)	*34*	*34*	
7,8-Dehydro-coelobillardierine (**7**)	+41° (*34*)	*34*	*34*	
Deoxyrhexifoline (**24**)		*35*		
Dihydrojasminine (**101**)	+300° (*27*)	*27*		
Dinklageine (**65**)	+60° (*37,38*)	*37,38*	*37,38*	
7,8-Epoxyracemigerine (**21**)	0° (*39*)	*39*		
N-Ethyl-gentioflavine (**300**)		*58*		
Euphrosine (**25**)	+3.3° (*40*)	*40*	*40*	
Gentiananine (**93**)		*41*		
Gentianidine (**79**)		*95*		
Gentianine (**81**)		*95,141,151*	*174*	
Gentiocrucine (**86**)		*216*		
10-Hydroxycantleyine (**312**)	−54° (*223*)	*223*		
10-*O-cis*-(4-Hydroxycinnamoyloxy)cantleyine (**18**)		*34*[b]	*34*	
10-*O-trans*-(4-Hydroxycinnamoyloxy)cantleyine (**19**)	−121° (*34*)	*34*[b]	*34*	
10-*O-trans*-(4-Hydroxycinnamoyloxy) tetrahydrocantleyine (**309**)	+13° (*223*)	*223*		
7-Hydroxy-5,6-dehydroskytanthine (**58**)		*42*	*42*	
10-Hydroxy-7-*O-trans*-(4-hydroxycinnamoyl) cantleyine (**308**)	−55° (*223*)	*223*		
10-Hydroxy-7-*O-trans*-(4-Hydroxycinnamoyl) tetrahydrocantleyine (**310**)	+10° (*223*)	*223*		
5*β*-Hydroxy-incarvilline (**43**)	−20.4° (*43*)	*43*	*43*	*43*
4-Hydroxy-*β*-phenethyl-3-carbomethoxy-5-ethyl-4-pyridinyl acetate (**100**)				

TABLE III (*continued*)

Alkaloid	Optical Rotation	^{1}H NMR	^{13}C NMR	X-ray
5β-Hydroxy-skytanthine (**44**)		*42*	*42*	*46,47*
4-Hydroxy-tecomanine (**59**)		*42*	*42*	
10-Hydroxy-tetrahydrocantleyine (**311**)	+23° (*223*)	*223*		
Incarvillateine (**34**)				*48*
Incarvilline (**35**)	−8° (*49*)	*49*	*49*	*49*
Incarvine A (**38**)		*50*	*50*	
Incarvine B (**41**)	+14° (*51*)	*51*	*51*	
Incarvine C (**42**)	−20.8° (*51*)	*51*	*51*	
Isocantleyine (**17**)	+18.2° (*52*)	*52*	*52*	
Isoplectrodorine (**27**)	0° (*53*)	*53*	*53*	
Jasminidine (**96**)	−3.2° (*54*)	*54*		
Jasminine (**97**)	−29.8° (*54*)	*54*		
Kinabalurine A (**46**)	+26° (*55,56*)	*55,56*	*55,56*	*55,56*
Kinabalurine B (**47**)	−100° (*56*)	*56*	*56*	
Kinabalurine C (**48**)	+25° (*56*)	*56*	*56*	
Kinabalurine D (**49**)	−13° (*56*)	*56*	*56*	*56*
Kinabalurine E (**50**)	+134° (*56*)	*56*	*56*	
Kinabalurine F (**51**)	+56° (*56*)	*56*	*56*	
Kopsilactone (**53**)	+43° (*57*)	*57*	*57*	
Kopsirachine (**77**)	+65.8° (*58*)	*58*	*58*[c]	
Kopsone (**53**)	+132° (*57*)	*57*	*57*	
Leptorhabine (**4**)	0° (*80*)	*80*		
Lindenialine (**60**)	+20° (*59*)	*59*	*59*	
Lindeniamine (**61**)	−26° (*59*)	*59*[d]	*59*[d]	
Loxylostosidine A (**91**)	+248.3° (*60*)	*60*	*60*	
Loxylostosidine B (**92**)	+287° (*60*)	*60*	*60*	
4-Methyl-5,5′-[(1-methyltrimethylene) di] (methylnicotinoate) (**98**)		*28*		
4-Methyl-2,6-naphthyridine (**104**)		*62,63*		
Neozeylanicine (**70**)		*64*		
7-*O*-Nicotinoyl-strychnovoline (**66**)	+24° (*39*)	*39*		
7-*O*-Nicotinoyl-tetrahydrocantleyine (**67**)	+59° (*39*)	*39*		
δ-*N*-Normethylskytanthine (**32**)	−21.5° (*36*)	*36*	*36*	*36*
Oxerine (**8**)	−11° (*65*)	*65*		
Plectrodorine (**26**)	0° (*53*)	*53*		
(3-Pyridyl)-1-ethanol (**111**)	0° (*66*)	*66*		
Racemigerine (**20**)		*39*		
Rhexifoline (**23**)	+18° (*35*)	*35*		
Scaevodimerine A (**71**)	+31° (*69*)	*69*		
Scaevodimerine B (**72**)	+39° (*69*)	*69*		
Scaevodimerine C (**73**)	−18° (*69*)	*69*		
Scaevodimerine D (**74**)	+48° (*69*)	*69*		
Scaevoline (**22**)	0° (*39*)	*39*		
Schultesia guianensis alkaloid (**87**)		*70*		*70*
β-Skytanthine (**76**)			*58*	

(*continues*)

TABLE III (*continued*)

Alkaloid	Optical Rotation	^{1}H NMR	^{13}C NMR	X-ray
δ-Skytanthine (**33**)			*58*	
Spicatine (**85**)		*33*		
Strychnovoline (**64**)	+98° (*38*)	*38*	*38*	
Tecomanine (**55**)		*42*	*42*	*46,47*
Tetrahydrocantleyine (**16**)	+108° (*74*)	*39,74*	*39*	
Valerianine (**13**)	−10.5° (*75*)	*75,117*		
	+36° (*66*)			
Venoterpine (**12**)	+13° (*161*), *124*	*158,161,165*	*126*	
Venoterpine-related glucoside (**11**)		*76*		
7-*O*-(5-Vinylnicotinoyl)tetrahydrocantleyine (**68**)	+36° (*39*)	*39*		
Xylostosidine (**88**)	289.4° (*78*)	*78*	*60,78*	

[a] For alkaloids not listed, data are given in the earlier review (*1*), or no proton or carbon-13 data are available.
[b] Data also reported for the diacetate derivative.
[c] Data also reported for the acetate-dimethyl ether derivative.
[d] Data also reported for the acetylated and reduced forms.

and boschniakine (**121**) were examined either as their picrate or methyl iodide derivatives, and some of the major fragments are shown in Table IV. A scheme explaining the generation of representative ions from δ-skytanthine (**33**) was proposed (Scheme 47).

V. Biosynthesis and Biogenesis

No experimental work has been conducted on the biosynthetic derivation of the monoterpene pyridine alkaloids since the last review (1). Major questions therefore remain concerning the key steps in the pathways to many of these alkaloids, and with the discovery of several new alkaloid skeleta, biogenetic pathways to these alkaloids are evolving that also require experimental evaluation. The fundamental aspects remain valid, that there are two basic types of monoterpene pyridine alkaloid: (i) those produced from an iridodial type of precursor (actinidine type, skytanthines, tecomanines), and (ii) those produced from a secologanin (**2**) type of precursor, in which the cyclopentane ring of an iridoid precursor, such as loganin (**1**), has been cleaved. These alkaloids include the jasminine (**97**), naphthyridine, and gentioflavine (**129**) derivatives. It is worth noting that in the case of the conversion of loganin (**1**) to secologanin (**2**), this conversion is still not well understood

TABLE IV
PRINCIPAL MASS SPECTRAL FRAGMENTS OF SELECTED MONOTERPENE PYRIDINE AKALOIDS[a]

Alkaloid	Principal Fragments[b]
δ-Skytanthine (**33**)[c]	167 (M^+, 41), 166 (75), 122 (6), 110 (11), 107 (4), 84 (17), 68 (12), 58 (100), 44 (75)
5β-Hydroxy-skytanthine (**44**)[c]	183 (M^+, 36), 166 (20), 122 (11), 107 (23), 84 (39), 58 (93), 44 (100)
5,6-Dehydroskytanthine (**123**)	165 (M^+, 66), 164 (41), 150 (16), 122 (14), 107 (42), 93 (39), 91 (39), 58 (100), 44 (64)
δ-*N*-Normethylskytanthine (**32**)[c]	153 (M^+, 28), 138 (27), 122 (37), 107 (12), 96 (23), 70 (25), 44 (100), 30 (89)
Tecostanine (**45**)	193 (M^+, 49), 182 (90), 100 (28), 84 (18), 70 (18), 58 (94), 44 (100)
Tecomanine (**55**)	179 (M^+, 81), 164 (46), 150 (35), 137 (40), 122 (26), 121 (42), 108 (40), 93 (50), 91 (51), 84 (22), 58 (60), 57 (100), 44 (50)
Boschniakine (**121**)	161 (M^+, 100), 160 (35), 146 (96), 132 (31), 118 (29), 117 (38), 116 (6), 91 (35)

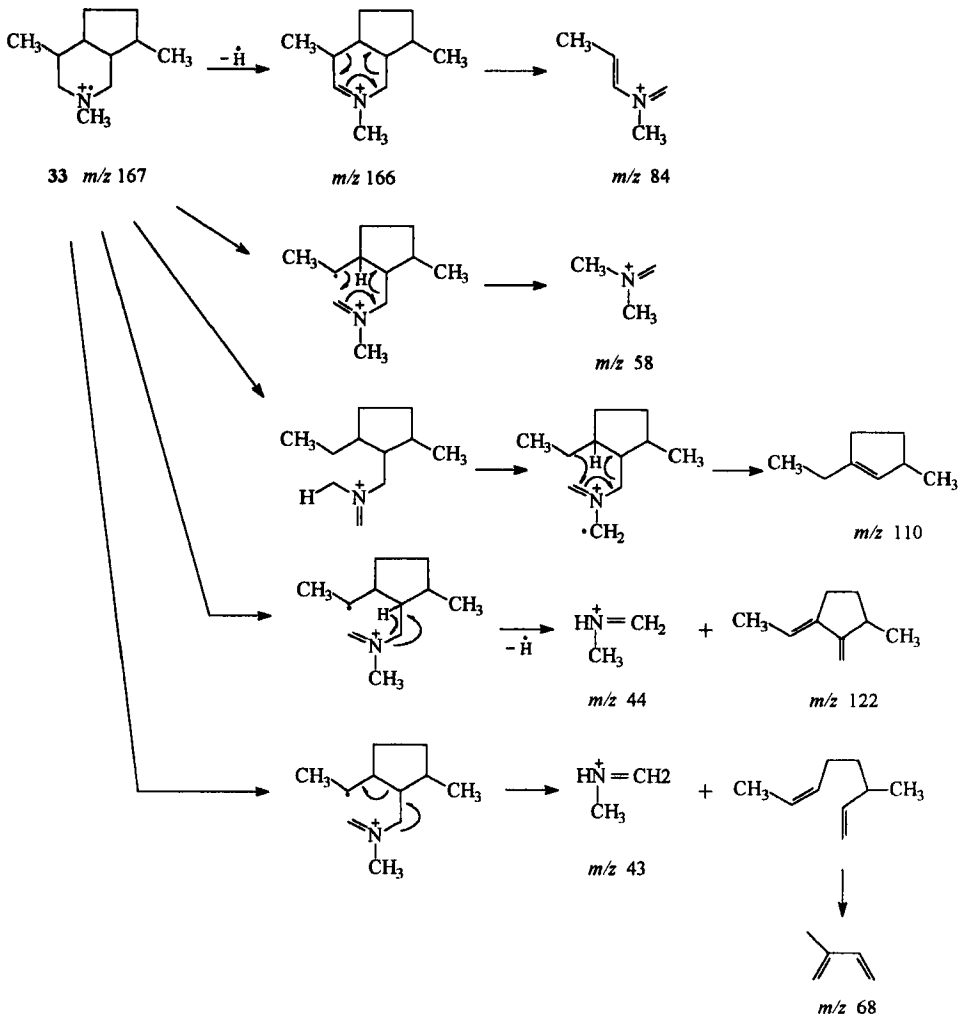
[a] Data are from ref. *238*.
[b] % of base peak in parentheses.
[c] Data rescaled to an alkaloid-derived base peak.

(*239*). As noted in the discussion of the *in vitro* conversion of the iridoids to the monoterpene pyridine alkaloids (see Section III.G), frequently the iridoid corresponding to the alkaloid is a co-metabolite in the isolation process or a direct progenitor, based on the isolation procedure when ammonia is used. Similarly, one can envisage, with the studies on the planned generation of alkaloids from iridoids (see Section III.H), that alkaloids can be produced semisynthetically that may subsequently be found in nature.

In the last review, the overall biogenesis of these alkaloids was assembled for the first time (*1*). The range of new alkaloid skeleta isolated since that time challenges the veracity of those suggestions, and thus brief comment will be made here on how the proposed pathway can be extended to accommodate the recently isolated alkaloids.

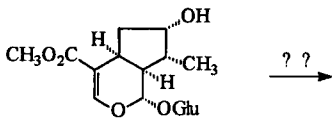
Recent isolation studies have afforded the jasurosides A–D (*240*) and E–G (*241*) from the leaves and stems of *Jasminium urophyllum*. A representative structure of jasuroside E (**380**) is shown. The interesting feature of these iridoids is the manner in which the iridodial-derived groups remain reduced and uncyclized.

If we look beyond the cleavage of the cyclopentane ring, there is an analogous alkaloid. Although not a simple monoterpene alkaloid, but rather a monoterpene indole alkaloid, deppeaninol (**381**) from *Deppea blumena-*

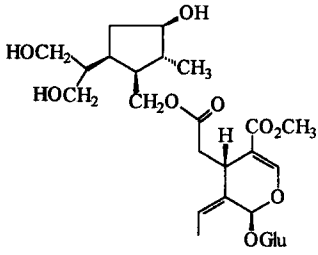


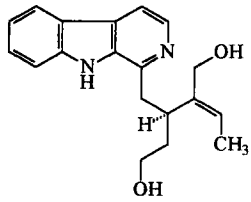
SCHEME 47. Mass spectral fragmentation of δ-skytanthine (**33**) (*238*).

viensis (Rubiaceae) (*242*) represents an excellent example of what was previously postulated to be a key aspect of the biogenesis of the monoterpene alkaloids (*1*), namely, that a completely opened monoterpene such as **382** is responsible for the molecular versatility of the monoterpenes and therefore the variety of the resulting alkaloids. One can envisage that deppeaninol would be derived from tryptamine through the condensation with an aldehyde such as **383,** followed by dehydrogenation.

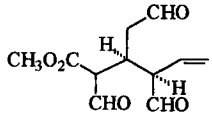


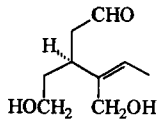
1 Loganin 2 Secologanin





380 Jasuroride E 381 Deppeaninol



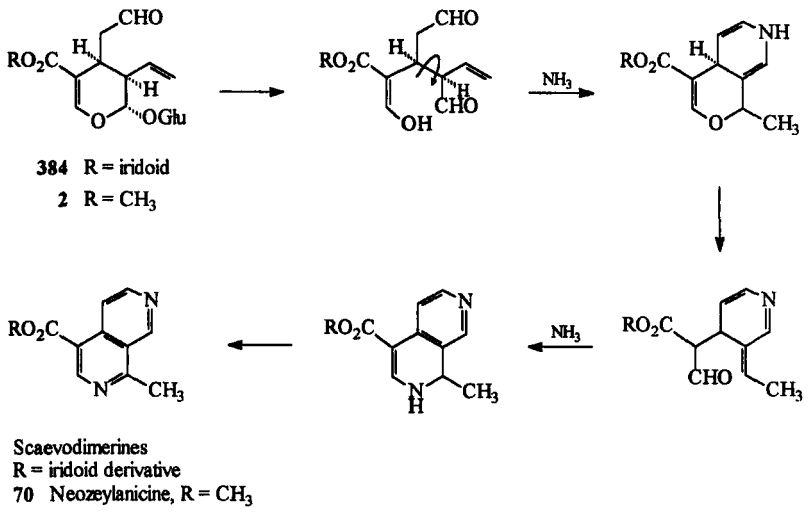


382 383

One of the new groups of alkaloids to have been isolated recently is the naphthyridines, and examples with both a 2,6- and a 2,7-naphthyridine skeleton have been described.

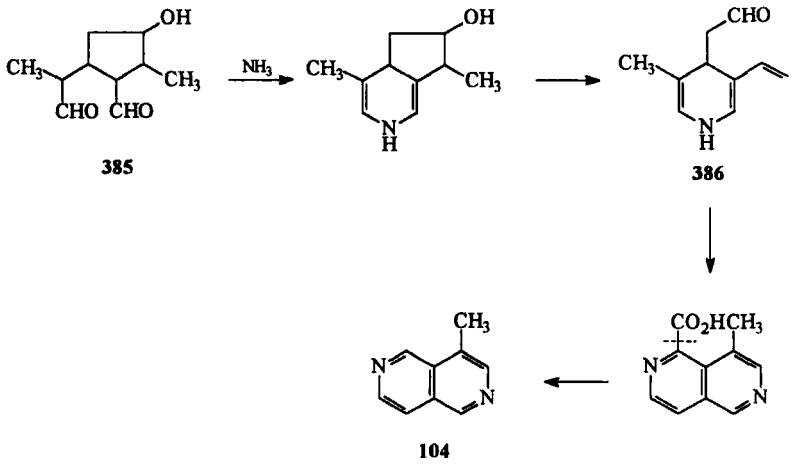
The scaevodimerines A–D were isolated from *Scaevola racemigera* following treatment of the extract with ammonia. The authors considered that these bis-monoterpene alkaloids were derived from the corresponding bis-iridoids (*69*) and proposed a scheme (Scheme 48) that would explain the formation of the 2,7-naphthyridine unit from an esterified secologanin **384.** If instead of R being another iridoid-derived unit, it is a methyl group; that is, the precursor is secologanin (**2**) itself, the product is neozeylanicine (**70**), which was subsequently isolated (*64*).

4-Methyl-2,6-naphthyridine (**104**) may be derived as shown in Scheme 49. An iridodial such as **385** is cleaved in a manner similar to the formation of **2** to afford a *seco*-cyclopentano-dihydro-actinidine **386,** which can be oxidized and decarboxylated to **104.**

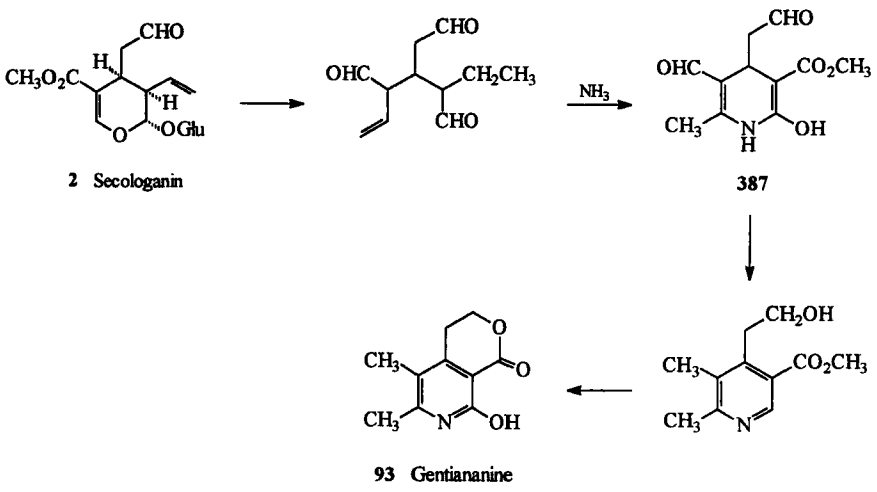


SCHEME 48. Biogenesis of scaevodimerines and neozeylanicine (**70**) (*69*).

Gentiananine (**93**) represents the first of a new series of monoterpene alkaloids in which the pyridine ring is fully substituted. Biogenetically, the alkaloid may arise from a secologanin precursor through complete opening,



SCHEME 49. Biogenesis of 4-methyl-2,6-naphthyridine (**104**).



SCHEME 50. Biogenesis of gentiananine (**93**).

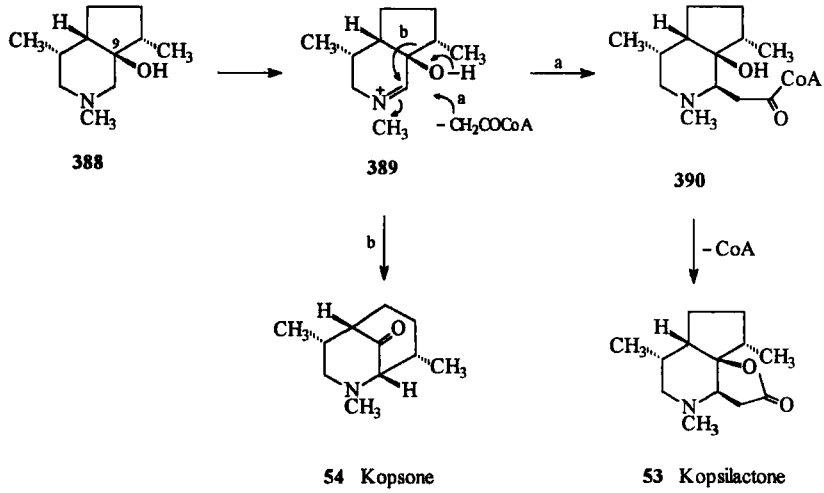
recyclization to a gentioflavine-type intermediate **387,** and a series of reduction and oxidation reactions (Scheme 50).

Kopsone (**54**) represents a rearranged monoterpene skeleton and it was suggested that this occurs through the pathway shown in Scheme 51 (*57*) from 9-hydroxyskytanthine (**388**). The key reaction is viewed as a [3.3] sigmatropic rearrangement initiated by the hydroxy group on the iminium ion **389.** An intermediate such as **389** would also be susceptible to attack by acetate (or acetoacetate) and the product **390** cyclized (and decarboxylated) to afford kopsilactone (**53**), which co-occurs (*57*).

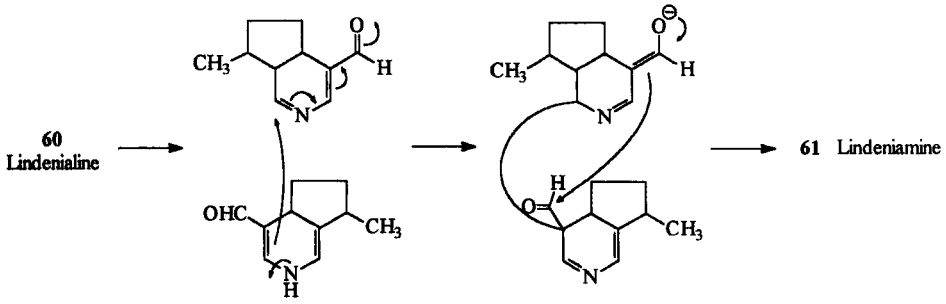
Lindeniamine (**61**) was isolated following ammonia treatment of the leaves of *Antirrhinum majus* (*59*). The formation of **61** from the co-occurring lindenialine (**60**) was viewed as taking place through an oxidative dimerization process (Scheme 52) (*59*).

Kopsirachine (**77**) (*58*) is presumably derived from the condensation of catechin (**75**) with an iminium species such as **391.** Several alkaloids in other series (ficine, borelline, etc.) are derived from various iminium species in a similar manner.

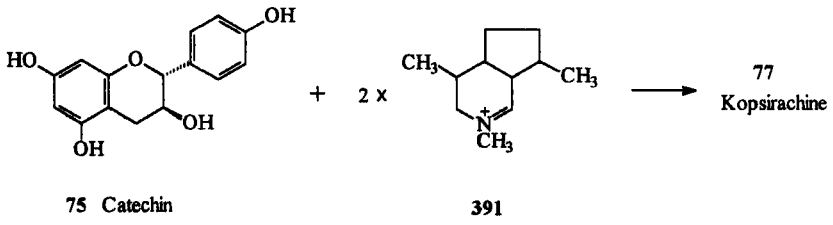
Surprisingly few studies have been carried out of the formation of monoterpene alkaloids in plant tissue culture. Indeed the only work published appears to be that by Dohnal (*89,243*) from over 20 years ago. Using *Tecoma stans* cultures grown on media supplemented with mevalonic acid, lysine, or quinolinic acid, alkaloid production was very limited or nonexis-

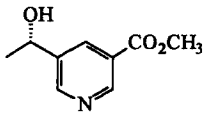


SCHEME 51. Biogenesis of kopsone (**54**) and kopsilactone (**53**) (*57*).

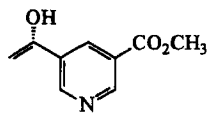


SCHEME 52. Biogenesis of lindeniamine (**61**) (*59*).

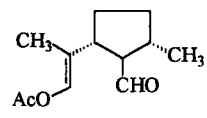




283



113



392

tent compared with the field-grown leaf material. Seven alkaloids, including actinidine (**14**), 4-noractinidine (**95**), boschniakine (**121**), tecomanine (**55**), two skytanthine derivatives [probably δ-skytanthine (**33**) and tecostanine (**45**)], and one unidentified alkaloid, were detected from the leaf material (*89*). However, the callus tissue grown from the leaves on M-L medium gave only a complex mixture of very polar alkaloids, and from the callus grown on the Murashige–Skoog medium the polar skytanthine alkaloid mixture, tecomanine (**55**) and actinidine (**14**) were detected, and in the presence of quinolinic acid, boschniakine (**121**) was also demonstrated (*89*).

VI. Pharmacology

The alcohol **283** and the vinyl compound **113** showed weak activity against Gram-positive bacteria and fungi in an agar diffusion assay (*213*). No MIC values or organisms were presented.

Iridodial β-monoenol acetate (**392**) and actinidine (**14**) were evaluated for antifungal activity against a range of organisms (*114*). The former compound was isolated from the essential oil of *Nepeta leucophylla* and the latter from *N. clarkei.* Both plants were collected in the Kumaon Himalayan region at an altitude of 2000 m based on the antifungal use of the essential oils of these species. Activity for both compounds against *Aspergillus flavus, Aspergillus ochraceus, Penicillum citrinum,* and *Penicillium viridicatum* was weak or nonexistent. However, moderate activity was observed for both compounds against *Sclerotium rolfsii* and *Macrophomina phaseolina;* thus **392** showed MIC values of 160 and 240 ppm, respectively. Actinidine (**14**) was more active than nystatin against *M. phaseolina* (*114*).

A decoction of the leaves and twigs of *Fagraea fragrans* is used in Malay traditional medicine for the treatment of dysentery, and a bark preparation is used for malaria. Wan and co-workers (*244*) have evaluated gentianine

(**81**) from this plant for a variety of biological responses. An oral dose of 300 mg/kg in mice produced no overt behavioral effects, and doses of 0.5 and 1.0 mg/kg in cats did not lower mean arterial blood pressure. No hypoglycemic activity was noted at 100 mg/kg in guinea pigs. Some weak analgesic activity was observed in rats at 100 mg/kg, and weak diuretic activity was observed at 25 mg/kg (*244*).

Japanese workers have examined the pharmacological effects of *Swertia japonica* extracts, swertiamarin (**299**) and gentianine (**81**) (*245*). Gentianine (**81**) showed a depressive effect on the central nervous system at a dose of 30 or 50 mg/kg through *per os* administration in mice. Swertiamarin was inactive. In the water immersion test of rats, gentianine (**81**) also showed antiulcerogenic activity at 50 and 100 mg/kg *per os*. Weak antigastric ulcer activity was observed in pylorus-ligated rats, and no activity as a sedative, analgesic, or laxative agent (*245*). Sweriamarin was similarly inactive in these assays.

The whole plant of *Incarvillea sinensis* is used in traditional Chinese medicine as an antirheumatic and analgesic (*88*). Examination of the alkaloid content led to a number of new monoterpene pyridine alkaloids discussed earlier (see Section II.A.20–22). Biological evaluation of the isolates indicated that incarvillateine (**34**) at 10 mg/kg i.p. inhibited both the first and second stages of formalin-induced pain and reduced spontaneous motor activity. At lower doses (1–5 mg/kg), the analgesic activity was maintained without sedative activity (*88*).

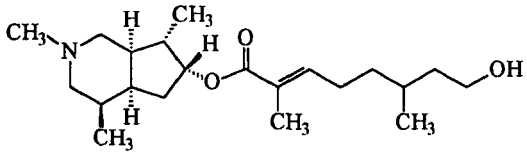
Two alkaloids were isolated from the aerial parts of *Spigelia anthelmia* (Loganiaceae) by Wagner and co-workers, one of which was isoquinoline and the second of which was partially characterized as being isomeric with actinidine. A series of choline derivatives was isolated from the aqueous extract. Preliminary biological evaluation indicated that the alkaloids are involved with the cardiotonic activity reported for the plant (*246*).

Polyzonimine (**119**) had powerful ant-repellant activity, and on closer contact the ants displayed intense cleaning activities, as though **119** was acting as an irritant (*111*). The alkaloid was also assayed as an irritant to cockroaches (*Periplaneta americana*) and was effective at levels down to 10^{-4} *M*, and in a fly (*Phormia regina*) **119** was active in producing a proboscis cleaning response at 0.1 *M*. These data support the defensive activity of **119** corresponding to estimates of 0.5 *M* to 1 *M* for the concentration of **119** in the exudate of the milliped *Polyzonium rosalbum* (*111*).

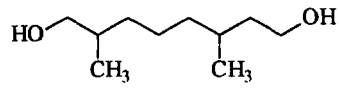
Addendum

Incarvilline Derivatives

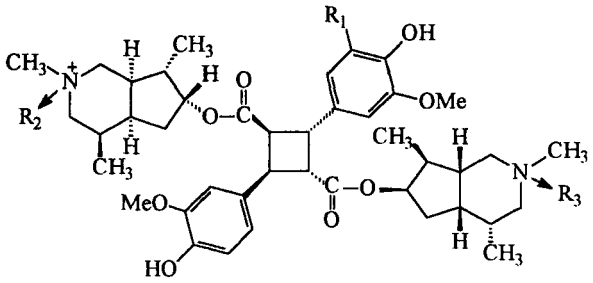
Additional studies on the aerial parts of *Incarvillea sinensis* led to the isolation of four new monoterpene alkaloids (*247*). Incarvine D (**393**), $[\alpha]_D$ −4.2°,



393



394



	R_1	R_2	R_3
395	OCH_3	—	—
396	H	O	—
397	H	—	O
398	H	O	O

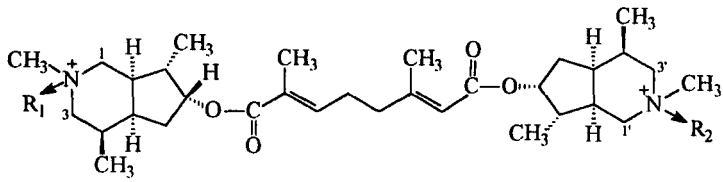
showed a M^+ at *m/z* 351 and base peaks at *m/z* 182 [incarvilline-H]$^+$ and 166 [incarvilline-OH]$^+$. The ^1H and ^{13}C NMR spectra showed a series of resonances indicating the presence of incarvilline (**35**), leaving ten carbon resonances, which, through heteronuclear correlation spectroscopy, were assigned to a methyl, an olefinic methyl, an olefinic proton, six methylene protons, and two oxygenated methine protons. This moiety was characterized as tetrahydroalcohol **394,** corresponding to Hildebrandt's acid (**39**). The HMBC spectrum established the linkage between C–1′ of the monoterpene and H-7 of the incarvilline unit, and thus incarvine D has the structure **393** (*247*).

Methoxyincarvillateine (**395**), $[\alpha]_D$ −4.0°, showed an M^+ at *m/z* 748 and the ^{13}C NMR spectrum indicated the presence of a cycobutane ring, as in incarvillateine (**34**). The additional 30 amu compared with **34** was traced

to a methoxy group (δ_H 3.90; δ_C 56.2 ppm) at the 5-position on a 3,5-dimethoxybenzyl unit. HMBC spectroscopy established these relationships, and thus the structure of methoxyincarvillateine was shown to be **395** (*247*).

Incarvillateine *N*-oxide (**396/397**), $[\alpha]_D$ −19.2°, displayed (FAB-MS) a $(M + 1)^+$ at *m/z* 751. The NMR spectrum was quite similar to that of **34,** although substantial shifts were observed for the *N*-methyl groups (to δ_H 3.09 from 2.17 ppm; to δ_C 61.44 from 46.0 ppm) and the adjacent methylene resonances, indicating the presence of an *N*-oxide moiety. The multiplicity of the signals indicated that the isolate was a mixture, and treatment with *m*-CPBA gave a product, **398,** identical to that derived from the similar treatment of **34.** Thus in **398** both N and N′ were oxidized, whereas the isolate was a mixture of **396** and **397** in which one each of the N atoms was oxidized (*247*).

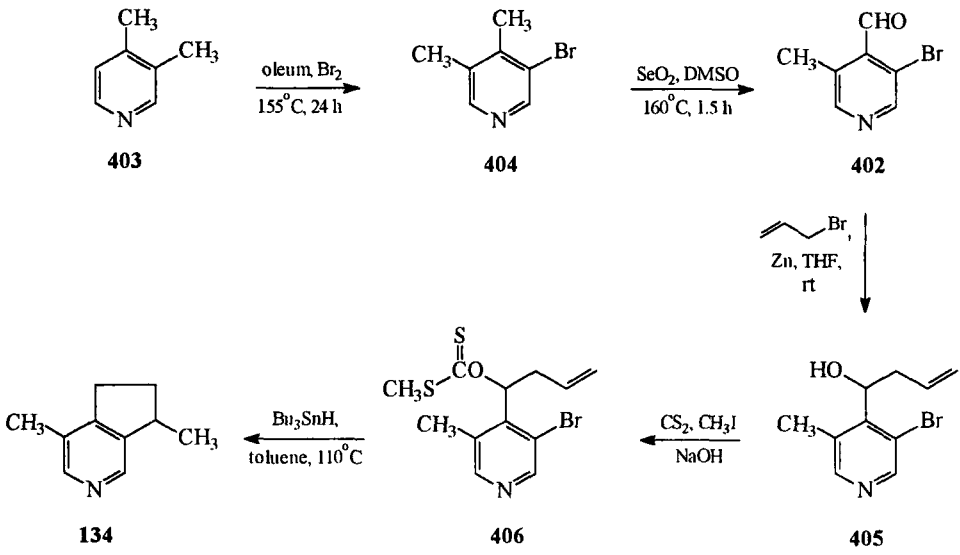
The fourth isolate described was incarvine A *N*-oxide (**399/400**), $[\alpha]_D$ −14.8°, showing a FAB-MS M^+ at *m/z* 544, and whose ^1H NMR spectrum was very similar to that of **38** except that the *N*-methyl group was shifted downfield by 1.05 ppm, as were the adjacent methylene protons. The ^{13}C NMR spectrum also showed corresponding shifts of the *N*-methyl groups by 15.35 ppm to 61.25 ppm, and for the methylene groups at C-1/1′ by 10.13 ppm to 67.23 ppm and at C-3/3′ by 8.86 ppm to 66.16 ppm. Once again, the NMR spectrum suggested that the isolate was a mixture of the two mono-*N*-oxides **399** and **400,** and this was confirmed when incarvine A *N*-oxide and incarvine A (**38**) yielded the same *N,N′*-dioxide **401** (*247*).



	R_1	R_2
399	O	—
400	—	O
401	O	O

Synthesis of (±) Actinidine (**134**)

A new synthesis of (±)-actinidine (**134**) has been described by Jones and Escudero-Hernandez using a pyridine radical cyclization as the



SCHEME 53. Jones and Escudero-Hernandez synthesis of (±)-actinidine (**134**) (*248*).

crucial step (*248*). This is an extension of earlier work on the synthesis of (±)-oxerine (**8**) (*188*). The key intermediate, 3-bromo-4-formyl-5-methylpyridine (**402**) was synthesized from 3,4-dimethyl-pyridine (**403**). Bromination under forcing conditions (oleum at 155°C) gave the 3-bromo derivative **404,** which was oxidized with SeO_2 in DMSO at 160°C to afford **402.** Reaction with allyl bromide and activated zinc gave the homoallylic alcohol **405** in 86% yield. Further reaction under phase transfer conditions with NaOH, CS_2, CH_3I, and catalytic Bu_4NHSO_4 afforded the xanthate **406** in 79% yield, which could by cyclized with an excess of tributyltin hydride in 66% yield to (±)-actinidine (**134**) (Scheme 53) (*248*).

Acknowledgments

The author is greatly indebted to Ms. Kyong Hee Lee for her excellent assistance in the development of the literature background for this manuscript and also for the preparation of the structures and schemes.

References

1. G. A. Cordell, *Alkaloids* **16,** 432 (1977).
2. G. M. Strunz and J. A. Findlay, *Alkaloids* **26,** 89 (1985).
3. G. A. Cordell, "Introduction to Alkaloids: A Biogenetic Approach," J. Wiley & Sons, New York, New York, 1981.
4. V. A. Snieckus, *Alkaloids* (*London*) **5,** 56 (1975).
5. A. R. Pinder, *Alkaloids* (*London*) **6,** 54 (1976).
6. A. R. Pinder, *Alkaloids* (*London*) **7,** 35 (1977).
7. A. R. Pinder, *Alkaloids* (*London*) **8,** 37 (1978).
8. A. R. Pinder, *Alkaloids* (*London*) **9,** 35 (1979).
9. A. R. Pinder, *Alkaloids* (*London*) **10,** 30 (1981).
10. A. R. Pinder, *Alkaloids* (*London*) **11,** 29 (1981).
11. A. R. Pinder, *Alkaloids* (*London*) **12,** 35 (1982).
12. A. R. Pinder, *Alkaloids* (*London*) **13,** 44 (1983).
13. A. R. Pinder, *Nat. Prod. Rep.* **1,** 225 (1984).
14. A. R. Pinder, *Nat. Prod. Rep.* **2,** 181 (1985).
15. A. R. Pinder, *Nat. Prod. Rep.* **3,** 171 (1986).
16. A. R. Pinder, *Nat. Prod. Rep.* **4,** 527 (1987).
17. A. R. Pinder, *Nat. Prod. Rep.* **6,** 67 (1989).
18. A. R. Pinder, *Nat. Prod. Rep.* **6,** 515 (1989).
19. A. R. Pinder, *Nat. Prod. Rep.* **7,** 447 (1990).
20. A. R. Pinder, *Nat. Prod. Rep.* **9,** 17 (1992).
21. A. R. Pinder, *Nat. Prod. Rep.* **9,** 491 (1992).
22. A. O. Plunkett, *Nat. Prod. Rep.* **11,** 581 (1994).
23. D. O'Hagan, *Nat. Prod. Rep.* **14,** 637 (1997).
24. K. P. Tiwari, P. K. Minocha and M. Masood, *Pol. J. Chem.* **54,** 857 (1980).
25. M.-M. Janot, J. Guilhem, O. Contz, G. Venera, and E. Cionga, *Ann. Pharm. Fr.* **37,** 413 (1979).
26. A. Takahashi, S. Kurasawa, D. Ikeda, Y. Okami, and T. Takeuchi, *J. Antibiot.* **42,** 1556 (1989).
27. R. Benkrief, Y. Ranarivelo, F. Tillequin, M. Koch, A.-L. Skaltsounis, J. Pusset, and T. Sévenet, *Phytochemistry,* in press, 1998.
28. M. Willems, *Arch. Pharm.* (*Weinheim*) **320,** 229 (1988).
29. M. Willems, *Arch. Pharm.* (*Weinheim*) **320,** 1245 (1987).
30. J. W. McCoy and F. R. Stermitz, *J. Nat. Prod.* **46,** 902 (1983).
31. J. L. Pousset, J. Levesque, A. Cavé, F. Picot, P. Potier and R. R. Paris, *Plantes méd. phytothér.* **8,** 51 (1974).
32. D. Bishay and P. J. Hylands, *J. Pharm. Pharmacol.* **30,** 80P (1978).
33. D. W. Bishay, S. A. Ross, and P. J. Hylands, *Planta Med.* **37,** 253 (1979).
34. J. L. Lopez, J. Pusset, and A. San Feliciano, *J. Nat. Prod.* **51,** 829 (1988).
35. M. R. Roby and F. R. Stermitz, *J. Nat. Prod.* **47,** 846 (1984).
36. G. H. Harris, E. C. Finman, F. R. Stermitz and L. Castedo, *J. Nat. Prod.* **51,** 543 (1988).
37. A.-L. Skaltsounis, S. Michel, F. Tillequin, and M. Koch, *Tetrahedron Lett.* **25,** 2783 (1984).
38. S. Michel, A.-L. Skaltsounis, F. Tillequin, M. Koch, and L. Aki Assi, *J. Nat. Prod.* **48,** 86 (1985).
39. A.-L. Skaltsounis, S. Michel, F. Tillequin, M. Koch, J. Pusset, and G. Chauvière, *Helv. Chim. Acta* **68,** 1679 (1985).

40. C. A. Boros, F. Stermitz, and G. H. Harris, *J. Nat. Prod.* **53,** 72 (1990).
41. A. Abdusamatov, A. Samatov, and S. Yu Yunusov, *Chem. Nat. Comp.* **12,** 116 (1976).
42. A. P. Lins and J. D'arc Felicio, *Phytochemistry* **34,** 876 (1993).
43. Y.-M. Chi, F. Hashimoto, W.-M. Yan, T. Nohara, M. Yamashita, and N. Marubayashi, *Chem. Pharm. Bull.* **45,** 495 (1997).
44. L. B. de Silva, W. H. M. W. Herath, K. M. Navaratne, Atta-ur-Rahman, I. I. Vohra and M. I. Choudhary, *Proc. Sri Lanka Assoc. Adv. Sci.* **43,** 201 (1987).
45. E. M. Dickinson and G. Jones, *Tetrahedron* **25,** 1523 (1969).
46. G. Jones, G. Ferguson, and W. C. Marsh, *J. Chem. Soc., Chem. Commun.,* 994 (1971).
47. G. Ferguson and W. C. Marsh, *J. Chem. Soc., Perkin Trans. II* 1124 (1975).
48. Y.-M. Chi, W.-M. Yan, and J.-S. Li, *Phytochemistry,* **29,** 2376 (1990).
49. Y.-M. Chi, W.-M. Yan, D.-C. Chen, H. Noguchi, Y. Iitaka, and U. Sankawa, *Phytochemistry,* **31,** 2930 (1992).
50. Y.-M. Chi, F. Hashimoto, W.-M. Yan, and T. Nohara, *Phytochemistry* **40,** 353 (1995).
51. Y.-M. Chi, F. Hashimoto, W.-M. Yan, and T. Nohara, *Phytochemistry,* **39,** 1485 (1995).
52. H.-Y. Zhang, W.-M. Yan, and D.-C. Chen, *Yaoxue Xuebao* **27,** 113 (1992).
53. D. Gournelis, A.-L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and S. Labarre, *J. Nat. Prod.* **52,** 306 (1989).
54. H. Ripperger, *Phytochemistry* **17,** 1069 (1978).
55. T.-S. Kam, K. Yoganathan, and C. Wei, *Nat. Prod. Lett.* **8,** 231 (1996).
56. T.-S. Kam, K. Yoganathan, and C. Wei, *J. Nat. Prod.* **60,** 673 (1997).
57. C. Kan-Fan, T. Sévenet, H. A. Hadi, M. Bonin, J.-C. Quiron, and H.-P. Husson, *Nat. Prod. Lett.* **7,** 283 (1995).
58. K. Homberger and M. Hesse, *Helv. Chim. Acta* **67,** 237 (1984).
59. H. E. A. Saad, R. Anton, J. C. Quiron, G. Chauviere, and J. Pusset, *Tetrahedron Lett.* **29,** 615 (1985).
60. R. K. Chaudhari, O. Sticher, and T. Winkler, *Tetrahedron Lett.* **22,** 559 (1981).
61. S. S. Popov, N. L. Marekov, and L. Evststieva, *Izv. Khim.* **14,** 175 (1981).
62. K. J. Harkiss and D. Swift, *Tetrahedron Lett.* 4773 (1970).
63. K. J. Harkiss, *Planta Med.* **20,** 108 (1971).
64. Atta-ur-Rahman, I. I. Vohra, M. I. Chaudhary, L. B. de Silva, W. H. M. W. Herath and K. M. Navaratne, *Planta Med.* 461 (1988).
65. R. Benkrief, A.-L. Skaltsounis, F. Tillequin, M. Koch and J. Pusset, *Planta Med.* **57,** 79 (1991).
66. S. Baassou, H. Mehri, A. Rabaron, M. Plat and T. Sévenet, *Ann. Pharm. Fr.* **39,** 167 (1981).
67. S. Baassou, H. Mehri, and M. Plat, *Ann. Pharm. Fr.* **45,** 49 (1987).
68. F. R. Stermitz, G. H. Harris and W. Jing, *Biochem. Syst. Ecol.* **14,** 499 (1986).
69. A.-L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and G. Chauviere, *Heterocycles* **26,** 599 (1987).
70. E. M. Nobrega, A. A. Craveiro, J. T. Welch, T. Nicholson, and J. A. Zubieta, *J. Nat. Prod.* **51,** 962 (1988).
71. P. Thepenier, M.-J. Jacquier, G. Massiot, L. Le Men-Olivier, and C. Delaude, *Phytochemistry* **29,** 686 (1990).
72. K. Ghedira, M. Zeches-Hanrot, B. Richard, G. Massiot, L. Le Men-Oilivier, T. Sévenet and S. H. Goh, *Phytochemistry,* **27,** 3955 (1988).
73. G. Massiot, A. Boumendjel, J.-M. Nuzillard, B. Richard, L. Le Men-Olivier, B. David, and H. A. Hadi, *Phytochemistry* **31,** 1078 (1992).
74. T. Sévenet, A. Husson and H.-P. Husson, *Phytochemistry* **15,** 576 (1976).
75. B. Franck, U. Petersen, and F. Hüper, *Angew. Chem. Int. Ed. Engl.* **9,** 891 (1970).
76. K. Biswas and G. S. Saharia, *Ind. J. For.* **1,** 66 (1978).

77. R. K. Chaudhuri and O. Sticher, *Planta Med.* **39,** 217A (1980).
78. R. K. Chaudhuri and O. Sticher, *Helv. Chim. Acta* **63,** 1045 (1980).
79. Kh. A. Kadyrov, V. I. Vinogradova, A. Abdusamatov, and S. Yu Yunusov, *Khim. Prir. Soedin.* **10,** 683 (1974).
80. Kh. A. Kadyrov, A. Abdusamatov, and S. Yu Yunusov, *Chem. Nat. Comp.* **11,** 286 (1975).
81. M. R. Roby and F. R. Stermitz, *J. Nat. Prod.* **47,** 854 (1984).
82. A. Abdusamatov. S. Khakimdzhaov, and S. Yu Yunusov, *Khim. Prir. Soedin.,* **5,** 457 (1969).
83. S. Khakimdzhanov, A. Abdusamatov, and S. Yu Yunusov, *Khim. Prir. Soedin.* **6,** 142 (1970).
84. D. Gross, W. Berg, and H. R. Schütte, *Phytochemistry* **12,** 201 (1975).
85. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.* **34,** 2543 (1969).
86. I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.* **113,** 4092 (1991).
87. A. J. Birch, M. Kocor, N. Sheppard, and J. Winter, *J. Chem. Soc.* 1503 (1962).
88. Y.-M. Chi, F. Hashimoto, T. Nohara, M. Nakamura, T. Yoshizawa, M. Yamashita, and N. Marubayashi, *Proc. 38th Symp. Chem. Nat. Prod. Sendai, Japan, October, 1996* 48 (1996).
89. B. Dohnal, *Acta Soc. Bot. Pol.* **45,** 369 (1976).
90. Y. Hammouda and M. M. Motawi, *Egypt. Pharm. Bull.* **41,** 73 (1959).
91. G. Jones, H. M. Fales and W. C. Wildman, *Tetrahedron Lett.* 397 (1963).
92. Y. Hammouda, M. Plat, and J. Le Men, *Ann. Pharm. Fr.* **21,** 699 (1963).
93. F. Murai and M. Tagawa, *Chem. Pharm. Bull.* **28,** 1730 (1980).
94. A. Takahashi, D. Ikeda, H. Nakamura, H. Naganawa, S. Kurasawa, Y. Okami, T. Takeuchi, and Y. Iitaka, *J. Antibiot.* **42,** 1562 (1989).
95. X.-T. Liang, D.-Q. Yu, and F.-Y. Fu, *Sci. Sinica* **14,** 869 (1965).
96. H. Inouye, S. Ueda, and N. Shimokawa, *Yakugaku Zasshi,* **86,** 1202 (1966).
97. D. W. Bishay, W. H. Shelver, and S. K. Wahba Khalil, *Planta Med.* **33,** 422 (1978).
98. H. Inouye, T. Yoshida, Y. Nikamura, and S. Tobita, *Chem. Pharm. Bull.* **18,** 1889 (1970).
99. R. P. Rooney and S. A. Evans, *J. Org. Chem.* **45,** 180 (1980).
100. R. Lett and A. Marquet, *Tetrahedron* **30,** 3379 (1974).
101. A. Samatov, S. T. Akramov and S. Yu Yunusov, *Khim. Prir. Soedin.* 182 (1967).
102. N. K. Hart, S. R. Johns and J. K. Lamberton, *Aust. J. Chem.* **21,** 1321 (1968).
103. N. K. Hart, S. R. Johns and J. K. Lamberton, *Aust. J. Chem.* **24,** 1739 (1971).
104. G. Giacomello, F. Gualtieri, F. M. Riccieri, and M. L. Stein, *Tetrahedron Lett.* 1117 (1965).
105. R. Tan and A. Taurins, *Tetrahedron Lett.* 2737 (1965).
106. N. Ikehawa, *Chem. Pharm. Bull.* **6,** 269 (1958).
107. A. Taurins and R. T. Li, *Can. J. Chem.* **52,** 843 (1974).
108. S. McLean and D. G. Murray, *Can. J. Chem.* **48,** 867 (1970).
109. E. Demole and C. Demole, *Helv. Chim. Acta* **58,** 523 (1975).
110. N. A. Adibatti, P. Thirugnanasambanathan, C. Kulothungan, S. Viswanathan, L. Kameswaran, K. Balakrishna, and E. Skumar, *Phytochemistry* **30,** 2449 (1991).
111. J. Smolanoff, A. F. Kluge, J. Meinwald, A. McPhail, R. W. Miller, K. Hicks and T. Eisner, *Science,* **188,** 734 (1975).
112. G. Purevsuren, Z. Koblocová, and J. Trojánek, *Cesk. Farm.* **36,** 32 (1987).
113. Y. Hirose, K. Yonemitsu, and T. Sonoda, *Shoyakugaku Zasshi* **32,** 121 (1978); *Chem. Abstr.* **90,** 51471v (1979).
114. J. Saxena and C. S. Mathela, *Appl. Environ. Microbiol.* **62,** 702 (1996).
115. A.-K. Borg-Karlson, F. O. Englund, and C. R. Unelius, *Phytochemistry,* **35,** 321 (1994).
116. E. Cionga, V. Popesco, O. Contz and L. Boniforti, *Adv. Mass Spectrom. Biochem. Med.* **1,** 299 (1976).

117. A. Bučková, E. Eisenreichová, M. Haladová, and J. Tomko, *Ann. Fac. Pharm. Univ. Comen.* **31,** 29 (1977).
118. A. Bučkova, K. Grznár, M. Haladová, and E. Eisenreichová, *Cesk. Farm.* **26,** 308 (1977).
119. M.-M. Janot, J. Guilhem, O. Contz, G. Venera, and E. Cionga, *Ann. Pharm. Fr.* **37,** 413 (1979).
120. Y. Imakura, S. Kobayashi, Y. Yamahara, M. Kihara, M. Tagawa, and F. Murai, *Chem. Pharm. Bull.* **33,** 2220 (1985).
121. R. L. Arsianian and F. R. Stermitz, *Phytochem. Anal.* **2,** 35 (1991).
122. S. I. Balbaa, M. S. Kargwya, and M. S. Afifi, *U. A. R. J. Pharm. Sci.* **12,** 35 (1971).
123. Z. F. Ahmed, A. M. Rizk and F. M. Hammouda, *Postep Dziedzinie Leku Rosl., Pr. Ref. Dosw. Wygloszone Symp.* 20 (1972); *Chem. Abstr.* **78,** 94856u (1973).
124. H. Ripperger, *Pharmazie* **34,** 577 (1979).
125. Yu. D. Sadykov, M. Khodzhimatov, and V. A. Degtyarev, *Dokl. Akad. Nauk Tadzh. SSR* **27,** 452 (1984); *Chem. Abstr.* **102,** 201177m (1985).
126. T. Ravao, B. Richard, M. Zeches, G. Massiot, and L. Le Men-Olivier, *Tetrahedron Lett.* **26,** 837 (1985).
127. G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, H. Jacquemin, and S. K. Kan, *J. Nat. Prod.,* **46,** 708 (1983).
128. H. Ripperger, *Pharmazie* **35,** 235 (1980).
129. E. Seguin, F. Hotellier, M. Koch and T. Sévenet, *J. Nat. Prod.* **47,** 687 (1984).
130. G. Massiot, P. Thepenier, M.-J. Jacquier, L. Le Men-Olivier, and C. Delaude, *Phytochemistry,* **31,** 2873 (1992).
131. M. Bruix, A. Rumbero and P. Vasquez, *Phytochemistry* **33,** 1257.
132. A. Pande and V. N. Shukla, *Fitoterapia* **66,** 467 (1995).
133. P. V. Sharma, *Indian J. Pharm. Sci.* **44,** 36 (1982).
134. P. V. Sharma, *Indian Drugs* **21,** 395 (1984).
135. A. N. Aliev, I. S. Movsumov and E. Kh. Bagirov, *Chem. Nat. Comp.* **11,** 708 (1975).
136. T. U. Rakhmatulaev, *Khim Prir. Soedin* **7,** 114 (1971).
137. A. M. Aliev and I. S. Movsumov *Zerb. Med. Zh.* **58,** 36 (1981); *Chem. Abstr.* **97,** 88682k (1982).
138. N.-J. Sun and C.-F. Xia, *Zhongyao Tongbao* **9,** 33 (1984); *Chem. Abstr.* **100,** 171576e (1984).
139. J. Vercauteren, G. Massiot, T. Sévenet, B. Richard, V. Lobjois, L. Le Men-Olivier, and J. Lévy, *Phytochemistry* **20,** 1411 (1981).
140. B. Legseir, A. Cherif, B. Richard, J. Pusset, S. Labarre, G. Massiot, and L. Le Men-Olivier, *Phytochemistry* **25,** 1735 (1986).
141. D. W. Bishay, W. H. Shelver, and S. K. Wahba Khalil, *Planta Med.* **33,** 422 (1978).
142. A. Kun-Anake, and C. Ragvatin, *Bull. Dept. Med. Sci. Mahidol Univ.* **18,** 1 (1976).
143. C. Delaude, *Bull. Soc. R. Sci. Liege* **54,** 18 (1985).
144. C. Delaude and E. Darimont, *Bull. Soc. R. Sci. Liege* **54,** 127 (1985).
145. L. I. Topuriya, *Chem. Nat. Compd.* **14,** 353 (1978).
146. S. Ghosal, A. A. K. Singh and K. Biswas, *Planta Med.* **49,** 240 (1983).
147. S.-Y. Yang, W.-W. Wang, M.-S. Huang, and Z.-P. Li, *Chung Ts'ao Yao* **12,** 7 (1981).
148. S. Michel, F. Tillequin, M. Koch, and L. Ake Assi, *J. Nat. Prod.* **45,** 489 (1982).
149. F. Asai, M. Iinuma, T. Tanaka, and S. Matsuura, *Yakugaku Zasshi* **102,** 690 (1982).
150. S. Ghosal, P. V. Sharma, R. K. Chaudhuri, and S. K. Bhattacharya, *J. Pharm. Sci.,* **62,** 926 (1973).
151. X.-F. Guo, and C. P. Chen, *Chung Ts'ao Yao* **13,** 200 (1986). *Chem. Abstr.* **94,** 71293 (19??).
152. T.-S. Wu, H.-J. Tien, and C.-N. Lin, *J. Chin. Chem. Soc. (Taipei)* **23,** 53 (1976); *Chem. Abstr.* **85,** 2572s (1976).

153. L.-L. Hou, M.-Q. Chen, and H. Zhu, *Zhongcaoyao* **12,** 352 (1981). *Chem. Abstr.* **96,** 139646 (1982).
154. B. Achari, E. Ali, P. P. Ghosh Dastidir, R. R. Sinha and S. C. Pakrashi, *Planta Med. Suppl. 5* (1980).
155. M.-J. Chen, L.-L. Hou, and H. Zhu, *Chi Wu Hsueh Pao* **22,** 257 (1980); *Chem. Abstr.* **94,** 12818b (1981).
156. S.-C. Liu and A. B. Segelman, *Abstr. Int. Res. Cong. Nat. Prod. Abstr.* 15 (1975).
157. S.-C. Liu and A. B. Segelman, *Diss. Abstr.* **46,** 810 (1985).
158. L.-T. Lin, T.-Y. Chao, and J.-S. Hsu, *Acta Chim. Sinica* **35,** 227 (1977).
159. J.-S. Hsu, T.-Y. Chao, L.-Z. Lin, C.-F. Hsu, *Hua Hsueh Hsueh Pao,* **35,** 193 (1977); *Chem. Abstr.* **90,** 28930k (1979).
160. S.-J. Yang, Z.-Z. Wu and H.-H. Ren, *Zhongguo Yaoke Daxue Xuebao* **24,** 281 (1993); *Chem. Abstr.* **120,** 50155w (1994).
161. J. Kunitomo, M. Oshikata, K. Miyata, and K. Masui, *Shoyakugaku Zasshi* **37,** 294 (1983).
162. S. Baassou, H. Mehri, and M. Plat, *Phytochemistry,* **17,** 1449 (1978).
163. S. Sakai, N. Aimi, K. Takahashi, M. Kitagawa, K. Yamaguchi, and J. Haginiwa, *Yakugaku Zasshi* **94,** 1274 (1974).
164. M. Baoua, J.-M. Bessiere, B. Pucci, and J.-P. Rigaud, *Phytochemistry* **19,** 718 (1980).
165. A. Chatterjee, A. Banerji, and M. Chakrabarty, *Planta Med.* **28,** 109 (1975).
166. G. W. K. Cavill, P. L. Robertson, J. J. Brophy, D. V. Clark, R. Duke, C. J. Orton, and W. D. Plant, *Tetrahedron* **38,** 1931 (1982).
167. J. W. Wheeler, T. Olagbemiro, A. Nash and M. S. Blum, *J. Chem. Ecol.* **3,** 241 (1977).
168. K. Dettner and G. Schwinger, *Z. Naturforsch. C* **46,** 366 (1986).
169. M. Lorenz, W. Boland, and K. Dettner, *Angew. Chem. Int. Ed. Engl.* **32,** 912 (1993).
170. H. R. Arthur and S. N. Loo, *Phytochemistry,* **5,** 977 (1966).
171. L. A. Mitscher, A. B. Ray, and A. Chatterjee, *Experientia* **27,** 16 (1971).
172. T. Sévenet, B. C. Das, J. Parello, and P. Potier, *Bull. Soc. Chim. Fr.* 3120 (1970).
173. J. W. McCoy, M. R. Roby, and F. R. Stermitz, *J. Nat. Prod.* **46,** 894 (1983).
174. F. Bailleul, P. Delaveau, A. Rabaron, M. Plat, and M. Koch, *Phytochemistry,* **16,** 723 (1977).
175. S. McLean and D. G. Murray, *Can. J. Chem.* **50,** 1478 (1972).
176. T. Sakan, A. Fujino, F. Murai, A., Suzui and Y. Butsugan, *Chem. Bull. Soc. Japan* **32,** 1155 (1959); T. Sakan, A. Fujino, F. Murai, A, Suzui, Y. Butsugan, and Y. Terashima, *Chem. Bull. Soc. Japan* **33,** 712 (1960).
177. J. D. Wuest, A. M. Madonik, and D. C. Gordon, *J. Org. Chem.* **42,** 2111 (1977).
178. L. B. Davis, S. G. Greenberg and P. G. Sammes, *J. Chem. Soc., Perkin Trans. I* 1909 (1981).
179. M. Nitta, A. Sekiguchi, and H. Koba, *Chem. Lett.* 933 (1981).
180. J. Cossy and D. Belotti, *Tetrahedron Lett.* **29,** 6113 (1988).
181. Y. Ranarivelom F. Hoetlier, A.-L. Skaltsounis, and F. Tillequin, *Heterocycles,* **31,** 1727 (1990).
182. J. Cossy, D. Belotti, and C. Leblanc, *J. Org. Chem.* **58,** 2351 (1993).
183. M.-J. Shiao, W.-L. Chia, C.-J. Peng, and C.-C. Shen, *J. Org. Chem.* **58,** 3162 (1993).
184. S. A. Achmad and G. W. K. Cavill, *Aust. J. Chem.* **16,** 858 (1963).
185. J. Zsindely and H. Schmid, *Helv. Chim. Acta* **51,** 1510 (1968).
186. J. Cossy, D. Belotti and J. P. Pete, *Tetrahedron Lett.* **28,** 4545 (1987).
187. Y. Aoyagi, T. Inariyama, Y. Arai, S. Tauchida, Y. Mtuda, H. Kobayashi, A. Ohta, T. Kurihara, and S. Fujihara, *Tetrahedron,* **50,** 13575 (1994).
188. K. Jones and A. Fiumana, *Tetrahedron Lett.* **37,** 8049 (1996).
189. J. Cossy and C. Leblanc, *Tetrahedron Lett.* **32,** 3051 (1991).
190. W. Opplozer, R. Pitteloud and H. F. Strauss, *J. Am. Chem. Soc.* **104,** 6476 (1982).

191. W. Oppolzer and E. J. Jacobson, *Tetrahedron Lett.* **27,** 1141 (1986).
192. C. G. Casinovi, J. A. Garbarino, and G. B. Marini-Bettolo, *Chem. Ind. (London)* 253 (1961).
193. M. M. Cid, U. Eggnauer, H. P. Weber, and E. Pombo-Villar, *Tetrahedron Lett.* **32,** 7233 (1991).
194. S. M. Roberts, C. Smith, and R. J. Thomas, *J. Chem. Soc., Perkin Trans. I* 1493 (1990).
195. M. M. Cid and E. Pombo-Villar, *Helv. Chim. Acta* **76,** 1591 (1993).
196. T. Tsunoda, F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto and S. Itó, *Tetrahedron Lett.* **37,** 2463 (1996).
197. T. Tsunoda, S. Tatsuki, K. Kataoka and S. Itŏ, *Chemistry Lett.* 543 (1996).
198. D. Tanaka, T. Yoshino, I. Kuono, M. Miyashita, and H. Irie, *Tetrahedron,* **49,** 10253 (1993).
199. Y. Hammouda and M. S. Amer, *J. Pharm. Sci.* **55,** 1452 (1966).
200. T. Mamose, M. Kinoshita and T. Imanishi, *Heterocycles* **12,** 243 (1979).
201. M. Alam, J. D. Baty, G. Jones and C. Moore, *J. Chem. Soc., Sect. C* 1520 (1969).
202. T. Imanishi, N. Yagi and M. Hanaoka, *Tetrahedron Lett.* **22,** 667 (1981).
203. T. Imanishi, N. Yagi and M. Hanaoka, *Chem. Pharm. Bull.* **31,** 1243 (1983).
204. T. Kametani, Y. Suzuki, C. Ban, and T. Honda, *Heterocycles* **26,** 1491 (1987).
205. M. Miyashita, D. Tanaka, T. Shiratani, and H. Irii, *Chem. Pharm. Bull.* **40,** 1614 (1992).
206. G. Vidari, M. Tripoloni, P. Novella, P. Allegrucci, and L. Garlaschelli, *Tetrahedron: Assymetry* **8,** 2893 (1997).
207. J.-L. Brayer, J.-P. Alazard, and C. Thal, *Tetrahedron Lett.* **29,** 643 (1988).
208. J.-L. Brayer, J.-P. Alazard, and C. Thal, *Tetrahedron Lett.* **24,** 4193 (1983).
209. J.-P. Alazard and C. Thal, *Tetrahedron Lett.* **27,** 1319 (1986).
210. J.-L. Brayer, J.-P. Alazard, and C. Thal, *Tetrahedron* **46,** 5187 (1990).
211. J.-P. Alazard, A. Leboff, and C. Thal, *Tetrahedron* **47,** 9195 (1991).
212. F. Bracher and K. Mink, *Annalen* 645 (1995).
213. F. Bracher and T. Papke, *Monatsch. Chem.* **126,** 805 (1995).
214. Unpublished work, cited as personal correspondence in ref. 216.
215. S. Ghosal, R. K. Chaudhuri, M. P. Tiwari, A. K. Singh and F. W. Wehrli, *Tetrahedron Lett.* 403 (1974).
216. B. Ganem, *J. Am. Chem. Soc.* **98,** 224 (1976).
217. T. Hayashi and M. Higashino, *Yakugaku Zasshi,* **96,** 362 (1976).
218. F.-Y. Fu and N.-C. Sun, *Yao Hsueh Hsueh Pao* **6,** 198 (1958); *Chem. Abstr.* **53,** 8310 (1959).
219. J.-F. Zhong and J.-H. Lin, *Acta Pharm. Sinica* **23,** 601 (1988).
220. G. Büchi and R. E. Manning, *Tetrahedron Lett.* 5 (1960).
221. H. Inouye, S. Tobita and M. Moriguchi, *Chem. Pharm. Bull.* **24,** 1406 (1976).
222. S. S. Popov, N. L. Marekov, and T. N. Do, *J. Nat. Prod.* **51,** 765 (1988).
223. R. Benkrief, A.-L. Skaltsounis, F. Tillequin, M. Koch and J. Pusset, *J. Nat. Prod.,* **54,** 532 (1991).
224. S. M. Fredericksen and F. R. Stermitz, *J. Nat. Prod.* **59,** 41 (1996).
225. M. Hattori, Y. Kawata, K. Inoue, Y.-Z. Shu, Q.-M. Che, T. Namba, and K. Kobashi, *Phytother. Res.* **4,** 66 (1990).
226. H. Franzyk, S. M. Fredericksen, and S. R. Jensen, *J. Nat. Prod.* **60,** 1012 (1997).
227. Y. Kawata, M. Hattori, T. Akao, K. Kobashi, and T. Namba, *Planta Med.* **57,** 536 (1991).
228. A. I. El-Sedawy, Y.-Z. Shu, M. Hattori, K. Kobashi, and T. Namba, *Planta Med.* **55,** 147 (1989).
229. F. Guillier, F. Nivoliers, J. Bourguignon, G. Dupas, F. Marsais, A. Godard, and G. Quéguiner, *Tetrahedron Lett.* **33,** 7355 (1992).
230. T. R. Kelly and J. J. Walsh, *J. Org. Chem.* **57,** 6657 (1992).
231. K. Matsuo and T. Arase, *Chem. Pharm. Bull.* **42,** 715 (1994).

232. K. Matsuo and T. Arase, *Chem. Pharm. Bull.* **43,** 2091 (1995).
233. K. Matsuo, M. Kobayashi, and K. Sugimoto, *Heterocycles* **45,** 1191 (1997).
234. K. Mori and K. Fukamatsu, *Liebigs Ann. Chem.* 489 (1992).
235. H. Hong and D. L. Comina, *J. Org. Chem.* **61,** 391 (1996).
236. D. Villemin and L. Lian, *Tetrahedron Lett.* **37,** 8733 (1996).
237. T. Sugahara, Y. Komatsu, and S. Takano, *J. Chem. Soc., Chem. Commun.* 214 (1984).
238. W. Berg, D. Gross, H. R. Schütte and M. Herrmann, *Pharmazie* **32,** 41 (1977).
239. J. Bruneton, "Pharmacognosy, Phytochemistry, Medicinal Plants," Lavoisier Publishing, Paris, 1995, p. 478.
240. Y.-C. Shen and P.-W. Hsieh, *J. Nat. Prod.* **60,** 453 (1997).
241. Y.-C. Shen and P.-W. Hsieh, *Phytochemistry* **46,** 1197 (1997).
242. C. Kan-Fan, J. A. Zuanazzi, J.-C. Quiron, H.-P. Husson and A. Henriques, *Nat. Prod. Lett.* **7,** 317 (1995).
243. B. Dohnal, *Acta Soc. Bot. Pol.* **45,** 93 (1976).
244. A. S. C. Wan, E. Macko, and B. Douglas, *Asian J. Med.* **8,** 334 (1972).
245. J. Yamahara, T. Konoshima, T. Sawada, and H. Fujimura, *Yakugaku Zasshi* **98,** 1446 (1978).
246. H. Wagner, K. Seegert, M. P. Gupta, M. Esposito Avella, and P. Solis, *Planta Med.* 378 (1986).
247. Y.-M. Chi, F. Hashimoto, W.-M. Yan, and T. Nohara, *Phytochemistry* **46,** 763 (1997).
248. K. Jones and M. L. Escudero-Hernandez, *Tetrahedron* **54,** 2275 (1998).

CUMULATIVE INDEX OF TITLES

This Page Intentionally Left Blank

INDEX

ISBN 0-12-469552-3