THE ALKALOIDS

Edited by
ARNOLD BROSSI

VOLUME 28

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Chemistry and Pharmacology

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Chemistry and Pharmacology

Edited by
Arnold Brossi
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PREFACE

The editor-in-chief of this treatise notes with great pleasure that scientists from 18 different countries have contributed to the writing of articles in the last eight volumes, attesting to the fact that the study of alkaloids is a multidisciplinary and international affair.

The diverse group of isoquinoline alkaloids, discussed by Šantavý in Vol. 17 of this text under the heading "Papaveraceae Alkaloids," has been broken up further. "Rhoeadine Alkaloids," discussed in this volume, represent the newest subgroup, including until now about 40 individual representatives of largely unknown pharmacological potential. "The Protoberberine Alkaloids," on the other hand, discussed twice before, have been brought up to date. The chapter also includes a discussion of pharmacological properties of representative alkaloids. The third chapter, "Simple Indolizidine and Quinolizidine Alkaloids," avoids discussion of representatives with fused polycyclic ring systems, such as "Phenanthroindolizidine and Phenanthroquinolizidine Alkaloids," and alkaloid families, such as "Lupine Alkaloids," "Elaeocarpus Alkaloids," "Lythraceae Alkaloids," and "Nuphar Alkaloids," which will be discussed separately. The alkaloids discussed here are representatives of a cross-section of natural sources, including fungi, higher plants, insects, amphibians, and mammals, and the chapters concentrate on chemical synthesis, stereochemical aspects, and some intriguing biological properties of these interesting molecules.

Arnold Brossi

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— CHAPTER 1 —

RHOEADINE ALKALOIDS

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I. Introduction

The rhoeadine alkaloids are always classified with the big isoquinoline family of alkaloids to which they are closely related biogenetically, although in structural terms they differ in having a 3-benzazepine entity. Since 1965, when the correct structure for rhoeadine emerged in the literature, the rhoeadine alkaloids' plant sources, chemistry, biosynthesis, and other concerns have been incorporated into review papers on Papaveraceae or isoquinoline alkaloids, such as those by Manske (*99*) or Šantavý (*177, 178*) in this series. Others from Pfeifer's group (*93, 129, 140*) put more emphasis on history and early chemistry as well as on botanical and phytochemical aspects. Shamma in his books on the isoquinoline alkaloids (*194, 196*) dealt with substantial chemistry, synthesis, and biosynthesis of the rhoeadine alkaloids and, together with Montgomery *et al.* (*105*), provided a useful compilation of their structural, physical, and spectral data. A similar listing that was combined with an outline of their basic chemistry had already been made available by Kametani (*73*). Döpke's (*35*), Cordell's (*29*), or Robinson's (*160*) books dealing with the field of alkaloids include concise reports on chemistry and/or biosynthesis. The *Specialist Periodical Report* series on alkaloids (*11, 50, 103*) has given brief reference as to occurrence, chemistry, and biosynthesis of rhoeadine alkaloids for each year since 1971. Chemotaxonomic aspects of Papaveraceae alkaloids, among them the rhoeadines, have been discussed by Preininger (*151a*).

Being the first treatise on the rhoeadine alkaloids of their own, at least in this series, this review should gather all pertinent information from the literature or previous reports to be as comprehensive as feasible. This, however, does not mean that early chemistry and historical or phytochemical aspects are to be considered in every detail; instead, the reader is referred to previous reviews. Parallel work that merely repeats previous original studies has been outlined briefly or even omitted.

II. Alkaloids and Plants

A. Structural Overview

The rhoeadine group of alkaloids is best presented by rhoeadine itself (**2a**, Table I), which was isolated by Hesse (*51*) from *Papaver rhoeas* L., the common field poppy, in 1865. This review also deals with the *N*-norrhoeadines, notorious as papaverrubines, a name introduced by Pfeifer (*125*) for their deep red coloration developed if treated with dilute mineral acid. The first papaverrubine isolated was porphyroxine, which was found in opium by E. Merck (*104*) as early as 1837. It was later renamed papaverrubine D (**4k**). By contrast, all *N*-methyl alkaloids with concentrated sulfuric acid give a characteristic coloration that changes red → brown → green (*125*). Members of the two groups often co-occur in nature, are difficult to separate, and it was not until 1957 that Awe and Winkler (*5, 7*) showed that pure rhoeadine was not responsible for the red color reaction.

The basic structure common to both groups is made up of a tetrahydro-3-benzazepine entity connected to an isochroman structure*, which inevitably incorporates an acetal or a hemiacetal carbon. The latter character was easily detected in early work, and several structures had been suggested for rhoeadine until Šantavý, and a mass spectroscopic team in a joint paper (*180*) arrived at the structure for rhoeadine (**2a**) in combining degradative work with proton-NMR and mass spectroscopy.

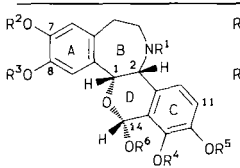
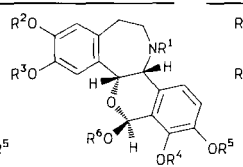
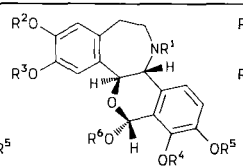
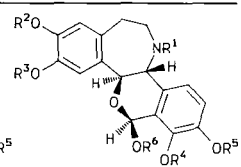
As to structural variation in the rhoeadine group, four oxygen substituents are always present on positions 7, 8, 12, and 13 to show methoxyl, methylenedioxy, or, in a few cases, hydroxy groups. Two of the three chiral centers, namely, C-1 and C-14, are another source of variability, and the *R* configuration consistently observed for the third one (C-2) might be responsible for the positive optical rotation of all naturally occurring rhoeadine alkaloids.

According to Table I, which includes the absolute stereochemistry of the rhoeadine alkaloids, there are two main series, which differ in relative configuration at C-1 and C-2, providing B/D-ring conjuncture, the B/D-trans or the B/D-cis series, with the former being transformed to the latter by boiling 1 *N* mineral acid. The two series each split into two subseries having opposite chirality at C-14, the acetal carbon. Thus in the B/D-trans series there are two types of methyl acetals, the less stable type (**4**) and the more stable one (**3**) showing a 14*S* or 14*R* configuration, respectively, while the hemiacetals (**3**) always have the 14*R* configuration. Apart from this, the B/D-cis series invariably includes methyl acetals of the stable type (**2**), and the hemiacetals (**1**) in general assume the opposite chirality at C-14, i.e., 14*R*. It should be premised that the chirality at C-14 in hemiacetals (**1**) is a special case in that it depends on certain conditions, which are discussed in detail in Section III,D,2,b. Series **4** comprises all less

* The basic skeleton may be referred to as benz[*d*]isochromano[4,3-*b*]azepine.

TABLE I

The Rhoeadine Alkaloids and Their Absolute Configurations at C-1, C-2, and C-14

							B/D-cis (1*R*,2*R*)		B/D-trans (1*S*,2*R*)	
										
	R^1	R^2	R^3	R^4	R^5	R^6	**1** (14*R*)	**2** (14*S*)	**3** (14*R*)	**4** (14*S*)
a	CH_3	CH_2		CH_2		CH_3	—	Rhoeadine	Epiisorhoeadine[a]	Isorhoeadine
b	CH_3	CH_2		CH_2		H	Rhoeagenine	—	Isorhoeagenine	—
c	CH_3	CH_2		CH_2		Glucose	—	—	Isorhoeagenine D-glucoside	—
d	H	CH_2		CH_2		CH_3	—	Papaverrubine E	Epipapaverrubine A[a]	Papaverrubine A
e	CH_3	CH_3	CH_3	CH_2		CH_3	—	Oreodine	Epiglaudine	Glaudine
f	CH_3	CH_3	CH_3	CH_2		H	Oreogenine	—	Glaucamine	—
g	H	CH_3	CH_3	CH_2		CH_3	—	Papaverrubine F	Papaverrubine H[b]	Papaverrubine B
h	CH_3	CH_3	H	CH_2		CH_3	—	*N*-Methyl-*cis*-porphyroxine[a,c]	*N*-Methylepiporphyroxine	*N*-Methylporphyroxine
i	CH_3	CH_3	H	CH_2		H	*N*-Methyl-*cis*-porphyroxigenine[d]	—	*N*-Methylporphyroxigenine[e]	—
k	H	CH_3	H	CH_2		CH_3	—	—	Papaverrubine C	Papaverrubine D[f]
l	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	—	*O*-Methyl-*cis*-alpinigenine[a]	Epialpinine[g]	Alpinine
m	CH_3	CH_3	CH_3	CH_3	CH_3	H	*cis*-Alpinigenine[a]	—	Alpinigenine	—
n	H	CH_3	CH_3	CH_3	CH_3	CH_3	—	—	Epipapaverrubine G[a]	Papaverrubine G

[a] Semisynthetically prepared from related rhoeadines.

[b,c,d,e] Names used for these alkaloids in the original literature were: [b]epipapaverrubine B, [c]*cis*-*N*-methylepiporphyroxine, [d]*cis*-*N*-methyl-14-*O*-demethylepiporphyroxine, [e]*N*-methyl-14-*O*-demethylepiporphyroxine.

[f] The former name was porphyroxine.

[g] Another name is *O*-methylalpinigenine.

stable B/D-trans-(14*S*)-methyl acetals, the only source of which occurred in nature until recently (cf. Section IV,B,4). They may easily be transformed to more stable 14*R* epimers (**3**), even if only catalytic amounts of acid are present. The acetals of type **3**, often recognized from the prefix "epi" or "14-epi" in their names, may be obtained semisynthetically from the corresponding hemiacetals of general formula **3**. They have been given the prefix "*O*-methyl . . ." when not found in plants previously. Alkaloids in Table I prepared by partial synthesis are always indicated in this way. The occurrence of *O*-ethyl acetals in plants has never been verified. At least four ethyl acetals of different rhoeadine alkaloids have been described in connection with the use of ethanol in the isolation procedure and therefore most probably are artifacts, which are listed in Table X.

B. Occurrence

There are approximately 25 naturally occurring rhoeadine alkaloids whose plant origin is substantially confined to the genus *Papaver* L., Papaveraceae. However, two related genera represented by *Bocconia frutescens* L. and several Himalayan *Meconopsis* species were shown to contain them, even though only in traces (*214, 216*). The rhoeadine alkaloids are very common and widespread in the genus *Papaver,* yet are far from ubiquitous; some species not containing them can be seen from previous reviews (*177, 178*). The rhoeadines appear as the major alkaloids in the sections *Orthorhoeades (Rhoeadium)* and *Argemonerhoeades (Argemonidium),* in some plants of the sections *Pilosa* and *Glauca,* and in *Papaver somniferum* (*117*). The papaverrubines (norrhoeadines) in many species do occur in traces detectable by thin layer chromatography (TLC) using an extremely sensitive method for staining (vapors of hydrogen chloride) (*130*).

Natural rhoeadines in Table II are arranged in alphabetical order, with prefixes like "epi" or "iso" being incorporated into the name. Most characteristically, thermodynamically more stable 14-epi compounds (**3**) are rare in nature or even lacking. Epiisorhoeadine (**3a**) and the epipapaverrubines A (**3d**) and G (**3n**) have been obtained only by chemical transformation, while epiglaudine (**3e**), epialpinine (**3l**), or epipapaverrubine B (**3g**) each were identified in singular cases. Moreover, methyl acetals of general formula **3** may be artifacts for two reasons: first they may be formed from hemiacetals of general formula **3** when methanol is used in the isolation process or, second, when methyl acetals of general formula **4** come into contact with acid.

Another problem was that assignments to general formulas **3** or **4** have been made in the literature, which rely on TLC or mass spectroscopy, although proton NMR and/or optical rotation would have been required for this. In Table II, detections of rhoeadines and papaverrubines depending mainly on TLC or methods of similar significance are indicated by reporting the specific method applied.

TABLE II
Naturally Occurring Rhoeadines

Name	Plant sources and references
Alpinigenine (**3m**)	*Papaver alpinum* L. ssp. *alpinum (134)*, ssp. *burseri* (Crantz.) Fedde *(101)*, ssp. *kerneri* (Hayek) Fedde *(101)*, ssp. *rhaeticum* (Ler.) Mgf. *(134)*, ssp. *sendtneri* (Kern.) Schinz et. Keller *(134)*, ssp. *tatricum* Nyar. *(101)*; *P. bracteatum* Lindl. *(39, 95)*; *P. fugax* Poir. *(148)*; *P. floribundum* Desf. *(148)*; *P. orientale* L. *(68, 147, 192)*; *P. pseudo-orientale* (Fedde) Medw. *(147)*
Alpinine (**4l**)	*Papaver alpinum* L. ssp. *alpinum (134)*, ssp. *burseri* (Crantz.) Fedde *(101)* TLC, ssp. *kerneri* (Hayek) Fedde *(134)*, ssp. *rhaeticum* (Ler.) Mgf. *(134)*, ssp. *sendtneri* (Kern.) Schinz et Keller *(134)*, ssp. *tatricum* Nyar. *(101)* TLC; *P. anomalum* Fedde *(145)*; *P. bracteatum* Lindl. *(94, 229)*, MS detection
Epialpinine (**3l**)	*Papaver alpinum* L. ssp. *kerneri* (Hayek) Fedde *(229d)*, ssp. *tatricum* Nyár *(229d)*; *P. bracteatum* Lindl. *(33, 229, 229a)*
Epiglaudine (**3c**)	*Papaver glaucum* Boiss. et Hauskn. as glaupavine that may contain some glaudine *(210)*; *P. tauricola* Boiss. *(187)*
Glaucamine (**3f**)	*Papaver fugax* Poir. *(148)*; *P. glaucum* Boiss. et Hauskn. *(24, 210)*; *P. nudicaule* L. var. *leiocarpum* (Turcz.) Fedde *(101)*; *P. rhoeas* L. *(156)*; *P. tauricola* Boiss. *(187)*
Glaudine (**4e**)	*Papaver anomalum* Fedde *(145)*; *P. armeniacum* (L.) D.C. *(148)*; *P. fugax* Poir. *(148)*; *P. glaucum* Boiss. et Hauskn. *(24, 137)*; *P. rhoeas* L. *(128)*; *P. somniferum* L. *(128)*; *P. tauricola* Boiss. *(187)*
Isorhoeadine (**4a**)	*Meconopsis betonicifolia* Franch. *(216)*; *M. horridula* Hook. f. et Thoms. *(216)*; *M. napaulensis* D.C. *(216)*; *M. rudis* Prain *(216)*; *Papaver arenarium* Marsch.-Bieb. *(156)* TLC; *P. argemone* L. *(156)* TLC; *P. commutatum* Fisch. et Mey. *(116)*; *P. dubium* L. ssp. *lecoquii* (Lamotte) Fedde *(156)*; *P. oreophilum* Rupr. *(136, 230)* TLC; *P. rhoeas* L. *(116, 235)*, var. *decaisnei* Hochst. et Steud. *(156)* TLC, var. *flore albo (156)* TLC, var. *flore pleno (156)* TLC; *P. rupifragum* Boiss. et Reut. *(219)* TLC; *P. syriacum* Boiss. et Blanche *(215)*
Isorhoeagenine (**3b**)	*Papaver commutatum* Fisch. et Mey. *(116)*; *P. rhoeas* L. *(116)*
Isorhoeagenine-D-glucoside (**3c**)	*Papaver commutatum* Fisch. et Mey. *(116)*; *P. rhoeas* L. *(113, 116)*, var. *decaisnei (152)*
N-Methylporphyroxigenine (**3i**)	*Papaver somniferum* L. *(26)*
Oreodine (**2e**)	*Papaver armeniacum* (L.) DC. *(185)*; *P. fugax* Poir. *(148)*; *P. oreophilum* Rupr. *(136, 138)*; *P. tauricola* Boiss. *(187)*; *P. triniifolium* Boiss. *(186)*

(*continued*)

TABLE II (*Continued*)

Name	Plant sources and references
Oreogenine (**1f**)	*Papaver fugax* Poir. *(148); P. oreophilum* Rupr. *(138, 230); P. tauricola* Boiss. *(187)*
Papaverrubine A (**4d**)	*Meconopsis betonicifolia* Franch. *(216); M. napaulensis* DC. *(216); M. paniculata* (D. Don) Prain *(216); M. rudis* Prain *(216); Papaver albiflorum* ssp. *austromoravicum* Kubat *(218)* TLC; *P. atlanticum* Ball. *(130)* TLC; *P. californicum* A. Gray *(116)* TLC; *P. caucasicum* Marsch.-Bieb. *(130)* TLC; *P. commutatum* Fisch. et Mey. *(116)* TLC; *P. decaisnei* Hochst. *(209)* TLC; *P. dubium* L. *(116, 130)* TLC; *P. glaucum* Boiss. et Hauskn. *(130, 155)* TLC; *P. heldreichii* Boiss. *(130)* TLC; *P. latericium* C. Koch *(130)* TLC; *P. lecoquii* Lamotte *(218)* TLC; *P. litwinowii* Fedde ex Bornm. *(217)* TLC; *P. macrostomum* Boiss. et Huet *(130)* TLC; *P. oreophilum* Rupr. *(130, 138)* TLC; *P. pilosum* Sibth. et Smith *(130)* TLC; *P. rhoeas* L. *(19),* var. *flore pleno (152); P. rupifragum* Boiss. et Reut. *(130, 219)* TLC; *P. strigosum* (Bönningh.) Schur. *(130)* TLC; *P. syriacum* Boiss. et Blanche *(215)* TLC
Papaverrubine B (**4g**)	*Papaver alpinum* L. ssp. *kerneri* (Hayek) Fedde *(229d); P. anomalum* Fedde *(145); P. atlanticum* Ball. *(130)* TLC; *P. bracteatum* Lindl. *(152)* TLC; *P. californicum* A. Gray *(116)* TLC; *P. caucasicum* Marsch.-Bieb. *(130)* TLC; *P. commutatum* Fisch. et Mey. *(116)* TLC; *P. feddei* Schwz. *(130)* TLC; *P. fugax* Poir. *(152)* TLC; *P. glaucum* Boiss. et Hauskn. *(126); P. heldreichii* Boiss. *(130, 155)* TLC; *P. hybridum* L. *(130)* TLC; *P. latericium* C. Koch *(130)* TLC; *P. macrostomum* Boiss. et Huet *(130)* TLC; *P. nudicaule* L. *(130)* TLC; *P. oreophilum* Rupr. *(130, 138)* TLC; *P. orientale* L. *(130)* TLC; *P. persicum* Lindl. *(90)* TLC; *P. pilosum* Sibth. et Smith *(130)* TLC; P. *polychaetum* Schott et Kotschy *(90)* TLC; *P. pseudocanescens* M. Pop. *(145); P. radicatum* Rottb. *(19, 130)* TLC, ssp. *hyperboreum* Nordhagen *(130)* TLC; *P. rhoeas* L. *(130)* TLC; P. *rupifragum* Boiss. et Reut. *(130, 219)* TLC; *P. setigerum* DC. *(130)* TLC; *P. somniferum* L. *(63, 128); P. strigosum* (Bönningh.) Schur. *(130)* TLC; *P. triniaefolium* Boiss. *(130, 152)* TLC; *P. urbanianum* Fedde *(154)* TLC
Papaverrubine C (**3k**)	*Meconopsis betonicifolia* Franch. *(216); M. horridula* Hook. f. et Thoms *(216); M. napaulensis* DC. *(216); M. paniculata* (D. Don) Prain *(216); M. robusta* Hook f. et Thoms *(216); M. rudis* Prain *(216); Papaver albiflorum* ssp. *austromoravicum* Kubat *(218)* TLC; *P. anomalum* Fedde *(144, 145); P. alboroseum* Hulten *(143)* TLC; *P. atlanticum* Ball. *(142); P. caucasicum* Marsch.-Bieb. *(64); P. commutatum* Fisch. et Mey. *(116)* TLC; *P. decaisnei* Hochst. *(209)* TLC; *P. dubium* L. *(116); P. glaucum* Boiss. et Hauskn. *(155)* TLC; *P. lecoquii* Lamotte *(218)* TLC; *P litwinowii* Fedde ex Bornm. *(217)* TLC; *P. orientale* L. *(32, 130)* TLC; *P. rhoeas* L. *(116); P. rupifragum* Boiss. et Reut. *(219)* TLC; *P. somniferum* L. *(64)*

Papaverrubine D (**4k**)	*Meconopsis betonicifolia* Franch. *(216); M. horridula* Hook. f. et Thoms. *(216); M. paniculata* (D. Don) Prain *(216); M. robusta* Hook. f. et Thoms. *(216); M. rudis* Prain *(216); M. sinuata* Prain *(216); Papaver albiflorum* ssp. *austromoravicum* Kubat *(218)* TLC; *P. alboroseum* Hulten *(143); P. alpinum* ssp. *alpinum (134)* TLC, ssp. *kerneri* (Hay.) Fedde *(134)* TLC, ssp. *rhaeticum* (Ler.) Mgf. *(134)* TLC, ssp. *sendtneri* (Kern.) Schinz et Keller *(134)* TLC; *P. anomalum* Fedde *(144); P. argemone* L. *(130)* TLC; *P. atlanticum* Ball. *(142); P. bracteatum* Lindl. *(130, 152)* TLC; *P. californicum* A. Gray *(116)* TLC; *P. caucasicum* Marsch.-Bieb. *(92); P. commutatum* Fisch. et Mey. *(116)* TLC; *P. croceum* Ledeb. *(229d)* TLC; *P. decaisnei* Hochst. *(209)* TLC; *P. dubium* L. *(116, 130)* TLC; *P. feddei* Schwz. *(130)* TLC; *P. fugax* Poir. *(152)* TLC; *P. glaucum* Boiss. et Hauskn. *(155)* TLC; *P. heldreichii* Boiss. *(130)* TLC; *P. hybridum* L. *(130)* TLC; *P. latericium* C. Koch *(130)* TLC; *P. lecoquii* Lamotte *(218)* TLC; *P. litwinowii* Fedde ex Bornm. *(217)* TLC; *P. macrostomum* Boiss. et Huet *(130)* TLC; *P. nudicaule* L. *(130)* TLC; *P. oreophilum* Rupr. *(130, 138)* TLC; *P. orientale* L. *(32, 130); P. pavoninum* Fisch. et Mey. *(130)* TLC; *P. persicum* Lindl. *(90, 130)* TLC; *P. pilosum* Sibth. et Smith *(130)* TLC; *P. polychaetum* Schott et Kotschy *(90)* TLC; *P. pseudo-canescens* M. Pop. *(145); P. radicatum* Rottb. *(19, 130)* TLC, ssp. *hyperboreum* Nordhagen *(130)* TLC; *P. rhoeas* L. *(130)* TLC; *P. rupifragum* Boiss. et Reut. *(130, 219)* TLC; *P. setigerum* DC. *(130)* TLC; *P. somniferum* L. *(141)*, var. *paeoniflorum* Alef. *(125)* TLC; *P. strigosum* (Bönningh.) Schur. *(130)* TLC; *P. triniaefolium* Boiss. *(130, 152)* TLC
Papaverrubine E (**2d**)	*Bocconia frutescens* L. *(214); Meconopsis betonicifolia* Franch. *(216); M. horridula* Hook. f. et Thoms. *(216); M. paniculata* (D. Don) Prain *(216); M. robusta* Hook f. et Thoms. *(216); M. rudis* Prain *(216); Papaver albiflorum* ssp. *austromoravicum* Kubat *(218)* TLC; *P. argemone* L. *(130)* TLC; *P. atlanticum* Ball. *(142); P. bracteatum* Lindl. *(130, 152)* TLC; *P. californicum* A. Gray *(116)* TLC; *P. caucasicum* Marsch.-Bieb. *(130)* TLC; *P. commutatum* Fisch. et Mey. *(116)* TLC; *P. decaisnei* Hochst. *(209)* TLC; *P. dubium* L. *(116, 130)* TLC; *P. feddei* Schwz. *(130)* TLC; *P. fugax* Poir. *(152)* TLC; *P. heldreichii* Boiss. *(130)* TLC; *P. hybridum* L. *(130)* TLC; *P. latericium* C. Koch *(130)* TLC; *P. lecoquii* Lamotte *(218)* TLC; *P. macrostomum* Boiss. et Huet *(130)* TLC; *P. oreophilum* Rupr. *(130, 138)* TLC; *P. orientale* L. *(130)* TLC; *P. pavoninum* Fisch. et Mey. *(130)* TLC; *P. pilosum* Sibth. et Smith *(130)* TLC; *P. pseudocanescens* M. Pop. *(145); P. radicatum* Rottb. ssp. *hyperboreum* Nordhagen *(130)* TLC; *P. rhoeas* L. *(116, 131); P. rupifragum* Boiss. et Reut. *(130, 219)* TLC; *P. setigerum* DC. *(130)* TLC; *P. somniferum* L. *(157)* TLC; *P. strigosum* (Bönningh.) Schur. *(130)* TLC; *P. syriacum* Boiss. et Blanche *(215)* TLC; *P. tauricolum* Boiss. *(155)* TLC

(*continued*)

TABLE II (*Continued*)

Name	Plant sources and references
Papaverrubine F (**2g**)	*Papaver commutatum* Fisch. et Mey. *(116)* TLC; *P. dubium* L. *(116)* TLC; *P. oreophilum* Rupr. *(138)*
Papaverrubine G (**4n**)	*Papaver alpinum* L. ssp. *alpinum (134)*, ssp. *kerneri* (Hay.) Fedde *(134)*, ssp. *rhaeticum* (Ler.) Mgf. *(134)*, ssp. *sendtneri* (Kern.) Schinz et Keller *(134)* TLC; *P. anomalum* Fedde *(144, 145)*
Papaverrubine H (**3g**)	*Papaver anomalum* Fedde *(145)*
Rhoeadine (**2a**)	*Bocconia frutescens* L. *(214, 223)*; *Meconopsis betonicifolia* Franch. *(216)* TLC; *M. horridula* Hook. f. et Thoms. *(216)* TLC; *M. napaulensis* DC. *(216)* TLC; *M. paniculata* (D. Don.) Prain *(216)* TLC; *M. rudis* Prain *(216)* TLC; *Papaver albiflorum* ssp. *austromoravicum* Kubat *(218)*; *P. anomalum* Fedde *(100)*; *P. arenarium* Marsch.-Bieb. *(156)*; *P. argemone* L. *(156)*; *P. armeniacum* (L.) DC. *(185)*; *P. atlanticum* Ball. *(156)*; *P. californicum* A. Gray *(116, 182)*; *P. commutatum* Fisch. et Mey. *(211)*; *P. cyclindricum* Cullen *(184)*; *P. decaisnei* Hochst. *(209)*; *P. dubium* L. *(116)*, ssp. *lecoquii* (Lamotte) Fedde *(156)*; *P. fugax* of Turkish origin *(146, 148)*; *P. glaucum* Boiss. et Hauskn. *(182)*; *P. gracile* Boiss. *(156)*; *P. intermedium* (Becker) O. Ktze. *(182)*; *P. latericium* C. Koch *(182)*; *P. lecoquii* Lamotte *(218)*; *P. macrostomum* Boiss. et Huet *(156)*; *P. monanthum* Trautv. *(156)*; *P. nudicaule* L. ssp. *rubro-aurantiacum* Fedde *(101)*, ssp. *xanthopetalum* (Trautv.) Fedde *(100)*; *P. oreophilum* Rupr. *(136)*; *P. paeoniflorum* Hort. *(23)*; *P. pavoninum* Fisch. et Mey. *(182)*; *P. pilosum* Sibth. et Smith *(156)*; *P. pseudocanescens* M. Pop. *(145)*; *P. rhoeas* L. *(5, 51)*, var. *decaisnei* Hort. *(156)*, var. *flore albo* Hort. *(156)*, var. *flore pleno* Hort. *(156)*; *P. rupifragum* Boiss. et Reut. *(219)*; *P. strigosum* (Bönningh.) Schur. *(182, 210)*; *P. syriacum* Boiss. et Blanche *(215)*; *P. tauricola* Boiss. *(187)*; *P. triniifolium* Boiss. *(186)*
Rhoeagenine (**1b**)	*Papaver arenarium* Marsch.-Bieb. *(156)*; *P. argemone* L. *(156)*; *P. atlanticum* Ball. *(156)*; *P. californicum* A. Gray *(116)*; *P. commutatum* Fisch. et. Mey. *(211)*; *P. dubium* L. *(116)*; *P. latericium* C. Koch *(182)*; *P. nudicaule* L. ssp. *rubro-aurantiacum* Fedde *(101)*; *P. oreophilum* Rupr. *(136)*; *P. pilosum* Sibth. et Smith *(156)*; *P. rhoeas* L. *(5, 206)*, var. *decaisnei (156)*, var. *flore pleno (156)*; *P. rupifragum* Boiss. et Reut. *(219)*; *P. strigosum* (Bönningh.) Schur. *(210)* *P. syriacum* Boiss. et Blanche *(215)*; *P. tauricola* Boiss. *(187)*

Botanical names used in this review are consistent with those in the original paper, irrespective of the possibility that the botanical identity of any species may have later been doubted or even failed to be verified. For each natural source of any alkaloid in Table II at least one reference to an original paper was provided, but it was generally impossible to consider the priority in each case.

III. Structure Elucidation and Related Chemistry

A. Introduction

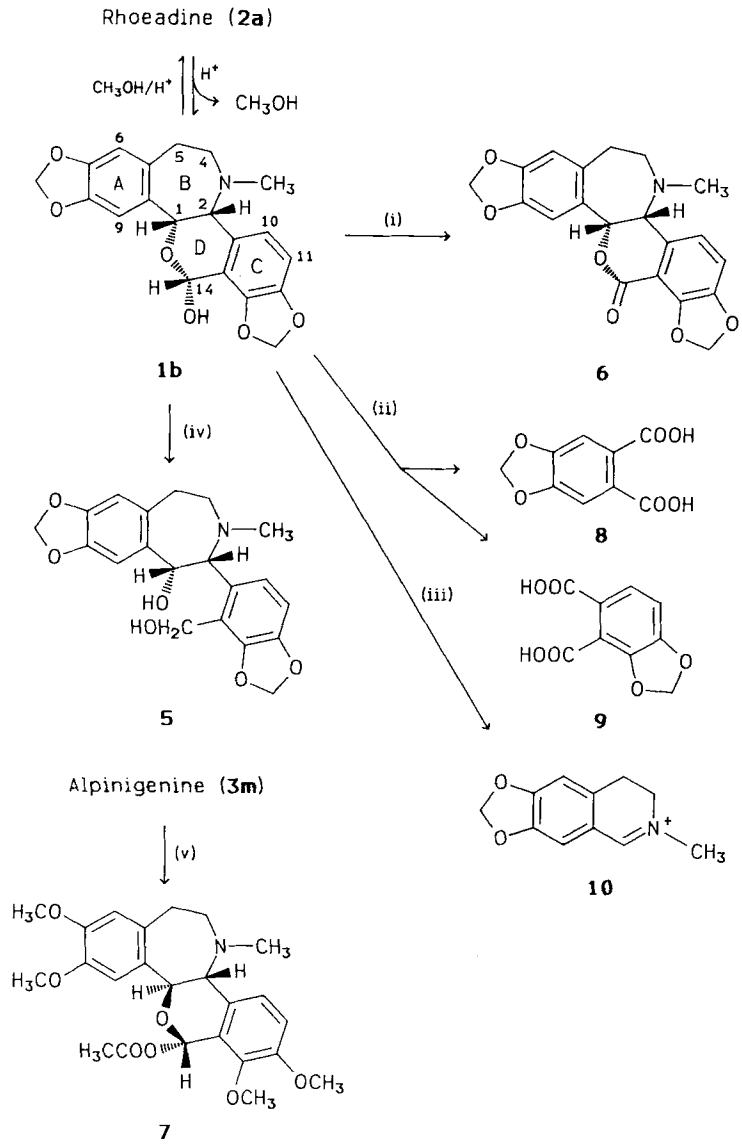
The six-membered acetal or hemiacetal building block present in all rhoeadine and papaverrubine alkaloids shows itself by some typical reactions. Mild acid hydrolysis (0.1 *N* hydrochloric acid/100°C/60 sec) (*134*) yields methanol, which was identified by Slavík (*206*) prior to 1959, in addition to a "genine" like rhoeagenine (**1b**) (Scheme 1). Acid-catalyzed remethylation or O-alkylation (*115*) for completion normally requires a dry alcohol and less than 2 hr of heating (*172*). There is never a CO frequency in the IR spectrum of any hemiacetal, but owing to ring–chain tautomerism, the formation of a dinitrophenylhydrazone or the oxime (**17**) from rhoeagenine (**1b**) (*222*) and alpinigenine (**3m**) (*161, 168*), respectively, is possible (see Schemes 4, 11). Opening of the hemiacetal ring can also be effected by means of lithium aluminum hydride or by catalytic hydrogenation (*180*) to prepare a diol, e.g., rhoeageninediol (**5**).

Mild oxidation of rhoeagenine (**1b**) or diol **5,** using chromium trioxide or manganese dioxide, gave a low yield of oxyrhoeagenine (**6**) (*180*), which showed a carbonyl frequency in the IR spectrum at 1725 cm^{-1}. An IR absorption in this region is suggestive of a δ-lactone rather than of a γ-lactone, as had to be expected, however, when the basic structure of rhoeadine was still regarded as belonging to the phthalidisoquinoline type; a report on that early structural work can be found in this series (*177*). In order to acetylate alpinigenine, success was achieved by using acetic anhydride in pyridine at room temperature. The lactol ester **7** formed exhibited an IR absorption for the ester carbonyl at 1753 cm^{-1} (*172*).

In early oxidative experiments done on **1b** alkaline permanganate (*181*) gave 4,5- and 3,4-methylenedioxyphthalic acids (**8** and **9**, respectively), while application of nitric acid (*234*) resulted in hydrastinine (**10**). The first result provided a clue to the arrangement of methylenedioxy groups on the two aromatic rings, but the isolation of the 3,4-dihydroisoquinoline **10** turned out to be misleading with regard to the elucidation of the basic skeleton of the rhoeadine alkaloids (cf. *8, 177*).

B. Degradative Studies and Basic Structure

The idea that a benz[*d*]isochromano[4,3-*b*]azepine affords the basic skeleton for rhoeadine (**2a**) and isorhoeadine (**4a**) was elaborated by Šantavý in common



SCHEME 1. i, CrO_3/AcOH; ii, $KMnO_4/OH^-$; iii, HNO_3; iv, $LiAlH_4$/THF/reflux or H_2/Pt/AcOH; v, Ac_2O/Py/room temp.

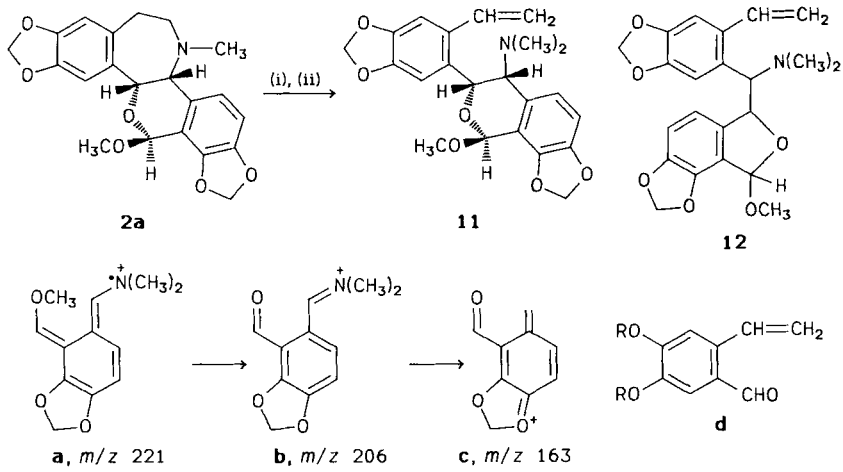
with the Dolejš–Hanuš MS team in 1965 (*180*). The new structure was mainly derived from an analysis of the mass spectra of **2a, 4a,** and rhoeagenine (**1b**) as well as the Hofmann products obtained from **2a** and rhoeageninediol **5** (see next paragraph). At the same time in joint papers also with Dolejš and Hanuš, Pfeifer

(*132*) reported on the structures of the papaverrubines, and Slavík (*212*) on those of glaucamine (**3f**) and *O*-methylglaucamine (**3e**). Therefore, mass spectroscopy of the rhoeadines will be summarized in Section VI,A. The numbering system adopted in Scheme 1 and throughout this review is the original one (*180*), although a numbering more consistent with *Chemical Abstracts* practices and the name rheadane (rhoeadane) has since been suggested (*73, 84*).

An important feature exhibited by proton NMR is the existence of a benzylic coupling system due to protons at C-1 and C-2. Vicinal coupling constants $J_{1,2}$ are indicative of B/D ring fusion (cf. Section III,D,1). Furthermore, proton-NMR spectroscopy of rhoeadine (**2a**) and isorhoeadine (**4a**) (*180*) and their congeners showed each aromatic ring to bear two protons, with one of the two (A or C) having two ortho protons, which in most cases is obvious from a pair of doublets ($J_{AB} \cong 8.5$ Hz). Other degradative work on rhoeageninediol described in this section revealed a substitution pattern with the two ortho protons being located on ring C.

1. Hofmann Degradation of Rhoeadine

The Hofmann degradation of rhoeadine (**2a**) led predominantly to the styrene derivative **11** (*6, 180, 181*) (Scheme 2). The styrene nature of this so-called desrhoeadine was early recognized from its UV spectrum, having maxima at 207, 222(sh), 269, and 294 nm. On electron impact in mass spectrometry, the methine **11** by benzylic cleavage most specifically yielded a strong fragment **a,** which proved to be incompatible with the historical formulation for **11** as a phthalidisoquinoline-related methine (cf. **12**). As evidenced from a metastable

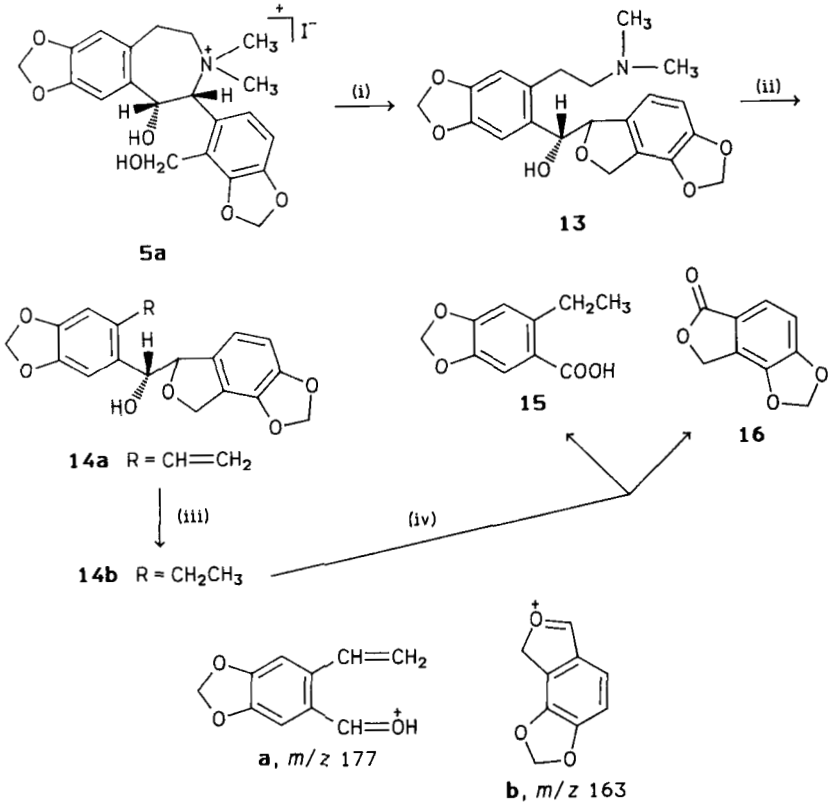


SCHEME 2. i, CH_3I/MeOH/reflux; ii, Ag_2O, then 40% KOH/reflux.

transition at *m/z* 192, fragment **a** loses a methyl radical to form daughter ion **b,** the base peak, which in turn gives rise to the less abundant species **c.** More recently, the neutral species **d** (R = CH_3), indetectable by electron-impact MS, was found in low-energy electron-attachment mass spectrometry of *O*-methylalpinigeninemethine (**44**) (*167*) (see Scheme 17). For a general discussion of Hofmann elimination processes in the B/D-cis and B/D-trans series, see Section IV,A,1.

2. Attempted Hofmann Degradations on Rhoeageninediol and Alpinigenine Oxime

Attempted Hofmann degradation of rhoeageninediol as its methiodide (**5a**) was reported by Šantavý *et al.* (*180*) to proceed in the first step by an intramolecular attack by the 14-hydroxy group at carbon 2 to form the cyclic ether **13,** designated as desrhoeageninediol (Scheme 3). Such an intramolecular nu-



SCHEME 3. i, Ag_2O, then OH^-/heat; ii, Hofmann sequence; iii, H_2/Pt; iv, CrO_3/AcOH.

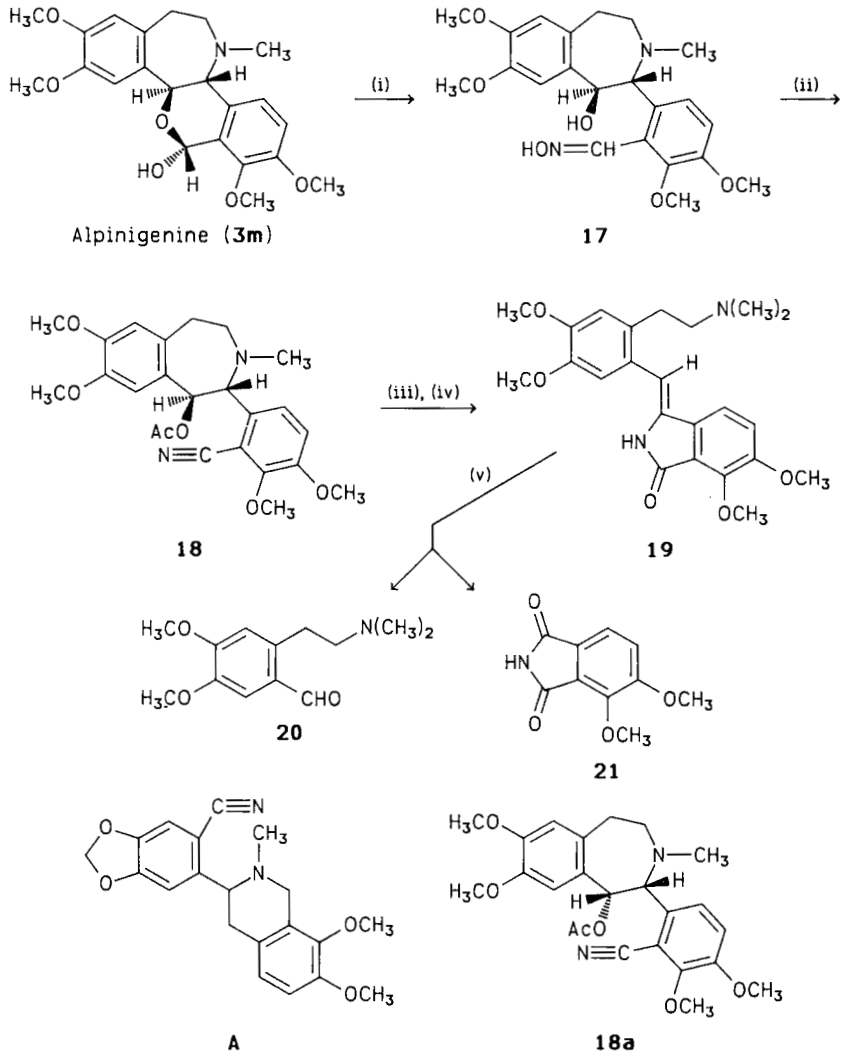
cleophilic substitution by an alkoxy anion at the carbon-bearing nitrogen rather than elimination of β-hydrogen is not an uncommon alternative for systems possessing a nucleophilic group in a proper position (*28, 194*). In the following step a normal elimination of triethylamine from **13** took place to give the Hofmann product desdesrhoeageninediol (**14a**) in a low overall yield. On mass spectrometry, the latter formed a molecular ion that again broke along the benzylic bond with the formation of fragment ions **a** and **b** competing for the positive charge.

Oxidative fission of **14b** obtained from **14a** by catalytic hydrogenation was a high-yielding process forming the known compounds **15** and **16,** which together are evidence for the precise positions of the substituents on rings A and C, respectively.

For the degradation of multiply labeled alpinigenine (**3m**) isolated from feeding experiments with radioactive biosynthetic precursors, a sequence was developed by Rönsch (*161, 168*) that allowed the individual hydrogen atoms bound to C-1, C-2, and C-14, as well as specific ^{14}C labels to be analyzed independently for their levels of radioactivity (Scheme 4). Hot acetic anhydride was chosen to prepare the nitrile **18** from the aforementioned alpinigenine oxime (**17**) by dehydration and simultaneous O-acetylation. Attempted Hofmann degradation of **18** methiodide, using mild conditions, resulted in the optically inactive, yellow phthalimidine **19,** whose formation is reminiscent of that of **13** as to the intramolecular reaction mechanism. Furthermore, the neighboring hydroxy function at C-1 is vitally involved in this "multicenter process." Little or no phthalimidine is formed if this OH group is absent in model compound **A,** or if its stereochemistry is inappropriate as in the corresponding nitrile **18a** derived from *cis*-alpinigenine (**1m**). Similarly, no phthalimidine derivative was reported to be formed when this sequence was applied to rhoeagenine (**1b**) by Tani and Tagahara (*227*). Lemieux–Johnson oxidation of **19** was very effective in producing the aldehyde **20** as well as hemipinimide (**21**), two known compounds showing the substitution patterns on rings A and C, respectively, of alpinigenine.

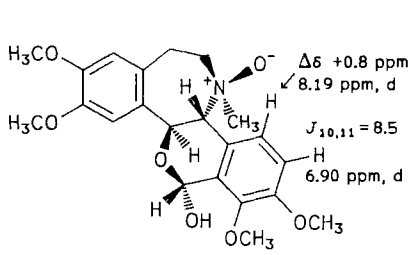
3. Other Structural Work

a. Alpinigenine (3m). Additional evidence for the position of methoxy groups in alpinigenine (**3m**) was early extracted from the NMR spectra of its *N*-oxide (**22**) (*39*). If the framework of the rhoeadines was thought to be devoid of methoxy groups and all possible conformations of the seven-membered N-heterocyclic ring were taken into account, there was only one proton out of eight, that at C-10, that could be deshielded by the oxygen of the *N*-oxide group (Scheme 5). Comparing the NMR spectra of **3m** and **22** in the latter spectrum due to proximity of the *N*-oxide oxygen to 10-H, one can see a strong downfield shift by +0.8 ppm with the A part of the aromatic AB system.



SCHEME 4. i, $NH_2OH \cdot HCl/Py/100°C$; ii, $Ac_2O/120°C$; iii, CH_3I/acetone/reflux; iv, 1 *N* KOH/80°C; v, $NaIO_4$/catalytic amount of OsO_4/pH 2/20°C.

b. *N*-Methylporphyroxigenine (3i). This opium alkaloid was isolated by Brochmann-Hanssen *et al.* (*26*) and named *N*-methyl-14-*O*-demethylepiporphyroxine. It is one of the three well-characterized phenolic rhoeadines known. The position of its phenolic hydroxy group, which corresponds to that of papaverrubine D (**4k**) and papaverrubine C (**3k**) (*25, 64*), was derived from pH-shift



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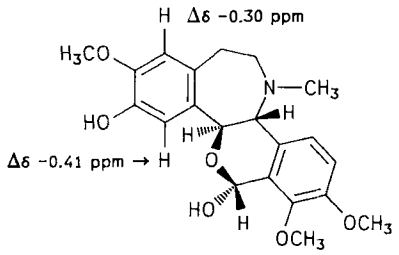
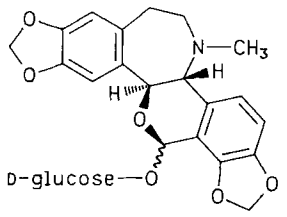


3i



3c

SCHEME 5

measurements by proton NMR in DMSO-d_6/NaOD. The protons in positions 6 and 9 experienced upfield shifts by $\Delta\delta = -0.30$ or -0.41 ppm, respectively, characteristic of their position relative to the phenolic anion. In the aporphine field, upfield shifts of aromatic protons on anion formation had usually been found to be as follows: ortho 0.47–0.54 ppm, meta 0.25–0.42 ppm, and para 0.86 ppm (*121*).

c. (+)-Isorhoeagenine D-Glucoside (3c). Alkaloidal glycosides in general are rare in most groups, an exception being Solanum. (+)-Isorhoeagenine D-glucoside (**3c**) was isolated from *Papaver rhoeas* by Němečková *et al.* (*113, 116*) and has been a singular case in the rhoeadine family until now. Acid hydrolysis in dilute sulfuric acid afforded a sugar portion identified as D-glucose as well as rhoeagenine (**1b**), which, however, was formed by a B/D trans → cis isomerization from the original aglycon constituting the alkaloidal portion of **3c** (Scheme 5). The involvement of isorhoeagenine (**3b**) was deduced from the NMR spectrum of the glycoside, which showed the large coupling $J_{1,2} = 9.5$ Hz indicative of a B/D-trans configuration. The configuration at the anomeric carbon was not yet established, and the other NMR data have not been published.

Klyne's rule has been used to assign the α configuration for the glycosidic linkage, although this method was applied in an inconclusive way. In order to compare with the molar rotation $[M]_D$ of the natural glycoside, $[M]_D$ values were calculated for isorhoeagenine α- and β-glucosides, implying a 14*R* configuration

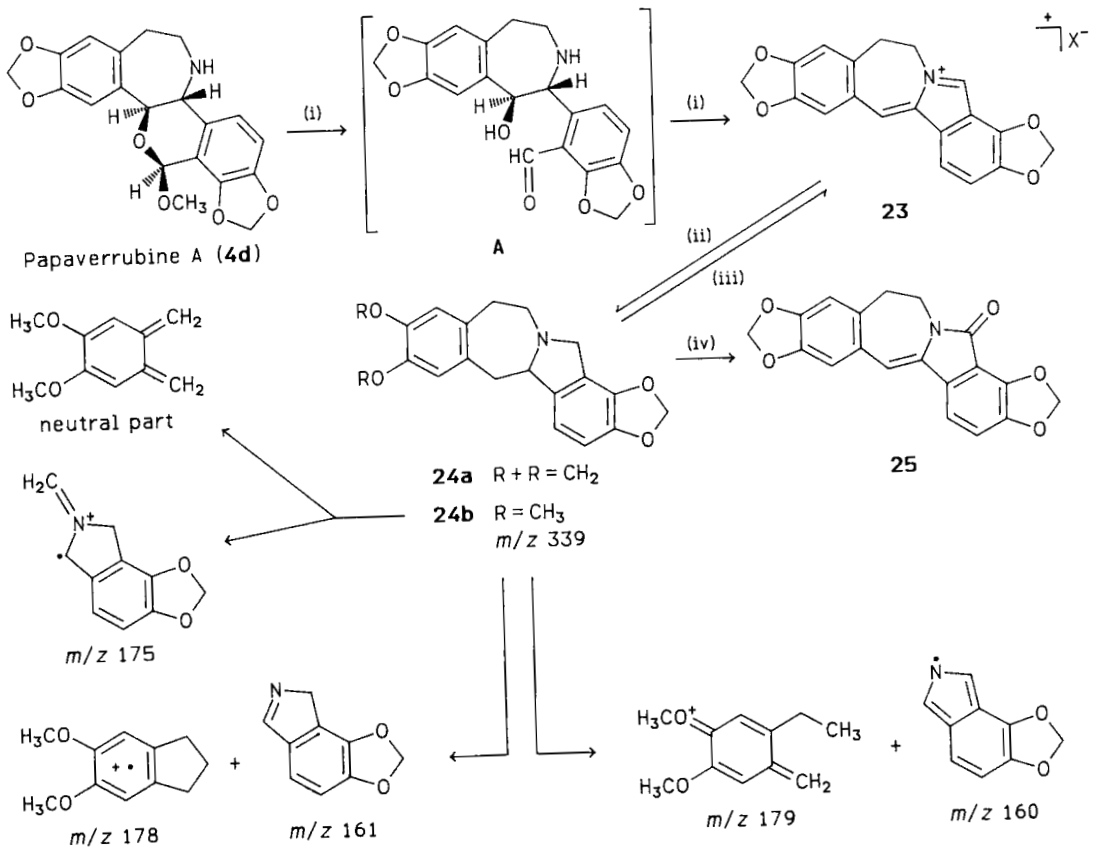
for both the free aglycon and the two possible glucosides. It seems, however, inadmissible to do so before determining the configuration at C-14 in **3c.**

C. Papaverrubines (Norrhoeadines)

All of the 10 papaverrubines known (Table I) are methyl acetals, which in acid solution below pH 3 produce an intense red coloration. The development of color depends on time, temperature, pH, and structure of the papaverrubines (*137, 141*). Papaverrubines are always present in opium and their color reaction has been made an instrument in the analysis of this drug as to its origin (*38, 124*); furthermore, it allows the chromatographic detection of papaverrubines even in traces as low as 0.1 μg (*125, 130*).

The chemical examination of the red products formed from papaverrubines has long been baffled by their formation as a mixture and their instability (*140*), but eventually Walterová and Šantavý (*232*) in a brief note reported on the isolation of the quaternary isoindolobenzazepine **23** from papaverrubine A (**4d**) after acid treatment (Scheme 6). Hydrolytic formation of a hemiacetal and subsequent cyclization by way of the tautomeric oxoform **A** to a Schiff base are assumed to be the essential steps in this transformation. Catalytic hydrogenation of **23** furnished the colorless tertiary base **24a.** Air oxidation regenerated the red product **23,** while with mercuric acetate the red five-membered lactam **25** (ν_{CO} 1685 cm^{-1}) was formed. Additional evidence for the structure of the saturated base of type **24** was contributed by Pfeifer and Thomas (*145*) who studied the mass spectral fragmentation of **24b,** an analog obtained from papaverrubine B (**4g**). The main fragmentation mode of this analog, which has two methoxy groups in place of the one methylenedioxy entity on ring A of **24a,** was verified by high resolution technique and metastable peak analysis as outlined in Scheme 6. As reported very recently, the isoindolobenzazepine ring system present in the red product **23** has been found to be the basic skeleton for a number of lactam alkaloids occurring in South American members of the Berberidaceae (*229c*).

The mass spectral behavior of papaverrubine bases themselves (*132*) was found to be very similar to that of the corresponding tertiary rhoeadine alkaloids discussed in Section VI,A. An N-methylation, for instance, of papaverrubine F (**2g**) may simply be done by using methyl iodide in tetrahydrofuran at room temperature, and the oreodine **2e** formed was isolated in a low yield (*138*). Alternatively, heating papaverrubine A (**4d**) in methanol with formic aldehyde resulted in 90% of isorhoeadine (**4a**) accompanied by 10% of rhoeadine (**2a**), which had to be separated by column chromatography (*183*). Proton-catalyzed isomerization at the anomeric carbon (epimerization at C-14) of a less stable B/D-*trans* papaverrubine was managed in boiling methanol containing less than one equivalent of hydrogen chloride and a trace of water (*64*), so that papaverrubine D (**4k**) (porphyroxine), after separating 9% of red product and some



SCHEME 6. i, H^+; ii, H_2/Pt; iii, air; iv, Hg(II) acetate.

unchanged **4k,** yielded 68% of the B/D-trans 14-epimer papaverrubine C (**3k**) (14-epiporphyroxine).

D. Stereochemistry

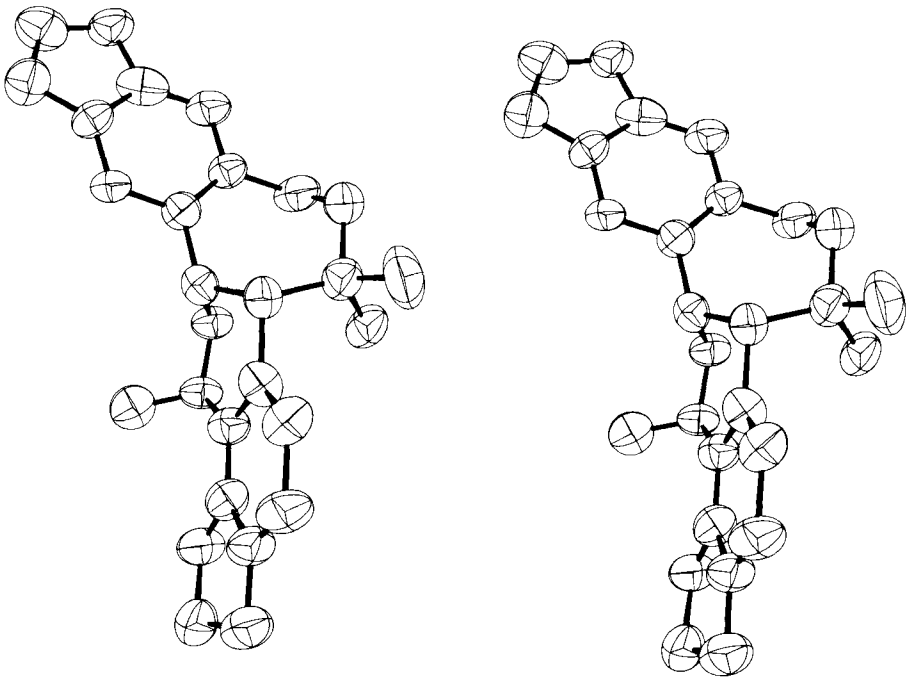
1. Relative and Absolute Configuration at Carbons 1 and 2

The benz[*d*]isochromano[4,3-*b*]tetrahydroazepine skeleton common to all rhoeadine alkaloids includes three chiral carbons, and the chirality at nitrogen has to be considered in some *N*-oxides. The two chiral centers C-1 and C-2, which provide the conjunction between the benzazepine and the isochroman part, give rise to two diastereomeric series, the thermodynamically more stable B/D-cis series [general formulas **1** and **2** (Table I)], as well as the B/D-trans series (general formulas **3** and **4**), irreversibly isomerizing in 1 *N* mineral acid to the former.

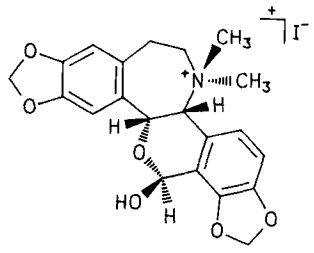
The existence of these two series was first recognized by the Šantavý team (*180*) when studying rhoeadine (**2a**) and isorhoeadine (**4a**) by proton-NMR spectroscopy. Similar results have been obtained, for example, by Cross *et al.* (*30, 31*) for the oreodine group. The 1-H and 2-H protons generally show up as two doublets having either a small spin–spin coupling for the B/D-cis series ($J_{1,2} \sim$ 1.0–2.5 Hz) or a larger one for the B/D-trans series ($J_{1,2} \sim$ 7.0–9.5 Hz). The listing of the rhoeadine and papaverrubine alkaloids as arranged in Table I is consistent with this NMR criterion.

From Table I it can be realized that 2*R* chirality is a constant character of both the B/D-cis and B/D-trans rhoeadine alkaloids. As to the alkaloids from the cis series, this assignment is based on an X-ray analysis done by Huber (*61*) with rhoeagenine methiodide (**2o**) in 1970 (Scheme 7). The X-ray results directly show that this methiodide and its related tertiary alkaloids rhoeagenine (**1b**) and rhoeadine (**2a**) should be assigned the 1*R*, 2*R* configuration. The other alkaloids showing the cis criterion in their NMR spectra have been included in general formulas **1** or **2** (Table I) simply for the reason of exhibiting a positive optical rotation. The X-ray data regarding the spatial arrangement around C-1 and C-2 are evidence for a dihedral angle ranging from 62 to 72°, which is in accord with the small vicinal couplings always observed for 1-H and 2-H protons within the B/D-cis series.

The assignment of a 2*R* configuration also to the alkaloids of the B/D-trans series has been a point of discussion for a certain period and implies that it is carbon 1 rather than carbon 2 that changes chirality during B/D-trans → cis isomerization. At the outset of the stereochemical studies in this group, Šantavý (*179*) in an empirical analysis compared the ORD spectra of rhoeadine, isorhoeadine, and related compounds with those of some phthalidisoquinoline alkaloids, the sterochemistry of which had already been elucidated. The conclusions drawn from this work favored the 1*S*, 2*R* configuration for the B/D-trans series in addition to the 1*R*, 2*R* configuration for the cis-fused alkaloids as shown in Table I.



A stereoscopic view of the organic cation in **2o**.



2o

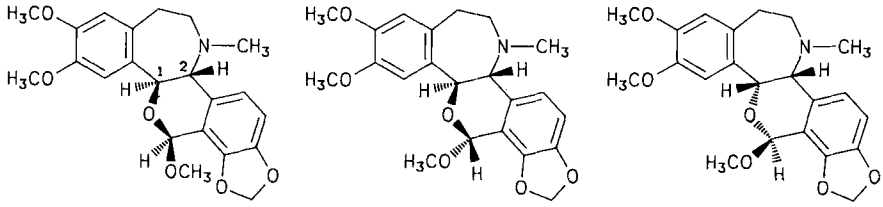
SCHEME 7. X-ray Analysis on rhoeagenine methiodide (**2o**).

Next, without knowledge about Huber's X-ray studies on rhoeagenine methiodide, Shamma *et al.* (*197*) applied the aromatic chirality method to a complete set of stereoisomeric methyl acetals represented by the two B/D-trans alkaloids glaudine (**4e**) and epiglaudine (**3e**) as well as the corresponding cis acetal oreodine (**2e**). The critical point as to the applicability of this method is, first, sufficient proximity between the two aromatic chromophores within a molecule and, second, a Cotton effect strong enough to enable chromophore interaction. In such a case in the circular dichroism spectrum, a Davydov splitting of Cotton effects can be observed (*48*, *49*).

If taken in hexane rather than ethanol, the CD spectra of each member of the triad consisting of **4e, 3e,** and **2e** in the allowed A → B transition band around 200 nm showed a splitting of the Cotton effect, which was attributed to the existence of chromophore interaction (Scheme 8). On this basis, the 2*R* chirality for each of these three alkaloids was derived from the positive sign of the first Cotton effect. The absolute configuration at the other carbon, C-1, was deduced from the known configurational relationships between the two, in accordance with the NMR criterion already discussed. Thus the 1*R*, 2*R* configuration of all B/D-cis fused alkaloids was confirmed, while the configuration in the B/D-trans series was suggested to be 1*S*, 2*R*.

Considering the historical point of view, the work discussed above led to the acceptance of the absolute configurations at carbons 1 and 2 as outlined in Table I. Some years later Hrbek *et al.* (*59*) proposed that the positive couplets observed within the ^{1}B band cannot be considered as an indication of Davydov splitting between two aromatic chromophores and hence cannot be interpreted as an evidence for the 2*R* chirality in the rhoeadine alkaloids. Fortunately, this contradictory interpretation of experimental results was of no consequence with regard to the assignment of configurations for the rhoeadine alkaloids. Furthermore, the Emde degradations of *O*-methylalpinigenine and *O*-methyl-*cis*-alpinigenine investigated by Rönsch in 1972 (*164, 172*) provided independent evidence for the 1*S*, 2*R* configuration as already accepted for the B/D-trans series (cf. Scheme 15). X-Ray analysis on alpinigenine has conclusively established this (*96*).

The absolute stereochemistry established for the two main series of rhoeadine alkaloids suggests that the acid B/D-trans → cis isomerization has to proceed through the intermediacy of C-1 rather than C-2. In practice, this change in



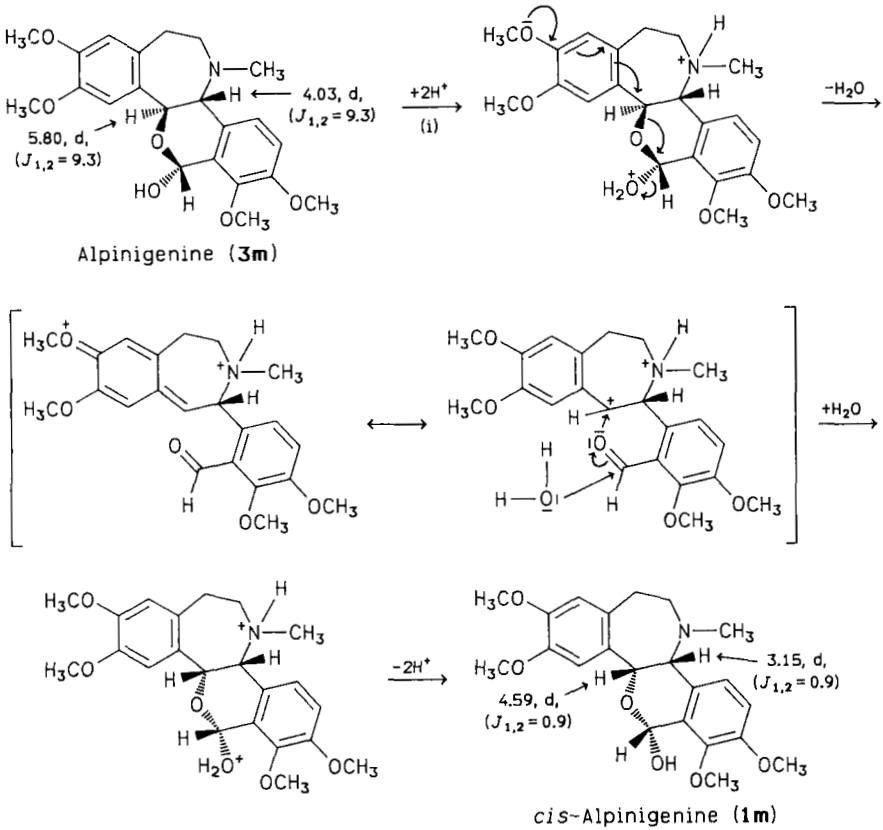
CD Extremes at room temperature, (nm) ($\Delta\epsilon$) (*197*)

195 (−5.00), 222 (+5.7)	207 (+7.25)[a]	193 (−7.5),	207(+9.4)[a]	197 (−10.0),	207(+12.5)[a]
250 (−2.0)[b]		250 (−1.3)[b]		238 (−3.00)[b]	
290 (+5.3)[b]		270 (+5.7)[b]		288 (−3.9)[b]	

[a] Split Cotton Effect in hexane, [b]normal Cotton Effect in dry ethanol.

SCHEME 8. CD data for a triad of methyl acetals (a, split Cotton effect in hexane; b, normal Cotton effect in dry ethanol).

chirality has always been accomplished by means of hot aqueous 1 *N* hydrochloric acid (*98, 138*) with acetals, e.g., isorhoeadine (**4a**), simultaneously undergoing hydrolytic cleavage. In another experiment using alpinigenine (**3m**), it was shown that even with a slightly prolonged reaction time a small amount of the starting B/D-trans compound was recovered (*172*). The mechanism proposed for this isomerization at C-1 considers the specific capability of stabilizing a positive charge on a benzylic carbon to acquire a trigonal state, a provision for a thermodynamically controlled change in chirality (Scheme 9).



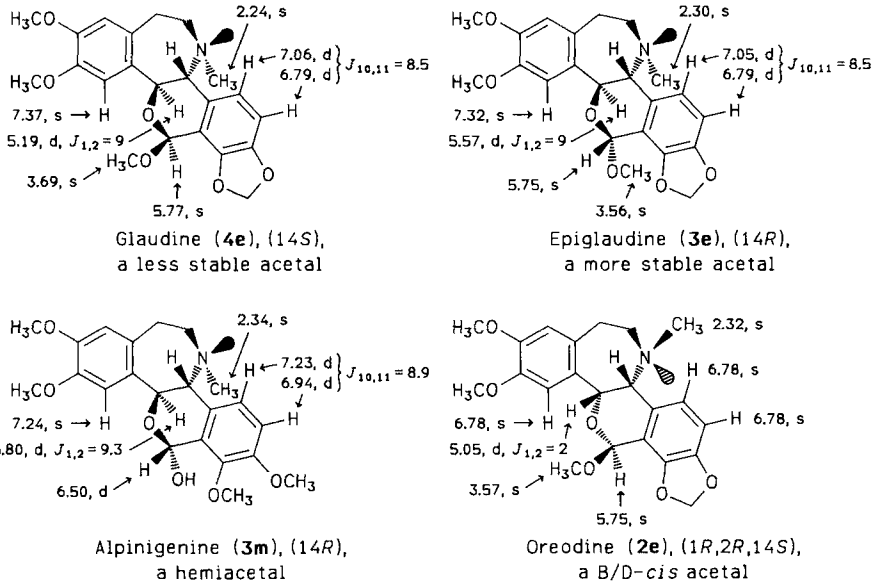
SCHEME 9. i, 1 *N* HCl/reflux/90 min/58%; figures added to individual protons are proton-NMR data obtained in $CDCl_3$/200 MHz, δ values (ppm) relative to TMS (*158*).

2. Specification of Configuration at Carbon 14

a. Epimerism at Carbon 14 in the B/D-trans Series. The relative stereochemistry of stable acetals and less stable ones has been studied by Shamma *et*

al. (*194, 201*), and some time later, when the chirality at carbons 1 and 2 had been revealed, it became possible to express the results in terms of absolute configuration at C-14. In this study, kinetic and proton-NMR data of a triad of identically substituted acetals comprising glaudine (**4e**), epiglaudine (**3e**), and also the B/D-cis fused oreodine (**2e**) were discussed, adding arguments derived from stereo models. Since Shamma has omitted hemiacetals from discussion, it seems to be more convenient to include alpinigenine (**3m**) in discussion for which related data are available now. The formulas in Scheme 10, drawn on the basis of molecular models, constitute a schematic view that provide an idea of the most important intramolecular interactions, and NMR data relevant for discussion are included.

Kinetic data were obtained from N-methylation experiments measuring the rate of quaternization by methyl iodide. The very hindered nature of the nitrogen in both glaudine (**4e**) and epiglaudine (**3e**) is reflected in the very slow pseudo first-order rates of 1.6×10^{-4} sec^{-1} or 2.1×10^{-4} sec^{-1}, respectively. The corresponding kinetic data for the cis compound oreodine (**2e**) were found to be 23.1×10^{-4} sec^{-1}. In the epimeric acetals **4e** and **3e,** owing to the close proximity of nitrogen and the aromatic proton 10-H, the *N*-methyl group may be forced to the rear side of the molecule into an axial position, while the nonbonding N-orbital makes this proton shift downfield by $\sim +0.3$ ppm. Alternatively in



SCHEME 10. Epimerism at carbon-14 in the B/D-trans series. Figures attached to individual protons are proton-NMR data obtained in $CDCl_3$; **2e, 3e,** and **4e** (*194, 201*); **3m** 200 MHz (*158*).

oreodine (**2e**), there is sufficient distance between nitrogen and 10-H to show no additional deshielding and to make it equivalent to 11-H.

Independent of the conformation of ring B, which probably is a chair, ring D might always be a half-chair and nearly coplanar with the aromatic ring C, with the ring oxygen being arranged above this plane in the B/D-trans series, while it lies below this plane in the B/D-cis series. In the case of B/D-trans fusion only, this oxygen is approximately in plane with the other aromatic ring A. Such a relationship is indicated by a downfield shift as large as $\sim +0.6$ ppm for the aromatic 9-H proton in alkaloids **4e, 3e,** and **3m,** as well as all the other B/D-trans alkaloids, where the interatomic distances between 9-H and ring-D oxygen are much smaller than in any B/D-cis base, e.g., **2e**.

Evidence for the assignment of the 14*S* configuration to a less stable B/D-trans methyl acetal, e.g., **4e,** or of the 14*R* configuration to a stable one, e.g., **3e,** was obtained as follows.

1. The anomeric methoxy group should be (quasi) equatorial in the less stable epimer **4e** or (quasi) axial in its stable counterpart **3e** as indicated by the more upfield resonance in the latter ($\Delta\delta = -0.12$ ppm), which is required from the anomeric effect (*36*).
2. The anomeric effect also favors an axial epimer, and therefore the axial acetal **3e** should be more stable than **4e**, which is indeed the case. As was already mentioned in Section III,C, the epimerization of acetals at the anomeric carbon is an irreversible process catalyzed by acid in boiling methanol that transforms a labile 14*S* compound to a stable 14*R* epimer, such as **4e** to **3e.**
3. The axial nature of the anomeric methoxyl is convincingly shown from the chemical shifts of benzylic C-1 protons in **4e** and **3e;** owing to 1,3-diaxial interaction with the 14-OCH_3 group, there is a clear downfield shift by $\Delta\delta = +0.38$ ppm for 1-H in the stable acetal **3e.**
4. Even the protons of the (probably) axially oriented *N*-methyl group of **3e** may be influenced by an axial rear-side oxygen at C-14. The chemical shift differences for the *N*-methyl protons in **4e** and **3e** are small but significant, $\Delta\delta = +0.06$ ppm.

In the four known B/D-trans hemiacetals alpinigenine (**3m**), glaucamine (**3f**), isorhoeagenine (**3b**), and *N*-methylporphyroxigenine (**3i**), the configuration at the anomeric carbon logically is identical to that of the stable acetals in this series, namely, 14*R*. In addition, there is experimental evidence for this. First, in proton NMR a 1,3-diaxial relationship between 1-H and 14-OH is again indicated by the very low-field resonance of any 1-H proton, which is comparable to and even more pronounced than in the (14*R*)-methyl acetals discussed above. Second, no significant molar rotation differences $\Delta[M]_D$ are observed for a hemiacetal and its related stable methyl acetal (*172*) as predicted from Hudson's Second Rule (Table III).

TABLE III
Molar Rotation Differences $\Delta[M]_D$ for O-Methylation of B/D-trans Hemiacetals

Compound	$[\alpha]_D$ (°) (Solvent)	$[M]_D$ (°)	$\Delta[M]_D$ (°)	Ref.
Alpinigenine (**3m**)	+306 (MeOH)	+1228	+24	*172*
Epialpinine (**3l**)	+302 (MeOH)	+1252		*172*
Alpinigenine methiodide	+188 (MeOH)	+1021	+36	*172*
Epialpinine methiodide (**33**)	+189 (MeOH)	+1057		*172*
Alpinigenine *N*-oxide (**22**)	+138 (MeOH)	+595	+71	*172*
Epialpinine *N*-oxide (**47**)	+149 (MeOH)	+666		*172*
Glaucamine (**3f**)	+298 ($CHCl_3$)	+1148	+136	*210*
Epiglaudine (**3e**)	+254 ($CHCl_3$)	+1012		*210*

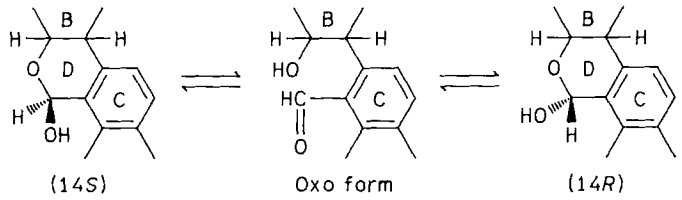
Table III includes all couples of hemiacetals and corresponding stable acetals for which optical rotations are available in the literature. Apparently, the low optical rotation for epiglaudine does not fit. This might be due to experimental error. On the other hand, the high $\Delta[M]_D$ values shown in Table IV for several 14-epimeric couples of B/D-trans methyl acetals are characteristic of the contribution to molar rotation provided by different chirality at carbon 14.

TABLE IV
Molar Rotation Differences $\Delta[M]_D$ for B/D-trans Acetals Epimeric at Carbon 14

Compound	$[\alpha]_D$ (°) (Solvent)	$[M]_D$ (°)	$\Delta[M]_D$ (°)	Ref.
Alpinine (**4l**)	+412 (MeOH)	+1710	−493	*134*
Epialpinine (**3l**)	+293 (MeOH)	+1217		*134*
Glaudine (**4e**)	+455 ($CHCl_3$)	+1815	−803	*127*
Epiglaudine (**3e**)	+254 ($CHCl_3$)	+1012		*210*
Papaverrubine B (**4g**)	+398 ($CHCl_3$)	+1537	−348	*93*
Epipapaverrubine B (**3g**)	+308 ($CHCl_3$)	+1189		*64*
Papaverrubine D (**4k**)	+391 ($CHCl_3$)	+1443	−400	*141*
Papaverrubine C (**3k**)	+283 ($CHCl_3$)	+1043		*64*

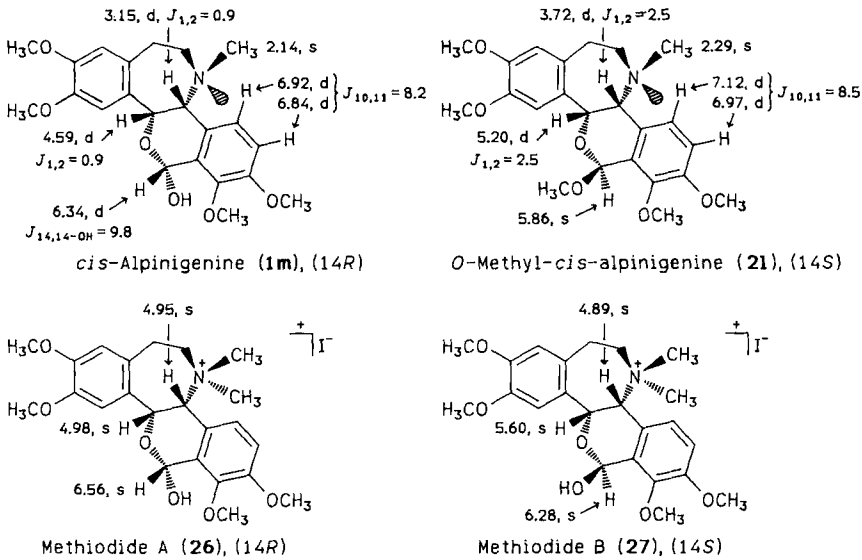
b. Epimerism at C-14 in the B/D-cis Series. In the B/D-cis series no less stable methyl acetals are known. It has been assumed initially that hemiacetals like rhoeagenine (**1b**) and their corresponding methyl acetals (general formulas **2**) have an identical configuration at the anomeric carbon. Moreover, some confusion has developed in the literature from the inadmissible extension of the 14*S* configuration—established for crystalline rhoeagenine methiodide (**2o**) by an X-ray analysis (*61*, *62*)—over all the tertiary B/D-cis hemiacetals.

It has been pointed out by Rönsch *et al.* (*172*) that rhoeadine alkaloid hemiacetals, in analogy to monosaccharides, are involved in ring–chain tautomerism. Because of this tautomeric equilibrium, configuration around carbon 14 becomes



SCHEME 11. Ring–chain tautomerism.

a point subject to variation (Scheme 11). A change in chirality at the anomeric carbon can conceivably occur very easily by way of the ring D-open oxoform. A priori, either of the two epimers may be favored thermodynamically, but which one actually is preferred should depend on the conditions determined by various influences, for example, the structural characters of the specific alkaloid, the nature of the solvent used, the inter- and intramolecular forces existing in a crystal lattice, or simply the presence of an additional substituent at the nitrogen atom, e.g., an additional methyl group or an oxygen atom. In this regard, it was no surprise when *cis*-alpinigenine (**1m**) and its less stable methiodide (**26**) were found to show mutarotation (*172*). In aprotic solvents, such as acetone, **1m** with methyl iodide formed a uniform methiodide A (**26**), which on recrystallization, especially from protic solvents, was always recovered as a mixture containing high amounts of its 14-epimer (Scheme 12). Complete epimerization of methiodide A (**26**) to the



SCHEME 12. Figures attached to individual protons are ^{1}H-NMR data taken from ref. *172* or *158*.

more stable methiodide B (**27**) was effected by hot aqueous tetrahydrofuran. Compound **26** in a variety of protic solvents or in pyridine showed mutarotation, which was largest in chloroform/methanol or most rapid in water/methanol (Table V). The maximal change in molar rotation is of the same size as the molar rotation difference $\Delta[M]_D$ measured for the pure epimers **26** and **27.** By the way, it is very similar to the $\Delta[M]_D$ values found for 14-epimeric couples of acetals in the B/D-trans series (cf. Table IV).

A rapid mutarotation was also determined with *cis*-alpinigenine in methanol/chloroform. Although appreciably smaller, the amount of mutarotation was yet significant and points to the fact that even in protic or polar solvents only partial epimerization seems to be possible at the maximum. The mutarotation found for both **26** and **1m** has a positive sign. These data allow the specification of absolute configuration to be 14*R* in **26** and **1m** or 14*S* in **27** (*65, 172*).

In addition to mutarotation, other arguments have been advanced to assign the absolute configuration at C-14 depicted in Scheme 12 as follows.

1. A 1,3-diaxial relationship between 1-H and 14-OCH_3/OH is present in *O*-methyl-*cis*-alpinigenine (**2l**) and the more stable methiodide B (**27**) as well, but it is absent in both the less stable methiodide A (**26**) and *cis*-alpinigenine (**1m**) itself. This relationship is very well documented by a strong downfield shift by $\Delta\delta \sim -0.65$ ppm in the NMR spectra for 1-H in the (14*S*)-B/D-cis compounds **2l** in chloroform or **27** in chloroform/methanol 4:1 solution (Scheme 12). Alternatively, the NMR spectrum of the less stable counterpart **26,** run under the same conditions, within 3 days will turn into a spectral mixture that consists of the two anomers **26** and **27.** No

TABLE V
Mutarotation of *cis*-Alpinigenine (**1m**) and *cis*-Alpinigenine Methiodide A (**26**)[a]

Compound	Solvent	$[M]_D$ (°) outset	$[M]_D$ (°) equilibrium	$\Delta[M]_D$ (°)	Time (hr)	
(**1m**)	$CHCl_3$	+322	+324	—	18	
	$CH_3OH/CHCl_3$ 19:1	+356	+428	+72	3	
	Pyridine	+432	+432	—	50	
	$DMSO/H_2O$ 19:1	+284	+291	—	25	
(**26**)	H_2O	+673	+844	+171	10	$[M]_D$ values for **27** (°)
	H_2O/CH_3OH 4:1	+656	+867	+211	4	—
	Pyridine	+581	+809	+228	22	+809
	CH_3OH	+643	+860	+217	75	+870
	$CHCl_3/CH_3OH$ 19:1	+564	+864	+300	240	+863

[a] t = 23–32°C, c = 0.6–0.8 *(172)*.

TABLE VI
Molar Rotation Differences $\Delta[M]_D$ for O-Methylation of B/D-cis Hemiacetals

Compound	Configuration at C-14	$[M]_{\beta}$ (°)	$\Delta[M]_D$ (°)	Ref.
cis-Alpinigenine (**1m**)	*R*	+322 (C)	+371	*172*
O-Methyl-*cis*-alpinigenine (**2l**)	*S*	+693 (C)		*172*
cis-Alpinigenine methiodide A (**26**)	*R*	+643 (M)	+397	*172*
O-Methyl-*cis*-alpinigenine methiodide (**28**)	*S*	+1040 (M)		*172*
Rhoeagenine (**1b**)	*R*	+406 (C)	+493	*170*
Rhoeadine (**2a**)	*S*	+899 (C)		*180*
cis-Alpinigenine methiodide B (**27**)	*S*	+870 (M)	+170	*172*
O-Methyl-*cis*-alpinigenine methiodide (**28**)	*S*	+1040 (M)		*172*
Rhoeagenine methiodide (**2o**)	*S*	+786 (C)	+191	*180*
Rhoeadine methiodide	*S*	+977 (W)		*181*

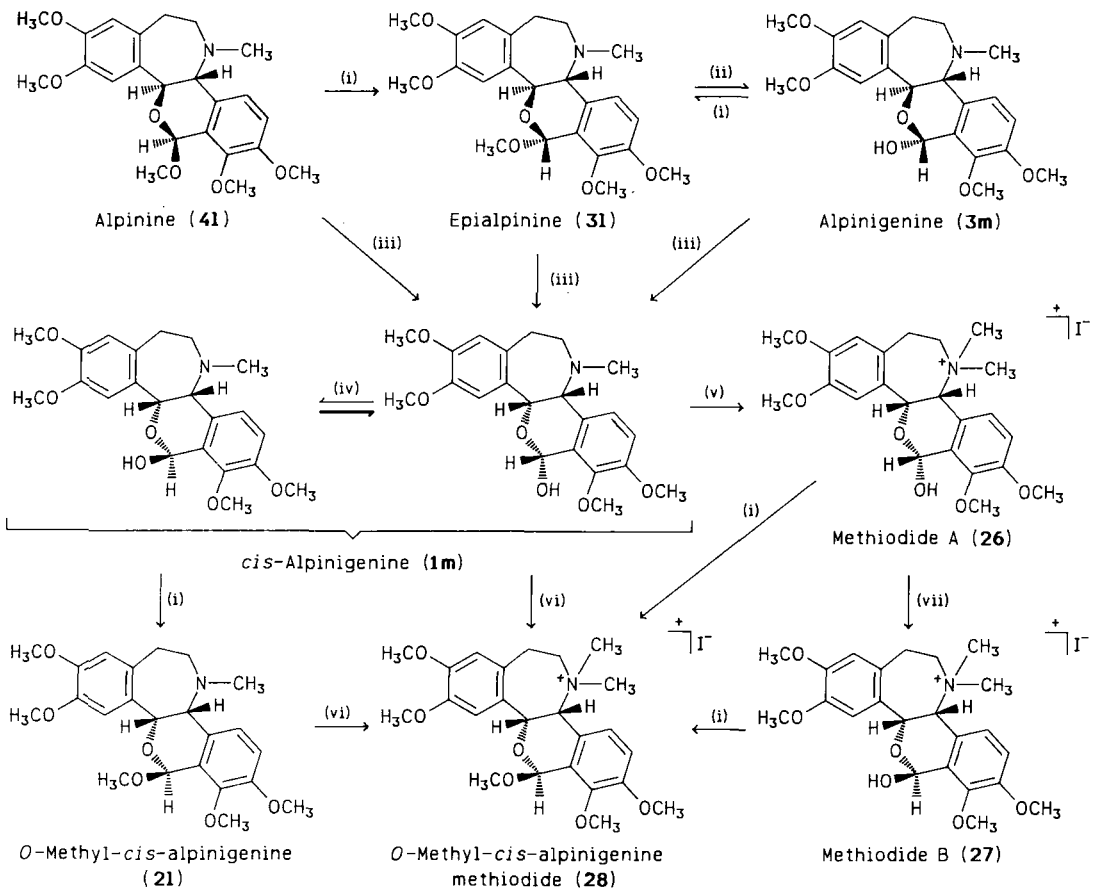
[a] C = chloroform, M = methanol, W = water.

time-dependent changes were observed in the NMR spectra of *cis*-alpinigenine (**1m**) in chloroform or acetone solution, and there is no conflict with the formation of the less stable methiodide A from **1m** in the latter solvent because the chirality existing at carbon 14 is maintained during the course of N-methylation.

2. The transformation of a B/D-cis hemiacetal, e.g., **1m,** to the corresponding methyl acetal, e.g., **2l,** is combined with a large positive molar rotation difference ranging between $\Delta[M]_D$ +350 and +400°. These values contrast sharply with those found for trans hemiacetals (cf. Table III) and are due to concurrent inversion at the anomeric carbon. In Table VI all pertinent examples available in the literature have been collected (upper part) and, alternatively, two couples that represent O-methylation without inversion have been included (lower part). Important chemical and stereochemical relationships encountered among the members of the alpinigenine subfamily have been summarized in Scheme 13.

As to the other known B/D-cis hemiacetals, rhoeagenine (**1b**), oreogenine (**1f**), and *cis*-*N*-methylporphyroxigenine (**1i**), extensive studies similar to those done with *cis*-alpinigenine (**1m**) and its congeners have not been undertaken. However, some missing NMR data for **1b** and **1f** have been provided (*187*). The generalization taken by suggesting the general formula **1** for the B/D-cis hemiacetals **1b, 1f, 1i,** and **1m** is based on the identity of their specific NMR characteristics.

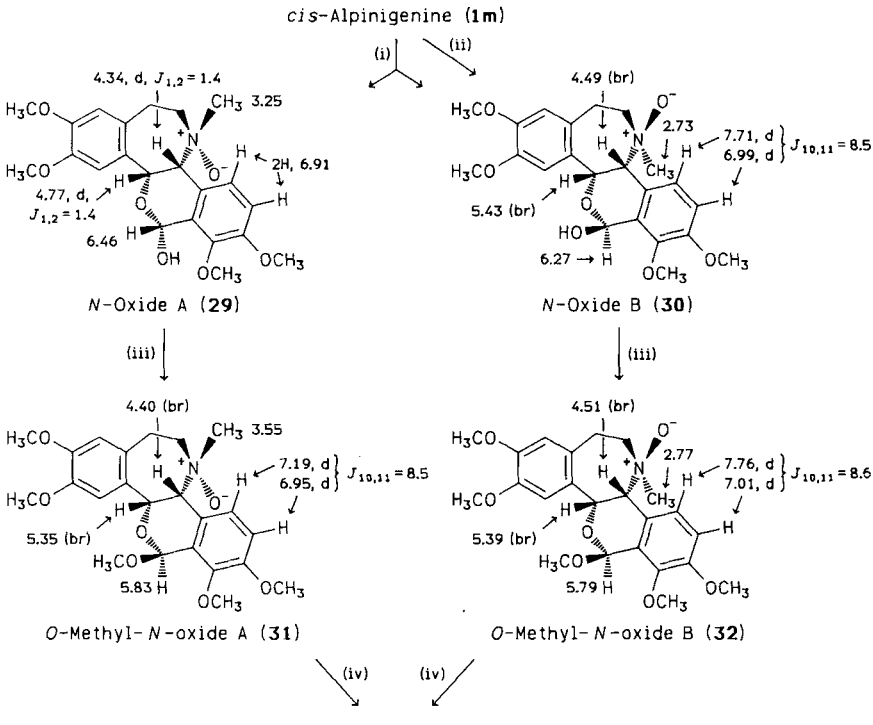
c. *N*-Oxides. The two *N*-oxides A (**29**) and B (**30**) were simultaneously formed in similar yields when *cis*-alpinigenine (**1m**) was treated with perbenzoic



SCHEME 13. i, H^+/MeOH/heat; ii, H^+/H_2O/heat; iii, 1 *N* HCl/reflux; iv, equilibrium in MeOH/$CHCl_3$ 19:1; v, CH_3I/acetone/reflux; vi, CH_3I/MeOH/reflux; vii, THF/H_2O/reflux.

acid at low temperature (*167, 172*) (Scheme 14). They differ in their configurations not only at the anomeric carbon but also at the quarternary nitrogen atom. Proton-NMR evidence for their opposite chirality at C-14 is again the strong difference in chemical shift observed for 1-H, which is due to a 1,3-diaxial relationship between 1-H and 14-OH in the (14*S*)-*N*-oxide B (**30**). *N*-Oxide A (**29**), in which the original 14*R* configuration characteristic of the starting compound **1m** is retained, is yet a very stable compound that neither shows mutarotation nor is liable to rearrange to its apparently more stable isomer B (**30**). Conforming with this, the latter greatly dominates in the alternate N-oxidation of **1m** at boiling temperature, using hydrogen peroxide in methanol.

The opposite chirality at nitrogen for the *N*-oxides A (**29**) and B (**30**) is obvious from the strong deshielding that the aromatic 10-H experiences only in the latter isomer, $\Delta\delta = +0.8$ ppm. Evidence for this was confirmed by chemical



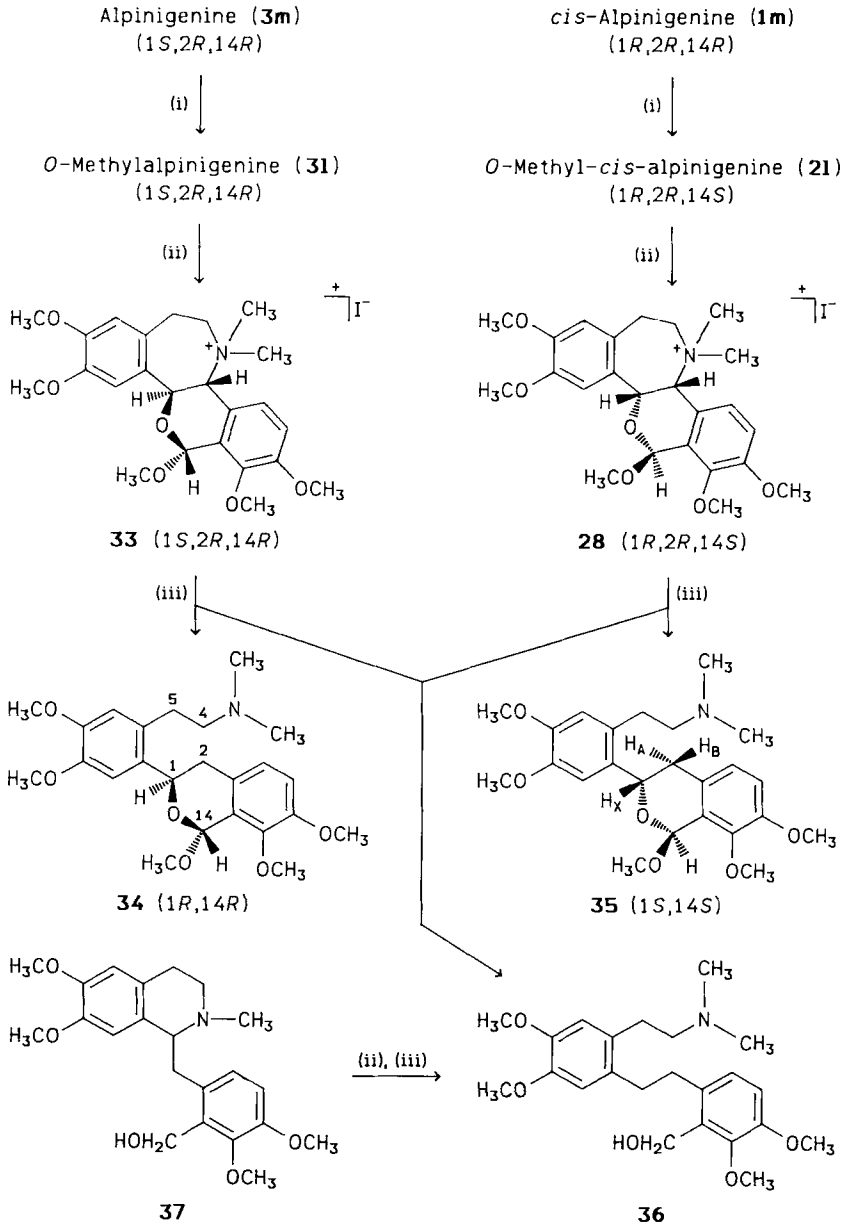
SCHEME 14. i, Perbenzoic acid/$CHCl_3$/5°C; ii, H_2O_2:EtOH: H_2O = 1:7:2/reflux; iii, 0.1 *N* HCl in dry MeOH/room temp; iv, $LiAlH_4$/THF/reflux. Figures attached to individual protons are proton-NMR δ values in $CDCl_3$ at 60 MHz (**29, 30**) or at 200 MHz (**31, 32**); br = broadened signal, half width ~1.5 Hz. (*167, 173*).

transformation. Mild H^+-catalyzed O-methylation at room temperature of the two *N*-oxides **29** and **30** afforded the methyl acetals **31** or **32,** which differ exclusively in their configurations at nitrogen. The chiral uniformity at C-14 was proved for both **31** and **32** by deoxygenative transformation to *O*-methyl-*cis*-alpinigenine (**2l**), using lithium aluminum hydride (*167*). In addition, the different chirality at nitrogen in *N*-oxide methyl acetals **31** and **32** is combined with a molar rotation difference $\Delta[M]_D$ as large as 435°.

3. Independent Evidence for 1*S* Configuration in the B/D-trans Series

Emde degradation at ambient temperature of the two stable acetals epialpinine and *O*-methyl-*cis*-alpinigenine as methiodides **33** and **28**, respectively, removed chirality from carbon 2 and afforded in good yield the two enantiomeric 3-arylisochroman methyl acetals (**34,** dextrorotatory, or **35,** levorotatory, respectively) [Rönsch, 1972 (*164*)] (Scheme 15). Benzylic fission of the C-4/C-5 bond (rhoeadine numbering), forming the base peak *m/z* 58 (C_3H_8N), dominates the mass spectra of the Emde products **34** and **35.** In proton NMR, 1-H shows up as the X part of an ABX system consisting of the protons at C-1 and C-2 (δ = 5.41 ppm, d × d, J_{AX} = 11 Hz, J_{BX} = 5 Hz). In all other data, including melting point, IR, NMR, and MS, but except for optical rotation and circular dichroism, **34** and **35** proved to be identical. The enantiomeric relationship between these two products of hydrogenolysis was established by preparing the racemate, which readily crystallized when equal amounts of each **34** and **35** were united in cyclohexane/hexane solution.

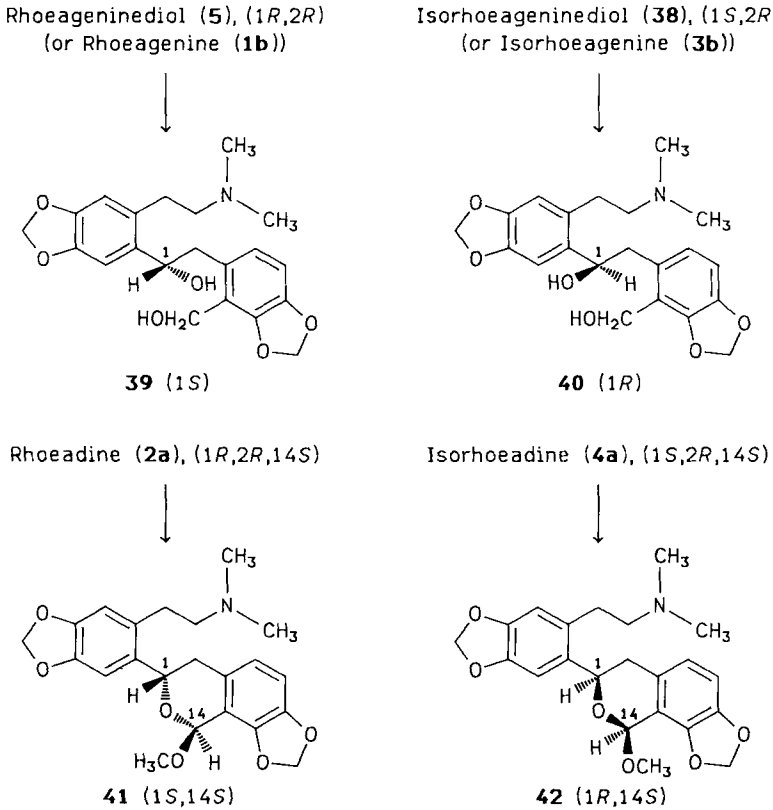
Being independent of optical methods, the above results have provided an alternate basis for the assignment of a 1*S* configuration to alpinigenine **3m** and all the other B/D-trans rhoeadines covered by general formulas **3** or **4** (*164, 172*). The argument was presented as follows: methiodide **28** originates in *cis*-alpinigenine (**1m**), the 1*R*,2*R* configuration of which is based on an X-ray analysis as shown in Section C,1. According to the NMR criterion, alpinigenine (**3m**), the percursor of the other methiodide (**33**), has an opposite relative configuration and therefore a priori may have an opposite chirality on either C-1 or C-2. The unique case, however, that the two isochromans (**34** and **35**) are mirror images means that they have opposite chirality on both C-1 and C-14, and this unequivocally determines **33, 3l,** and alpinigenine (**3m**) to have 1*S* chirality. The possibility that inversion may have occurred on any carbon during Emde degradation was excluded from the very mild alkaline reaction conditions. In addition, the two Emde products and therefore the two methyl acetals **3l** and **2l** differ in chirality at the anomeric carbon, which had already been assigned by other methods (see Section III,D,2,a). The structure of the optically inactive dibenzyl derivative **36,** formed as a trace product in the B/D-trans series or as the second



SCHEME 15. Emde degradation and stereochemical correlation of alpinigenine and *cis*-alpinigenine. i, MeOH/H^+/reflux; ii, CH_3I; iii, Na amalgam/H_2O/stirring, 25°C.

main product from the B/D-cis compound **28,** was confirmed by partial synthesis from the canadaline analog **37** (*172*).

Independently, Emde degradation was also applied to rhoeadine (**2a**), isorhoeadine (**4a**), and a variety of related compounds by Šimánek *et al.* from the Šantavý group (*59, 202–204*). An enantiomeric couple was formed again when rhoeageninediol (**5**) and isorhoeageninediol (**38**) as methiodides were split hydrogenetically between carbon 2 and nitrogen, with the chiral center maintained in the products **39** and **40** solely at C-1 (Scheme 16). The same products were similarly formed from rhoeagenine (**1b**) or isorhoeagenine (**3b**). These results are a confirmation for those obtained in the alpinigenine subfamily and the stereochemical conclusions drawn above. It should be noted that the diastereomeric Emde products **41** and **42** obtained from rhoeadine (**2a**) or isorhoeadine (**4a**), respectively, gave CD spectra that were nearly mirror images of each other (*202*), although their chiralities are opposite as to C-1 only. In a joint paper with



SCHEME 16. Emde degradation in the rhoeadine subfamily.

the Šantavý group (*59*), Snatzke discussed the very complex CD spectra of various rhoeadine alkaloids, including rhoeadine (**2a**), isorhoeadine (**4a**), alpinigenine (**3m**), and papaverrubine A (**4d**), as well as of a wide variety of Hofmann and Emde degradation products.

IV. Chemistry Excluding Synthesis

A. Further Degradative Reactions

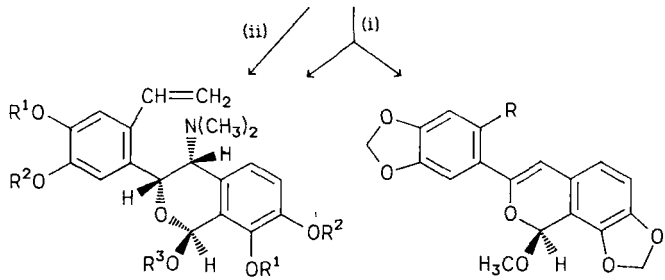
1. Hofmann Degradation in the B/D-cis and B/D-trans Series

The formation of the styrene **11** (rhoeadine methine A) by Hofmann degradation of rhoeadine (**2a**) has already been mentioned in Section III,B,1 (*6, 181*). Considering the presence of a β-hydrogen having the optimal staggered conformation relative to nitrogen, a prerequisite for Hofmann elimination required by theory (*28*), one would expect the two Hofmann products **11** and **43a** to be formed in equal amounts (Scheme 17). It was later shown by Hrbek *et al.* (*59*) that the latter isochromene (**43a**), designated as methine B, was actually formed, although in a very low yield, which might be due to steric hindrance hampering the attack of the hydroxy anion on the proton at C-1. Treatment of rhoeadine methochloride with sodium in liquid ammonia produced exclusively (**11**).

On the other hand, no anomaly was involved with Hofmann degradation in the B/D-trans series when epialpinine (**3l**) regiospecifically afforded the styrene **44** (*167*). In **44** and *O*-methyl-*cis*-alpinigenine methine (**11a**) the vicinal couplings for protons 1 and 2 were found to be $J_{1,2}$ = 11 or 2.5 Hz, respectively (*170*). These data differ slightly but significantly from those characteristic of the original benzazepine alkaloids **3l** or **2l,** and they may be a hint of the ring strain present in the benzazepine portion of the two steric series of rhoeadine alkaloids, which is destroyed on opening of ring B.

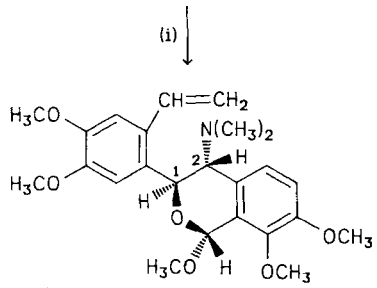
The Hofmann degradation of a hemiacetal, namely, of rhoeagenine methiodide (**2o**), has been studied by Rozwadowska and ApSimon (*175*). From the complex mixture formed, four compounds were isolated and structurally characterized (Scheme 18). The main product (**11c**) has the expected styrene structure and presumably is identical with a hemiacetal formerly prepared from rhoeadine methine (**11**) by acetal hydrolysis (*181*). Compound **11c** has been assigned the 14*S* configuration by analogy to the starting compound, but a trace product was claimed to be the related 14*R* compound **11d.** In our opinion, however, the published data, especially the NMR spectrum of **11d,** exhibiting a downfield shift for 1-H are prohibitive for such an assignment. The structures of the irregular Hofmann products **45** and **46** have been thoroughly evaluated, and a mechanism for their formation has been suggested. Compound **45** was also formed

Rhoeadine methiodide or **28**



11	$R^1 + R^2 = CH_2$, $R^3 = CH_3$	**43a**	$R = CH_2CH_2N(CH_3)_2$
11a	$R^1 = R^2 = R^3 = CH_3$	**43b**	$R = CH{=}CH_2$
11b	$R^1 = R^2 = CH_3$, $R^3 = H$	**43c**	$R = C_2H_5$

Epialpinine methiodide (**33**)



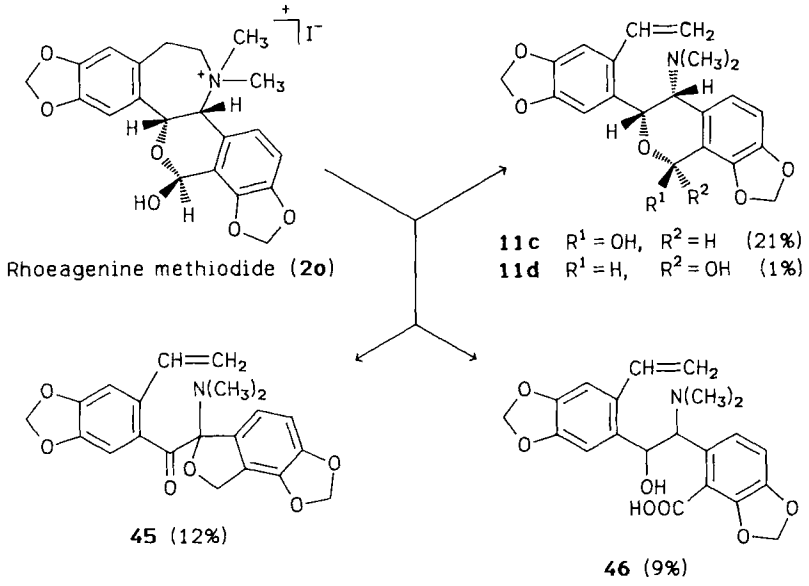
44

SCHEME 17. i, Ag_2O, then KOH/reflux; ii, after transformation to the methochloride: Na/liquid NH_3/−70°C.

when rhoeagenine methine (**11c**) was heated with base in the presence of air, similar conditions to those applied in this Hofmann degradation.

2. Thermal Rearrangement of *N*-Oxides

The thermal behavior of rhoeadine alkaloid *N*-oxides has been studied by Rönsch and Preiss (*167, 173*) for methyl acetals of the cis and trans series as well as for a hemiacetal (Scheme 19). The acetal *N*-oxides **47** and **32,** obtained from epialpinine (**3l**) or *O*-methyl-*cis*-alpinigenine **2l,** respectively, were heated at 100–120°C to give specifically the Meisenheimer products **48a** or **49.** No elimination product was detected. The hemiacetal *N*-oxide **22** required for thermolysis a higher temperature, and two compounds were formed: the Meisenheimer product **48b** in addition to the Cope product **50,** the latter being formed



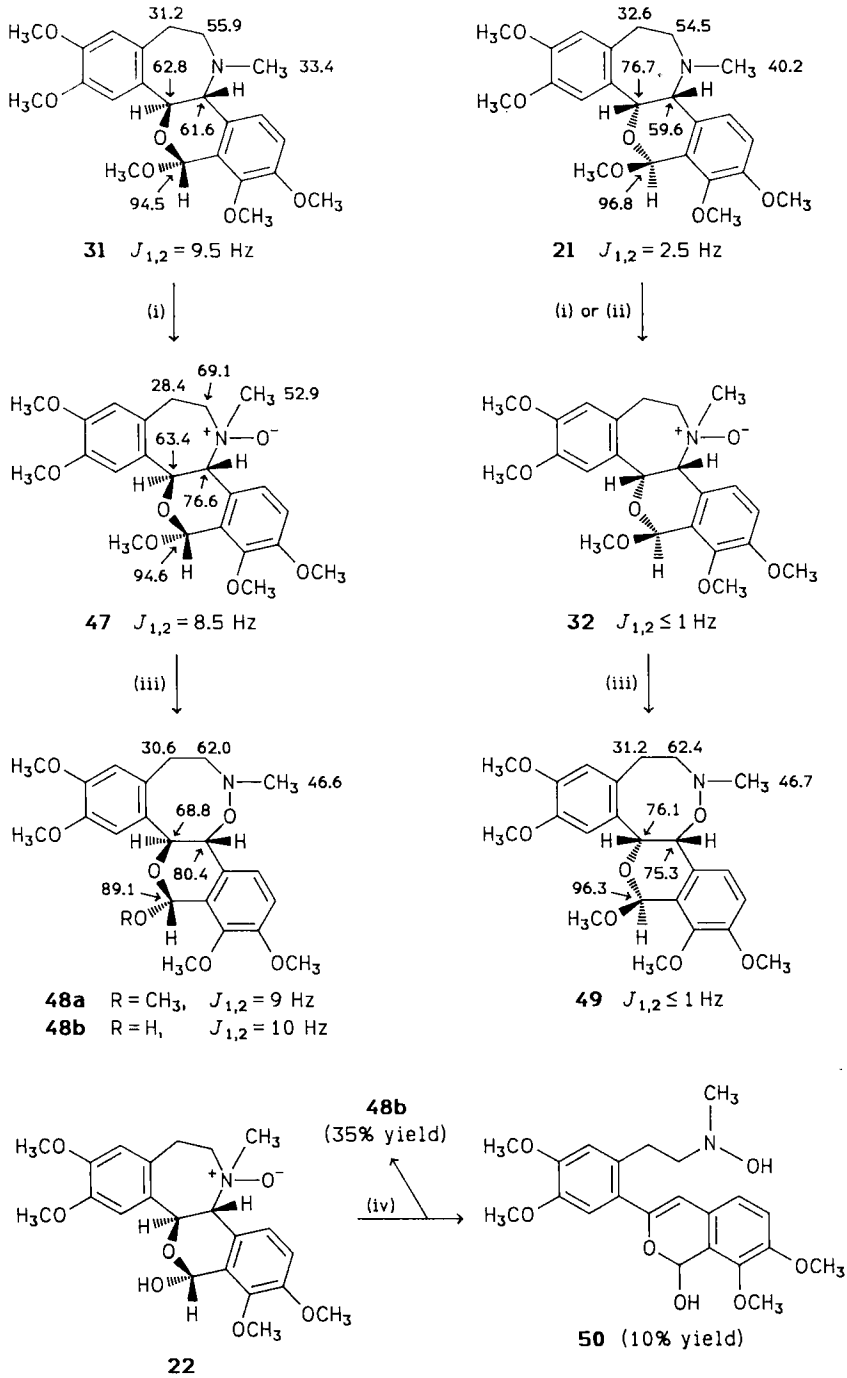
SCHEME 18. Yields are in parentheses.

by β-elimination in a side reaction. Meisenheimer rearrangement and Cope elimination are regarded to be competitive reaction types in the thermolysis of heterocyclic *N*-oxides (*70, 71*).

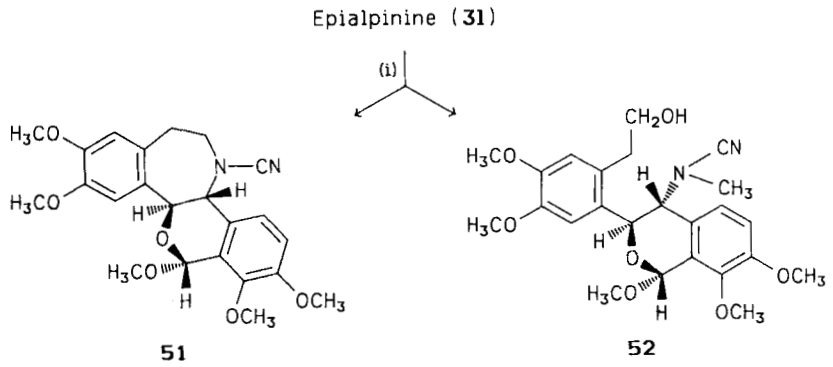
It is remarkable that during the course of rearrangement the chirality at carbon 2 is maintained in both the B/D-*trans*-benzoxazocine (**48a**) and the cis compound **49.** Evidence for this again came from proton-NMR vicinal couplings $J_{1,2}$, which did not change after ring enlargement in either series (see Scheme 19). That it is C-2 rather than C-4 that is the central carbon where the *N*-oxide oxygen is incorporated into ring B was verified from carbon-13 NMR, and relevant data were added to the formulas shown. These results support the view discussed in Johnstone (*70*) that the Meisenheimer rearrangement is a cleavage recombination process.

3. Solvolytic Cyanogen Bromide Reaction

The solvolytic cyanogen bromide reaction (*3, 162*) was developed as a more feasible variation to von Braun degradation. In an application to epialpinine (**3l**), however, a complex mixture was formed from which the two main components **51** and **52** were isolated in low yields (*167*) (Scheme 20). The structures proposed are suggestive of the probability that at least in the B/D-trans series this reaction proceeds predominantly through nucleophilic attack on nonbenzylic positions, instead of C-2 as had been expected.



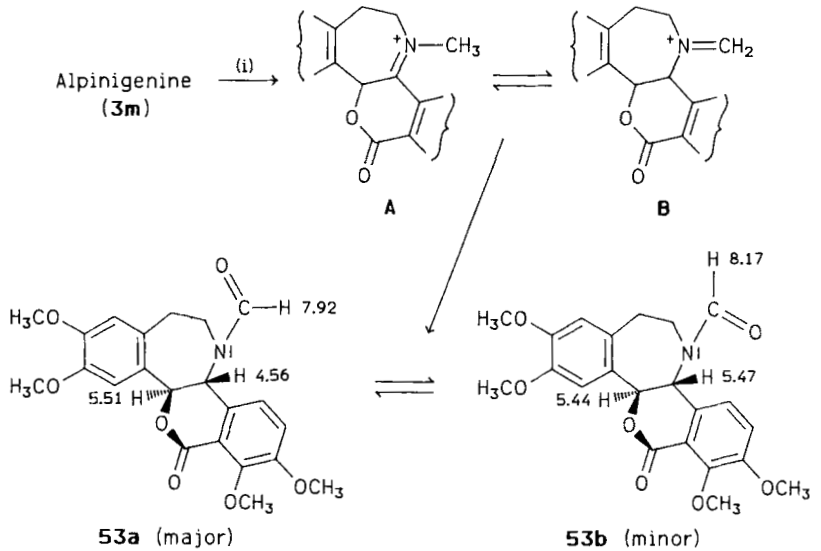
SCHEME 19. i, Perbenzoic acid/$CHCl_3$/5°C; ii, H_2O_2/MeOH/reflux; iii, 120°C/ 1 torr; iv, 180°C/1 torr; figures added to individual carbons are ^{13}C chemical-shift data in $CDCl_3$.



SCHEME 20. i, BrCN/THF/H_2O/MgO/3 hr reflux.

4. Two Rotamers of *N*-Formyloxynoralpinigenine

Jones oxidation of alpinigenine (**3m**), unlike rhoeagenine under similar conditions (Scheme 1), provided the pure rotamer **53a** of a lactonic *N*-formylalpinigenine derivative [Lavie *et al.* (*96*)]. In chloroform solution, the half of this amide rotamer (**53a**) was long enough to allow a proton-NMR spectrum to be done, but within 2 hr an equilibrium consisting of **53a** and **53b** was reached (Scheme 21). The formation of **53** was explained by benzylic dehydrogenation to



SCHEME 21. i, CrO_3/H_2SO_4/acetone/room temp; figures added to individual protons are ^{1}H-NMR data.

an immonium salt **A,** subsequent double-bond shift to **B,** water addition, and further oxidation. The attribution of structures **53a** and **53b** to the major and minor rotamers, respectively, was possible on the basis of proton- and carbon-13-NMR data as included in Scheme 21.

B. Transformation of Rhoeadines to Other Alkaloids

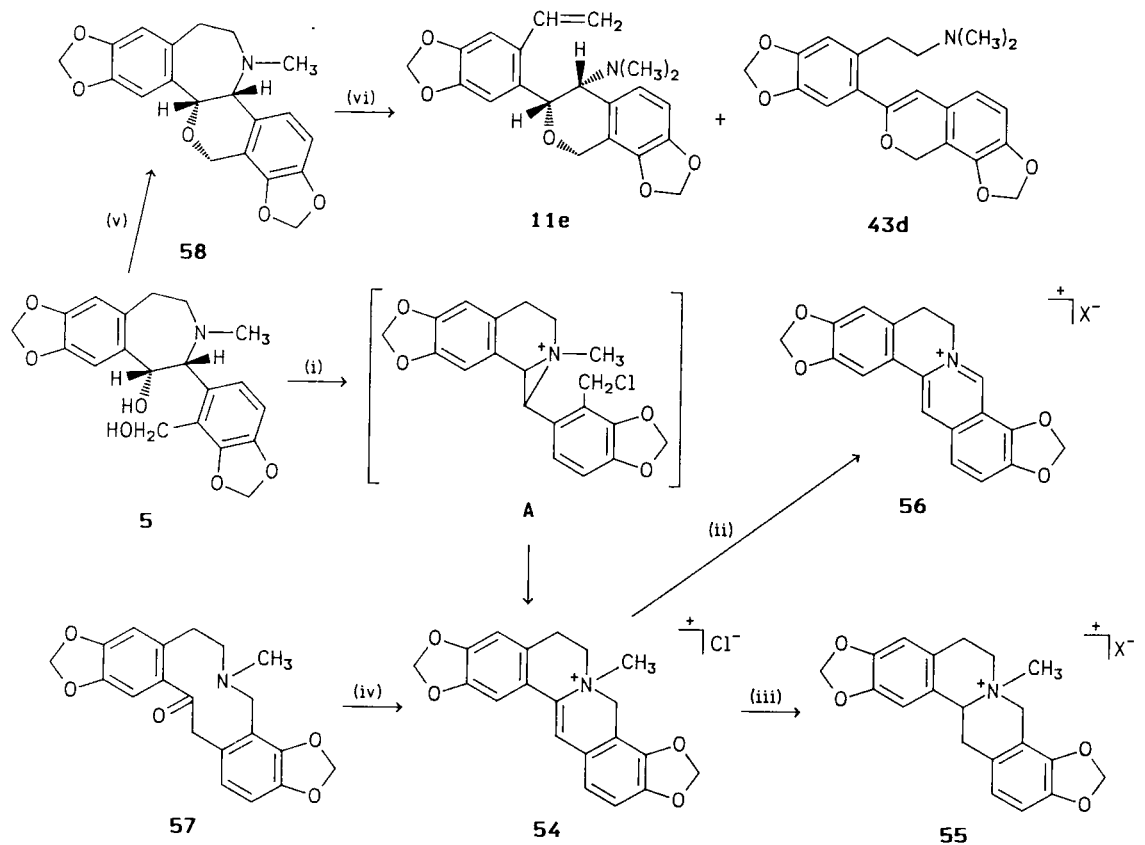
1. To Protoberberines

Treatment of rhoeageninediol (**5**) with boiling thionyl chloride resulted simultaneously in ring contraction, dehydration, and closure of an additional ring as shown from the product, the quaternary enamine **54,** which has a partially hydrogenated protoberberine structure [Klásek *et al.* (*83*)] (Scheme 22). Compound **54** was identified by transformation to tetrahydrocoptisine methiodide (**55**) as well as to coptisine (**56**). The complex series of reactions leading to **54** has not yet been studied, but Shamma (*194*) has advanced the plausible suggestion that the aziridinium species **A** might be involved. The coptisine derivative **54** has long been known as isoprotopine chloride and can either be prepared from protopine (**57**), using phosphoryl chloride according to Perkin (*123*), or from 7,8-dihydrocoptisine by way of dimethyl sulfate methylation (*118*).

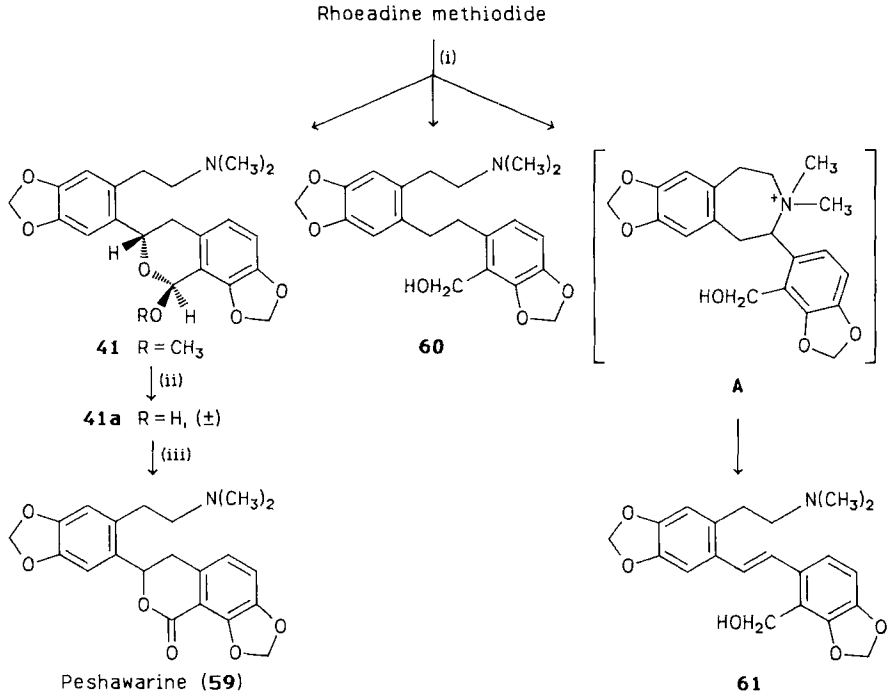
In this context, a related acid transformation of diol **5,** found by Hrbek *et al.* (*60*), should be mentioned briefly. In hot 2 *N* hydrochloric acid, **5** readily and stereospecifically recyclized to give the rhoeadine-like isochroman **58,** which lacks an oxygen substituent at C-14. This acid treatment did not destroy the chirality at any carbon, and **58** proved to be identical with 14-demethoxyrhoeadine, which had been prepared previously from rhoeadine by Suszko and Rozwadowska (*222*), using the lithium aluminum hydride/aluminum chloride reagent. Hofmann degradation of **58,** leading to the methines **11e** and **43d** took a course similar to that of rhoeadine (cf. Scheme 17).

2. To Secoberbines

The transformation of rhoeadine (**2a**) to peshawarine (**59**) has been described by Šimánek *et al.* (*205*) (Scheme 23). Peshawarine is a lactonic member of the small group of secoberbine alkaloids reported in the 1970s, which are formally derived from tetrahydroprotoberberine alkaloids if the carbon-8/nitrogen bond of the latter is split (*195*). Emde degradation of rhoeadine methiodide, already mentioned in Section III,D,3, was again applied in Šantavý's laboratory to give a mixture, which in this case included the three main products **41, 60,** and **61.** The regular Emde product **41** was subjected to acetal hydrolysis with concomitant



SCHEME 22. i, $SOCl_2/CHCl_3$/reflux; ii, sodium *p*-tolylthiolate/EtCOMe/O_2/reflux; iii, H_2/Pt; iv, $POCl_3$; v, 2 *N* HCl/reflux; vi, Hofmann sequence.



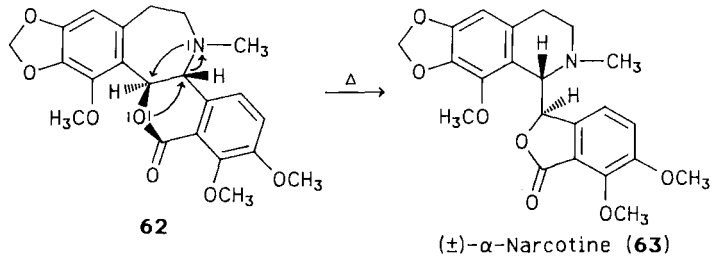
SCHEME 23. i, Na–Hg/MeOH/H_2O/48 hr/22°C/no stirring (according to ref. *202*); ii, 0.1 *N* HCl; iii, $CrO_3/H_2O/H_2SO_4$/acetone.

racemization forming hemiacetal (±)-**41a.** Treatment of **41a** with the Jones reagent afforded a high yield of racemic peshawarine (**59**).

The irregular product **61,** not mentioned in previous reports on the Emde degradation of rhoeadine (cf. *202* or *59*) might be formed via intermediate **A** by a combination of Emde and Hofmann processes during an unusually long reaction time.

3. To Phthalidisoquinolines

A ring contraction of another type was observed by Hohlbrugger and Klötzer (*54*) when the nonnatural B/D-trans lactone **62** was heated above its melting point (Scheme 24). The product formed was α-narcotine (**63**), crystallizing from the melt. This nucleophilic exchange reaction should be inhibited by N-protonation, and, indeed, heating **62** in 1 *N* hydrochloric acid effected the normal B/D-trans → cis isomerization to the corresponding cis lactone (not shown). The scope of this unique reaction has not yet been studied. It seems possible that

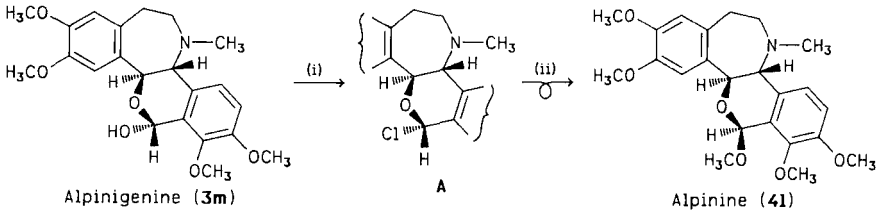


SCHEME 24

strong steric strain between ring-D oxygen and the unusual 9-methoxy group is the main driving force in this rearrangement.

4. Transformation of Alpinigenine to Alpinine, a Less Stable Methyl Acetal

Scheme 25 shows the course of the main reaction that occurred when alpinigenine (**3m**) was treated with thionyl chloride, followed by sodium methoxide. Since the sterospecificity was less than 75%, a mixture was formed, which consisted of alpinine (**4l**) and the stable acetal epialpinine (**3l**) in a ratio ranging between 2:1 and 3:1. Theuns *et al.* (*229, 229a*) assume that it is the first step leading to the anomeric chloride **A,** not isolated, that lacks stereospecificity, especially in the presence of pyridine, while the reaction with a methoxide anion should proceed with Walden inversion. Although a complete separation of the epimeric acetals **4l** and **3l** was difficult, this sequence makes available for the first time **4l** and other less stable acetals whose only source until now has been the plant.



SCHEME 25. i, $SOCl_2$/THF/0°C; ii, NaOMe/THF/0°C.

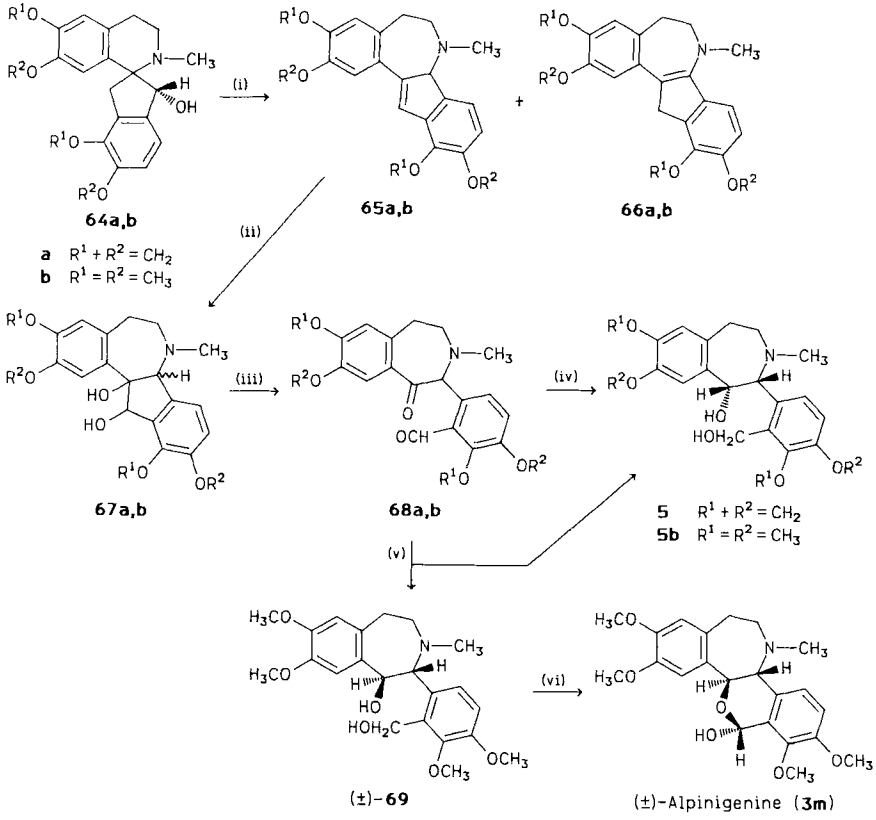
V. Synthesis

Synthetic work on rhoeadine alkaloids has been last reviewed in 1978 by Shamma (*196*) in his second book on the isoquinoline alkaloids. Earlier reviews

also including syntheses of structurally related benzazepines are by Shamma (*194*) or Kametani (*74*). A general report on benzazepines was published by Kasparek (*82*), and a new synthesis for 2-phenyl-3-benzazepines potentially useful as starting materials appeared in 1984 (*220*).

A. From Spirobenzylisoquinolines

The state of synthetic art in this field had appeared to lie dormant until 1970 when Irie *et al.* (*66*) succeeded in the synthesis of rheoageninediol (**5**), and the synthesis of alpinigenine (**3m**) followed soon (*67*). Essentially, this synthesis involves a skeletal rearrangement of the synthetically available spirobenzylisoquinoline alcohol **64** that was induced by methanesulfonyl chloride in triethylamine to form a mixture of the two benz[*d*]indeno[1,2-*b*]azepine derivatives **65** and **66** (Scheme 26). The major isomer, the β,γ-enamine **65,** unstable as free



Scheme 26. i, $CH_3SO_2Cl/Et_3N/THF/0°C/58\%$; ii, OsO_4/Et_2O/room temp/86%; iii, $NaIO_4$/pH 4–5/room temp; iv, $NaBH_4$/aq EtOH; v, lithium perhydro-9*b*-boraphenalenyl hydride/dry THF/0°C/90%; vi, activated $MnO_2/CHCl_3$/room temp/1%.

base, was hydroxylated to the diol **67,** which in turn was treated with sodium periodate and a complex hydride. Depending on the steric requirements of the reductant used, the intermediate ketoaldehyde **68a** with sodium borohydride gave predominantly (±)-rhoeageninediol (**5**), while lithium perhydro-9*b*-boraphenalenyl hydride reduction of **68b** afforded a 4:5 mixture consisting of the trans diol **69** plus **5b.** After separating the mixture, final oxidation of the trans diol **69,** using activated manganese dioxide, led to (±)-alpinigenine (**3m**) in very low yield.

B. From Phthalidisoquinolines

1. Rhoeadine

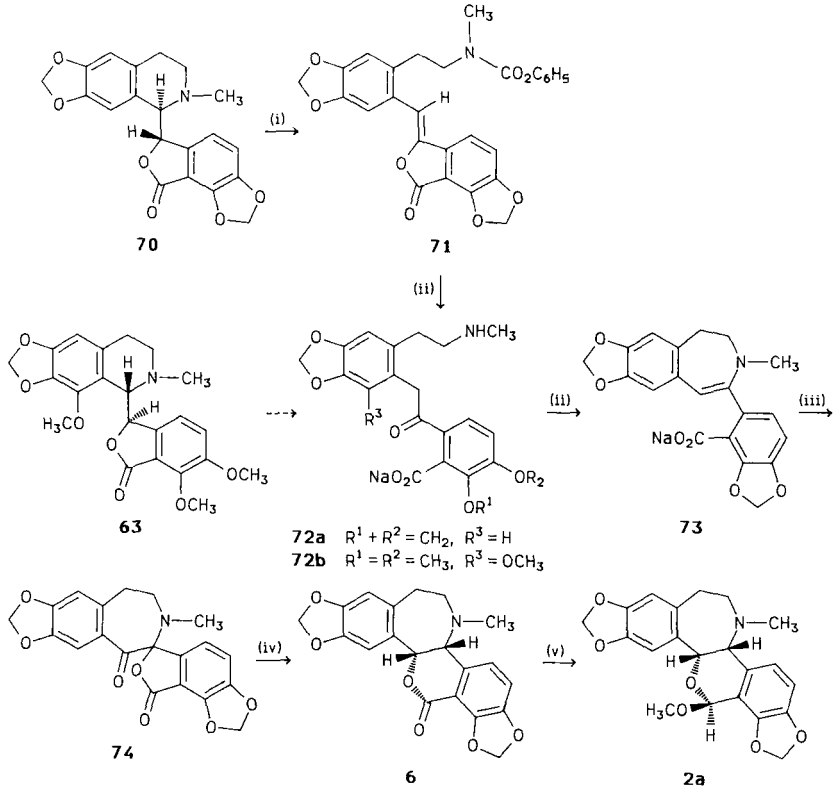
Prior to the elucidation of the biogenetic pathway leading to rhoeadine structures, alkaloids of the phthalidisoquinoline type had been considered to be precursory of them (*78, 180*). A laboratory procedure for the transformation of bicuculline (**70**) to rhoeadine (**2a**), elaborated by Klötzer *et al.* (*86, 87*), is reminiscent of such a suggestion.

A modified chloroformate degradation on **70** and subsequent dehydrohalogenation of an intermediate chloro compound (not shown) led to the benzylidenephthalide **71,** whose structure was ascertained by an X-ray analysis (Scheme 27). After carbamate hydrolysis, using hot alkali, the resulting fragment, probably the unstable nornarceine analog **72a,** rearranged to a 2-phenyl-3-benzazepine derivative isolated as the sodium salt (**73**). Spirolactonization of the latter in acidic medium and spontaneous air oxidation readily provided the ketolactone **74,** which by borohydride reduction and subsequent relactonization gave the known oxyrhoeagenine **6** in an overall yield amounting to 40%. After resolving the racemic product, enantiomeric **6** was treated with sodium bismethoxyethoxyaluminum hydride (Red-Al) at low temperature. The resulting mixture, which was said to consist of two anomeric hemiacetals characterized by R_F values only, was acetalized in acidic methanol to give uniform (+)-rhoeadine (**2a**).

The above synthesis was modeled starting from α-narcotine (**63**), and an efficient synthesis for the crucial intermediate nornarceine (**72b**) was developed (*84, 85, 88*). It seems interesting to note that the modified Hofmann sequence used for this did not work with the 8-nonsubstituted starting compound **70,** which instead was transformed to **72a** as described in the preceding paragraph.

2. Papaverrubine E

After publishing a model sequence (*52*), Hohlbrugger and Klötzer (*53*) achieved the first total synthesis of a natural papaverrubine alkaloid in 1979, with bicuculline (**70**) again being the starting point (Scheme 28). The key step was a

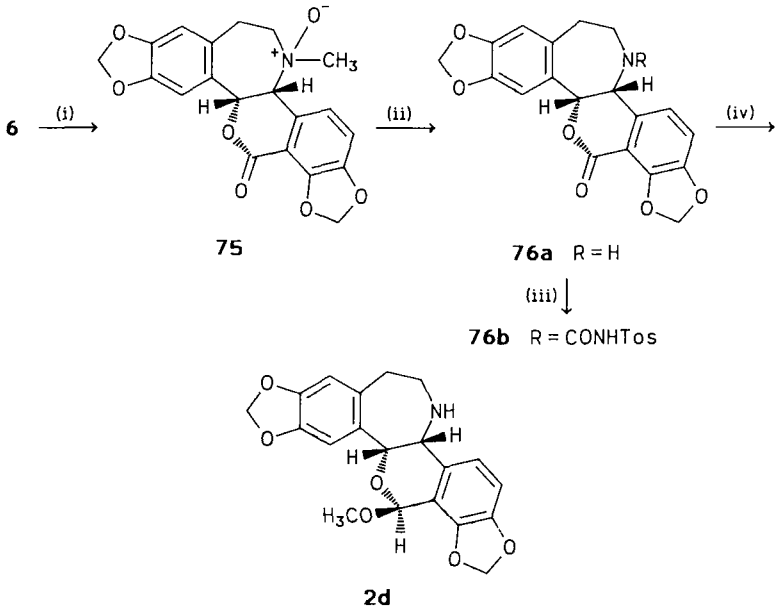


SCHEME 27. i, ClCOOPh/EtN(*i*-Pr)$_2$/benzene/20°C, then EtN(*i*-Pr)$_2$/DMSO/100°C/78%; ii, 2 *N* NaOH/THF/reflux temp/93%; iii, dil AcOH, then EtOH/air/65%; iv, $LiBH_4$/THF/0–24°C,then dil AcOH/100°C/85%; v, Red-Al/Py/THF/−70°C, then MeOH/H^+/20°C/60%.

modified Polonovsky demethylation on the *N*-oxide **75,** using trifluoroacetic anhydride at low temperature. The latter was obtained from **70** via oxyrhoeagenine (**6**). An N protection by the tosylcarbamoyl group before Red-Al reduction and O-methylation was essential for the preservation of the norrhoeadine structure, which was finally regenerated with boiling methanol to form papaverrubine E (**2d**). Another norrhoeadine compound formed an intermediate in a synthesis described in Section V,E (Scheme 38).

3. A B/D-cis → trans Conversion

There are few possibilities for the synthesis of B/D-trans alkaloids. Devising a procedure for the retransformation of the nonnaturally substituted cis lactone **77,** Hohlbrugger and Klötzer (*54*) provided a useful addition to the variety of syn-



SCHEME 28. i, *m*-Chloroperbenzoic acid/$CHCl_3$/0–20°C/84%; ii, TFAA/$CHCl_3$/N_2/−40–0°C/31%; iii, *p*-$MePhSO_2NCO$/THF/0°C/99%; iv, Red-Al/THF/0°C, then $CH(OCH_3)_3$/MeOH/H^+/0°C, then MeOH/$NaHCO_3$/reflux/38%.

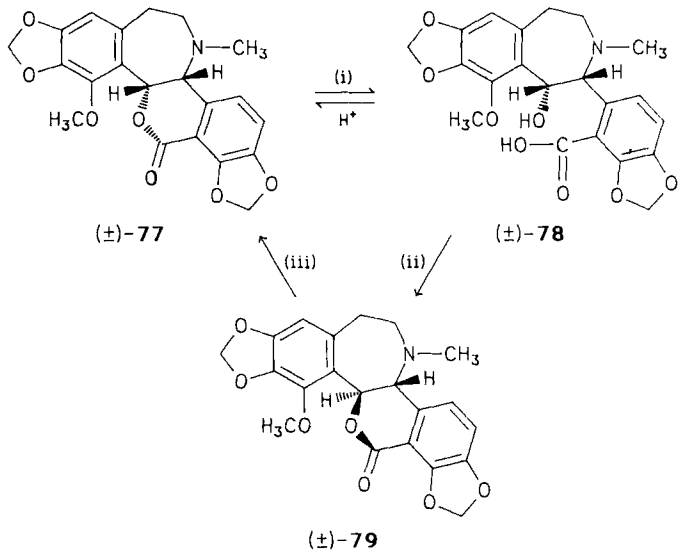
thetic work in the rhoeadine field. The B/D-cis → trans conversion is substantially a reversal of the thermodynamically favored isomerization of a tertiary B/D-trans compound.

In the system triphenylphosphine/diethyl azodicarboxylate, the free hydroxy acid **78,** obtained by alkaline hydrolysis from **77,** recyclized in moderate yield with inversion at C-1 to the trans lactone **79** (Scheme 29). In addition to the stereochemistry of B/D-ring fusion, this *trans*-rheadane* (**79**) is further destabilized by the unusual methoxy group at C-9 to such an extent that B/D-trans → cis isomerization in hot 1 *N* mineral acid requires a few minutes only. Consequently, the trans acid corresponding to **78** (not shown) failed to give **79** and rather isomerized to **77.**

4. An Alternate Transformation

Holland *et al.* (*55*) have reported on a series of reactions shown in Scheme 30, which constitute a formal conversion of a phthalidisoquinoline to a rhoeadane

* The term "rheadane" has been coined by Kametani (*73*) and was widely used by the Klötzer–Brossi team.

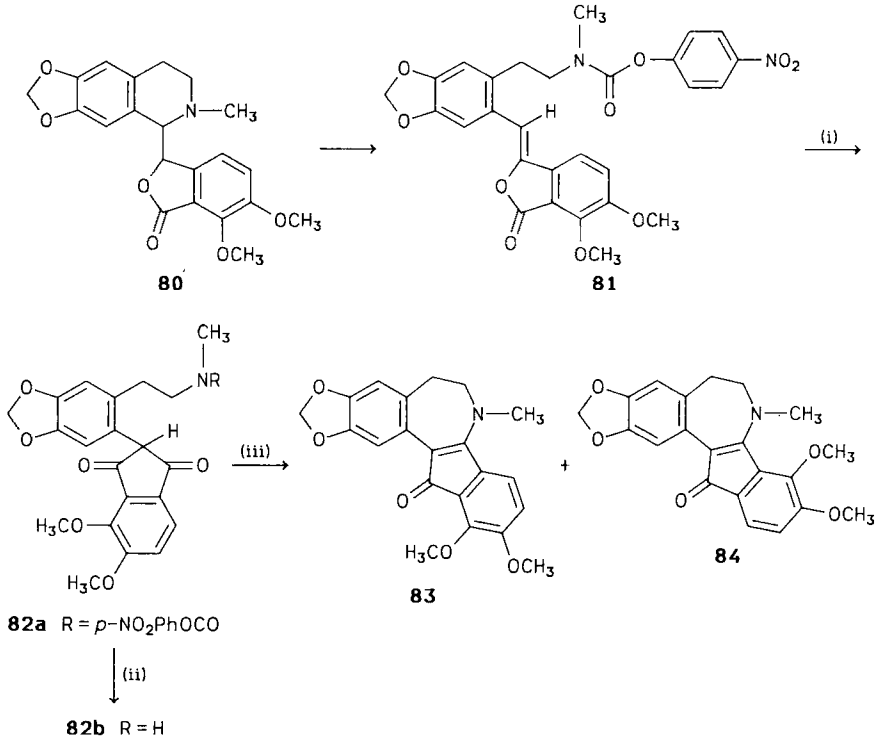


SCHEME 29. i, 2 *N* NaOH/MeOH/2 min/65°C, then pH 5–6/81%; ii, $Ph_3P/N_2(CO_2Et)_2$/THF/20°C/26%; iii, 1 *N* HCl/a few min of heating on a water bath.

compound, thus providing an alternative to previous work covered in this section. The benzylidenephthalide **81** was obtained from easily available hydrastine (**80**) in a manner similar to that shown for bicuculline (**70**) in Scheme 27. Sodium methoxide in methanol catalyzed a benzylidenephthalide/indan-1,3-dione rearrangement, and subsequent alkaline saponification of the carbamate function gave an excellent yield of the secondary amine **82b,** which in turn was cyclized via dehydration to a separable mixture of the two isomeric indenobenzazepines (**83** and **84**). The predominant isomer **83,** formed from **80** in an overall yield of 46%, has a substitution pattern corresponding to that of the natural rhoeadines. Further transformations of indenobenzazepines to rhoeadines will be described (Scheme 30) in Section V,D.

C. From Protoberberines and Tetrahydroprotoberberines

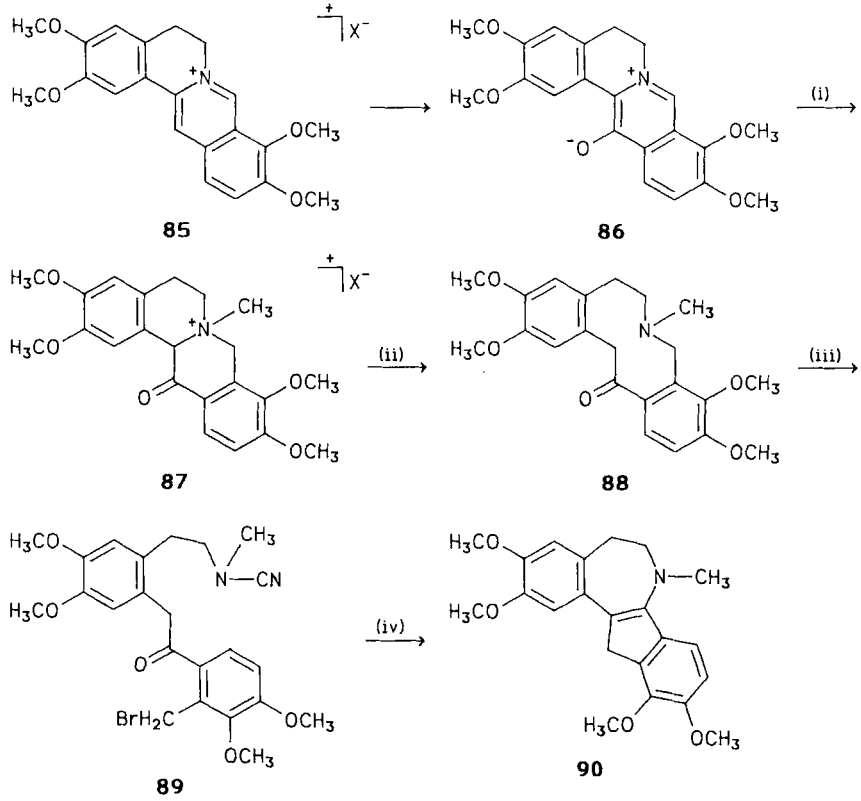
Protoberberines or tetrahydroprotoberberines are involved in the biosynthesis of a wide variety of isoquinoline alkaloid types. Also, they are precursors for the benzazepine bases of the rhoeadine relationship. Those synthetic sequences for rhoeadines that start from tetrahydroprotoberberines are therefore of special interest.



SCHEME 30. i, NaOMe/MeOH/N_2/reflux/95%; ii, aq NaOH/DMSO/100°C/98%; iii, *p*-$MePhSO_3H$/MePh/reflux/Dean–Stark trap/63% **83** + 14% **84.**

1. A Biogenetically Patterned Synthesis

Under this title Nalliah *et al.* (*110*) reported on the first chemical access to a benzazepine alkaloid from a tetrahydroprotoberberine (Scheme 31). The 13-oxoberbine methosalt **87** was prepared from the 13-phenol betaine **86** (*111*), a type of compound that is accessible from protoberberines, e.g., palmatine (**85**) or tetrahydroprotoberberines, by a variety of methods (*41*, *69*, *193*). Hydrogenolysis of the methosalt **87** furnished the 13-oxygenated analog **88** of the protopine alkaloids, which with cyanogen bromide underwent a predicted benzylic fission to give the "narceine equivalent" **89.** In analogy to experiments already discussed in Scheme 27, a cyclization to the indenobenzazepine (**90**) was achieved by using hot potassium hydroxide. The synthesis of rhoeadine alkaloids via indenobenzazepines had been described previously by Orito *et al.* (*120*) (see Section V,D).



SCHEME 31. i, $LiAlH_4$/THF, then Me_2SO_4/N_2; ii, Zn/30% aq MeCOOH/57%; iii, BrCN/THF/47%; iv, KOH/EtOH/reflux.

The idea of this biogenetically patterned synthesis was to show how a tetrahydropalmatine methosalt already established as an intermediate for alpinigenine (**3m**) (*163*) may be further transformed. Evidence from feeding experiments discussed in Section VII favors, however, the introduction of oxygen into the 14 position of the quarternary intermediate, which leads to a protopine type.

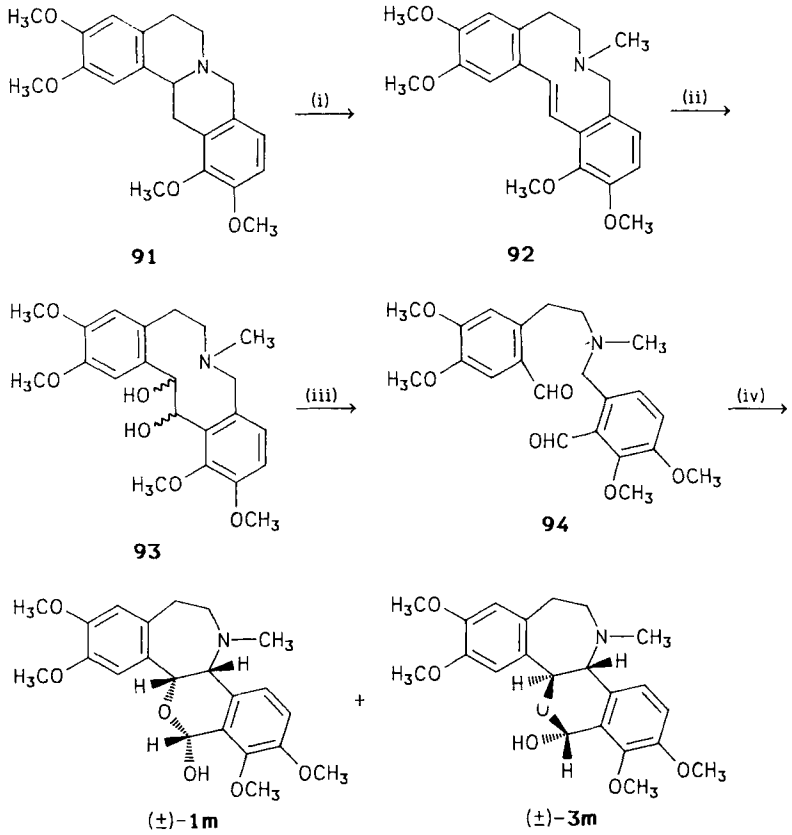
2. A Photochemical Double Cyclization for Both (±)-*cis*-Alpinigenine and (±)-Alpinigenine

The aminoaldehyde **94** required for the photochemical process was obtained by Prabhakar *et al.* (*149, 150*) from the nonnaturally substituted tetrahydroprotoberberine **91** via diol **93,** using a sequence originally described by Russel (*176;* also cf. *193*). The original procedure for the hydroxylation of the styrene-type methine base **92** provided a practical access to the starting diol **93** simply by

increasing the acidity of the reaction medium (Scheme 32). Diol **93** was readily cleaved with periodic acid. The photocyclization of the dialdehyde **94** thus formed required anaerobic conditions, and from the mixture of photoproducts (±)-*cis*-alpinigenine (**1m**) in addition to traces of (±)-alpinigenine (**3m**) were separated.

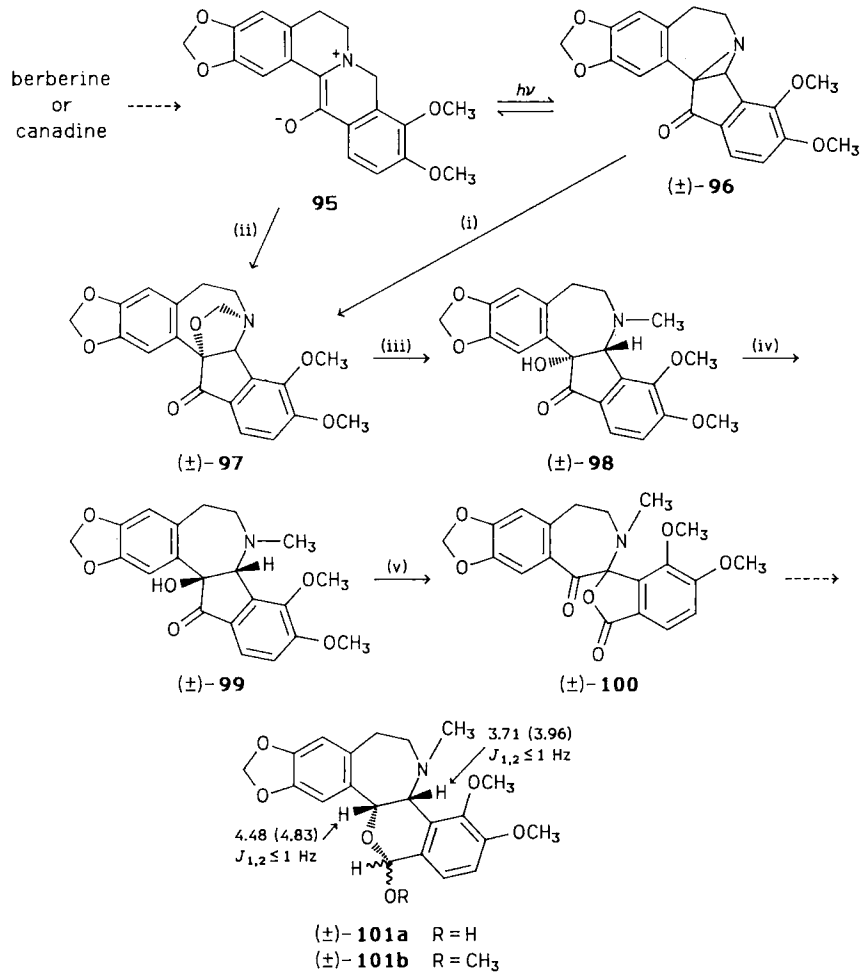
3. An Efficient Conversion to a Nonnaturally Substituted *cis*-Rhoeadane

An alternate sequence, starting again from a 13-phenol betaine, viz., **95,** was developed by Murugesan *et al.* (*108*) at Pennsylvania University in 1981. Use was made of a previously discovered photoequilibrium (*47*) existing between **95**



SCHEME 32. i, A Hofmann sequence modified by preventing a methohydroxide from CO_2 and heating it *in vacuo*/65%; ii, 1 *N* HCl/*N*-bromosuccinic imide/0°C/60%; iii, H^+/HIO_4/5°C/95%; iv, *hv*/dry *t*-BuOH/37°C/N_2/44%.

and the isolable ketoaziridine **96.** Treatment of aziridine **96** with formaldehyde or irradiation of betaine **95** in the presence of formaldehyde produced the bridged indenobenzazepine **97** in yields amounting to 90 or 60%, respectively (Scheme 33). Borohydride reduction of **97** and subsequent acid isomerization of **98** at room temperature gave an excellent yield of the more stable cis ketol **99.** Structures **97** through **99** were verified by carbon-13 NMR. Periodic-acid cleavage of **99** furnished a ketospirolactone (**100**) of a type familiar from previous synthetic



SCHEME 33. i, CH_2O/MeOH/90%; ii, $h\nu$/CH_2O/MeOH/60%; iii, $NaBH_3CN$/aq MeOH/pH ~3/~100%; iv, H_3O^+/room temp; v, $NaIO_4$/dil HCl/50%; figures added to formula **101** are proton-NMR δ values, with those in parentheses being for **101.**

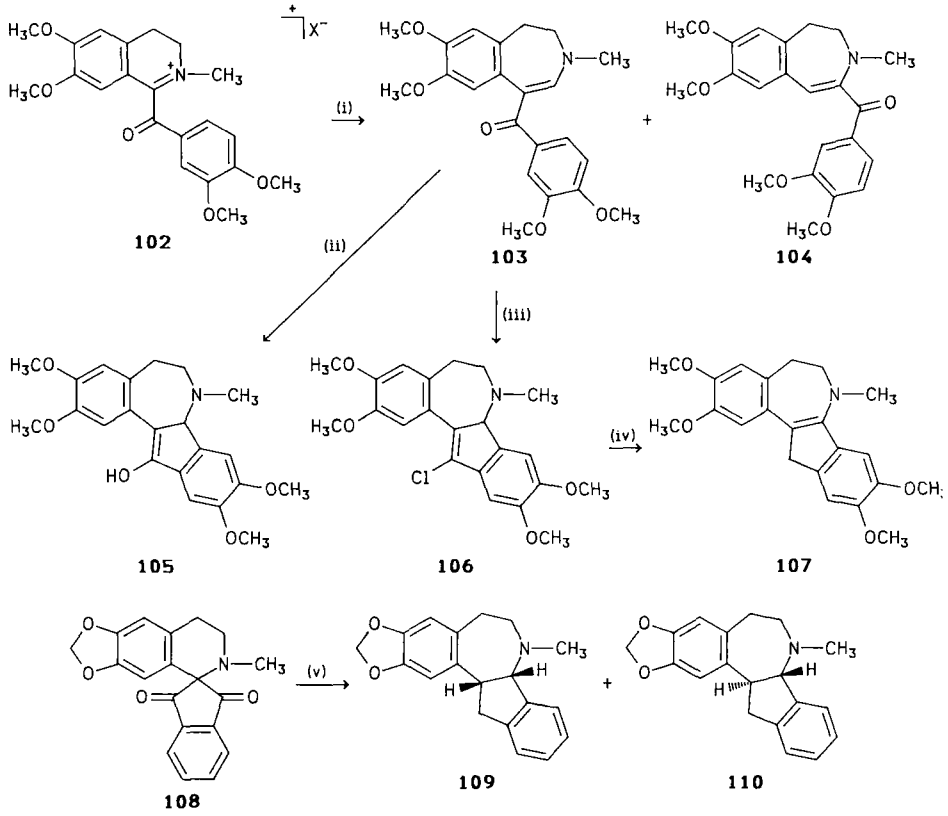
work dealt with in Section B,1. The remaining steps in this synthesis follow these precedents (*87*) as well as those to be reported in Section D,3. The overall yield through steps **96** → **101** was approximately 35%.

The relative stereochemistry at C-14 of both the racemic hemiacetal **101a** and acetal **101b** has been specified in the original paper without any discussion of the spectral data given for the 14*S*, 2*R* configuration. Contrary to this, in Scheme 33 the stereochemistry was not specified for the anomeric carbon because the spectral data published do not allow this. Due to the very-high-field chemical shift of the proton at C-1 in hemiacetal **101a,** it seems even more probable that the two compounds **101a** and **101b** have a different chirality at C-14 similar to the situation established for the hemiacetal *cis*-alpinigenine (**1m**) and its *O*-methyl derivative (**2l**) (cf. Section III,C,2).

D. Generation of Rhoeadines by Way of Benz[*d*]indeno[1,2-*b*]azepines

1. The Kametani Approach

The unique benz[*d*]isochromano[4,3-*b*]azepine framework of the rhoeadine alkaloids has been a great challenge for many workers interested in alkaloid total synthesis. Being intermediary in the rhoeadine syntheses reported above, the benz[*d*]indeno[1,2-*b*]azepine skeleton, sometimes referred to as indeno[2,1-*a*]-3-benzazepine or dibenzcyclopent[*b*]azepine, has acquired a pivotal role for a variety of synthetic approaches to the rhoeadines, among them that of T. Kametani. The Sendai group studied the utilization of the long-known 3,4-dihydropapaveraldine methiodide (**102**), which was found to react very smoothly with diazomethane at low temperature under regioselective ring expansion (*77, 78*). The 4,5-dihydro-3*H*-3-benzazepine derivative **103,** forming the main product, besides the unwanted isomer **104** (*79*), was isolated in high yield (Scheme 34). The nature and yield of the two benz[*d*]indeno[1,2-*b*]azepines (**105** and **106**), both of which were produced with phosphoryl chloride, were highly dependent on the reaction conditions applied: in boiling benzene the enol **105** was obtained in very low yield, while the higher temperature of refluxing toluene gave rise to an excellent yield of the 12-chloro compound **106.** The latter was dehalogenated by means of sodium borohydride in an alkaline medium. This sequence described by Kametani provides a convenient access to 5,6,7,12-tetrahydrobenz[*d*]indeno[1,2-*b*]azepines, which have the same framework as the key intermediate for the total synthesis of *cis*-alpinigenine (**1m**) by Orito *et al.* (*119*), described in the next paragraph. Other model syntheses using diketospirobenzylisoquinolines (e.g., **108**) gave a 1:3 mixture of *cis*- and *trans*-benzindenoazepines **109** and **110** (*75, 76*).

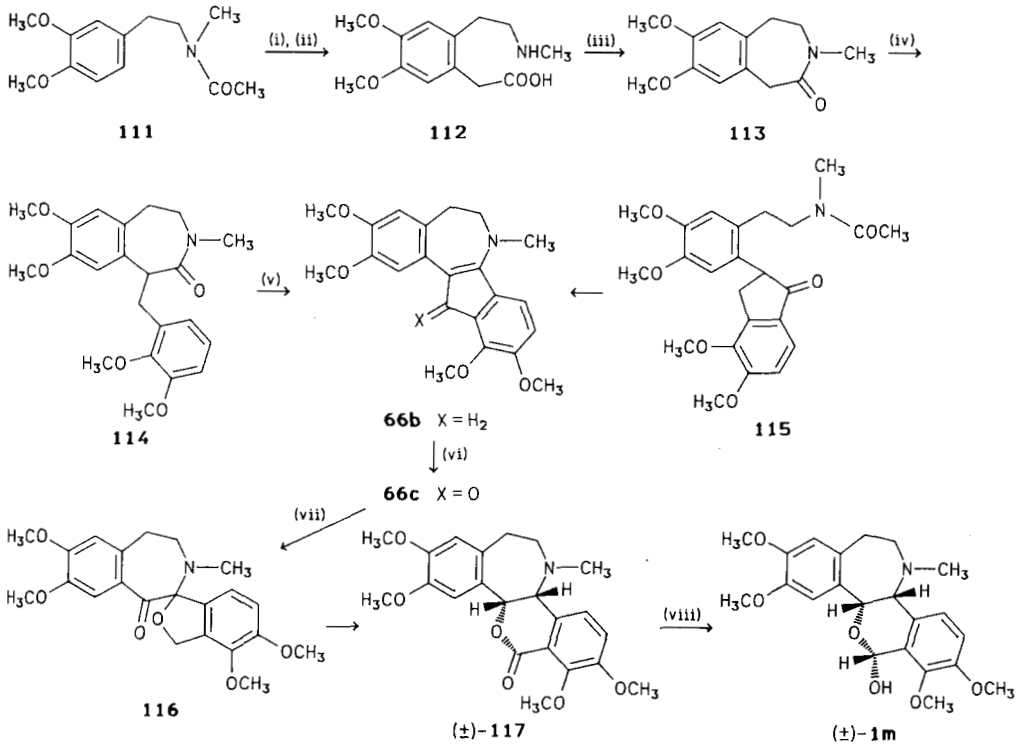


SCHEME 34. i, CH_2N_2/MeOH/0°C/90%; ii, $POCl_3$/benzene/78°C/12%; iii, $POCl_3$/toulene/108°C/89%; iv, $NaBH_4$/MeOH/NaOH/room temp/80%; v, Zn/MeCOOH/reflux/75%.

2. A Total Synthesis of (±)-*cis*-Alpinigenine

The original sequence for a synthesis of (±)-*cis*-alpinigenine (**1m**) via the benzindenoazepine derivative **66b** was outlined by Orito *et al.* (*120*) in a preliminary communication in 1974. It was later reinvestigated and thus extended to a ready access to this key intermediate (*119*). The total synthesis of **1m** is shown in Scheme 35 as its most efficient variety.

The acid **112** obtained from the acetamide **111** via chloromethylation, subsequent nitrile formation, and hydrolysis was smoothly cyclized by dehydration in boiling xylene. The 3-benzazepinone **113,** thus formed in 63% yield based on **111,** was α-alkylated in the presence of sodium hydride, using 2,3-dimethoxybenzyl bromide. The intermediate ketone **114** readily cyclized with phosphoryl



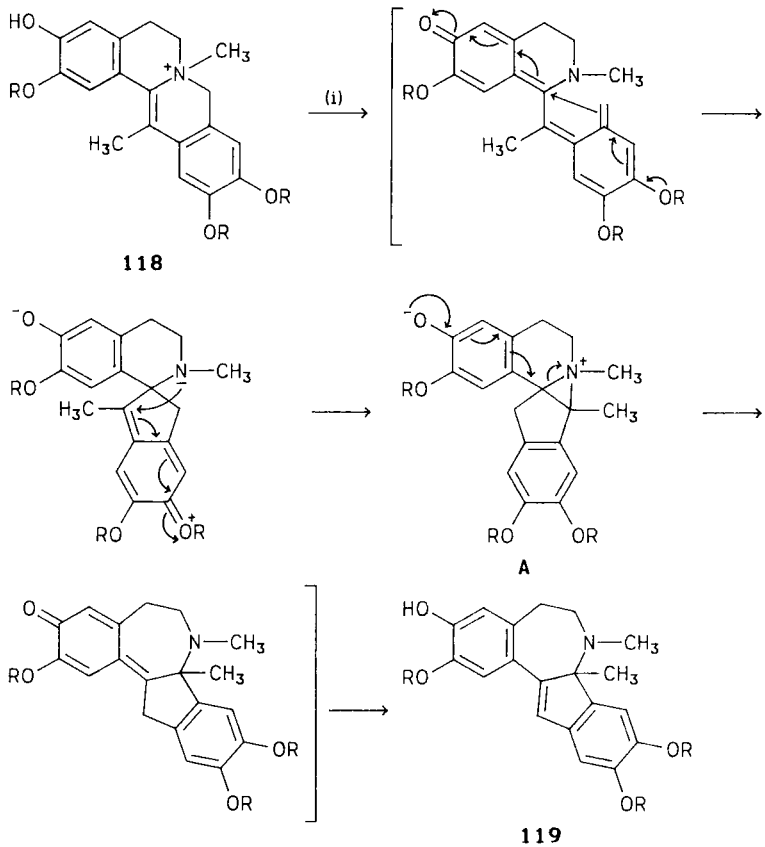
SCHEME 35. i, Aq $CH_2O/CHCl_3/HCl$ gas/$-10°C$, then NaCN/DMSO/78%; ii, NaOH/50% EtOH/reflux; iii, boiling xylene/Dean–Stark trap/81%; iv, 2,3-dimethoxybenzyl bromide/NaH/DMF/THF/N_2/80°C/86%; v, $POCl_3$/toluene/reflux/83%; vi, O_2/Triton B/pyridine/79%; vii, $h\nu/O_2$/Rose Bengal/37%; viii, Dibal/toluene/94%.

chloride to give the tetramethoxylated benzindenoazepine **66b** having the proper substitution pattern required for rhoeadine alkaloid synthesis. By the way, compound **66b** was the unwanted side product in Irie's synthesis (Scheme 26) and had been obtained from **115** previously by Orito *et al.* (*120*).

The oxidation of the enamine **66b** by molecular oxygen was facilitated by Triton B in pyridine to form the purplish 12-keto derivative **66c** in good yield. Subsequently, Rose Bengal-sensitized photooxidation gave a moderate yield of the keto lactone **116,** an analog of which had been previously synthesized from phthalidisoquinoline precursors (Scheme 27). An application of the known sodium borohydride transformation (*86*) to the keto lactone **116** led to *cis*-oxyalpinigenine (**117**), and the synthesis of (±)-*cis*-alpinigenine (**1m**) was then accomplished very efficiently by using diisobutylaluminum hydride (Dibal) for the final reduction of the lactone **117** to the hemiacetal **1m.**

3. From Protoberberines

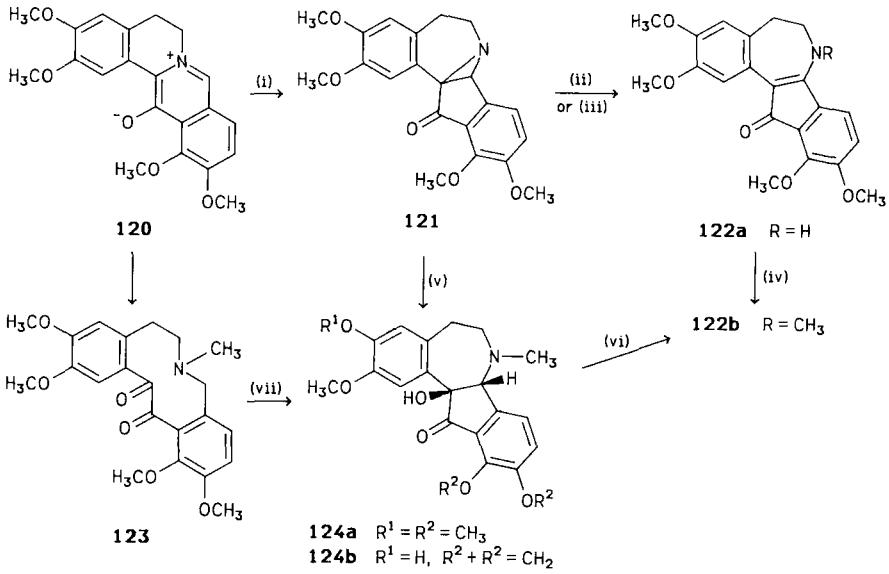
A photolytic and a biogenetically patterned conversion of protoberberines or berbines, respectively, have already been discussed in Section V,C. It has been found by Shamma and Nugent (*198*) that the base-catalyzed rearrangement of certain phenolic 7,8-dihydroprotoberberine quarternary salts leads to either the spirobenzylisoquinoline or the benzindenoazepine framework, depending on the position of the hydroxyl group. Those 7,8-dihydroprotoberberinium salts (e.g., **118**) that do not have a phenolic function on ring D will rearrange in alkaline medium via the aziridinium ion **A** to benzindenoazepines (e.g., **119**) (Scheme 36) rather than to spirobenzylisoquinolines. The involvement of an 8,14-cycloberbine as a mechanistic intermediate for the closely related spirobenzylisoquinoline → benzindenoazepine transformation also has been discussed by



SCHEME 36. i, 5×10^{-4} *N* NaOH/EtOH/reflux/N_2/4 days/41%.

Shamma and coworkers (*14, 15, 198*), and Irie's synthesis described in Scheme 26 was included.

Compounds possessing a benzindenoazepine skeleton have been found to occur in nature and thus form a new class of isoquinoline alkaloids, one example of which, viz., fumarofine (**124b**) (*16*), is included in Scheme 37. The utility of 8,14-cycloberbines for the synthesis of benzindenoazepines as key intermediates of rhoeadine-type alkaloids has been demonstrated by the work of Hanaoka *et al.* (*41–43, 46, 47*) as well as Blasko *et al.* (*13*), which is summarized in Scheme 37. The nonnaturally substituted protoberberinephenol betaine **120** afforded the cycloberbine **121** by anaerobic photoisomerization in good yield. For the transformation of an aziridine of type **121** to a benzindenoazepine there are a variety of possibilities, two of which are to be indicated. Treatment of **121** with *p*-toluenesulfonic acid in dry benzene led to a regioselective 14/N bond fission and was followed by an N-methylation of enamino ketone **122a** in the presence of sodium hydride to afford a total yield of 45% for **122b.** An iodine-induced valence isomerization of a compound of type **121** gave an improved yield of **122a** (*13*). Alternatively, cycloberberine (**121**) in aqueous acidic tetrahydrofuran added water to form two diastereomeric ketols, and a treatment of this mixture with methyl iodide led exclusively to the N-methylated *cis*-benzindenoazepine ketol **124a** with the trans isomer left unchanged. A direct transformation of



SCHEME 37. i, *hν* (Hg pressure lamp, pyrex filter)/MeOH/N_2/78%; ii, *p*-TsOH/benzene/reflux/58%; iii, I_2/$MeCl_2$/77%; iv, Me_2SO_4/HMPA/NaH/78%; v, CH_3SO_3H/aq THF/room temp, then CH_3I/CH_3CN/room temp/51%; vi, boiling AcOH; vii, h*ν* (sun light)/*t*-BuOH/*t*-BuOK/40%.

compounds of type **124** to rhoeadines has been described by Shamma (see Scheme 33), and that of type **122b** by Orito (Scheme 35).

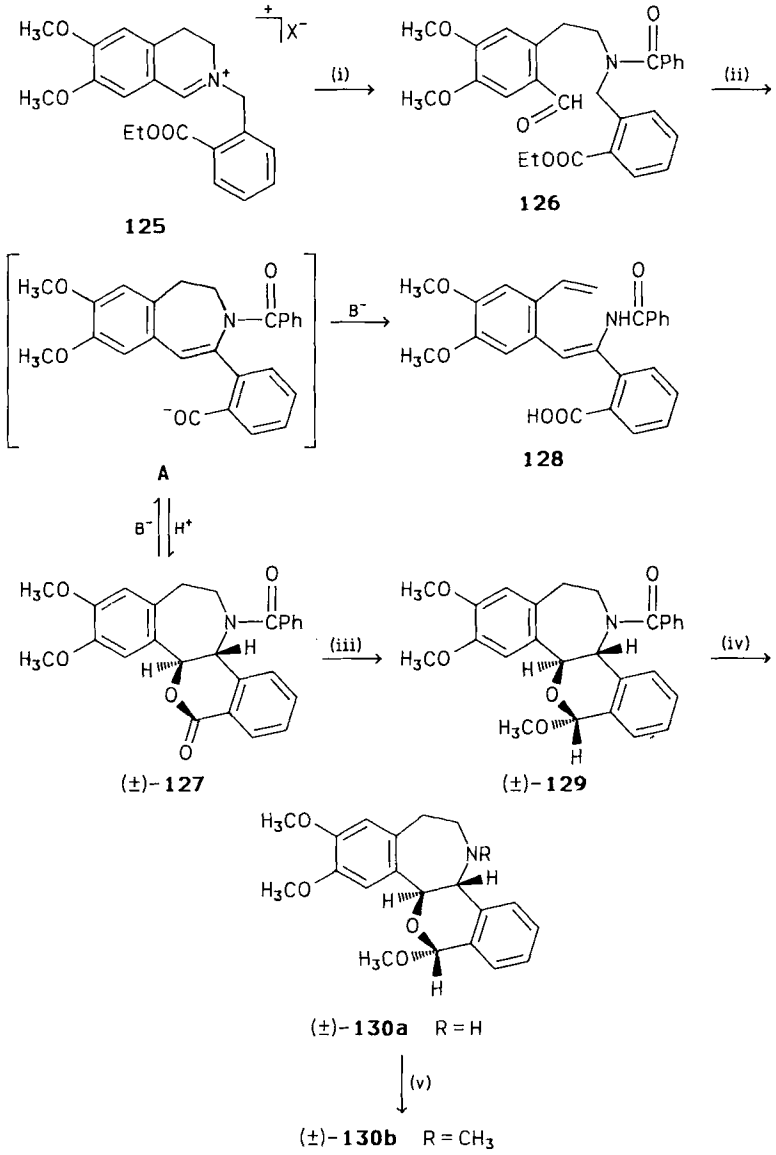
The work of Blasko *et al.* (*13*) offers still another approach to enamino ketone **122b.** The appropriately substituted 13-oxoprotopine **123** required for this might be made available from 13-phenol betaine **120** by a process that is indicated by the sequence **85** through **87** in Scheme 31, with the latter type of compound being capable of being oxidized in air to form **123.** The crucial step is the phototransformation of such a 13-oxoprotopine type to the cis-B/C-fused benzindenoazepine ketol **124a.** According to Hanaoka *et al.* (*43*), the final conversion of **124a** to **122b** can be realized in hot acetic acid.

The nonnaturally substituted protoberberine (not shown) required for these syntheses as a starting material has been made available from natural palmatine (**85**) by a novel ring-D inversion methodology (*44*).

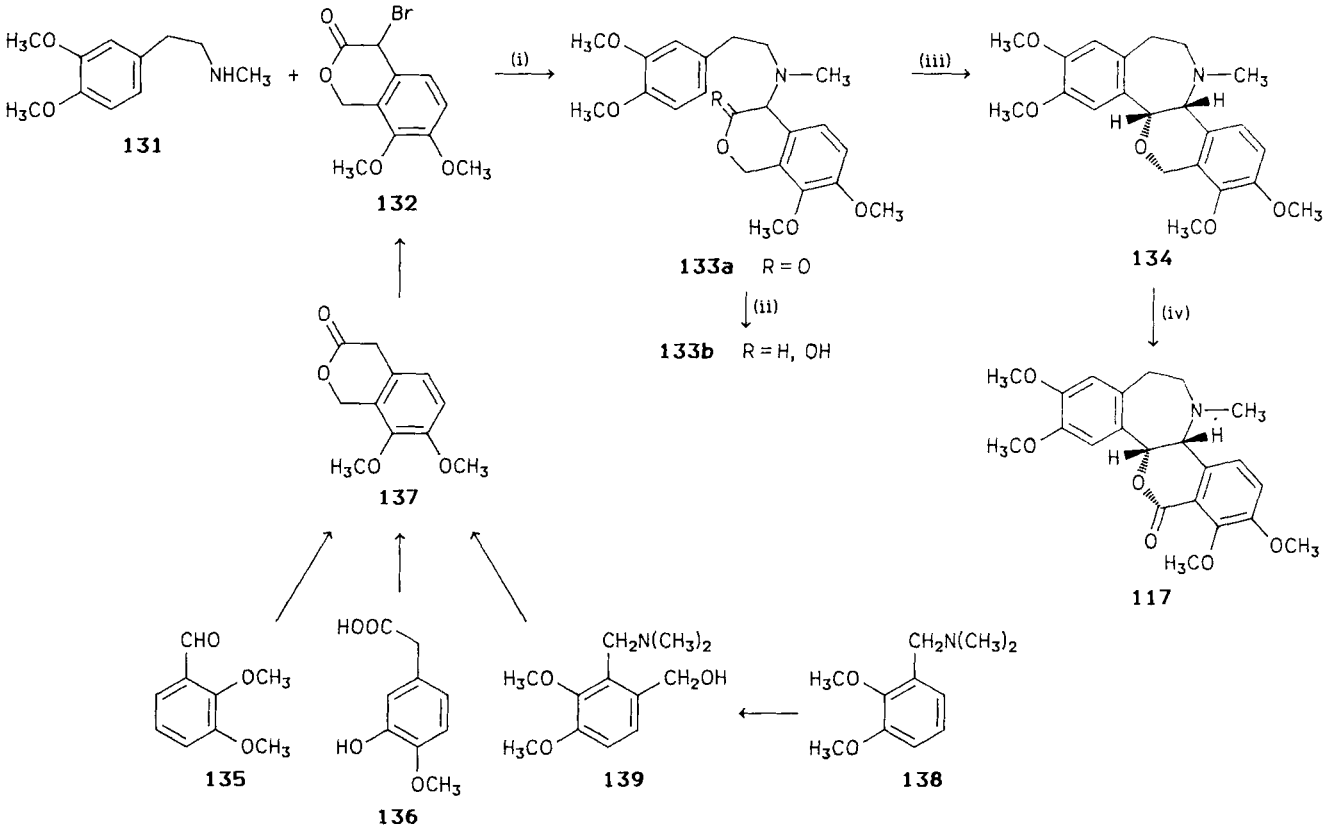
E. General Synthesis from *N*-Benzyl-3,4-Dihydroisoquinolines

A versatile route from readily available isoquinolines to 7,8-disubstituted B/D-*trans*-benz[*d*]isochromano[4,3-*b*]azepines has been published by Shamma and Töke (*199, 200*) and is another example of the high activity encountered in the field of rhoeadine preparations in the early 70s. The simple starting material for this model synthesis, the *N*-benzyl-3,4-dihydroisoquinolinium salt **125** was cleaved with benzoyl chloride under Schotten–Baumann conditions to give an excellent yield of the aldehydo amide **126** with the ester function being saved (Scheme 38). This rather neglected type of reaction known since 1899 (*174*) is assumed to proceed via an N-acetylated pseudobase. The amide **126** has an activated methylene group that is susceptible to intramolecular aldol condensation, which succeeded best by using dimsyl anion. Subsequent acidification afforded a mixture consisting of 56% of the lactone **127** in addition to the bicyclic acid **128.** Being incapable of forming an imonium salt, the intermediary enamide species **A** unlike the structurally related enamine **73** from the Brossi synthesis (cf. Scheme 27), apparently cyclizes to the δ-lactone **127**, which already shows the basic structure of the rhoeadine alkaloids.

The relationship existing between **127** and species **A** is a reversible one, showing that the B/D-trans fusion present in the amide **127** is thermodynamically more stable than the corresponding cis fusion. Generation of the hemiacetal entity using Red-Al reduction, followed by acetal formation, were prerequisites essential for removing the N-acyl group, for which this complex hydride again proved to be the reagent of choice. Thus treatment of acetal **129** with Red-Al in tetrahydrofuran gave the papaverrubine analog **130a,** which in acid developed a red coloration as expected. Reductive N-methylation eventually led to the trans-fused rhoeadine analog **130b,** having the stable 14-epi configuration. Appar-



SCHEME 38. i, PhCOCl/aq NaOH/0°C/97%; ii, DMSO/*t*-BuOK/5°C/56%; iii, Red-Al/Py/4°C/N_2, then $CH(OCH_3)_3$/MeOH/pH 2/90%; iv, Red-Al/THF/15°C/90%; v, CH_2O/EtOH/reflux/2 days, then $NaBH_4$/EtOH/90%.



SCHEME 39. i, Benzene/room temp/80%; ii, Dibal/toluene/−15°C/95%; iii, neat $(HPO_3)_n$/ 100°C/51%; iv, CrO_3/dil AcOH/0°C → 20°C/7%.

ently, the synthesis of a rhoeadane properly substituted in ring D has not been accomplished until now by this interesting sequence.

F. A Novel Entry into the Rhoeadines from Isochromanons

In 1982 Ahmad and Snieckus (*2*) have contributed interesting work to the total synthesis of (±)-*cis*-alpinigenine. The rhoeadine skeleton was constructed from phenethylamine and isochroman building blocks (**131** and **132**), respectively (Scheme 39). The resulting amino lactone **133a** was reduced to the lactol **133b** before cyclization. Polyphosphoric acid was used for this and 14-deoxy-*cis*-alpinigenine (**134**) was obtained in an overall yield as high as 39%. Unfortunately, introducing oxygen at C-14 was hampered in that, after several abortive trials using modern oxidation technology, a chromic acid oxidation at low temperature yielded only 7% of lactone **117**. The final step to (±)-*cis*-alpinigenine (**1m**) is well documented in the literature (e.g., *87*) (cf. Scheme 27).

The isochroman building block **132** has been made available from three sources: first, by these authors' multistep process from 2,3-dimethoxybenzaldehyde (**135**); second, in gram quantities from homoisovannillic acid (**136**), which was hydroxymethylated regiospecifically in the presence of benzeneboronic acid to give the isochroman **137** after usual O-methylation (*2, 109*); and third, a process reported by Narasimhan *et al.* (*112*), which included a highly effective heteroatom-directed lithiation reaction applied to the benzylamine **138** as well as four additional steps for the transformation of **139** to the desired isochroman **137.**

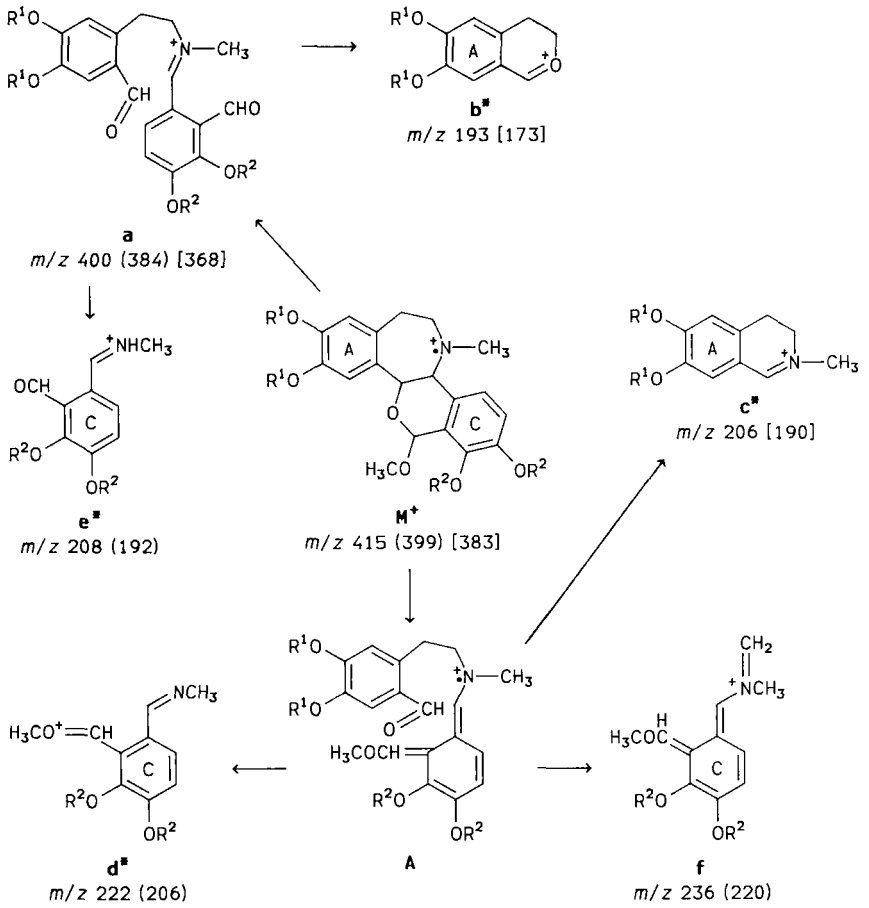
VI. Spectroscopy

A. Mass Spectroscopy

Apart from proton NMR, mass spectrometry has had major impact on the structural elucidation of rhoeadine as well as on the structural correlation among the individual members of the rhoeadine family. The basic paper on rhoeadine alkaloid mass spectroscopy was published by Dolejš and Hanuš (*34*) in 1967 when more specialized work done in common with other laboratories already had appeared, such as that on the structures of rhoeadine/isorhoeadine (*180*), of the papaverrubines (*132*), of oreodine/oreogenine (*139*), of glaucamine (*212*), of alpinigenine (*39, 102*), or of homologuous *O*-alkyl derivatives of rhoeagenine (*213*). The relatively wide range of different structures considered in this work, in addition to the application of high resolution and metastable peak techniques, has laid the basis for the now well-established structure of the rhoeadine al-

kaloids. The paper on *N*-methylporphyroxigenine (**3i**) by Brochmann-Hanssen *et al.* (*26*) independently constitutes an important contribution.

The mass spectra of the acetal alkaloids, which differ significantly from those of the hemiacetals, have been interpreted as depicted in Scheme 40. An abundant molecular-ion peak as well as abundant fragment ions **a** and **b** are most characteristic of the acetal derivatives. The fact that both rhoeadine (**2a**) and its *O*-alkyl homologs invariably show fragment **a** at *m/z* 368 (*213*) is evidence for an initial *O*(14)-alkyl splitting, which is followed by a series of bond shifts that lead to further splitting of rings B and D. Ion **b** thus originates in **a** as indicated by a metastable transition. Regarding less abundant species **c, d, e,** and **f,** ion **e** also



SCHEME 40. Mass spectral fragmentation of acetal rhoeadines; mass numbers are for $R^1 = R^2 = CH_3$, or for $R^1 = CH_3$, $R^2 + R^2 = CH_2$ (in parentheses), or for $R^1 + R^1 = R^2 + R^2 = CH_2$ (in brackets); *indicates high resolution.

derives from **a,** while a retrograde Diels–Alder process in the molecular ion gives rise to species **A.** The latter produces ion **c** representing ring A in addition to ions **d,** and **f,** which contain ring C. Depending on the nature of R^1 and/or R^2 in the individual alkaloids, the masses of most fragment ions vary in a typical way, some possibilities being indicated in Scheme 40. For example, in oreodine (**2e**), $R^1 = CH_3$, $R^2 + R^2 = CH_2$, the peak at *m/z* 206 becomes a doublet including fragment ions **c** and **d.** *N*-Norrhoeadines (papaverrubines) behave like other methyl acetals (*132*). Mass spectra are independent of the mode of B/D annulation and, accordingly, rhoeadine (**2a**) and isorhoeadine (**4a**) exhibit an almost identical fragmentation pattern.

Mass spectra of hemiacetal alkaloids are distinguished for a molecular ion of low intensity as well as for three abundant fragment ions **g, h,** and **i.** Unlike in the acetals, a retro-Diels–Alder process becomes the main fragmentation mode leading to species **B** (Scheme 41). The latter decomposes in the α or the β manner, forming the nitrogen-containing ions **g** or **h,** respectively, both of which show the ring C substitution pattern. Fragment ion **h** loses methyl methylenimine to form ion **i.** On the other hand, fragment **c** containing ring A is directly formed as a less abundant ion, similar to the behavior of acetal rhoeadines.

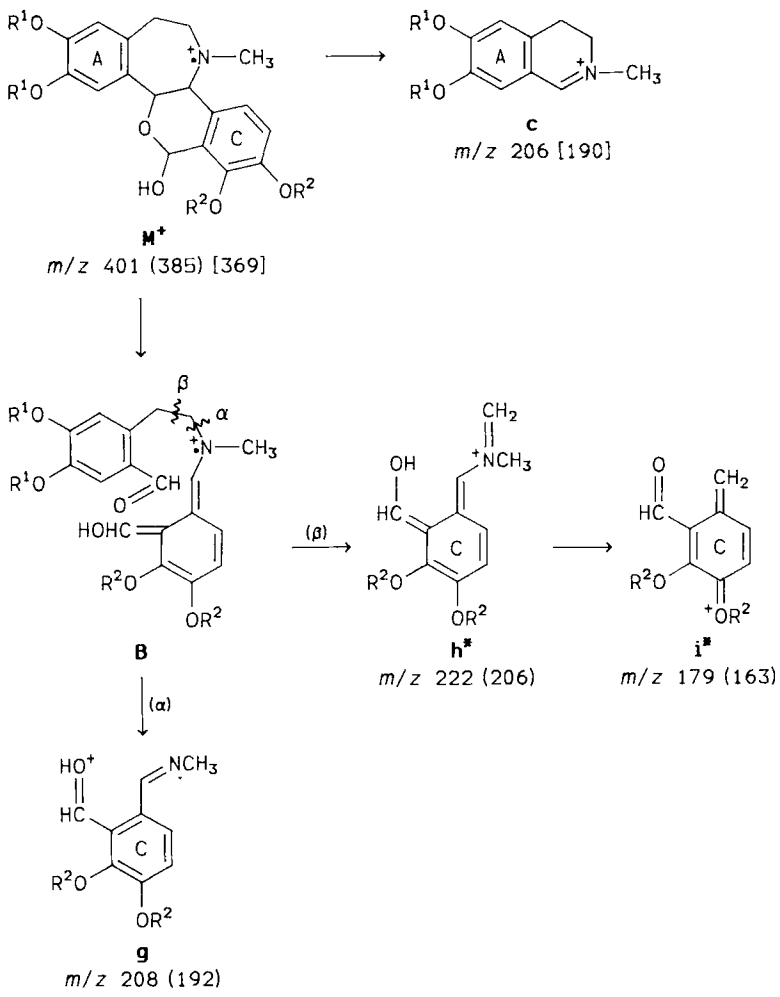
B. Nuclear Magnetic Resonance

1. Proton NMR

An assignment of individual protons has been made for *cis*-alpinigenine (**1m**) in full (*158*). Provided that ring B assumes a relatively rigid chair conformation, the results of spectral analysis may be presented as shown in Table VII or Scheme 42. Spectral analysis was aided by the two axial/equatorial couplings being very small or even undetectable. The $J_{a,a}$ and $J_{e,e}$ couplings exhibited by the four protons at C-4/C-5 in Table VII have been compared to those calculated from the dihedral angles measured on Dreiding models and using the Karplus equation. The extremely low-field position of the axial 5α proton is in agreement with the accepted equatorial position of the *N*-methyl group, which should result in an additional deshielding of the axial 5-H, probably due to nonbonding interaction with the lone pair at nitrogen. On the contrary, the other axial protons, both 4β-H and 2-H, are shifted high-field according to their trans diaxial position relative to the lone pair at nitrogen. A magnetic anisotropy due to the nitrogen lone pair has been discussed, for example, by Uskokovic *et al.* (*229b*).

2. Carbon-13 NMR

Carbon-13-NMR data have been made available for rhoeadine (**2a**) (*227*) and several alkaloids of the alpinigenine series as shown in Table VIII (*96, 158, 229*). The B/D-trans hemiacetal **3m** and the cis acetal **2a** are illustrated in



SCHEME 41. Mass spectral fragmentation of hemiacetals; mass numbers are for $R^1 = R^2 = CH_3$, or for $R^1 = CH_3$, $R^2 + R^2 = CH_2$ (in parentheses), or for $R^1 + R^1 = R^2 + R^2 = CH_2$ (in brackets); * indicates high resolution.

Scheme 42. The assignment of spectral data obtained in different laboratories has been accomplished by using the analysis of single-frequency, off-resonance, decoupled (SFORD) spectra including long-range and secondorder effects and a correlation to the ^{1}H-NMR signals. A discussion of the methods used in the identification of individual carbons in the alpinigenine series has been provided (*158*).

The availability of ^{13}C-NMR data for all chiral types of rhoeadine alkaloids

TABLE VII
Coupling Systems in 200-MHz Proton NMR of *cis*-Alpinigenine (**1m**) in $CDCl_3$

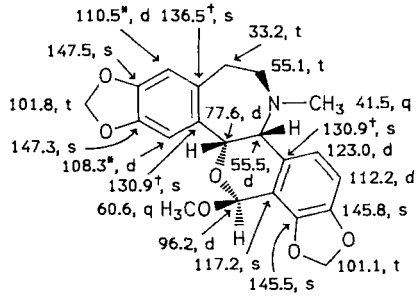
Couple of protons		Geminal and vicinal couplings		
			^3J (Hz)	
No.	No	^2J (Hz)	Observed	Predicted[a]
1	2		0.9	1–4.5
4α	4β	12.3	—	—
4α	5β		6.9	2–6
4α	5α		~0.5	0.5–4
4β	5β		<0.5	0.5–4
4β	5α		11.2	9.5–14
5β	5α	15.3	—	—
10	11		8.3	—
14	OH		9.9	—

[a] Calculated by means of the Karplus equation from the dihedral angles taken from Dreiding molecular models.

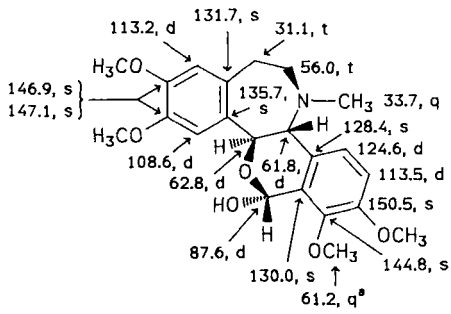
has rendered possible an independent approach to the conformational analysis of this interesting ring system (*96, 158*). In the B/D-trans series, the axial orientation of the *N*-methyl group derived from proton-NMR and quaternization rate data (cf. Section III,D,2) has now been ascertained from the γ(gauche) interactions between *N*-methyl, C-1, and C-5 carbons, which are reflected in a high-field location of their carbon-13 resonances. Thus the *N*-methyl signal is found around δ = 34 ppm in the B/D-trans series, while in the cis series it ranges between 40.2 ppm for (**2l**) and 45.3 ppm for (**1m**) (Table VIII). Similarly, C-1 and C-5 do appear more upfield in the first series or more downfield in the latter one, though C-5 responds much less.

From a cis 1,3-diaxial position of an axial substituent at C-14 relative to the 1-H proton, carbon 1 gains an additional γ(gauche) effect in ^{13}C NMR. Such an additive γ effect for C-1 is obviously present in the trans series with both alpinigenine (**3m**) and its stable acetal (**3l**) as well as in the cis acetals **2a** and **2l**. By contrast, there is no additional shielding, neither in the trans series with the less stable acetal alpinine (**4l**) nor in the cis series with the hemiacetal *cis*-alpinigenine (**1m**). In Table VIII, these considerations can be easily realized from the relatively downfield positions of C-1 observed in the latter two compounds (**4l** and **1m**). These findings fall in line with the established stereochemistry of these alkaloids and are further evidence for the epimerism at C-14 existing between acetals and hemiacetals in the B/D-cis series.

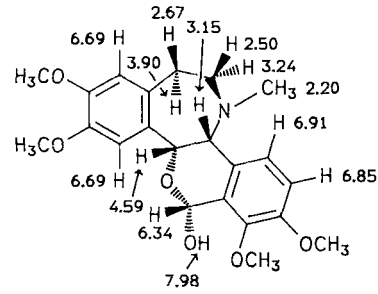
The shielding of the anomeric C-14 is much stronger in the two hemiacetals



Rhoeadine (**2a**)



Alpinigenine (**3m**)



cis-Alpinigenine (**1m**)[b]

SCHEME 42. ^{1}H and ^{13}C NMR of some rhoeadine alkaloids; figures added to individual atoms are δ values obtained at 200 MHz for ^{1}H or at 50 MHz for ^{13}C in $CDCl_3$; *,† signals may be interchanged; [a]other OCH_3 signals between δ 56.0 and 56.4 ppm; [b]OCH_3 signals at δ 3.81, 3.89, 3.90, and 3.92 ppm.

3m and **1m** than in all of the acetals. This has been attributed to the influence of the methoxy substituent at the aromatic C-13 (*96*).

C. UV SPECTROSCOPY

Typical UV data of several alkaloids have been gathered in Table IX. So far as reported in the literature, all rhoeadines, including the papaverrubines in methanol or ethanol solution, exhibit two maxima, which are in the range between 230 and 245 nm or 281 and 294 nm. The intensities of the two maxima are nearly equal for rhoeadine and the other bismethylenedioxy substituted compounds. Stepwise substitution of these groups for two or four methoxy residues, e.g., in **2e** or **2l**, respectively, causes the higher wavelength extreme to decrease gradually in intensity, while the other is increased. Concomitantly, both maxima are shifted to shorter wavelengths. Due to the presence of a phenolic hydroxy group

TABLE VIII
Carbon-13 NMR Data[a] for Alpinigenine (**3m**), Alpinine (**4l**), and Epialpinine (**3l**), as Well as Rhoeadine (**2a**), *cis*-Alpinigenine (**1m**), and *O*-Methyl-*cis*-Alpinigenine (**2l**)

Identification of carbon	B/D-trans			B/D-cis		
	(**3m**) *(96)*	(**3l**) *(229)*	(**4l**) *(229)*	(**2a**) *(227)*	(**2l**) *(158)*	(**1m**) *(158)*
1	62.8	62.6	70.1	77.6	76.7	83.5
2	61.8	61.7	61.7	55.5	59.6	66.3
4	56.0	55.7	54.0	55.1	54.5	58.3
5	31.1	30.9	31.5	33.2	32.6	33.9
5a	131.7	131.0	130.6	136.5[b]	134.5	135.4
6	113.2	113.1	113.0	110.5[c]	113.5	113.4
7	146.9[b]	147.1[b]	147.0[b]	147.5	146.8[b]	146.9[b]
8	147.1[b]	146.8[b]	146.9[b]	147.3	148.3[b]	148.8[b]
9	108.6	108.3	108.8	108.3[c]	115.7	115.2
9a	135.7	134.9	134.5	130.9[b]	129.5[c]	129.2
10	124.6	124.4	123.5	123.0	125.4	123.1
10a	128.4	129.7	130.0	130.9[b]	129.5[c]	131.6
11	113.5	113.4	113.0	112.2	112.7	111.2
12	150.8	150.9	151.3	145.8	151.8	152.8
13	144.8	145.0	145.7	145.5	149.1	145.9
13a	131.0	129.7	130.6	117.2	128.9[c]	131.0
14	87.6	94.5	98.3	96.2	96.8	89.7
N-Me	33.7	33.5	34.5	41.5	40.2	45.3
7-, 8-, 12-OMe	56.0–56.4	55.6–55.9[c]	55.8	—	—	56.1
13-OMe	61.2	61.0	61.0	—	60.7	61.7
14-OMe	—	55.6[c]	55.8	60.6	—	—
Ring A O—CH_2—O	—	—	—	101.8	—	—
Ring C O—CH_2—O	—	—	—	101.1	—	—

[a] Chemical shifts (δ values) in $CDCl_3$.
[b,c] Same letters in the same column indicate interchangeable signals.

TABLE IX
UV Data of Some Rhoeadine Alkaloids

Compound	λ_{max} (log ε)[a]	λ_{max} (log ε)	Ref.
Rhoeagenine (**1b**)	243 (3.97)	290 (3.96)	*138*
Papaverrubine A (**4d**)	240 (3.91)	289 (4.03)	*57*
Oreodine (**2e**)	235 (4.19)	285 (3.94)	*138*
Glaucamine (**3f**)	238 (4.0)	286 (3.8)	*210*
N-Methylporphyroxigenine (**3i**)	238	288	*26*
Alpinigenine (**3m**)	230 (4.19)	284 (3.79)	*102*
O-Methyl-*cis*-alpinigenine (**2l**)	237 (4.34)	283 (3.80)	*172*
Papaverrubine G (**4n**)	230	281	*133*

[a] All spectra have been recorded in methanol, except for (**3i**) taken in EtOH.

in the opium constituent *N*-methylporphyroxigenine (**3i**), the two maxima on addition of sodium hydroxide encounter a bathochromic shift by 4–5 nm (*26*).

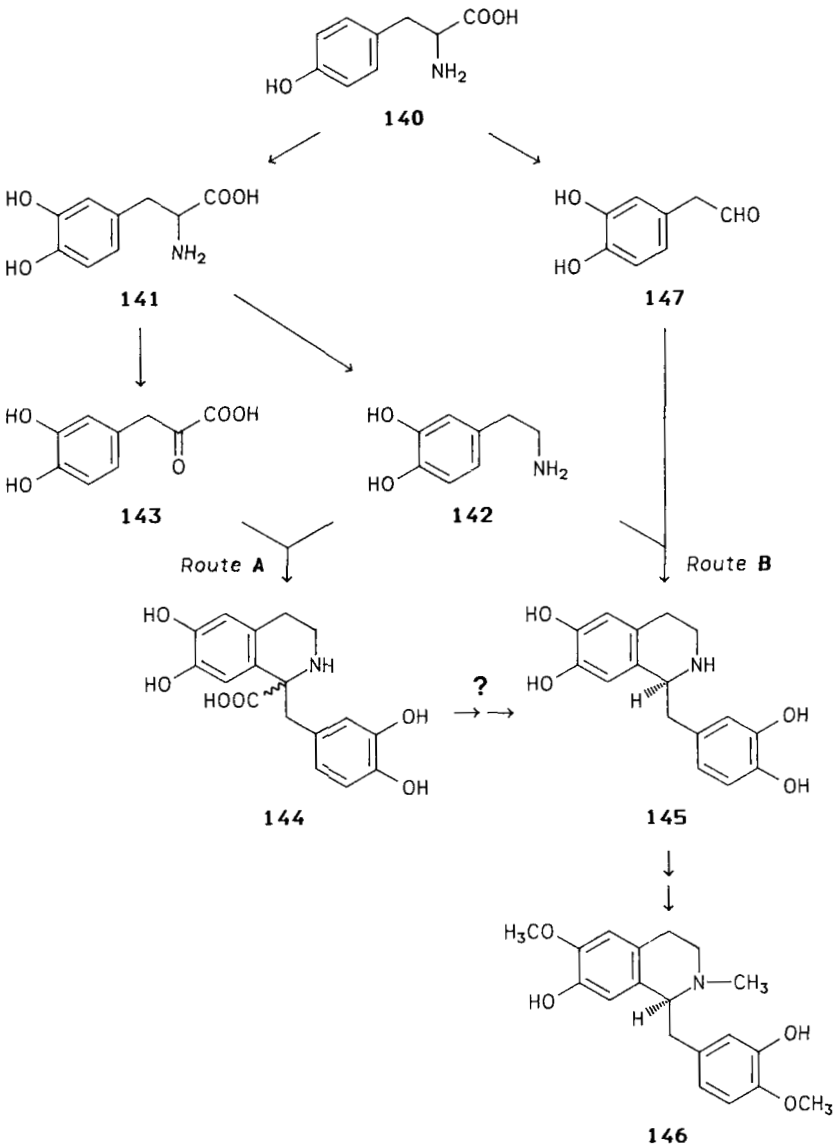
VII. Biosynthesis

A. Introduction

Alkaloids, like terpenes, sterols, flavanols, and others, are secondary plant products, the formation, transformation, and degradation of which, as well as their translocation and storage in the plant, are processes that are distinguished from primary metabolism. Unlike the latter, which is very uniform and general in the plant kingdom, this secondary metabolism is characteristic of its diversity of metabolic pathways, leading to a plenitude of natural products, which in many cases are obviously lacking any important specific function in the plant (*106*). A species from the genus *Papaver* is an organism often distinguished for a great capability of synthesizing a wide range of different isoquinoline alkaloids. The rhoeadine alkaloids are only one type among more than 20 different isoquinoline-related structures. So far as hitherto established, all of them have the same origin in primary metabolism, the amino acid L-tyrosine (**140**), and most of them are formed via reticuline (**146**), a diphenolic 1-benzyltetrahydroisoquinoline alkaloid. Thus the rootstock of the pedigree for the isoquinoline alkaloids is the biosynthesis of reticuline as outlined in Scheme 43.

The gross elaboration of a biogenetic scheme for the most important isoquinolines is one of the earliest examples of experimental work on the natural formation of alkaloids that made use of the administration of radioactive precursors to the plant. The state of the art has recently been discussed by Robinson (*160*) and more comprehensively by Schütte (*190, 191*). In particular, the initial steps, i.e., those between L-tyrosine (**140**) and reticuline (**146**) are far from being completely understood. Recently, Schumacher *et al.* (*189*) have envisaged two alternative routes, A and B, leading to norlaudanosoline (**145**), both of which incorporate L-DOPA (**141**) as well as dopamine (**142**) (Scheme 43).

A decision in favor of route A, which is distinguished by a condensation of 3,4-dihydroxyphenylpyruvic acid (**143**) and **142,** had, however, become possible as early as 1975, when the implication of the previously hypothetical norlaudanosoline-1-carboxylic acid (**144**) was proved by experiments done at the same time on *Papaver orientale* (*233*), *P. somniferum* (*9*), and *Litsea glutinosa* (Lauraceae) (*12, 228*). Alternatively, Schumacher *et al.* (*189*) reported on the isolation of (*S*)-norlaudanosoline synthase from cell cultures of an *Eschscholzia* species (Papaveraceae). This well-characterized enzyme is capable of promoting and stereospecifically controlling the slow self-condensation between dopamine and 3,4-dihydroxyphenylacetaldehyde (**147**) to form (*S*)-norlaudanosoline (**145**) in the direct way, i.e., by route B.



SCHEME 43. Two routes from L-tyrosine (**140**) to (*S*)-reticuline (**146**).

Subsequent transformation of **145** to (*S*)-reticuline (**146**) requires three methylation steps, the final one of which has been found in *Litsea glutinosa* (*12*) to be N-methylation. The enzymology of these processes has been explored in detail (*236*). The two enantiomeric forms of reticuline are an important branching in the biosynthetic pedigree of the isoquinoline alkaloids (*190, 191*).

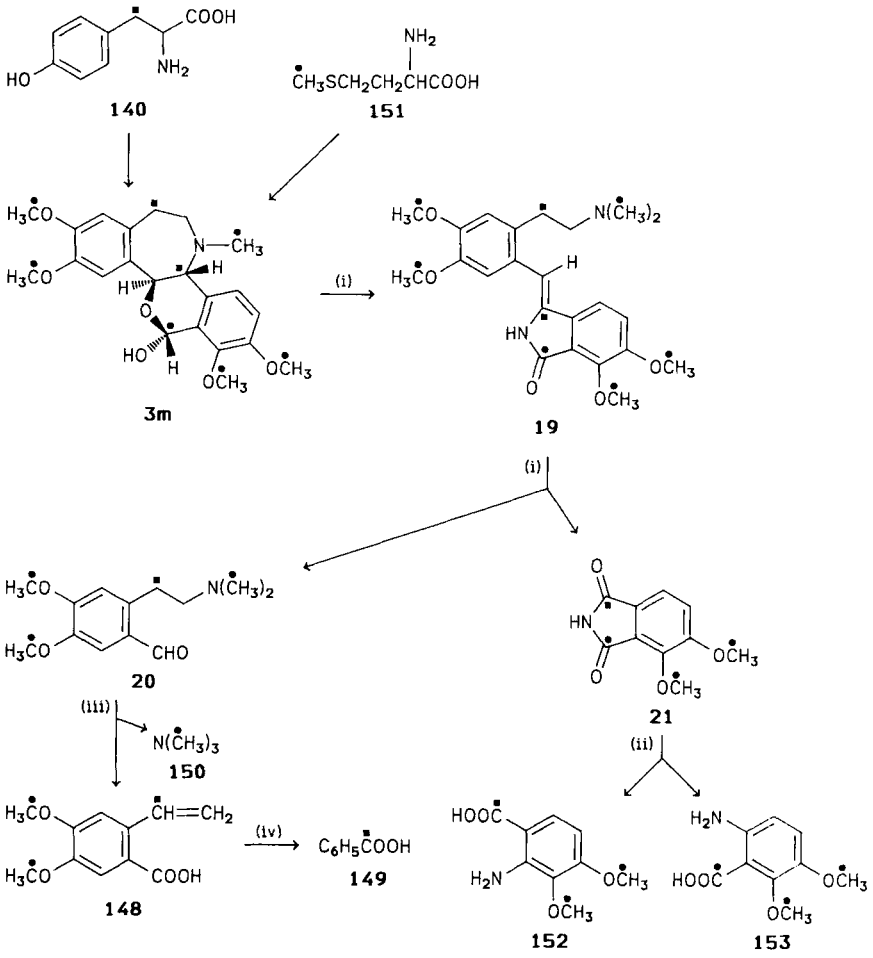
B. Experiments on the Biosynthesis of Alpinigenine and Rhoeadine

1. Alpinigenine

The perennial *Papaver bracteatum* Lindl. is a stately ornamental poppy, which in its leaves and poppy heads accumulates the morphinane alkaloid thebaine. A certain variety of this plant (*17*), however, is interesting for a relatively high amount of the rhoeadine alkaloid alpinigenine (**3m**) formed besides thebaine (*39*). Administration of (±)-tyrosine-*3*-^{14}C (**140**) to flowering plants belonging to this chemovariety was reported by Böhm and Rönsch (*21*) to result in the incorporation of radioactivity into alpinigenine. The localization of radioactivity on carbons 2 and 5 of **3m** suggested both a utilization of two molecules of this amino acid and a mode of biosynthesis that branches out from the isoquinoline rootstock at some point. The positions labeled in the alpinigenine **3m** obtained from feeding experiments have been identified by degradation according to Scheme 4 (Section III,B,2), which led to the veratric aldehyde **20** in addition to hemipinimide **21** (Scheme 44) (*171*). The two fragments **20** and **21,** representing the "upper" isoquinoline and the "lower" benzyl portion, respectively, of any intermediary 1-benzylisoquinoline precursor, were each shown to carry the label from one of the two tyrosine molecules required for the construction of alpinigenine (**3m**). There was no equal distribution of radioactivity over the fragments **20** and **21,** which showed relative radioactivities of 63 or 37%, respectively. This result might be due to the different pathways by which the two tyrosine molecules are incorporated into an isoquinoline alkaloid (cf. Scheme 43). Precisely localizing the radioactive carbons of **20** and **21** was traced back to the identification of individual carbons by further degradation, as can be easily realized from Scheme 44. All of the radioactivity present in **20** was finally recovered with benzoic acid **149.** That of **21** was retained with **152,** one of the two anthranilic acids simultaneously formed on Hofmann amide degradation, while the other one (**153**), having lost the original alpinigenine C-2, was completely nonradioactive.

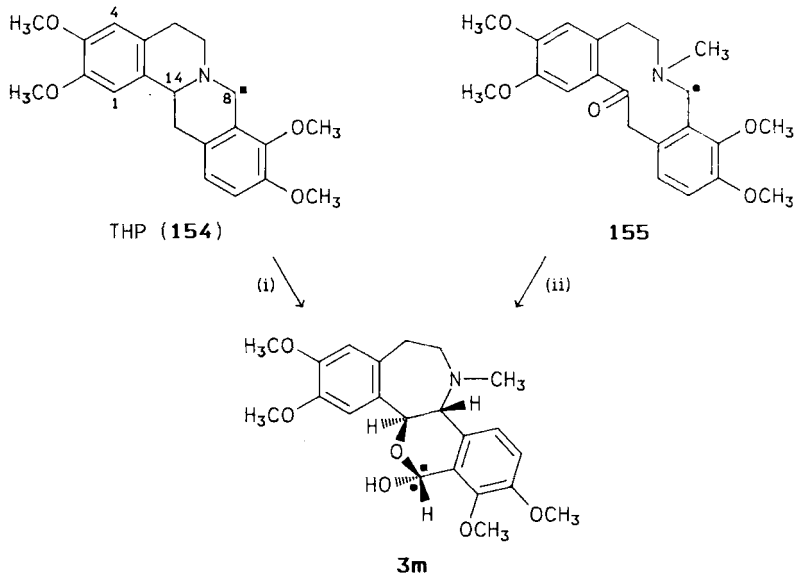
Also included in Scheme 44 was a feeding experiment using methionine-*S-methyl*-^{14}C (**151**), which usually renders radioactive all *O*- and *N*-methyl groups. A similar degradation again led to the two anthranilic acids **152** and **153,** which in this case had radioactivities corresponding to 2/6 or 3/6, respectively, of the original radioactivity incorporated in the starting alpinigenine (**3m**). This extra radioactivity, localized apparently in the carboxy carbon of compound **153,** is evidence for an incorporation of methionine radioactivity into C-14 of **3m** (*171*).

To explain the origin of this extra carbon, an experiment was devised by Rönsch (*163*) who used labeled tetrahydropalmatine (THP) (**154**), which has such an extra carbon at C-8. Radioactive THP specifically labeled on this carbon,



SCHEME 44. Two feeding experiments on *Papaver bracteatum*; ■ indicates the label incorporated into alpinigenine (**3m**) by using L-tyrosine-*3*-^{14}C (**140**), ● that of methionine-*S-methyl*-^{14}C (**151**); i, degradation according to Scheme 4; ii, NaOBr; iii, Hofmann sequence; iv, (a) $NaBH_4$, (b) $OsO_4/NaIO_4$, (c) C_6H_5MgBr, (d) CrO_3/H^+.

the so-called "berberine bridge," which originates in the *N*-methyl group of reticuline (**146**) (cf. Scheme 49), was incorporated into alpinigenine (**3m**) with a very high efficiency. The site of labeling was determined by the usual degradation of **3m** to be C-14 (Scheme 45). Tetrahydroprotoberines, as well as protopine or phthalidisoquinoline intermediates, have early been suggested to be potential precursors in rhoeadine alkaloid biosynthesis (*91, 177, 190*). Evidence was then obtained from another feeding experiment using ^{14}C-labeled muramine (**155**),



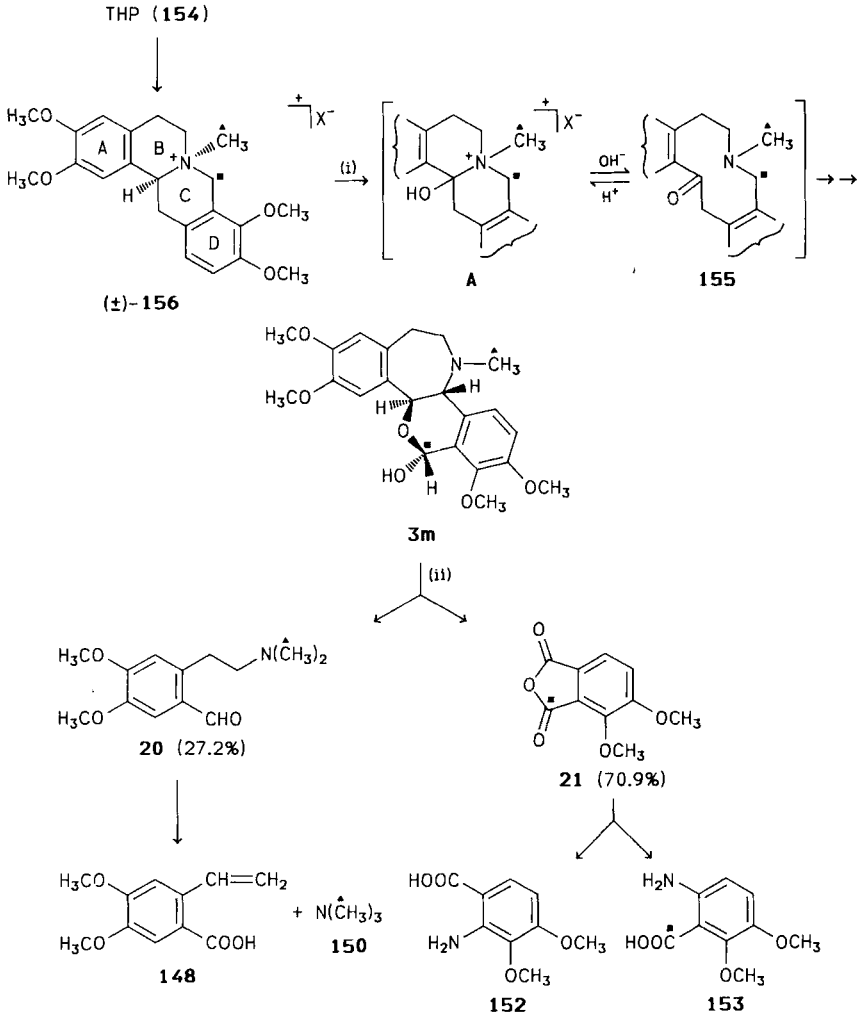
SCHEME 45. i, Rate of incorporation of radioactivity 14.8%; ii, incorporation rate 22.6%.

revealing that it is a protopine- rather than a phthalidisoquinoline-type alkaloid that is precursory of alpinigenine in *Papaver bracteatum* (*165, 166*). The incorporation of radioactivity into **3m** from specifically labeled **155**-*8*-^{14}C was again very high.

The outcome of the latter experiments is that among the two sites of ring opening required for the biogenetic transformation of a tetrahydroprotoberberine to a rhoeadine, nature gives precedence to N/C-14 fission over N/C-8 fission. Up to this time, however, mode and sequence of the steps following muramine in the biogenetic chain leading to alpinigenine have remained obscure, although considerable effort has been devoted to this purpose (*166, 167*). These unexplored steps include at least a ring fission at the N/C-8 site and an appropriate functionalization of C-13 (THP numbering) (see Section VII,C for a brief discussion).

Next, the putative transformation of THP (**154**) to muramine (**155**) is to be considered. An N/C-14 bond fission as discussed above was shown to proceed by way of N-methylation and subsequent hydroxylation at C-14 of a THP methosalt (**156**) as an intermediary (*163, 166, 167*). The quaternary carbinolamine species **A** is involved in a pH-dependent, nonenzymatically controlled equilibrium with the protopine species **155,** i.e., muramine, the biogenetic transformation of which into alpinigenine (**3m**) was already established. This was ver-

ified by feeding experiments on *P. bracteatum*, mainly by using the doubly labeled methosalt **156**, which carries radioactivity on the skeletal C-8 atom as well as on the *N*-methyl group (Scheme 46). The ratio of the two labels, which had been introduced into the precursor **156** by chemical synthesis (*166*) was obtained from the two fragments **20** and **21** recovered after the usual degradation



SCHEME 46. i, The ratio of the labels applied in this feeding experiment was ■:▲ = 71.7:28.3; ii, degradation according to Schemes 4 and 44, numbers in parantheses are percent of total radioactivity.

of the isolated alpinigenine. The specificity of labeling was further demonstrated by subsequent degradation of the veratric aldehyde **20,** which gave the nonradioactive veratric acid **148** in addition to trimethylamine (**150**), incorporating the complete amount of radioactivity present in **20.** Similarly, hemipinimide (**21**) yielded the inactive acid **152** besides an active one (**153**). Since neither a deviation from the prescribed ratio nor any scattering of label among other carbons was observed, this result is strong evidence for the novel mechanism shown in Scheme 46. It involves a selective oxygenation at a nonactivated carbon, viz., C-14. This type of reaction is seldom encountered in organic chemistry, though a photochemical process resembling the sequence **156** → species **A** → **155** has been described (*45*).

The appropriate relative configuration at C-14 and nitrogen being present in the α-methosalt **156** (i.e., B/C-cis) has been proved to be decisive for any utilization in biosynthesis. This was later discovered (*167*), however, when the corresponding β-diastereomer (not shown) was found to be rejected by the plant. Similar results showing the involvement of tetrahydroprotoberberinium α-methosalts in the biosynthesis of rhoeadine were obtained in Japan (*227*) (cf. Section VII,B,2). A preparative route to uniform berbine methosalts of both the α and the β form was reported in 1984 (*169*). The biogenetic impact of berbine α-methosalts on the biosynthesis of protopine- and benzophenanthridine-type alkaloids has been exemplified by similar findings on *Macleaya cordata* (*225*) and *Corydalis incisa* (*224, 226*). As mentioned above, besides the alpinigenine strain of *P. bracteatum,* there is another one forming exclusively thebaine in its mature plants (*17*). Seedlings and immature plants up to an age of 2 months in the two strains always produce the full alkaloid spectrum including thebaine, alpinigenine, and a number of tentatively identified bases. Böhm also found (*18*) that in mature plants of the thebaine strain the biosynthetic chain leading to alpinigenine (**3m**) lacks a link, which is present in the other one. Feeding THP (**154**), an established intermediate for **3m**, to mature plants of this strain led to an experimental "normalization" of the alkaloid character, i.e., to the formation of **3m** in addition to thebaine. The link naturally missing in mature thebaine plants appears to be the so-called "berberine bridge enzyme," which is capable of cyclizing reticuline (**146**) to form scoulerine (**157**) (*20, 159*). Subsequently, great success in isoquinoline alkaloid enzymology has been achieved by Zenk (*236*) by using cultivated plant cells. In the course of these intensive studies the berberine bridge enzyme was again isolated from cell cultures of *Berberis beaniana* (*221*). Among the enzymes newly characterized in Munich, (*S*)-scoulerine-9-*O*-methyltransferase (*107*) may well be important for the biotransformation of scoulerine to THP (**154**) in *P. bracteatum* as well.

Working with plant-cell cultures has often led to results not easy to rationalize. Alpinigenine was completely absent from cultured cells of *P. bracteatum,* and thebaine was detected in traces only. Instead, coptisine, the unsaturated counter-

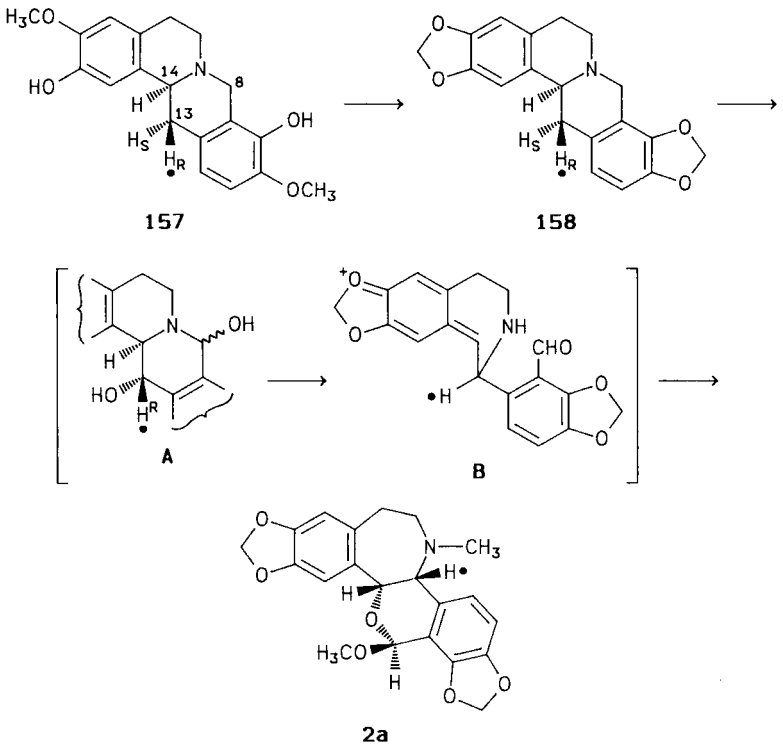
part of stylopine (**158**), and protopine (**57**), not known to be constituents of this plant species, were found to be formed at a notable level (*80, 81*). In early stages of subculturing, however, thebaine was formed.

2. Rhoeadine

Tracer experiments on the biosynthesis of rhoeadine (**2a**) have been undertaken with the common field poppy *Papaver rhoeas* L. In the first study, Battersby and Staunton (*10*) in feeding experiments used the two stereospecifically labeled (*S*)-scoulerines (*13S-t* and *13R-t*) (**157**), having an additional carbon label at some site not specified in that more general paper, as internal references. The two precursors were incorporated into rhoeadine (**2a**) and the two products were analyzed for their $^{14}C/^{3}H$ ratios. Losses of tritium were encountered to different degrees, which constitute good evidence for a stereospecific removal of the pro-*S* hydrogen from C-13 of (*S*)-scoulerine (**157**) or some other intermediate on the pathway from **157** to **2a**. On the basis of these results, the biotransformation of **157** was envisaged to proceed via stylopine (**158**), as well as the 8,13-dihydroxylated carbinolamine species **A**, which has already lost the pro-*S*-H from C-13 (Scheme 47). Ring opening at the N/C-8 site and subsequent skeletal rearrangement leading to the benzazepine species **B** were suggested to be other features of the enzymatic process. The construction of rhoeadine would then be accomplished by an N-methylation and a hydroxylation at C-1 (rhoeadine numbering). It should be stressed that apart from this discussion Battersby's results imply no logic contradiction to the preceding experiments done on *Papaver bracteatum*, as well as those on *P. rhoeas* described in the following paragraph, which give precedence to N-methylation and oxygenation at C-14 over any functionalization of carbons 8 and/or 13 at the tetrahydroprotoberberine stage.

For the other two feeding experiments, Tani and Tagahara (*227*) used protopine-*13-t* (**57**) and stylopine-*N-methyl*-^{13}C α-methochloride (**159**) to obtain rhoeadine-*2-t* (**2a**) or rhoeadine-*N-methyl*-^{13}C, respectively. These results are summarized in Scheme 48. In an attempt to localize the tritium incorporated into **2a**, a degradative sequence according to Scheme 4 had to be interrupted on the nitrile stage (**160**), because in the B/D-cis series even low yields of any phthalimidine related to **19** are difficult to obtain, as was later confirmed with *cis*-alpinigenine (**1m**) (*168*). The tritium-labeled rhoeadine was then transformed to rhoeagenine-diol (**5**), which was oxidized, using nitric acid to give the nonradioactive fragments **10** and **161.** This result provides evidence that the localization of label in **2a**-*t* is confined at least to 1H and/or 2-H. On the other hand, the ^{13}C label enriched in the *N*-methyl group of (**2a**) was easily determined by ^{13}C NMR.

Conspicuously, the rate of incorporation was 0.03% for protopine-*t* (**57**), which is much lower than that of the quarternary precursor **159,** amounting to 1% approximately. This result contrasts sharply to the corresponding findings ob-

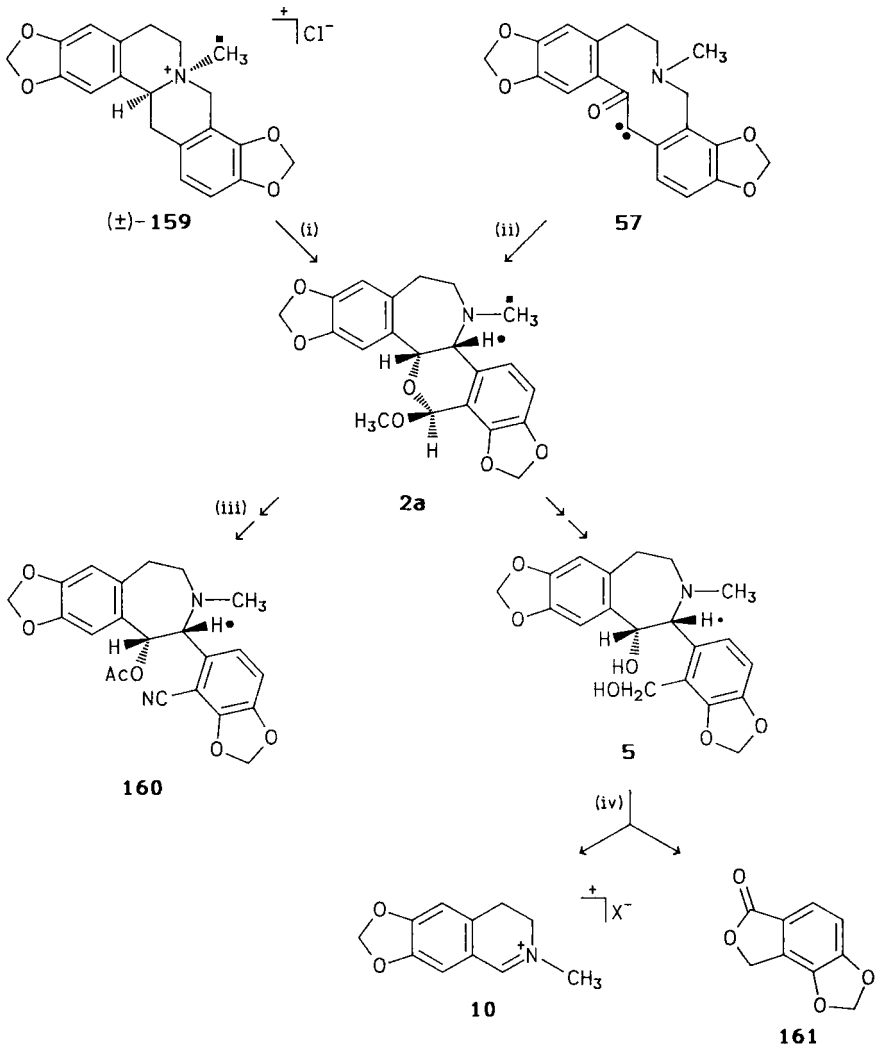


SCHEME 47. ●, Indicates (13*R*)-tritium label.

tained for alpinigenine (**3m**) in *P. bracteatum*. A possible explanation would be that nonspecific tritium loss from **57**-*t*, lacking an internal ^{14}C reference, cannot be excluded. The isolation of the quaternary salt **159** from *P. rhoeas* has been reported by Preininger *et al.* (*153*).

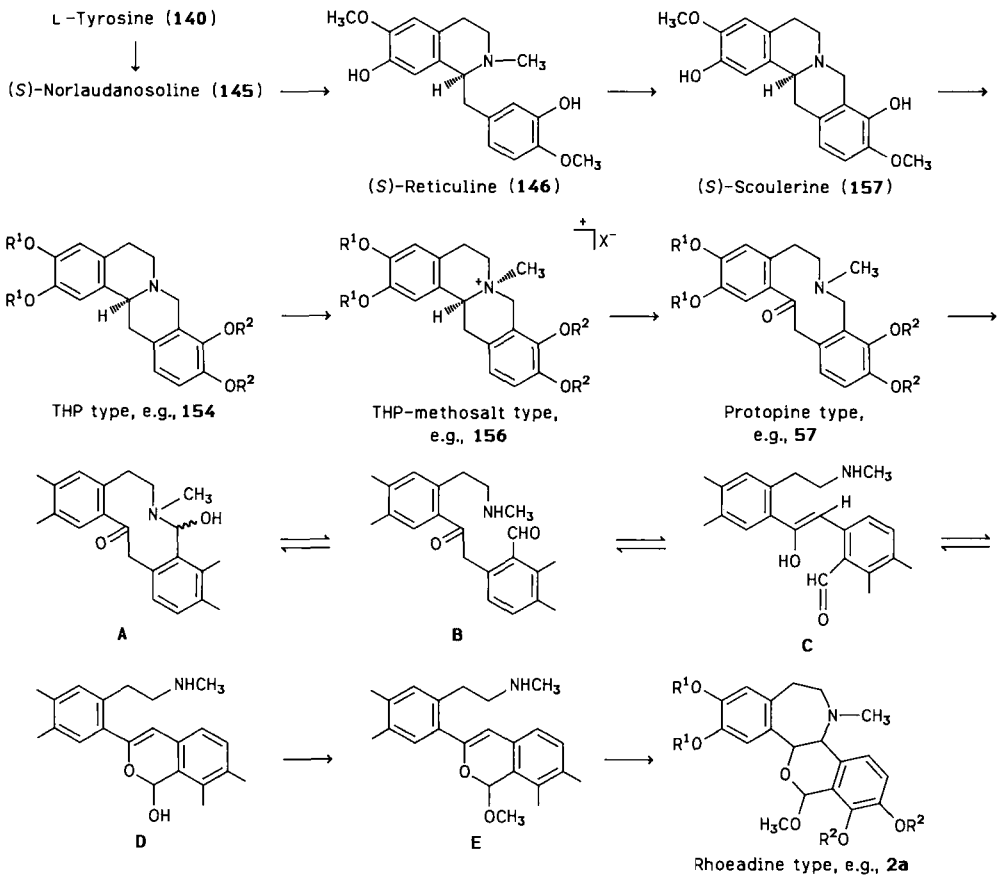
C. Biogenetic Scheme for Rhoeadine Alkaloids

The results discussed in the preceding paragraphs, as well as the ideas advanced by various workers in this field, have been gathered to design a biogenetic scheme for rhoeadine alkaloids, which naturally must increase in its hypothetical character as the postprotopine-type stages are being considered (Scheme 49). The natural source for all rhoeadine and papaverrubine alkaloids can be assumed to be the amino acid L-tyrosine (**140**). It is very probable, furthermore, that the pathway between **140** and (*S*)-reticuline (**146**) can be deduced from the general outline made in Scheme 43. The latter compound has been administered to *P. bracteatum*, affording radioactive alpinigenine (*167*),



SCHEME 48. Two feeding experiments on *Papaver rhoeas*; ■, ●, denote ^{13}C or ^{3}H label, respectively; i, enhancement of NCH_3 spectral intensity above natural abundance 1:2.02; ii, incorporation 0.03%; iii, (a) acetal hydrolysis, (b) attempted degradation according to Scheme 4; iv, HNO_3.

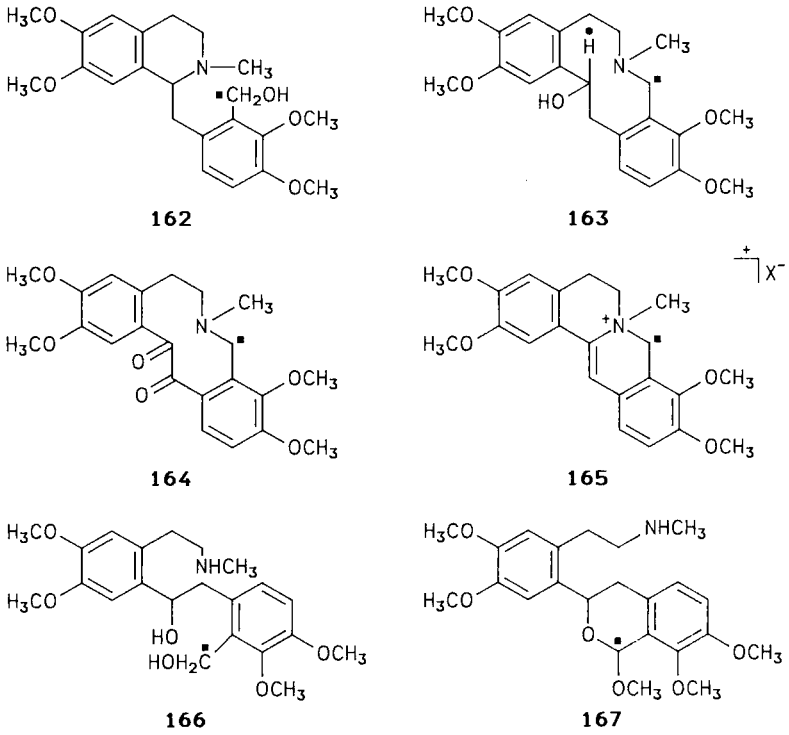
while the intermediacy of the berbine alkaloid (*S*)-scoulerine (**157**) has been ascertained in *P. rhoeas*. After O-methylation or formation of methylenedioxy entities from **157** there apparently follows an N-methylation of a nonphenolic THP type, e.g., **154**, although the feeding of a scoulerine methosalt as a probe



SCHEME 49. A biogenetic sequence for rhoeadine alkaloids. $R^1 = R^2 = CH_3$, alpinigenine group; $R^1 = CH_3$, $R^2 + R^2 = CH_2$, oreodine group; $R^1 + R^1 = R^2 + R^2 = CH_2$, rhoeadine group.

into the specificity of the quaternization step has not yet been performed. The novel hydroxylation of a quaternary precursor, e.g., **156**, leading to a protopine species has been accounted for by a range of experiments done on *P. bracteatum* and *P. rhoeas* as well.

As to the stages beyond the protopine type, one can make some profit of a number of attempted feeding experiments with *P. bracteatum*, the compounds applied being put together in Scheme 50. These nonprecursors may suggest how biosynthesis does not proceed (*166, 167*). 2′-Hydroxymethyllaudanosine (**162**) was not incorporated into **3m**, as expected. Dihydromuraminol (**163**) was incorporated with a low efficiency; but the tritium contained at C-14 was lost, showing that **163** is outside the natural pathway leading to **3m**. Feeding of either 13-



SCHEME 50. ■, ●, indicate ^{14}C or ^{3}H label, respectively.

oxomuramine (**164**) or the Δ^{13}-unsaturated methosalt **165,** two C-13 functionalized compounds, did not produce any radioactive **3m** (*166*). Moreover, neither secomuraminol (**166**), nor the methyl acetal **167,** even though offering a preconstructed isochroman skeleton, were incorporated into **3m** (*167*).

Finally, a different approach was made by feeding multiply labeled THP (**154**) and THP methosalt (**156**), both carrying tritium labels at C-8, C-13, and C-14. The tritium incorporated into radioactive alpinigenine (**3m**) was traced down by stepwise degradation (*166*). According to expectations, the tritium localized on C-14 was removed, while one of the two tritium atoms bound to each C-8 and C-13 atom was always retained over all the hypothetical steps connecting a protopine species and **3m.**

The hypothetical postmuramine intermediates **A** through **E** should conform to all of these findings. The notion is that hydroxylation at C-8 on the protopine stage gives rise to a carbinolamine species **A,** which might enter a series **B** through **D** of equilibrating species, with the latter being trapped by an O-methylation step leading to **E.** Final addition of the secondary amine function onto the

activated double bond may accomplish the enzyme-controlled formation of rhoeadine alkaloids.

VIII. Biological Activity

From the structural point of view, the rhoeadine alkaloids are complex compounds having a 3-benzazepine skeleton. Among the benzazepines in general, the 1-benzazepines in particular were the first to emerge in the literature as a pharmacologically attractive group, and Kasparek (*82*) in his review refers to some 30 publications, most of them patent specifications in this field, as early as 1974. This interest in the 3-benzazepines has continued, and synthetic work was stimulated (*27, 122, 220*). Kaiser and his group (*1, 72*) have reported on the strong dopaminergic activity accompanied by a potent antihypertensive activity of a relatively simple 1-phenyltetrahydro-3*H*-3-benzazepine as well as on the dopamine receptor antagonist and neuroleptic activity of related 3-benzazepines.

In view of this background, it is surprising that the pharmacological data hitherto available for rhoeadine alkaloids are confined to rhoeadine itself. Most of this work, except for one paper (*231*) published later, has been briefly reported by Preininger (*151*) in his review on the pharmacology of the papaveraceae alkaloids in this series.

Awe (*4*) was the first who studied the physiological activity of presumably pure rhoeadine (**2a**) to observe spasms. Lieb and Scherf (*97*) in a detailed examination of 16 papaveraceae alkaloids including rhoeadine recorded their very diverse activities upon intraocular pressure, mydriasis, and general behavior in the rabbit after intravenous administration. Rhoeadine was found to produce an immediate strong response of the intraocular pressure, combined with mydriasis and a slight stimulation of respiration. The intraocular pressure within 10 min dropped to half its initial value and slowly normalized after 100 min. The results have been discussed in terms of a central action on both the extrapyramidal and hypothalamus hypophysis systems.

Walterová *et al.* (*231*) determined the medium lethal dose of rhoeadine to be $LD_{50} = 530 \pm 20$ mg/kg in the female rat after intraperitoneal administration. In the course of her study, urine, feces, liver, kidney, and brain were examined for their content of rhoeadine metabolites. Among the five metabolites detected in urine, using thin-layer chromatography, were rhoeagenine (**1a**) and papaverrubine E (**2d**), showing that O- and N-dealkylation are the most prominent processes in the biotransformation of rhoeadine. The remaining more polar metabolites, not yet identified, probably result from splitting off the methylenedioxy bridge(s).

The uptake of oxygen by ascitic tumor cells in mice was slightly inhibited by rhoeadine (*188*). The finding that the intraocular pressure in rabbits was in-

TABLE X
Physiocochemical Data for Rhoeadine Alkaloids, Functional Derivatives, and Degradation Products

Name	Formula No.	mp (°C)	$[\alpha]_D$, (°) Solvent[a]	References	
				^{1}H-NMR	MS
Alpinigenine	**3m**	193–195 *(102)*	+286, M *(102)*	*(102, 172)*	*(102, 172)*
		187–188 *(172)*	+306, M *(172)*		
(±)-Alpinigenine	**3m**	172–173 *(67)*	—	—	—
Alpinigeninediol	**69**	151–152 *(172)*	+18, M *(172)*	*(172)*	*(172)*
(±)-Alpinigeninediol	**69**	(characterized in ref. *67* as the picrate, mp 189–191°)			
benzoxazocine derivative[b]	**48b**	187–188 *(167, 173)*	+258, M *(167, 173)*	*(167, 173)*	*(167, 173)*
Cope product	**50**	186–189 *(167)*	optically inactive	—	*(167)*
hydrochloride	—	161–163 *(172)*	+210, M *(172)*	—	—
methiodide	—	185–187 *(172)*	+188, M *(172)*	*(172)*	—
N-Formyloxynoralpinigenine	**53a**	263–264 *(96)*	+146, C *(96)*	*(96)*	*(96)*
nitrile[c]	**18**	161–162 *(168)*	+11, M *(168)*	*(168)*	*(168)*
nitrile methiodide	—	224–228[d] *(168)*	+54, M/C=2:1 *(168)*	—	*(168)*
N-oxide	**22**	176–178 *(172)*	+138, M *(172)*	*(172)*	*(172)*
O-Acetylalpinigenine	**7**	amorphous *(172)*	+282, M *(172)*	—	*(172)*
phthalimidine derivative[e]	**19**	161–162 *(168)*	optically inactive	*(168)*	*(168)*
Alpinine	**6l**	amorphous *(134)*	+412, M *(134)*	*(229)*	*(229)*
methiodide	—	166–167 *(134)*	—	—	—
***cis*-Alpinigenine**	**1m**	175–176 *(172)*	+110, M; +80, C	*(172)*	*(172)*
			+108, Py *(172)*		
(±)-*cis*-Alpinigenine	**1m**	183–184 *(120)*	—	*(120)*	—

(continued)

TABLE X (*Continued*)

Name	Formula No.	mp (°C)	$[\alpha]_D$, (°) Solvent[a]	References	
				^{1}H-NMR	MS
(±)-*cis*-14-Deoxyalpinigenine	**134**	164–166 *(2)*	—	*(2)*	*(2)*
(±)-*cis*-Oxyalpinigenine	**117**	195–196 *(120)*	—	*(120)*	—
methiodide A	**26**	214–217[d] *(172)*	+104, C/M=19:1 *(172)*	*(172)*	*(172)*
methiodide B	**27**	228–230[d] *(172)*	+160, M *(172)*	*(172)*	*(172)*
nitrile[f]	**18a**	144–145 *(168)*	−143, M *(168)*	*(168)*	*(168)*
N-oxide A	**29**	176–178 *(172)*	+141, M *(172)*	*(172)*	*(172)*
N-oxide B	**30**	195–197 *(172)*	+139, M *(167)*	*(172)*	*(172)*
***cis*—Alpinine** (See *O*-methyl-*cis*-alpinigenine)					
Dubirheine (*O*-ethylrhoeagenine)	—	236–237 *(207)*	+236, C *(207)*	*(187)*	*(187, 213)*
Epialpinine	**31**	122–123 *(172)*	+302, M *(172)* +288, C *(102)*	*(102, 172)*	*(102, 172)*
benzoxazoxine derivative[g]	**48a**	200–202 *(167)*	+244, M/C=9:1 *(167, 173)*	*(167, 173)*	*(167, 173)*
compound **52**	**52**	amorphous *(167)*	−27, M *(167)*	*(167)*	*(167)*
Emde product[h]	**34**	86–88 *(172)*	+14, M *(172)*	*(172)*	*(172)*
methine[i] (Hofmann product)	**44**	104–105 *(167)*	−23, M *(167)*	*(167)*	*(167)*
methiodide	**33**	186–190[d] *(172)*	+189, M *(172)*	—	—
N-Cyano-*N*-norepialpinine	**51**	176–184 *(167)*	+335, M *(167)*	*(167)*	*(167)*
N-oxide	**47**	123–125 *(172)*	+149, M *(172)*	*(172)*	*(172)*
O-Ethylalpinigenine	—	amorphous *(148)*	—	—	*(148)*
Epiglaudine (glaupavine)	**3e**	98–101 *(210)*	+250, C *(138)* +254, C *(210)*	*(138, 187)* *(201)*	*(34, 138)* *(187)*
hydrobromide	—	252–254 *(210)*	—	—	—
methiodide	—	158–161 *(64)*	—	—	—

Epiisorhoeadine	**3a**	—	—	—	*(138)*
Epipapaverrubine B	**3g**	70–71 *(145)* 71–74 *(64)*	+308, C *(64)*	—	*(145)*
Epipapaverrubine G	**3n**	(characterized in ref. *134* by TLC)			
Glaucamine	**3f**	222–223 *(210)* 222–224 *(56)*	+298, C *(210)* +300, C *(56)*	*(31, 187)*	*(34)*
hydrobromide	—	202–204 *(37)*	—	—	—
hydrochloride	—	215–217 *(37)*	—	—	—
hydriodide	—	203–205 *(127)*	—	—	—
O-Ethylglaucamine	—	—	—	—	*(148)*
oxalate	—	150 *(137)*	—	—	—
perchlorate	—	197–199 *(37)*	—	—	—
Glaudine	**4e**	103–105 *(127)*	+455, C *(127)*	*(187, 201)*	*(187)*
hydrochloride	—	185–187 *(127, 137)*	—	—	—
hydriodide	—	180–182 *(127, 137)*	—	—	—
oxalate	—	152 *(127, 137)*	—	—	—
perchlorate	—	178–181 *(127, 137)*	—	—	—
Isorhoeadine	**4a**	159–161 *(114, 180)* 165–167 *(235)*	+314, C *(114, 180)* +435, C *(57)*	*(180)*	*(34)*
Emde product	**41**	amorphous *(202)*	+39, M *(202)*	*(202)*	—
methine (Hofmann product)	—	amorphous *(59)*	−25, Et *(59)*	*(59)*	—
dihydromethine	—	amorphous *(59)*	—	*(59)*	*(59)*
Isorhoeagenine	**3b**	182–185 *(116)* 215–216 *(208)*	+292, C *(116)* +258, C *(208)*	—	—
D-glucoside	**3c**	240–242 *(113)*	+225, Py *(113)*; +250, C/M *(179)*	*(113)*	—
Isorhoeageninediol	**38**	153–155 *(180)*	+72, C; +33, M *(180)*	*(180)*	—
Emde product (from **38**)	**40**	135–136 *(202)*	−110, M; −61, C *(202)*	*(202)*	—

(*continued*)

TABLE X (*Continued*)

Name	Formula No.	mp (°C)	$[\alpha]_D$, (°) Solvent[a]	References	
				^{1}H-NMR	MS
***N*-Methyl-*cis*-porphyroxigenine**	**1i**	(characterized in ref. *138* by TLC)		—	—
***N*-Methyl-*cis*-porphyroxine**	**2h**	(characterized in ref. *138* by TLC)		—	—
***N*-Methylepiporphyroxine**	**3h**	(characterized in ref. *138* by TLC)		*(26)*	—
***N*-Methylporphyroxigenine**	**3i**	217–218 *(26)*	+340, M *(26)*	*(26)*	*(26)*
***N*-Methylporphyroxine**	**4h**	—	—	*(25, 26)*	—
***O*-Methylalpinigenine** (see epialpinine)					
***O*-Methyl-*cis*-alpinigenine**	**2l**	106–107 *(172)*	+193, M; +167, C*(172)*	*(172)*	*(172)*
benzoxazocine derivative[k]	**49**	164–166 *(173)*[l]	+197, M *(173)*[l]	*(173)*[l]	*(173)*[l]
Emde product[m]	**35**	86–87 *(172)*	−15, M *(172)*	*(172)*	*(172)*
Emde product[n] (optically inactive)	**36**	121–123 *(172)*	—	*(172)*	*(172)*
methine[o] (Hofmann product)	**11a**	112–113 *(170)*	−52, M *(170)*	*(170)*	*(170)*
14-*O*-demethylmethine[p]	**11b**	151–152 *(170)*	−53, M *(170)*	*(170)*	*(170)*
methiodide	**28**	210–211[d] *(172)*	+186, M *(172)*	*(172)*	*(172)*
N-oxide A	**29**	220–224[d] *(173)*	+243, M *(173)*[l]	*(173)*[l]	*(173)*[l]
N-oxide B	**30**	amorphous *(173)*[l]	+150, M *(173)*[l]	*(173)*[l]	*(173)*[l]
***O*-Methylglaucamine** (see epiglaudine)					
***O*-Methylisorhoeagenine** (see epiisorhoeadine)					
Oreodine	**2e**	184–186 *(138)*	+224, C *(138)*	*(138)*	*(34, 138)*
methiodide	—	186–189 *(138)*	—	—	—
Oreogenine	**1f**	amorphous *(138)*	—	*(138)*	*(138)*
methiodide	—	173–175 *(138)*	—	—	—
O-Ethyloreogenine	—	–	—	—	*(187)*
Papaverrubine A	**4d**	223–224 *(131)*	+410, C *(131)*	—	*(34, 132)*
		226 *(57)*	+520, C *(57)*		
picrolonate	—	170–173 *(131)*	—	—	—

Papaverrubine B	**4g**	201–203 *(63, 126)*	+398, C *(140)*	*(63)*	*(34, 63, 132)*
Papaverrubine C	**3k**	190–192 *(64)*	+283, C *(64)*	*(64, 135)*	*(135)*
Papaverrubine D	**4k**	237–239 *(135)*	+391, C *(58, 141)*	*(26)*	*(25, 132)*
picrate	—	241–244 *(141)*	—	—	—
Papaverrubine E	**2d**	229–231 *(53)*	+326, C *(53)*	*(53)*	*(34, 132)*
		231 *(131)*	+331, C *(131)*		
(±)-Papaverrubine E	**2d**	216–218 *(53)*	—	—	—
(+)-Oxypapaverrubine E[a]	**76a**	225–230 *(53)*	+120, C *(53)*	*(53)*	*(53)*
(±)-Oxypapaverrubine E	**76a**	140–143 *(53)*	—	—	—
picrate	—	155–157 *(131)*	—	—	—
picrolonate	—	176–178 *(131)*	—	—	—
Papaverrubine F	**2g**	223–225 *(138)*	—	—	*(138)*
Papaverrubine G	**4n**	amorphous *(134)*	+397, M *(134)*	—	—
Papaverrubine H (see epiapaverrubine B)					
Porphyroxine (see papaverrubine D)					
Rhoeadine	**2a**	251–253 *(180)*	+235, C *(180)*	*(180)*	*(34)*
		252–254 *(138)*	+174, Py *(181)*		
(−)-Rhoeadine	—	253–254 *(87)*	−228, C *(87)*	—	—
(±)-Rhoeadine	—	222–224 *(87)*	—	—	—
14-Demethoxyrhoeadine	**58**	117–119 *(60)*	+118, C; +124, M *(60)*	*(87)*	*(87)*
methiodide (from **58**)	—	217–220 *(60)*	—	—	—
Emde product (from **58**)	—	125–127 *(202)*	−85, M *(202)*	*(202)*	—
methine A (from **58**)	**11e**	amorphous *(60)*	−128, C *(60)*	*(60)*	*(60)*
methine B (from **58**)	**43d**	110–112 *(60)*	0, C *(60)*	*(60)*	*(60)*
Emde product	**41**	134–135 *(202)*	+15, M; +22, C *(202)*	*(59)*	—
hydrobromide	—	228–230 *(181)*	+210, C *(181)*	—	—
hydrochloride	—	224–226 *(181)*	+214, C *(181)*	—	—
hydriodide	—	228–230 *(181)*	+206, C *(181)*	—	—

(*continued*)

TABLE X (*Continued*)

Name	Formula No.	mp (°C)	$[\alpha]_D$, (°) Solvent[a]	References	
				^{1}H-NMR	MS
methine A (Hofmann product)	**11**	156–158 *(181)*	−27, C *(181)*	*(59)*	*(180)*
			−50, Et *(59)*		
bismethine	**43b**	144–146 *(181)*	+17, C *(181)*	—	—
dihydrobismethine	**43c**	104–106 *(181)*	+60, C *(181)*	—	—
dihydromethine A	—	146–148 *(181)*	−55, C *(181)*	*(59)*	—
Emde product (from dihydromethine)	—	207–209 *(59)*	+49, C *(59)*	*(59)*	*(59)*
methine B (Hofmann product)	**43a**	135–136 *(59)*	+49, C *(59)*	*(59)*	*(59)*
methiodide	—	215–217 *(181)*	+186, H_2O *(181)*	—	—
Rhoeagenine	**1b**	236–238 *(56, 138)*	+130, Py *(138)*	*(187)*	*(34)*
			+110, C *(170)*		
			+170, AcOH *(56)*		
hydrochloride	—	205–207 *(181)*	+233, C *(181)*	—	—
hydriodide	—	207–209 *(181)*	+228, C *(181)*	—	—
methine (Hofmann product)	**11c**	177–178 *(175)*	−35, Et *(175)*	*(175)*	*(175)*
		170–171 *(181)*	−37, C *(181)*		
14-epimethine	**11d**	216–217 *(175)*	+13, Et *(175)*	*(175)*	*(175)*
irregular Hofmann product (from **1b**)	**45**	132–133 *(175)*	0, C *(175)*	*(175)*	*(175)*
irregular Hofmann product	**46**	180–182 *(175)*	+139, C *(175)*	*(175)*	*(175)*
methiodide	**2o**	255–258 *(180)*	+154, C *(180)*	—	—
		230–235 *(175)*	+169, M *(175)*		
nitrile[r]	**160**	—	—	*(227)*	*(227)*
2,4-dinitrophenylhydrazone	—	203–205 *(222)*	—	—	—

Oxyrhoeagenine	**6**	220–222 *(180)*	+61, C *(180)*	*(180)*	—
(±)-Oxyrhoeagenine	—	241–243 *(87)*	—	*(87)*	*(87)*
(±)-Oxyrhoeagenine *N*-oxide	**75**	195–200 *(53)*	—	—	—
Rhoeageninediol	**5**	131–133 *(180)*	−50, C; −99, M *(180)*	*(180, 227)*	*(227)*
		134–135 *(227)*	−10, C *(222)*		
(±)-Rhoeageninediol	—	142–143 *(67)*	—	—	—
diacetate	—	93–95 *(180)*	−96, C *(180)*	*(180)*	—
methiodide	**5a**	243–245[d] *(180)*	−108, M *(180)*	—	—
		192 *(227)*			
Desrhoeageninediol	**13**	amorphous *(180)*	+58, C *(180)*	*(227)*	*(180, 227)*
methiodide (from **13**)	—	262–265 *(180)*	+15, M *(180)*	*(227)*	—
Desdesrhoeageninediol	**14a**	115–117 *(180)*	+25, C *(180)*	*(180)*	*(180)*
Dihydrodesdesrhoeageninediol	**14b**	amorphous *(180)*	+86, C *(180)*	—	*(180)*
Emde product	**39**	135–136 *(202)*	+112, M; +63, C *(202)*	*(202)*	—

[a] M = methanol, C = chloroform, Et = ethanol, Py = pyridine.

[b] **48b** = (1*S*, 2*R*, 15*R*)-15-hydroxy-8,9,13,14-tetramethoxy-4-methyl-1,2,5,6,-tetrahydro-4*H*-isochromano[3,4-*a*]benz[*c*]oxazocine.

[c] **18** = (1*S*, 2*R*)-1-acetoxy-2-(2-cyano-3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine *(161)*.

[d] Decomposition.

[e] **19** = 3-[2-(β-dimethylaminoethyl)-4,5-dimethoxybenzylidene]-6,7-dimethoxyphthalimidine *(161)*.

[f] **18a** = (1*R*, 2*R*)-1-acetoxy-2-(2-cyano-3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine.

[g] **48a** = (1*S*, 2*R*, 15*R*)-8,9,13,14,15-pentamethoxy-4-methyl-1,2,5,6-tetrahydro-4*H*-isochromano[3,4-*a*]benz[*c*]oxazocine.

[h] **34** = (1*R*, 3*R*)-3-[2-(β-dimethylaminoethyl)-4,5-dimethoxyphenyl]-1,7,8-trimethoxyisochroman *(167)*.

[i] **44** = (1*R*, 3*S*, 4*R*)-4-dimethylamino-1,7,8-trimethoxy-3-(4,5-dimethoxy-2-vinylphenyl)isochroman *(167)*.

[k] **49** = (1*R*, 2*R*, 15*S*)-8,9,13,14,15-pentamethoxy-4-methyl-1,2,5,6-tetrahydro-4*H*-isochromano[3,4-*a*]benz[*c*]oxazocine.

[l] Also see ref. *(167)*.

[m] **35** = (1*S*, 3*S*)-3-[2-(β-dimethylaminoethyl)-4,5-dimethoxyphenyl]-1,7,8-trimethoxyisochroman *(167)*.

[n] **36** = 2-(β-dimethylaminoethyl)-2′-hydroxymethyl-4,5,3′,4′-tetramethoxydibenzyl *(167)*.

[o] **11a** = (1*S*, 3*R*, 4*R*)-4-dimethylamino-1,7,8-trimethoxy-3-(4,5-dimethoxy-2-vinylphenyl)isochroman.

[p] **11b** = (1ξ, 3*R*, 4*R*)-4-dimethylamino-1-hydroxy-3-(4,5-dimethoxy-2-vinylphenyl)-7,8-dimethoxyisochroman.

[q] **76a** = (+)-2,3:10,11-bis(methylenedioxy)-6,15-*cis*-rheadane-8-one *(53)*.

[r] **160** = 1-acetoxy-2-(2-cyano-3,4-methylenedioxyphenyl)-3-methyl-7,8-methylenedioxy-1,2,4,5-tetrahydro-3*H*-3-benzazepine.

creased after the administration of seed oil and extracts from poppy heads of *Papaver rhoeas* (*40*) cannot be envisaged as an activity due to rhoeadine. The observation (*89*) that cattle avoid *P. rhoeas* is another nonspecific effect caused by the intake of plants containing rhoeadine alkaloids.

It may be worth noting that a series of isoindolobenzazepines, which in structural terms are closely related to the red products readily formed from papaverrubine alkaloids on acid contact, exhibits potent cytotoxic activity toward leukemia P388 cells, and *in vitro* these compounds behave like synergists of certain clinically administered anticancer substances (*158a*). As to the pharmacology of the papaverrubines themselves, no work seems to be published.

IX. Physicochemical Data of Rhoeadine Alkaloids and Derivatives

Table X is a compilation of rhoeadine alkaloids, functional derivatives, and degradation products, which lists the chemical formula number if available, melting point, optical rotation, as well as literature references for proton-NMR and mass spectroscopy. Compounds from synthetic sequences have been included occasionally, for example, if their structures were closely related to the basic skeleton of the rhoeadine alkaloids.

The body of material is arranged in alphabetical order, using generally accepted trivial names for all natural and semisynthetically prepared alkaloids, which are printed in boldface type. Derivatives of any individual alkaloid are indented and again arranged alphabetically. The names adopted in this list are mainly those used in the original papers referred to. The simple name "methine" or the prefix "des . . ." are extensively used for products of Hofmann's exhaustive methylation. No attempt has been made to introduce into this field IUPAC systematical nomenclature, although, if systematic names are given in an original paper, these are added as footnotes.

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— CHAPTER 2 —

PROTOBERBERINE ALKALOIDS

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I. Introduction

The protoberberine alkaloids were first reviewed by Manske and Ashford in 1954 in Volume IV of this treatise. After 13 years Jeffs' review appeared in Volume IX and protoberberine alkaloids of Papaveraceae were reviewed by Manske in Volume X, and by Šantavý in Volumes XII and XVII.

Recent years have witnessed an upsurge in scientific information on protoberberine alkaloids and some facets were reviewed (*1–4*). Several new sources of protoberberine alkaloids were explored and though relatively few new bases were isolated, some possess unusual structures.

^{13}C-NMR spectroscopy coupled with circular dichroism techniques (CD) have been frequently employed for determination of conformation and absolute configuration.

There has been much interest in the chemistry of protoberberines, and their basic skeleton was transformed chemically into several biogenetically related structures. Several successful syntheses of protoberberine alkaloids were achieved, often by new approaches.

Production of protoberberine alkaloids in callus cultures of plants was studied. The biosynthesis of several protoberberine alkaloids were investigated thoroughly, and biosynthetic pathways were traced, including aberrant biosynthetic pathways. In recent years biochemists have paid attention to enzymatic processes, and at least two pure enzymes were isolated that formed the berberine bridge and converted berbines to protoberberines. Protoberberine alkaloids were reported to exhibit a variety of biological and pharmacological effects.

II. Occurrence*

The protoberberine alkaloids isolated from plants since the appearance of earlier reviews are listed in Tables I to III. Table I shows known protoberberine

* This material supplements material presented in this treatise, Volume 9, pages 44–50, and Volume 17, pages 390–396.

TABLE I
Botanical Distribution of Known Protoberberine Alkaloids

Plant (Reference)	Alkaloid
Annonaceae	
Enantia chlorantha Oliver *(14)*	Columbamine, jatrorrhizine, palmatine
Mitrella kentii Miq. *(15)*	Aequaline
Schefferomitra subaequalis (16)	Aequaline, schefferine
Berberidaceae	
Berberis aristata DC[l]. *(17)*	Berberine
B. asiatica Rox. ex DC. *(18)*	Berberine
B. jaeschkeana Schneid. *(19)*	Palmatine
B. julianae Schneid[h] *(20, 21)*	Berberine, jatrorrhizine, palmatine
B. lycium Royle *(22, 23)*	Berberine, oxyberberine
B. oblonga (24, 25)	Berberine, columbamine, jatrorrhizine, palmatine
B. petiolaris Wall. ex G. Don *(26)*	Berberine, palmatine
B. vulgaris L. *(27–29)*	Berberine, columbamine, jatrorrhizine, palmatine
Leontice leontopatalum Linn. *(29)*	Palmatine, tetrahydropalmatine
Mahonia aquifolium Nutt. *(30)*	Berberine, canadine, corypalmine
Fumariaceae	
Fumaria officinalis L. *(31)*	(−)-Sinactine
F. parviflora[i] *(32)*	Coptisine, (−)-stylopine
F. schleicheri Soy. Will. *(33)*	(±)-Sinactine
F. vaillantii Loisel[i] *(34)*	(−)-Cheilanthifoline, (−)-scoulerine, (+)-stylopine
Leguminosae	
Erythrina orientalis Murr. *(35)*	(+)-Coreximine, scoulerine
Menispermaceae	
Arcangelisia flava (L.) Merr[a,l] *(36)*	Berberine, jatrorrhizine, palmatine
Cocculus carolinus DC. *(37)*	Palmatine
Coscinium wallichianum (38)	Berberine, jatrorrhizine, palmatine
Legnephora moorii Miers *(39)*	Dehydrocorydalmine
Menispermum cannadense Linn. *(40)*	Dehydrocheilanthifoline
Stephania glabra (Roxb.) Miers[d] *(40–42)*	Corydalmine, dehydrocorydalmine, jatrorrhizine, palmatine, palmatrubine, stepharinine, stepholidine, tetrahydropalmatine
S. japonica Miers[a,b] *(43)*	Cyclanoline, steponine
S. kwansiensis[d] *(44)*	(−)-Tetrahydropalmatine
Tinospora crispa (L.) Hk.f. & Th.[a] *(45)*	Berberine, palmatine
T. glabra[a,b] *(45)*	Berberine, palmatine
T. sagittata[a] *(45)*	Palmatine
Papaveraceae	
Chelidonium majus L.[b,i] *(46)*	Berberine, coptisine, corysamine, (±)- and (−)-stylopine, (−)-(α)-stylopine methiodide

(continued)

TABLE I (*Continued*)

Plant (Reference)	Alkaloid
Corydalis cava (L.) Schw. et Koert[f] *(47, 48)*	(+)-Canadine, copnoidine, coptisine, (+)-corybulbine, corycavine, (+)- and (±)-corycavidine, corydaline, corypalmine, corysamine, dehydrocorydaline, (+)- and (±)-isocorypalmine, (+)-stylopine, (+)- and (±)-tetrahydropalmatine, (+)- and (±)-thalictricavine
C. marschalliana Pers. *(49)*	Sinactine, stylopine
C. ophiocarpa Thoms[f] *(50–52)*	Berberine, (−)-canadine, (−)-cheilanthifoline, coptisine, (−)-corycarpine, (−)-corypalmine, dehydrocheilanthifoline, (−)isocorypalmine, (−)-ophiocarpine, (−)-stylopine
C. solida (L) Swartz[i] *(53)*	Corydaline, stylopine
Dicranostigma lactucoides Hook f. et. Thoms[i] *(54)*	Berberine, coptisine
D. leptopodum (Maxim.) fedde[f] *(54)*	Berberine, coptisine
Glaucium corniculatum (L.) Rud.[a,b,c,m] *(55)*	Berberine
Hunnemannia fumariaefolia Sweet[f] *(56)*	Berberine, coptisine, corysamine, (−)-scoulerine,
Meconopsis cambrica Vig.[b] *(57, 58)*	Mecambridine
Papaver albiflorum var. *austromoravicum*[f] *(59)*	Berberine
P. albiflorum var. *albiflorum*[f] *(59)*	Berberine
P. lecoquii Lamotte[f] *(59)*	Berberine
P. orientale L.[i] *(60)*	Mecambridine, orientalidine
P. pseudoorientale[v] *(56, 57)*	Mecambridine, orientalidine
P. rhoeas L. *(56)*	Berberine, coptisine, β-stylopine methiodide
P. rupifragum Boiss et. Reut[f] *(61)*	Coptisine
Ranunculaceae	
Aquilegia olympica Boiss *(62)*	Berberine
Coptis groenlandica (63)	Berberine, coptisine, isocoptisine
C. japonica Makino *(64, 65)*	Berberine, coptisine, jatrorrhizine
C. japonica Makino (Callus culture) *(66)*	Berberine, jatrorrhizine
C. japonica Makino var. *dissecta (67)*	Berberine
C. quinavefolia Miq. *(64)*	Berberine, columbamine, coptisine, jatrorrhizine
C. teeta Wall. *(28)*	Berberine
C. spp. *(68)*	Berberastine, epiberberine, groenlandicine, oxyberberine, thalifendine
Hydrastis canadensis L. *(24, 69, 70)*	Berberine, canadaline, canadine
Thalictrum fendleri Engelm. *(71)*	Tetrahydrothalifendine
T. foliolosum DC.[d] *(72, 73)*	Berberine, jatrorrhizine, palmatine
T. lucidum (74)	Berberine, jatrorrhizine

(*continued*)

TABLE I (*Continued*)

Plant (Reference)	Alkaloid
T. minus Race B[i] *(75, 76)*	Berberine, oxyberberine, palmatine
T. polygamum Muhl.[f] *(77)*	Berberine, berberrubine deoxythalidastine, thalifendine
T. revolutum DC.[b] *(78)*	Berberine, jatrorrhizine
T. rugosum (79, 80)	Columbamine, deoxythalidastine, thalidastine, thalifendine
Phellodendron wilsonii (71)	Berberine
Zanthoxylum monophyllum Lam.[a,c] *(81, 82)*	Berberine
Z. ocumarense (83)	*N*-Methylcanadine

[a] Stem; [b]root; [c]leaf; [d]rhizome or tuber; [e]fruit; [f]whole plant; [g]callus culture; [h]seed; [i]aerial parts; [j]bark; [k]stem bark; [l]root bark; [m]flower; [n]capsule.

alkaloids isolated from known sources. Table II records new sources of known protoberberine alkaloids. In Table III new alkaloids are shown.

Quaternary berberines often have been isolated as salts, but in what form they occur in nature is not precisely known. The anion may be an organic acid, etc. The occurrence of some berbines in racemic, (+), and (−) forms in plants and their co-occurrence with their corresponding dehydro bases are of biogenetic interest.

TABLE II
New Botanical Sources of Known Protoberberine Alkaloids

Plant (Reference)	Alkaloid
Annonaceae	
Annona muricata Linn.[b,c,k] *(84)*	Coreximine
Desmos tiebaghiensis (Daniker) R. E. Fr.[i] *(85)*	(−)-Discretamine, (−)-stepholidine
Duguetia calycina Benoist Guianese *(86)*	Discretamine, xylopine
D. obovata (87)	(−)-Discretine, (−)-xylopinine
Guatteria discolor[k] *(88)*	Corypalmine, discretamine, discretine, *O*-demethyldiscretine
G. ouregou Dun.[d] *(89)*	(−)-Coreximine, (−)-demethylxylopinine
G. scandens (90)	(−)-Discretine, (−)-xylopinine
Pachypodanthium staudtii Engl. & Diels[j] *(91)*	Corypalmine, discretine
Polyalthia nitidissima Benth. *(92)*	Stepholidine
P. oligosperma Danguy Diels[j] *(93)*	Kikemanine, xylopinine
Xylopia buxifolia Baill *(94)*	Discretamine, xylopinine

(*continued*)

TABLE II (*Continued*)

Plant (Reference)	Alkaloid
Berberidaceae	
Berberis empetrifolia Lam.[a] *(95, 96)*	Berberine, oxyberberine
Mahonia repens (Lindl) G. Don[a,b] *(97)*	Berberine, jatrorrhizine, columbamine, palmatine
Fumariaceae	
Fumaria densiflora DC[i] *(98)*	Coptisine, palmatine, (±)-sinactine
F. judaica Boiss.[i] *(99)*	Cheilanthifoline, coptisine, stylopine (fumjudaine)
F. kraliki Jordan[i] *(32)*	Berberine, (−)-canadine, coptisine, (−)-stylopine
F. parviflora Lam.[f] *(32, 100, 101)*	(−)-Cheilanthifoline, coptisine, dehydrocheilanthifoline, 8-oxocoptisine, (−)-stylopine
F. schleicheri Soy.-Will. *(102, 104)*	Sinactine, stylopine, (−)-stylopine
F. schrammii Nym. *(105)*	(±)-Sinactine, (−)-Stylopine
F. vaillantii Loisel. *(106)*	Stylopine
Lauraceae	
Cryptocarya longifolia Kostermans[a] *(107)*	(−)-Scoulerine
Menispermaceae	
Anamirta cocculus (L.) W. & A.[a,b] *(109)*	Berberine, columbamine, palmatine
Arcangelisia flava (L.) Merr.[a,l] *(36)*	Dehydrocorydalmine,8-hydroxyberberine, thalifendine
A. lourerii (38)	Berberine, jatrorrhizine, palmatine
Chasmanthera dependens[a] Hochst. *(108)*	Columbamine, coreximine, govanine [≡ (−)-tetrahydropseudocolumbamine], jatrorrhizine, palmatine, tetrahydropalmatine
Fibraurea chloroleuca Miore[a,l] *(109)*	Berberine, berberrubine, columbamine, dehydrocorydamine, jatrorrhizine, palmatrubine, pseudocolumbamine, pseudojatrorrhizine, tetrahydrojatrorrhizine, tetrahydropalmatine
Heptacyclum zenkeri Engl.[a,b] *(110)*	Dehydrodiscretine
Limaciopsis loangensis[e] *(111)*	8-Oxopalmatine
Stephania cepharantha Hayata[h] *(112)*	Crebanine, dehydrocrebanine, stesakine
S. elegans Hk.f. & Th[a,b,c] *(113)*	Cyclanoline
S. glabra (Roxb.) Miers[d] *(41)*	Capaurine, corynoxidine
S. japonica var. *australis*[a,d] *(114)*	Cyclanoline, oxostephamiersine, stephabyssine, thalrugosine
S. kwansiensis H. S.[d] *(44, 115, 116)*	(−)-Capaurine, palmatine, stephanine,
S. sasakii[a,b] *(117)*	(−)-Tetrahydropalmatine
Tinospora baenzigeri[a] *(45)*	Berberine, jatrorrhizine
T. cordifolia (Willd.) Hk.f. & Th.[c] *(45)*	Palmatine
T. crispa (L.) Hk.f. & Th[a] *(45)*	Jatrorrhizine

(*continued*)

TABLE II (*Continued*)

Plant (Reference)	Alkaloid
T. glabra[b] *(45)*	Jatrorrhizine
T. merrilliana[a] *(45)*	Berberine, jatrorrhizine, palmatine
T. sinensis (Lour.) Merr.[a] *(45)*	Palmatine
T. smilacina Benth.[a] *(45)*	Berberine
Papaveraceae	
Chelidonium majus Linn.[f] *(46)*	Mecambridine, (−)-β-stylopine methiodide
C. gortschakovii Schrenk[i] *(118)*	Stylopine
C. meifolia Wall.[a,c]	Apocavidine, (+)-cavidine, cheilanthifoline, (+)-sinactine, stylopine
C. ophiocarpa Hook. f. et Thoms *(50–52)*	Carpoxidine, dehydroisocorypalmine, 13-β-hydroxystylopine, ophiocarpine-*N*-oxide
Dicranostigma lactucoides Hook. f. et Thoms *(54)*	Corysamine
D. leptopodum (Maxim) Fedde[f] *(54)*	Corysamine
Glaucium grandiflorum Boiss. et Huet[a,c,m] *(55)*	Berberine
G. pulchrum Stapi[i] *(119)*	*N*-Methyllindcarpine[o]
G. vitellinum Boiss and Buhse[i] *(120)*	Tetrahydropalmatine[p]
Hunnemannia fumariaefolia Sweet[f] *(56)*	(−)-Cyclanoline iodide, (−)-α-Scoulerine
Hypecoum procumbens L.[f] *(121)*	(−)-Scoulerine
Papaver albiflorum sub. spp. *austromoravicum*[f] *(59)*	Canadine, (−)-α-canadine methohydroxide, coptisine, corysamine, scoulerine α-stylopine methohydroxide
P. albiflorum sub. spp. *albiflorum (59)*	Canadine, (−)-α-canadine methohydroxide, coptisine, corysamine, scoulerine, α-stylopine methiodide
P. bracteatum Lindl.[g] *(5)*	Orientalidine
P. confine Jord. *(56)*	Coptisine
P. lecoquii Lamotte[f] *(59)*	Canadine, coptisine, scoulerine, stylopine, α-stylopine methohydroxide
P. macrostomum Boiss. et Huet[a,c,m] *(55)*	Cheilanthifoline
P. pseudo-orientale (Fedde) Medw. *(56)*	Alborine, coptisine, palmatine
P. rhoeas L. *(56, 122)*	Mecambrine
P. rupifragum Boiss. et Reut[f] *(61)*	Corysamine, (−)-stylopine
P. tauricola (123)	Sinactine, scoulerine
P. trinifolium[i] *(124)*	Cheilanthifoline, scoulerine, sinactine
Rannunculaceae	
Hydrastis canadensis L. *(70)*	(−)-Corypalmine, bis-*O,O'*-dimethyl derivative of (−)-tetrahydropalmatine, (−)-isocorypalmine
Thalictrum alpinum L.[b] *(125)*	Berberine, columbamine, jatrorrhizine, oxyberberine, palmatine, thalifendine
T. baicalense Turcz. *(126)*	Berberine

(*continued*)

TABLE II (*Continued*)

Plant (Reference)	Alkaloid
T. foliolosum DC[b] *(73, 127)*	Columbamine, dehydrodiscretamine, oxyberberine, (berlambine)[o], thalidastine, thalifendine
T. javanicum Blume[a,b] *(128)*	Berberine, columbamine, jatrorrhizine, palmatine
T. longistylum DC[b] *(129)*	Berberine, columbamine, jatrorrhizine, oxyberberine, palmatine, 8-trichloromethyldihydroberberine (artifact)
T. minus L. Race B[b] *(76)*	Columbamine, jatrorrhizine, thalifendine
T. minus L[j] *(130)*	Berberine, *N*-methylcanadine hydroxide
T. minus var. hypoleucum[g] *(131)*	Berberine, columbamine, desoxythalidastine, jatrorrhizine, palmatine, thalidastine, thalifendine
T. podocarpum Humb.[b] *(132)*	Berberine, columbamine, jatrorrhizine, oxyberberine, palmatine, thalifendine, 8-trichloromethyldihydroberberine (artifact)
T. polygamum Muhl.[f] *(77)*	Palmatrubine
T. revolutum DC[b] *(78)*	Columbamine, deoxythalidastine, palmatine, thalifendine

[a] Stem; [b]root; [c]leaf; [d]rhizome or tuber; [e]fruit; [f]whole plant; [g]callus culture; [h]seed; [i]aerial part; [j]bark; [k]stem bark; [l]root bark; [m]flower.

[n] First report of the isolation of berbines from Lauraceae.

[o] First report of the isolation from Papaveraceae.

[p] First report of the isolation from *Glaucium* spp.

Protoberberine alkaloids have been isolated from callus cultures of some plants, and orientalidine was obtained from a cell culture of *Papaver bracteatum* (*5*), and capauridine and capaurimine were detected in redifferentiated plantlets of *Corydalis pallida* (*6*). (−)-Coptisine was isolated from seeds of *Fumaria indica* (*7*), with the racemic alkaloid being known to be a constituent of the whole plant (*8*). It was confirmed that (−)-α-stylopine methohydroxide was present in *Argemone ochroleuca, A. platycerus, Eschscholtzia oregana,* and *E. californica,* and the β-form in *Glaucium corniculatum, Papaver rhoeas,* and *P. syriacum* (*9*).

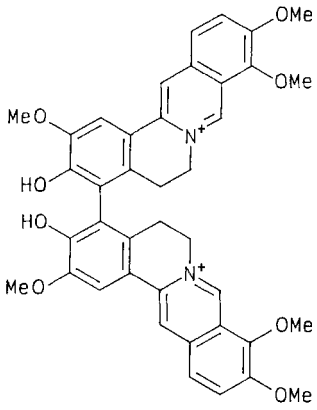
The alkaloid content of *Argemone mexicana* and particularly the presence of the four quaternary bases, (−)-scoulerine methohydroxide, (−)-cheilanthifoline, and α- and β-methohydroxides of (−)-stylopine, suggests a close relationship between this plant and *A. ochroleuca* and *A. albiflora* (*10*). Similarly, the presence of (−)-scoulerine in *A. polyanthemos* confirms its close relationship to *A. albiflora* (*11*).

The first known dimeric protoberberine alkaloid, bisjatrorrhizine (**1**), was

TABLE III
Botanical Distribution of New Protoberberine Alkaloids

Plant (reference)	Alkaloid	mp (°C)	$[\alpha]_D$ (°)
Alangiaceae			
Alangium lamarckii[h] Thw. *(133)*	Bharatamine	182–183	0
Annonaceae			
Duguetia calycina Benoist Guianese[a] *(86)*	(−)-10-Demethyl xylopinine	—	—
Guatteria ouregou Dun. *(89)*	(−)-10-Demethyl xylopinine	—	—
Pachypodanthium staudtii Engl. & Diels *(134)*	Staudine	205–206	0
Berberidaceae			
Berberis asiatica DC.[b] *(18)*	Karachine	146–148	—
Fumariaceae			
Fumaria officialis L.[f] *(31)*	*N*-Methylsinactine	318–320	−260 (H_2O)
Menispermaceae			
Anamirta cocculus (L.) W. & A.[a,b] *(107)*	(−)-8-Oxotetrahydropalmatine	—	—
Cocculus pendulus (Forsk.) Diels[a,c] *(135)*	(+)-Ophiocarpinone	217–218	+265 ($CHCl_3$)
Stephania elegans (Roxb.) Miers[a,b,c] *(113)*	*N*-Methylcorydalmine	190	
S. kwansiensis H. S. Lo[d] *(136)*	Dehydropalmatine	—	—
Papaveraceae			
Corydalis cava (L.) Shw. et Koert.[f] *(47)*	Dehydroapocavidine,	300–308	—
	α-tetrahydrocorysamine methiodide	285–293	—
C. meifolia Wall.[a,c] *(119)*	Dehydrocavidine	248–252	—
C. ochotensis Turcz. *(137)*	(−)-Lienkonine	166–167	−180 (EtOH)
C. solida (L.) Swartz *(53)*	Solidaline	197	—
C. tashiroi[f] *(138)*	Dehydrodiscretamine chloride	205–206	—
Rannunculaceae			
Thalictrum faurii Hayata[f] *(139)*	Dehydrodiscretine,	230–234	—
	thalifaurine	258–260	—
T. foliolosum DC[b] *(73)*	Dehydrodiscretamine chloride	205–206	—
T. javanicum Blume B[a,b] *(128)*	Demethyleneberberine	225	—

[a] Stem; [b]root; [c]leaves; [d]rhizome; [e]fruit; [f]whole plant; [g]callus culture; [h]seed.



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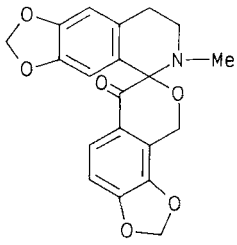


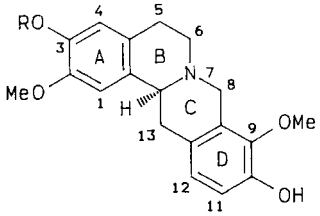
2

obtained from the roots of *Jatrorrhiza palmata* (Lam.) Miers. (Menispermaceae) (*12*). Corydalispirone (**2**), an alkaloid from *Corydalis incisa*, was suggested to be a metabolite of coptisine (*13*).

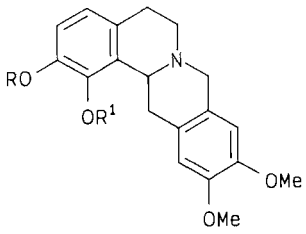
III. Revised Structures

A. Aequaline and Schefferine

The structures of aequaline and schefferine proposed by Pai *et al.* (*140*) were found to be incorrect. (−)-Aequaline and (−)-schefferine were found to be identical with discretamine and kikemanine, and their correct structures were established as **3** and **4,** respectively (*141*).



3 R = H
4 R = Me



5 R = Me, R^1 = H
6 R = H, R^1 = Me

B. Caseadine

Caseadine, isolated from *Corydalis caseana* A. Gray (*142*) was initially assigned structure **5** (*143*). Later, Kametani *et al.* (*144*) synthesized a substituted berbine having structure **5.** The *O*-methyl derivative of synthetic **5** and the *O*-methyl ether of natural caseadine, however, differed, and caseadine, therefore, was assigned structure **6.** Govindachari *et al.* (*145*) synthesized a compound of this structure. The ^{1}H-NMR spectra of synthetic and natural compounds were found to be similar but not identical. Natural caseadine was, therefore, reassigned the earlier structure **5.** Structure **5** of caseadine needs to be reexamined by X-ray analysis.

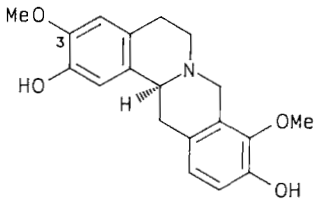
C. *Corydalis* L.

An alkaloid of structure **7,** isolated from *Corydalis* L., was synthesized as a racemate (*146*).

IV. New Alkaloids

A. Bharatamine

Bharatamine [**8,** $C_{18}H_{19}NO_2$, M 281, mp 182–183°C light petroleum–$CHCl_3$)], a novel racemic protoberberine alkaloid, unoxygenated at ring D, was isolated from the seeds of *Alangium lamarckii* Thw. (Alangiaceae) (*133*). The IR (Nujol) band at 3160 cm^{-1} (br) in conjunction with the UV absorption [λ_{max} (EtOH): (log ϵ) 206 (5.08), 290 (2.77) nm; λ_{max} (0.01 *N* NaOH): (log ϵ) 206 (4.85), 295 (3.91), 310 (2.71) nm] indicated that bharatamine had a phenolic tetrahydroprotoberberine skeletal structure. The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) of the base exhibited a three-proton singlet for one aromatic methoxy group (δ 3.84), two one-proton singlets (δ 6.60, 6.84) for a tetrasubstituted benzene, a four-proton multiplet (δ 7.74) for a disubstituted benzene, and a multiplet (δ 2.48–4.12) for nine aliphatic protons. The mass spectrum of bharatamine (M^+ *m/z* 281, 86%), besides the primary fragments at $M^+ - 1$ (100%) and $M^+ - Me$ (15%), had prominent and significant peaks at *m/z* 176 (46%) and 104 (60%) assignable to ions *i* and *ii,* respectively, conceivably arising by way of retro-Diels–Alder cleavage of ring C. From the above data, the base could have two alternative structures, 2-hydroxy-3-methoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a,g*]quinolizine (**8**) or its 2-methoxy-3-hydroxy isomer **9.** Treatment of bharatamine with diazomethane gave *O*-methylbharatamine (**10**), identical to synthetic 2,3-dimethoxyberbine (**10**). The position of the methoxy group at C-3 in bharatamine was finally established by an unambiguous synthesis (*133*).



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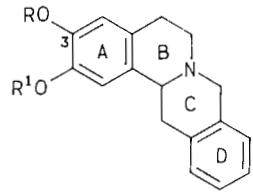
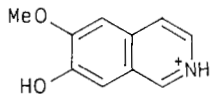


8 R = Me, R^1 = H
9 R = H, R^1 = Me
10 R = R^1 = Me



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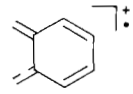
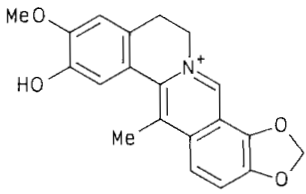


ii

Bharatamine is the first protoberberine alkaloid without an oxygen function in ring D. A plausible biogenetic route from deacetylipecoside or its equivalent to bharatamine was suggested (*133*).

B. Dehydroapocavidine

From *Corydalis cava* Schw. et Koerte (syn. *C. tuberosus*) the quaternary base dehydroapocavidine[**11**, $C_{20}H_{18}NO_4^+$, M 336 (ion), base iodide mp 300–308°C decomp] (*147*) was isolated as its iodide salt. Its mass spectrum had characteristic ions at *m/z* 339 (M^+), 204, 178, 176, and 162 (base peak).



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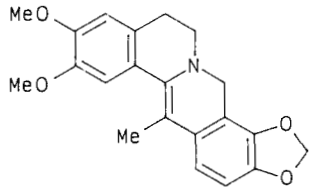


12

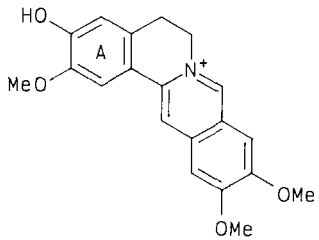
C. Dehydrocavidine

Dehydrocavidine [**12**, $C_{21}H_{20}NO_4$, M 350, mp 248–252°C (MeOH)] was isolated from the stems and leaves of *C. meifolia* (*119*). The ^{1}H-NMR spectrum

of the base had signals for one *C*-methyl (δ 2.92), two aromatic methoxy, and one methylenedioxy groups in the molecule. The C-8 protons appeared as a singlet at δ 10.4. The mass spectrum of the base had peaks at *m/z* 191, 177, and 145. Sodium borohydride reduction of the base yielded (+)-cavidine (*147*).

D. Dehydrodiscretine

Dehydrodiscretine [**13** chloride, $C_{20}H_{20}NO_4^+$, M 338 (ion), base chloride mp 230–234°C (MeOH), base iodide mp 243–245°C (decomp) (MeOH),] was first isolated from *Thalictrum fauriei* Hayata (*139*) and subsequently from the stems and roots of *Heptacyclam zenkeri* (*110*). The ^{1}H-NMR spectrum of the base had signals for three methoxy groups and six aromatic protons. A comparison of the ^{1}H-NMR spectral data of the base with thalifaurine (**30**) suggested dehydrodiscretine to be a 2,3,10,11-oxygenated protoberberine alkaloid. In the chemical ionization mass spectrum of dehydrodiscretine with isobutane as the reagent gas, the molecular ion M^+ *m/z* 338 was weak. The peaks at *m/z* 177, 178, and 176 suggested the presence of hydroxy and methoxy groups on ring A. A comparison of an authentic sample of pseudocolumbamine with the isolated base ruled out that dehydrodiscretine had a 2-hydroxy-3,10,11-trimethoxy substitution (*148*). Sodium borohydride reduction of **13** yielded (±)-discretine (**14**), and oxidation of **14** afforded dehydrodiscretine (**13**).



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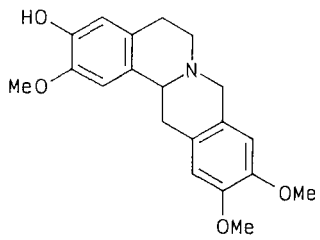

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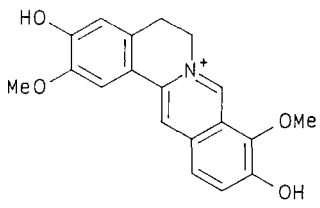
E. Dehydrodiscretamine

Dehydrodiscretamine [**15** chloride, $C_{19}H_{18}NO_4^+$, M 329 (ion), base chloride mp 205–206°C (decomp)] was isolated for the first time from *Corydalis tashiori* (*138*). Subsequently the base was also isolated from the roots of *T. foliolosum* DC. (*73*). UV-spectral data suggested it to be a phenolic protoberberine alkaloid. Sodium borohydride reduction of **15** yielded (±)-discretamine (**16**).



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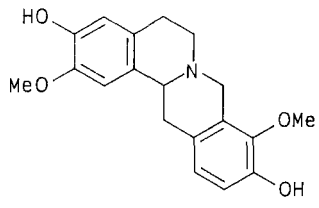
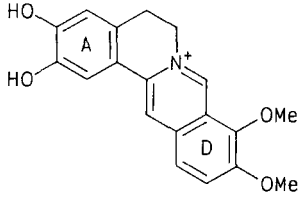


16

F. DEMETHYLENEBERBERINE

Demethyleneberberine [**17** chloride, $C_{19}H_{18}NO_4^+$, M 324 (ion), base chloride mp 225°C] was isolated from *T. javanicum* Bl. (*128*). A bathochromic shift in the presence of alkali in its UV spectrum suggested it to be a phenolic compound. The ^{1}H-NMR spectrum of the alkaloid showed the presence of two methoxy groups in the molecule. Mass spectral data of the base, its reduced product, its diacetyl and *O,O*-diethyl derivatives confirmed that two hydroxy and two methoxy groups in the molecule were in rings A and D, respectively. Treatment of the base with diazomethane afforded palmatine.



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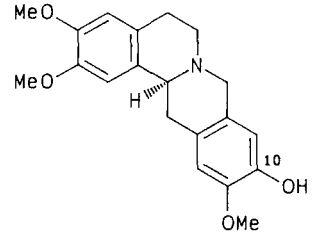
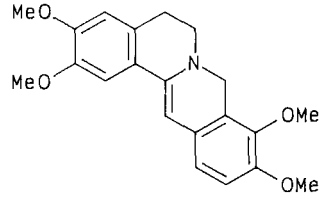


18

G. (−)-10-DEMETHYLXYLOPININE

(*S*)-(−)-10-Demethylxylopinine (**18,** $C_{20}H_{23}NO_4$, M 341) was isolated from the stem bark of *Duguetica calycina* Benoist Guianese (*86*). The ^{1}H-NMR and mass spectral data of the base suggested the presence of a hydroxy group at C-10. Treatment of the base with diazomethane gave (−)-xylopinine.



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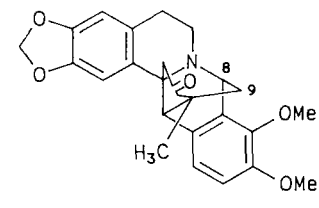


20

H. Dehydropalmatine

Cheng *et al.* (*136*) isolated dehydropalmatine (**19**) from the bulbs of *Stephania kwansiensis*. Sodium borohydride reduction of the base yielded (±)-tetrahydropalmatine. It is the first report of the occurrence of dehydropalmatine in nature.

I. Karachine

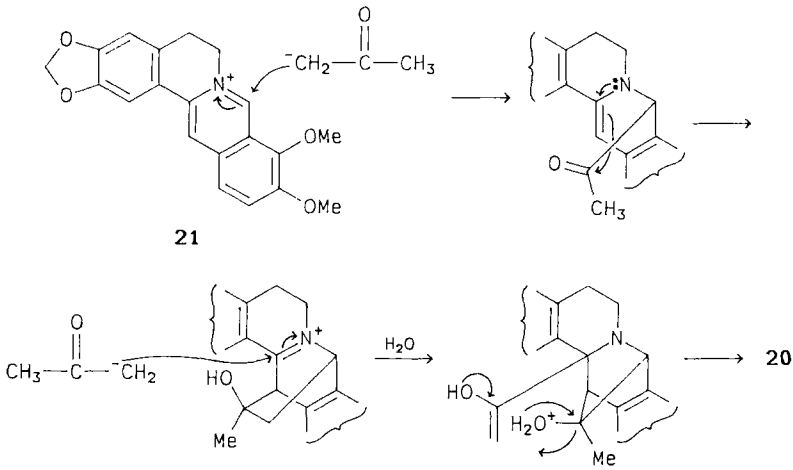
Karachine [**20**, $C_{26}H_{27}NO_5$, M 433, mp 146–148°C (EtOAc), $[\alpha]_D$ 0°], a naturally occurring berbinoid incorporating acetone units, was isolated from *Berberis aristata* DC (Berberidaceae), a shrub found in the northern mountainous regions of Pakistan and India (*18*). The UV spectrum λ_{max} (EtOH) 226 (sh) and 285 nm (log ϵ 3.90 and 3.62) of karachine was suggestive of a tetrahydroprotoberberine. The mass spectrum of the base showed a molecular ion at *m/z* 433 and a base peak at *m/z* 336. The latter peak fitted exactly for the molecular ion of berberine and was formed by loss of 97 mass units from the molecular ion via cleavage α to the nitrogen atom (C-13a to C-ϵ bond), followed by a retro-Diels–Alder process. The *m/z* 97 fragment corresponded to C_6H_9O or, more specifically, to 2 mol of acetone minus the elements of water. A sharp absorption band at 1710 cm^{-1} in the IR spectrum of karachine denoted the presence of a nonconjugated carbonyl. The structure **20** of karachine was assigned tentatively by the study of 360-MHz FT-NMR-spectral data. Supporting evidence for the substitution pattern was obtained by NOE studies. Irradiation of the C-10 methoxy singlet at δ 3.77 resulted in an 11.6% increase in the area (δ 6.52 and 6.55) of the ring-D aromatic doublet of doublets assigned to C-8 protons and a 5.6% increase of the singlet at δ 3.07 assigned to H-13. However, no observable NOE effect was noticed for the methoxy absorptions when either H-1 or H-4 singlets at δ 6.73 and 6.17 were irradiated.

Karachine (**20**) is the first example of the natural occurrence of a protoberberine alkaloid incorporating acetone moieties. A plausible mechanism of the formation of karachine (**20**) from berberine (**21**) was suggested (*18*) (Scheme 1).

Sodium borohydride reduction of karachine gave dihydrokarachine ($C_{26}H_{29}NO_5$, M 435). It was assumed that the reducing agent had approached from the less hindered side of the carbonyl function, giving rise to dihydrokarachine. In the mass spectrum of the dihydro derivative, the base peak again appeared at *m/z* 336, as in the parent base. The 360-MHz ^{1}H-NMR spectrum of dihydrokarachine along with the NOE studies further confirmed the structure of dihydrokarachine. That karachine is a true alkaloid and not an artifact was shown by reisolation of the base from the plant material with solvents free from acetone.

J. Lienkonine

Lienkonine [**22**, $C_{21}H_{25}NO_4$, M 355, mp 166–167°C (EtOH), $[\alpha]_D$ −180° (EtOH)] was isolated from *Corydalis ochotensis* Turz (*137*). The IR and UV

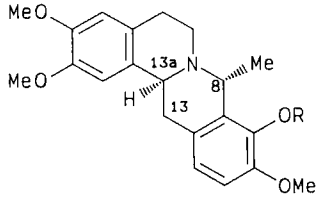


SCHEME 1. Formation of karachine from berberine.

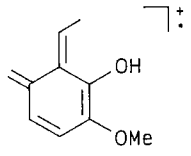
spectra of lienkonine suggested it to be a phenolic berbine derivative. The ^{1}H-NMR (60 MHz, $CDCl_3$) spectrum of lienkonine showed the presence of three methoxy groups at δ 3.85 (6H, s, 2 × OMe) and 3.88 (3H, s, 1 × OMe), four aromatic protons at δ 6.65 (1H, d, J = 6.5 Hz), 6.62 (1H, s), 6.69 (1H, s), and 6.77 (1H, d, J = 6.5 Hz), one secondary methyl group centered at δ 1.43 (3H, d, J = 6.5 Hz), and one hydroxy group at δ 5.75 (1H, br, s). Thus lienkonine was of the 2,3,9,10-oxygenated berbine type. Methylation of lienkonine with diazomethane produced *O*-methyllienkonine (**23**). The mass spectrum (70 eV) of lienkonine exhibited a molecular ion at *m/z* 355 (M^+) and fragment ions at *m/z* 340, 192, 190, and 164, which indicated that one hydroxy group must be attached to ring D. On the other hand, the signals for methyl groups centered at δ 1.43 in the ^{1}H-NMR spectrum and the fragment at *m/z* 164 (ion, *iii*) in the mass spectrum of lienkonine suggested that a methyl group may be located at C-8 or C-13.

The stereochemistry of 13-methylberberines, such as corydaline and mesocorydaline, having 2,3,9,10-oxygenated substituents, has been studied (*149*). A comparison of the spectral data of *O*-methyllienkonine with those of corydaline showed little resemblance. The IR and ^{1}H-NMR spectral data of the *O*-methyllienkonine, however, when compared with *O*-methylcorytenchirine (*150*), an 8-methylberbine derivative, showed close similarity. The C-8 methyl signal in *O*-methylcorytenchirine was at δ 1.40 (3H, d, J = 6.5 Hz) and in *O*-methyllienkonine at δ 1.43 (3H, d, J = 6.5 Hz). The IR spectrum of both compounds lacked Bohlmann bands in the 2800–2700-cm^{-1} region. The B/C ring junction in *O*-methyllienkonine was thus cis, and the steric relationship of hydrogens at the C-8 and C-13a positions in **23** were trans, as in *O*-methylcorytenchirine. Since *O*-methyllienkonine exhibited levorotation, both asymmetric

centers, C-8 and C-13a, in *O*-methyllienkonine (**23**) and lienkonine (**22**) were assigned an *S* configuration (*151*). A synthesis of (±)-lienkonine by Mannich condensation of 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline with acetaldehyde was reported (*152*).



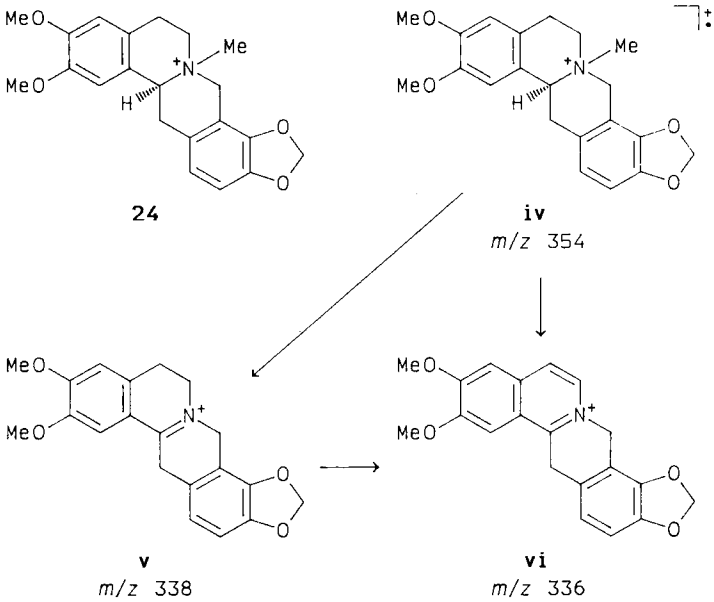
22 R = H
23 R = Me



iii

K. *N*-Methylsinactine

Mardirossian *et al.* (*31*) isolated the quarternary tetrahydroprotoberberine alkaloid *N*-methylsinactine [**24** hydroxide $C_{21}H_{24}NO_4^+$, M 354 (ion), base hydroxide mp 318–320° (EtOH–$CHCl_3$), $[\alpha]_D$ −260° (H_2O)] from *Fumaria officinalis* of Bulgarian origin. The mass fragmentation of *N*-methylsinactine was very informative (Scheme 2). The ions at *m/z* 190 and 148 suggested that *N*-

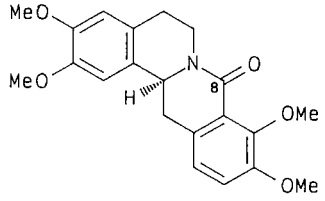


SCHEME 2. Mass fragmentation of *N*-methylsinactine (**24**).

methylsinactine had a protoberberine skeleton. The peaks at *m/z* 338 and 336 were due to the usual fragment ions. The ^{1}H-NMR spectrum of *N*-methylsinactine showed the presence of one *N*-methyl, two methoxy, and one methylenedioxy groups in the molecule. The structure **24** for N-methylsinactine was finally confirmed by its synthesis from sinactine.

L. (*S*)-(−)-8-Oxotetrahydropalmatine

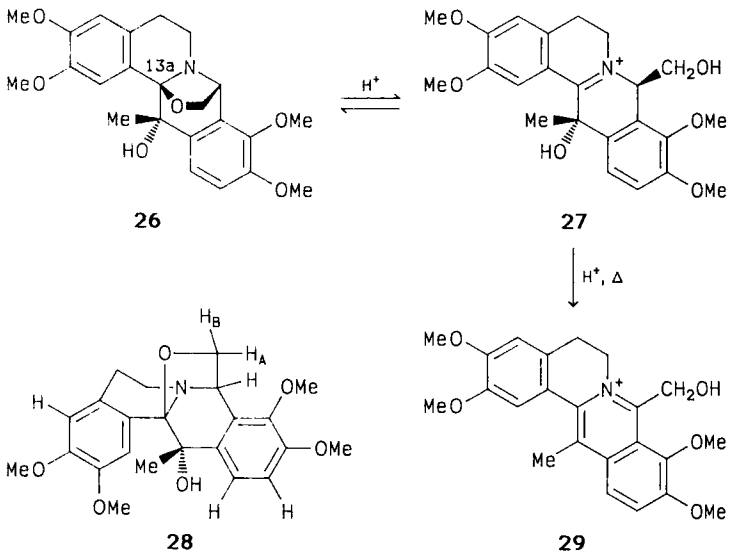
(*S*)-(−)-8-Oxotetrahydropalmatine (**25**, $C_{21}H_{23}NO_5$, M 369) was isolated from the stems and roots of *Anamirta cocculus* (*107*). The ^{1}H-NMR spectrum of the compound showed the presence of four methoxy groups and four aromatic protons in the molecule. There was an AB doublet for two aliphatic protons and a singlet for two aromatic protons. The ^{1}H-NMR spectral data in conjunction with IR and UV spectral data suggested that the compound had a protoberberine skeleton. The presence of a carbonyl function in the molecule was indicated by its IR spectrum and confirmed by ^{13}C-NMR spectral data. The position of a carbonyl function at C-8 in the molecule was concluded by analysis of ^{13}C-NMR spectral data of the compound. Finally, lithium aluminum hydride reduction of the compound yielded (*S*)-(−)-tetrahydropalmatine.



25

M. Solidaline

Solidaline [**26**, $C_{23}H_{27}NO_6$, M 413, mp 198°C ($CHCl_3$–MeOH)], an unusual base, was isolated from *C. solida* (L.) Swartz (*53*). Intense peaks at *m/z* 206, 207, and 191 due to fragmentation in the mass spectrum suggested that solidaline had a protoberberine skeleton. The presence of a nonphenolic hydroxyl, one tertiary *C*-methyl, and four methoxy groups and two tetrasubstituted aromatic rings in the molecule were shown by the ^{1}H-NMR spectrum of solidaline. The tentative structure **26** for the base was assigned by ^{1}H- and ^{13}C-NMR spectral data, including NOE and spin decoupling studies. Irradiation at δ 1.73 caused a 21–24% NOE enhancement of the signals for H-1 and H-12, suggesting the relative stereochemistry at C-13 and C-13a as shown in **28**, in which the β-methyl group was located close to both H-1 and H-12. Inspection of the model also suggested β-C-13 methyl rather than the α form (Scheme 3). A reversible

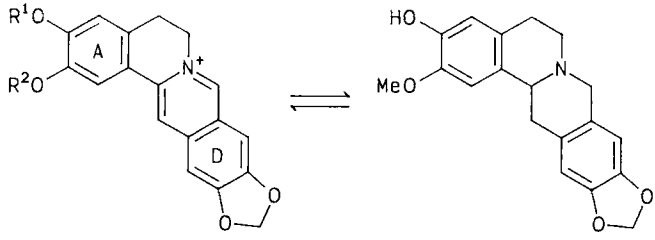


SCHEME 3. Solidaline and its chemical conversions.

immonium ion (**27**) and carbinolamine ether (**26**) equilibrium was observed in the UV spectrum of solidaline upon addition of acid at room temperature. On heating further in the presence of acid, an irreversible change occurred with the formation of the berberine-like product **29.**

N. THALIFAURINE

Thalifaurine [**30** chloride, $C_{19}H_{16}NO_4^+$, M 322 (ion), pale yellow needles, base chloride mp 258–260°C; $[\alpha]_D$ 0° (MeOH)] was isolated from *Thalictrum fauriei* Hayata (*139*). The UV spectrum of the base was characteristic of a quaternary protoberberinium salt. A bathochromic shift in the UV spectrum in alkali indicated the presence of a phenolic hydroxy group. The ^{1}H-NMR spectrum of thalifaurine showed signals for one methoxy and one methylenedioxy groups and six aromatic protons. A comparison of the chemical shift of the aromatic protons of pseudopalmatinium and pseudoepiberberinium salts with those of thalifaurine supported a 2,3,10,11-oxygenation pattern in the molecule. The chemical ionization mass spectrum of thalifaurine suggested the presence of a hydroxy and methoxy groups in ring A and a methylenedioxy group in ring D. Thus the 3-hydroxy-2-methoxy-10,11-methylenedioxyberberinium (**30**) and the 2-hydroxy-3-methoxy-10,11-methylenedioxyberberinium (**31**) structures were possible for thalifaurine. Direct comparison of an authentic sample of 2-hydroxy-3-methoxy-10,11-methylenedioxyberberinium chloride ruled out struc-



30 $R^1 = H$, $R^2 = Me$
31 $R^1 = Me$, $R^2 = H$

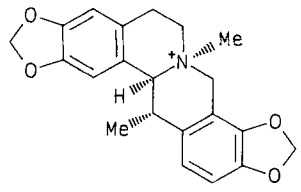
32

SCHEME 4.

ture **31** for thalifaurine. Sodium borohydride reduction of thalifaurine afforded 3-hydroxy-2-methoxy-10,11-methylenedioxytetrahydroberberine (**32**) (*153*) (Scheme 4). Again, oxidation of **32** with mercuric acetate yielded the protoberberinium salt identical in all respects to thalifaurine. A synthesis of thalifaurine (**30**) was reported (*153*).

O. α-TETRAHYDROCORYSAMINE METHIODIDE

Tetrahydrocorysamine [**33,** $C_{21}H_{22}NO_4$, M 352, base methiodide mp 285–293°C (MeOH)] was isolated as a methiodide from the quaternary alkaloidal fraction of *C. cava* (L.) Schw. et Koerte (*47*). The mass spectrum of the base had peaks at *m/z* 337 ($M^+ - MeI$), 176, 174, 162 (base peak), 142 (MeI), 127 (I). Treatment of (±)-tetrahydrocorysamine with methyl iodide afforded the corresponding methiodide.



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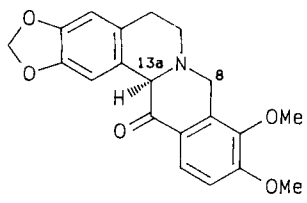

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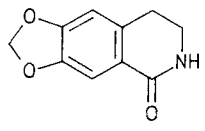

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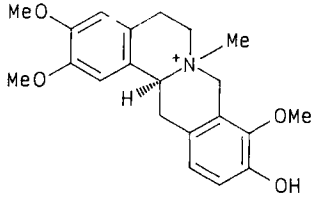


36

P. Ophiocarpinone

(+)-Ophiocarpinone [**34,** $C_{20}H_{19}NO_5$, M 353, mp 217–218°C (MeOH), $[\alpha]_D$ +265° ($CHCl_3$)] was isolated from *Cocculus pendulus* (Forsk) Diels (*135*). The UV spectrum suggested that the base had a protoberberine skeleton. The IR spectrum of ophiocarpinone showed the presence of a carbonyl function (1662 cm^{-1}). The ^{1}H-NMR spectrum of ophiocarpinone was very similar to that of canadine except that H-1 and H-12 were very much deshielded (δ 2.03 and 3.31, respectively) in ophiocarpinone, and the C-8 methylene protons appeared as two multiplets centered at δ 5.63 and 6.52, respectively. The H-13a signal was also much deshielded (δ 5.11), and there was no signal for the C-13 methylene protons in the spectrum. Ophiocarpinone, when oxidized with alkaline potassium permanganate, yielded neooxyhydrastine (**35**), suggesting thus the presence of a carbonyl function at C-13 in the molecule. Further lanthanide shift reagents caused deshielding of H-12 and H-13a. The mass spectrum of ophiocarpinone did not show the characteristic fragment ions of tetrahydroprotoberberines. Oxidation of (−)-(13*R*,13a*R*)-ophiocarpine afforded a compound identical in all respects (including optical rotation) with natural ophiocarpinone. The base was assigned the *R* configuration. A synthesis of ophiocarpinone from berberine is reported (*135*).

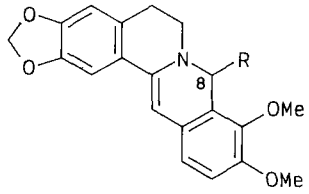
Q. (*S*)-*N*-Methylcorydalmine

(*S*)-*N*-Methylcorydalmine [**36,** $C_{21}H_{26}NO_4^+$, M 356 (ion), base chloride mp 190°C] was isolated from *Stephania elegans* as a chloride (*113*). The UV spectrum of the base suggested the compound to be a protoberberine alkaloid containing one phenolic hydroxy group. The ^{1}H-NMR spectrum evidenced the presence of one *N*-methyl and three aromatic methoxy groups. The mass fragmentation pattern also supported structure **36** for the base. Final confirmation of structure **36** was obtained by the comparison of physical and spectroscopic data of the base chloride with an authentic sample of *N*-methylcorydalmine chloride prepared from corydalmine.

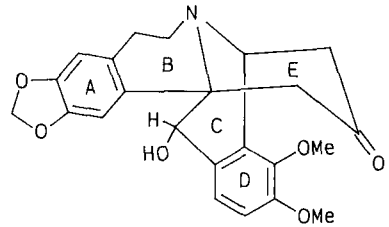
V. Chemical Reactions

A. Berberine Oxime

The structure of berberine oxime prepared by Gadamer was established as the cyclic N-substituted hydroxylamine **37.** A Schiff base obtained from berberinol and 4-(dimethylamino)aniline was shown to be a cyclic aminal (**38**) (*154*). This was confirmed by preparation of various derivatives and spectroscopically there was no indication of the existence of an aldehydic form of berberine.



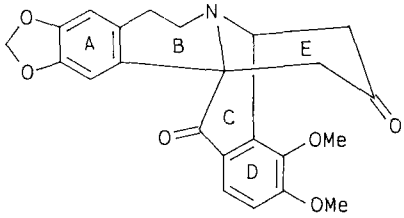
37 R = NHOH
38 R = *p*-$Me_2NC_6H_4NH$
39 R = CH_2COCH_3



40

B. Neooxyberberineacetone

Berberine sulfate in refluxing aqueous acetone when treated with aqueous sodium hydroxide formed berberineacetone (**39**) (*155*). Oxidation of **39** with aqueous potassium permanganate in acetone afforded neooxyberberineacetone, which was formulated as **40** by chemical, spectroscopic, and X-ray crystallographic studies, as having the hydroxy group and the 2′-oxopropano bridge cis to each other (*156*). Chromic acid oxidation of **40** gave diketone **41.**



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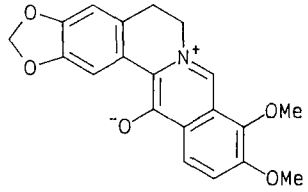

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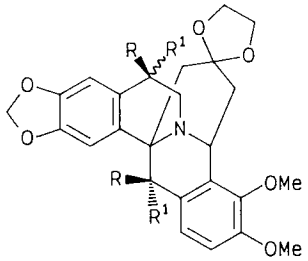
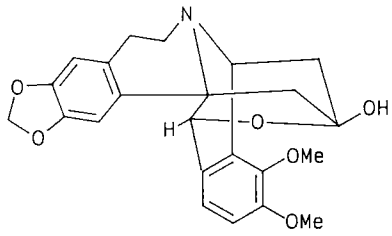
The ^{1}H-NMR spectrum of **41** showed selective and marked deshielding of H-12, demonstrating that rings B and C must be cis-fused, thus giving a trans geometry for the fusion of rings B and E containing the 2′-oxopropano bridge. Reduction of neooxyberberineacetone, followed by acid treatment, yielded berberinephenol betaine (**42**).

The ethylene ketal of **40** on oxidation gave a product formulated as **43.** In its ^{1}H-NMR spectrum H-4 was highly deshielded. The H-8 methine proton underwent the maximum downfield shift to δ 6.55. The mass spectrum of the compound had peaks *m/z* 479 in addition to the ion at *m/z* 451. The sodium borohydride reduction product of **43** was reformulated as **44.** The IR spectrum of **43** had strong absorption at 1640 cm^{-1}. The molecular ion in its mass spectrum was at *m/z* 483.

The 90-MHz spectrum of neooxyberberineacetone showed that it was a mixture of **40** and the hemiketal **45** in solution in a ratio of 7:3. In **45** H-13 appeared



43 $R - R^1 = O$
44 $R = H;\ R^1 = OH$

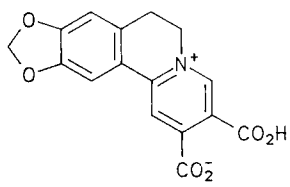


45

as a singlet at δ 5.03. The most pertinent observation in the spectrum was a singlet at δ 5.03 integrating for 0.3 proton. In **40** H-1 and H-12 were deshielded by 0.25 ppm as compared to the positions of these protons in **45.** Models of the two possible structures showed that the hydroxy group at C-13 in **40** could exert the deshielding effect on H-1 and H-12. However, the deshielding effect will not be operative in the formation of a cyclic hemiketal. The ^{1}H-NMR spectrum of neooxyberberineacetone in $CDCl_3$ and DMSO-d_6 had signals for both structures **40** and **45.** The 360-MHz spectrum of the tetrahydro derivative and the deuterated product also showed the presence of two species. The solid-state X-ray crystallographic studies indicated a weak intermolecular O—H---OC bonding. Since the compound was sharp melting, it was concluded that the equilibrium between **40** and **45** was set up in solution. The mass spectrum also supported the presence of two species.

C. Berberidic Acid

Resplandy (*157*) was the first to prepare berberidic acid (**46**) by oxidation of berberine with hot nitric acid. The structure **46** for the acid was confirmed by Chinnasamy and Shamma (*158*).



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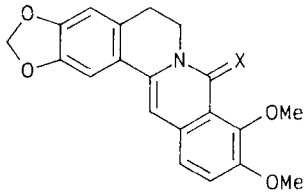
D. 8-Chloroberbines

8-Chloroberbines are very useful intermediates for the preparation of 8-substituted berberine and canadine derivatives. When oxyberberine (**47**) was

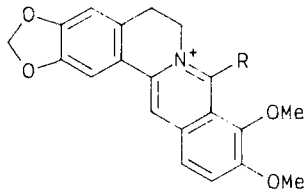
refluxed with phosphorus oxychloride, 8-chloroberberine (**54**) was formed (*159*). Previously the product was considered to be the 8-dichloro derivative **51** (*160*), but the high-resolution mass spectrum of **54** showed the molecular ion at *m/z* 370 for $C_{20}H_{17}ClNO_4$, and the only difference between the ^{1}H-NMR spectra of berberine (**53**) and 8-chloroberberine (**54**) was the absence of H-8 at δ 10.1 in **54.**

Because of the high reactivity of 8-chloroberberine (**54**) toward oxygen nucleophiles, several reactions had been carried out with primary amines, carbanions, and the Grignard reagent. Treatment of **54** with anhydrous ammonia gave 8-berberinylideneimine (**48**), which on acetylation afforded **57.** Compound **57** underwent hydrolysis with sodium bicarbonate to regenerate **48.** Treatment of **54** with primary amines such as methylamine, *n*-propylamine, aniline, and *p*-toluidine led to the formation of corresponding 8-berberinylideneimine derivatives (**49**). Methylation of **48** with methyl iodide produced **49,** R = Me, identical with the compound obtained by treatment of **54** with methylamine. The imine base **49** underwent hydrolysis with sodium hydroxide to 8-oxoberberine (**47**), while reduction with sodium borohydride yielded canadine.

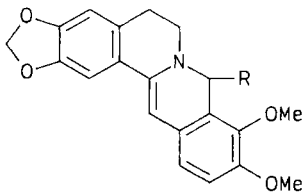
8-Chloroberberine reacted with carbanions such as malononitrile, ethyl acetoacetate, and diethyl malonate anions to yield the corresponding 8-



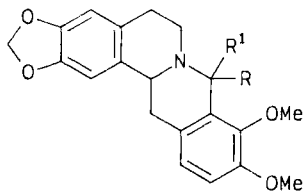
47 X = O
48 X = NH
49 X = NR
50 X = CR_2
51 X = Cl_2
52 X = R_2



53 R = H
54 R = Cl
55 R = CH_2CO_2H



56 R = CH-C_6H_5
57 R = N-COMe



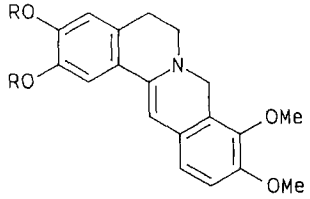
58 R = H, R^1 = H
59 R = $CH_2C_6H_5$, R^1 = H
60 R = Et, R^1 = Et
61 R = CH_2CO_2H, R^1 = H

SCHEME 5. Reaction products of 8-chloroberberine (**55**).

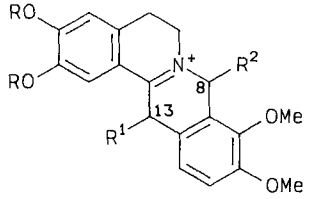
berberinylidene derivatives (**50**). Acid hydrolysis of **50,** R = CO_2Et, followed by decarboxylation, afforded the orange 8-berberinylacetic acid (**55**). Sodium borohydride reduction of **55** furnished 8-canadinylacetic acid (**61**). 8-Chloroberberine also reacted with Grignard reagents such as methyl magnesium iodide and ethyl magnesium iodide to produce the corresponding 8,8-dialkyldihydroberberine (**52**). Reduction of **52,** R = Et, with sodium borohydride afforded 8,8-diethylcanadine (**60**). Monoalkylation of **54** with benzyl magnesium bromide furnished **56,** which in turn was converted to 8-benzylcanadine (**59**) by treatment with sodium borohydride (Scheme 5).

E. Dehydroberbines

Reduction of palmatine and berberine with sodium borohydride gave dehydro derivatives **62** and **63,** respectively (*161*). Owing to the enamine character of dehydroberbines, many C-8 and C-13 derivatives were prepared from **62** and **63,** including 8,13-dehydroberberinium salts (**64–66**), the berbines 13-methyltetrahydropalmatine (**67**), 13-methylcanadine (**68**), and 8-benzylcanadine, and the diester **69** in which ring C of protoberberine had expanded to an eight-membered ring.



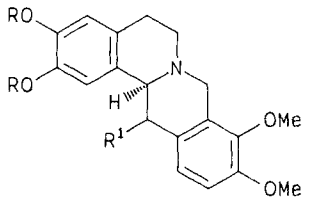
62 R = Me
63 R – R = CH_2



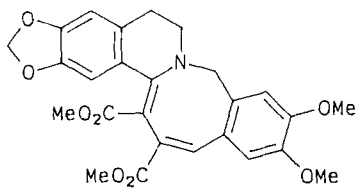
64 R^1 = $PhCH_2$, R^2 = H
65 R^1 = R^2 = $PhCH_2$
66 R^1 = $PhCOCH_2$, R^2 = H

F. Oxybisberbines

Dimers of berberinium and protoberberinium derivatives have been prepared by oxidation of berberine. Oxybisberberine was likewise prepared by the po-



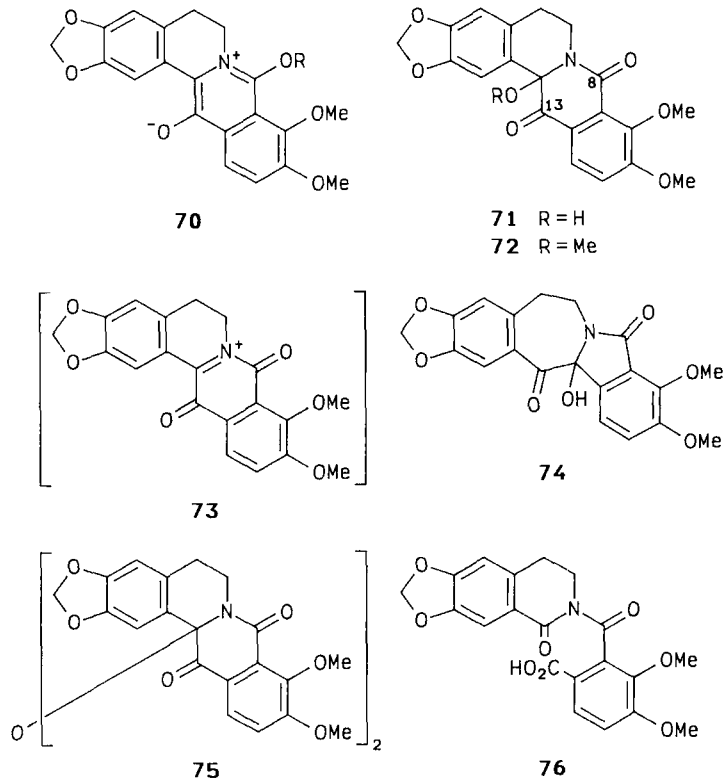
67 R = R^1 = Me
68 R – R = CH_2, R^1 = Me



69

tassium ferricyanide oxidation of berberine (*162*). The exact structure of oxybisberberine is still unknown but much is known about its chemistry (*162–165*).

Oxybisberbine when treated with methanolic/ethanolic hydrogen chloride gave 8-methoxy/ethoxy, berberine phenolbetaine (**70**), and berberine (*164*). Treatment of the compound with pyridine hydrochloride in pyridine cleaved the dimer. The nucleophile present in the reaction mixture, workup procedure, and the pH of the reaction medium dictated the nature of the product formed. The dimer, only with pyridine hydrochloride in pyridine (nonnucleophilic medium) yielded berberine and a red solution, which on treatment with aqueous acid gave 8,13-dioxo-13a-hydroxycanadine (**71**). Compound **71** on further treatment with anhydrous methanolic hydrogen chloride formed a transient deep violet iminium salt (**73**), which gave 8,13-dioxo-13a-methoxycanadine (**72**) by solvation with methanol present (Scheme 6). Thus compounds **71** and **72** underwent rapid interconversion in acidic medium. If the salt **73** was allowed to stand with concentrated hydrochloric acid, dimer **75** was formed. 8,13-Dioxo-13a-hydroxycanadine (**71**) was generated from either **72** or **75** by treatment with

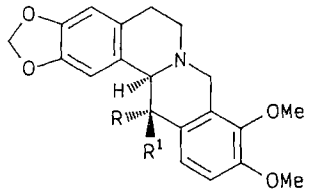


SCHEME 6. Reaction products of oxybisberberine (**75**).

concentrated hydrochloric acid and water. In a buffer system, **74** was obtained. Compound **74** was also prepared from **71** by treatment with ammonium hydroxide (*163, 164*), while with strong alkali oxidative rupture of the C-13—C-13a bond in **71** occurred, which led to the formation of Perkin's anhydroberberidic acid (**76**) and its hydrolyzed product noroxyhydrastine.

β-Norhydrastine on reduction with diisobutylaluminum hydride gave racemic, unnatural epiophiocarpine (**77**). Reduction of **70** with sodium borohydride yielded natural ophiocarpine (**78**) (*162*).

13-Hydroxyoxoberberine was obtained as a major product when oxybisberberine was cleaved with dry hydrogen chloride in pyridine and methanol. Sodium borohydride reduction of **72,** followed by loss of methanol, also generated 13-hydroxyoxoberberine (*163*).

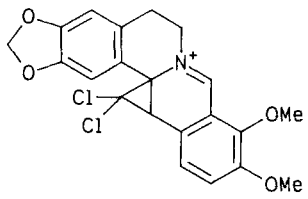


77 R = OH, R^1 = H
78 R = H, R^1 = OH

G. Reaction with Dichlorocarbenes

Many unusual derivatives, including 13-formyloxyberberine, were prepared by the reaction of dichlorocarbene with oxyberberine and berberine (*166*). Addition of dichlorocarbene to oxyberberine formed dichloro adduct **79.** Refluxing **79** with dilute hydrochloric acid in methanol furnished the hitherto unknown oxyberberine-13-carboxaldehyde (**80**) via the intermediacy of **81.** Compound **79,** when heated with hot concd hydrochloric acid, yielded two products. The major product was **83,** while the minor product was oxyberberine-13-carboxaldehyde (**80a**). Compound **80a** was also prepared by the hydrolysis of **83** with dil hydrochloric acid. Reduction of **79** with zinc and hot acetic acid afforded 13-methyloxyberberine (**82**), while with lithium aluminum hydride in hot tetrahydrofuran ring C expansion occurred and *C*-homoberberine (**84**) was formed (Scheme 7). Interestingly, **79** with hot aqueous pyridine generated the keto lactam **85.** The structure of **85** was confirmed by its oxidation to the known imide **86.**

Dichlorocarbene adds to berberine, giving the pentachloro derivative **87,** which when refluxed with hydrochloric acid in methanol formed the aldehyde **88** with the trichloromethyl moiety at C-8. Reduction of **88** with sodium borohydride afforded the alcohol **89,** while oxidation furnished the dichloro derivative **90** without affecting the aldehyde group.



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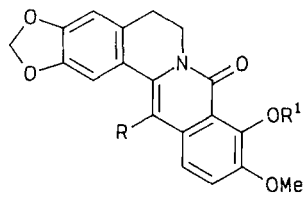
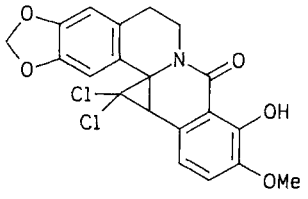
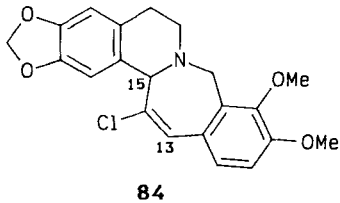


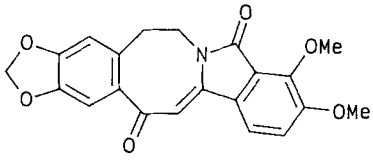
80 R = CHO, R^1 = Me
80a R = CHO, R^1 = H
81 R = $CHCl_2$, R^1 = Me
82 R = Me, R^1 = Me



83



84



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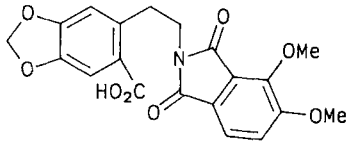

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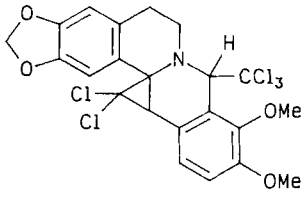
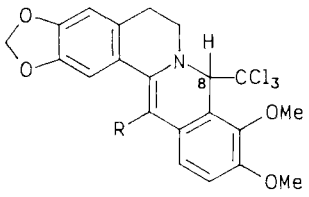
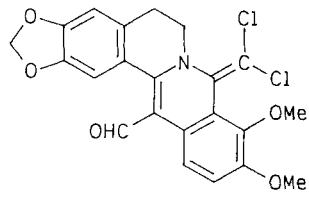


87

SCHEME 7. Reaction products of oxyberberine and berberine.



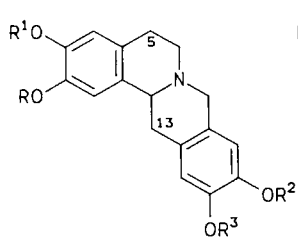
88 R = CHO
89 R = CH_2OH

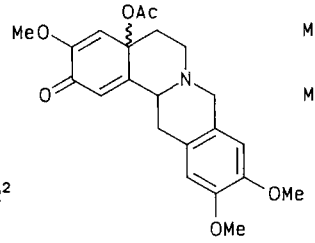


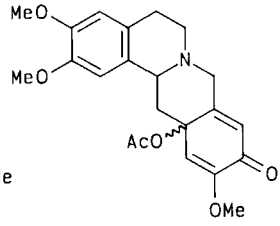
90

H. Lead Tetraacetate Oxidation of Berbines

Lead tetraacetate oxidation of racemic govanine (**91**), 10-hydroxy-2,3,11-trimethoxytetrahydroprotoberbine (**92**), discretine (**93**), and corytencine (**94**) afforded corresponding berbines substituted at C-5 or C-13 with acetoxy groups via the intermediacy of quinol acetate **95** or **96** (*167*) and is being reviewed by Umezawa elsewhere in *The Alkaloids* (Scheme 8).







91 R = H, $R^1 = R^2 = R^3 = Me$
92 R^2 = H, $R = R^1 = R^3 = Me$
93 R^1 = H, $R = R^2 = R^3 = Me$
94 R^3 = H, $R = R^1 = R^2 = Me$

95 **96**

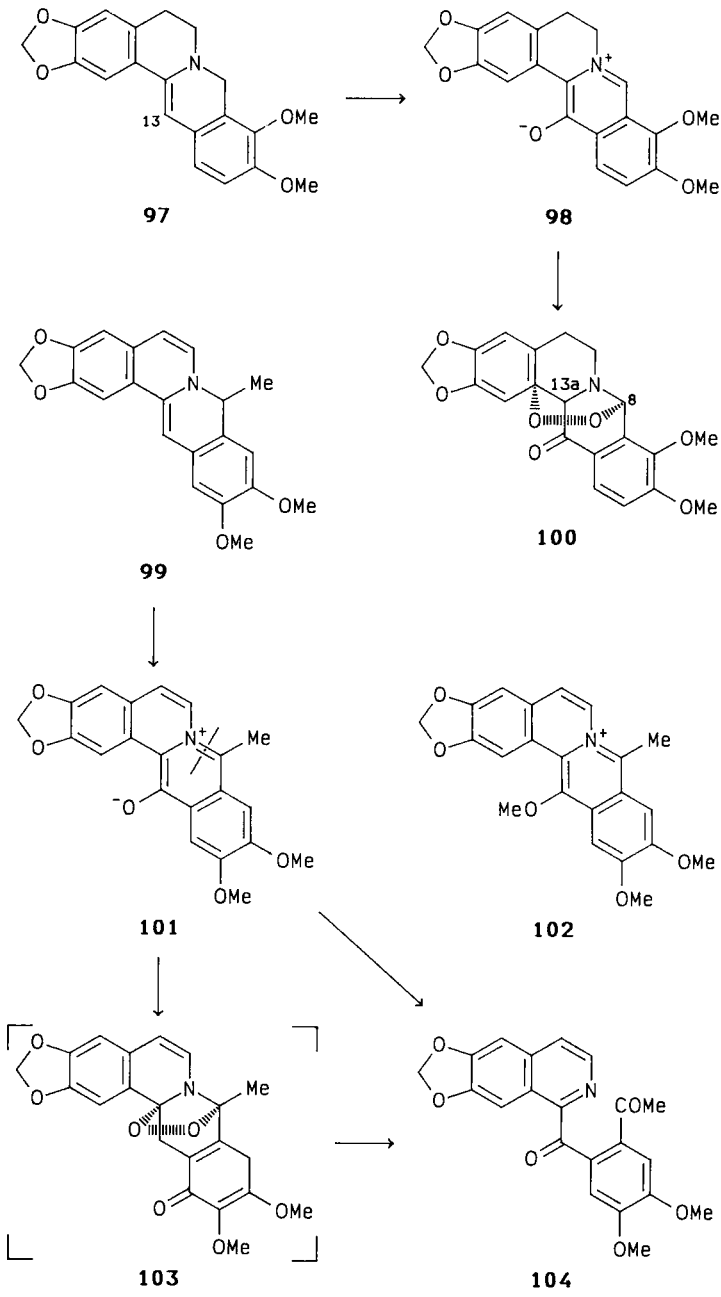
SCHEME 8. Lead tetraacetate oxidation products of berbines.

I. Regiospecific Photooxygenation

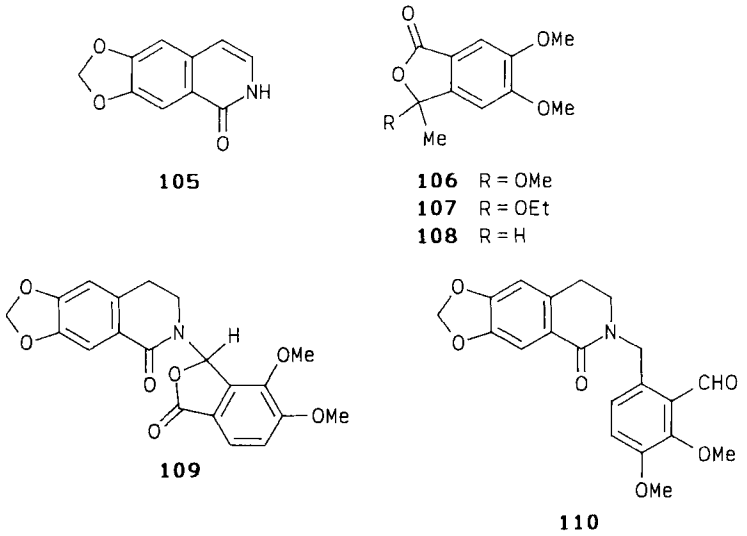
Kondo *et al.* (*168–170*) have introduced an oxygen function at C-13 in protoberberines by photooxygenation. Irradiation of a solution of dehydroberbine (**97**) in methanol in the presence of rose bengal under oxygen afforded a mixture of 13-oxidoberberine (**98**) and berberine. The use of a sensitizer increased the proportion of **98.** On the other hand, 7,8-dehydrocoralyne (**99**) underwent autooxidation in hot ethanol to 13-oxidocoralyne (**101**) in almost quantitative yield. A solution of **98** in the presence of rose bengal when irradiated gave the dibenzo[*a*,*g*]quinolizidine (**100**) in 90% yield. In contrast, **101** yielded 2′-acetylpapaveraldine (**104**) instead of the expected epidioxide, although the intermediacy of **103** was suggested (Scheme 9).

Irradiation of the hot alcoholic solution of either **99** or **101,** containing sodium methoxide under oxygen, gave 6,7-dimethoxyisoquinolone (**105**) and 3,5,6-trimethoxy3-methylisobenzofuran-1-[3*H*]one (**106**). A reaction mechanism that involved the initial formation of an epidioxy intermediate was evidenced and was supported by the observation that the photolysis of **101** when carried out in the presence of borohydride gave **105** and **108.** Also, the irradiation of **101** in caustic alkali yielded only **105.**

A one-pot synthesis of 13-hydroxytetrahydroprotoberberine from dehydroberberine was achieved (*169*). Thus reduction of **98** with sodium borohydride afforded a mixture of (±)-epiophiocarpine and (±)-ophiocarpine, the ratio depend-



SCHEME 9. Regiospecific photooxidation of protoberberine alkaloids.

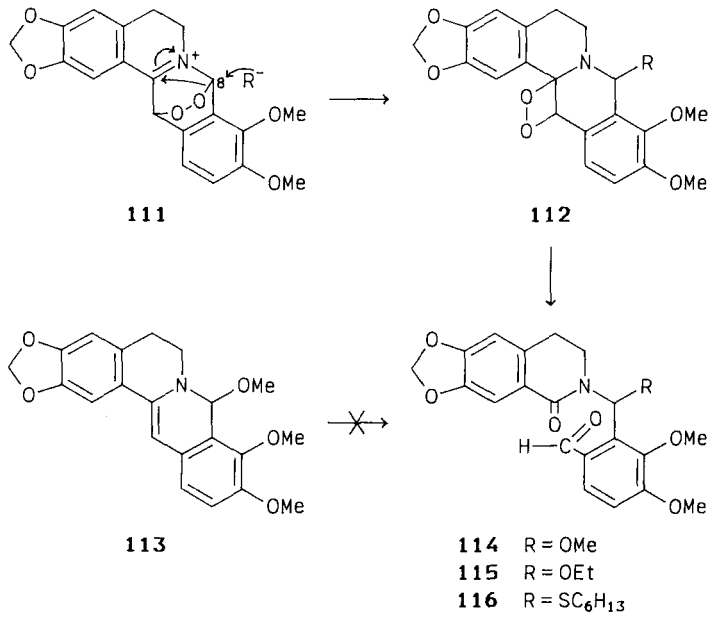


SCHEME 10. Photooxidation products of protoberberine alkaloids.

ing on the type of alcohol used. Similarly, irradiation of **100** led to the formation of berberal **109** and the isoquinolin-1[2*H*]-one **110** in 72 and 4% yields, respectively (Scheme 10). This transformation took place even in the solid state at room temperature, by heating, or by the use of ferrous ions. Naturally occurring isoquinolones are believed to be formed in nature from enzymatic oxidation of benzylisoquinoline and berbine alkaloids (*171*). However, the exact mechanism is still unknown.

J. PHOTOOXIDATION

Nonsensitized photochemical oxidation of berberine, catalyzed by basic reagents and in alcoholic solution with and without quenchers of singlet oxygen, were studied by Contreras *et al.* (*172*). Irradiation of a methanolic solution of berberine with a four-molar excess of the basic reagents formed the lactam aldehyde **114** instead of the phenol betaine. Compound **115** was obtained when ethanolic solution was used. Compound **116** was formed together with di-*n*-hexyl sulfide in the presence of sodium *n*-hexylmercaptide. That the reaction did not proceed via the intermediacy of dihydroberberine derivative **113,** as suggested earlier (*173*), was shown by direct irradiation of **113** separately when no lactam aldehyde was formed. Use of different nucleophiles did not alter the structure of compound **114,** thus establishing that no direct reaction of nucleophile and berberine took place. It was proposed that initially a berberine–oxygen complex was formed. Nucleophilic attack at C-8 in the intermediate **111,**

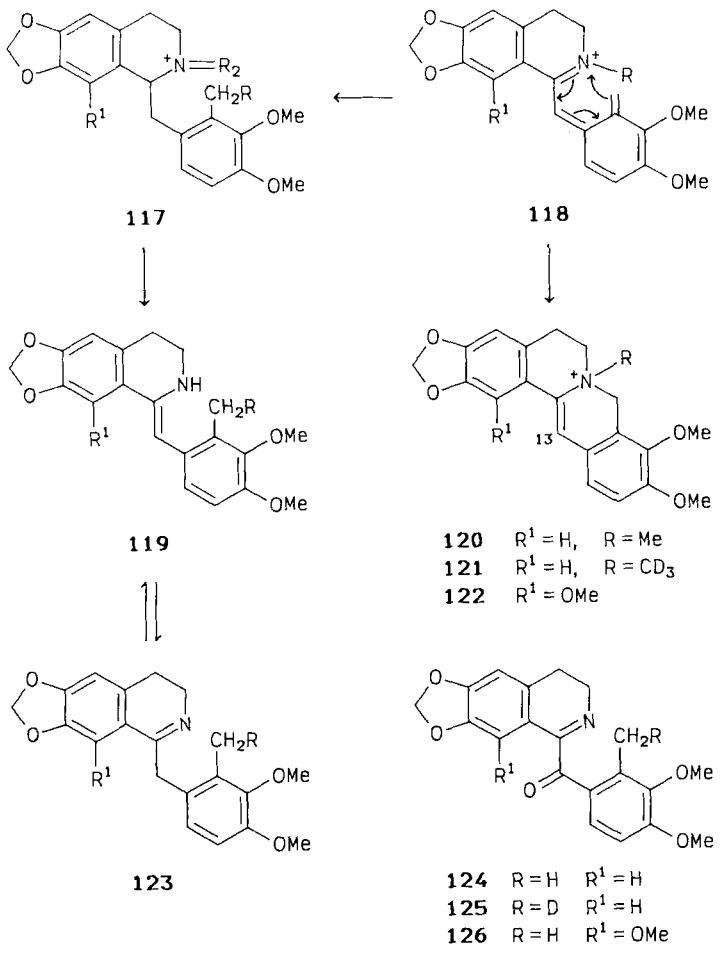


SCHEME 11. Photooxidation of berberine.

followed by an internal rearrangement, furnished the dioxoketene **112,** which in turn yielded **114** (Scheme 11). Thus the participation of both dihydroberberine and singlet oxygen as reactive species in these reactions was completely excluded.

N-Methyldihydroberberine salts (**120, 122**) unsubstituted at C-13, when exposed to sunlight, produced the corresponding benzylisoquinoline imino ketones **124** and **126** (Scheme 12).

On the other hand, C-13-methylated derivatives **130–132** produced the corresponding spirobenzylisoquinolines (**133**) (*174*). Thus the 13-methylated dihydroisoquinoline salts could also be transformed to the spirobenzylisoquinolines contrary to the previously reported transformation of salts having at least one phenolic group (*175, 176*). The transformation probably took place through the intermediacy of the *O*-quinodimethide **118** as shown in Scheme 12. Later, Kessar *et al.* (*177*) proposed an alternative pathway for this transformation. The deuterium-labeled salt substrate **121** was prepared. Product **125** obtained from **121** had reduced intensity of the methyl signal in its ^{1}H-NMR spectrum, thus ruling out the possibility of the first route as the major reaction pathway. If irradiation of **124** was followed by sodium borohydride reduction, **129** was obtained with the transposed ring D substituents (*178*) (Scheme 13). This reaction thus afforded a sequence for transposition of ring D substituents in protoberberinium alkaloids.



SCHEME 12. Photooxidation products of berberine.

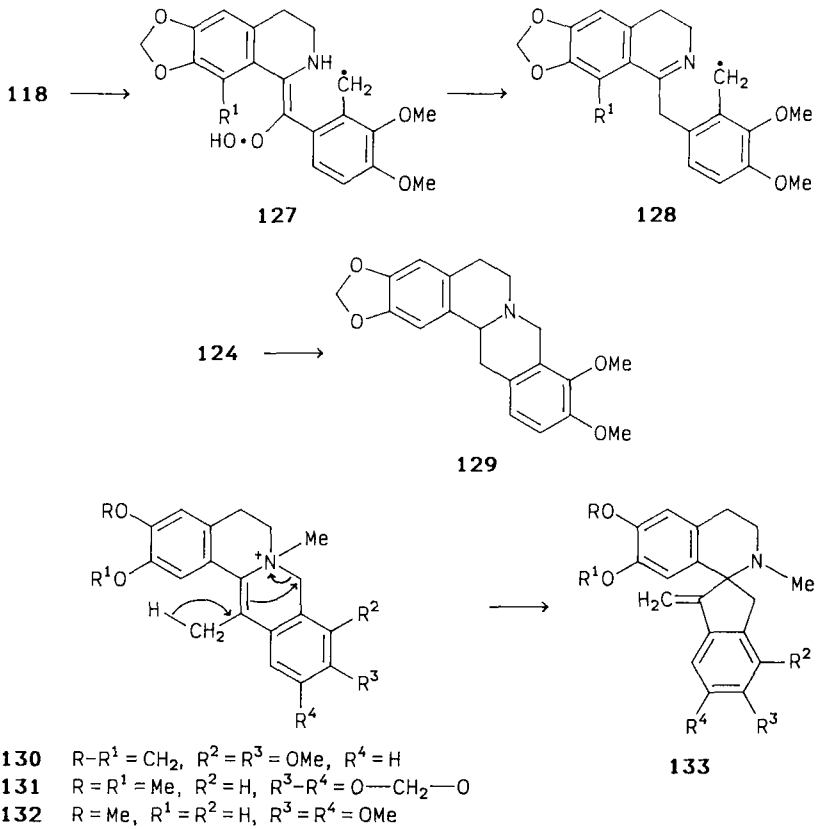
K. REDUCTION–OXIDATION OF BERBERINE *N*-OXIDES

Oxidation of berbines with *m*-chloroperbenzoic acid affords the corresponding *N*-oxides (*179*). Both *cis*-**135** and *trans*-**134** N-oxides were obtained by oxidation of canadine, xylopinine, nandinine, and thalictricavine, whereas only *cis*-*N*-oxide was formed with mesothalictricavine (Scheme 14).

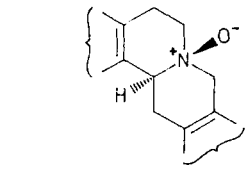
Reduction–oxidation of *trans*-canadine *N*-oxide in aerated liquid ammonia afforded nitrone **136** in 70% yield with the amine **137** as a minor product (5%). The imide **137** was obtained by reaction of **136** with acetic anhydride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine. The pho-

tolysis of **136** afforded three products, **140, 142,** and **143.** Compounds **140** and **143** were also obtained by the direct photolysis of *trans*-canadine *N*-oxide (*180*). The *cis*-canadine *N*-oxide when subjected to reduction–oxidation under similar conditions gave the nitrone **136** and the amine **137** in trace amounts, and the *trans*- and *cis*-xylopinine *N*-oxides gave only the corresponding amine **138** (Scheme 14). The reason for the formation of lactam **138** was explained with the intermediacy of **145,** which is resonance stabilized in strong acid by a quinone methide system shown in **147.** The analogous resonating form, present in canadine, would be the less favored *o*-quinone methide **146** (Scheme 15).

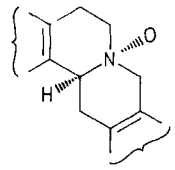
The *trans*-xylopinine *N*-oxide on direct photolysis generated **138** and **144** via the intermediate oxaziridine **148.** No characterizable product was obtained by irradiation of *cis*-xylopinine *N*-oxide. *Trans*-Nandinine *N*-oxide gave 2% of nitrone and 10% of the amine, but the *cis*-*N*-oxide afforded the nitrone only in 2%



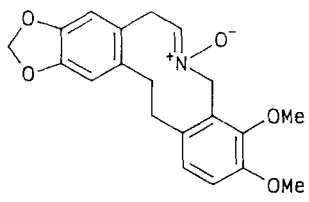
SCHEME 13. Transformation of the protoberberine skeleton to a spirobenzylisoquinoline system.



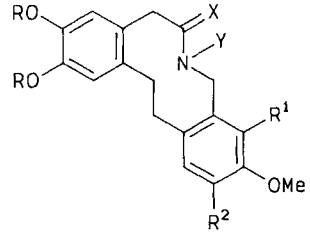
134
trans-N-Oxide

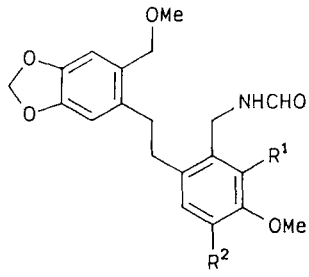


135
cis-N-Oxide



136





142

137 R-R = CH_2, R^1 = OMe, R^2 = Y = H, X = 2H

138 R = Me, R^1 = Y = H, R^2 = OMe, X = 2H

139 R-R = CH_2, R^1 = OMe, R^2 = H, X = O, Y = Ac

140 R-R = CH_2, R^1 = OMe, R^2 = Y = H, X = O

141 R = Me, R^1 = Y = H, R^2 = OMe, X = O

SCHEME 14. Reduction–oxidation products of berberine *N*-oxides.

yield. The yield of nitrone was curtailed by the presence of the C-13 methyl group in the *N*-oxide. For example, *trans*-thalictricavine *N*-oxide gave only 1% of nitrone. Hydroxylamine **149** was formed together with the nitrone by reduction–oxidation of *cis*-mesothalictricavine *N*-oxide (*180*).

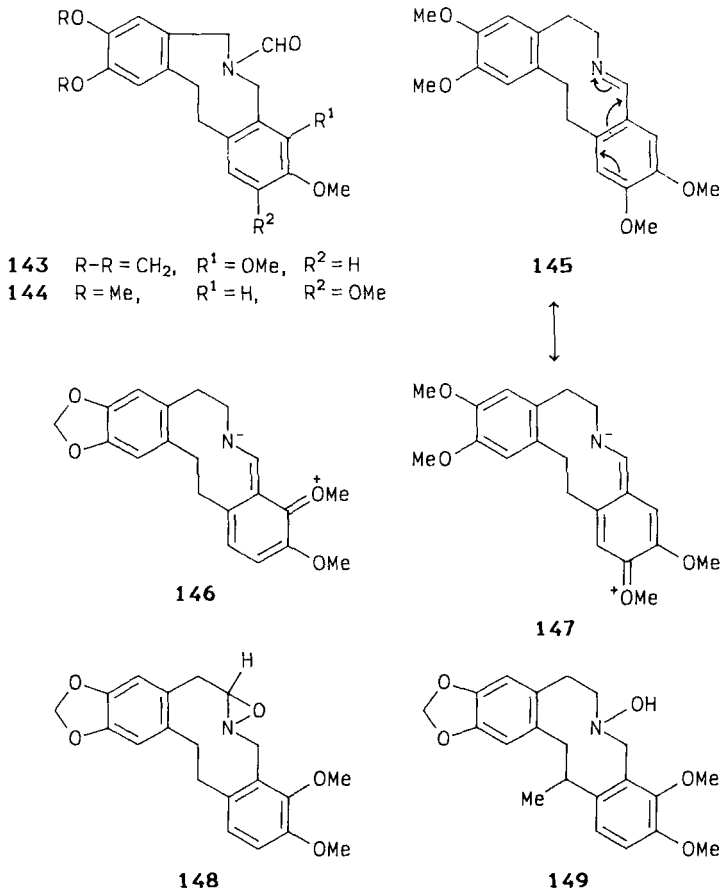
L. CLEAVAGE OF THE C-8—N BOND

Treatment of berbines **150** with an excess of ethyl chloroformate cleaved the C—N bond to give a mixture of compounds **151** and **152** generated through C-8—N and C-6—N bond cleavages, respectively (*181–184*). An electron-donating group in ring D must be present for the cleavage. The substituent present at C-1 or C-13 also affected the reaction as it changed the B/C ring

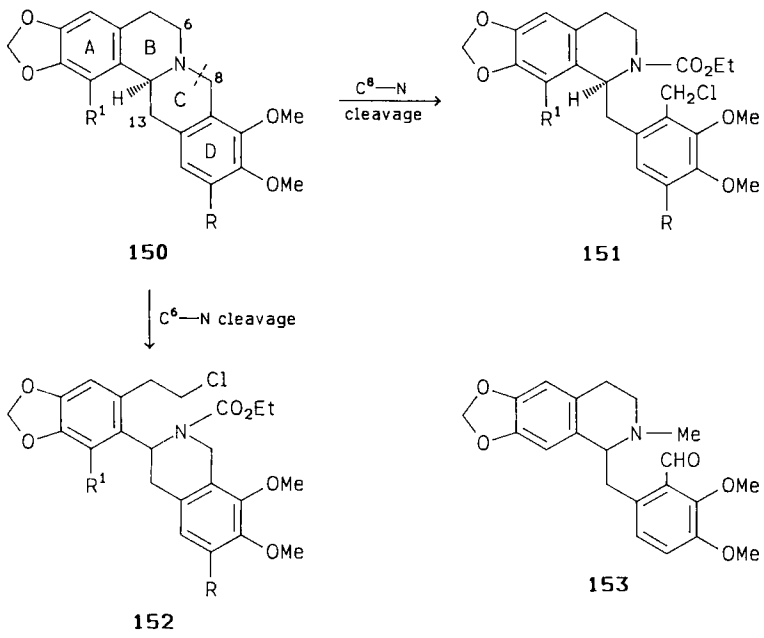
conformation. A secoberbine alkaloid, (±)-canadaline (**153**), was synthesized via regioselective C-8—N bond cleavage of canadine, using ethyl chloroformate (*64*, *185*) (Scheme 16).

Treatment of canadine with ethyl chloroformate yielded the urethane **154** (*183*), which when refluxed with aqueous ethanolic potassium hydroxide, formed the amino alcohol **155** and the retroprotoberberine **156** by a Mannich reaction (*185*, *186*) (Scheme 17). Oxidation of palmatine (**157**) with *m*-chloroperbenzoic acid gave polycarpine (**159**) (*187*). Compound **160** was obtained from coptisine chloride (*158*).

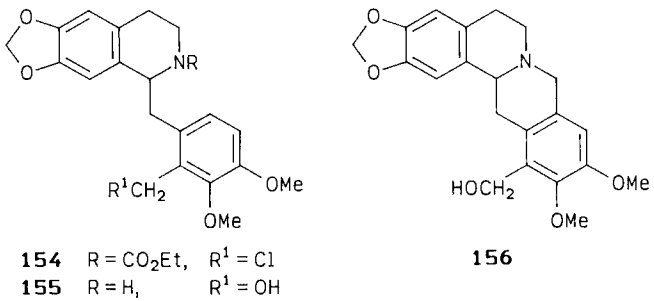
The racemic modification and each enantiomer of coreximine diacetate were cleaved with ethyl chloroformate and then converted to the racemic 6′-



SCHEME 15. Reduction–oxidation products of berberine *N*-oxides.

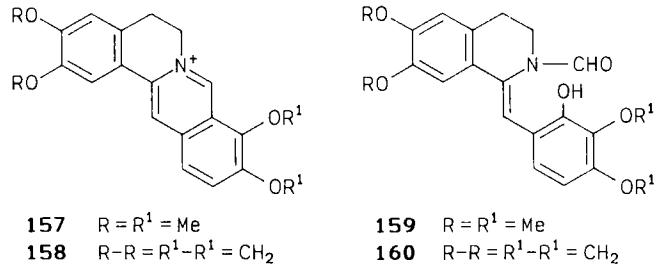


SCHEME 16. C-6—N and C-8—N cleavage products of berbines.



154 R = CO_2Et, R^1 = Cl
155 R = H, R^1 = OH

156

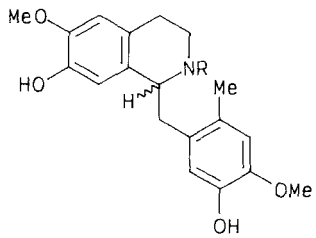


157 $R = R^1$ = Me
158 $R-R = R^1-R^1 = CH_2$

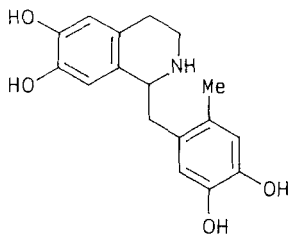
159 $R = R^1$ = Me
160 $R-R = R^1-R^1 = CH_2$

SCHEME 17. Ethyl chloroformate degradation products of berberine.

methylreticuline (**160a**) and the racemate and both enantiomers of 6′-methylnorreticuline (**160b**). It is interesting to note that **160b** corresponding in absolute configuration to (*R*)-(+)-norreticuline showed a negative specific rotation, which may indicate a substantially different solution conformation of (*R*)-(−)-**160b** relative to (*R*)-(+)-*N*-norreticuline. O-Demethylation of **160b** finally afforded **160c** (*188*).



160a R = Me
160b R = H
S = H
R = H



160c

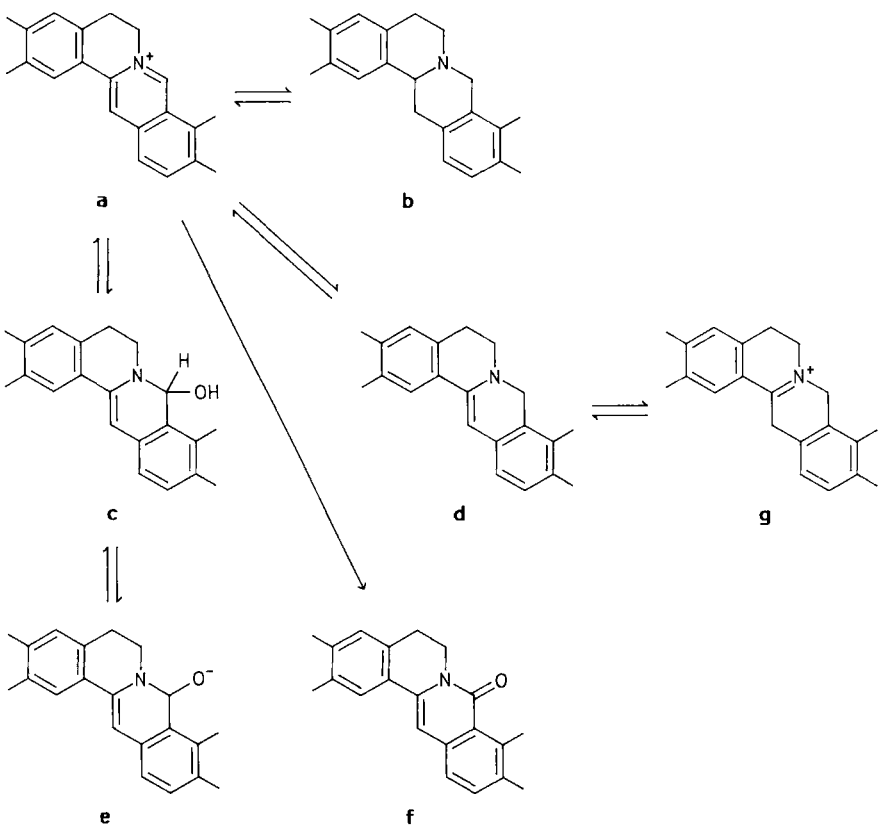
M. Oxidation and Reduction

The dihydroprotoberberines **d** and tetrahydroprotoberberines **b** could be oxidized to the corresponding quaternary protoberberines **a** with iodine, mercuric acetate, or simply by standing in air (*294*) (Scheme 17a). The quaternary protoberberines **a** could be reduced to the parent tetrahydroprotoberberines **b** with a variety of reducing agents such as mixed metal hydride, zinc/hydrochloric acid, and catalytic reduction in the presence of platinum. If, however, the reduction is carried out with a mixed hydride in a dry aprotic solvent, the reaction stops at the dihydroprotoberberine (**d**) stage. Quaternary protoberberine salts **a** are unstable in the presence of concentrated alkali. They form oxo derivative **f** and dihydro derivative **d** by hydrogen transfer. Oxo derivatives (**f**) are exclusively formed from the quaternary protoberberine salts **a** by oxidation with potassium ferricyanide (Scheme 17a).

The dihydroprotoberberine derivative **d** remains in equlibrium with its immonium form **g** in a protic medium. The immonium form **g** is unstable and undergoes rapid disproportionation to a mixture of the quaternary protoberberine salt **a** and tetrahydroprotoberberine **b** (*294*).

N. Chemical Transformation of Protoberberines

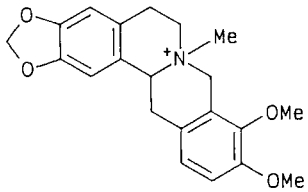
The conversion of protoberberine alkaloids to a variety of other isoquinoline alkaloids, including phthalidisoquinolines, benzophenanthridines, spirobenzylisoquinolines, and rhoeadines, had been accomplished (*184, 189, 190*) and are discussed separately in a forthcoming chapter.



SCHEME 17A. Oxidation and reduction of protoberberines.

1. Allocryptopine

A biomimetic one-step synthesis of allocryptopine (**162**) from the tetrahydroberberine methiodide **161** by photooxygenation was achieved (*191*). Though the yield was rather low, the synthesis, however, provided a simpler and more convenient route for the preparation of protopine alkaloids.



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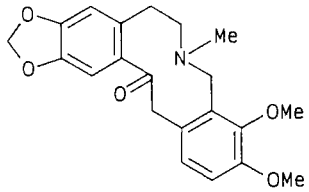
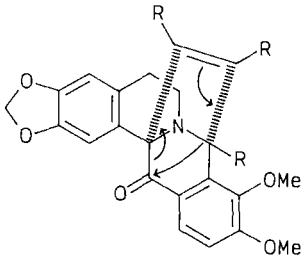


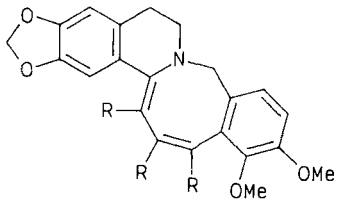
162

2. 8*H*-Isoquino[2,1-*b*]benzocines

1,3-Dipolar cycloaddition of 8-methoxyberberinephenol betaine with various acetylenic compounds gave the cycloadducts **163,** which on heating in ethanol formed the 8*H*-isoquino[2,1-*b*]benzocines (**164**) (*192, 193*).



163a R = OMe
163b R = H
163c R = CH_2COMe

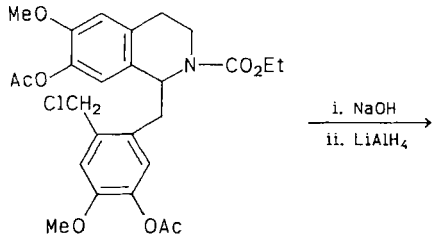


164a R = OMe
164b R = CH_2COMe

The cycloadduct **163a** isomerized to the azocine **164a** by an electrocyclic reaction as shown in **163a.** The reaction of 8-methoxyberberinephenol betaine was also carried out with other acetylenes. While the 8-acetonyl adduct **163c** was similarly isomerized to the azocine **164b,** the 8-hydrogen adduct **163b,** however, was not.

3. Benzo[5,6]cyclohept[1,2,3,*i,j*]isoquinolines

Coreximine diacetate, when refluxed with ethyl chloroformate in chloroform, formed carbamate **165,** which was converted to 1,2,3,7,12,12a-hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohept[1,2,3,*i,j*]-*N*-methylisoquinoline (**166**) by treatment with sodium hydroxide, followed by lithium aluminum hydride reduction (*194*).



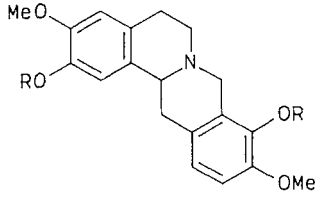
165 **166**

VI. Synthesis of Berbines

A large number of berbines have been synthesized during the period. Some new synthetic methods of berbines have been developed.

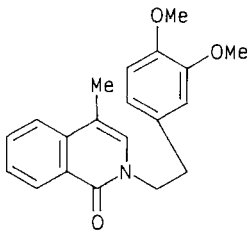
A. Mannich Condensation

The Mannich reaction is one of the oldest methods of synthesis (*195*, *196*). It is very convenient and still in use. The main drawback of the method is that it is not very regiospecific. A 1-benzylisoquinoline with a phenolic hydroxy group at C-3′ in the 1-benzyl moiety affords a mixture of 9,10- and 10-11-substituted berbines. The ratio of the isomers depends on the pH of the reaction medium (*197–200*). (±)-Scoulerine (**167**), (±)-coreximine, and (±)-tetrahydropalmatine (**168**) and their 1-bromo and 1,12-dibromo derivatives were synthesized by Mannich condensations. A bromine atom was used for blocking the reactive site in order to get the desired product (*201*). Debromination of 1-bromo and 1,12-dibromo derivatives of scoulerine and coreximine with lithium aluminum hydride in THF afforded the desired berbines. The bromo derivatives of tetrahydropalmatine were debrominated with zinc and sodium hydroxide.

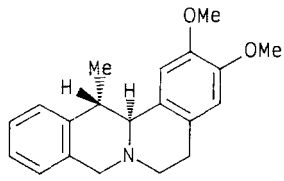


167 R = H
168 R = Me

trans-13-Methyltetrahydroprotoberberine (**170**) was synthesized by reduction of 4-methyl-2-[β-(3,4-dimethoxyphenyl)ethyl]isocarbostyril (**169**) with lithium aluminum hydride, followed by treatment with 12 *N* hydrochloric acid at 100°C for 1 h (*202*).

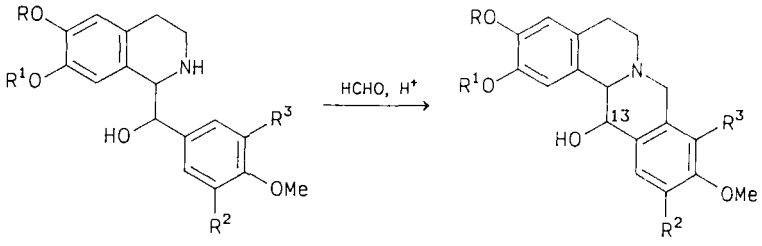


169

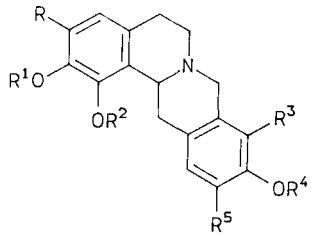


170

13-Hydroxyberbines (**172** R = R^1 = Me; RR^1 = CH_2; R^2,R^3 = H, OH, OMe) were prepared by cyclization of **171** with HCHO (*203*). (±)-Govadine (**173**) and (±)-caseadine (**173a**) were similarly synthesized (*145, 204*).



171 **172**



173 R = R^3 = OMe, R^1 = R^2 = R^4 = R^5 = H

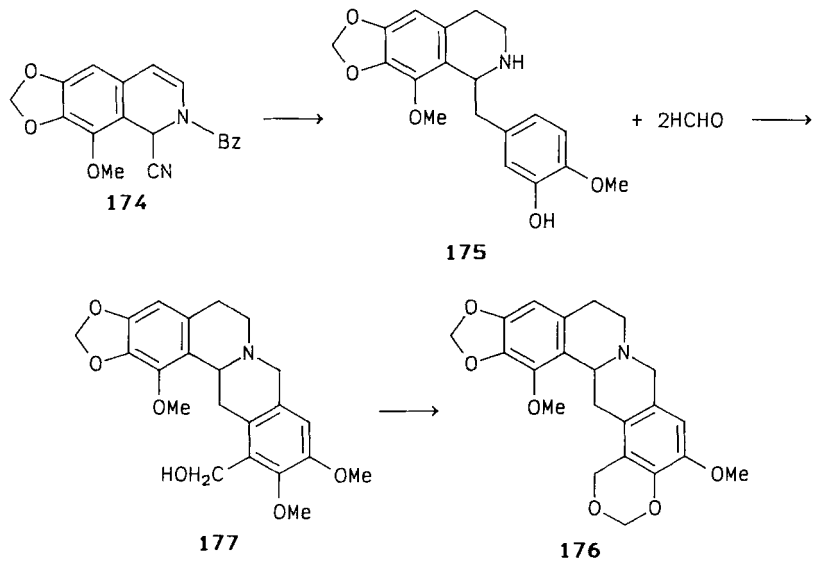
173a R = R^2 = R^3 = H, R^1 = R^4 = Me, R^5 = OMe

(±)-Mecambridine (**177**) was synthesized from **174** and 3-benzyloxy-4-methoxybenzyl chloride via **175** with HCHO. Compound **177** was further converted to orientalidine (**176**) (*205*) (Scheme 18).

Cyclization of (±)-norlaudanidine (**178**) with an acetaldehyde and acetic acid mixture afforded (±)-11-hydroxy-2,3,10-trimethoxy-8-methylberbine (**179**) (*206*). A similar reaction with optically active tetrahydropapaverine to give optically active coralydine and *O*-methylcorytenchirine was carried out by Brossi *et al.* (*150*).

B. The Pictet–Spengler Cyclization

Tetrahydropapaveroline (**180**), when subjected to an acid or base Pictet–Spengler cyclization with formaldehyde, formed **181** and **182.** A study of the reaction in aqueous buffer at 37.5°C and pH 2–10 indicated that the reaction was sufficiently vigorous under physiological conditions, and **181** and **182** were

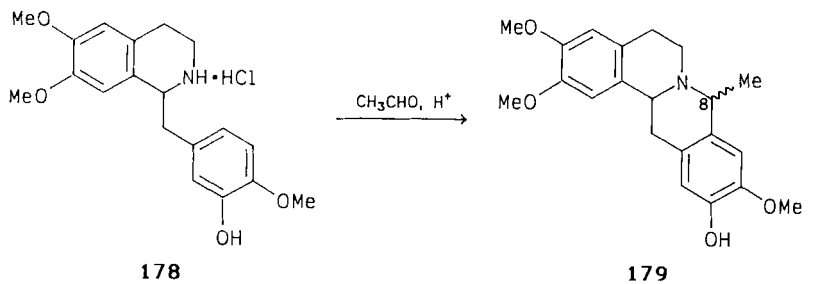


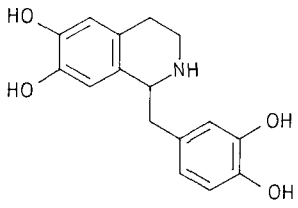
SCHEME 18. Reissert synthesis of (±)-mecambridine (**177**) and (±)-orientalidine (**176**).

produced in a ratio of 35:65. At low pH (~2) the reaction proceeded much more slowly, and 93% of **182** was produced, while at higher pH (~10) the reaction rate was maximum, producing an almost 1:1 ratio of **181** and **182** (*207*).

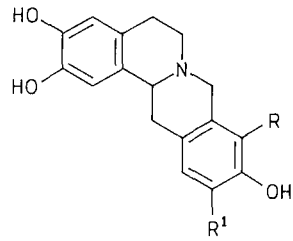
C. VARIANTS OF THE BISCHLER–NAPIERALSKI CYCLIZATION

The Mannich reaction of 1-benzyltetrahydroisoquinolines sometimes fails to give the desired berbines. The *N*-formyl derivatives of 1-benzyltetrahydroisoquinolines in such cases can often be cyclized with phosphoryl chloride, forming dihydroisoquinolines, which when reduced with sodium borohydride gave the desired berbines (*208*). Since the Mannich reaction in general gave mixtures of 9,10- and 10-11-substituted berbines, bromine was used to block the reactive



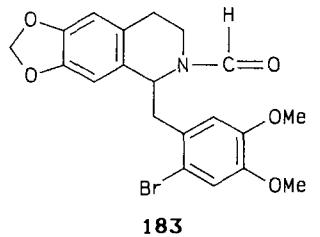


180

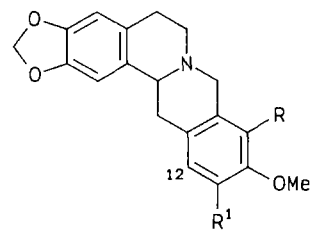


181 R = OH, R^1 = H
182 R = H, R^1 = OH

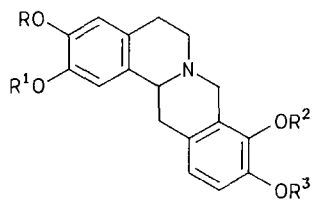
site. Cyclization of **183** by phosphoryl chloride, followed by reduction with sodium borohydride, yielded 12-chlorocanadine and tetrahydro-ψ-berberine (**185**) (*208*). Attempts to replace the chlorine by hydrogen remained unsuccessful. To check halogen exchange possibility, phosphoryl bromide was used as the cyclizing agent, affording 12-bromocanadine and 12-bromotetrahydro-ψ-berberine in a ratio of 1:3, and treatment with H_2 in the presence of 10% Pd/C yielded (±)-canadine (**184**) and **185.** (±)-Sinactine (**186**), (±)-stylopine (**187**), (±)-stepholidine (**188**), and (±)-13-methyltetrahydropseudocoptisine (**189**) were also prepared likewise (*4, 209*) (Scheme 19).



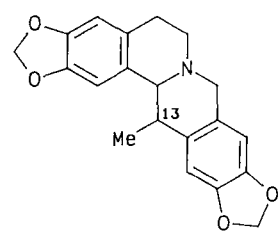
183



184 R = OMe, R^1 = H
185 R = H, R^1 = OMe



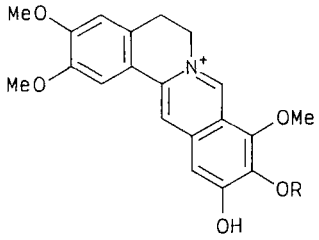
186 R = R^1 = Me, R^2–R^3 = CH_2
187 R–R^1 = CH_2, R^2–R^3 = CH_2
188 R = R^2 = Me, R^1 = R^3 = H



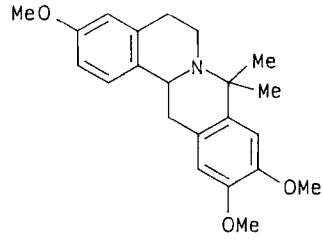
189

SCHEME 19

Glabrine (**190**) and glabrinine (**191**), the quaternary protoberberines with three oxygen functions in ring D, were synthesized for the first time utilizing the above sequence (*210*). A mixture of phosphorus pentoxide and phosphorus tribromide was used (*209*). Condensation of the isoquinoline with acetone afforded 8,8-dimethyl-substituted berbines (**192**) (*211*).



190 R = H
191 R = Me



192

D. Via Lactones

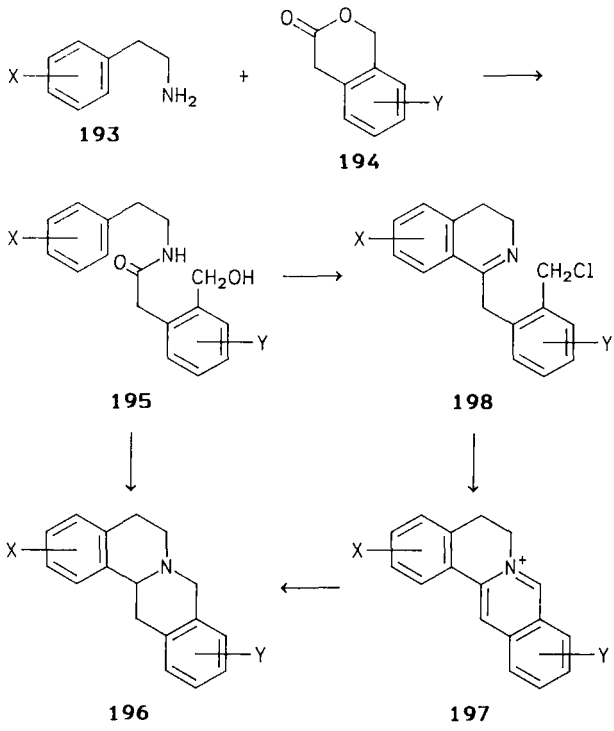
Berbine alkaloids had also been prepared with lactones as substrates (*212, 213*). Condensation of 3-isochromanones (**194**) with phenethylamines (**193**) furnished the tamide **195.** Desired berbines **196** were then prepared from **195** either by cyclization with phosphoryl chloride, followed by reduction with sodium borohydride, or by treating the dihydroisoquinoline **198** with ammonia followed by sodium borohydride reduction of **197** (Scheme 20).

Utilizing the reactions outlined above, several novel and naturally occurring berbines such as (±)-xylopinine (*214, 215*), (±)-govanine (*216*), and stepholidine (*217*), and 2,3,9,10,11-pentamethoxyprotoberberinium salt were synthesized (*215*).

(±)-Tetrahydropalmatine (**168**) was prepared from the keto acid **199** via the lactone **201** (*218*). Treatment of **201** with ammonia gave **202.** Lithium aluminum hydride reduction of **202** yielded the corresponding tetrahydroisoquinoline derivative **203,** which on Mannich condensation afforded **168** (*219*). In a separate synthesis of (±)-tetrahydropalmatine, the intermediate **202** was prepared from the bromo ester **200** by treatment with ammonia (*220*) (Scheme).

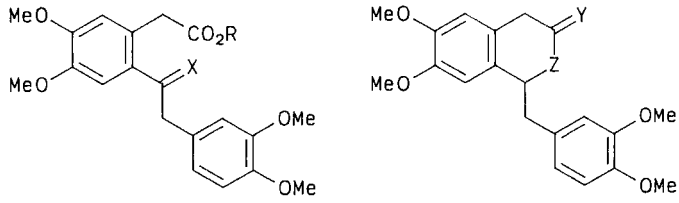
Pandey and Tiwari (*221–225*) synthesized racemic alkaloids xylopinine, govanine, scoulerine, isocoptisine, canadine, 3-hydroxy-9,10-dimethoxyberbine, 2,3,10-trimethoxyberbine, and 2,3,11-trimethoxyberbine as shown in Scheme 22.

Condensation of bromo ester **206,** obtained from lactone **204** with amine **207** prepared from bromide **208,** furnished the tricyclic lactone **209.** Berbines **210** were obtained in good yield from **209** by cyclization with phosphorus oxy-



SCHEME 20

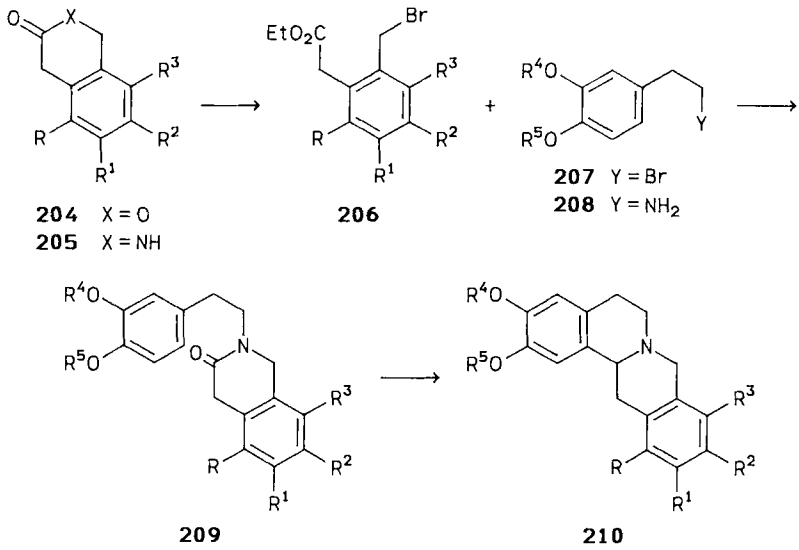
chloride, followed by reduction with sodium borohydride. The substitution pattern in ring D of the berbine nucleus is determined by the substitution of the bromo ester **206.** The key intermediate **209** was also prepared from **204** by reaction with ammonia and N-alkylation of **205** with substituted phenethyl bromides. It was applied in a synthesis of (±)-xylopinine (*226*).



199 X = O, R = H
200 X = H / Br, R = Et

201 Y = O, Z = O
202 Y = O, Z = NH
203 Y = H_2, Z = NH

SCHEME 21



204 X = O
205 X = NH

206

207 Y = Br
208 Y = NH_2

209 **210**

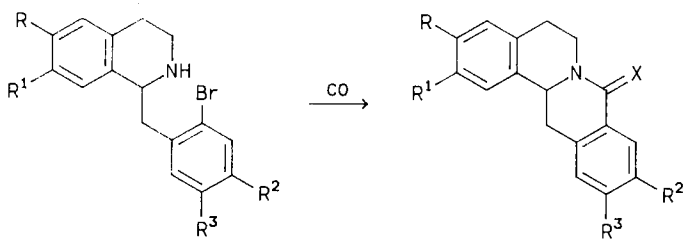
SCHEME 22

E. PALLADIUM-CATALYZED INSERTION OF CARBON MONOXIDE

Palladium-catalyzed carbonylation was used for the synthesis of benzolactam **212** (*227*). The carbon monoxide was inserted by heating the bromo-1-benzyltetrahydroisoquinoline **211** at 95–100° under a carbon monoxide atmosphere with a catalytic amount of palladium diacetate (4–6 mol %) and triphenylphosphine (6 mol %) in the presence of tri-*n*-butylamine for 30–140 h. The 8-oxoberbines **212** obtained were reduced with lithium aluminum hydride to get the desired berbines **213.** By the above procedure, the following racemic alkaloids were synthesized: 2,3-dimethoxy-10,11-methylenedioxyberbine, 2,3-dimethoxyberbine, xylopine, and pseudoepitetrahydroberberine (*228, 229*) (Scheme 23).

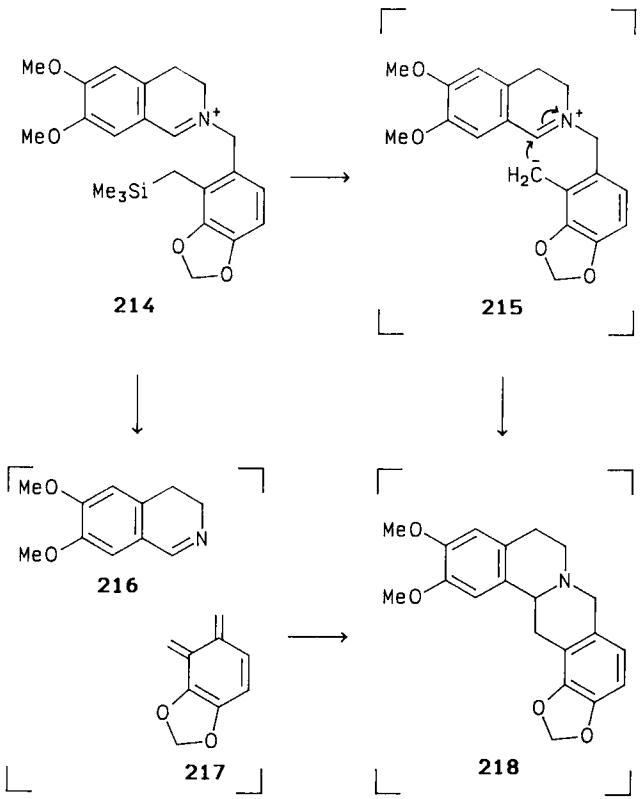
F. SILICON-MEDIATED SYNTHESIS

Berbines such as (±)-xylopinine and **218** were synthesized by an intra–inter-nucleophilic addition of an organosilicon compound to a carbon–nitrogen double bond (*230,231*). The intermediate 2-trimethylsilylmethylbenzylisoquinolinium salt **214** could give **218** by an intramolecular cyclization of **214** with cesium fluoride in ethanol via betaine **215.** Alternatively, **218** could be formed by an elimination cycloaddition mechanism (Scheme 24). Since no sinactine was detected in the reaction mixture, it was assumed that the reaction proceeded ex-

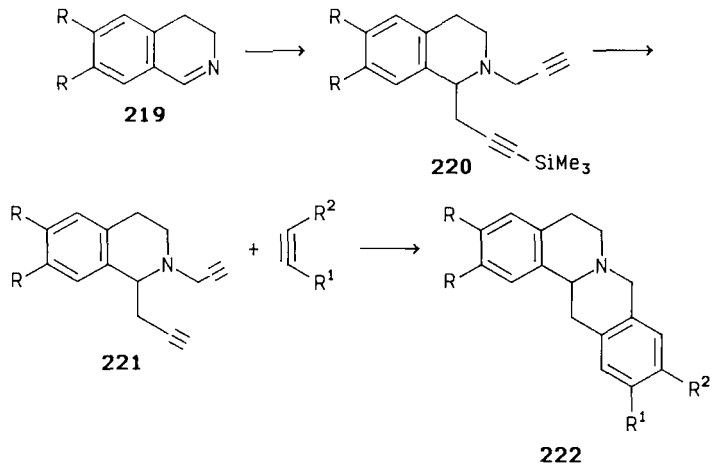


SCHEME23

clusively intramolecularly via the betaine intermediate **215.** No cyclization product was obtained in aprotic solvents such as dimethylformamide, acetonitrile, tetrahydrofuran or dichloromethane.



SCHEME 24



SCHEME 25. Cobalt-mediated synthesis of berbines.

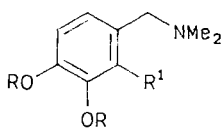
G. COBALT-CATALYZED SYNTHESIS

Rings C and D of berbines were generated by taking advantage of η^5-cyclopentadienyldicarbonylcobalt to effect oligomerization of α,ω-diynes with monoalkynes to give annulated benzenes. Since it provides access to a defined and varied substitution pattern in the D ring of the protoberberine structure, the method significantly widens its synthetic capability.

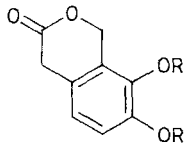
The synthesis of **221** was carried out by addition of Grignard reagent to **219,** followed immediately by N-propargylation in the presence of HMPA followed by hydrolysis with KOH in ethanol (Scheme 25). Reaction of **221** with bis(trimethylsilyl)ethyne and $CpCo(CO)_2$ gave berbines **222** in excellent yield after protodesilylation with HBr in CH_2Br_2 (*232*).

H. VIA LITHIATION REACTION

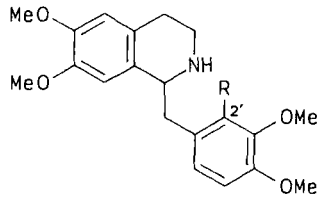
Isochroman-3-ones of type **225** are important substrates in the synthesis of berbines. However, the synthesis of some substituted isochromanones itself is difficult, and in some cases the desired compounds are not obtained by acid-catalyzed reaction with amines. The difficulty to get compounds with the desired substitution pattern was overcome with a lithiation reaction. For this purpose 3,4-dimethoxy- and methylenedioxy-substituted *N*-dimethylbenzylamines were lithiated, and the organolithium product was treated with formaldehyde to obtain the *O*-hydroxymethyl substituent. Isochromanones **225** were prepared from **224** by treating the quaternary salt of *224* with cyanide and hydrolysis of the nitrile.



223 $R^1 = H$
224 $R^1 = CH_2OH$



225



226a R = H
226b R = Li
226c $R = CH_2OH$

SCHEME 26

The racemic berbines tetrahydropalmatine, canadine, sinactine, stylopine, and xylopinine were prepared from isochromanones **225** (*233*, *234*).

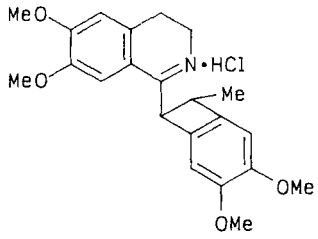
Direct lithiation of 1-benzyltetrahydroisoquinoline was also achieved (*235*). In the lithiation of laudanosine (**226a**) with *n*-BuLi, lithiation occurred at C-2′, and (±)-tetrahydropalmatine was synthesized by this procedure (Scheme 26).

I. THERMOLYSIS OF BENZOCYCLOBUTENES

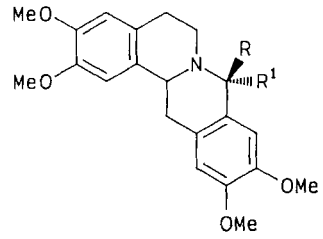
Benzocyclobutene derivatives open up when heated to afford the reactive *o*-quinodimethides, which react with enamines or imines to produce isoquinolines (*236*). Utilizing this approach, the benzocyclobutene hydrochloride **227** was pyrolyzed in bromobenzene at 150–160°C to give the 8-methylprotoberberinium salt, which on reduction with sodium borohydride afforded (±)-coralydine (**228**) together with (±)-*O*-methylcorytenchirine (**229**) (*237*) (Scheme 27).

J. FROM REISSERT COMPOUNDS

Reissert compounds undergo alkylation in the presence of strong base. A number of benzylisoquinoline alkaloids have been synthesized through Reissert



227

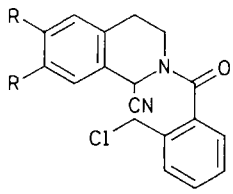


228 R = Me, $R^1 = H$
229 R = H, $R^1 = Me$

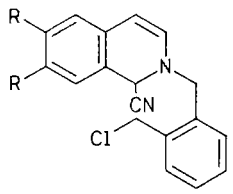
SCHEME 27

compounds (*238*), and this approach was also chosen for the syntheses of 8-oxoprotoberberine, dehydro-8-oxoberberine, unsubstituted 8-oxoprotoberberine, and their corresponding tetrahydroprotoberberines (*239, 240*). The Reissert compounds **230** were prepared by the reaction of 3,4-dihydroisoquinoline with acid chloride and trimethylsilyl cyanide in methylene chloride. Reaction of **230** with sodium hydride in dimethylformamide at room temperature gave 13,13a-dehydro-8-oxoprotoberberines. However, when a catalytic amount of aluminum chloride was used in the preparation of the Reissert compound, the dihydroisoquinolinaldonitrile **231** was formed, which on subsequent treatment with sodium hydride in dimethylformamide gave 5,6,13,13a-dehydro-8-oxoprotoberberine (*239*) (Scheme 28).

The berbines were obtained from 8-oxoberberines by reduction with lithium aluminum hydride, followed by sodium borohydride (*240*).



230



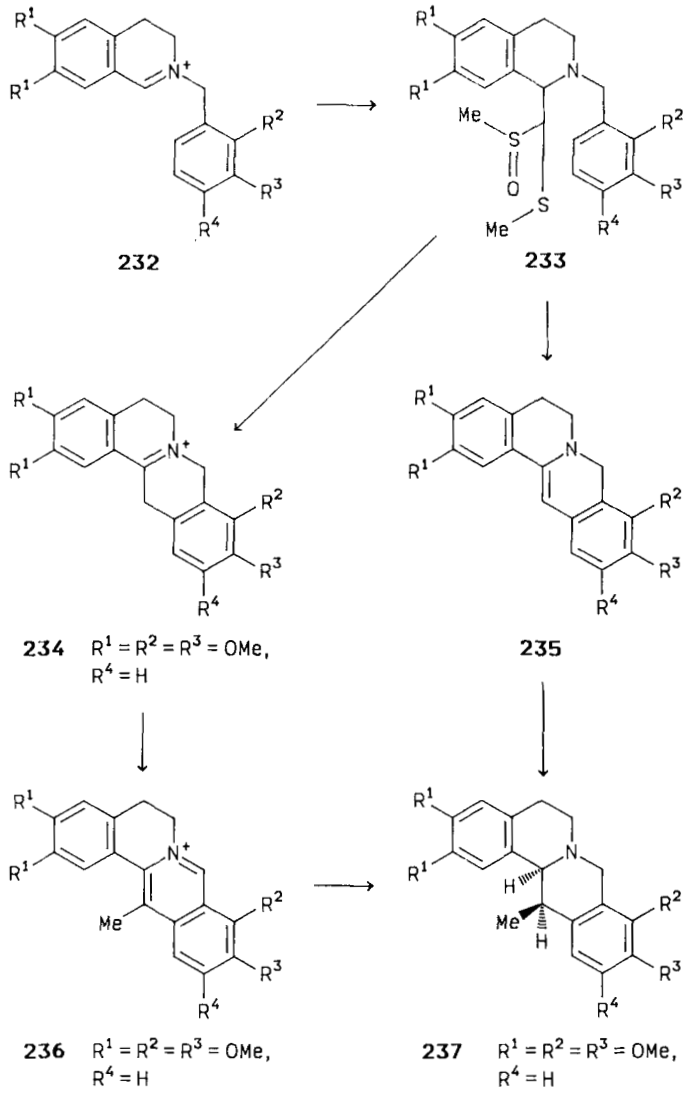
231

SCHEME 28

K. VIA DIHYDROISOQUINOLINE INTERMEDIATES

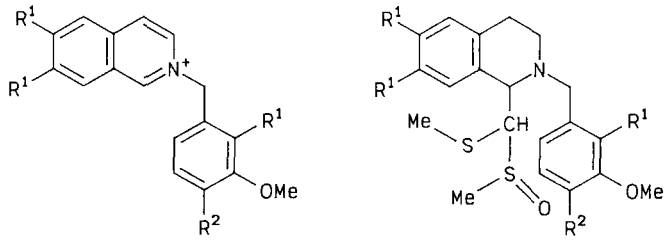
Regiospecific synthesis of various berbines from dihydroisoquinolines (**232**) as the starting materials had been reported by Kiparissides *et al.* (*241*) (Scheme 29).

The one-carbon unit required in the dihydroisoquinoline system, which becomes C-13 of protoberberines, was introduced by the reagent lithiomethyl methylthiomethyl sulfoxide (LiMMTs). The adduct **233,** so formed, was treated in two ways to get the desired berbines. First, the adduct **233,** when treated with concd HCl, afforded the iminium salt **234,** which on heating with formaldehyde in aqueous acetic acid and sodium acetate, followed by treatment with sodium iodide, gave dehydrocorydaline iodide (**236**). Borohydride reduction of **236** yielded exclusively (±)-corydaline (**237**). This is a very convenient and short synthetic route to C-13 methylberbines. In the second method, the adduct **233** was treated with concd HCl after cooling and treatment with NaOH to give the dihydroprotoberbine **235.** Sodium borohydride reduction of **235** furnished the desired berbines **237.** (±)-Tetrahydropalmatine, xylopinine, and sinactine were synthesized by this route (*241*).



SCHEME 29. Regiospecific synthesis of 13-methyltetrahydroprotoberberines.

Protoberberines not obtainable by the Bischler–Napieralski approach could be prepared by this method, using isoquinolines **238** as intermediates (*241*). Reduction of isoquinolines **238** was carried out with cyanoborohydride instead of sodium borohydride (Scheme 30). Palmatine iodide was prepared by oxidation of tetrahydropalmatine (*241*).



238 **239**

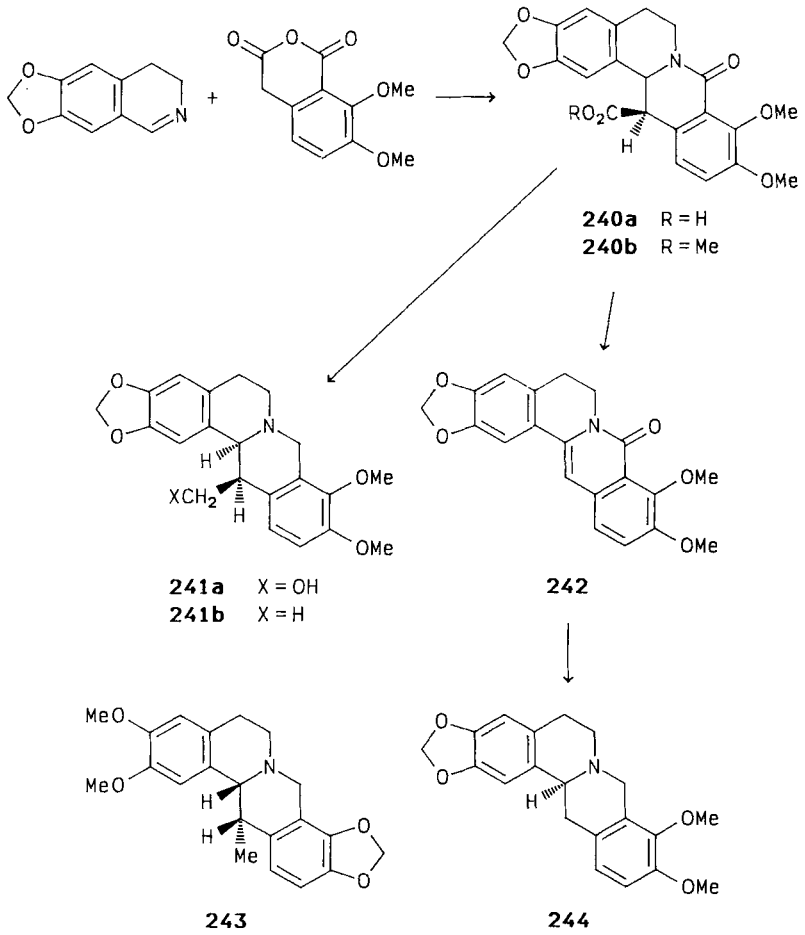
SCHEME 30

L. FROM HOMOPHTHALIC ANHYDRIDE

The 9,10-oxygenated berbines were obtained from appropriately substituted homophthalic anhydride (*242*). Condensation of 2,3-dimethoxyhomophthalic anhydride with norhydrastinine gave first a mixture of *cis*- and *trans*-13-carboxyberbines, which were then converted to the more stable cis acid **240a.** Decarboxylation of **240a** with lead tetraacetate in the presence of cupric acetate, potassium acetate, and acetic acid yielded berlambine (**242**). Aluminum hydride reduction of **242** gave (±)-canadine (**244**). Treatment of the cis acid **240a** with diazomethane furnished the methyl ester **240b,** which on reduction with lithium aluminum hydride afforded the amino alcohol **241a.** The mesylate of **241a** on treatment with sodium borohydride furnished (±)-thalictricavine (**241b**) (*242*) (Scheme 31).

Resolution of (±)-**240a** gave the (+)-acid, which was converted to (+)-thalictricavine and also to (+)-canadine (*243*). When lactam **242** was reduced with lithium aluminum hydride, (±)-canadine was formed. Since the absolute configuration of (−)-canadine was known, the absolute configuration of the (+)-acid and of (+)-thalictricavine (**241b**) must be 13*S*,13a*R* (*244*). The (+)-acid was converted to natural (+)-thalictrifoline and (+)-cavidine (**243**) (*244*), and the absolute configuration of (+)-cavidine (**243**) was established (*245*). The racemic alkaloids thalictrifoline, sinactine, cavidine, and corydaline were synthesized by similar routes (*246, 247*).

Several *cis*- and *trans*-13-carboxyberbines were synthesized from homophthalic anhydrides and cyclic imines (*248*). Compounds **248** were cyclized to **247b** with H_3PO_4 and reduced to **249b** with sodium borohydride (*249*). A one-pot synthesis of **249a** from homophthalic anhydride **246** and lactam **245** was achieved (*250*) (Scheme 32). Racemic caseadine was also synthesized by this approach (*251*).



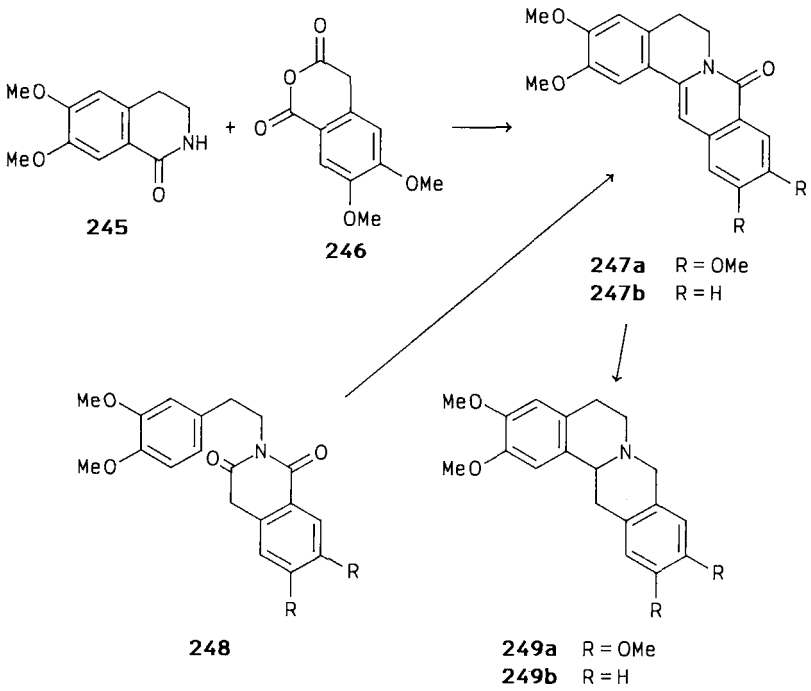
SCHEME 31. Synthesis of berlambine (**242**), (±)-canadine (**244**), and (+)-thalictricavine (**241a**).

M. VIA *N*-OXIDE INTERMEDIATE

(±)-Coreximine and (±)-scoulerine were prepared by treatment of reticuline N-oxide (**250**) with ferrous sulfate, and berbine **252** was similarly formed from orientaline *N*-oxide (**251**) (*252–254*) (Scheme 33).

N. FROM IMMONIUM AND IMINIUM SALTS

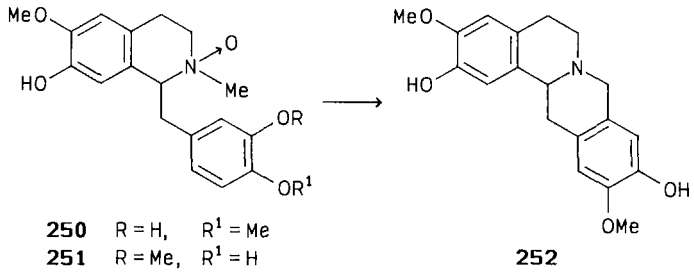
Shono *et al.* (*255*) developed a new electroreductive annelation method, which gave cyclized products without contamination with isomers. Electroreduction of



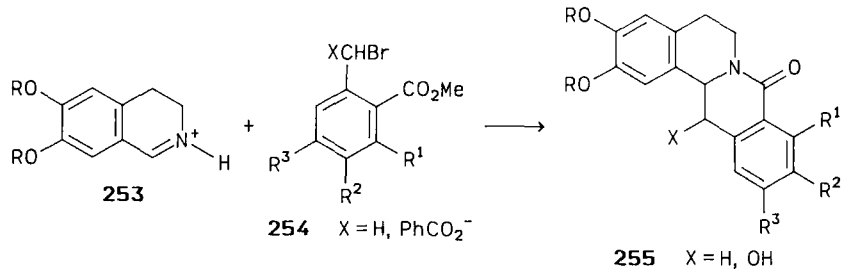
SCHEME 32. Synthesis of (±)-xylopinnine.

immonium salts **253** and bromide **254** in DMF at room temperature (−1.8 V) yielded the 8-oxoberbines **255** and the racemic alkaloids 8-oxosinactine, -xylopinine, -canadine, and -stylopine were prepared by this method (*255*). The synthesis of 13-hydroxyberbine was also accomplished (*256*) (Scheme 34).

The racemic alkaloids 2,3-dimethoxyberbine, norcoralydine, xylopinine, 1,2,3,10,11-pentamethoxyberbine, and tetrahydropalmatine were synthesized from the carboxylic acids **256** via regiospecific decarbonylation to iminium salts,

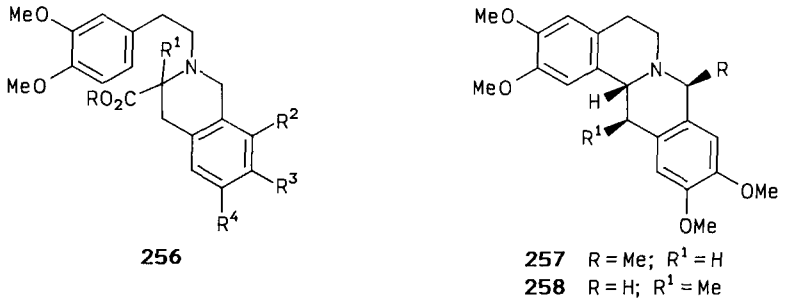


SCHEME 33



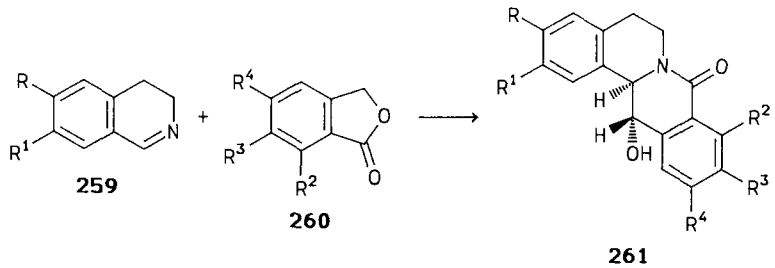
SCHEME 34

followed by acid-catalyzed cyclization (*257*). Similarly prepared were racemic *O*-methylcorytenchirine (**257**) and the *trans*-13-methyl isomer **258** (*258*).



13-Hydroxyberbines were synthesized by the reaction of phthalides **260** with 3,4-dihydroisoquinolines **259,** and the oxoberbine intermediate **261** was reduced with lithium aluminum hydride to the desired product (*259*) (Scheme 35).

The hydrogen atoms at C-13 and C-13a are trans to one another, and the relative configuration of the OH group is epimeric to that in ophiocarpine and 13-hydroxystylopine (*259*). The high degree of stereoselectivity in this reaction implied that the two components must interact in an endo fashion during the formation of the bonds between C-13 and C-13a and between C-8 and N.

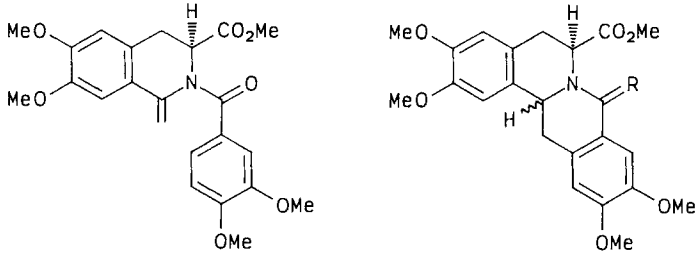


SCHEME 35

O. Photocyclization

Ninomiya had discussed the synthesis of berbines by photocyclization of enamides in Volume 22 of this treatise.

Kametani *et al.* (*260, 261*) synthesized xylopinine by 1,3-asymmetric induction through photolysis. Irradiation of enamide **262** in dry benzene at 20–30°C for 5 h afforded the 8-oxoberbine **263a,** which on treatment with phosphoryl chloride and reduction with sodium borohydride gave **263b.** The carboxyl unit at C-6 in **263b** was removed to give (±)-xylopinine (Scheme 36). The optically active 13-methylberbin-8-ones were obtained by asymmetric synthesis (*262*).



262 **263a** R = O
263b R = H

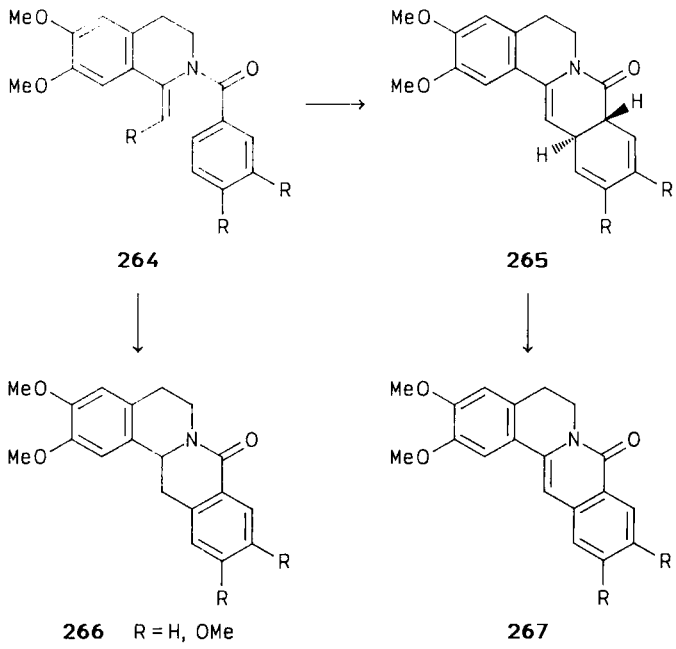
Scheme 36

Nonoxidative photocyclization of enamides **264** (R = H) at room temperature gave a new type of lactams (**265**), which were readily transformed to stable dehydrolactones **267** (R = H) (*263*) (Scheme 37).

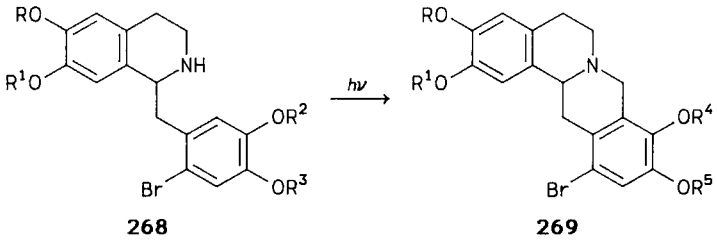
Irradiation of **264** (R = OMe) in the presence of sodium borohydride in benzene containing methanol afforded the saturated lactam **266** (R = OMe). (±)-Xylopinine was synthesized from the corresponding saturated lactam in 80% yield.

Photolysis of the phenolic 2′-bromo-1-benzyl-1,2,3,4-tetrahydroisoquinolines (**268**) afforded 12-bromotetrahydroprotoberberines (**269**), 12-bromoschefferine, 12-bromocorytenchirine, and 12-bromoaequaline, and other bromoberbines were prepared likewise by irradiating the corresponding 2′-bromo-1-benzyltetrahydroisoquinolines. Debromination of 12-bromotetrahydroprotoberberines with 10% Pd/C afforded the corresponding tetrahydroprotoberberines (*264–266*) (Scheme 38).

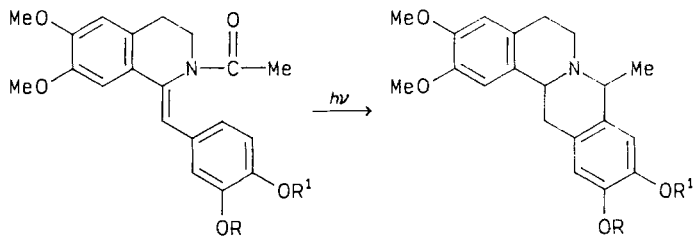
8-Methylberbine derivatives **271** and **272** were obtained by irradiation of a mixture of **270** and HIO_4 in a methanol–dioxane mixture, followed by reduction and debenzylation of benzylethers (*267*) (Scheme 39).



SCHEME 37



SCHEME 38



270 **271** R = Me, R^1 = H
272 R = H, R^1 = Me

SCHEME 39

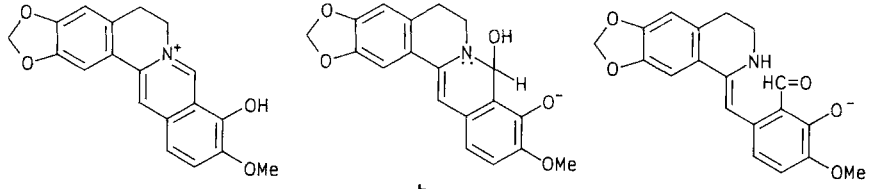
P. THE WITTIG–HORNER REACTION

Intramolecular Wittig–Horner reaction of the isoquinoline phosphate afforded a dibenzoquinolizinone in fairly good yield (*268*).

VII. Spectroscopic Properties

A. UV SPECTROSCOPY

The effect of hydroxy, methoxy, and methylenedioxy groups substituted in different positions of the aromatic nucleus on the UV spectra of aromatic and heterocyclic protoberberines was reviewed (*269*). Petlichnaya *et al.* (*270*) published a study of IR and UV spectra of condensation products of berberine with ketones. Hückel MO calculations for the three possible tautomeric forms, the iminium salt **a,** the carbinolamine **b,** and the open amino aldehyde **c** of berberine, jatrorrhizine, berberrubine, and jatrorubine were studied under the influence of acid and base (*271*).



The absorption maxima of berberubine at 441–450 and 348–359 nm, due to the quarternary iminium form, disappeared in basic solution, and three new maxima appeared at 328–333, 380–399, and 490–516 nm, due to the dissocation of a phenolic hydroxy group in the molecule. Neither carbinolamine nor amino aldehyde forms of berberrubine in solution were observed. Moreover,

because of the charge distribution in the molecule, the amino aldehyde form **c** is unlikely to exist, but the presence of carbinolamine **b** in stronger alkaline solution than that investigated cannot be ignored (*272*). The hypsochromic shift in the spectrum was proportional to the polarity of the solvent. The hydroxy group of berberrubine in propanol became totally dissociated, while in other solvents both forms were present.

B. ^{1}H-NMR Spectroscopy

Chiri *et al.* (*273*) studied ^{1}H-NMR spectra of 28 berbines and suggested that the oxygen-substitution pattern (2,3,9,10 or 2,3,10,11) together with the type of substitution could be deduced from the chemical shift values of the aromatic protons. Salient features of their findings are: (a) the signals for H-1 and H-4 protons in 2,3,9,10-tetrasubstituted protoberberines can be ascertained because H-11 and H-12 usually appeared as AB doublets or as a two-proton singlet; (b) the 3-hydroxy-2-methoxy substitution could be differentiated from the 2-hydroxy-3-methoxy substitution as the values for H-1 and H-4 differed by $\simeq \delta$ 0.05 ppm in the former case, whereas in the latter case a difference of δ 0.2 ppm was observed; (c) a two-proton singlet for H-11 and H-12 appeared in both 9-hydroxy-10-methoxy- and 9-methoxy-10-hydroxy-substituted compounds, however, the signal ($\simeq\delta$ 6.82 ppm) was more downfield in the latter than the signal at $\simeq\delta$ 6.72 ppm in the former; (d) two distinct sets of shifts were observed for H-9 and H-12 in the 10-hydroxy-11-methoxy-and 10-methoxy-11-hydroxy-substituted bases (in the former a two-proton singlet appeared at $\simeq\delta$ 6.63 ppm, but two singlets at $\simeq\delta$ 6.71 and δ 6.56 ppm were observed in the latter); (e) an upfield shift of the H-12 singlet ($\simeq\delta$ 6.53–6.63 ppm) was observed in 10,11-substituted bases as compared to H-11 and H-12 signals in 9,10-substituted compounds; (f) the methylenedioxy protons appeared at $\simeq\delta$ 5.86 to δ 6.06 ppm, whereas the signals for the methoxy groups were observed at δ 3.73 to δ 3.90 ppm.

The 270-MHz ^{1}H-NMR spectra of xylopinine, tetrahydropalmatine, and *O*-methylcapaurine have been analyzed, and the conformtions of coralydine (**228**) and *O*-methylcorytenchirine (**229**) were established (*274*).

The 90-MHz ^{1}H-NMR spectra of both *cis*- and *trans*-13-methyl-9,10- and -10,11-substituted berines have been studied. It has been suggested that the stereochemistry of the B/C ring junction in 10,11-disubstituted 13-methylberbines could be established by chemical shifts of the C-13 methyl doublets (*275*). The C-8 protons appeared as an AB quartet irrespective of the stereochemistry at the B/C ring junction in 10,11-substituted 13-methylberbines. However, in *cis*-quinolizidines the center of the AB quartet is shifted downfield by 0.15–0.20 ppm. Further, the signals are separated from each other by about 0.45–0.48 ppm as compared to 0.40–0.48 ppm in *trans*-quinolizidines. In 9,10-substituted compounds these are separated by 0.13–0.16 and 0.55–0.72 ppm, respectively. The

C-13a proton in 13-methylberbines appeared at ≈δ 3.70 in *trans*-quinolizidines and at much lower field than in *cis*-quinolizidines. The most important difference in the spectra of the two series is shown by C-13-methyl groups. The *cis*-quinolizidines give signals between δ 1.43 and 1.48 as compared to *trans*-quinolizidines (δ 0.88–0.99). Meniot and Shamma (*276*) have studied ^{1}H-NMR spectra of several reduced isoquinolines and observed that the ring-B methylene protons appeared as triplets if nitrogen inversion was precluded and as complex multiplets if the nitrogen atom underwent inversion. The chemical shift of the proton on the carbons adjacent to nitrogen was dependent on the state of the nitrogen atom.

C. ^{13}C-NMR Spectroscopy

^{13}C-NMR spectrometry has become an important tool for the determination of conformation of the quinolizidine system in berbines (*277, 278*). In 9,10- and 10,11-substituted berbines the chemical shift of the C-5 atom is a reliable indicator for the presence of the unusual B/C cis-fused conformation (*279*). The conformation of 13-hydroxyprotoberberines, ophiocarpine, epiophiocarpine, their acetates, and the corresponding *N*-metho salts have been determined by ^{13}C-NMR spectrometry (*279, 280*). NOE studies on structural elucidation problems of protoberberine alkaloids were reviewed (*281*).

D. Mass Spectroscopy

Positive and negative ion spectra of berbines under chemical ionization conditions, using ammonia gas, have been studied (*282*). The results showed the complementary nature of the two techniques. The positive ion spectra showed exclusively the $(M + H)^+$ ion, whereas the negative ion spectra gave $(M - H)^-$ ions with a few intense fragment ions, indicative of the functional groups present in the molecule. As expected, no NH_4^+ adduct ions were observed in positive chemical ionization mass spectrometry (CIMS) of the alkaloids. The preferred site of protonation is the nitrogen atom of the quinolizidine ring. Minor fragment ions due to loss of H_2O from the $(M + H)^+$ ions were also observed in phenolic compounds (presumably protonation occurred on phenolic oxygen). The other peaks in the spectra corresponded to products of the usual retro-Diels–Alder fragmentation. In negative CIMS, no molecular-ion peak is observed. Instead, all of the compounds exhibit $(M - H)^-$ ions, presumably formed by dissociative electron capture. The phenolic compounds give very intense $(M - H)^-$ ions (83%), as resonance-stabilized phenoxide anions are formed by loss of hydrogen.

The appearance of an M − 14 peak rather than the expected molecular ion in the mass spectrum of berberine has been shown to be due to its thermal disproportion to dihydroberberine and oxyberberine (*283*).

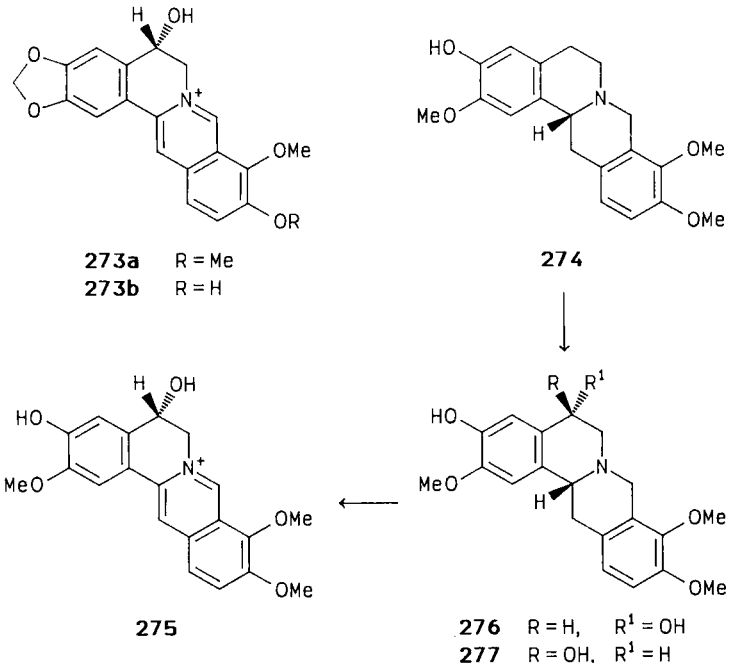
VIII. Absolute Configuration

The absolute configurations of 13-methylberbines (+)-thalictricavine (**241b**) and (+)-thalictrifoline were determined as 13*S*,13a*R* and 13*R*,13a*R*, respectively, by correlation with (+)-canadine (*243–245*). (+)-Sinactine has been assigned the *R* configuration at C-13a by chemical correlation with (+)-tetrahydropalmatine, comparing optical rotations and biosynthetic considerations (*284*).

Berberastine (**273a**) and thalidastine (**273b**), isolated from *Berberis baluchistanica* (*285*, *286*), are thus far the only members of quaternary berberine alkaloids that possess a hydroxy group at C-5, but the chirality remained undefined because of paucity of material and facile dehydration leading to aromatization of ring B. The absolute configurations of these bases, however, has now been determined as follows: jatrorrhizine was reduced to (±)-tetrahydrojatrorrhizine, which was resolved to give (+)-tetrahydrojatrorrhizine (**274**); lead tetraacetate oxidation of **274** afforded the diastereoisomeric C-5 monoacetates; hydrolysis of the monoacetates with 10% hydrochloric acid gave the separable mixture of the isomeric alcohols **276** and **277** in a ratio of 2:1. The relative and absolute stereochemistry of both alcohols was established by NMR studies. Oxidation of **276** gave the corresponding quaternary protoberberinium salt **275,** which was found to be dextrorotatory (Scheme 40). Since berberastine (**273a**) and thalidastine (**273b**) were also dextrorotatory, these bases must possess the same absolute configuration at C-5 (*287*).

Circulation dichroism (CD) techniques were used extensively in determining the absolute configuration of berbine alkaloids as it gives maximum information of the substitution pattern by the sign of Cotton effects (CE) for a particular absolute configuration. Ringdahl *et al.* (*288*) studied the absolute configurations of 10 protoberberines and their salts by the CD technique and concluded that tetraoxygenated berbines with different substitution patterns could be differentiated by CD. Thus 2,3,9,10-tetrasubstituted bases having an *S* configuration showed a positive CE within the 285-nm absorption band, which become negative when the nitrogen was protonated. In contrast, 2,3,10,11-tetrasubstituted bases with an *S* configuration showed a negative CE, which remained unchanged on protonation. Also a larger magnitude of the second CE (~235 nm) occurred in the latter case. It was inferred that all berberines with an *S* configuration show a negative CE for the ^{1}Lb band of protonated species. The CD spectra of 1-substituted compounds do not differ appreciably from those of the unsubstituted ones except that an extra shoulder band at 230 nm occurs. The sign of CE at 206–210 nm of all the bases and their salts is found independent of the oxygen substitution pattern (2,3,9,10- or 2,3,10,11-), the nature of the B/C ring junction, and the protonation of nitrogen.

The conformation of the B/C ring junction in protoberberine alkaloids was determined by X-ray analysis and by the rate of methiodide formation. X-Ray



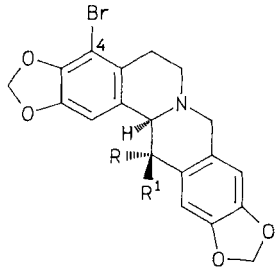
273a R = Me
273b R = H

274

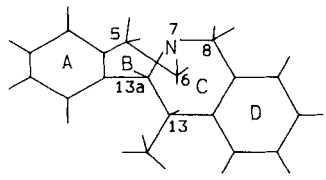
SCHEME 40

crystallographic studies have shown that the heterocyclic rings of ophiocarpine and ophiocarpine *N*-oxide were trans-fused, having a half-chair conformation (*289*). Physical and kinetic data suggested that 4-bromo-13-methyltetrahydropseudocoptisine (**278**) and 4-bromo-13-methyltetrahydropseudoepiberberine (**279**) and *cis*- and *trans*-quinolizidine systems, respectively. Rogers *et al.* (*290*) have confirmed this assignment by X-ray data. Of the two possible conformations A and B for the cis-fused compound, it was found that it existed only in conformation A with the lone pair on nitrogen axial and H_B equatorial to the quasi chair of ring B. The position of the bromine atom was fixed at C-4 in Ring A (*290*).

The rate of methiodide formation of a number of berbines and 13-methylberbines has been studied (*291*). It has been observed that the rate was much faster with 13-substituted *cis*-quinolizidines as compared to *trans*-quinolizidines. No appreciable change in the rate occurred in the trans series. Introduction of bromine into the aromatic rings did not alter the rate constant for trans compounds, which again was decreased in the cis series. A faster rate was found for 10,11-substituted compounds compared to 9,10-substituted compounds. However, the rate of quaternization was enhanced by the presence of a free phenolic hydroxy



278 R = Me, R^1 = H
279 R = H, R^1 = Me



Conformation A

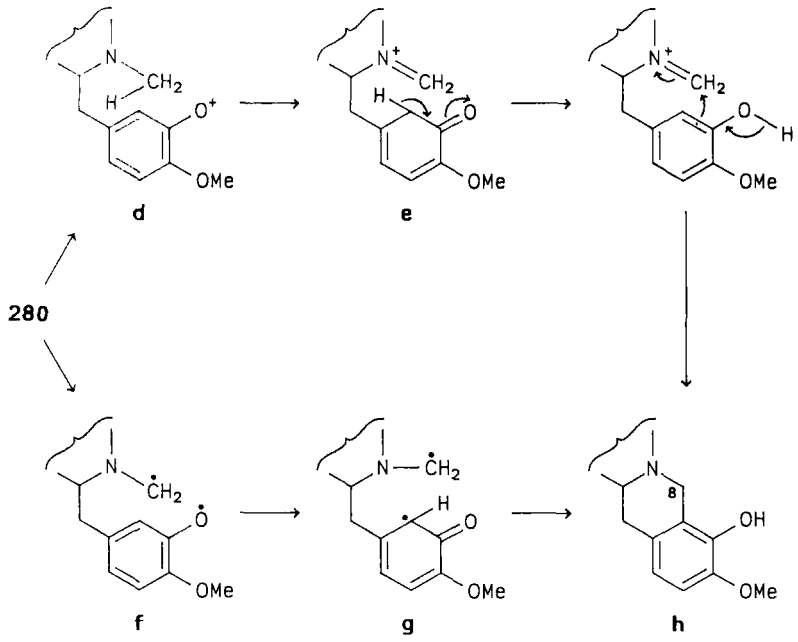
group as compared to the corresponding O-alkylated derivatives. In the cases of tetrahydrojatrorrhizine and caseadine it reaches to almost the values of the cis conformers of the 13-methyl series. These results show that a careful assignment of the stereochemistry can be made by measuring quaternization rates of isomers.

IX. Biosynthesis

A. Normal Biosynthesis

The biogenesis of protoberberine alkaloids was discussed earlier (*292–294*). The relationship of 1-benzyltetrahydroisoquinolines and protoberberines was recognized quite early (*292*). That berberine (**282**) had a modified 1-benzyltetrahydroisoquinoline nucleus was shown when labeled (±)-norlaudanosoline was converted to berberine in *Berberis japonica* (*295*). The two units accounted for all but one of the carbon atoms in the protoberberine molecule. Tyrosine thus enters into two sites in the skeleton of these alkaloids. This hypothesis has been tested by several tracer experiments. The radioactive bases obtained from plants to which (±)-tyrosine-2-^{14}C had been administered showed a labeling pattern that was in complete conformity with the predictions.

In several tracer experiments the activity was found almost equally divided between the two labeled centers, and these results appeared to support the hypothesis. However, later observation invalidated this assumption (*296*). Unequal distribution of activity was found between the two labeled centers in tyrosine-derived alkaloids. Direct evidence was obtained when it was found that dopamine was only incorporated into one of the two "halves" of berberine (*297*). The incorporation of only one dopamine unit into these alkaloids suggested that the enzyme system controlling the oxidative deamination of dopamine was not active in these plants. Dopa was shown to be incorporated into berberine in *Hydrastis canadensis* (*296*). Since reticuline was shown to be a biological pre-



SCHEME 41. Mechanism of berberine bridge formation.

cursor of protoberberine alkaloids, the early stages of biosynthesis of these alkaloids from reticuline was studied (*298, 299*).

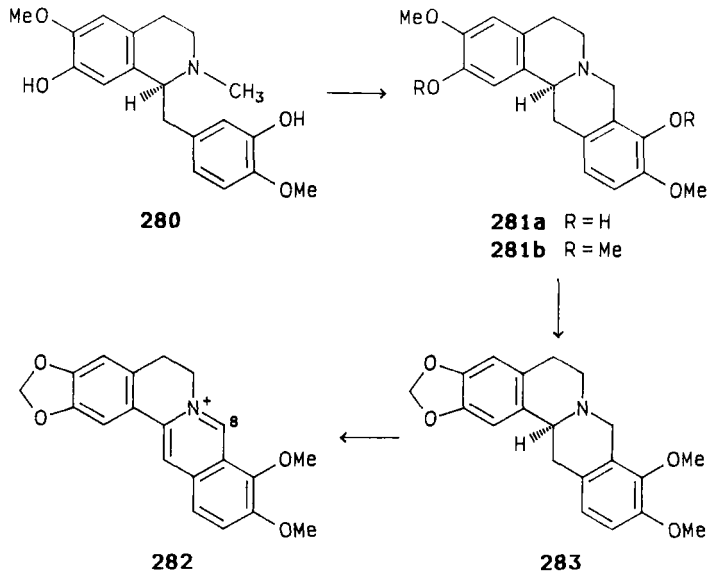
The C-8 atom of protoberberine and berbine alkaloids is known as the "berberine bridge." It has been suggested that this bridge could be formed in nature by oxidative modification of an *N*-methyl group (*300–302*). Plausible mechanisms of the reaction are shown in Scheme 41.

Two-electron oxidation of a suitable precursor such as reticuline (**280**) could give the phenoxonium ion **d** from which **e** could be derived by intramolecular hydrogen transfer. In an alternative mechanism, one-electron oxidation of **280** could furnish a phenolate radical. A hydrogen atom could then be transferred from the *N*-methyl group to oxygen, which could be oxidized to the biradical **g.** Coupling of radicals could then lead to ring closure to give **h** as in normal C—C bond formation in phenolate oxidation reactions. Experimental support in favor of the hypothesis was put forward by Barton, Battersby, and coworkers directly and by Gupta and Spenser indirectly. Barton *et al.* (*303*) fed reticuline labeled with ^{14}C in its *N*-methyl group to *Hydrastis canadensis*. Biosynthetically synthesized berberine (**282**) was degraded unambiguously and essentially all of the radioactivity was found at C-8 of the alkaloid. Battersby's group (*304*) by using laudanosoline labeled with ^{14}C in the methyl group had confirmed the above

results. Gupta and Spenser (*305*) had provided evidence from experiments with methionine-^{14}C.

Barton and co-workers (*306*) have studied biosynthesis of berberine in detail. Feeding doubly labeled reticuline, they confirmed that C-8 of berberine was derived from the *N*-methyl group of the precursor. Further, it was demonstrated that the methylenedioxy group in berberine (**282**) was also formed as in other cases (*307, 308*) by oxidative cyclization of a catechol-*O*-methyl ether. Parallel feeding of both the labeled enantiomers of reticuline showed that (+)-reticuline (**280**) was converted to **282** 15 times more efficiently than (−)-reticuline in *H. canadensis* plants (Scheme 42). (−)-Canadine (**283**) occurs in *H. canadensis*. Efficient incorporation (8.9%) of (±)-canadine into berberine by the plants established its intermediacy. Protosinomenine, however, was not incorporated into **282** in the plants.

The berberine bridge carbon in palmatine had been shown to be derived from formate (*309*). High incorporation of (±)-reticuline into coreximine in opium poppies showed that 2,3,10,11-tetrasubstituted tetrahydroberberines were also derived from reticuline. (+)-Reticuline (**280**) was efficiently incorporated into (−)-scoulerine (**281a**), which in turn acted as an efficient precursor of stylopine in *Chelidonium majus* (*310*). Reticuline was also shown to be a precursor of stylopine in this plant. Labeled (±)-reticuline was converted specifically to corydaline by *Corydalis cava* (*311*). It followed that C-13-methylated berbines



SCHEME 42. Biosynthesis of berberine.

were also derived, like the non-C-13-methylated species, from the same 1-benzyltetrahydroisoquinoline precursor.

(−)-Sinactine and (±)-sinactine with established structure had been isolated from several plant species. (+)-Sinactine had been obtained by resolution of (±)-sinactine. However, (+)-sinactine as a natural product was isolated recently for the first time from *Corydalis meifolia* Wall (*119*). The biosynthetic pathways of (+)-sinactine (**286b**) were traced (*284*).

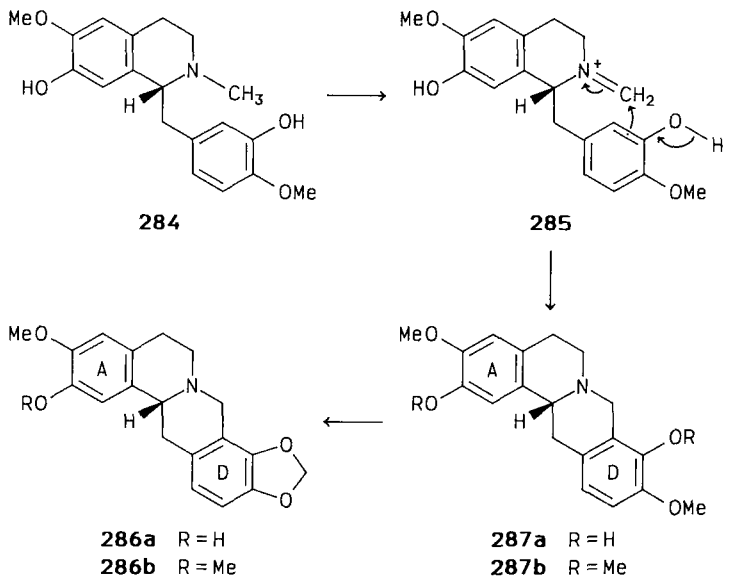
Initial feeding of tyrosine-L-*U*-^{14}C to young cut branches of *Cocculus laurifolius* DC showed that the plants were actively biosynthesizing (+)-sinactine (**286b**) at the time of feeding. Parallel feeding of (±)-reticuline, -norreticuline, and -nororientaline demonstrated that reticuline and norreticuline were efficiently incorporated into sinactine in *C. laurifolius* plants, while nororientaline was very poorly metabolised to form **286b.** Doubly labeled (±)-reticuline was then fed to young cut branches of *C. laurifolius,* and sinactine was isolated. The ratios of the ^{14}C:^{3}H labels in the precursor was 1:9, while in the biosynthetic sinactine 1:8 was present, demonstrating that the H atom at the asymmetric center C-13a essentially remained unaffected during the biotransformation. The regiospecificity of the label in the biosynthetic **286b** was determined by Hofmann degradation and oxidation, affording labeled breakdown products.

Atom C-8 in (+)-sinactine (**286b**) was shown to be introduced by oxidative cyclization of the NMe group of reticuline in *C. laurifolius*. The biosynthetic sinactine formed was isolated, treated with BCl_3 in dry CH_2Cl_2, and the phenols were methylated with CH_2N_2 to furnish (+)-tetrahydropalmatine (**287b**), having essentially the same molar radioactivity as **284.** Radioactive **287b** was oxidized with I_2 to radioactive palmatine without loss of radioactivity. Treatment of palmatine with phenylmagnesium bromide afforded radioactive 8-phenyldihydropalmatine, which after chromic acid oxidation gave radioactive benzoic acid containing 97% of the original activity.

The foregoing experiments established that sinactine in *C. laurifolius* was biosynthesized from reticuline. Further C-8 in sinactine was formed by oxidative cyclization of the NMe group of reticuline as shown in Scheme 43.

Feeding of (+)-scoulerine (**287a**) established its intermediacy in the biosynthesis of (+)-sinactine (**286b**). Selective O-methylation of the phenolic function of ring A in **287a** could afford tetrahydropalmatrubine which in turn could be converted to **286b** by transformation of the *O*-methoxyphenol in ring D to a methylenedioxy group. Alternately, the methylenedioxy group in ring D in **287a** could first be formed to give cheilanthifoline (**286a**), which by O-methylation could finally be converted to (+)-sinactine (**286b**). Parallel feedings of tritiated scoulerine (**287a**) and tritiated tetrahydropalmatrubine supported the second route.

Parallel feedings with (*R*)-(−)- and (*S*)-(+)-reticuline demonstrated that ster-



SCHEME 43. Biosynthesis of sinactine (**286b**).

eospecificity was recognized in the bioconversion of 1-benzyltetrahydroisoquinolines to (+)-sinactine. (*R*)-(−)-Reticuline was incorporated about 15 times more efficiently than its (*S*)-(+) isomer. The *R* configuration of (+)-sinactine (**286b**) was confirmed by its chemical conversion to (*R*)-(+)-tetrahydropalmatine (**287b**) after treatment with BCl_3 and O-methylation. (*R*)-(−)-Reticuline was isolated from *C. laurifolius* (*351*), and the results, therefore, strongly support the biosynthesis of (+)-sinactine in this plant to proceed as follows: L-tyrosine → norreticuline → (*R*)-reticuline → scoulerine → cheilanthifoline → (*R*)-sinactine.

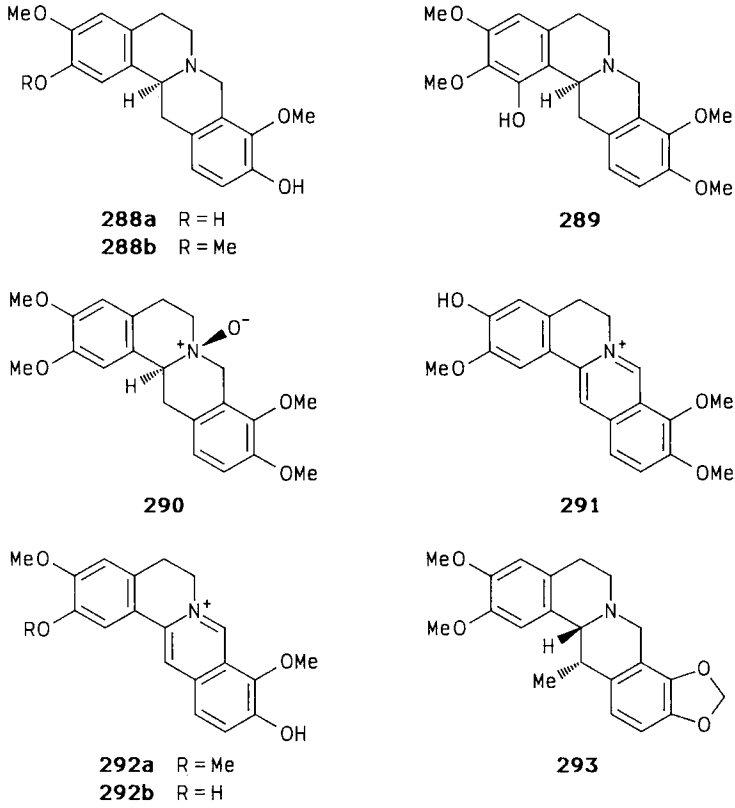
Tetrahydropalmatine occurs in nature in optically active (*312*) and racemic (*313*) forms. The incorporation of norlaudanosoline, norprotosinomenine, nororientaline, norlaudanidine, reticuline, and laudanosine, studied as racemic mixtures into palmatine and tetrahydropalmatine was reported (*314*).

Feeding of radiolabeled (±)-reticuline demonstrated that C-8 of tetrahydropalmatine and palmatine was formed by oxidative cyclization of the NMe group. Parallel experiments with labeled (*R*)- and (*S*)-reticuline demonstrated specific incorporation of the *R* isomer, revealing also that the plant converted tetrahydropalmatine to palmatine with high efficiency. Incorporation of dehydroreticuline into tetrahydropalmatine and palmatine in *C. laurifolius* was demonstrated, and parallel feedings of (*R*)- and (*S*)-reticuline showed specific incorporation to afford either (*R*)- or (*S*)-tetrahydropalmatine. Feeding of doubly

labeled reticuline suggested that reticuline was not converted first to dehydroreticuline in this plant and that racemization of optically active tetrahydropalmatines via dehydrotetrahydropalmatine did not occur (*314, 315*).

Tetrahydroprotoberberines and berberines isolated from *Stephania glabra* are (*S*)-(−)-stepholidine (**288a**), (*S*)-(−)-corydalmine (**288b**), (*S*)-(−)-capaurine (*289*), (*S*)-(−)-corynoxidine (**290**), jatrorrhizine (**291**), tetrahydropalmatine, palmatine, stepharanine (**292b**), and dehydrocorydalmine (**292a**). Their biosynthetic correlation is of interest (Scheme 44).

Initial feeding of labeled tyrosine to *S. glabra* showed that this plant was actively biosynthesizing stepholidine, corydalmine, scoulerine, tetrahydropalmatine, palmatine, dehydrocorydalmine, and jatrorrhizine (*316*). Feeding norlaudanosoline, norreticuline, reticuline, nororientaline, protosinomenine, norlaudanidine, coclaurine, and *N*-methylcoclaurine showed that only norlaudan-



SCHEME 44. Alkaloids of *Stephania glabra*.

osoline, norreticuline, and reticuline were efficient precursors of stepholidine and corydalmine.

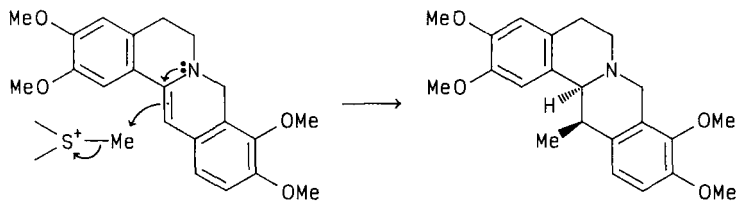
The regiospecifity of labeling in the biosynthetic stepholidine (**288a**) derived from reticuline was established by exhaustive degradation, affording radioactive formaldehyde and maintaining 95% of original radioactivity. Similarly, corydalmine (**288b**), obtained from feeding of labeled norreticuline, afforded radioactive formaldehyde containing 98% of the original activity (*316*). Atom C-8 of stepholidine (**288a**) and corydalmine (**288b**) was shown to be derived from the NMe group of reticuline.

The foregoing experiments established that reticuline was specifically incorporated into stepholidine (**288a**) and corydalmine (**288b**), but the positions of OH and OMe groups in reticuline and derived berbines **288a** and **288b** had changed. This change in position of functional groups during biotransformation could have taken place either by an O-demethylation–remethylation process or by methyl migration. When doubly labeled norreticuline was fed to young cut branches of *C. laurifolius* and stepholidine (**288a**) and corydalmine (**288b**) was isolated, it was found that both alkaloids were essentially devoid of the labels, and it was suggested that a change in the position of OH and OMe groups probably had occurred by an O-demethylation–remethylation process (*316*). Feeding of labeled scoulerine (**281a**) suggested that this process occurred after the formation of **281a.** It was also demonstrated that in the biosynthesis of stepholidine (**288a**) and corydalmine (**288b**) in *C. laurifolius* the asymmetric center in reticuline remained unaffected during its biotransformation to berbines. However, parallel feedings with labeled (*S*)- and (*R*)-reticuline demonstrated that the configurations were kept in their biotransformation to stepholidine (**288a**) and corydalmine (**288b**). (*S*)-Reticuline was incorporated about 40 and 30 times more efficiently than its *R* isomer. Tritiated corydalmine (**288b**) and stepholidine (**288a**), when fed to young *S. glabra* plants, were incorporated efficiently into the protoberberine dehydrocorydalmine (**292a**) and stepharanine (**292b**).

Tritiated tetrahydropalmatine when fed to the plants was poorly transformed to capaurine (**289**) and corynoxidine (**290**), suggesting that either tetrahydropalmatine was not on the direct biosynthetic pathway or did not reach the site of biosynthesis. Feeding results demonstrated that protoberberinium salts in nature were formed by dehydrogenation of berbine alkaloids, but their rate of conversion was different. In some plants both berbines and protoberberine alkaloids coexist. For example, in *S. glabra* tetrahydropalmatine and palmatine, corydalmine and dehydrocorydalmine, and stepholidine and stepharinine occur together. The other quaternary protoberberines, jatrorrhizine palmatrubine, glabrine, and glabrinine were also isolated from *S. glabra;* however, the corresponding berbines have not yet been obtained. It appears that the rate of conversion of berbines to protoberberine alkaloids in plants is very fast.

Incorporation of the racemic alkaloids protosinomenine, nororientaline, and norlaudanidine into cavidine **293** was studied (*317*). Feeding of racemic reticuline and norreticulne showed that both were efficient precursors of **293,** and feeding of doubly labeled norreticuline gave labeled cavidine. The label ratios in precursor and product thus established that the H atom at C-1 in norreticuline was not lost during its bioconversion. Parallel feedings of (*S*)- and (*R*)-reticuline demonstrated that (*R*)-reticuline was incorporated more efficiently than its *S* enantiomer.

Early stages of biosynthesis of berberine (**282**) and corydaline (**295**) were examined by feeding of labeled dopa to *Hydrastis canadensis, Corydalis solida,* and *C. ochotensis.* The isolated bases **282** and **295** were found radioactive (*318*). The degradation results demonstrated predominant incorporation of dopa into the upper half (isoquinoline part) of the alkaloids. Late stages in the biosynthesis of corydaline (**295**) in *C. solida* were studied by feeding labeled tetrahydropalmatine and labeled palmatine. Only palmatine was specifically utilized by the plants to form **295.** It was established previously that no reversible oxidation–reduction of corydaline (**295**) occurred in *C. solida,* and possibly with tetrahydropalmatine in *C. solida* (*318*). The methyl group at C-13 was perhaps added at the dehydroprotoberberine (**294**) stage, arising from palmatine, but this has to be verified (Scheme 45).



294 **295**

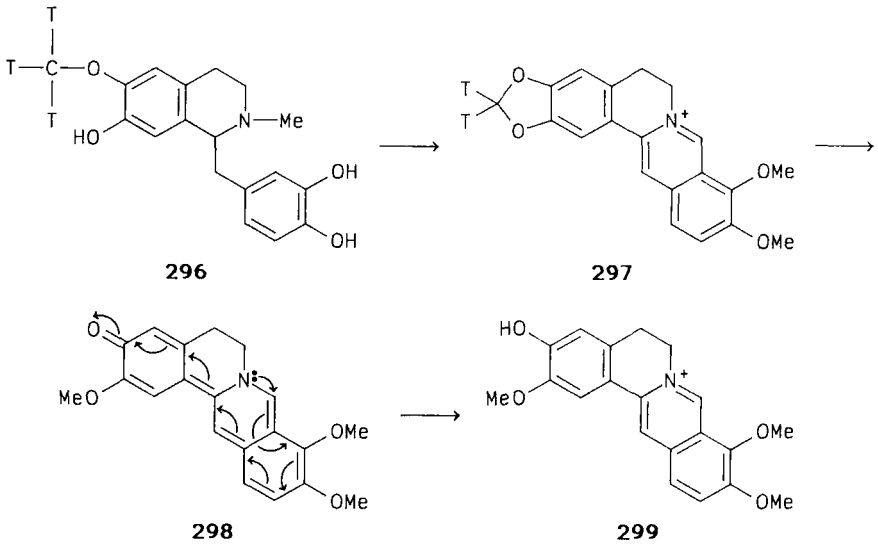
SCHEME 45. Biosynthesis of corydaline (**295**).

Battersby and coworkers (*319*) demonstrated that (±)-scoulerine in the *Chelidonium majus* plant was converted to protopine, stylopine, and chelidonine, and (*S*)-(−)-scoulerine **281a** was incorporated more efficiently into all three alkaloids.

Beecher and Kelleher (*320*) have shown high incorporation (12.8%) of labeled berberine (**282**) into jatrorrhizine (**299**) in a 14-day-old *Berberis aggregata* callus culture and proposed a possible mechanism for the bioconversion (Scheme 46).

Hydride attack at the methylenedioxy carbon of berberine (**282**) promotes an electron shift, affording the quinonemethide **298,** which accepts a proton and affords the quaternary salt of jatrorrhizine (**299**).

Zenk and coworkers (*321*) have studied in detail the biosynthesis of berberine



SCHEME 46. Biosynthesis of jatrorrhizine (**299**).

(**282**). Parallel feeding of (*S*)-reticuline and (*S*)-protosinomenine showed a predominant incorporation of the former (4.4%) over the latter (0.73%) into jatrorrhizine (**299**) in calluses of *B. stolonifera,* indicating a preference for the reticuline pathway. Parallel feeding of 6-*O*-methylnorlaudanosoline (**296**) and 7-*O*-methylnorlaudanosoline showed that the former was incorporated (4%) with greater efficiency than the latter (incorporation 0.6%). Reduction of labeled jatrorrhizine (**299**) with $NaBH_4$, followed by O-demethylation showed that no transfer of the label to a methoxy group had occurred. It was suggested that transformation of the precursor **296** to jatrorrhizine (**299**) must involve an internal transfer of the methyl group from the C-6 position in (*S*)-reticuline to give the C-2 position in jatrorrhizine. This was proved with a doubly labeled precursor of **296** prepared enzymatically with methyl-tritiated and ^{14}C-labeled (*S*)-adenosylmethionine to label the 6-*O*- and *N*-methyl-groups, respectively. When supplied to *B. stolonifera* callus for 48 h, incorporation into jatrorrhizine (**299**) occurred (0.6%), and the isotope ratio corresponded to a loss of one-third of the tritium label of the original 6-OCH_3 of **296.** Berberine, which was also isolated from this callus showed 0.6% incorporation and the same isotope ratio as found in jatrorrhizine. This finding suggested that jatrorrhizine was formed from berberine by reopening of the methylenedioxy group. Indeed, berberine-^{14}C was incorporated by *Thalictrum minus* callus to an extent of 1.6% into jatrorrhizine, providing evidence that the major biosynthetic route to jatrorrhizine went through berberine.

B. Aberrant Biosynthesis

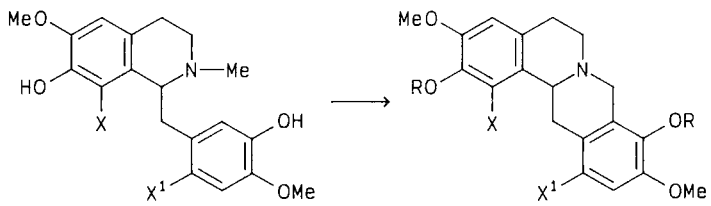
Transformations where an "unnatural precursor" is converted to an "unnatural product" or an "unnatural precursor" is converted in a living system to a "natural product" is called "aberrant biosynthesis." This area of research is relatively unexplored in higher plants.

The bioconversion of several substituted 1-benzyltetrahydroisoquinoline derivatives to the corresponding substituted berbines was studied (*322*). Tritiated 6′- and 8-bromoreticulines (**300** and **301,** respectively) fed separately to *Stephania glabra* and *Cocculus laurifolius* was found to be efficiently incorporated into 12-bromoscoulerine (**303**) and 1-bromoscoulerine (**305**) in both plants (Scheme 47).

Labeled **303,** when treated with CH_2N_2, afforded 12-bromotetrahydropalmatine (**304**) and after debromination, tetrahydropalmatine, which was dehydrogenated to radioactive palmatine (*322*). These experiments established that 6′-bromoreticuline was specifically converted to 12-bromoscoulerine in *S. glabra.*

Tracer experiments with labeled dibromoreticuline (**302**) showed that this compound was specifically converted to 1,12-dibromoscoulerine (**307**) and 1,12-dibromotetrahydropalmatine (**308**) in plants (*322*).

Tritiated 6′-nitroreticuline, when fed to young cut branches of *C. laurifolius,* afforded tritiated 12-nitroscoulerine and 12-nitrotetrahydropalmatine (*322*). Radiolabeled (±)-6′-aminoreticuline, when fed to young cut branches of *C. laurifolius,* afforded 12-aminoscoulerine and 12-aminotetrahydropalmatine in radioactive form (*322*). These experiments suggest that some enzymes in *S. glabra* and *C. laurifolius* involved in the biotransformation of 1-benzyltetrahydroisoquinoline derivatives to the corresponding berbines appear to be nonspecific with regard to substitution in the aromatic moieties and are able to synthesize un-



300 X = H, X^1 = Br
301 X = Br, X^1 = H
302 X = Br, X^1 = Br

303 R = H, X = H, X^1 = Br
304 R = Me, X = H, X^1 = Br
305 R = H, X = Br, X^1 = H
306 R = Me, X = Br, X^1 = H
307 R = H, X = Br, X^1 = Br
308 R = Me, X = Br, X^1 = Br

Scheme 47. Aberrant biosynthesis of berbines.

natural alkaloids from unnatural precursors. No abnormal precursor in these experiments was found to give a normal protoberberine alkaloids.

C. Enzymatic Studies

Holland reviewed both the microbial and *in vitro* enzymatic transformation of alkaloids (*323*). The studies have been carried out with enzyme preparations of mammalian origin and with cell-free plant extracts. Biotransformation of (±)-reticuline to scoulerine and coreximine with rat liver homogenate was demonstrated (*322, 324, 325*). The yields of the alkaloids were significantly increased by the presence of cofactors (e.g., NAD, NADP, or NADPH). The stereochemistry of 1-benzyltetrahydroisoquinoline precursor (*S*)-reticuline was retained during its biotransformation to (−)-scoulerine and (−)-coreximine in rat liver microsomes (*326*). However, incubation of (±)-reticuline afforded racemates of the above alkaloids, thus demonstrating nonstereospecificity of the rat liver microsomes.

Incubation of (±)-reticuline *N*-oxide in rat-liver microsomes yields scoulerine and coreximine in high yield, detected by preparative thin-layer chromatography (*327*). Since reticuline *N*-oxide can easily be converted to protoberberine with acid and since (±)-reticuline *N*-oxide is a mixture of four optically active entities, no conclusion can be drawn for its intermediacy in such biotransformation.

Incubation of hexadeuterioreticuline in rat-liver homogenate was demonstrated (*325, 326*). Partial loss of deuterium occurred in the biotransformation of reticuline to scolulerine and coreximine, suggesting that N-demethylation of reticuline occurred first to form norreticuline, which then was converted to berbines. That C-8 in berbines originated from (*S*)-adenosylmethionine was shown by incubating a mixture of (±)-reticuline and (*S*)-methionine-*S-methyl*-^{14}C (*326, 328*).

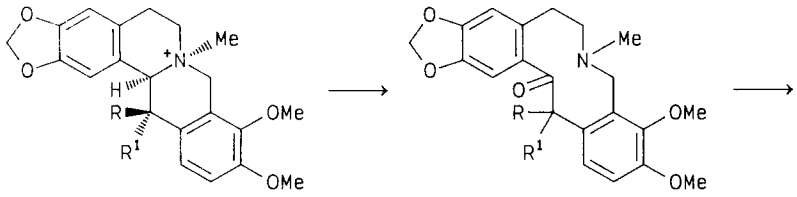
O-Methylation of racemates and the optical isomers of laudanosoline and 2,3,10,11-tetrahydroxyberbine were studied with catechol *O*-methyltransferases from rat liver (*329*), producing a mono-O-methylated major product and a di-O-methylated product in trace amounts. The position of O-methylation is affected by the stereochemistry of the substrate used.

Berberine bridge-forming enzymes were isolated from the cell cultures of *Berberis beaniana* Schneid and purified to homogenity (*330*). The enzyme was found to be enantiospecific for 1-benzyltetrahydroisoquinoline substrates requiring *S* configuration. In the presence of oxygen and stoichiometric amounts of hydrogen peroxide the enzyme was shown to catalyze the transformation of (*S*)-reticuline, (*S*)-protosinomenine, and (*S*)-laudanosoline to the corresponding berbines. Enzyme activity was monitored with labeled reticuline, affording (*S*)-scoulerine devoid of one-third of the radioactivity of reticuline. Neither (*S*)- nor R-reticuline N-oxide was transformed by the enzyme. The enzyme was found

inactive for the transformation of orientaline, nororientaline, and laudanidine to berbines (*330*). An enzyme responsible for the conversion of berbines to protoberberinium alkaloids was isolated and found enantiospecific for the oxidation of the *S*-enantiomer (*331*).

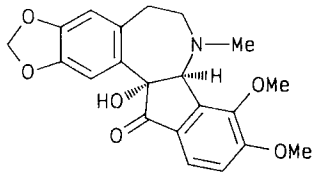
The enzyme failed to oxidize canadine to berberine in the presence of $NaBD_4$, and one atom of deuterium at C-13a was incorporated in the canadine isolated. Since 13,13a-dehydrocanadine and canadine methosalts were not oxidized by the enzyme, it is established that dehydrogenation of canadine occurred at C-13a generating first a 7,13a-dehydroberberinium species, which aromatizes to a protoberberinium species. Introduction of a methyl group at C-8 or at C-13 in berbines rendered them unsuitable for the enzymatic oxidation. The enzyme was shown to catalyze the oxidation of 20 different *S*-configurated berbines to the corresponding protoberberines. This enzyme was isolated first from *Berberis wilsonae* var. *subcaulialata* Schnied and subsequently from other *Berberis* species, which produce a considerable amount of berbine alkaloids but are also found in *Papaver somniferum* (*331*).

Iwasa *et al.* (*332*) studied the biotransformation of 13-hydroxyberbines, in callus cultures of *Corydalis* spp. Callus from *C. ophiocarpa*, when grown on a solid medium containing tritiated epiophiocarpine α-*N*-methyl chloride (**309**) with a cis-fused quinolizidine ring, produced a tritium-enriched (87–90%) 13-hydroxyallocryptopine (**311**), 13-oxoallocryptopine (**312**), and tritiated epiophiocarpine-α-*N*-methyl chloride. This established the utilization of only the levorotatory form of epiophiocarpine-α-*N*-methyl chloride in this biotransforma-



309 R = H, R^1 = OH
310 R = OH, R^1 = H

311 R = H, R^1 = OH
312 RR^1 = O



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SCHEME 48. Biosynthetic pathways of benzindanoazepine (**313**).

tion. Similarly, callus preparations from *C. ochotensis* var. *raddeana,* when grown on agar medium with tritiated epiophiocarpine α-*N*-methyl chloride (*309*), produced **311** and **312.** However, tritiated epiophiocarpine-β-*N*-methyl chloride (**309**) with a trans-fused quinolizidine ring was not metabolized by the callus culture from *C. ophiocarpa* (Scheme 48).

(±)-Ophiocarpine-α-*N*-metho salt (**310**) with a cis-fused quinolizidine ring was biotransformed to the benzindanoazepine alkaloid **313** via **312** in a callus culture from *C. ophiocarpa.* This demonstrates that the α-*N*-metho salts of both (±)-epiophiocarpine and (±)-ophiocarpine with trans and cis configuration were utilized. The experiments defined the following biosynthetic pathway: (±)-epiophiocarpine-α-*N*-metho salt (**309**) or (±)-ophiocarpine-α-*N*-metho salt (*310*) → 13-hydroxyallocryptopine (**311**) → 13-oxoallocryptopine (**312**) → benzindanoazepine (**313**).

X. Pharmacological Properties

Protoberberines and their relatives exhibit several types of biological activities (*2*). However, to date berberine alone was found to be of clinical value and is being used in the treatment of gastrointestinal disorders.

Sado (*333*) examined systematically antibacterial activity of berberine chloride, iodide, and palmatine iodide against *Vibrio, Eberthella, Salmonella,* and *Escherichia* organisms and observed that the antibacterial action of berberine chloride was virtually invariant between pH 5 and 9. Berberine sulfate inhibited the growth of *Candida tropicalis* and *Xanthomones citri* at a concentration of 3.1 μg/ml and of *Pseudomonas* and *Salmonella* at a concentration >100 μg/ml (*334, 335*). Lahiri and Dutta (*336*) have recommended the use of berberine as an adjunct to isotonic saline and electrolyte replacement therapy in acute cholera (*336*). Berberine is reported to depress intestinal peristalsis and to remove inflammatory congestion of the mucosal surface of the intestine. Berberine has been found effective also in the treatment of diarrhea of infancy and childhood (*337*). Krey and Hahn (*338*) have observed that berberine formed a complex with DNA, probably intercalating into supercoiled mitochondrial DNA to produce configurational changes in DNA.

Better antibacterial activity than berberine has been demonstrated by salts of berberine and sulfanilamide (*339*). However, appropriate comparisons with standard antibacterials are lacking. Berberine chloride is found to eliminate *Syphacia obvelata* from the intestine of mice (*340*). Berberine is also found effective in the treatment of cutaneous leshmaniasis (*341*). Antifungal and antiarrhythmic activities have been shown by a number of 8-substituted berberines (*342*). Berberine sulfate and tetrahydropalmatine inhibit the respiratory chain by interfering with the action of NADH oxidase (*343*). Berberrubine chloride isolated from

Thalictrum polygamum is found to possess antimicrobial activity against *Mycobacterium smegmatics* at 100 μg/ml (*344*).

Suffness and Cordell (*345*) have reviewed anticancer activity of protoberberines. Berberine has been reported to possess cytotoxic (*346*) and neoplasm inhibitory activity (*347*) against KB and Ehrlich ascite tumor cells. Coralyne chloride, a 8-methylhexadehydroberberinium salt, is found to possess antileukemic activity against both P-388 and L-1210 strains in mice (*348*). A number of coralyne salts and analogs have been synthesized, and structure–activity relationship has been studied (*349*). The 8-ethyl homologs are found to have better activity than the 8-methyl compounds, while the 8-propyl derivative is found ineffective. There is a slight decrease in antileukemic activity when one or both of the O-dimethoxy groups are replaced by methylenedioxy groups. The two (8-methyl and 8-ethyl) bis(methylenedioxy) analogs exhibit activity against human epidermoid carcinoma of the nasopharynx (KB) *in vitro* in contrast to the dimethoxy compound. Although different salts of coralyne have comparable activity, coralyne acetosulfate is found most active. The planarity and rigidity of molecules of these types are found critical to activity. Coralyne formed a stable complex with thymus DNA *in vitro,* which is found responsible for its activity. The activity of coralyne against L-1210 is shown to be schedule independent. An adduct of berberine and thiophosphoric acid exhibits anticancer, analgesic, and antiinflammatory activities (*350*). *C*-x-Alkyl derivatives of tetrahydropalmatine and tetrahydroberberine show anticancer activity in rats (*351*).

Cardiovascular and CNS activities are reported for many tetra- and trisubstituted berbines (*352*). A large number of berbines substituted in rings A and D exhibit marked tranquilizing properties in initial tests (*353*). Berberine has transient hypotensive activity in rats, which can be prolonged by substituting the *C*-9-OMe group with *O*-*n*-C_4H_9 or *O*-*n*-C_5H_{11} (*354*). (−)-Canadine methochloride also exhibits some hypotensive activity in anesthetized cats and dogs (*355*). (−)-Tetrahydrocoptisine has been found to possess antipsychotic and neuroleptic activities in mice and rats (*356*). Hypotensive as well as sedative and analgesic activities are found in (±)-11-hydroxy-2,3,10-trimethoxy-8-methyl-13α*H*-berbine (*167*). (−)-Tetrahydroberbine-*d*-camphor sulfonate is reported to be an effective antipsychotic drug with minimal side effects (*357*). Oral administration of a dose of 25 mg/kg of the drug to mice shows sedation within 30 min. Aminoberbine derivatives are reported to exhibit analgesic activity in mice (*358*).

Contractive activities of tertiary and quaternary berberine-type alkaloids have been studied on isolated uteri of mice (*359, 360*). Quaternary protoberbines including berberine, palmatine, jatrorrhizine, coptisine, and dehydrocorydaline cause marked contraction of uterine muscles, but only a weak spasmolytic activity is exhibited on isolated intestines of mice. On the contrary, berbines including canadine, tetrahydropalmatine, and tetrahydrojatrorrhizine show

strong papaverine-like action, although their contractive activities on uteri are transitory. Dehydrocorydaline chloride is found to possess considerable gastric antisecretary activity (*361*). When administered orally to rats and guinea pigs, it prevents gastric and duodenal ulcers (*362*).

Berberineacetone derivatives have been claimed to possess antihistamine and antiinflammatory activities (*363*). The *cis*- and *trans*-norcoralydine methiodides have shown neuromuscular blocking activity (*364*). The 2,3,10,11-substituted protoberberines and their derivatives exhibit analgesic, vasodilating, and antihypertensive properties (*365*). Dehydrocorydaline shows a significant adrenergic neuron-blocking effect (*366*). Replacement of hydrogen by deuterium in *cis*-and *trans*-norcoralydine derivatives enhance their neuromuscular blocking activity (*367*).

8,13-Dibenzyldihydroberberine *in vitro* exhibits antistaphylococcal activity; however, the base *in vivo* is found inactive. Weak antitubercular activity *in vitro* is shown by a number of dihydroberberines (*368*). The long-lasting and relatively strong adrenergic alpha-blocking effects of xylopinine on the blood pressure of rabbits, cats, and dogs has been established (*369*). Berberine markedly inhibits acetylcholinesterase (*370*) both *in vivo* and *in vitro,* resulting in the temporary decrease of blood pressure. The base also inhibits the action of tyrosine decarboxylase (*371*) and tryptophanase (*372*), acting as an antagonist of the coenzyme pyridoxal phosphate. Coralyne salts are proved to be more potent inhibitors of catechol-*O*-methyltransferase than pyrogallol (*349*).

Pavelka and Kovar (*373*) have studied the liver alcohol dehydrogenase activity of several protoberberine alkaloids. 13-Ethylberberine has been found to be the most active inhibitor of liver alcohol dehydrogenase (*373*). The compound is bound more firmly to the enzyme at pH 10 than NAD and NADH (*373*). Salts of palmatrubine esters specifically inhibit xanthine oxidase (*374*). The quaternary protoberberine alkaloids, berberine, coptisine, and substituted berbines are found to be weak inhibitors of butyrylcholinesterase in human serum, whereas jatrorrhizine and columbamine are found to be more potent (*375*).

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— CHAPTER 3 —

SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS

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I. Introduction

The indolizidine and quinolizidine ring systems are found in bewildering profusion in nature. Inspection of a recent compendium of alkaloid structures (*1*) reveals that between 25 and 30% of all alkaloids incorporate these structures or various unsaturated versions of them. How, then, is the reviewer to interpret a mandate to discuss "simple" indolizidine and quinolizidine alkaloids?

We have adopted the following policy in preparing the material for this chapter:

1. If the azabicyclic nucleus is embedded within a fused polycyclic ring system, the alkaloid is no longer considered to be simple. This effectively excludes a huge variety of compounds, ranging from a few tricyclic alkaloids to some highly complex structures like those of the Aspidosperma alkaloids and many steroidal alkaloids. The only exceptions we have admitted are the unique Streptomyces and sponge metabolites discussed in Sections III,E and IV,C, respectively. Of course, many simple indolizidine and quinolizidine alkaloids bear additional rings as substituents, and these compounds fall within the ambit of this chapter.

2. Several families of alkaloids include a few simple indolizidines and quinolizidines among their members. In most cases, these families have formed the subject of previous chapters in this treatise. The alkaloid families falling into this category include Elaeocarpus, Lythraceae, Nuphar, and lupine alkaloids, as well as compounds obtained from amphibians. In our endeavors to provide a comprehensive catalog of alkaloids containing isolated indolizidine and quinolizidine nuclei, we could not avoid duplicating material that may be found elsewhere in these volumes. For these compounds, we have done little more than list their structures and natural sources and have included biosynthetic and synthetic discussion only where such material updates that in the previous reviews.

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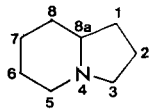
3. Several other simple indolizidine and quinolizidine alkaloids, for example, those from species of *Dendrobium* and *Poranthera,* have been treated cursorily in the past in the chapters entitled "Alkaloids Unclassified and of Unknown Structure." These compounds will be dealt with more fully in this review.

Our rigorously limited view of what constitutes a simple alkaloid inevitably entails artificial exclusion of certain compounds that have obvious structural and biogenetic relationships to those under discussion. The bicyclic compound porantherilidine, for instance, should ideally be discussed alongside its tri- and tetracyclic relatives. On the other hand, an alkaloid like septicine, which is merely a seco version of the phenanthroindolizidine alkaloid tylophorine, was excluded on structural grounds from the recent chapter on phenanthroindolizidine alkaloids (*2*) but will find an appropriate home in this review.

Those alkaloids that remain within the scope of this chapter nevertheless form a large group and comprise an impressive diversity of structural types. There are representatives from a cross section of natural sources, including fungi, higher plants, insects, amphibians, and mammals. In order to keep the volume of subject matter in this chapter to manageable proportions, we have dispensed with most of the detail on the isolation and separation of alkaloids from their source materials, and also much of the minutiae of structural proofs based on chemical degradations and interconversions, or on the interpretation of spectra. The greater part of the literature on the systems of interest deals with their synthesis, and this is reflected in our review. Biosynthetic work, on the other hand, is sparse; and pharmacological or other biochemical studies, with the notable exception of the indolizidines slaframine, swainsonine, and castanospermine, are virtually nonexistent. We have endeavored to include all references up to the end of 1984, and publications from the early 1985 literature have also received coverage.

There are a few other fairly general reviews available, which survey facets of the chemistry of simple indolizidine and quinolizidine alkaloids. Foremost among these is the indispensable Royal Society series *The Alkaloids* (*3*), an annual current awareness series, which highlights important developments in all aspects of alkaloid chemistry. This series has recently (1984) been absorbed into a bimonthly publication, sections of which have already been devoted to indolizidine and quinolizidine alkaloids (*4,5*). Other reviews on the alkaloids of interest are also available (*6–9*); reviews on specific classes of these alkaloids are referenced in the appropriate sections of this chapter. There are several reviews



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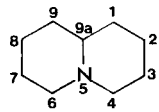

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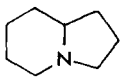
dealing wholly or in part with the spectroscopy of indolizidine and quinolizidine alkaloids (*10–16*). Finally, the important and complex subject of the stereochemistry and conformation of indolizidine- and quinolizidine-containing compounds has also been reviewed (*17*).

In the following chapter, we shall be using the *Chemical Abstracts* numbering system for indolizidines and quinolizidines as shown in **1** and **2**. The most commonly seen variant of this system designates position 8a in **1** and 9a in **2** as 9 and 10, respectively.

II. δ-Coniceine

There is a persistent misconception that δ-coniceine (**3**) is an alkaloid. In fact, the only naturally occurring coniceine is γ-coniceine (**4**), a hemlock alkaloid isolated from *Conium maculatum* L. (*18*). δ-Coniceine is a purely synthetic material, obtained as long ago as 1885 (*19*) from the cyclization of *N*-bromoconiine (**5**) with sulfuric acid. The origins of the misconceptions are obscure, but that it has persisted is surprising in view of the quite unambiguous statements in previous volumes of this treatise (*20–22*) as to its origin.



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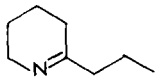

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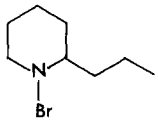

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As the parent ring system for the indolizidine alkaloids, however, **3** possesses intrinsic interest. Many syntheses of the compound, some showing a high degree of originality, have been reported, and several of these have expressly been designed as models for the synthesis of more complex indolizidine alkaloids. It is therefore appropriate to begin this review with a brief discussion of recent synthetic approaches to the unadorned indolizidine skeleton. Since the last coverage of the topic in this treatise extended only to 1959, we have had to be selective in our choice of material, and some of the more routine approaches have received only passing mention. Supplementary information may be found in two old reviews and summaries (*23,24*) and among the material contained in a 1978 review (*25*).

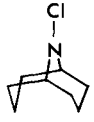
1. The Hofmann–Löffler–Freytag Reaction

The classic synthesis of δ-coniceine from *N*-bromoconiine (**5**) and concentrated sulfuric acid (*19,26*) has been optimized to give (±)-**3** in 50% yield and

greater than 95% purity (*27*). When optically active coniine is used to prepare **5**, the synthesis can be made to yield either enantiomer of δ-coniceine. Gas-chromatographic analysis of the *N*-trifluoroacetyl-L-prolyl derivatives of the resulting products indicates at least 99% optical purity. This work provides the best values to date for the optical rotations of both antipodes of **3** and also establishes their absolute configurations. (−)-Coniine gives (+)-δ-coniceine ($[\alpha]_D$ +9.3 ± 0.6°, *c* 1.77, ethanol); and (+)-coniine gives (−)-δ-coniceine ($[\alpha]_D$ −10.2 ± 0.6°, *c* 1.76, ethanol); since (+)-coniine has been correlated with D-pipecolic acid (*28*), (−)-δ-coniceine belongs to the *R* series. Incidentally, it is somewhat ironic that the only syntheses of optically active δ-coniceines should be by this relatively unsophisticated old procedure.

A transannular version of the Hofmann–Löffler–Freytag reaction on *N*-chloroazacyclononane has been used to prepare (±)-δ-coniceine (**3**) (*29,30*). The reaction is induced by silver(I) under both homogeneous and heterogeneous conditions. The presence of free secondary amine markedly enhances the product yield, the best obtained being 68%. The authors find no evidence for the intermediacy of discrete nitrenium ions: in fact, yields are drastically reduced in the presence of oxygen, and nitrogen-centered radicals can be trapped by adding 2-methyl-2-nitrosopropane to the reaction mixture (*31*).

Nitrenium ions, on the other hand, appear to be involved in the silver-induced rearrangement of *N*-chlorogranatinine (**6**) to (±)-**3** (*32*). When the reaction is performed with silver tetrafluoroborate in benzene, it appears, on the basis of NMR evidence, that the iminium ion **7** is an intermediate (*33*). On treatment of the crude product with sodium borohydride, (±)-**3** is obtained in 92% yield. When the reaction is performed with silver nitrate in methanol, followed by treatment with sodium cyanoborohydride and acetic anhydride, only the pyrrolizidine **8** and *N*-acetylgranatine are obtained in yields of 25 and 50%, respectively.



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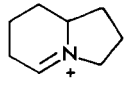

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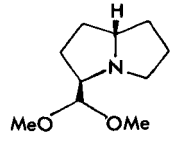

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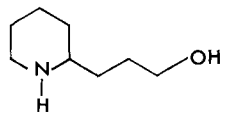
2. Intramolecular Cyclo-*N*-alkylation and Cyclo-*N*-acylation of 2-Substituted Piperidines and Pyrrolidines

The cyclization of 2-(3-hydroxypropyl)piperidine (**9**), generally obtained by reduction of the corresponding pyridine derivative, to δ-coniceine has been per-



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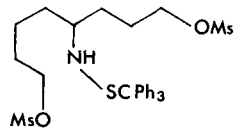

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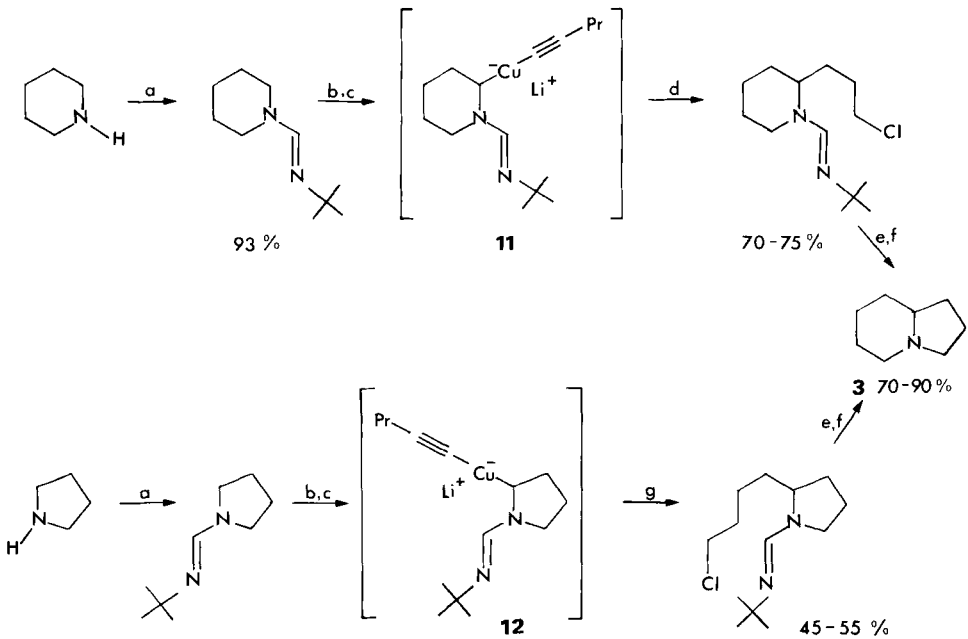
formed in innumerable ways since its first description in 1909 (*34*). In the past quarter century, the cyclization has been carried out in 48% yield with hydrogen bromide followed by base workup (*35*), in 85% yield with Raney nickel (*36*), in 80% yield with *N,N*-dimethylaminophosphodichloridate (*37*), and in 42% yield with triphenylphosphine and tetrachloromethane in the presence of triethylamine (*38*). In a similar vein, (±)-**3** is formed in 75% yield on reductive cyclization of ethyl 3-(2-piperidyl)propionate with lithium aluminum hydride (*39*) and on treatment of 2-(3-hydroxypropyl)pyridine with thionyl chloride, followed by hydrogenation over platinum dioxide (*40*). Azamonocyclic intermediates are also undoubtedly involved in the synthesis of **3** from 2-(4-aminobutyl)tetrahydrofuran over an alumina–zirconia catalyst at 325–330°C (*41*) and in a rather lengthy



SCHEME 1. Synthesis of δ-coniceine by Edwards and Meyers (*43*). Reagents: (a) *N,N*-dimethyl-*N'*-*t*-butylformamidine; (b) *t*-BuLi, ether–THF, −78 to −20°C; (c) pentynylcopper, THF; (d) $ClCH_2CH_2CH_2I$; (e) Na_2S, H_2O, H^+; (f) KOH, MeOH–H_2O, 55°C; (g) $ClCH_2CH_2CH_2CH_2I$.

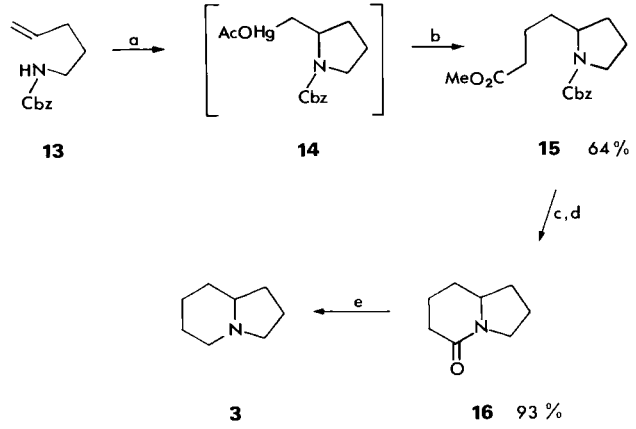
procedure, which has as key step the treatment of the dimesylate **10** with trimethylsilyl iodide and base (*42*). The synthesis of δ-coniceine in the latter case is only incidental; the main thrust of the report is on the use of tritylsulfenyl as a protecting group for amines.

Of greater interest is the versatile formamidine methodology developed by Meyers (Scheme 1), which provides a neat and general route to 1-azabicyclo[m.n.o]alkanes via 2-(ω-chloroalkyl)piperidines and -pyrrolidines (*43*). The *N*-*t*-butylformamidine derivatives of both pyrrolidine and piperidine undergo α-metalation with *t*-butyllithium. The lithiated species may be converted to the cuprates **11** and **12**, which, on treatment with the appropriate α,ω-chloroiodoalkanes, yield crude products, which cyclize directly to 1-azabicycles in the presence of base.

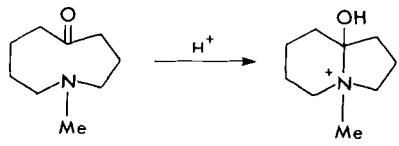
The novelty in Danishefsky's four-step synthesis of (±)-δ-coniceine (Scheme 2) lies in the initial steps rather than in the final cyclo-*N*-acylation (*44*). Intramolecular ureidomercuration of **13** with mercury(II) acetate gives a crude product formulated as **14**. The radical species resulting from the reduction of **14** with sodium trimethoxyborohydride can be trapped with methyl acrylate, giving the ester **15**. When the protecting group on nitrogen is removed by hydrogenolysis and the resulting product is warmed, bicyclic lactam **16** is formed in excellent yield. The synthesis of (±)-δ-coniceine (**3**) is completed by reducing **16** with lithium aluminum hydride.

3. Transannular Cyclizations on to Nitrogen

Medium-ring compounds tend to possess a degree of strain resulting from transannular interactions and often undergo rather unexpected transformations in

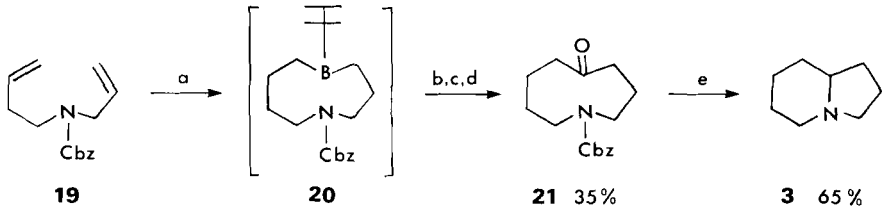


SCHEME 2. Synthesis of δ-coniceine by Danishefsky and co-workers (*44*). Reagents: (a) $Hg(OAc)_2$; (b) $Na(MeO)_3BH$, CH_2Cl_2, $H_2C{=}CHCO_2Me$; (c) hydrogenolysis; (d) Δ; (e) $LiAlH_4$, THF.



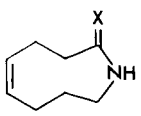
order to relieve this strain. In a compound like *N*-methylazacyclononan-5-one (**17**), for example, the carbonyl group is lost on protonation, as evinced by the disappearance of the C=O signal in the IR spectrum. The effect is ascribed to the ready formation of the species **18**, containing a transannular bond (*45*). The ease of transannular bond formation has been exploited by several groups in their syntheses of δ-coniceine; one example, the transannular Hofmann–Löffler–Freytag cyclization of *N*-chloroazacyclononane, has already been quoted (*30*).

Garst and Bonfiglio set up an azacyclononan-5-one system by hydroborating the N-protected diene **19** with thexylborane (Scheme 3) (*46,47*). The resulting boracycle **20** may be carbonylated to ketone **21** with great regioselectivity, though only in 35% yield. Hydrogenolysis of **21** over palladium catalyst completes this simple synthesis of (±)-δ-coniceine (**3**).

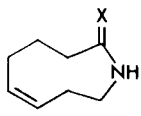


SCHEME 3. Synthesis of δ-coniceine by Garst and Bonfiglio (*46,47*). Reagents: (a) thexylborane, THF; (b) KCN, $(CF_3CO)_2O$: (c) NaOAc, H_2O_2, H_2O; (d) Jones oxidation; (e) H_2 (355 kPa), 10% Pd–C, MeOH.

The approach adopted by Wilson and Sawicki (*48*) depends on electrophilically initiated transannular attack by nitrogen on to the double bond of an azacyclononene mixture, **22** and **23**. Treatment of this mixture with bromine in dichloromethane gives a single bicyclic product **24** in 61% yield, the structure of which has been established by an X-ray diffraction study of its picrate salt. Reduction to δ-coniceine is accomplished in 43% yield, using lithium aluminum hydride. A more efficient synthesis (53% overall yield) results from treatment of the **22/23** mixture with mercury(II) chloride in tetrahydrofuran, followed by reduction of the organomercurial intermediate with sodium borohydride. This approach tolerates substituents on the azacyclononene ring and also works well on the lactam mixture **25/26**. In this case, the mercury(II) method gives the bicyclic lactam **16** in 85% yield. Reduction of **16** to (±)-δ-coniceine (**3**) with lithium aluminum hydride proceeds in 82% yield.



22 X = H_2
25 X = O

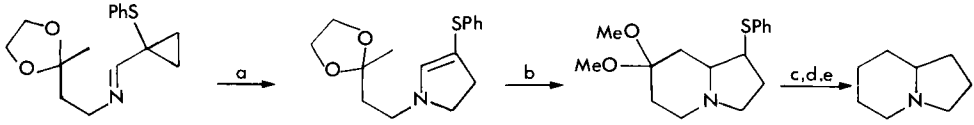


23 X = H_2
26 X = O

24

4. Intramolecular Cyclizations α to Nitrogen

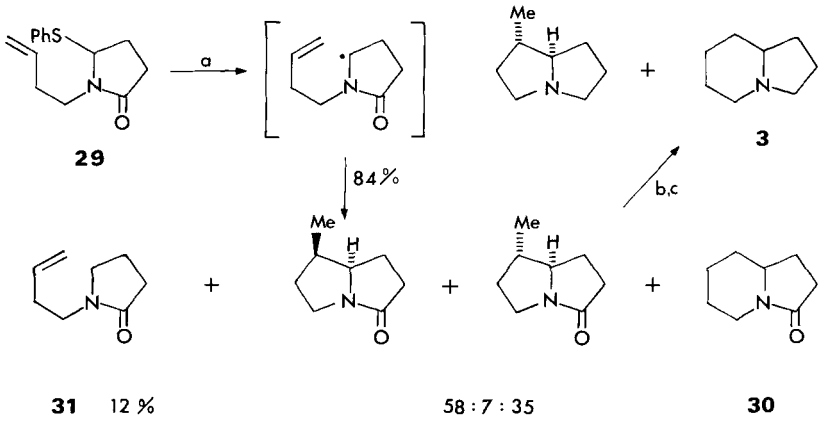
The generalized approach to alkaloid synthesis developed by R. V. Stevens has been tremendously successful in terms of the range of structures to which it permits access (*49*). The distinguishing feature of the method is the rearrangement of a cyclopropylimine to a Δ^2-pyrroline, which may then be elaborated in various ways to the desired alkaloid systems. The main features of its application to (±)-δ-coniceine are shown in Scheme 4 (*50*); other alkaloids made by the Stevens approach may be found in Section V,F of this chapter. In the present case, the role of the SPh group is to stabilize the endocyclic enamine **27**, a type of compound that is otherwise extremely susceptible to polymerization. The ring closure to the bicyclic system, **27** to **28**, effectively completes a Mannich reaction.



27 88 % **28** 90 % **3**

SCHEME 4. Synthesis of δ-coniceine by Stevens and co-workers (*50*). Reagents: (a) NH_4Cl, xylene, Δ; (b) HCl, MeOH; (c) Raney Ni (85% yield); (d) hydrolysis; (e) Wolff–Kishner reduction.

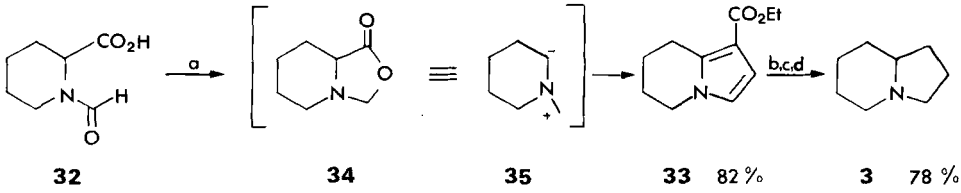
Hart has developed a generalized approach to heterocyclic synthesis, which employs α-acylamino radical cyclizations. The method is related to the well-known cyclization of α-acyliminium ions, studied extensively both by Hart and by Speckamp (*51*). In Hart's synthesis of (±)-δ-coniceine (*52,53*), the radical cyclization procedure is not seen to particular advantage since the key cyclization, induced by radical abstraction of phenylthio from **29** (Scheme 5), shows poor regioselectivity. The desired indolizidinone **30** makes up only about a quarter of the product mixture. In addition, since only the lactam **31** and the major pyrrolizidinone isomer can be separated from the product mixture, completion of the synthesis by reduction with lithium aluminum hydride must be performed on a mixture of indolizidinone **30** and the minor pyrrolizidinone isomer. The reduced products can, however, be separated as their picrate salts. The same product ratio results when the *S*-methyl analog of **29** is used initially, although the reaction proceeds at a much slower rate (*53*).



SCHEME 5. Synthesis of δ-coniceine by Hart and Tsai (*52*, *53*). Reagents: (a) Bu_3SnH, AIBN, benzene, Δ; (b) $LiAlH_4$, ether, Δ (32% combined yield); (c) picric acid, EtOH, fractional crystallization.

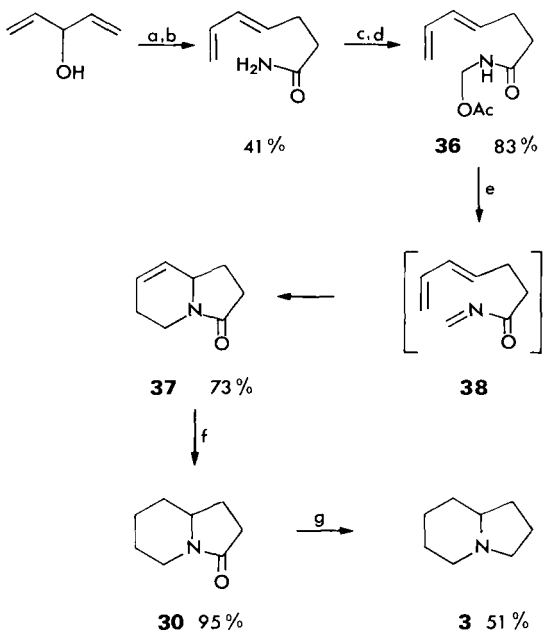
5. Heterocyclic Synthesis by Cycloaddition

An unusual 1,3-dipolar cycloaddition has been used by Pizzorno and Albonico in a general synthesis of 5,6,7,8-tetrahydroindolizines (*54*). In the example of interest (Scheme 6), when *N*-formylpipecolic acid (**32**) is heated with ethyl propiolate and acetic anhydride, the pyrrole **33** is obtained in 82% yield. The reaction proceeds via the intermediacy of **34**, effectively the equivalent of the 1,3-dipole **35**. Hydrolysis, decarboxylation, and hydrogenation over palladium complete the synthesis of (±)-δ-coniceine (**3**) in 62% overall yield based on **32**.



SCHEME 6. Synthesis of δ-coniceine by Pizzorno and Albonico (*54*). Reagents: (a) Ac_2O, ethyl propiolate. 120°C; (b) KOH, MeOH–H_2O, Δ; (c) 240°C; (d) H_2 (3 atm), 10% Pd–C, EtOH.

The intramolecular imino Diels–Alder reaction has been developed to a fine art by Weinreb, who has used it in the synthesis of a wide variety of alkaloids (*55*). In his synthesis of δ-coniceine (Scheme 7), the methylol acetate **36** is pyrolyzed over glass beads at 370–390°C. Formation of the bicyclic lactam **37** is presumably by way of the transient intermediate **38**. Hydrogenation of **37** yields the known lactam **30**, reduction of which with diborane completes the synthesis (*56*,*57*).



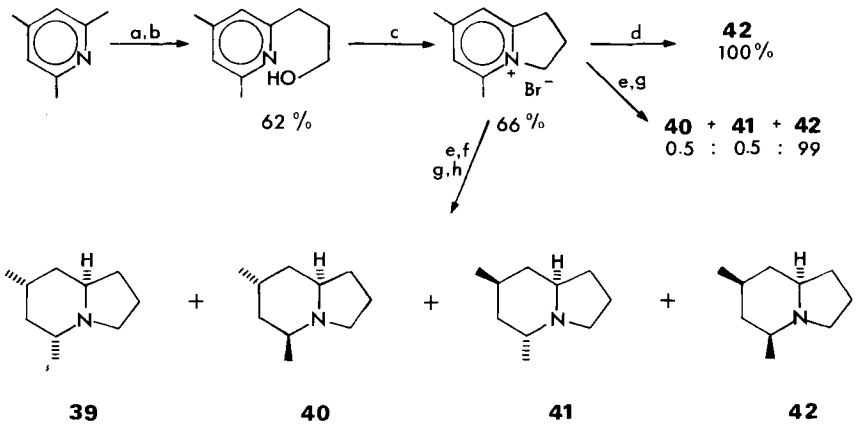
SCHEME 7. Synthesis of δ-coniceine by Weinreb and co-workers (*56,57*). Reagents: (a) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$ (cat.), 130–135°C; (b) Me_2AlNH_2, C_6H_6, Δ; (c) 37% aq H_2CO, 5% NaOH–H_2O, glyme; (d) Ac_2O, py; (e) $C_6H_5CH_3$, 370–390°C, glass helices; (f) H_2 (1 atm), 5% Pd–C, EtOAc; (g) BH_3, THF.

III. Alkyl, Functionalized Alkyl, and Acylindolizidine Alkaloids

A. DENDROPRIMINE

There is a noteworthy structural diversity among the alkaloids isolated from plants of the genus *Dendrobium* (family Orchidaceae). Three of these, two simple indolizidines and a bisindolizidine, fall within the scope of this chapter. These compounds have been described in passing in this treatise in chapters on "Alkaloids Unclassified and of Unknown Structure" (*58,59*). The alkaloid dendroprimine (**39**), a 5,7-dimethylindolizidine, will be discussed here, while the remaining two compounds, which bear aromatic rings as substituents, will be treated in Section V,A.

Dendroprimine (**39**) has been isolated from the species *Dendrobium primulinum* Lindl. as a colorless oil ($[\alpha]_D$ −38° *c* 1.0, chloroform) (*60*). The gross structure of the compound was deduced from its NMR and mass spectra, and from its dehydrogenation with selenium to 2,4-dimethyl-6-propylpyridine. The

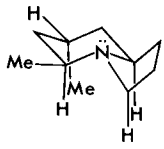


SCHEME 8. Synthesis of the four diastereomers of dendroprimine by Lüning and Lundin (*61*). Reagents: (a) PhLi; (b) ethylene oxide; (c) 48% HBr; (d) H_2 (50 atm), PtO_2, EtOH; (e) $LiAlH_4$, Et_2O, (f) Li, NH_3, Et_2O; (g) H_2 (1 atm), PtO_2, HOAc; (h) preparative GLC, 20% SE-52, 100°C.

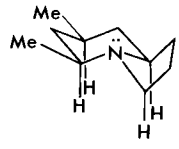
relative stereochemistry of the substituents was elucidated by comparing the natural material with synthetic samples of the four possible racemic diastereomers **39–42** (*61*). These compounds were synthesized as shown in Scheme 8.

Having the full set of diastereomers **39–42** affords a rare opportunity for investigating substituent effects on the conformations of indolizidines in a coherent fashion. The relative axial/equatorial orientations of the methyl groups on a chair-like piperidine ring follow from their chemical shifts and also from selected decoupling experiments on the signals for the methyl groups and the signals for hydrogen atoms adjacent to nitrogen. The stereochemistry of ring fusion may be deduced from the presence or absence of Bohlmann bands (*62*) in the IR spectra. Both **40** and **42** have strong Bohlmann bands; this fact, taken in conjunction with the NMR data, suggests conformations **43** and **44**, respectively, for these compounds. Compound **41** has weak Bohlmann bands; when this is interpreted along with the broadness of certain NMR signals and the doubling up of the signal for the C-5 methyl group, the existence of **41** as an equilibrium mixture of conformers **45a** and **45b** seems likely. Finally, the diastereomer **39**, spectroscopically identical to natural dendroprimine, completely lacks Bohlmann bands, and conformation **46** is proposed. The stereochemistry of ring junction in this compound appears to be preserved on protonation and N-methylation, again as judged by NMR effects.

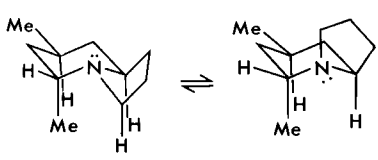
Some years after the relative configuration of dendroprimine was deduced, its absolute configuration was established as 5*R*,7*S*,8a*R* (*63*), as shown in **39**. This assignment was based on a sequence of Hofmann degradation/hydrogenation



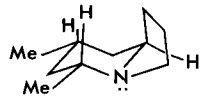
43=40



44=42



45a = 41 = 45b



46=39

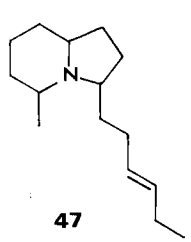
steps to (*S*)-(+)-4-methylnonane, a compound that had previously been correlated with (−)-shikimic acid. The CD curve of an intermediate in the degradation scheme, (+)-(2*S*)-methyl-1-[1-methyl-(2*R*)-pyrrolidinyl]pentane, shows a mirror-image relationship to that of a model compound, (*R*)-(−)-1,2-dimethylpyrrolidine, prepared from (*S*)-(−)-proline. This gives additional evidence for the *R* configuration at the pyrrolidine ring of the intermediate and hence at position 8a in dendroprimine (**39**).

B. Indolizidine Alkaloids from the Pharaoh Ant

1. Isolation and Synthesis

The Pharaoh ant, *Monomorium pharaonis* L., is a pest of tropical origin, which has become widely established in North America and western Europe. The insect is a persistent nuisance primarily in heated buildings; since it is a carrier of pathogenic bacteria, it presents a health hazard, particularly in hospitals where it can enter sophisticated isolation units and even penetrate bandages and sterile packs. The nests tend to be well hidden, and the usual insecticidal measures fail. The possibility of controlling this pest by pheromone manipulations was initiated by Ritter and co-workers at the instigation of the Dutch Ministry of Public Health and Environmental Hygiene (*64*).

A wide variety of rather simple alkaloids are produced by members of the Arthropoda, an extremely populous animal phylum (*65*). Among these animals, ants are well known as alkaloid producers, and a comprehensive listing of ant metabolites is contained in ref. *66*. The genus *Monomorium* is the source of various pyrrolidine alkaloids (*67*), but simple indolizidines appear to be unique to the Pharaoh ant (*68*). Several compounds have now been identified in the trail



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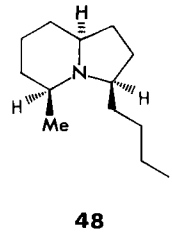
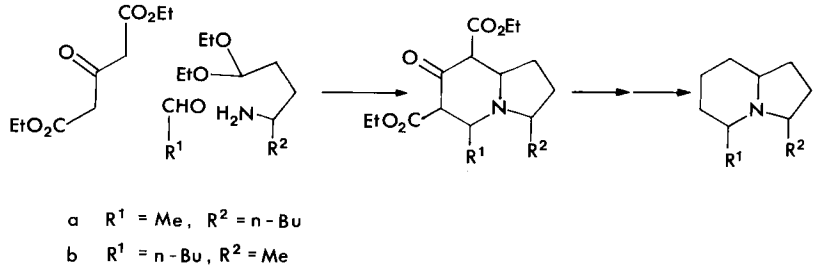


48

pheromone of this pest. The true attractant apears to be faranal, (3*R**,4*R**)-7,11-tetramethyl-(6*E*,10*Z*)-tridecadienal (*69*), which is found in Dufour's gland. The alkaloidal component includes four 2,5-disubstituted pyrrolidines (*67*) and the two compounds of interest for the present survey, the indolizidine **47** (*70*) (monomorine VI) and monomorine I (**48**) (*64,71,72*). The alkaloids are contained in various abdominal glands of the insect, including the poison and Dufour's glands, and are present in secretions collected directly from the insects' stings (*64*).

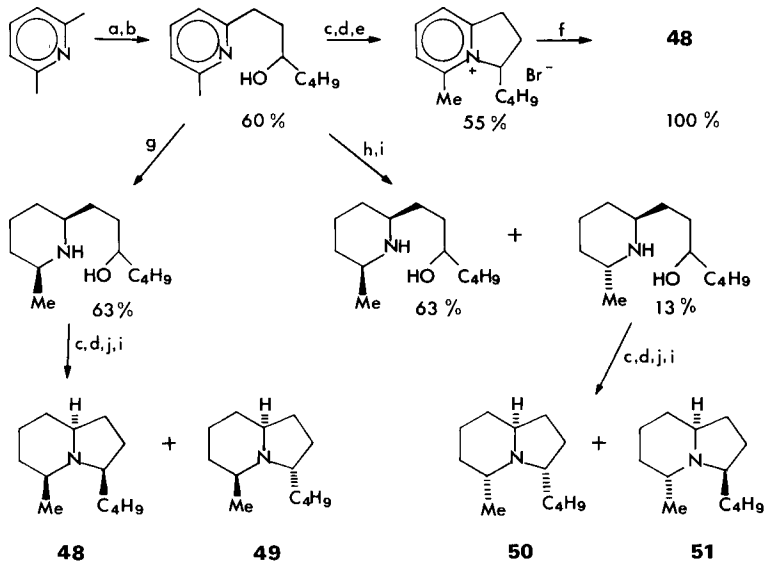
No further work seems to have been done on alkaloid **47**, and at the present time the relative stereochemistry in the compound is unknown. By contrast, work on monomorine I (**48**) has been extensive. This rather simple compound was originally isolated by preparative gas chromatography of the dichloromethane extract of about 6000 (1 g) homogenized ants (*71*). The natural compound is dextrorotatory (*64*); its optical rotation has been given as $[\alpha]_D$ +46.5° (*c* 0.032, hexane) (*73*), though the very small quantity of material available for the determination makes this value somewhat tentative. The gross structure was elucidated by spectroscopic techniques, especially mass spectrometry. The relative placement of the butyl and methyl side chains was confirmed by examining the mass spectra of various dehydrogenation products of both natural and synthetic materials (*72*) and by nonstereoselective syntheses of both the 3-butyl-5-methyl (*71*) and the 5-butyl-3-methyl isomers (*72*). These syntheses are outlined in Scheme 9.



a R^1 = Me, R^2 = n-Bu

b R^1 = n-Bu, R^2 = Me

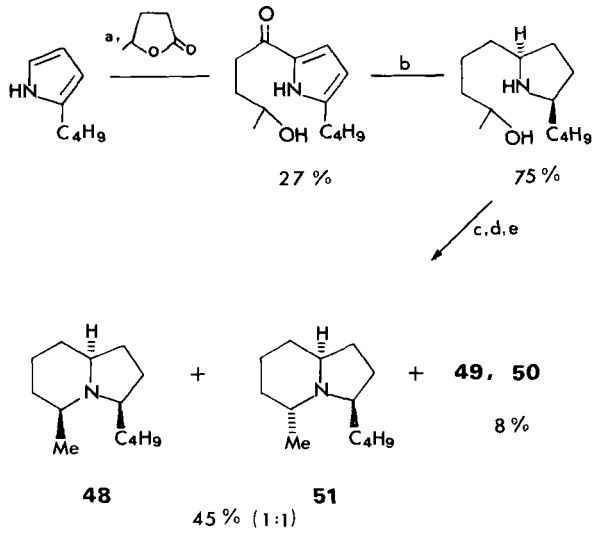
SCHEME 9. Nonstereoselective synthesis of 3-butyl-5-methylindolizidine and 5-butyl-3-methylindolizidine (*71,72*).



SCHEME 10. Synthesis of the four diastereomers of 3-butyl-5-methyl-indolizidine by Sonnet and Oliver (*74,75*). Reagents: (a) *n*-BuLi, C_6H_{14}; (b) 1,2-Epoxyhexane; (c) 48% HBr; (d) PPh_3, Br_2, MeCN, Δ: (e) Me_2CO, Δ; (f) H_2, PtO_2, EtOH, 45 psi; (g) H_2 (50 psi), PtO_2, HOAc; (h) Na, EtOH, Δ; (i) spinning band distillation; (j) NEt_3.

It was only after unambiguous synthesis of the four diastereomers of the compound by a number of alternative procedures that monomorine I was finally shown to have the all-cis stereochemistry shown in **48** (*74,75*). The two most successful synthetic routes are shown in Schemes 10 and 11: diastereomers were formed, which were generally separable by spinning-band distillation. A third synthetic method, using a Hofmann–Löffler cyclization on either *cis*- or *trans*-2-heptyl-6-methylpiperidine, was less satisfactory because of poor yields of bicyclic products (*75*). The structures of the diastereomers **48–51** were assigned on spectroscopic grounds and backed up by mechanistic arguments. Supporting structural evidence was later obtained by a detailed investigation, using ^{13}C NMR (*76*). The later studies also permitted the conformational assignment of the four compounds as **52–55**, respectively. Interestingly, the spectroscopic data for monomorine I itself are most satisfactorily interpreted on the basis of a boat-shaped piperidine ring.

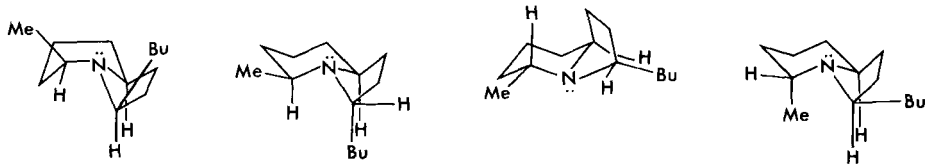
Stereoselective synthesis of monomorine I (**48**) has received limited attention. The important synthesis by Stevens and Lee (*77*) is outlined in Scheme 12. In this work, the cis stereochemistry between C-3 and C-8a is set up in the hydrogenation of **56** to **57**. More significantly, the stereochemistry at the remaining center, C-5, is introduced during the reduction of the iminium ion intermediate

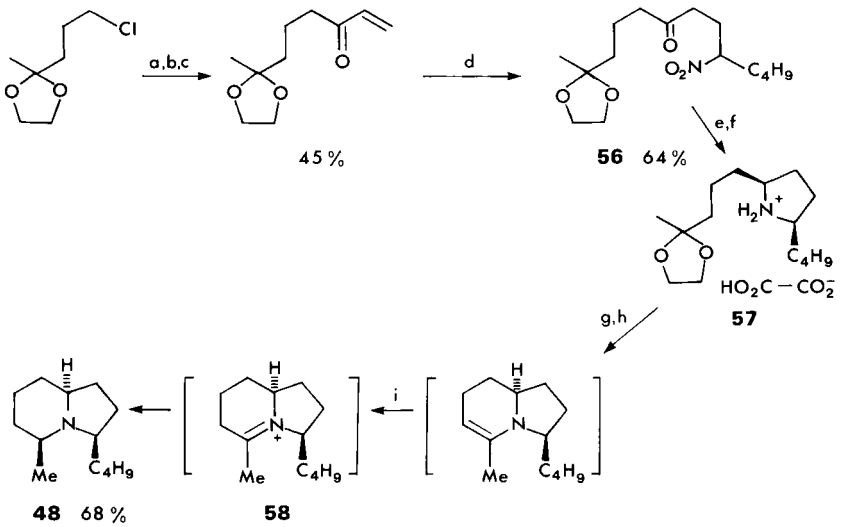


SCHEME 11. Alternative synthesis of two diastereomers of 3-butyl-5-methylindolizidine by Sonnet and Oliver (*75*). Reagents: (a) MeMgCl, Et_2O; (b) H_2 (50 psi), PtO_2, HOAc; (c) 48% HBr; (d) PPh_3, Br_2, MeCN, Δ; (e) NEt_3.

58 with sodium cyanoborohydride, a process that appears to be subject to remarkable conformational control. The rationale for the observed stereocontrol is shown in Scheme 13. There are four possible transition states for the reduction in which maximum orbital overlap with respect to the hydride reagent and the developing lone pair on nitrogen can be maintained. Two of these, represented by the dotted arrows, are kinetically disfavored as they entail boat-like transition states in order to fulfil stereoelectronic demands. A third, shown by the solid arrow in **59a**, has a severe peri interaction with the proton on C-2. The remaining interaction, given by the solid arrow in **59b**, leads to the desired stereoisomer of (±)-monomorine I (**48**). Stevens has also used this approach in the synthesis of a number of other alkaloids (*78*).

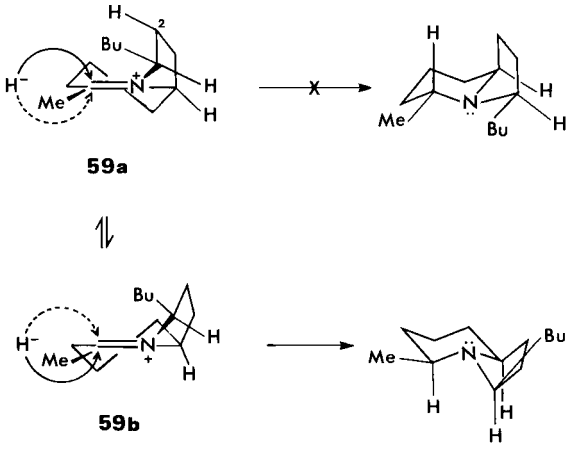
Royer and Husson (*73*) have recently accomplished a significant asymmetric synthesis of (−)-monomorine I (Scheme 14). The chiral intermediate **60**, pre-



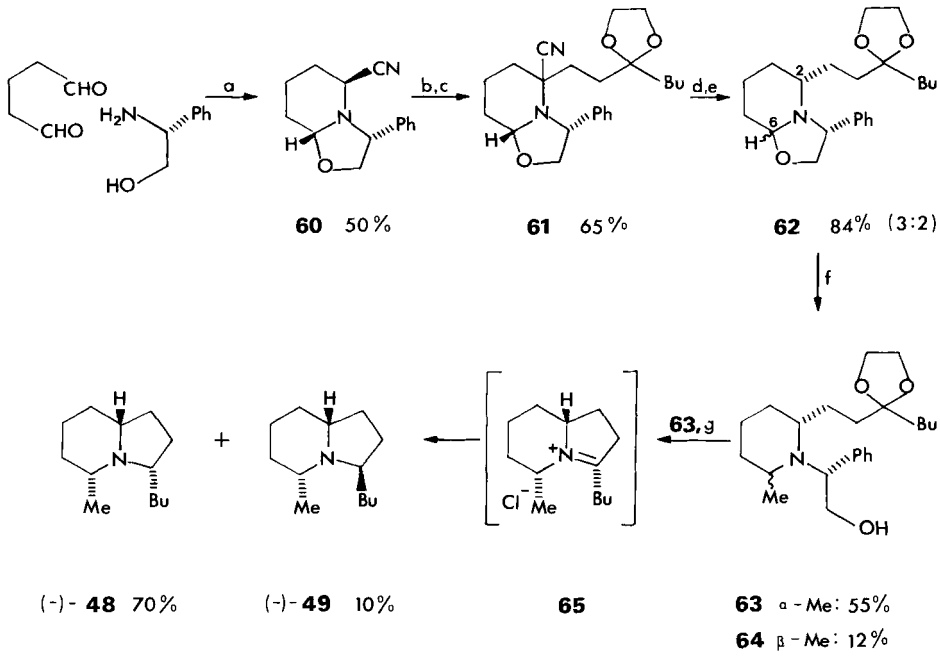


SCHEME 12. Synthesis of monomorine I by Stevens and Lee (*77*). Reagents: (a) Mg, THF; (b) $H_2C{=}CHCHO$; (c) MnO_2, or Py·HCl–CrO_3; (d) 1-nitropentene, tetramethylguanidine (cat.); (e) H_2, 10% Pd–C, anhyd Na_2SO_4; (f) oxalic acid; (g) H_3O^+; (h) OH^-; (i) $NaBH_3CN$, pH 3.8–5.4.

pared from (−)-phenylglycinol and glutaraldehyde in the presence of potassium cyanide (*79*), plays the central role in the synthesis. Alkylation of the anion of **60** with the ethylene glycol acetal of 1-iodo-3-heptanone yields a single product **61**, which, after silver-assisted elimination of cyanide ion and reduction of the result-



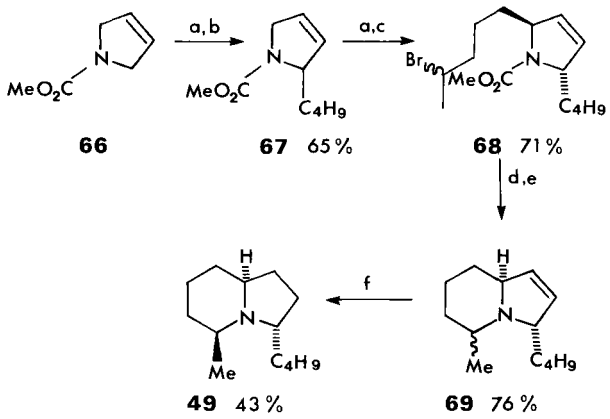
SCHEME 13. Transition state models for the stereochemistry of reduction of cyclic iminium ion intermediate **58** in the Stevens synthesis of monomorine I (*77*).



SCHEME 14. Synthesis of (−)-monomorine I by Royer and Husson (*73*). Reagents: (a) KCN, citric acid, H_2O, pH 3–4; (b) LDA, THF, −78°C; (c) 1-Iodo-3,3-(ethylenedioxy)heptane; (d) $AgBF_4$, THF; (e) $Zn(BH_4)_2$, Et_2O, −50°C; (f) MeMgI, Et_2O, −70°C; (g) H_2 (1 atm), 10% Pd–C, MeOH, 1% 1 *M* HCl.

ing iminium species, gives the oxazolidine isomer mixture **62**. This mixture is isomeric at C-6, that is, at a carbon atom formally at the aldehyde oxidation level and hence inevitably susceptible to epimerization. More importantly, C-2 (destined to become C-8a of the alkaloid) has the *R* configuration. Addition of methyl Grignard to **62** produces two separable amino alcohols, **63** and **64**, the former of which has the requisite cis orientation of side chains for monomorine I. Hydrogenolytic removal of the chiral auxiliary from **63** in acidic medium generates the isolable iminium intermediate **65**, which undergoes further reduction to a mixture of monomorine I (**48**) and its diastereomer **49**. Both products are obtained in optically active form: the former has $[\alpha]_D$ −35.8° (*c* 1.35, hexane), and the latter has $[\alpha]_D$ −69.2° (*c* 0.55, methanol). In terms of its origins, this synthetic (−)-monomorine I must have the 3*S*,5*R*,8a*R* absolute configuration. Naturally occurring (+)-monomorine I must therefore be 3*R*,5*S*,8a*S*. The ORD curves of natural (+)-monomorine I and synthetic (−)-monomorine I show excellent correlation.

A stereoselective synthesis (Scheme 15) of diastereomer **49** of monomorine I must also receive mention here (*80*). In this case, a trans relationship between



SCHEME 15. Synthesis of a diastereomer of monomorine I by Macdonald (*80*). Reagents: (a) LDA, THF, −40°C; (b) $CH_3CH_2CH_2CH_2Br$; (c) $BrCH_2CH_2CH_2CHBrCH_3$; (d) Me_3SiI, $CHCl_3$, 70°C; (e) Na_2CO_3, MeOH, Δ; (f) H_2, PtO_2, AcOH.

C-3 and C-8a is set up by means of two sequential alkylations of the anions derived from Δ^3-pyrrolines **66** and **67**. From the product **68** a 1:1 mixture of dehydroindolizidines **69** is obtained on cyclization. A noteworthy feature in this synthesis is the formation of a single product, **49**, on hydrogenation of the isomer mixture **69**. The reason for the selectivity is not understood.

2. Biological Activity

It has already been indicated that monomorine I is not the true attractant in the trail pheromone of *Monomorium pharaonis* (*69*). The compound and its diastereomers do, however, act as attractants for the Pharaoh ant. In the original article describing the isolation of the alkaloid, Ritter and co-workers provided the first description of pheromone-elicited, trail-following behavior in the species (*71*). Ants could be induced to follow trails made from a hexane extract of paper strips taken from their rearing boxes and from a crude extract of the homogenized insects. In simple choice tests, ants preferentially assembled in a tube containing paper impregnated with the extracts rather than in a tube containing blank paper. The tests were run by releasing 25 workers into the system and counting the number of ants in the two tubes at one-min intervals over a period of 15 min. The differences between the average numbers present in each tube were used as a measure of the activity of the pheromones. The activity of 10 μl of the crude insect extract was 5.8; for monomorine I as isolated by gas chromatography, the activity was measured as 10.2 for 25 μg, 13.2 for 3 μg, and 8.0 for 0.25 μg. In addition, trails made from the crude extracts were also followed by queen ants (*64*).

A more exhaustive evaluation of the attractancy of the four diastereomers of monomorine I, **48–51**, has been performed by Edwards and Pinniger (*81*), using a setup with light-dependent resistors, which respond whenever an insect crosses one of two target areas in a test arena. In one set of experiments, 0.05 mg of the test sample was applied to one of the target areas, and 20 worker ants were released into the arena. Monomorine I (**48**) was the only isomer that caused the insects to cross the dosed target area more frequently as well as to pause within the target area. Isomers **49** and **50** had no apparent attractant properties but had some arrestant effects. Isomer **51** appeared to be quite inactive.

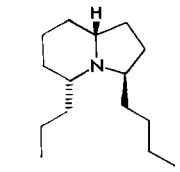
In a second set of experiments, entire nest cells were placed on the edge of the arena, and ants were allowed to choose between two food sources, one of which was placed at the end of an artificial trail created from a hexane solution of each of the isomers in turn. Only isomers **48** and **51** initiated trail-following behavior among foraging workers, although ants always formed natural trails to the food sources, which were more often followed than the artificial trail. Overall, the biological activity of the monomorine isomers is low compared with natural pheromones, suggesting that they may have little potential for use in control measures.

It seems clear that the synergistic effect of all components present in the natural pheromone is important in inducing trail-following behavior in the Pharaoh ant (*64*). The possibility that Pharaoh ant indolizidines may act as natural repellents toward other insects has been mooted by Ritter and Stein, although no evaluations have yet been performed (*82*).

C. Simple Indolizidine Alkaloids from Amphibians

1. The Alkaloids

One would be hard pressed to improve on the admirable treatment of this topic by Witkop and Gössinger in Volume 21 of this treatise (*83*). As far as simple indolizidines from the genus *Dendrobates* are concerned, there is little new information to add to the material in the earlier chapter. A few structural points have been clarified in the ensuing interval (*84*), and three publications describing chiral syntheses have appeared (*85–87*). In addition, an important publication on the isolation of indolizidine alkaloids from non-dendrobatid frogs has appeared (*88*). We include a list of amphibian indolizidines (Scheme 16), partly for ready-reference purposes, and partly to bring up to date the catalog of structures that have been elucidated either partially or totally. The reader should consult the earlier chapter (*83*) or the equally excellent review by Daly (*89*) for references to the original literature and for the sources from which the alkaloids have been isolated. In addition to the compounds in Scheme 16, there are several alkaloids that are suspected to be simple indolizidines but for which structural evidence is



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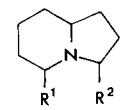
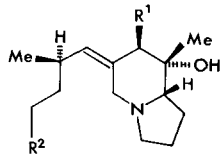
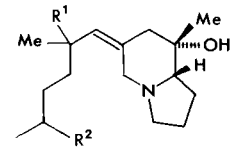


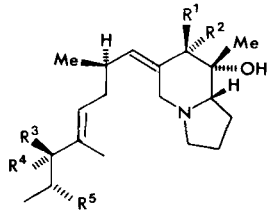
71 $R^1 = C_3H_6OH$, $R^2 = n\text{-}Bu$
72 $R^1 = n\text{-}Pr$, $R^2 = C_4H_8OH$



73 $R^1 = H$, $R^2 = Me$
74 $R^1 = H$, $R^2 = Et$
80 $R^1 = OH$, $R^2 = Me$
81 $R^1 = OH$, $R^2 = Et$



75 $R^1 = H$, $R^2 = OH$
76 $R^1 = OH$, $R^2 = H$



77,78 $R^1 = R^2 = R^5 = H$; $R^3, R^4 = H, OH$
79 $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = OH$
82,83 $R^1 = OH$; $R^2 = R^5 = H$; $R^3, R^4 = H, OH$
84 $R^1 = R^4 = R^5 = OH$; $R^2 = R^3 = H$
85 $R^1 = R^3 = H$; $R^2 = R^4 = R^5 = OH$

SCHEME 16. Simple indolizidine alkaloids from amphibians for which total or partial structures are known. Compound **70** = gephyrotoxin 223AB, **71** = gephyrotoxin 239AB, **72** = gephyrotoxin 239CD, **73** = pumiliotoxin 237A, **74** = pumiliotoxin 251D, **75** = pumiliotoxin 267C, **76** = pumiliotoxin 267D, **77** and **78** = pumiliotoxins 307A′ and 307A″ (formerly pumiliotoxin A), **79** = pumiliotoxin 323A (pumiliotoxin B), **80** = allopumiliotoxin 253A, **81** = allopumiliotoxin 267A, **82** and **83** = allopumiliotoxins 323B′ and 323B″, **84** = allopumiliotoxin 339A, **85** = allopumiliotoxin 339B.

so far lacking. For most of these, only mass spectral data and tentative molecular formulas are available, and a full list of these data is contained in ref. (*89*).

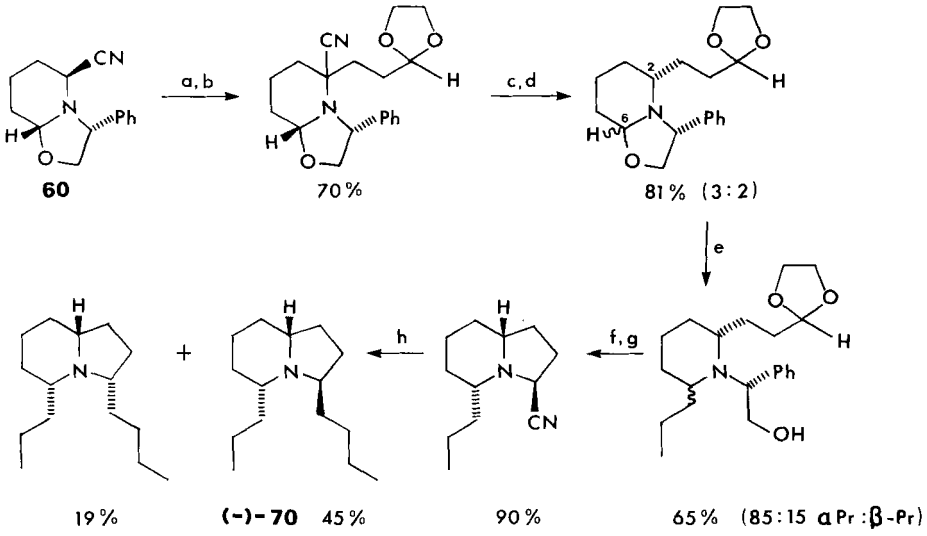
Some comments on the structures shown in Scheme 16 are in order. Daly and co-workers (*84*) have recently shown that the compound previously known as pumiliotoxin A actually consists of two substances, **77** and **78**, epimeric at C-15. These are now referred to as pumiliotoxins 307A′ and 307A″. The relative configurations at C-15 have not yet been determined, although the compounds can apparently be interconverted. Similarly, the compounds previously called allopumiliotoxins B′ and B″, thought to be epimeric at C-7, have been shown to contain an axial OH group at C-7; the epimeric position is in fact C-15. The

compounds **82** and **83** can also be interconverted; they should now be referred to as allopumiliotoxins 323B′ and 323B″. Finally, allopumiliotoxin 339 exists as a pair of noninterconverting isomers, which are epimeric at C-7. These should now be called allopumiliotoxins 339A (**84**) and 339B (**85**). At the time of the previous review (*83*) in this treatise, the absolute configurations of pumiliotoxin 251D (**74**) and the diol moiety of the side chain in pumiliotoxin B (**79**) were known; now, thanks to the spectacular enantioselective syntheses by Overman and coworkers (*86,87*), the full absolute configurations of pumiliotoxin B and of allopumiliotoxins 267A (**81**) and 339B (**85**) are known as well. The absolute configuration of gephyrotoxin 223AB (**70**) has also been established by total synthesis (*85*). The structural diagrams given in Scheme 16 show these absolute configurations.

Perhaps the most exciting recent development has been the discovery by Daly *et al.* that skin alkaloids of the pumiliotoxin and histrionicotoxin types are not unique to dendrobatid frogs (*88*); several taxa of small southern-hemisphere frogs also contain these compounds. The animals investigated include the Brazilian frog *Melanophryniscus moreirae* (family Bufonidae), the species *Mantella aurantica* and *Mantella madagascariensis* (family Ranidae, subfamily Mantellidae) from Malagasy, and the Australian frog *Pseudophryne semimarmorata* (family Myobatrachidae). The quantities of alkaloids isolated in this survey were exceptionally small—in the last two cases, the extraction was performed on a single skin—and the separation and identification of materials was mostly by a combination of gas chromatography and mass spectrometry. Nonetheless, the identity of previously known alkaloids from these new sources appears indisputable. The evidence for the gross structures of two new alkaloids, **75** and **76**, is also good; in fact, sufficient of the former was obtained for both proton- and ^{13}C-NMR spectra to be measured. The frog species investigated also yielded other new unidentified alkaloids, the mass spectral characteristics of which do not seem to support indolizidine structures. For the record, the four species of nondendrobatid frogs are the sources of the following simple indolizidine alkaloids: pumiliotoxin 267C (**75**), allopumiliotoxin 323B (**82/83**) (*Melanophryniscus moreirae*); pumiliotoxin 267D (**76**), pumiliotoxin 323A (**79**), allopumiliotoxin 323B (**82/83**), allopumiliotoxin 339A (**84**) (*Mantella aurantica*); allopumiliotoxin 323B (**82/83**) (*Mantella madagascariensis*); pumiliotoxin 267D (**76**), allopumiliotoxin 323B (**82/83**) (*Pseudophryne semimarmorata*).

2. Enantioselective Total Syntheses

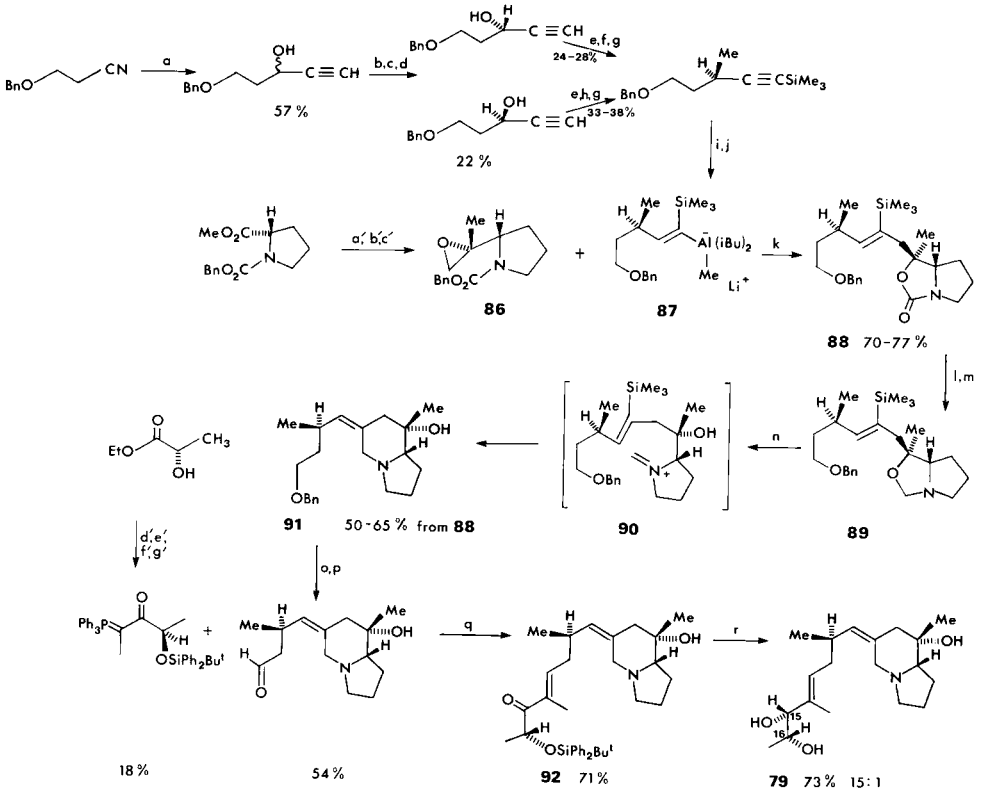
The first total synthesis of (−)-gephyrotoxin 223AB (**70**) (Scheme 17) has recently been accomplished by Royer and Husson (*85*). This synthesis parallels their synthesis of monomorine I (**48**) discussed in Section III,B (see Scheme 14) and in fact proceeds by way of the same chiral intermediate **60**. In terms of the



SCHEME 17. Synthesis of (−)-gephyrotoxin 223AB by Royer and Husson (*85*). Reagents: (a) LDA, THF, −78°C; (b) 2-(2-Bromoethyl)-1,3-dioxolan; (c) $AgBF_4$, THF; (d) $Zn(BH_4)_2$, −50°C; (e) *n*-PrMgBr, Et_2O, −50°C; (f) H_2, 10% Pd–C, MeOH; (g) KCN, 1 *M* HCl, CH_2Cl_2; (h) *n*-BuMgBr, Et_2O, 0°C.

synthetic route employed, the product **70** must have the 3*R*,5*R*,8a*R* absolute configuration. Its optical rotation is quoted as $[\alpha]_D$ −101° (*c* 2.3, hexane). Natural gephyrotoxin 223AB has not been obtained in sufficient quantity and purity for accurate measurement of its optical rotation, but it is also known to be levorotatory. This synthesis therefore establishes the absolute configuration of the natural product with a reasonable degree of certainty.

The enantioselective total synthesis of pumiliotoxin 251D (**74**) by Overman and Bell (*90*), discussed in the earlier chapter in this treatise (*83*), has now been published as a full paper together with the total synthesis of pumiliotoxin B (**79**) (*86*). Both syntheses proceed by way of a common intermediate, **86**, derived in three steps from L-proline. For pumiliotoxin B (Scheme 18), the intermediate **86** is coupled with the vinylsilane alanate **87** to give the cyclic carbamate **88**. In one of the key steps of the sequence, compound **89** is converted to **91** on heating with paraformaldehyde and an acid catalyst; the cyclization apparently involves intramolecular nucleophilic attack by the vinylsilane moiety on to the iminium ion in the intermediate **90**. At the end of the sequence, the stereochemistry in the side chain is established in a threo-selective (15:1) reduction of **92** to **79**, using lithium aluminum hydride. These isomers proved to be inseparable; however, in spite of the presence of a small quantity of the undesired isomer, the final product shows essentially identical optical rotation ($[\alpha]_D$ +19.3°, *c* 1.00, MeOH) and



SCHEME 18. Synthesis of (+)-pumiliotoxin B by Overman, Bell, and Ito (*86*). Reagents: (a) *i*-Bu_2AlH, lithium acetylide, THF, 0°C; (b) Cl_2CO, (*R*)-(+)-α-methylbenzylamine; (c) chromatographic separation of diastereomers; (d) Cl_3SiH; (e) MeLi, Me_3SiCl; (f) Ac_2O, py, DMAP; (g) $Me_2CuMgBr$, THF; (h) Ph_3P, DEAD, $C_6H_5CO_2H$, THF; (i) *i*-Bu_2AlH, C_6H_{14}; (j) MeLi, Et_2O; (k) THF, Δ; (l) KOH, EtOH–H_2O, Δ; (m) 37% aq H_2CO, MeOH; (n) $(CH_2O)_n$, MeCN, camphorsulfonic acid, 80°C; (o) Li, NH_3, THF; (p) DMSO, $(COCl_2)_2$; (q) CH_2Cl_2, Δ; (r) $LiAlH_4$, THF; then Na_2SO_4, $CHCl_3$. Supplementary steps: (a′) MeMgI, Et_2O; (b′) $SOCl_2$, Et_3N, −50°C; (c′) *m*-CPBA, CH_2Cl_2 (20% over 3 steps); (d′) PhP_3, DEAD, 4-O_2N-C_6H_4-CO_2H, THF; (e′) K_2CO_3, EtOH; then *t*-$BuPh_2SiCl$, imidazole, DMF; (f′) KOH, MeOH; then aq HCl; then DCC, EtOAc; then pyridine-2-thiol; (g′) *s*-BuLi, THF, $Ph_3PEt^+Br^-$ (18% over 4 steps).

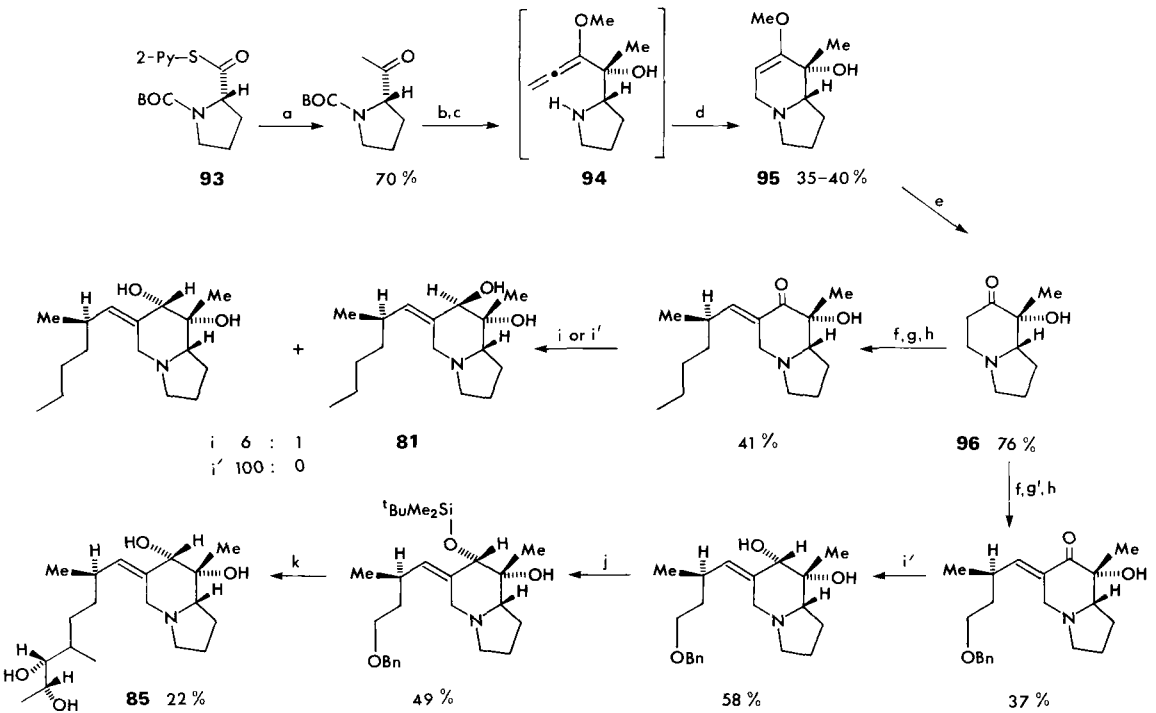
spectroscopic properties to an authentic sample of pumiliotoxin B (**79**). This synthesis establishes the absolute configuration of the alkaloid. To put the matter beyond doubt, the isomer of **79** with the *S,S* configuration at C-15 and C-16 has also been prepared, as has the C-11 epimer of **79**. Both compounds are clearly distinguishable from pumiliotoxin B by NMR spectroscopy.

Overman and Goldstein have also devised a somewhat different convergent synthesis of (+)-allopumiliotoxins 267A (**81**) and 339B (**85**) (Scheme 19), again starting with an L-proline derivative, **93** (*87*). Sequential treatment of this compound with lithium dimethylcuprate, trifluoroacetic acid, and 1-methoxyallenyllithium affords as sole product the labile adduct **94**. The addition of the allenyllithium proceeds with Cram cyclic diastereoselectivity. The crucial cyclization of **94** to **95** is induced by acid, and hydrolysis of **95** yields ketone **96** in greater than 95% enantiomeric excess. The alkylidene side chain is introduced by aldol condensation of the dianion of **96** with pure enantiomers of appropriate aldehydes, followed by dehydration. The syntheses are completed by further manipulations of ring and side-chain functionality. For allopumiliotoxin 339B (**85**), the latter steps are identical to those in the pumiliotoxin B synthesis described above. In particular, a threo-selective lithium aluminum hydride reduction sets up the diol portion of the side chain. Products **81** and **85** are spectroscopically identical to natural materials; however, the optical rotations obtained {$[\alpha]_D$ +12.8°, *c* 0.1, MeOH for allopumiliotoxin 267A (**81**), and $[\alpha]_D$ +8.8°, *c* 1.0, MeOH for allopumiliotoxin 339B (**85**)} are probably more reliable than those previously recorded on very dilute, possibly impure samples of the natural products.

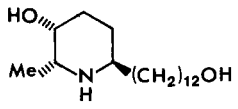
D. Juliprosopine and Juliprosine

Plants of the genus *Prosopis* are well known as producers of piperidine alkaloids (*91*). The discovery of indolizidines in some species of this genus is of recent date. Hesse and co-workers isolated from *Prosopis juliflora* A. DC. (family Leguminosae) four alkaloids, juliprosopine, isojuliprosopine, juliprosine, and isojuliprosine (*92*), the first and third of which have been structurally elucidated. The only alkaloids formerly isolated from this species have been 2-methyl-6-(12-hydroxydodecyl)piperidin-3-ol [julifloridine (**97**), absolute configuration shown] and related piperidinols (*93*). Juliprosopine has also been obtained from *P. glandulosa* Torr and *P. farcta* (Banks and Sol.) Macbride (*94*), the former of which also contains julifloridine (*95*).

Hesse's juliprosopine (**98**), isolated from the leaves of plants grown in Madras, was a colorless gum having $[\alpha]_D$ +0.7° (*c* 1.05, ethanol) or +10.0° (*c* 2.15, chloroform) (*92*). Its overall structure was deduced from spectroscopic data on the alkaloid itself, on some simple derivatives, and on the products obtained following a Hofmann degradation. The configurations of the piperidine



SCHEME 19. Synthesis of (+)-allopumiliotoxin 267A and (+)-allopumiliotoxin 339B by Overman and Goldstein (*87*). Reagents: (a) Me_2CuLi; (b) C_6H_5OMe, CF_3CO_2H, CH_2Cl_2; (c) 1-Methoxyallenyllithium, THF, −78°C; (d) *p*-TsOH, MeCN; (e) 5% aq HCl; (f) Ph_3CLi (2 equiv), Et_2O, 0°C; (g) (*R*)-2-Methylhexanal; (g′) (*R*)-4-benzyloxy-2-methylbutanal; (h) $(CF_3CO)_2O$, DBU, DMAP, 0°C; (i) $LiAlH_4$, THF, 0°C; (i′) $NaBH_4$, $CeCl_3$; (j) *n*-BuLi, HMPA, *t*-$BuMe_2SiCl$; (k) see Scheme 18, steps (o)–(r).



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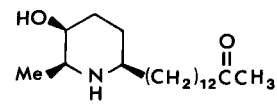

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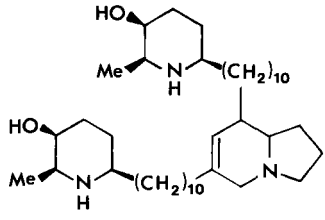

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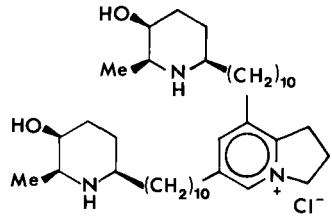

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rings appear to be unambiguous on the basis of NMR spectroscopy, especially when the data are compared with those of simple piperidinol alkaloids bearing essentially the same substituents and of the same configuration. At this stage the relative configurations at C-8 and C-8a remain unknown.

Hesse obtained the chloride salt of juliprosine (**99**) as an oil ($[\alpha]_D$ +11°, *c* 0.50, chloroform). The dihydroindolizinium nucleus was inferred after spectroscopic comparison of juliprosine and 1,3,5-collidinium chloride (*96*). Both juliprosine and juliprosopine give the same product on hydrogenation over platinum oxide, implying that the side chains are the same in both. The absolute configuration of juliprosine is probably that shown in the diagram, since the measured specific and molar optical rotations for the compound correlate well with those of a number of monocyclic piperidinol Prosopis alkaloids of known absolute configuration, for example, spectalin (**100**).

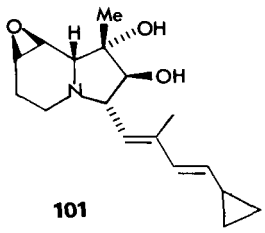
Hesse has speculated on the biogenesis of these alkaloids (*92*). They probably arise from two piperidinol alkaloids bearing 12-carbon side chains, and Δ^1-pyrroline. The occurrence of **97** alongside **98** and **99** in *P. juliflora* adds credence to the hypothesis, as does the fact that many known Prosopis alkaloids also have 6-dodecyl-2-methyl-3-piperidinol structures.

Both juliprosopine and the crude extracts from various Prosopis species have been reported to show antibacterial behavior (*94*).

E. Indolizidine Alkaloids from *Streptomyces* Species

1. Cyclizidine

The unique alkaloid cyclizidine (**101**) has been obtained from a previously undescribed *Streptomyces* species NCIB 11649, isolated from a hedgerow soil sample originating from the greater Manchester region of the United Kingdom



101

(*97*). The broth (37 L) resulting from laboratory culture of the organism under shake-flask aerobic conditions yielded cyclizidine (4.29 g) as a colorless crystalline solid (mp 184°C, $[\alpha]_D$ −46.3°, *c* 2.0, methanol), on recrystallization from ether. Spectroscopic investigation of the compound allowed partial structural elucidation, especially in the unprecedented side chain, but X-ray crystallography was necessary to solve the complete structure and to determine the relative stereochemistry. The absolute configuration was not established.

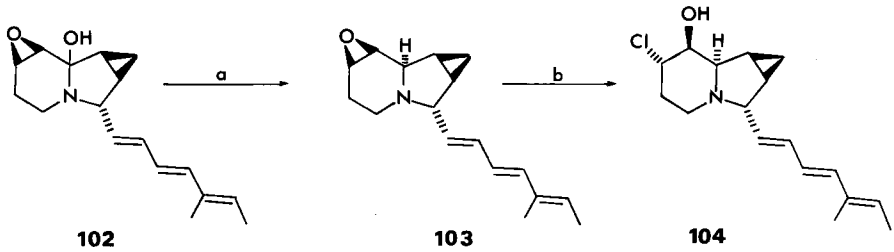
A number of interesting structural features emerge from the crystallographic study. The five- and six-membered rings adopt envelope and twist-boat conformations, respectively. The side chain is fully extended, and the cyclopropane ring adopts the energetically more favored bisected conformation relative to the conjugated double bonds. Neighboring molecules in the crystal appear to be associated by hydrogen bonding.

The compound is biologically active. The *Streptomyces* species shows low activity against *Botrytis allii,* though cyclizidine itself is not responsible for this activity. Cyclizidine does, however, show nonselective immunostimulatory properties, and its secondary monoacetate causes a reduction in frequency of beats of cultured heart cells, an effect shown by some β-blocking drugs.

2. Indolizomycin

The *Streptomyces* strain SK2-52, produced by protoplast fusion between non-antibiotic-producing mutants of *S. tenjimariensis* and *S. griseus*, is the source of a new antibiotic, indolizomycin (**102**) (*98*). The strain was cultured under shake-flask conditions; the alkaloid content in the broth (11.6 L) was determined as 88 μg/ml, using a paper-disc assay against *Bacillus subtilis* PCI219. Chromatography yielded the pure antibiotic (20.4 mg) as a thick, pale yellow oil ($[\alpha]_D$ −28.6°, *c* 0.5, MeOH).

The structure of indolizomycin was determined as **102** by a combination of spectroscopic techniques and the chemical interconversions shown in Scheme 20. Reduction of the carbinolamine in **102**, followed by treatment of the deoxygenated product **103** with hydrochloric acid gives the crystalline chlorohydrin derivative **104** (mp 157–158°C, $[\alpha]_D$ −116°, *c* 1, MeOH). X-Ray crystallography on **104** has yielded the structure and absolute configuration shown in the diagram; by exten-



SCHEME 20. Chemical transformations of indolizomycin. Reagents: (a) $NaBH_4$, MeOH; (b) HCl, MeOH, 50°C.

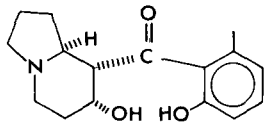
sion, therefore, indolizomycin (**102**) must have the 1*S*,2*R*,3*S*,7*R*,8*R* configuration. The orientation of the OH group of **102** at position 8a, however, remains unknown. As far as the derivative **104** is concerned, the crystal structure shows that the side-chain atoms of the double bond are fully extended in a plane that nearly bisects the C-2—C-3—N angle. The five- and six-membered rings adopt chair and envelope conformations respectively, and an intermolecular O—H···N hydrogen bond is observed.

The antibacterial activity of indolizomycin (**102**) is weak. A survey of its antibacterial spectrum toward 34 different microorganisms shows MIC values in the range 12.5–100 μg/ml. Its intraperitoneal acute LD_{50} in mice is 12.5–25 mg/kg. The compound, however, is labile; even on storage at −30°C, it lost 13% of its activity in 1 week, and 28% in 2 weeks.

F. Simple Elaeocarpus Indolizidine Alkaloids

No new simple indolizidine alkaloids have been discovered in plants belonging to the genus *Elaeocarpus* (family Elaeocarpaceae) since the publication of the review by Johns and Lamberton in an earlier volume of this treatise (*99*). The four alkaloids of interest, (+)-isoelaeocarpicine (**105**), (+)-elaeokanine A (**106**), and (−)-elaeokanines B and C (**107,108**), are essentially seco versions of polycyclic alkaloids like isoelaeocarpine (**109**) or elaeokanine E (**110**). The absolute configurations of these alkaloids have not been established; even the relative configuration of elaeokanine B (**107**) is not known, though a synthesis of the two diastereomers of **107** seems to suggest that the natural product may actually be a mixture of both (*57*).

Since 1975 there has been an unabated interest in the total synthesis of the Elaeocarpus indolizidines, especially the elaeokanines. The synthetic strategies developed have been quite varied, but most of them have a common feature: they begin with a substituted pyrrolidine system, and elaborate the six-membered ring on to it. For convenience, we have chosen to classify the syntheses of interest according to the bond formed in the final annulation reaction. The disconnections involved are shown in Scheme 21.



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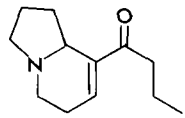

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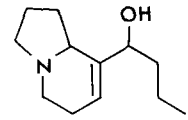

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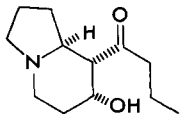

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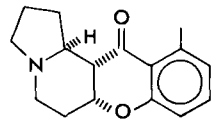

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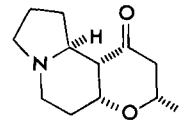

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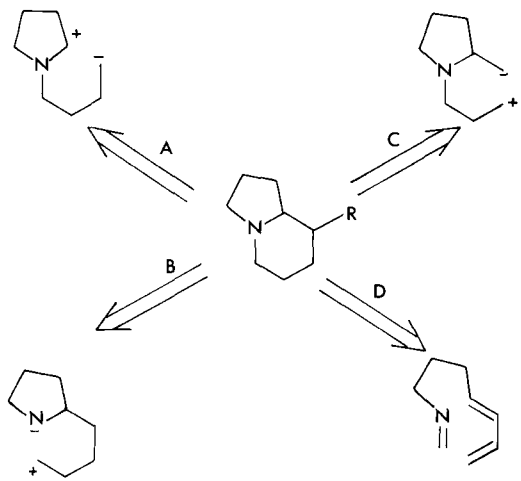
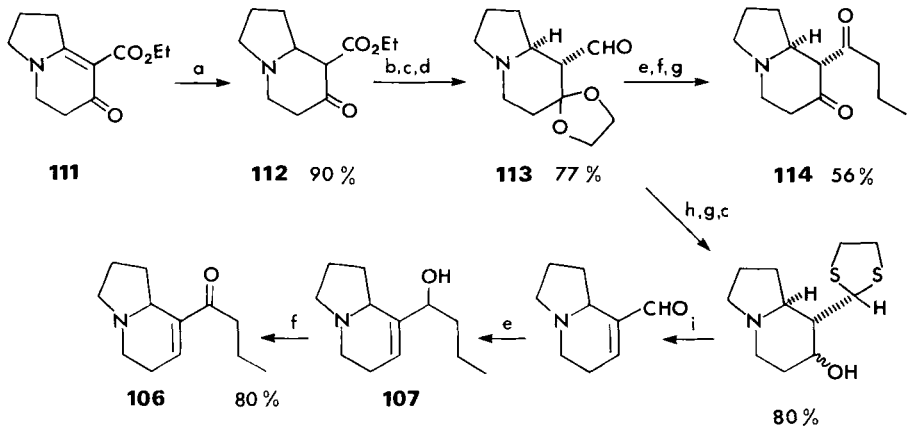
1. Disconnection A

The syntheses in this group all use iminium systems based on Δ^1-pyrroline as the electrophilic component, though the nucleophilic partner varies substantially. A convergent synthesis of the elaeokanines by Watanabe and co-workers (*100*), for example, proceeds through the unsaturated bicyclic compound **111,** prepared from 2-ethoxy-Δ^1-pyrroline and ethyl 3-oxopent-4-enoate, following the procedure described by Trost (*101*) for the synthesis of the corresponding quinolizidine. A key intermediate, the β-ketoester **112**, is obtained from **111** on reduction with lithium aluminum hydride (Scheme 22). Functional group manipulation yields the aldehyde **113**, which can be taken on either to elaeokanine C



SCHEME 21. Disconnections for reported syntheses of simple indolizidine Elaeocarpus alkaloids.

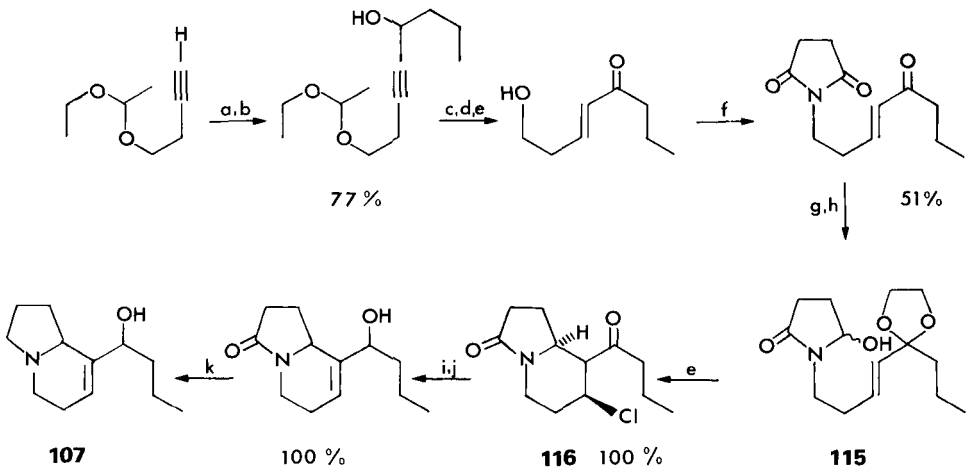


SCHEME 22. Synthesis of elaeokanines A, B, and C by Watanabe and co-workers (*100*). Reagents: (a) $LiAlH_4$, Et_2O–THF, −70°C; (b) $(HOCH_2)_2$, *p*-TsOH, C_6H_6; (c) $LiAlH_4$, Et_2O-THF, Δ; (d) Me_2S, NCS, $C_6H_5CH_3$–CH_2Cl_2, −25°C; (e) *n*-PrMgBr, Et_2O–THF, Δ; (f) Jones oxidation; (g) 47% HBr; (h) $(HSCH_2)_2$, BF_3, HOAc; (i) MeI, THF–MeCN, HCl, Δ.

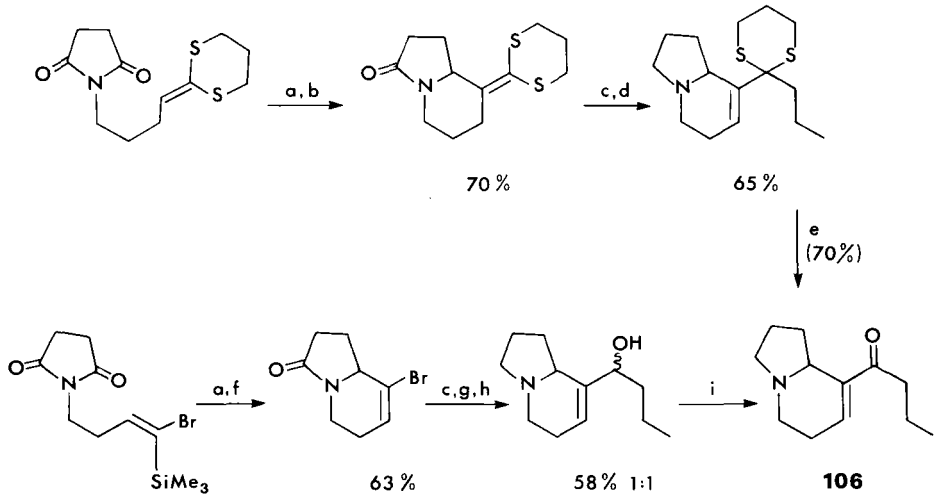
(**108**) or to elaeokanines A and B (**106,107**) as required. In the former case, a formal synthesis of **108** is achieved with the attainment of the diketone **114**, which had been prepared by Hart *et al.* in their early pioneering synthesis of the alkaloid (*102*). Watanabe has also described the use of aldehyde **113** in the synthesis of the tricyclic elaeokanines (*103*).

The Speckamp approach to elaeokanine B (**107**) (*104*) makes use of his well-known cyclization of acyliminium ions to construct the six-membered ring of the indolizidine system (Scheme 23). In the critical ring-closure step, **115** to **116**, the use of hydrogen chloride in methanol circumvents the formation of the side products found when formic acid is used. It is noteworthy that none of the pyrrolizidinone regioisomer is formed. The highly stereoselective capture of chloride ion is unexpected but may be due to a template-directing effect of the acetal protecting group functioning as the site for both proton and chloride ion involvement. The intriguing implication is that the three processes formally occurring in this step—dehydration of **115**, formation of the new C—C bond, and capture of the cation by the nearby chloride ion—may be nearly concerted. It would also seem to indicate that ring closure is faster than acetal hydrolysis.

Two other conceptually similar approaches to elaeokanines A and B (Scheme 24) also proceed by way of acyliminium intermediates but use as intramolecular nucleophiles vinyl groups bearing substituents whose directing effects enforce regiospecific ring closure. In the synthesis by Chamberlin and his group (*105*), a ketene dithioacetal provides the nucleophilic thrust for ring closure on to the acyliminium ion, which is generated *in situ* by the novel mesyl chloride-induced



SCHEME 23. Synthesis of elaeokanine B by Wijnberg and Speckamp (*104*). Reagents: (a) *n*-BuLi, Et_2O, −70°C; (b) butanal; (c) $LiAlH_4$, THF, Δ (88%); (d) CrO_3, py, CH_2Cl_2 (80%); (e) HCl, MeOH, 0–5°C; (f) Ph_3P, DEAD, succinimide; (g) $(CH_2OSiMe_3)_2$, Me_3SiOTf, −8–0°C; (h) $NaBH_4$, H^+ (100%); (i) DBN, $C_6H_5CH_3$, Δ; (j) $NaBH_4$, 0°C; (k) *i*-Bu_2AlH, Et_2O.

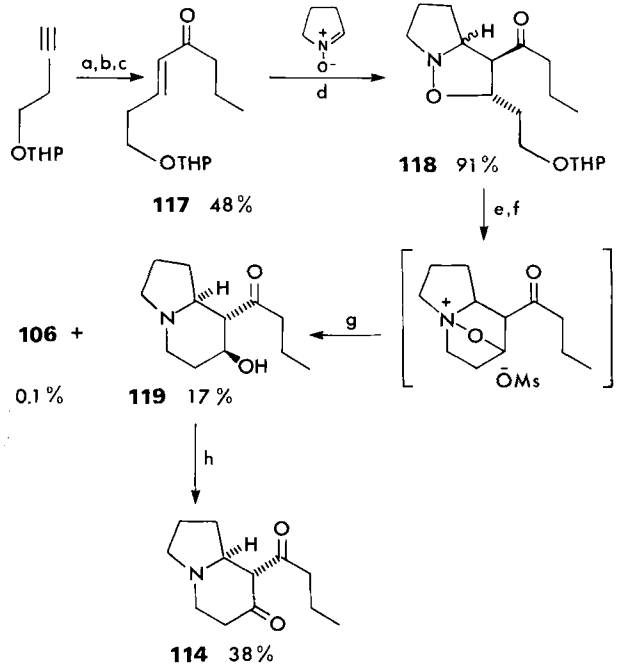


SCHEME 24. Alternative syntheses of elaeokanine, A employing acyliminium ion cyclizations (*105,106*). Reagents: (a) $NaBH_4$, MeOH, 0°C; (b) MsCl, NEt_3; CH_2Cl_2; (c) $LiAlH_4$, THF; (d) LDA, *n*-PrI, THF; (e) $HgCl_2$, $CaCO_3$, H_2O–MeCN, 50°C; (f) CF_3CO_2H, Δ; (g) *s*-BuLi, THF, −78°C; (h) butanal; (i) $(CF_3CO)_2O$, DMSO.

dehydration of a lactol. In the synthesis of elaeokanines A and B by Overman and co-workers (*106*), the nucleophilic species is a vinylsilane. The Overman synthesis provides the first example of a vinylsilane terminator in an acyliminium ion cyclization.

2. Disconnection B

Nitrone cycloadditions have played an increasingly important role in alkaloid synthesis over the past decade (*107*). Such a cycloaddition is at the heart of the synthesis of the elaeokanines (Scheme 25) by Kametani and his colleagues (*108,109*). The addition of Δ^1-pyrroline-1-oxide to the *trans*-enone **117** affords an inseparable mixture (2:3) of diastereomers of **118**. The cyclization and N—O bond cleavage of this material give **119** (epielaeokanine C) in low yield, as well as a trace of elaeokanine A (**106**). In these steps, epimerization α to the carbonyl group has obviously occurred. On using the cis rather than the trans isomer of **117** at the start of the sequence, a different diastereomeric cycloadduct is formed initially, but by the end of the reaction sequence the same hydroxy ketone **119** is



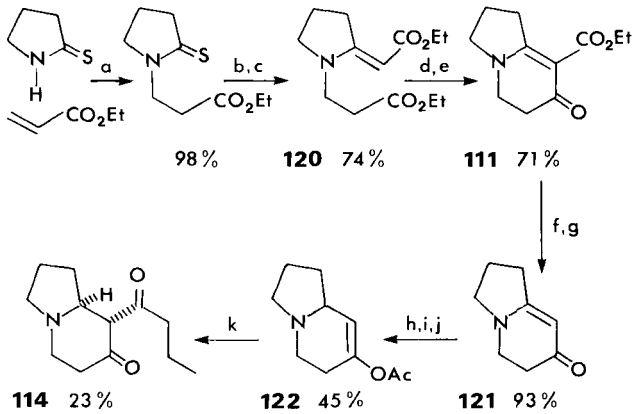
SCHEME 25. Formal synthesis of elaeokanine C by Kametani and co-workers (*108,109*). Reagents: (a) *n*-BuLi, butanal, THF; (b) $LiAlH_4$, Et_2O; (c) MnO_2, petroleum ether; (d) $C_6H_5CH_3$, Δ; (e) 1 *M* HCl, THF; (f) MsCl, py: (g) Zn, $HOAc–H_2O$, 50°C; (h) Jones oxidation.

isolated. With the oxidation of **119** to **114**, a formal synthesis of elaeokanine C (**108**), and hence A and B (**106, 107**), is accomplished.

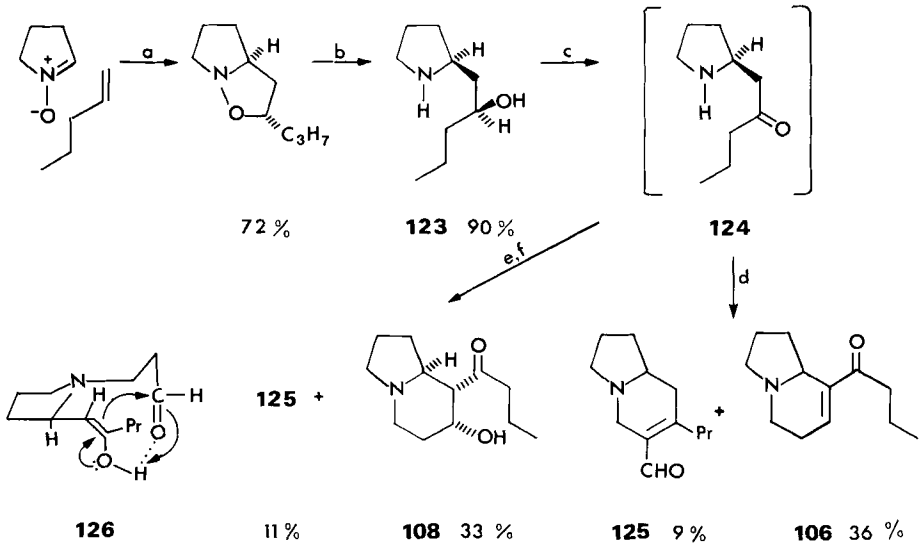
3. Disconnection C

The ubiquitous diketone **114** is again featured in a formal synthesis of the elaeokanines by Howard *et al.* (*110*). This synthesis uses the Eschenmoser sulfide contraction to construct vinylogous urethane **120**, whose nucleophilicity is exploited in an alternative synthesis of the intermediate **111** (Scheme 26). The vinylogous amide **121**, which results from hydrolysis and decarboxylation of **111**, is transformed regiospecifically to enol acetate **112**, from which a regiochemically unambiguous enolate can be generated on treatment with methyllithium. The acylation of the enolate is a troublesome step but can be effected with minimal competing reactions by using acyl cyanides rather than acyl halides (*111*). The acylation is still poor (23%) in the sequence leading to the elaeokanines via **114**, but is far more successful in a formal synthesis of elaeocarpine and isoelaeocarpine (**109**), where an aroyl cyanide serves as the acylating agent.

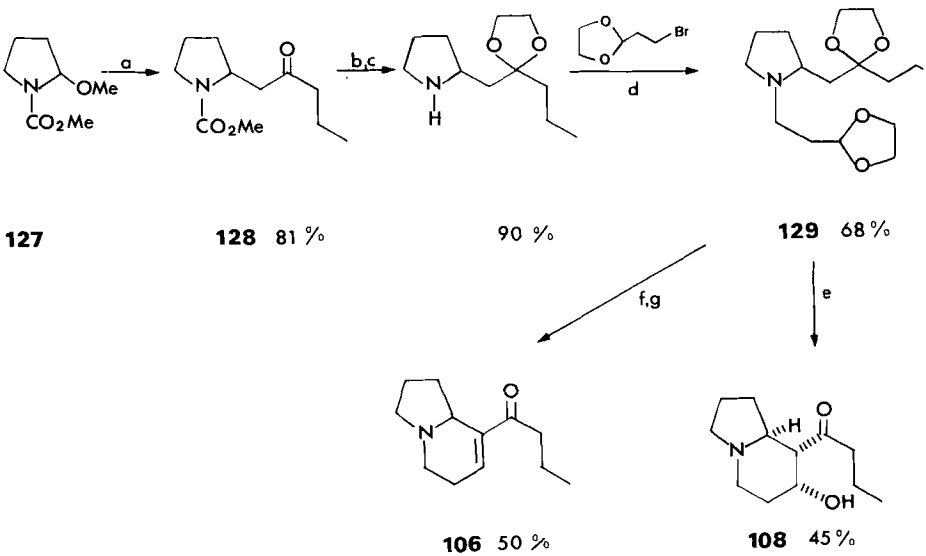
The "disconnection C" mode of cyclization is an important feature in a synthesis of elaeokanines A and C by Tufariello and Ali (*112*), which uses a nitrone cycloaddition to assemble the 2-substituted pyrrolidine **123** (Scheme 27). The thermally labile ketone **124** is pivotal in the synthesis since, depending on how its condensation with acrolein is carried out, either elaeokanine A (**106**) or elaeokanine C (**108**) can be produced alongside the product of alternative aldol condensation, **125**. In the latter case, **108** is thought to be the product of kinetic



SCHEME 26. Formal synthesis of the elaeokanines by Howard, Gerrans, and Meerholz (*110*). Reagents: (a) NaOH (cat.), THF; (b) $BrCH_2CO_2Et$, MeCN; (c) Ph_3P, NEt_3, MeCN; (d) NaOH, H_2O, Δ; (e) Ac_2O, MeCN; (f) KOH, H_2O, Δ; (g) HCl, H_2O, Δ; (h) AcCl, $AgClO_4$, MeCN; (i) $NaBH_4$, MeCN; (j) HOAc, Δ; (k) MeLi, $CH_3CH_2CH_2COCN$, THF, 0°C.



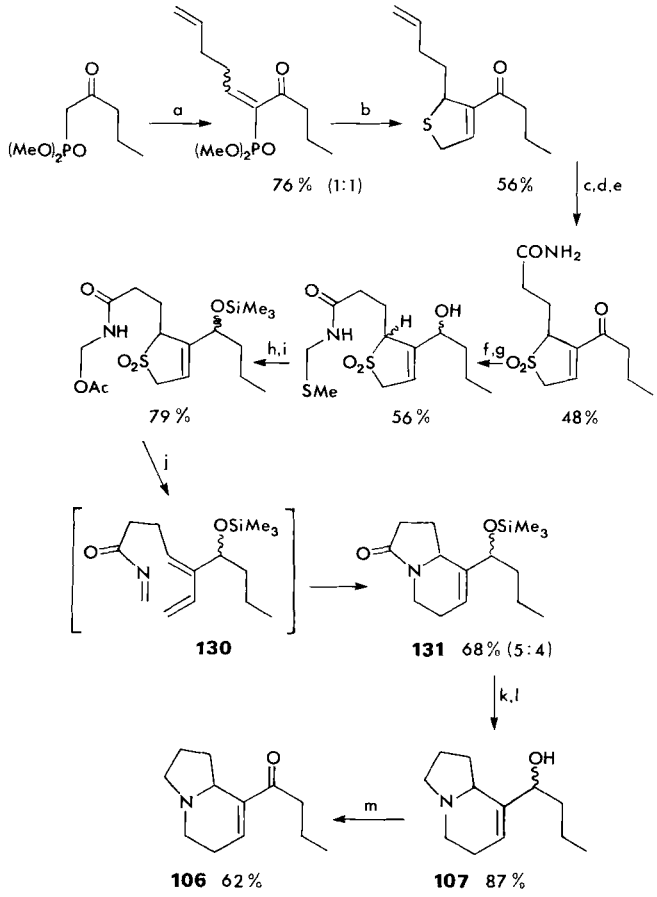
SCHEME 27. Synthesis of elaeokanines A and C by Tufariello and Ali (*112*). Reagents: (a) 110°C, sealed tube; (b) H_2, 10% Pd–C; (c) Jones oxidation; (d) *t*-BuOK, $H_2C{=}CHCHO$, C_6H_6; (e) $H_2C{=}CHCHO$, CH_2Cl_2; (f) concd HCl.



SCHEME 28. Synthesis of elaeokanines A and C by Shono and co-workers (*114*). Reagents: (a) $TiCl_4$, 2-trimethylsilyloxy-1-pentene, CH_2Cl_2, −70 to −20°C; (b) $(HOCH_2)_2$, $HC(OMe)_3$, *p*-TsOH, Δ; (c) H_2NNH_2, KOH, $(HOCH_2)_2$, Δ; (d) NaH, DMF; (e) concd HCl; (f) 1 *M* HCl, Δ; (g) 1 *M* NaOH, Δ.

control since, when a sample of it is exposed to concentrated hydrochloric acid, the material is unaffected; that is, retroaldol condensation does not occur. Attainment of the correct transition state for the observed cyclization is suspected to be facilitated by hydrogen bonding involving the enol of the side chain, as shown in **126**.

Tufariello has also used a very similar reaction sequence with 2-methoxy-4-methylstyrene rather than 1-pentene to make isoelaeocarpicine (**105**), the only



SCHEME 29. Synthesis of elaeokanines A and B by Weinreb and co-workers (*57,115*). Reagents: (a) 4-Pentenal, piperidine, HOAc, C_6H_6, Δ; (b) $HSCH_2CHO$, NEt_3, CH_2Cl_2, Δ; (c) *m*-CPBA, CH_2Cl_2; (d) CrO_3, H_5IO_6, aq Me_2CO; (e) $ClCO_2Et$, NEt_3, CH_2Cl_2, −15°C; then NH_3; (f) $ClCH_2SMe$, CF_3CO_2H, CH_2Cl_2; (g) $NaBH_4$, $CeCl_3$, MeOH: (h) $Hg(OAc)_2$, HOAc; (i) Me_3SiCl, py, $(Me_3Si)_2NH$; (j) $C_6H_5CH_3$, 370–390°C, glass helices; (k) 1 *M* HCl, H_2O–THF; (l) *i*-Bu_2AlH, THF; (m) $(CF_3CO)_2O$, DMSO, CH_2Cl_2, NEt_3, −78°C.

recorded synthesis of this compound (*113*). In this case, treatment of the appropriate analog of **124** with acrolein and concentrated hydrochloric acid gives, in 36% yield, the methyl ether of **105**, which can be demethylated (80%) with boron tribromide.

A somewhat different use of disconnection C is found in a biogenetically flavored synthesis of elaeokanines A and C by Shono *et al.* (*114*). The novel feature in this approach is the anodic oxidation of *N*-methoxycarbonylpyrrolidine in methanol to the α-methoxy compound **127**, a good enough electrophile to react with a silyl enol ether in the presence of a Lewis acid (Scheme 28). The product **128** is converted in three steps to the bisacetal **129**, acid-induced hydrolysis and aldol condensation of which yields elaeokanine C (**108**) almost exclusively, presumably for the same reasons as adduced by Tufariello. The alternative condensation product **125** can be detected but in very minor quantities.

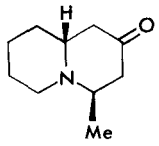
4. Disconnection D

Weinreb's imino Diels–Alder reaction represents a radically different approach to the construction of the indolizidine nucleus of the elaeokanines (*57,115*). The key cyclization, **130** to **131**, is an efficient process (68%), but the bulk of the synthetic effort (Scheme 29) obviously goes into setting up the highly functionalized precursor of **130**. As a point of structural interest, once the diastereomeric cycloaddition products **131** (4:5 ratio) are hydrolyzed, the free alcohols can be separated by medium-pressure liquid chromatography and then individually reduced to different diastereomers of elaeokanine B (**107**). From the data available, Weinreb speculates that natural elaeokanine B may actually be a mixture of the two diastereomers, though there is insufficient evidence for the matter to be settled beyond doubt.

IV. Alkyl and Functionalized Alkyl Quinolizidine Alkaloids

A. Myrtine and Epimyrtine

The European bilberry or whortleberry, *Vaccinium myrtillus* Cham. and Schlecht (family Ericaceae), is the source of two methylquinolizidinones, myrtine (**132**) and epimyrtine (**133**) (*116,117*). These compounds were isolated as optically active, colorless oils from the aerial parts of fresh plant material in 0.00175 and 0.00042% yields, respectively. The measured optical rotations were $[\alpha]_D$ +3.1° (*c* 2.1, chloroform) for myrtine, and −2.5° (*c* 1.2, chloroform) for epimyrtine. The structures and relative stereochemistries of these simple compounds were deduced from their spectra, especially their proton and ^{13}C-NMR



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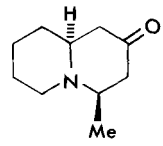

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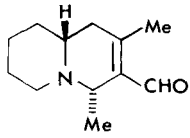
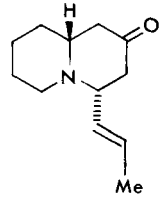


134

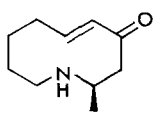


135

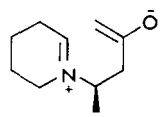
spectra. In addition, epimyrtine shows strong Bohlmann bands in its IR spectrum at 2790 and 2745 cm^{-1}, while myrtine has weak bands at 2810 and 2765 cm^{-1}. Both compounds thus preferentially adopt conformations in which the ring junction is trans.

The structures of the compounds have been confirmed by straightforward but inefficient biomimetic syntheses of their racemates, using a Mannich condensation between acetaldehyde and (±)-pelletierine (2-acetonylpiperidine). When the reaction is induced by base, myrtine is the kinetically preferred product (13:1), but the combined yield of the desired products is only 9%. The major product is the bicyclic aldehyde **134** (13%). Under acidic condensation conditions, myrtine is less favored than epimyrtine (15 and 20% yields, respectively); the ketone **135** (16%) is also isolated. The racemic alkaloids may be resolved with (−)-tartaric acid, whereupon the salts of (+)-myrtine and (−)-epimyrtine preferentially crystallize from an acetone–hexane mixture. The pure, optically active bases show markedly greater optical rotations than the natural products (myrtine, $[\alpha]_D$ +11.3°, *c* 2.7, chloroform, mp 41–43°C; epimyrtine, $[\alpha]_D$ −18°, *c* 5.4, chloroform), implying that the compounds isolated from the plant are partly racemized.

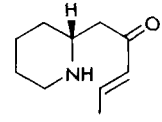
When the synthesis is repeated with (*R*)-pelletierine, the optically active products (+)-myrtine and (+)-epimyrtine are obtained. These results establish the



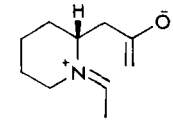
136a



136b



137a

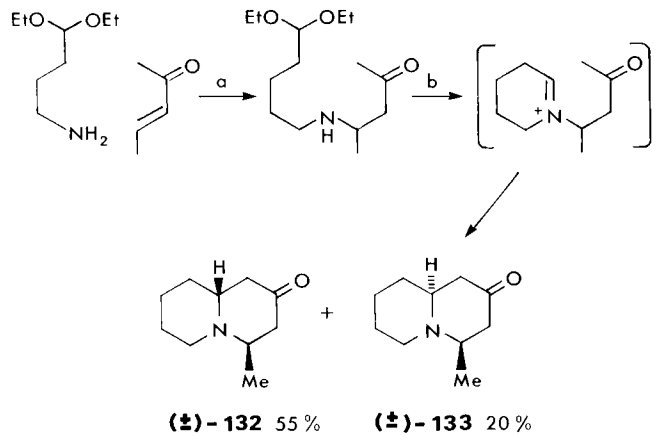


137b

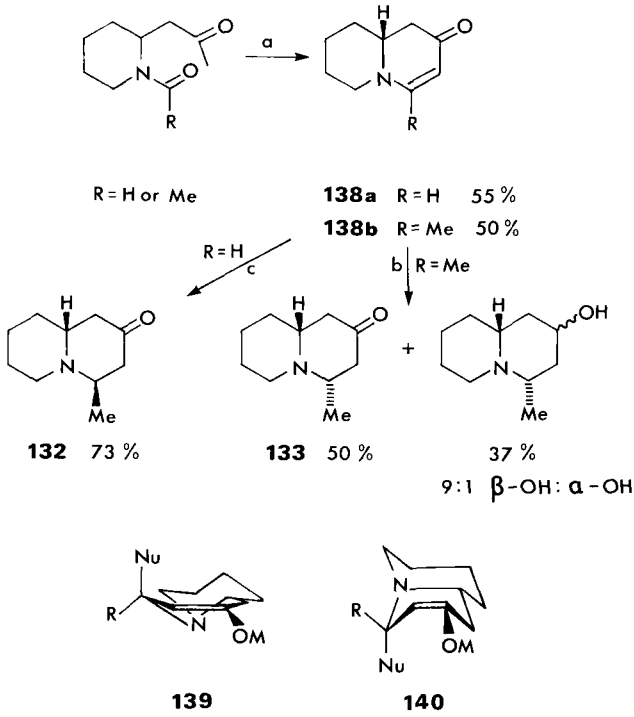
absolute configuration of (+)-myrtine as 4*R*,9a*R* (as shown in **132**), and strongly suggest that natural (−)-epimyrtine has the 4*R*,9a*S* absolute configuration. Further support for this suggestion comes from the positive Cotton effect that (−)-epimyrtine gives in isooctane.

Because the alkaloids are both Mannich bases, it is not surprising that they can be equilibrated under acidic or basic conditions, presumably by retro-Michael or retro-Mannich pathways. Epimyrtine (**133**) is, understandably, the thermodynamically more stable isomer, since it bears an equatorial methyl group. On prolonged heating of the racemates of either **132** or **133** with potassium carbonate in aqueous dioxan, a 3:7 mixture of myrtine and epimyrtine results, while on refluxing with 0.1 *N* hydrochloric acid solution, a 2:8 ratio is established. With pure (−)-myrtine, racemic products result under basic equilibration conditions; but under acidic conditions, only (−)-myrtine and (+)-epimyrtine are formed. The implication in the former case is that epimerization can occur by way of retro-Mannich or retro-Michael intermediates of types **136a** and **136b**, as well as **137a** and **137b**. In the latter case, however, only **136a** and **136b** can be involved, since only the stereochemistry at position 9a is affected.

In addition to the above Mannich syntheses of the alkaloids, two other syntheses have been published. In the first of these (Scheme 30), the key cyclization is by an alternative intramolecular Mannich reaction (*118*). In a one-pot procedure, 5-amino-1,1-diethoxypentane and pent-3-en-2-one react to give an intermediate Michael product, which cyclizes under acidic conditions to a mixture of (±)-myrtine (55%) and (±)-epimyrtine (20%). In view of what has been said above, it is somewhat surprising that myrtine should be the dominant product under these conditions.



SCHEME 30. Synthesis of myrtine and epimyrtine by King (*118*). Reagents: (a) Et_2O, room temperature; (b) 2 *M* HCl, 100°C.

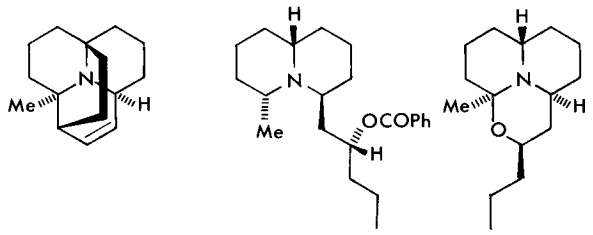


SCHEME 31. Synthesis of myrtine and epimyrtine by Slosse and Hootelé (*117,119*). Reagents: (a) $(t\text{-BuO})_3Al$, $C_6H_5CH_3$, Δ; (b) $LiAlH_4$, THF, 0°C; (c) MeMgI, C_6H_6.

In the second synthesis (Scheme 31), the feature of interest is the stereospecific addition of nucleophiles to enaminones **138a** and **138b**, formed by base-induced intramolecular condensation of *N*-formyl- or N-acetylpelletierine (*117,119*). The entering nucleophile (methylmagnesium iodide for **138a**, lithium aluminum hydride for **138b**) comes in cis to the hydrogen at C-9a. The reason for this selectivity is presumably that attack of the nucleophile from the upper face leads to an intermediate **139** with a pseudochair structure. The alternative mode of attack, from the α face of the molecule, would lead to the formation of the strained pseudoboat intermediate **140**.

B. PORANTHERILIDINE

The Australian shrub *Poranthera corymbosa* A. Brongn. (family Euphorbiaceae) is the source of a number of quinolizidine-containing alkaloids, six of which have been characterized (*120*). The compounds, of which porantherine (**141**) is the chief, are mainly 9b-azaphenalenes. Porantherilidine (**142**), the only



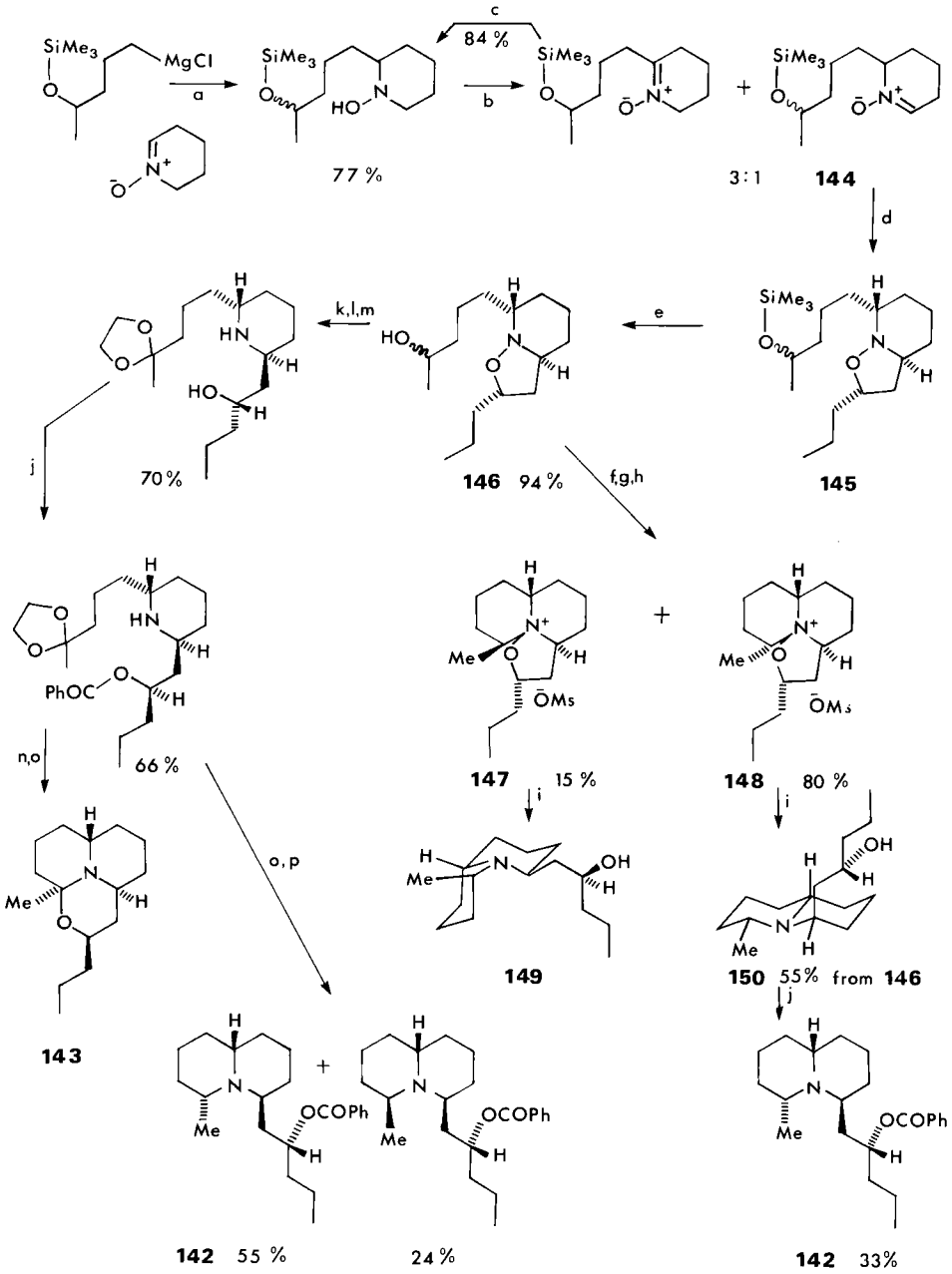
141 **142** **143**

simple quinolizidine in the group, is essentially a seco version of its relatives and has an obvious structural relationship to the oxatricyclic compound porantheridine (**143**). It has received brief mention in this treatise as an alkaloid of unclassified type (*121*). Porantherilidine (**142**) is a colorless oil ($[\alpha]_D$ −47°, *c* 0.75, chloroform), which forms a crystalline hydrobromide salt (mp 251–252°C, $[\alpha]_D$ −27°, *c* 0.46, methanol). Owing to the limited quantities of the natural product available to its isolators, its structural characterization was by means of X-ray crystallography on the hydrobromide salt (*122*). This study also established the absolute configuration shown in **142**. The stereochemistry of ring fusion in the salt is trans; more surprisingly in view of the bulky axial substituent on the ring, the stereochemistry in the free base appears to be trans as well, as judged by the appearance of Bohlmann bands at 2790 and 2760 cm^{-1} in the IR spectrum of a synthetic sample (*123*).

The biogenesis of the Poranthera alkaloids is suggested to be from the condensation of a C-16 polyketide chain with ammonia, followed by appropriate cyclizations and loss of the terminal carboxy group. The implication of the suggestion is that 2,6-disubstituted piperidines, themselves well known as alkaloids, are biosynthetic intermediates (*120*).

Two total syntheses of porantherilidine (Scheme 32) have been described by Gössinger. The first synthesis (*123*) employs a cycloaddition of the diastereomeric nitrone mixture **144** with 1-pentene to produce the isoxazolidines **145**, deprotection of which yields the key alcohol mixture **146**. Diastereomer mixtures are carried through the synthesis as far as the separable oxatricyclic compounds **147** and **148**, which result from the differential reactivities of the mesylate precursors during the final cyclization process. Reduction of these compounds to **149** and **150**, respectively, yields products whose spectra allow reasonably reliable structural assignment. Compound **149**, for instance, shows no Bohlmann bands in its IR spectrum but has a strong intramolecular hydrogen bond; the structure and conformation depicted in the diagram thus appear the most likely. Mitsunobu coupling of **150** with benzoic acid affords (±)-porantherilidine (**142**), chromatographically and spectroscopically identical with the natural product.

A variation on this route also uses the alcohol mixture **146** and yields both



SCHEME 32. Syntheses of porantheridine by Gössinger (*123, 124*). Reagents: (a) Et_2O; (b) HgO, $CHCl_3$, 45°C; (c) $NaBH_4$, MeOH, 0°C; (d) 1-Pentene, $CHCl_3$, 48°C; (e) Bu_4NF, THF, 45°C; (f) MsCl, py, 3°C; (g) Et_2O, aq $NaHCO_3$; (h) 60°C, vacuum; (i) $LiAlH_4$; (j) Ph_3P, DEAD, $C_6H_5CO_2H$, C_6H_6; (k) oxidation; (l) $(HOCH_2)_2$, *p*-TsOH; (m) H_2, Raney Ni; (n) KOH, EtOH; (o) HCl, THF–H_2O; (p) $NaBH_3CN$, pH 6, MeOH.

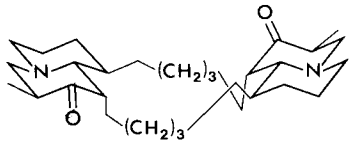
porantherilidine (**142**) and porantheridine (**143**) (*124*). In this route, the isoxazolidine ring is cleaved and Mitsunobu inversion in the side chain is effected before the second ring of the quinolizidine system is closed by cyclodehydration. The resulting iminium system is captured either by hydride or intramolecularly by OH to give **142** and **143**, respectively.

C. Bisquinolizidines from Sponges

The marine sponge *Petrosia seriata*, from Papua-New Guinea, has recently been shown to contain a number of novel ichthyotoxic bisquinolizidine alkaloids (*125,126*). The methanol extract of sun-dried specimens contains at least eight different alkaloids, three of which have now been elucidated structurally.

The principal alkaloid, petrosin (**151**), is an optically inactive crystalline solid, mp 215–216°C, of formula $C_{30}H_{50}N_2O_2$. The ^{13}C-NMR spectrum of the compound shows only 15 peaks, suggesting a degree of symmetry in the molecule. Bohlmann bands in the IR spectrum imply a trans-fused ring junction. Other spectroscopic data allow the assignment of the gross structure as well as some stereochemical deductions, but X-ray crystallography has been used for the unambiguous assignment of structure **151**. In the crystal, the molecules adopt chiral conformations, though two enantiomers coexist in the crystal to give the observed centrosymmetric space group $P2_1/c$. Each molecule possesses a twofold pseudoaxis of rotation passing through the middle of the macrocyclic pocket and perpendicular to the mean plane of this ring.

Two minor alkaloids, petrosin-A and petrosin-B, appear to be diastereomers of **151**. Both are noncrystalline but optically active; petrosin-A has $[\alpha]_D$ −5° (*c* 0.71, dichloromethane), and petrosin-B has $[\alpha]_D$ −12° (*c* 0.79, dichloromethane). The former shows the same coincidences of signals in its NMR spectra as



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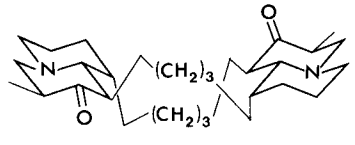

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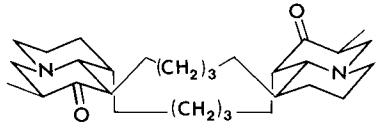

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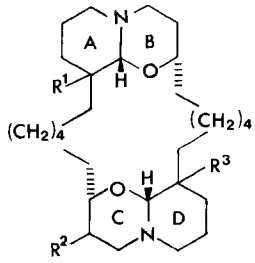


154 $R^1 = R^2 = R^3 = \alpha$-H, A/B = C/D = trans
155 $R^1 = \beta$-OH, $R^2 = \beta$-Me, $R^3 = \beta$-H, A/B = C/D = trans
156 $R^1 = \beta$-H, $R^2 = R^3 = \alpha$-H, A/B = cis, C/D = trans
157 $R^1 = \beta$-OH, $R^2 = R^3 = \alpha$-H, A/B = cis, C/D = trans

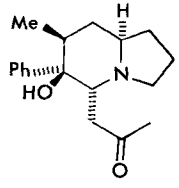
does petrosin (**151**), again suggesting a twofold rotation axis in the molecule. In contrast, petrosin-B has no element of symmetry. Both have trans-fused quinolizidine rings, as evinced by strong Bohlmann bands, and equatorial methyl groups, as shown by the appropriate chemical shifts and coupling constants. Homonuclear 2D-^{1}H-NMR experiments have been used to provide valuable information on the couplings in all three petrosins. In the light of available information, structures **152** and **153** appear to be the most likely for petrosins A and B, respectively.

It should be mentioned that the Australian sponge *Xestospongia exigua* has been shown to contain four alkaloids, xestospongins A, B, C, and D (**154–157**) (*127*). These compounds do not fall within the scope of this chapter but, in view of their similarity to the petrosins, are included here for comparison.

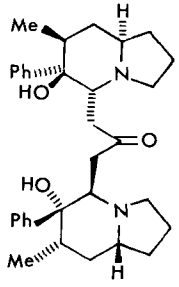
V. Arylindolizidine and Arylquinolizidine Alkaloids

A. Crepidamine and Dendrocrepine

The occurrence of simple indolizidine alkaloids within the Orchidaceae has already been discussed (Section III,A). The two compounds of interest for the present discussion, crepidamine (**158**) and dendrocrepine (**159**), have been ob-



158



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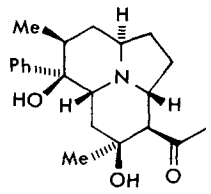


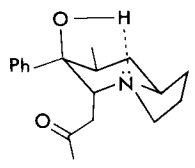
160

tained along with crepidine (**160**) from the species *Dendrobium crepidatum* Lindl. (*128*). From 8.6 kg of fresh plants, 0.08 g of crepidamine, 0.25 g of dendrocrepine, and 0.20 g of crepidine were recovered.

Crepidamine (**158**) is a crystalline solid, mp 107.5–109°C, which shows no optical activity in the range 200–600 nm. The structural assignment has been based on the analysis of spectroscopic data, which, as reported (*128*), appear somewhat inadequate for a full stereochemical assignment. The stereochemistry shown in **158** would seem to depend on structural comparison with dendrocrepine, for which the stereochemical evidence is firm as a result of an X-ray analysis (*129*). However, the solution IR spectrum (CCl_4) of crepidamine, possessing weak Bohlmann bands, supports a trans-fused ring junction. In addition, the position of the OH stretching absorption at 3470 cm^{-1} suggests an intramolecular O—H···N hydrogen bond. The predominant conformation is therefore most likely to be **161**.

Dendrocrepine (**159**), a unique bisindolizidine alkaloid, is an optically inactive crystalline solid, mp 158–163°C. That only a single diastereomer results from the reduction of dendrocrepine with lithium aluminum hydride argues against the existence of the compound in a meso form. The crystal structure of dendrocrepine hydrobromide confirms not only the structure and stereochemistry of the compound, but also its racemic nature (*129*). It also shows the same type of intramolecular OH···N hydrogen bonding postulated for crepidamine. The ^{13}C-NMR spectrum of dendrocrepine has a further surprising feature: there are six distinct resonances for the phenyl groups, highly suggestive of restricted rotation in the compound (*130*). At 57°C, the number of resonances is reduced to the expected four.

The axial nature of the ketone substituent in both **158** and **159** deserves some comment. Both compounds readily isomerize, either on heating in ethanol or on chromatography on neutral alumina, to the thermodynamically more stable compounds isocrepidamine and isodendrocrepine. These isomers are not simply the equatorial epimers at C-5, but are in fact the hemiacetals of these epimers,



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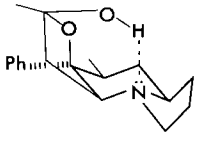

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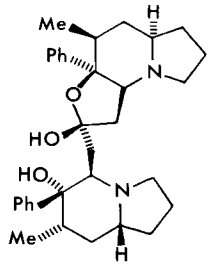


163

possessing strong O—H···N hydrogen bonds (*128*). The structure and predominant conformer of isocrepidamine is shown in **162**, while isodendrocrepine, in which only one C-5 site has epimerized, is shown in **163**. Since the alkaloids **158** and **159** are Mannich bases, the epimerization probably proceeds via retro-Michael or retro-Mannich reaction, followed by recyclization to the thermodynamically more stable isomers. As an interesting footnote, it had earlier been thought that both isocrepidamine and isodendrocrepine were also alkaloids of *Dendrobium crepidatum* (*131,132*). Since in the later work they were not isolated from fresh acidic plant extracts, the inference is that their earlier isolation must have been as artifacts produced during the isolation procedure (*128*).

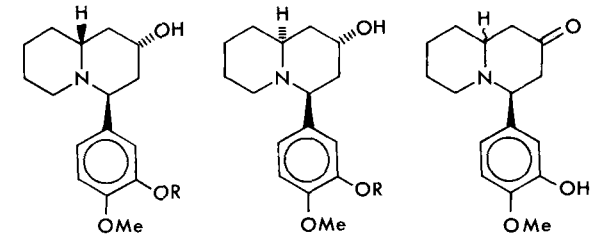
B. Simple Quinolizidine Alkaloids of the Lythraceae

1. The Compounds and Their Occurrence

Alkaloids from plants of the Lythraceae are sufficiently numerous to have merited a chapter of their own in this treatise (*133*). Among their number are the simple 4-arylquinolizidines listed in Table I, all of which were known at the time of the previous review, which should be consulted for the original references. The absolute configurations of these compounds have not been established. Later reports of biosynthetic and synthetic work on the simple Lythraceae quinolizidines are scant, and a very brief summary will suffice to bring the topic up to date.

Simple alkaloids like the demethyllasubines **164** and **165**, at least in the species *Heimia salicifolia*, have been isolated only from very young seedlings (1–2 weeks old) and vanish with time as the concentrations of more complex alkaloids like lythrine (**174**) and vertine (cryogenine) (**175**) increase (*134*). There are obvious biogenetic implications in this finding, and the most recently presented biogenetic hypothesis in this treatise (*133*) takes these findings into account. A study using tritium-labeled materials, however, shows that while the 3,4-dihydroxyphenyl trans compound **176** is specifically incorporated into lythrine and the corresponding cis compound **177** into vertine, the analogous monomethyl ethers **178–181** are not used in the biosynthesis of the macrolide alkaloids (*135*). It would therefore appear that compounds **164** and **165** represent end products of a metabolic chain of events rather than genuine biosynthetic intermediates.

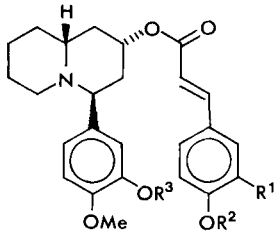
It is also worth mentioning that *in vitro*-grown shoots of *Heimia salicifolia*, which have been cultured on glucose or sucrose, still contain demethyllasubines I and II (**164** and **165**) when harvested 6–8 weeks after the last subculture (*136*). The shoots also contain significant quantities of 10-epidemethoxyabresoline



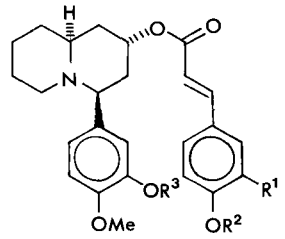
164 R = H
170 R = Me

165 R = H
171 R = Me

166



167 $R^1 = R^2 = R^3 = H$
172 R^1 = OMe, $R^2 = R^3$ = Me



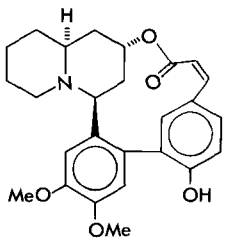
168 $R^1 = R^2 = R^3 = H$
169 R^1 = OMe, $R^2 = R^3 = H$
173 R^1 = OMe, $R^2 = R^3$ = Me

TABLE I
Simple Quinolizidine Alkaloids of the Lythraceae

Compound	Alkaloid	Ring junction	Source
164	Demethyllasubine I	cis	*a*
165	Demethyllasubine II	trans	*a*
166	(9a-α and/or β-H)		*a*
167	10-Epidemethoxyabresoline	cis	*a*
168	Demethoxyabresoline	trans	*a*
169	Abresoline	trans	*a*
170	(−)-Lasubine I	cis	*b*
171	(−)-Lasubine II	trans	*b*
172	(+)-Subcosine I	cis	*b*
173	(+)-Subcosine II	trans	*b*

[a] *Heimia salicifolia* Link and Otto.
[b] *Lagerstroemia subcostata* Kuehne.

(**167**) and demethoxyabresoline (**168**), compounds that are usually minor components of mature field-grown plants (*137*). By contrast, in vitro-grown callus or cell-suspension cultures of *H. salicifolia* show no detectable alkaloid content (*136*).



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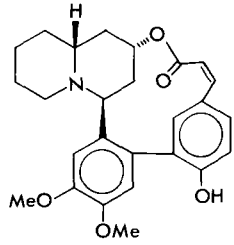

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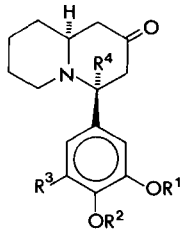
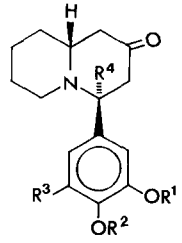


176 $R^1 = R^2 = R^3 = H$, $R^4 = T$
178 $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = T$
180 $R^2 = R^4 = H$, $R^1 = Me$, $R^3 = T$

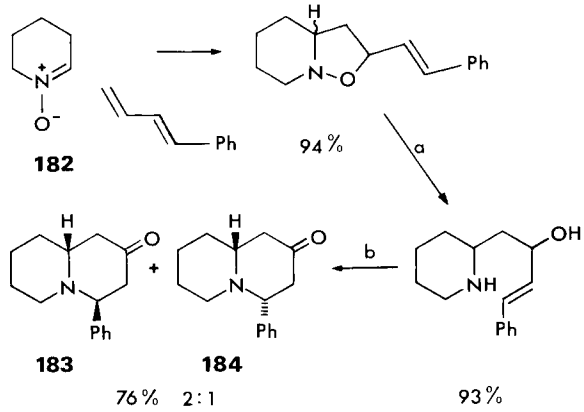


177 $R^1 = R^2 = R^3 = H$, $R^4 = T$
179 $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = T$
181 $R^2 = R^4 = H$, $R^1 = Me$, $R^3 = T$

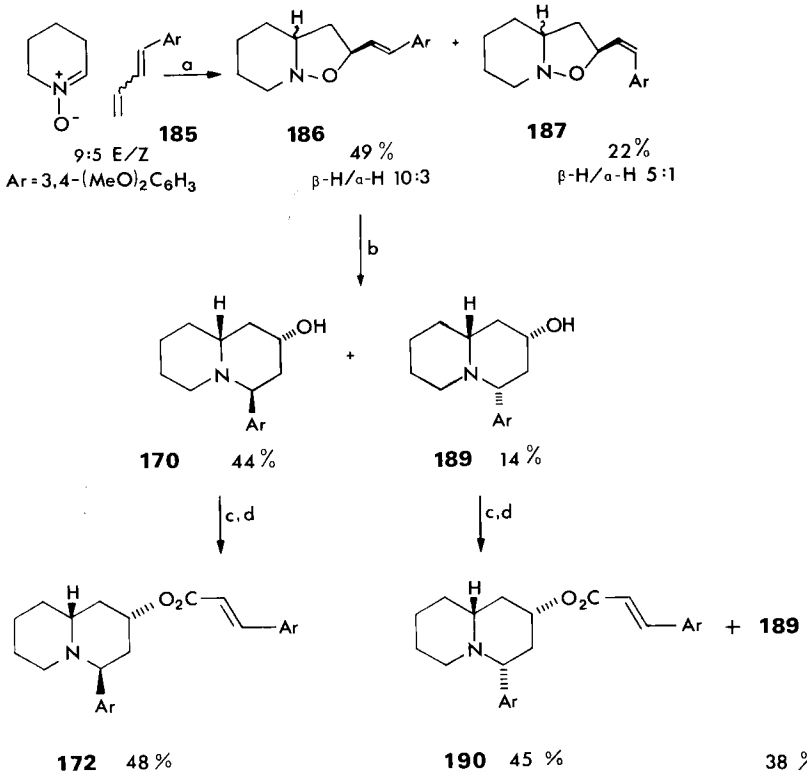
2. Synthesis

In contrast to earlier syntheses of simple Lythraceae quinolizidines, which mostly involve the Mannich reaction of pelletierine with appropriately substituted benzaldehydes (*133*), later syntheses of simple Lythraceae quinolizidines use nitrone cycloaddition methodology. The use of Δ^1-piperideine *N*-oxide (**182**) as the source of the unsubstituted piperidine ring in the quinolizidine system is common to all of these syntheses. In this regard, Tufariello and Gatrone (*138*) paved the way for later workers by developing a model sequence (Scheme 33) leading to the unsubstituted 4-phenylquinolizidin-2-ones **183** and **184**. Tufariello has reviewed his nitrone-based approach to alkaloid synthesis (*107*).

The stereochemistry of nitrone cycloaddition is of no concern in Tufariello's work, since oxidation of the alcohol function does away with an asymmetric carbon center. For most of the Lythraceae alkaloids, however, C-2 is at the alcohol oxidation level, and the stereochemistry of the cycloaddition process has a critical bearing on the course of the synthesis. The sorts of problems that may be encountered are clearly illustrated in a synthesis of lasubine I (**170**) and subcosine I (**172**) (Scheme 34) (*139,140*). This synthesis is complicated from the start by the inability to separate the *E* and *Z* dienes **185**, which serve as di-



SCHEME 33. Synthesis of 4-phenylquinolizidin-2-ones by Tufariello and Gatrone (*138*). Reagents: (a) Zn, 50% HOAc; (b) MnO_2, CH_2Cl_2.

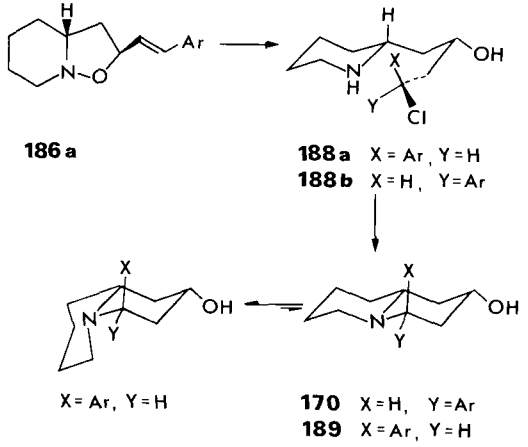


SCHEME 34. Synthesis of lasubine I and subcosine I by Iida, Tanaka, and Kibayashi (*139,140*). Reagents: (a) $C_6H_5CH_3$, Δ; (b) HCl, $CHCl_3$; then H_2 (1 atm), 10% Pd–C, EtOH; (c) *n*-BuLi, THF, −78°C; (d) $[3,4\text{-}(MeO)_2C_6H_3CO_2]_2O$, DMAP, dioxan.

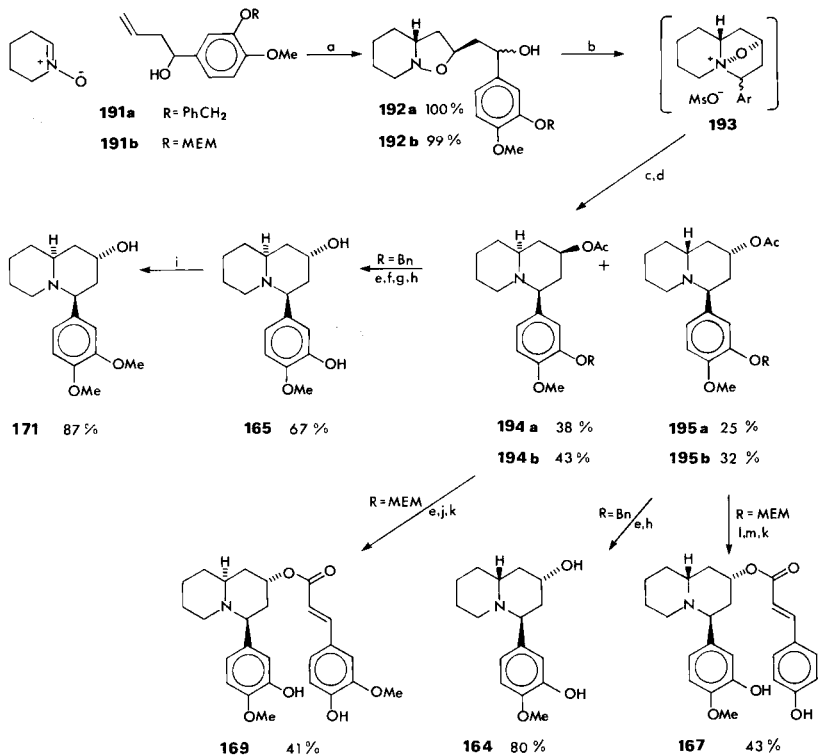
polarophiles in the initial cycloaddition. While the cycloaddition is regiospecific, it is not stereoselective; the *E* and *Z* isoxazolidines **186** and **187** are separable, but each consists of a pair of inseparable diastereomers. Lack of selectivity in a subsequent reaction of these products only aggravates the stereochemical difficulties. By the end of the synthesis, the yield of lasubine I (**170**) is understandably low, and the alternative product, 2-epilasubine II (**189**) is also isolated. Both products may be acylated with appropriate cinnamoyl derivatives, the former to subcosine I (**172**), and the latter to 2-episubcosine II (**190**).

In order to explain the final product distribution in Scheme 34, one must assume that the bridgehead β-H isomer **186a**, on treatment with hydrogen chloride gas, followed by hydrogenolysis of the N—O bond, gives both chloro intermediates **188a** and **188b**, the former yielding lasubine I (**170**) on cyclization and the latter, 2-epilasubine II (**189**) (Scheme 35). One might similarly expect the bridgehead α-H isomer of **186a**, present in the reaction mixture, to lead to lasubine II (**171**) and 4-epilasubine II, but these were not isolated. With the *Z*-isoxazolidine mixture **187**, similar arguments can be advanced, but in fact only lasubine I (**170**) has been isolated.

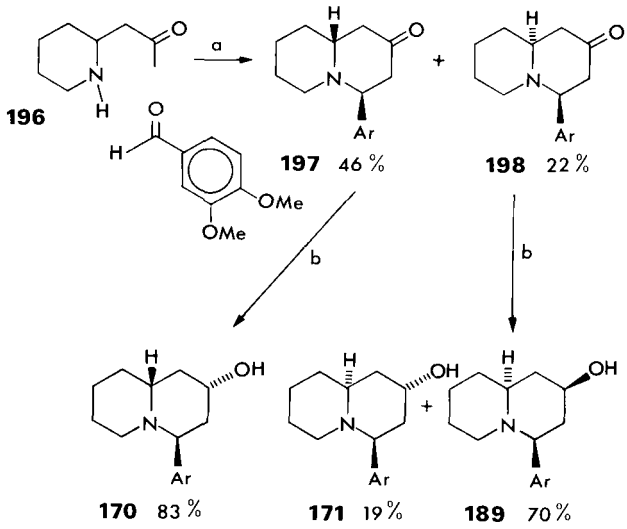
In a similar vein, dipolar cycloaddition of Δ^1-piperideine *N*-oxide (**182**) with the benzyl alcohol **191a** starts off a synthesis of the demethyllasubines I and II, **164** and **165** (Scheme 36) (*141,142*). In contrast to the previous synthesis, the cycloaddition is a highly stereoselective process, although there is no stereochemical control at the benzylic position. The diastereomeric mixture **192a** is carried through the synthesis, via intermediate **193**, to the acetates **194a** and **195a**, which can then be separated. The latter is readily transformed by hydrolysis and deprotection to alkaloid **164**. The former requires inversion of configu-



SCHEME 35. Stereochemistry of ring closure in the synthesis of lasubine I by Iida, Tanaka, and Kibayashi (*139,140*).



SCHEME 36. Synthesis of demethyllasubines I and II, lasubine II, abresoline, and 10-epidemethoxyabresoline by Takano and Shishido (*141,142,143*). Reagents: (a) $C_6H_5CH_3$, Δ; (b) MsCl, py; (c) Zn, 50% HOAc; (d) Ac_2O, py; (e) NaOH, H_2O–MeOH; (f) Ph_3P, DEAD, $C_6H_5CO_2H$, THF; (g) NaOMe, MeOH; (h) H_2 (1 atm), 10% Pd–C, MeOH; (i) CH_2N_2, MeOH; (j) 3-MeO-4-MEM-*O*-$C_6H_3CH{=}CHCO_2H$, Ph_3P, DEAD, THF; (k) CF_3CO_2H, CH_2Cl_2, 0°C; (l) LiOH, H_2O–MeOH; (m) py, DMAP, (4-MEM-*O*-$C_6H_4CH{=}CHCO)_2O$.



SCHEME 37. Mannich synthesis of lasubines I and II by Iida, Tanaka, and Kibayashi (*140*). Reagents: (a) 1% aq NaOH, THF, 70°C; (b) $NaBH_4$, MeOH.

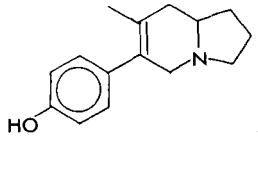
ration at the 2 position in order to complete a synthesis of **165**. This is most conveniently done on the corresponding alcohol by the Mitsunobu procedure, using benzoic acid as nucleophile. From compound **165**, lasubine II (**171**) is readily prepared by alkylation of the free phenolic group with diazomethane.

A parallel sequence starting with **191b** (R = MEM), also shown in Scheme 36, yields a similar mixture of cycloadducts **194b** and **195b** (*142,143*). Basic hydrolysis of the acetate group of **195b**, followed by reesterification with MEM-protected *p*-coumaric acid and subsequent removal of the MEM-protecting groups gives (±)-10-epidesmethoxyabresoline (**167**). On the other hand, application of the Mitsunobu inversion procedure to **194b**, using MEM-protected ferulic acid, followed by removal of MEM-protecting groups, results in the synthesis of (±)-abresoline (**169**).

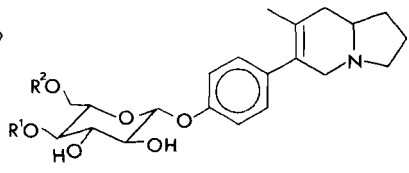
A more conventional synthesis of lasubines I and II uses Mannich methodology (*140*). The reaction of isopelletierine (**196**) and veratraldehyde gives rise to the ketone mixture **197** and **198**. Reduction of the former gives lasubine I (**170**) in 83% yield, while reduction of the latter gives lasubine II (**171**) and 2-epilasubine II (**189**) in 19 and 70% yields, respectively (Scheme 37).

C. IPALBIDINE AND RELATED INDOLIZIDINE ALKALOIDS

Simple indolizidine alkaloids have been isolated from two species of *Ipomoea* (family Convolvulaceae). From the basic extracts of the crushed seeds of



199



200 $R^1 = R^2 = H$
201 $R^1 = COCH{=}CHC_6H_4\text{-}4\text{-}OH$, $R^2 = H$
202 $R^1 = H$, $R^2 = COCH{=}CHC_6H_4\text{-}4\text{-}OH$

Ipomoea alba L. were isolated ipalbidine (**199**), (+)-ipalbine (**200**, absolute configuration not determined), and a minor unidentified base (*144*). The crushed seeds of *Ipomoea muricata* Jacq. gave ipalbidine (**199**) as the minor product (0.001% by mass) and a new alkaloid, (+)-ipomine, as the major (0.022%) (*145*).

The structure of ipalbidine (**199**), a crystalline solid of mp 147–148°C, was determined by a combination of spectroscopic techniques and chemical transformations, including partial and total hydrogenation and dehydrogenation over selenium (*144*). Ipalbidine is the aglycone of ipalbine (**200**), mp 118°C, from which it is readily obtained, along with β-D-glucose, on hydrolysis in dilute acid solution. Both compounds have received prior mention in this treatise as alkaloids of unclassified type (*146,147*).

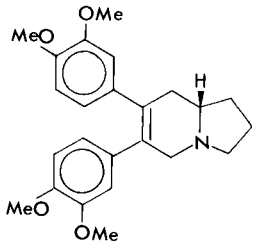
The structure of ipomine is less secure. The compound, a solid of mp 139°C, is hydrolyzed in dilute acid to ipalbidine (**199**), β-D-glucose, and *p*-coumaric acid. Enzymatic hydrolysis with emulsin also gives ipalbidine, thereby confirming that the phenolic hydroxy group of ipalbidine, and not *p*-coumaric acid, is linked to C-1 of glucose. When ipomine is methylated with dimethyl sulfate and the resulting product is hydrolyzed in acid, 2,3,6-tri-*O*-methyl-β-D-glucopyranose is isolated; on this basis, the attachment of *p*-coumaric acid to C-4 of glucose would seem to be unambiguous, implying structure **201** for ipomine (*145*). However, a subsequent ^{13}C-NMR spectroscopic study casts doubts on this structure (*148*); the data are more consistent with the attachment of coumaric acid to C-6 of glucose, and the alternative structure **202** has been suggested for ipomine. The matter is clearly in need of further clarification.

While optical rotations for both ipalbine ($[\alpha]_D$ +32.5°, *c* 0.3, EtOH) (*144*) and ipomine ($[\alpha]_D$ +46.4°, *c* 0.55) (*145*) have been measured, in neither of these studies was an optical rotation for natural ipalbidine (**199**) reported. This point was addressed in an early synthesis by Dolphin and co-workers (see Section V,F,3) in which both enantiomers of ipalbidine were made (*149*). These workers found substantial differences in the melting points of racemic **199** and (−)-**199** and also in those of their methiodide and picrate salts; the reported melting points of natural ipalbidine and its salts are significantly closer to those of the racemic

synthetic material. Furthermore, the hydrochloride salt of natural ipalbidine was found to be essentially optically inactive, whereas that of (−)-**199** gave $[\alpha]_D$ −70° (*c* 1, MeOH). In addition, synthetic (+)-ipalbine (**200**), prepared from synthetic (+)-ipalbidine and β-D-glucose, gave a markedly different optical rotation from the natural material ($[\alpha]_D$ +54.7°, *c* 1, MeOH), as well as a lower melting point, 95–98°C. On the basis of some model calculations, the authors conclude that natural ipalbine consists of an approximately 85:15 diastereomeric mixture of the β-D-glucosides of (+)- and (−)-ipalbidine, respectively. The implication is that racemic ipalbidine (**199**) is the biogenetic precursor of ipalbine (**200**) and that partial selectivity by the plant in forming the glucosides (or subsequent discrimination between the diastereomeric glucosides) leads to formation of the unequal mixture of diastereomers of ipalbine (**200**). Racemization of the ipalbidine nucleus during isolation can be ruled out, since (−)-ipalbidine emerges optically unscathed after subjection to hydrolysis conditions. The question of the diastereomeric nature of ipalbine (**200**) has not received further attention. The likelihood of a similar problem with ipomine has not been recognized, though it may not exist, since all peaks in the ^{13}C-NMR spectrum of the compound appear to be fully resolved (*145*).

D. Septicine and Related Indolizidine Alkaloids

(−)-Septicine (**203**) has the distinction of being the first simple indolizidine alkaloid to have been discovered. The report of its isolation dates from 1963 (*150*); in fact, it may actually have been isolated much earlier, since the compound (mp 136–137°C) may just be a purer version of the "amorphous base" (mp 125–130°C) isolated a quarter of a century earlier by Chopra *et al.* from *Tylophora asthmatica* (*151*). The alkaloid is a close relative of the phenanthroindolizidine alkaloids, which have received separate treatment in this treatise (*2,152*) and elsewhere (*9,153,154*). Septicine itself has been treated cursorily in



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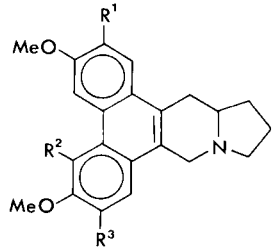


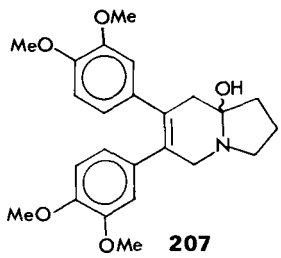
204 $R^1 = R^3 = OMe$, $R^2 = H$
205 $R^1 = R^2 = OMe$, $R^3 = H$
206 $R^1 = OMe$, $R^2 = R^3 = H$
209 $R^1 = R^2 = H$, $R^3 = OMe$

this treatise in the chapters entitled "Alkaloids Unclassified and of Unknown Structure" (*155–157*).

Septicine was isolated, along with (−)-tylophorine (**204**) and (+)-tylocrebrine (**205**), from the tree *Ficus septica* Forsk. (family Moraceae) (*150*). Its structure was deduced on the basis of chemical degradation, spectroscopic methods, and conversion to tylophorine, a known compound at that time. The structure was later confirmed by synthesis from L-prolinol (see Section V,F,1), a synthesis, incidentally, that established (−)-septicine as being of the *S* configuration, as shown in **203** (*158*). While the optical rotation of the natural material was not reported in the original paper, that of synthetic (−)-septicine—claimed to be identical to the natural product in all respects—was determined as $[\alpha]_D$ −16.2° (*c* 1, MeOH). In the light of the data presented in the following paragraph, this synthetic (−)-septicine may nevertheless be partly racemized. Interestingly enough, when a later group of workers reinvestigated the metabolites of the root and leaves of *Ficus septica,* they failed to isolate septicine, tylophorine, or tylocrebrine, and only obtained a quantity of partially racemic antofine (**206**) (*159*).

(−)-Septicine has also been isolated from *Tylophora crebriflora* S.T. Blake, an Australian vine belonging to the family Asclepiadaceae (taxonomically quite remote from the family Moraceae) in which it occurs alongside tylocrebrine (**205**) and five similar phenanthroindolizidine alkaloids (*160,161*). The optical rotation quoted for (−)-septicine in this work is $[\alpha]_D$ −42.5°. Strangely enough, (+)-septicine ($[\alpha]_D$ +38.8°, *c* 1, MeOH), has been obtained from another species, *Tylophora asthmatica* Wight et Arn [syn. *T. indica* (Burm) Merril] (*162*). A third species, *T. hirsuta,* contains a related alkaloid, (+)-8a-hydroxysepticine (**207**) {$[\alpha]_D$ +100° (*c* 0.4, MeOH)} (*163*). The orientation of the hydroxy group in this compound has not been determined, though the ring junction is probably cis. A demethoxy derivative of septicine, named hispidine (**208**), has been isolated from the leaves of *Ficus hispida* (*164*). Its optical rotation has not been determined. The compound is a seco version of (−)-deoxypergularine (**209**), with which it co-occurs.

The biosynthesis of septicine and related alkaloids, although not studied per se, must surely be intimately related to the biosynthesis of the phenanthroin-



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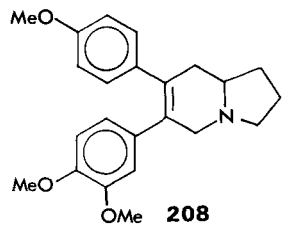

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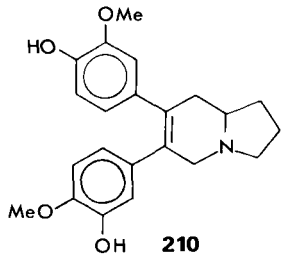
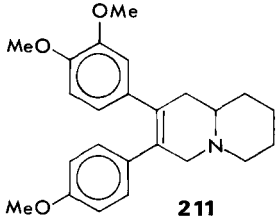


210

dolizidine alkaloids, a subject that has received a fair amount of attention (*2,165, 166*). Current thinking allocates a central role in the biosynthesis of these alkaloids to compound **210**, oxidative phenolic coupling within which leads to the fused pentacyclic alkaloids. The production of septicine (**203**) from **210** *in vivo* probably terminates a sequence of events, since septicine itself is not incorporated into alkaloids like tylophorine (**204**) (*165*).

E. Julandine and Kayawongine

Julandine (**211**), a minor alkaloid from *Boehmeria platyphylla* Don. (family Urticaceae) (*167*), is an example of that *rara avis,* a natural product that nobody was in a hurry to name. The present appellation was given as a matter of convenience a decade after the compound was first isolated (*168*), and there seems to be no obvious rationale for the name. The compound has previously



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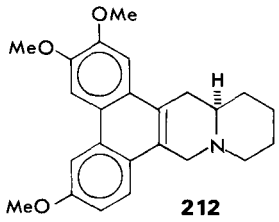

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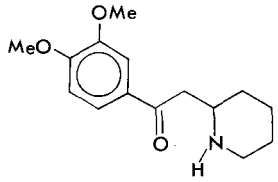

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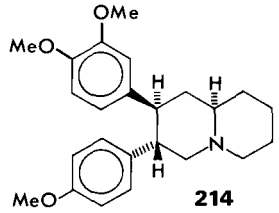


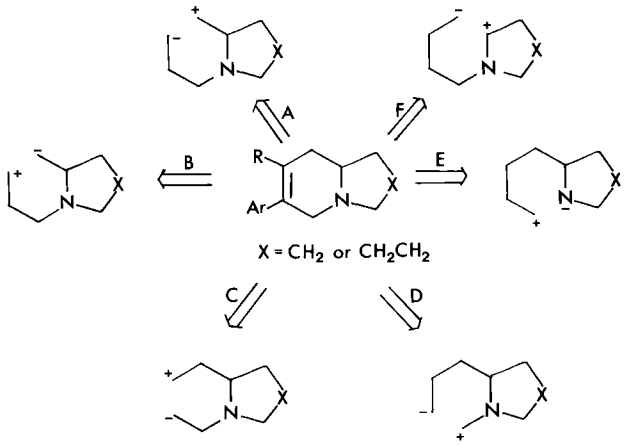
214

received passing notice in this treatise as an alkaloid of unclassified type (*169*). Julandine has a clear structural similarity to the phenanthroquinolizidine alkaloids [e.g., cryptopleurine (**212**)], which have excited interest as antimicrobial and antitumor agents; indeed, julandine occurs alongside cryptopleurine and their mutual precursor, 3,4-dimethoxy-ω-(2′-piperidyl)acetophenone (**213**). From 17 kg of the dried plant, only 10 mg of julandine was obtained (*167*); this seems to be the only record of the isolation of the natural material. Its presence could not be definitely established in extracts from *B. cylindrica* (L.) Sw. (*170*) or in *B. cylindrica* var. *drummondiana* Wedd. (*171*). The natural compound is a solid, mp 134.5–135.5°C, and, although it was obtained in optically active form ($[\alpha]_D$ +4.6°, *c* 0.5, chloroform), the similarity of behavior of natural julandine and a synthetic racemic sample raises the suspicion that the natural product may be largely racemic. The structure of julandine was deduced from spectroscopic data and by analogy to cryptopleurine and confirmed shortly after its isolation by synthesis (*172*).

The related alkaloid (−)-kayawongine (**214**) occurs with cryptopleurine (**212**) in the plant *Cissus rheifolia* Planch. (family Vitaceae), a native of northeast Thailand (*173*). The name of the alkaloid is derived from the Thai name of the plant, *ka-ya-wong*, which is translated as "vulture without hope." In the report describing the isolation of kayawongine, the legend behind the naming of the plant is recounted: a herd of cattle recovered from an unnamed disease after being fed rice that had been boiled with the root of the plant, thereby depriving the hopeful vultures of their anticipated feast. The alkaloid (mp 124–124.5°C; $[\alpha]_D$ −116°, *c* 0.85, chloroform) constituted 0.01% of the dried leaves of the plant. Its structure was assigned with the aid of extensive spectroscopic data; in particular, the relative stereochemistry of the substituents was inferred from the ^{1}H-NMR spectrum on the basis of coupling constant data and decoupling experiments. Although the absolute configuration of **214** could not be deduced from its circular dichroism spectrum, the authors favor the same 9a*R* configuration as has been assigned to cryptopleurine (**212**), and they cite biosynthetic analogies for their choice.

F. Syntheses of Ipalbidine, Septicine, and Julandine

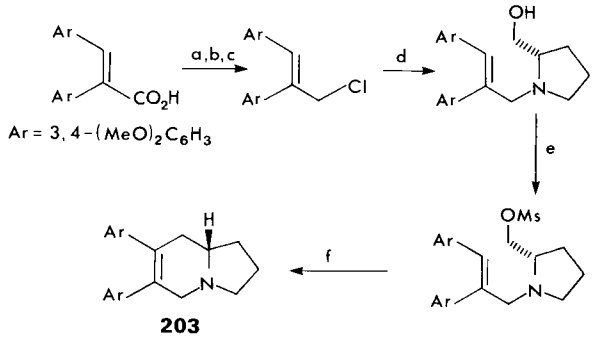
Ipalbidine (**199**), septicine (**203**), and, to a lesser extent, julandine (**211**) have all been exceedingly popular targets for total synthesis. In view of the obvious structural similarities between these compounds, it is not surprising that several common approaches to their synthesis have been developed. We have chosen to classify the documented syntheses of these compounds on the basis of the mode of ring closure of the aryl-substituted ring. Scheme 38 shows the disconnections involved.



SCHEME 38. Disconnections for reported syntheses of ipalbidine, septicine, and julandine.

1. Disconnection A

The interest in this route is largely historic. It was the first route by which septicine (**203**) was made and is in fact the only route to have led to the optically active alkaloid (*158*). The key feature is the use of L-prolinol to confer optical activity on the product; as mentioned before (Section V,D), however, the synthetic product may nevertheless be partly racemic, in view of the low $[\alpha]_D$ value obtained for it. The reaction sequence is summarized in Scheme 39.

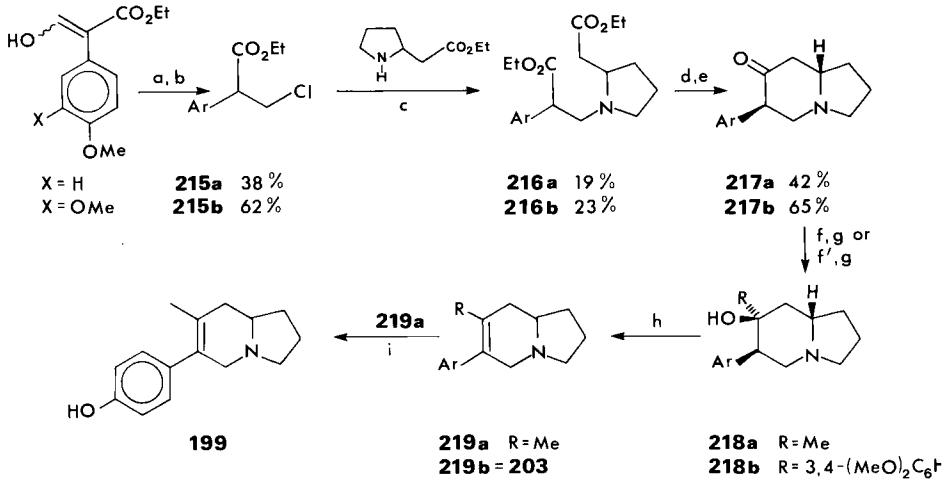


SCHEME 39. Synthesis of (−)-septicine by Russel and Hunziker (*158*). Reagents: (a) HCl, EtOH; (b) $LiAlH_4$, THF; (c) HCl, Et_2O, anhyd Na_2SO_4; (d) L-prolinol, DMF, py; (e) MsCl, py; (f) NaH, DMF.

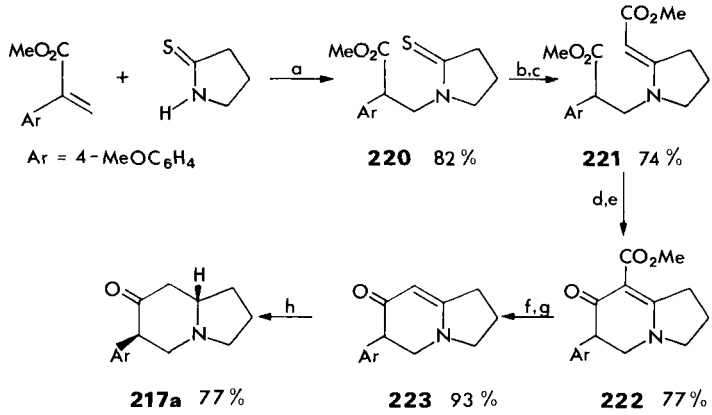
2. Disconnection B

A generalized route to both (±)-ipalbidine (**199**) (*174*) and (±)-septicine (**203**) (*175*) by Govindachari and co-workers uses a Dieckmann condensation to accomplish ring closure to the indolizidine ring system (Scheme 40). Ethyl 2-pyrrolidinylacetate serves as the precursor of the five-membered ring, and N-alkylation of this with the appropriate phenethyl chloride **215a** or **215b** produces the diesters **216a** and **216b** on which the condensations are carried out. Immediate hydrolysis and decarboxylation of the Dieckmann product effectively circumvents the problem of regiochemistry in the condensation. The resulting ketones **217a** and **217b** are very important intermediates, since several later formal syntheses converge to these compounds. The isomers shown appear to be the sole ones isolated, presumably owing to thermodynamic effects. The syntheses are completed by addition of the appropriate organolithium compound, followed by dehydration of the resulting alcohols **218a** and **218b**. The unsaturated product **219a** can be demethylated with boron tribromide to (±)-ipalbidine (**199**); product **219b** (= **203**) is septicine. The perdemethoxy analog of septicine has also been synthesized by this route (*175*).

Ketone **217a** is the objective of a later formal synthesis of (±)-ipalbidine (**199**), which employs disconnection B (*176*). The reaction sequence (Scheme 41) begins with Michael reaction of a 2-arylacrylic ester on to the nitrogen atom of pyrrolidine-2-thione. Methyl bromoacetate alkylates the resulting thiolactam



SCHEME 40. Syntheses of ipalbidine and septicine by Govindachari and co-workers (*174,175*). Reagents: (a) $NaBH_4$, MeOH; (b) $SOCl_2$; (c) K_2CO_3, $C_6H_5CH_3$, Δ; (d) Ph_3CK, Et_2O–THF; (e) 2 *M* HCl, Δ; (f) MeLi (for **119a**), Et_2O–THF; (f′) 3,4-$(MeO)_2C_6H_4Li$ (for **119b**), Et_2O–THF; (g) 2 *M* HCl; (h) H_2SO_4, H_2O, Δ; (i) $AlBr_3$, CS_2.

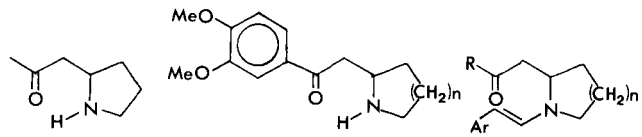


SCHEME 41. Formal synthesis of ipalbidine by Howard, Gerrans, and Michael (*176*). Reagents: (a) NaOH (cat.), THF; (b) $BrCH_2CO_2Me$, THF (c) Ph_3P, NEt_3, MeCN; (d) NaOH, H_2O, Δ (e) $ClCO_2Me$, Bu_4NI (cat.), THF; (f) KOH, H_2O, Δ; (g) HCl, H_2O, Δ; (h) $LiAlH_4$, THF.

220 on sulfur; when the ensuing salt is subjected to the sulfide contraction procedure, vinylogous urethane **221** is formed. Ring closure in this synthesis depends on the enamine-like nucleophilicity of vinylogous urethane **221**; it is effected once the saturated ester group has been converted to a mixed anhydride. Hydrolysis and decarboxylation of the cyclized product **222** yields the vinylogous amide **223**, which, on reduction under carefully controlled conditions, gives the target ketone **217a**.

3. Disconnection C: Biogenetically Patterned Synthesis

That pyrrolidine and piperidine rings in alkaloids originate from ornithine and lysine, respectively, is beyond argument, whatever the intermediate species en route may be. Δ^1-Pyrroline and -piperideine (or biological equivalents for them) are probably the first heterocyclic species in the biogenetic sequence of events, functioning as electrophiles for the attachment of side chains at their 2 positions. Simple heterocyclic bases like norhygrine (**224**), ruspolinone (**225**), and the piperidine analog of the latter (**226**) are all natural products which conform with this biogenetic hypothesis. One can in turn readily envisage these compounds, or



224 **225** n = 1 **226** n = 2 **227**

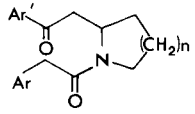
others very much like them, as easily accessible synthetic forerunners for ipalbidine (**199**), septicine (**203**), and julandine (**211**), respectively.

It is precisely on such a biogenetic model that Herbert and co-workers have fashioned economical syntheses of these three alkaloids (*168,177–181*). By the oxidation of putrescine or cadaverine with pea-seedling diamine oxidase in the presence of appropriate β-keto acids, the three monoheterocyclic alkaloids **224**, **225**, and **226** can be made in 88, 85, and 79% yields, respectively. When these compounds are treated with suitably substituted arylacetaldehydes, the enamines **227** result. These compounds need not be isolated; they undergo cyclization and dehydration merely on standing in methanolic solution, though the julandine synthesis benefits from Lewis acid catalysis (*179*). After reduction of the crude products with sodium borohydride, the desired bicyclic alkaloids are obtained in 20–29% yields. The method has been used by other workers for the synthesis of septicine analogs and, from them, tylophorine (**204**) (*182*).

Rather similar approaches have been devised, which rely on the intramolecular cyclization of keto amides **228** instead of enamines **227**. In these cases, cyclization must be induced with base (sodium ethoxide, potassium *t*-butoxide, or alcoholic alkali). The lactams **229**, which result from this condensation, may then be reduced with lithium aluminum hydride (with or without the addition of aluminum chloride) to the alkaloids septicine (**203**) (*183–185*) and julandine (**211**) (*172,185,186*), as well as to several unnatural analogs (*187,188*). The lactams **229** may also serve as precursors to phenanthroindolizidine and -quinolizidine alkaloids (*184–186,189*).

The synthesis of the keto amides **228** on which the cyclizations are carried out deserves some comment. The obvious routes just involve the acylation of the monocyclic alkaloids **225** and **226** with appropriate arylacetyl chlorides; the monocyclic alkaloids are in turn made by Δ^1-pyrroline methodology (*183*) or conventional pyridine chemistry (*172*). A more imaginative procedure, however, employs nitrone cycloadditions to create systems that can then be N-acylated and cyclized (*184–186*). The steps involved are shown in Scheme 42. While the nitrone cycloadditions proceed regiospecifically, the extent of their stereoselectivity depends on whether a five- or six-membered cyclic nitrone is used initially. The former gives more severe mixtures of isoxazolidine products, which, once cleaved and oxidized, afford the desired keto amides on which the biogenetically modeled cyclization is performed.

The synthesis of ipalbidine by Dolphin and co-workers (*149*), shown in



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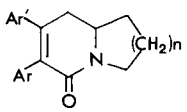

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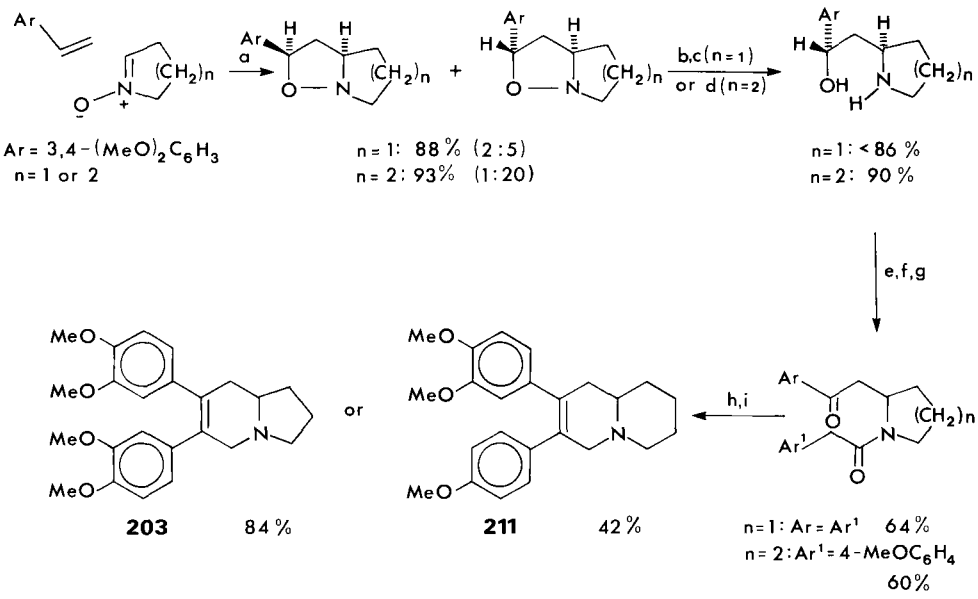
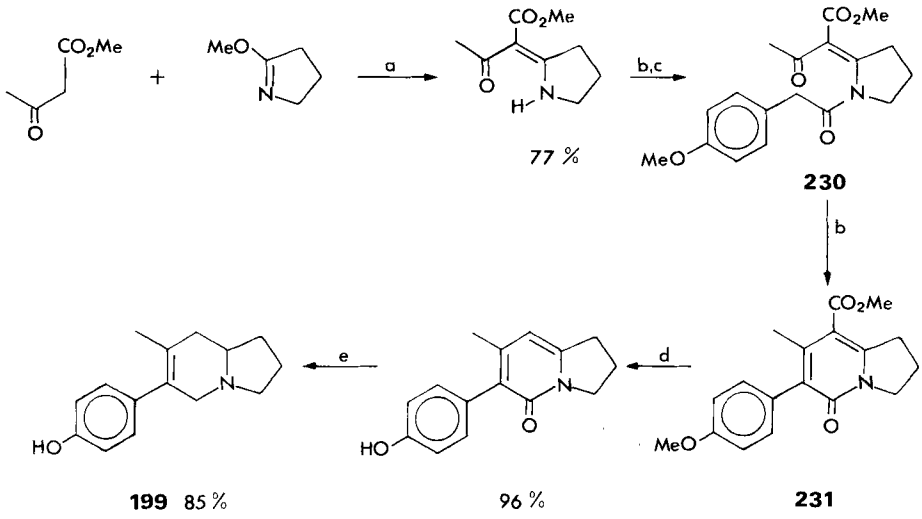


SCHEME 42. Syntheses of septicine and julandine by Kibayashi and co-workers (*184–186*). Reagents: (a) $C_6H_5CH_3$, Δ; (b) H_2 (1 MPa), 10% Pd–C, MeOH (80%); (c) repeated recrystallization; (d) Zn, 50% aq HOAc; (e) $Ar'CH_2COCl$, K_2CO_3, MeCN; (f) K_2CO_3, MeOH–H_2O, Δ; (g) Collins oxidation, CH_2Cl_2; (h) NaOEt, EtOH, Δ (for n = 2); 5% KOH, EtOH, Δ (for n = 1); (i) $LiAlH_4$, THF (for n = 2); $LiAlH_4$, $AlCl_3$, THF–Et_2O (for n = 1).

Scheme 43, has previously been referred to (Section V,C). Although not specifically designed with biogenetic principles in mind, it is included in this section because of the key cyclization step, **230** to **231**. More important, however, is the fact that the authors succeed in resolving their product, (±)-ipalbidine (**199**), via its *O*-acetyl derivative. This ester gives crystalline salts with both (+)- and (−)-di-*O*-*p*-toluyltartaric acid; the diastereomeric salts can then be crystallized to constant melting points and optical rotations. Liberation of the free base and mild basic hydrolysis allows the isolation of both (−)-ipalbidine ($[\alpha]_D$ −237°, *c* 1, chloroform; mp 82–84°C) and (+)-ipalbidine ($[\alpha]_D$ +233.5°, *c* 1, chloroform; mp 72–82°C). The (+)-enantiomer can in turn be converted to (+)-ipalbine (**200**) on treatment with β-D-glucose under mildly acidic conditions.

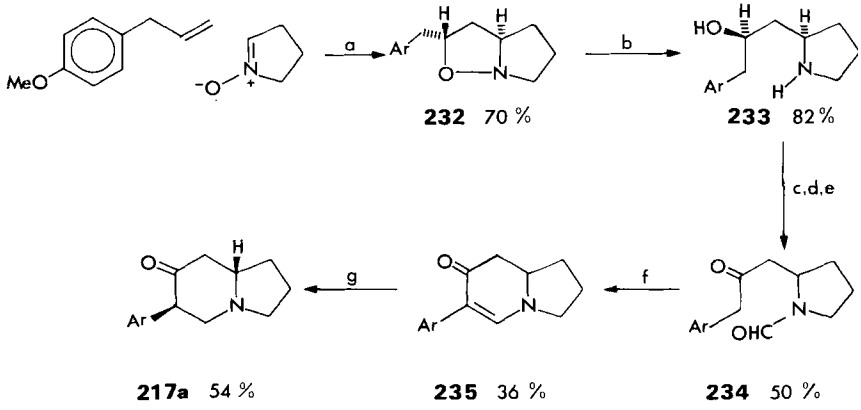
4. Disconnections D and E

The interesting features of two syntheses employing disconnections D and E are as much in the early stages as in the ring closures. Both make use of nitrone methodology to introduce a carbon chain into the 2 position of a pyrrolidine ring.

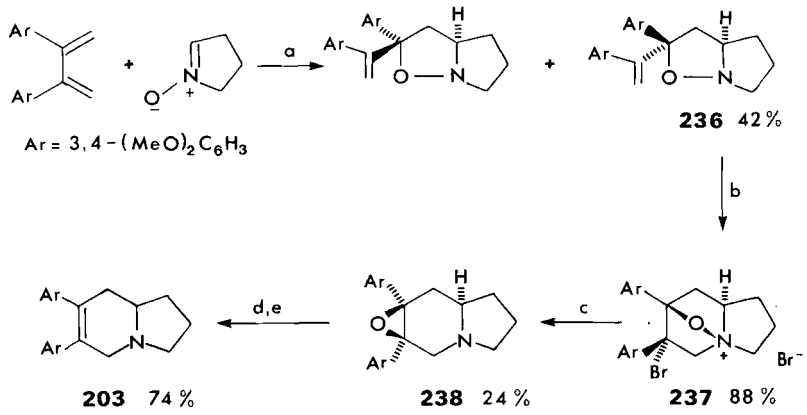


SCHEME 43. Synthesis of ipalbidine by Wick, Bartlett, and Dolphin (*149*). Reagents: (a) 85°C; (b) NaH, C_6H_6; (c) $ArCH_2COCl$, C_6H_6; (d) 48% HBr, 135°C; (e) $LiAlH_4$, $AlCl_3$, THF, Δ.

Scheme 44 outlines a recent formal synthesis of (±)-ipalbidine (**199**), which uses disconnection D (*190,191*). The reaction of Δ^1-pyrroline *N*-oxide with *p*-allylanisole gives isoxazolidine **232** as the sole product, hydrogenolysis of which yields the pyrrolidine **233**. A sequence of transformations leads to the *N*-formyl product **234**, which undergoes base-initiated cyclization to the vinylogous amide



SCHEME 44. Formal synthesis of ipalbidine by Iida, Watanabe, and Kibayashi (*190,191*). Reagents: (a) $C_6H_5CH_3$, Δ; (b) H_2, 5% Pd–C, MeOH; (c) HCO_2H, $C_6H_5CH_3$, Δ; (d) NH_3, MeOH; (e) Collins oxidation, CH_2Cl_2; (f) $(t\text{-BuO})_3Al$, xylene, Δ; (g) Li, NH_3, THF.



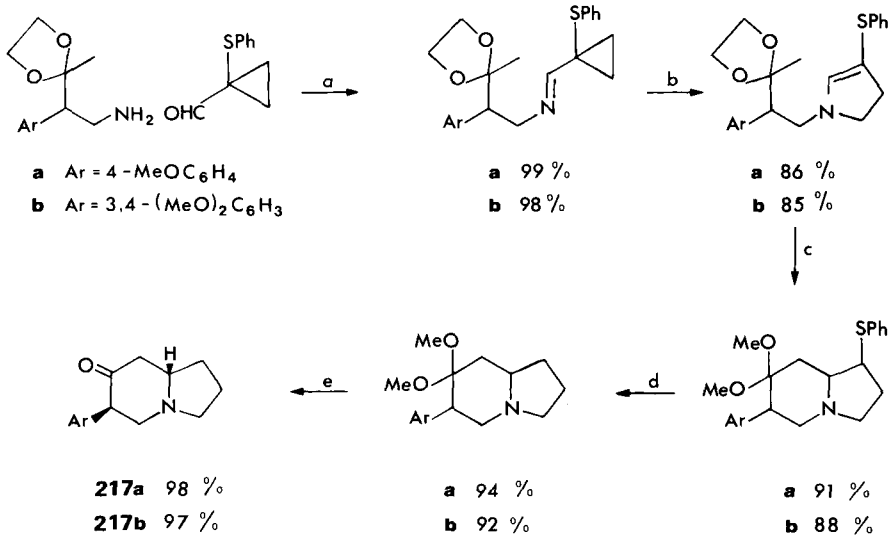
SCHEME 45. Synthesis of septicine by Iwashita *et al.* (*192*). Reagents: (a) $C_6H_5CH_3$, Δ; (b) Br_2, $CHCl_3$; (c) $LiAlH_4$, THF; (d) Me_3SiCl, $CHCl_3$; (e) Zn, HOAc–EtOH (1:10), Δ.

235. Selective reduction of the olefinic bond leads to the much-synthesized ketone **217a**, thereby completing a formal synthesis of ipalbidine (**199**).

Apart from the use of nitrone methodology, a synthesis of (±)-septicine (**203**) (*192*) uses a disconnection-E annulation procedure, which breaks away from the almost inevitable "condensation" which is so characteristic a feature of most of the syntheses described thus far (Scheme 45). The major isoxazolidine **236** from the dipolar cycloaddition undergoes bromination with intramolecular participation by nitrogen to set up the indolizidine system in **237**. Treatment of **237** with lithium aluminum hydride leads to regeneration of **236** in 43% yield and also, more importantly, to the formation of epoxide **238** in 24% yield. Septicine (**203**) is obtained in 74% yield from this compound by opening the epoxide ring with trimethylsilyl iodide, followed by zinc-assisted elimination of the elements of trimethylsilyl hypoiodite.

5. Disconnection F

The cyclopropylimine–Δ^2-pyrroline rearrangement, so ably exploited by Stevens (*49*), has been applied with excellent results to the synthesis of both (±)-ipalbidine (**199**) and (±)-septicine (**203**) (*193*). The sequence, which is a variation of the δ-coniceine synthesis discussed in Section II,4, is shown in Scheme 46. As in the earlier example, the chief synthetic interest lies in the rearrangement of cyclopropylimines to phenylthio-stabilized Δ^2-pyrrolines. The subsequent formation of the bicyclic systems is effectively accomplished by an intramolecular Mannich reaction. Ketones **217a** and **217b** are once again key intermediates, and from these intermediates the syntheses are completed essentially as described by Govindachari (*174,175*).



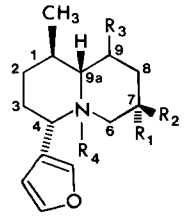
SCHEME 46. Syntheses of ipalbidine and septicine by Stevens and Luh (*193*). Reagents: (a) C_6H_6, Δ; (b) NH_4Cl, xylene, Δ; (c) HCl, MeOH, $(MeO)_3CH$; (d) H_2 (60 psi), Raney Ni, EtOH; (e) 1 *M* HCl, CH_2Cl_2.

VI. Sesquiterpenoid Indolizidine and Quinolizidine Alkaloids

A. NUPHAR ALKALOIDS

Alkaloids isolated from plants of the genus *Nuphar* (family Nymphaceae) have been reviewed twice before in this treatise (*194,195*), the latest covering the literature up to 1974. Another succint review (*196*) of later vintage includes the structures of all known Nuphar alkaloids, a group that embraces C_{15} piperidine and quinolizidine alkaloids (the former being seco derivatives of the latter) and C_{30} thiospirane alkaloids. The C_{15} alkaloids possess a regular sesquiterpenoid skeleton, part of which has been elaborated into a 3-substituted furan. The C_{30} alkaloids are essentially sulfur-bridged dimers of the simple quinolizidine systems. Six simple quinolizidines were known at the time of the review in Volume 16 of this treatise (*195*). A seventh, (+)-nupharopumiline (**246**), was reported in 1977 (*197*); and a further compound, 7-epinupharidine (**240**), while isolated from plant sources, is thought to be an artifact (*198*). The structures and sources of the simple Nuphar quinolizidines are listed in Table II. Unless stated otherwise, the appropriate references may be found in the earlier reviews (*194,195*) in this treatise.

Various chemical transformations have been used to establish configurational



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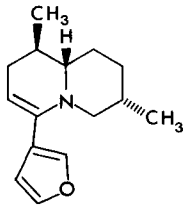

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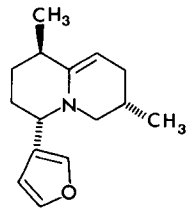

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TABLE II
Simple Nuphar Quinolizidine Alkaloids

Compound	Name	R_1	R_2	R_3	R_4	Ring junction	Source
239	(+)-Nupharidine	Me	H	H	O	cis	*a,b,c,d*
240	7-Epinupharidine	H	Me	H	O	trans	*d*
241	(−)-Deoxynupharidine	Me	H	H	—	trans	*a,b,c,d*
242	7-Epideoxynupharidine	H	Me	H	—	trans	*b,c,d*
243	(−)-Nupharolidine	Me	H	OH	—		*b*
244	(−)-Nupharolutine	Me	OH	H	—	trans	*b*
245	(+)-Dehydrodeoxynupharidine						*a*
246	(+)-Nupharopumiline						*d*

[a] *Nuphar japonica* L.
[b] *N. lutea* (L.) Sibth. and Sm.
[c] *N. lutea* ssp. *variegata.*
[d] *N. pumila* (Timm) DC.

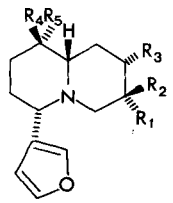
correlations among these compounds, and in most cases (−)-deoxynupharidine (**241**) has served as the configurational pivot. It was thus particularly unfortunate that its absolute configuration was for a long time mistakenly regarded as 1*S*,4*R*,7*R*,9a*R* (*199*). One needs to be cautious when reading the earlier Nuphar and related literature, since much of it incorporates this error. The correct 1*R* absolute configuration (*195*), as shown in the diagram, was proposed by La-Londe and co-workers (*200*) and confirmed by X-ray crystallographic analysis of (−)-deoxynupharidine hydrobromide (*201*). The 1*R* configuration was subsequently found for the hydrobromide salt of (+)-nupharidine (**239**) in an X-ray crystallographic study, which also showed that the rings in this compound are cis-fused chairs (*202*). This, incidentally, appears to be the only simple Nuphar quinolizidine not to contain a trans-fused ring junction (*203*).

The new alkaloid, (+)-nupharopumiline (**246**), represents about 0.15% of the total alkaloids of *Nuphar pumila* (Timm.) DC. (*197*). The compound is a solid {mp 195–197°C, $[\alpha]_D$ +27° (chloroform)}. Not surprisingly, its IR spectrum shows no Bohlmann bands. On catalytic hydrogenation, it is converted to (−)-deoxynupharidine (**241**); the absolute configuration of **246** is thus 1*R*,4*S*,7*S*.

B. Alkaloids from the Canadian Beaver

Castor oil, or castoreum, is a commercially valuable extract from the scent glands of the Canadian beaver, *Castor fiber* L. Its major use is as a fixative in perfumery. A comparatively early study (*204,205*) showed that the extract contains at least 40 compounds, mostly phenols, aromatic acids, and ketones. Also isolated was an amine, castoramine. A structure, based on some spectroscopic data and on deoxygenation to (−)-deoxynupharidine (**241**), was proposed for this compound 16 years after its first isolation (*206*). The gross structure was substantiated by synthesis shortly thereafter (*207*); but, as with other Nuphar alkaloids, the 1*S* absolute configuration originally assumed (*208*) is now known to be incorrect. The correct absolute configuration is shown in **247**. The early history of castoramine has been discussed in this treatise (*194*). There is speculation that the occurrence of castoramine in the beaver may be related to the diet of the animal (*206*): the base may be a product of metabolism of alkaloids ingested from *nuphar* species, although one study (*209*) casts doubts on the hypothesis.

An important study by Maurer and Ohloff in 1976 indicates that 14 other nitrogen-containing compounds besides castoramine also occur in the scent



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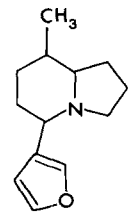

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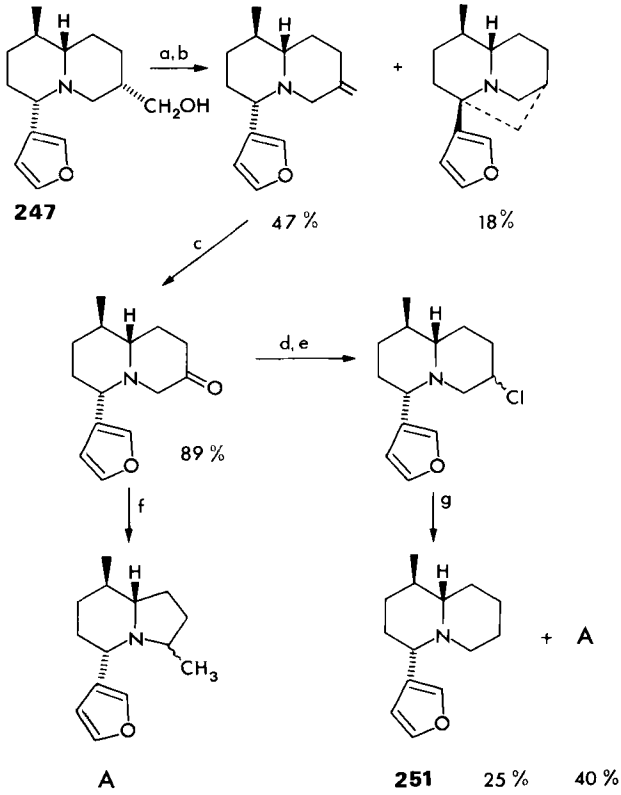
TABLE III
Simple Indolizidine and Quinolizidine Alkaloids from *Castor fiber*

Compound	Name	R_1	R_2	R_3	R_4	R_5	Conc. (%[a])	$[\alpha]_D$ (*c*, EtOH) (°)
241	Deoxynupharidine	Me	H	H	Me	H	0.008	−90(1.0)
242	7-Epideoxynupharidine	H	Me	H	Me	H	0.001	−75(1.0)
247	Castoramine	CH_2OH	H	H	Me	H	0.12	−80(1.0)
248	Isocastoramine	Me	H	OH	Me	H	0.024	−124(1.0)
249	1-Epideoxynupharidine	Me	H	H	H	Me	0.002	−36(0.5)
250	1-Epi-7-epideoxynupharidine	H	Me	H	H	Me	0.001	−70(1.0)
251	7-Demethyldeoxynupharidine	H	H	H	Me	H	0.002	−85(1.0)
252	(Nuphar indolizidine)						trace	

[a] Percentage by mass of dried extract of scent glands.

glands of *C. fiber*, some of them in vanishingly small quantities (*210*). Six of these new compounds are quinolizidines of the Nuphar type, one is an indolizidine, and the rest are mainly pyrazines. The compounds of interest are listed in Table III. Two of them, (−)-deoxynupharidine (**241**) and (−)-7-epideoxynupharidine (**242**), are identical to materials obtained from *nuphar* species, while two others, **249** and **250**, had previously been synthesized in racemic form (*208*). The structures of new compounds were determined by a combination of spectroscopic techniques and chemical interconversions. In particular, the absolute configuration of isocastoramine (**248**) was deduced by converting it to a mixture of (−)-deoxynupharidine (**241**) and (−)-7-epideoxynupharidine (**242**); and (−)-7-demethyldeoxynupharidine (**251**) was correlated with the series by synthesis from (−)-castoramine (**247**). This interconversion, which involves the



SCHEME 47. Conversion of (−)-castoramine to (−)-7-demethyldeoxynupharidine by Maurer and Ohloff (*210*). Reagents: (a) $ClCO_2Me$, py; (b) 500°C, quartz tube; (c) OsO_4, $NaIO_4$, Et_2O–THF–H_2O; (d) $LiAlH_4$, Et_2O; (e) $POCl_3$, py, 10°C; (f) Wolff–Kishner reduction; (g) H_2, 10% Pd–C, EtOH, KOH.

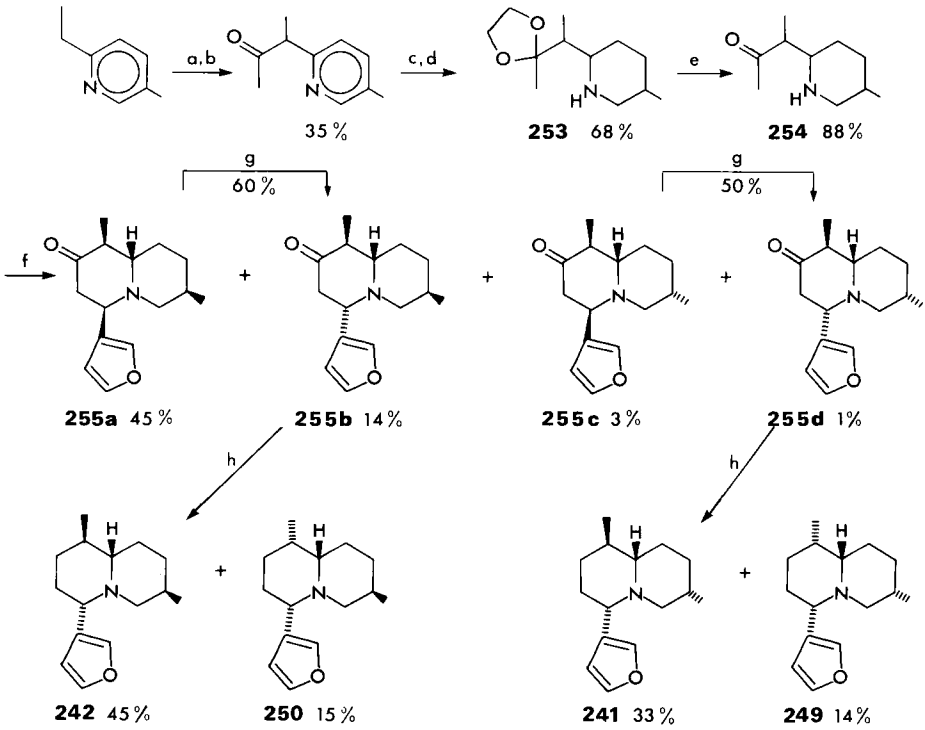
removal of a hydroxymethyl group, has intrinsic chemical interest, and the reaction sequence is shown in Scheme 47. The indolizidine **252** was obtained in such small quantities that its structural assignment had to be based on mass spectral evidence alone. While its absolute configuration and relative stereochemistry are unknown, later syntheses have confirmed its gross structure (*211,212*).

C. Syntheses

The older literature (*194,195*) contains relatively few syntheses of Nuphar and related alkaloids. The decade between the mid 60s and mid 70s was particularly quiet, but since 1977 there has been an increase in synthetic activity. These recent syntheses rely for the most part on the inevitable cyclo-N-acylation or condensation on to nitrogen to elaborate the second ring, but the earlier stages show a notable diversity of approach. Not surprizingly, the stereoselective introduction of the substituents on the quinolizidine system has always been problematic, and few syntheses to date have managed to avoid diastereomeric product mixtures.

Pyridines have been popular starting materials for the synthesis of Nuphar quinolizidines. The Mannich reaction is the key step in a recent synthesis of (±)-deoxynupharidine (**241**) and three of its diastereomers (Scheme 48) by Arata, one of the pioneers in the field of Nuphar chemistry (*213,214*). Unfortunately, the ketone **254** on which the Mannich reaction with furan-3-carbaldehyde is performed is itself a mixture of diastereomers, the exact composition of which varies according to the method used to deprotect the acetal **253** from which **254** is made. The percentage yields for Mannich products **255a–d** given in the scheme are those obtained by using the diastereomeric ketone mixture **254** deprotected with 10% aqueous hydrochloric acid. The lack of stereoselectivity in the Mannich reaction is not a major problem, however, since compounds **255a** and **255c**, in which the ring junction is cis, can be isomerized at the 4 position on treatment with sodium hydroxide in aqueous methanol to the trans-fused compounds **255b** and **255d** in 60 and 50% yields, respectively. Wolff–Kishner reduction of each of these in turn, on the other hand, again entails stereochemical scrambling; each gives rise to two diastereomers of the desired product. The final products, **241**, **242**, **249**, and **250**, are all racemates of known alkaloids. This method has also been used by Arata to synthesize 4-phenyl analogs of Nuphar alkaloids (*215*).

The same type of Mannich ring closure has been used in a synthesis of (±)-nupharolutine (**244**) (*216*), the most intriguing feature of which is the involvement of a dihydropyridine endoperoxide adduct (**256**) (*217*) as the source of the 7-hydroxy group (Scheme 49). Poor stereoselectivity again complicates various steps, especially the Mannich step. As in the previous example, the undesired Mannich product **257a**, possessing a cis-fused ring junction, can be isomerized at

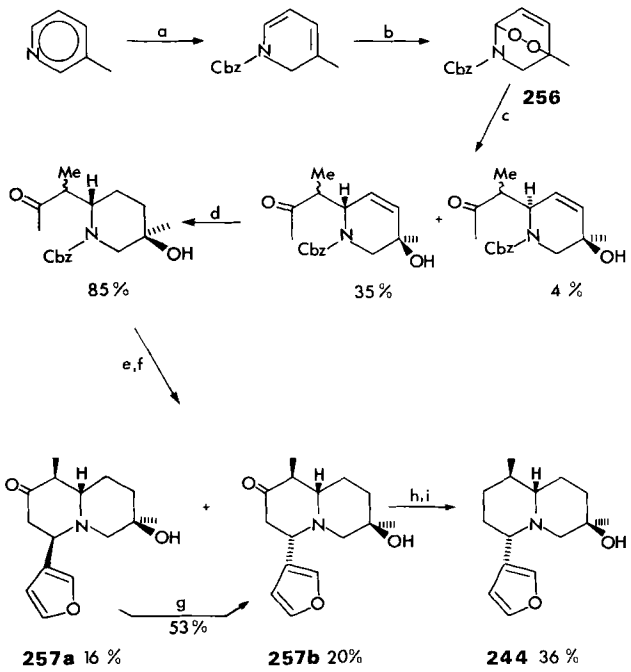


SCHEME 48. Synthesis of deoxynupharidine and three of its diastereomers by Yasuda, Hanaoka, and Arata (*213,214*). Reagents: (a) PhLi, Et_2O; (b) MeCN, then H^+; (c) $(HOCH_2)_2$, *p*TsOH, C_6H_6, Δ; (d) H_2, 5% Rh–Al_2O_3, HOAc; (e) 10% aq HCl; (f) furan-3-carbaldehyde, NaOH, aq MeOH; (g) NaOH, aq MeOH; (h) Wolff–Kishner reduction.

the 4 position with base to the trans-fused compound **257b**. Reduction of the tosylhydrazone of **257b** gives (±)-nupharolutine (**244**), apparently uncontaminated by isomers. Since nupharolutine has previously been converted to deoxynupharidine (**241**) (*218*), this method represents a formal synthesis of **241** and of a host of other Nuphar alkaloids, which can themselves be obtained by various transformations of **241**.

The problem of diastereomer production in the synthesis of Nuphar alkaloids was first overcome by Wròbel and co-workers in an approach that employs a remarkably stereoselective reduction of quinolizinium salts with sodium cyanoborohydride (Scheme 50) (*219*). The decahydroquinolizine **258**, unfortunately the less abundant product of the reduction, is easily epimerized by base to **259**, in which the stereochemistry at all positions is precisely that required for deoxynupharidine (**241**). Standard transformations complete the synthesis of **241**.

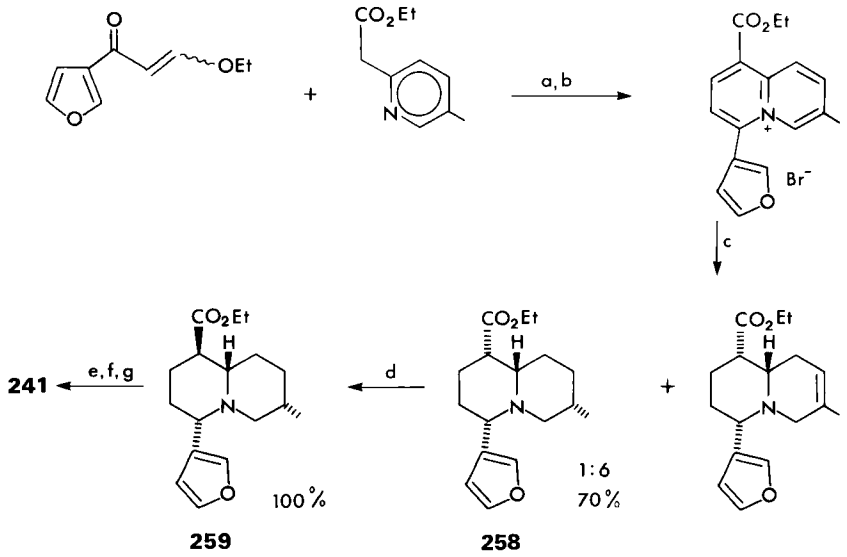
A later synthesis by Wróbel and co-workers (*220*) also uses a highly ster-



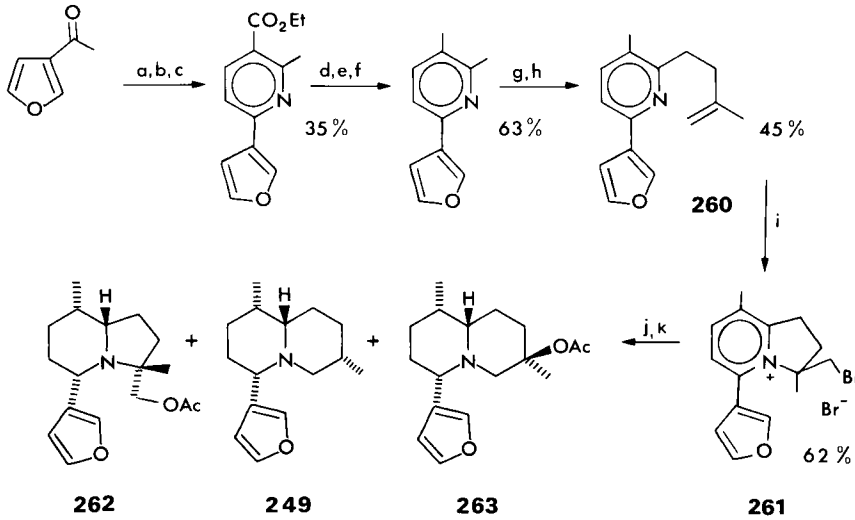
SCHEME 49. Synthesis of nupharolutine by Natsume and Ogawa (*216*). Reagents: (a) ref. *217*; (b) O_2, irradiation, photosensitizer; (c) 2-trimethylsilyloxy-2-butene, $SnCl_2$; (d) H_2, PtO_2, $(MeOCH_2)_2$; (e) H_2, 10% Pd–C, MeOH; (f) furan-3-carbaldehyde, 1% aq NaOH, aq MeOH; (g) 5% aq NaOH, aq MeOH; (h) *p*-$TsNHNH_2$; (i) $LiAlH_4$, THF, Δ.

eoselective reduction, this time of a dihydroindolizinium salt (Scheme 51). The key cyclization here occurs during the bromination of the intermediate **260** [previously used (*221*) in a synthesis of two nuphar piperidine alkaloids]; the reaction proceeds with intramolecular participation by nitrogen to give the dihydroindolizinium salt **261**. Platinum-catalyzed hydrogenation of this, followed by debromination with silver acetate, gives a mixture of indolizidine **262** and quinolizidines **263** and **249**, the last two presumably by way of a tricyclic aziridinium species. In this somewhat fortuitous manner, syntheses of (±)-1-epideoxynupharidine (**249**) and the acetate of 1-epinupharolutine were accomplished.

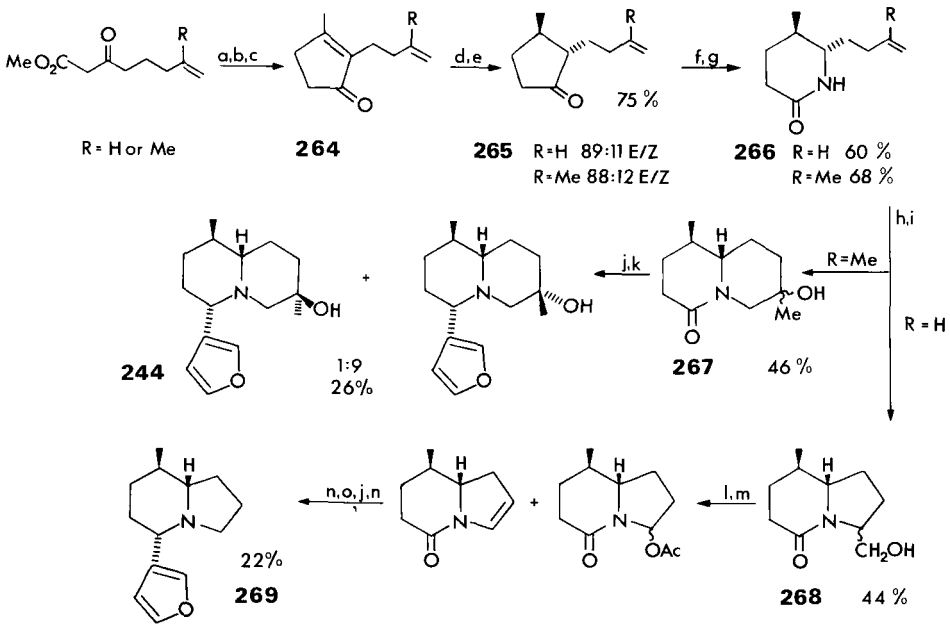
Syntheses of (±)-nupharolutine (**244**) and a single diastereomer of the castor indolizidine **252** by LaLonde and co-workers (*211*) make use of a Beckmann rearrangement to set up functionalized piperidone systems (Scheme 52). Some of the stereochemical questions are addressed at an early stage: reduction of the ketones **264** with lithium in ammonia followed by base-catalyzed equilibration produces mainly the trans-2,3-disubstituted cyclopentanones **265**, the small



SCHEME 50. Synthesis of deoxynupharidine by Wróbel and co-workers (*219*). Reagents: (a) CF_3CO_2H; (b) 45% HBr–HOAc; (c) $NaBH_3CN$, EtOH; (d) NaOEt, EtOH; (e) $LiAlH_4$; (f) $SOCl_2$, py; (g) $LiAlH_4$, glyme.



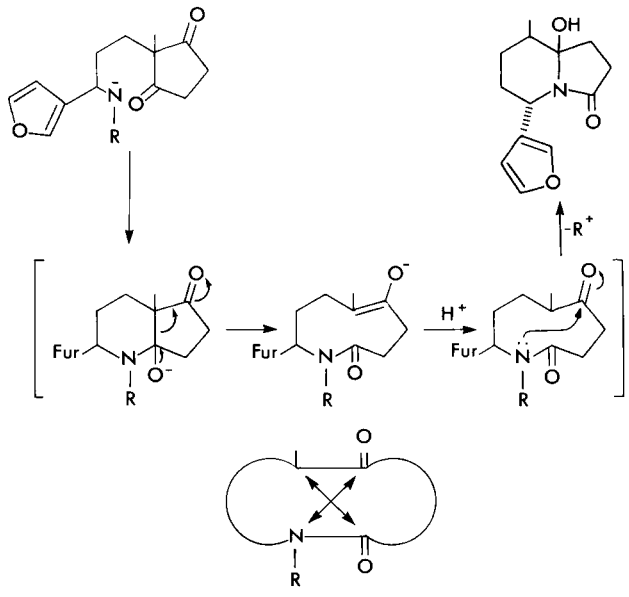
SCHEME 51. Synthesis of 1-epideoxynupharidine and nupharolutine acetate by Wróbel and co-workers (*220*). Reagents: (a) Na, HCO_2Et, Et_2O; (b) HOAc; (c) ethyl 3-aminocrotonate, C_6H_6; (d) $LiAlH_4$; (e) 60% HBr, Δ; (f) Zn, HOAc, Δ (g) $NaNH_2$, NH_3; (h) methallyl chloride; (i) Br_2, CCl_4; (j) H_2, PtO_2, EtOH; (k) AgOAc.



SCHEME 52. Synthesis of nupharolutine and the Nuphar indolizidine by LaLonde and co-workers (*211*). Reagents: (a) NaH, $BrCH_2COCH_3$, dioxan; (b) 3% aq NaOH, 70°C; (c) H_2SO_4, pH 4; (d) Li, NH_3, Et_2O; (e) equilibration; (f) $NH_2OH{\cdot}HCl$, py, $EtOH–H_2O$; (g) PCl_5, Et_2O; or *p*-TsCl, py; (h) *m*-CPBA, CH_2Cl_2; (i) NaH, C_6H_6, Δ; (j) 3-furyllithium, Et_2O; (k) $NaBH_4$, EtOH; (l) Jones oxidation; (m) $Pb(OAc)_4$, $Cu(OAc)_2$, py, C_6H_6; (n) $NaBH_3CN$, pH 3, MeOH; (o) H_2, 10% Pd–C, MeOH.

amounts of cis isomer present (11–12%) being carried through till the end of the syntheses. The Beckmann rearrangements to piperidones **266** proceed in the expected regiochemical sense. These products are converted to their epoxides, intramolecular cyclizations of which show an intriguing dependence on the nature of the group R. With R = methyl, only the quinolizidinone **267**, as a mixture of diastereomers, is formed; but with R = H, the indolizidinone **268**, also as a mixture of diastereomers, is the sole regioisomer formed. Of the remaining steps in the syntheses, addition of 3-furyllithium to the lactam carbonyl group is both the most important and also the poorest yielding. The synthesis of the indolizidine **269** is significant, however, since it provides some evidence for the structure and stereochemistry of Ohloff's natural product from castor (*210*), the reported mass spectrum of which is virtually identical to that of **269**.

The last synthesis to be described, that of two diastereomers of the Nuphar

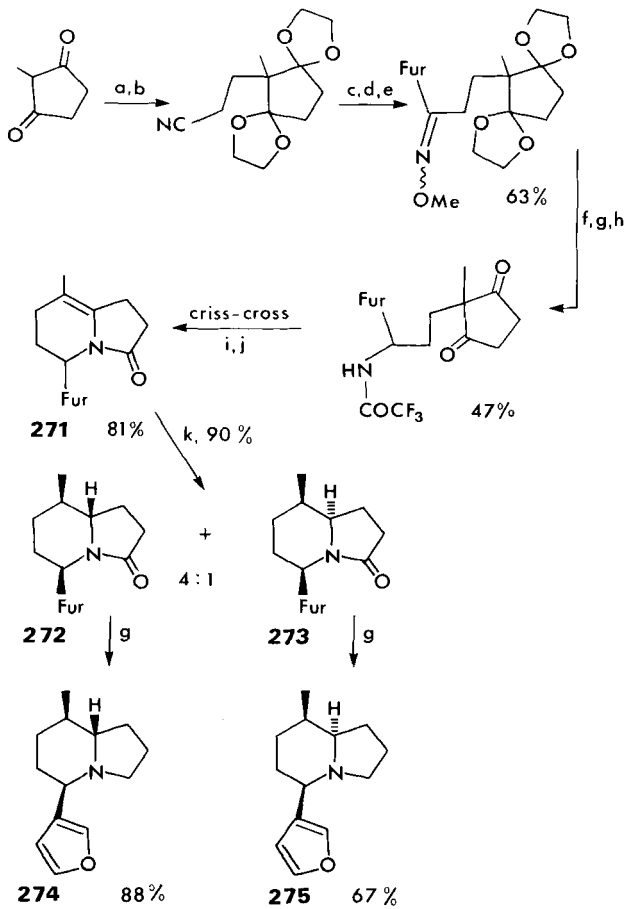


270

SCHEME 53. "Crisscross annulation" devised by Ban and co-workers (*212*).

indolizidine **252** by Ban and co-workers (*212*), is also the most innovative, since it breaks with tradition in its approach to the construction of the bicyclic skeleton. The transformation of central importance is what Ban refers to as a "crisscross annulation," and this is illustrated for the case of interest in Scheme 53. The interactions between electrophilic and nucleophilic sites in this reaction are shown in the sketch **270**, which clearly illustrates the "crisscross" nature of the process.

The reaction sequence leading to the indolizidines themselves is shown in Scheme 54. The crisscross product **271** is formed in 81% yield. This product is reduced with sodium cyanoborohydride in acidic medium to a 4:1 mixture of the indolizidinones **272** and **273**. The stereoselectivity of the reduction is rationalized on the basis of conformational effects involving $A^{1,3}$ strain between the 3-furyl substituent and the carbonyl group. Lithium aluminum hydride reduction of each lactam yields the indolizidine isomers **274** and **275**, respectively, the mass spectra of which are also almost identical to that reported by Maurer and Ohloff (*210*) for **252**. The stereochemistry of **274** has further been confirmed by an X-ray analysis of its picrate.



SCHEME 54. Synthesis of two diastereomers of the Nuphar indolizidine by Ban and co-workers (*212*). Reagents: (a) $H_2C{=}CHCN$, base; (b) $(HOCH_2)_2$, camphorsulfonic acid; (c) 3-furyllithium; (d) H_2O; (e) H_2NOMe; (f) $LiAlH_4$, THF; (g) $(CF_3CO)_2O$, py; (h) aq CF_3CO_2H; (i) LiOH, aq MeOH, 60°C; (j) aq HCl, MeOH; (k) $NaBH_3CN$, pH 3, THF.

VII. Alkaloids of the Papilionoideae: Simple Lupine Quinolizidines

The reviewer who has the task of surveying the quinolizidine alkaloids of the Papilionoideae—that formidable group of compounds commonly known as the lupine alkaloids—must surely approach the subject with a sense of hopelessness. The literature of these compounds is, in a word, overwhelming. That they have been investigated so intensively is a quite understandable reflection of the botani-

cal, ecological, and social importance of their plant sources. The Leguminosae, of which the Papilionoideae (also known as the Faboideae or the Lotoideae) form the most populous subfamily (the others being the Caesalpinioideae and the Mimosoideae), is the third largest family of flowering plants, and its geographical and climatic distribution is global. The economic importance of leguminous plants as food sources for both humans and livestock is probably superseded only by that of grain-bearing plants. The Leguminosae play a pivotal role in nitrogen fixation and soil conservation. On a more mundane level, many of its members provide a useful source of timber and fuel. From the chemist's point of view, the family serves as a source of oils and resins, and some of its secondary metabolites, notably the alkaloids, have both pharmacological potential and toxicological drawbacks.

The lupine alkaloids, found only in the more primitive genera of the Papilionoideae, include a hierarchy of structural types ranging from uncomplicated bispiperidines through simple quinolizidines (our particular concern here) to the fused arrays of rings found in numerous diazatetracyclic alkaloids and in even more complex polyazapolycyclic systems. The unusually rich catalog of known lupine alkaloids and their plant sources has in turn stimulated further research in a variety of specialist fields. There is, for example, seemingly limitless scope for biogenetic speculation on the interrelationships among these compounds, and biosynthetic studies in the Leguminosae form a flourishing field of endeavor. For the botanist, the wealth of available data provides a fruitful base for the chemotaxonomic study of the Papilionoideae, and for establishing phylogenetic relationships at generic and tribal levels in this subfamily. In human and veterinary pharmacology, the long-standing fascination with the effects of the alkaloids on the living organism provides the impetus for increasingly sophisticated research as the techniques of molecular biology become ever more refined.

It is all the more perplexing, therefore, that the last review on the lupine alkaloids in this treatise dates back to 1967 (*222*); up to that point, the topic had received regular coverage (*223,224*). To bring the topic up to date would be a labor of Herculean proportions—hence the feeling of hopelessness. Even though our present task is to cover no more than the simple quinolizidines of the Papilionoideae, to do a thorough job would swell this chapter very considerably. Fortunately, a separate chapter on the entire lupine family of alkaloids is intended for a future volume of this treatise, and we do not wish to preempt this projected review. All that we intend to do here is to give a comprehensive list of the known simple lupine quinolizidine alkaloids and their plant sources for the sake of having in a single review as complete a catalog as possible of all known simple indolizidines and quinolizidines of natural origin.

Attempts to provide comprehensive lists of known lupine quinolizidines, both simple and polycyclic, have been made (*225,226*). Pride of place must go to the 1984 review by Kinghorn and Balandrin (*227*), the only serious attempt in recent

times at a state-of-the-art overview of aspects of lupine alkaloid chemistry and biochemistry. This excellent compilation lists 161 lupine quinolizidines, and also gives succinct summaries on analytical methods for these compounds, their biogenetic relationships, chemotaxonomic implications, and their biological activity. Indeed, we include no references to the literature in the preceding paragraphs simply because everything of importance in these areas is referred to in the Kinghorn and Balandrin article. Their review, however, does not cover certain topics that a chemist would find particularly interesting; for example, spectroscopic studies on the lupine alkaloids, and their total synthesis, are not treated, although some key references are given.

Our own list of known and suspected simple lupine quinolizidines is given in Table IV. We can not claim that the list is complete or flawless; part of the problem is that the literature germane to the topic is disorganized and haphazard. The major problems with which we had to contend in compiling Table IV are as follows:

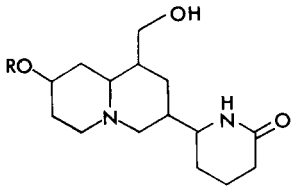
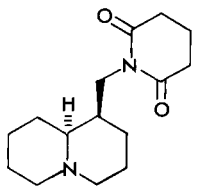
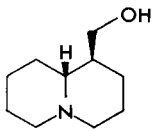
1. The identification of the alkaloid-bearing plant species is not always secure. This is true especially in the older literature, though it is becoming less serious as the practice of vouchering specimens is becoming standard. For example, the species *Lupinus digitatus*, *L. pilosus*, and *L. varius*, early sources of epilupinine (**281**) and its *N*-oxide (**289**), are now recognized to be the same, and are referred to as *L. cosentinii* (*228*). We have retained the genus and species names used by the authors of the appropriate papers unless corrections have been made at a later stage.

2. The detection or isolation of alkaloids from the Papilionoideae often appears to be a casual affair. New alkaloids have usually received full characterization, but the detection of standard alkaloids like lupinine (**294**) or epilupinine (**281**) in previously unexplored plant species often rests on no surer evidence than thin-layer chromatographic comparison or, more convincingly, gas chromatography–mass spectrometry. In many reports, the plants examined contain only traces of the compounds of interest. We have referenced all work in which relevant alkaloids have been claimed without any attempt at critical evaluation of the validity or otherwise of the claims.

3. The occurrence of specific alkaloids within the plant appears to depend very markedly on the time of year at which plants are harvested and on the stage of growth of the plant. The lupinyl esters **295–300**, for instance, appear at an early stage (4–8 days) of growth of *Lupinus luteus*, but decrease to very low levels thereafter (*229–233*). There are clear biogenetic implications in these and related findings, but few systematic studies on these factors have been performed.

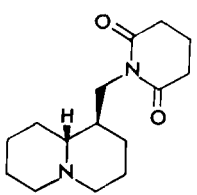
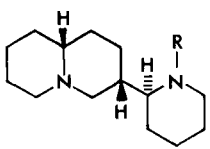
4. Even within a species, the occurrence of alkaloids seems to depend substantially on the geographical source of plant material (*234*, *235*). In the lupinus

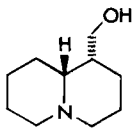
TABLE IV
Simple Lupine Quinolizidine Alkaloids

Structure	Compound	Name	Absolute configuration	Source	Reference
	**276**	Cadiamine (R = H)		*Cadia purpurea* Picc., Ait.	*237*
	277	Cadiamine 4-hydroxyphenylacetate (R = COC_6H_4-4-OH)		*Cadia purpurea* Picc., Ait.	*237*
	278	Cadiamine pyrrolyl-α-carboxylate (R = CO-α-pyrrolyl)		*Cadia purpurea* Picc., Ait.	*237*
	**279**	(−)-Epilamprolobine	1*R*,9a*S*	*Sophora chrysophylla* Seem.	*238*
				Sophora tomentosa L.	*239*
	280	(+)-Epilamprolobine *N*-oxide	1*R*,5*R*,9a*S*	*Sophora chrysophylla* Seem.	*238*
				Sophora tomentosa L.	*239*
	**281**	(+)-Epilupinine	1*S*,9a*R*	*Harpalyce formosa* Moc. and Sesse ex DC.	*240*
				Lupinus chamissonis Eschsch.	*241*
				Lupinus cosentinii Guss.	*228*
				Lupinus hirsutus L.	*242*
				Lupinus hispanicus Boiss. and Reuter var. *bicolor* Merino	*243*
				Sophora secundiflora (Ort.) Lag. ex DC.	*244*
				Templetonia egena (F. Muell.) Benth.	*240*
				Thermopsis barbata Benth.	*245, 246*
				Virgilia oroboides (Berg.) Salter	*247*

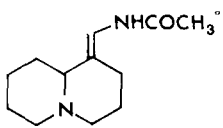
(*continued*)

TABLE IV (*Continued*)

Structure	Compound	Name	Absolute configuration	Source	Reference
	282	(±)-Epilupinine (tetralupine)		*Lupinus palmeri* S. Wats.	*223, 248*
		(+)-Epilupinine esters:			
	283	Acetate		*Lupinus cosentinii* Guss.	*228*
	284	4-Hydroxycinnamate		*Lupinus cosentinii* Guss.	*228*
	285	4-α-L-Rhamnosyloxycinnamate		*Lupinus cosentinii* Guss.	*228*
	286	4-Hydroxy-3-methoxycinnamate		*Lupinus cosentinii* Guss.	*228*
	287	4-α-L-Rhamnosyloxy-3-methoxycinnamate		*Lupinus cosentinii* Guss.	*228*
	288	4-Hydroxy-3-methoxycinnamate, dimer (bisepilupinyl ester of α-truxillic acid?)		*Lupinus cosentinii* Guss.	*228*
	289	(+)-Epilupinine *N*-oxide		*Lupinus cosentinii* Guss.	*228*
				Lupinus hirsutus L.	*242*
	290	(+)-Epilupinine *N*-oxide, acetate ester		*Lupinus cosentinii* Guss.	*228*
	**291**	(+)-Lamprolobine	1*R*,9a*R*	*Lamprolobium fruticosum* Benth.	*249, 250*
				Lupinus holosericeus Nutt.	*251*
				Sophora chrysophylla Seem.	*238*
				Thermopsis villosa (Walt.) Fern. and Schub.	*252*
	**292**	(+)-Leontiformidine (R = H)		*Leontice leontopetalum* L.	*253*
	293	(+)-Leontiformine (R = CHO)		*Leontice leontopetalum* L.	*254*
	294	(−)-Lupinine	1*R*,9a*R*	*Anabasis aphylla* L. [a]	*223*
				Genista abchasica Sachok.	*255*
				Goebelia pachycarpa Bunge ex Boiss.	*256*



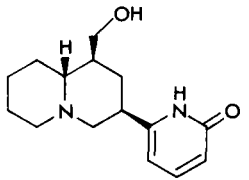
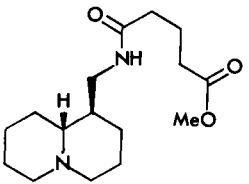
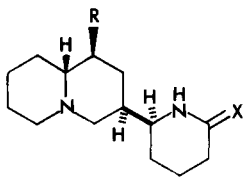
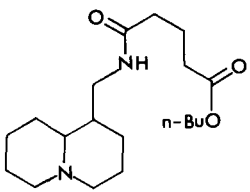
	(−)-Lupinine esters:	
295	4-Hydroxycinnamate	*Lupinus luteus* L. 229
296	4-α-L-Rhamnosyloxycinnamate	*Lupinus luteus* L. 230
297	4-β-D-Glucopyranosyloxy-cinnamate	*Lupinus luteus* L. 231
298	4-Hydroxy-3-methoxycinnamate	*Lupinus luteus* L. 264
299	4-α-L-Rhamnosyloxy-3-methoxycinnamate	*Lupinus luteus* L. 232
300	4-β-D-Glucopyranosyloxy-3-methoxycinnamate	*Lupinus luteus* L. 233



301	(+)-Lusitanine	*Cadia ellisiana* Baker 265
		Chamaecytisus austriacus Link subsp. *stefanoffii* (Stoj) Kuzm. 266
		Genista lusitanica L. 267
		Lupinus albus L. 235
		Lupinus angustifolius L. 235
		Lupinus bakeri Greene 257, 258
		Lupinus elegans H. B. and K. 259
		Lupinus formosus Greene 258
		Lupinus hispanicus Boiss. and Reuter var. *bicolor* Merino 243
		Lupinus linifolius Roth 260
		Lupinus luteus L. 223
		Lupinus mutabilis Sweet 261
		Lupinus niger Pharm. 223
		Lupinus palmeri S. Wats. 223
		Lupinus pilosus Murr. 260
		Lupinus polyphyllus Lindl. 235
		Lupinus subcarnosus Hook 260
		Lupinus westianus Small 262
		Thermopsis barbata Benth. 246
		Virgilia divaricata Adamson 263
		Virgilia oroboides (Berg.) Salter 263

(*continued*)

TABLE IV (*Continued*)

Structure	Compound	Name	Absolute configuration	Source	Reference
	**302**	(+)-Mamanine	3*R*,9a*R*	*Sophora chrysophylla* Seem.	*238, 268*
				Sophora flavescens Ait.	*269, 270*
	303	(−)-Mamanine *N*-oxide	3*R*,5*S*,9a*R*	*Sophora chrysophylla* Seem.	*238*
	**304**	1-(4-Methoxycarbonylbutanoyl)-aminomethylquinolizidine; artifact?		*Lamprolobium fruticosum* Benth.	*249, 250*
	305	1-(4-Methoxycarbonylbutanoyl)-aminomethylquinolizidine *N*-oxide; artifact?		*Sophora tomentosa* L.	*239*
	**306**	Methyl aphyllate (R = CO_2Me, X = H_2)		*Anabasis aphylla* L. [a]	*271*
	307	(−)-Pohakuline (R = CH_2OH, X = O)	1*S*,3*R*, 9a*R*,6′*S*	*Sophora chrysophylla* Seem.	*238, 268*
	**308**	(−)-Sophorine		*Sophora alopecuroides* L.	*272, 273*

[a] Family Chenopodiaceae.

species used as fodder crops, this factor no doubt has a bearing on the "sweetness" or "bitterness" of the crop, bitter plants being richer in alkaloid content and, as a consequence, more toxic to livestock.

5. There seems to be no general pattern of site specificity for the accumulation of quinolizidine alkaloids within their plant sources. While individual species show alkaloid buildup at certain locations, in general terms the compounds of interest have been detected in all parts of the plant, including fruit, seeds, flowers, inflorescence, wood, bark, twigs, leaves, and roots or tubers. Cell-suspension cultures can also biosynthesize quinolizidine alkaloids (*236*).

6. The correctness of the alkaloid structures in Table IV (*237–273*) is occasionally suspect. Kinghorn and Balandrin (*227*) list 19 simple quinolizidines in the Papilionoideae, whereas we have 33. Our list is certainly a less critical one and includes some compounds from unique isolations for which corroborative evidence is lacking as well as some compounds that are undoubtedly artifacts formed during the isolation process.

7. Optical rotations have certainly not been measured for alkaloids isolated from all of the plant sources listed in Table IV. We have not differentiated between cases in which rotations have and have not been measured. On the basis of the references quoted in the table, however, the enantiomer indicated is the only naturally occurring one.

8. In most cases the structures of the alkaloids are supported by spectroscopic data and even on occasion by X-ray crystallography. We have indicated those cases for which the correct relative or absolute configurations are known. In all determinable cases, the geometry of quinolizidine ring fusion appears to be trans, the minimum admissible evidence being the presence of Bohlmann bands in the IR spectra. With the cinnamoyl esters of lupinine and epilupinine there is, however, a problem with geometrical isomerism in the cinnamoyl portion; both cis and trans isomers coexist and are occasionally separable, but the former increases at the expense of the latter when the compounds are handled in sunlight. We have not treated these geometrical isomers as separate compounds.

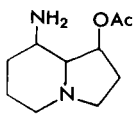
9. In the main, the references provided are to the first detection of an alkaloid in a given plant species, or to its first unambiguous characterization. For the alkaloids known before 1960, the reference is to their previous treatment in this treatise (*223*).

VIII. Slaframine

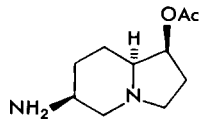
Slaframine has previously been mentioned briefly on several occasions in this treatise in chapters on "New Alkaloids" or "Alkaloids Unclassified and of Unknown Structure" (*274–276*). This chapter contains the first full treatment of the alkaloid in this treatise. General discussions of the chemistry and biological activity of slaframine are contained in a number of reviews (*277–280*).

A. Isolation and Structure

The natural source of slaframine is *Rhizoctonia leguminicola* Gough et E.S. Elliott, a fungus that infects ruminant forages, notably red clover hay (*281, 282*), giving rise to the disease known as "black patch." Ingestion of such infected forages causes cattle and sheep to salivate ("slobber") profusely—hence the name slaframine, from the Old Norse *slafra*, to slaver. More seriously, the animals go off their feed, suffer from diarrhea, and may indeed die. While the fungus contains several alkaloids (see Section IX,A), it is specifically the compound slaframine that is implicated in slobber syndrome. This compound, usually obtained from cultured *Rhizoctonia leguminicola*, though it has also been isolated directly from infected red clover (*283*), is an oil, which is most conveniently characterized as the dipicrate, mp 183–184°C, or as the *N*-acetyl derivative, mp 140–142°C (*284*). The optical rotation of slaframine does not appear to have been published, but that of the *N*-acetyl derivative has been given as $[\alpha]_D$ −15.9° (*c* 5, EtOH) (*286*).



309



310

Early structural investigations leaned heavily on the interpretation of spectra, particularly the mass spectrum, of slaframine itself and of various derivatives. These studies led to the proposal of structure **309** for the alkaloid (*284,285*). A more detailed analysis of the 100-MHz PMR spectrum of *N*-acetylslaframine, however, suggested the position of the amine group as C-6 rather than C-8; these results, considered in conjunction with the PMR spectra of the isomers of 1-acetoxyindolizidine, led to the proposal of the revised structure **310** for slaframine (*286*). The presence of relatively intense Bohlmann bands in the 2700–2800-cm^{-1} region of the IR spectra both of slaframine and *N*-acetylslaframine indicates that the rings are trans-fused (*287*).

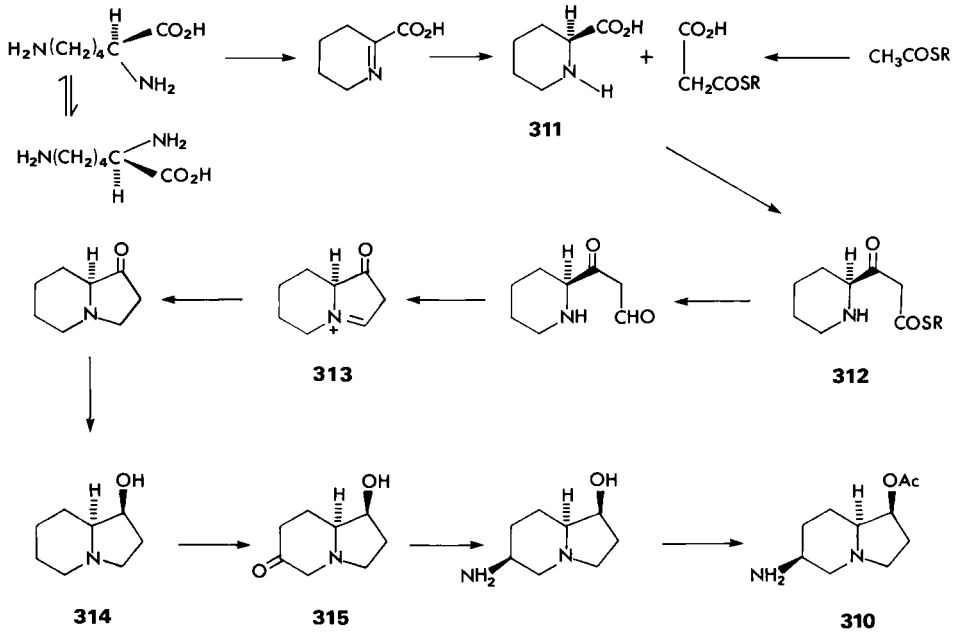
The absolute configuration of slaframine at C-1 was deduced to be as shown in **310** by the application of Horeau's procedure (*288*). Thus reaction of *N*-acetyl-*O*-deacetylslaframine with optically inactive 2-phenylbutyric acid anhydride leaves residual (−)-2-phenylbutyric acid, a result that empirically leads to the assignment of the 1*S* configuration to the alcohol, and hence of the 1*S*,8a*S* configuration for the alkaloid as a whole (*286*). No other degradative or synthetic studies having a bearing on the absolute configuration of slaframine appear to have been undertaken.

B. Biosynthesis

The present state of knowledge of biosynthesis of slaframine in *R. leguminicola* as outlined in Scheme 55 is due to the efforts of Broquist and Harris and their co-workers (*289–294*).

In broad outline, C-1 and the piperidine ring of the alkaloid are derived from lysine, while the rest of the pyrrolidine ring comes from acetate. Feeding of DL-lysine-*1*-^{14}C and DL-lysine-*6*-^{14}C to *R. leguminicola* has shown that, in contrast to the situation with other lysine-derived alkaloids, such as those of the Lythraceae (*133*), the entire carbon skeleton of the amino acid is incorporated into pipecolic acid (**311**), and thence into slaframine (*290*); pipecolic acid itself is incorporated into the alkaloid about 100 times more efficiently than lysine is. In addition, the use of ^{15}N-labeled lysine has made it clear that it is the nitrogen atom on C-6 that is retained, while that on C-2 is lost (*291*). Finally, the additional two carbon atoms of the slaframine skeleton arise from acetate via malonate (*292*).

A careful study (*291*) of the catabolism of lysine in *Rhizoctonia leguminicola* has revealed the involvement of a lysine racemase, which appears to dictate stereospecific events of lysine metabolism. When the action of this enzyme is blocked by the addition of hydroxylamine to the culture medium, L-lysine gives



SCHEME 55. Biosynthesis of slaframine.

rise to L-pipecolic acid (**311**), while D-lysine is converted to D-N^6-acetyllysine prior to further catabolism. Under normal circumstances, D-lysine competes significantly with DL-lysine-^{14}C in pipecolate synthesis. The results with ^{15}N-labeled lysine referred to above suggest that L-pipecolic acid is formed via Δ^1-piperideine-2-carboxylic acid rather than the 6-carboxylic acid isomer. Support comes from experiments aimed at reduction of these two compounds, using cell-free extracts of the organism; only the former undergoes conversion to pipecolic acid (*291*).

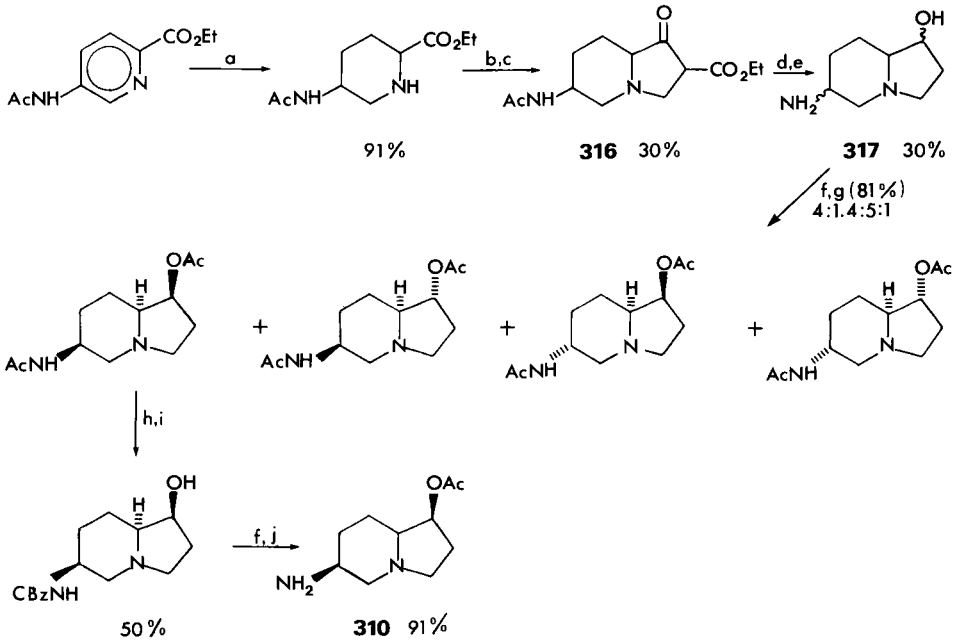
The elaboration of the pyrrolidine ring from L-pipecolic acid (**311**) and acetate has also been investigated in detail (*292*). Both acetate and malonate are incorporated into the nucleus of slaframine, the former slightly less efficiently than the latter. More importantly, the acylation of malonate by pipecolate appears to occur with simultaneous loss of the carboxyl group to give **312**; indeed, a pipecolate-dependent loss of radioactivity from carboxy-labeled malonate has been detected, using cell-free extracts of *R. leguminicola*, though an assay system that completely avoids nonspecific decarboxylase activity has not yet been found. The acylated intermediate **312** [incidentally, also a postulated intermediate in the biosynthesis of swainsonine (Section IX,B)], is suggested to undergo reduction to the aldehyde level, giving the iminium ion **313**. This postulate is preferred to one involving cyclization at the acyl level, since the lactam which would result from the cyclization of **312** is known not to be incorporated into slaframine (*293*).

As regards the late steps in the biosynthesis of slaframine, tritiated 1-oxoindolizidine, *cis*- and *trans*-1-hydroxyindolizidine, and 1,6-dihydroxyindolizidine are all incorporated into slaframine; furthermore, *cis*-1-hydroxyindolizidine follows 1-oxoindolizidine in the biosynthesis, since a tritium label at C-1 in **314** is retained in slaframine (*290*). The involvement of the intermediate **315** follows from incubation experiments with *R. leguminicola* and pipecolic acid perdeuterated on the carbon atoms of the ring; the slaframine isolated was found to have lost two deuterium atoms from C-6, thus implicating a carbonyl group at this position (*294*). Finally, acetylcoenzyme A has been shown to be the source of the 1-acetoxy group (*290*).

C. Synthesis

Four syntheses of slaframine have been published to date. Three of these follow the same general approach: construction of the carbon skeleton by means of the Dieckmann reaction and the use of reductions to establish the three asymmetric carbon centers.

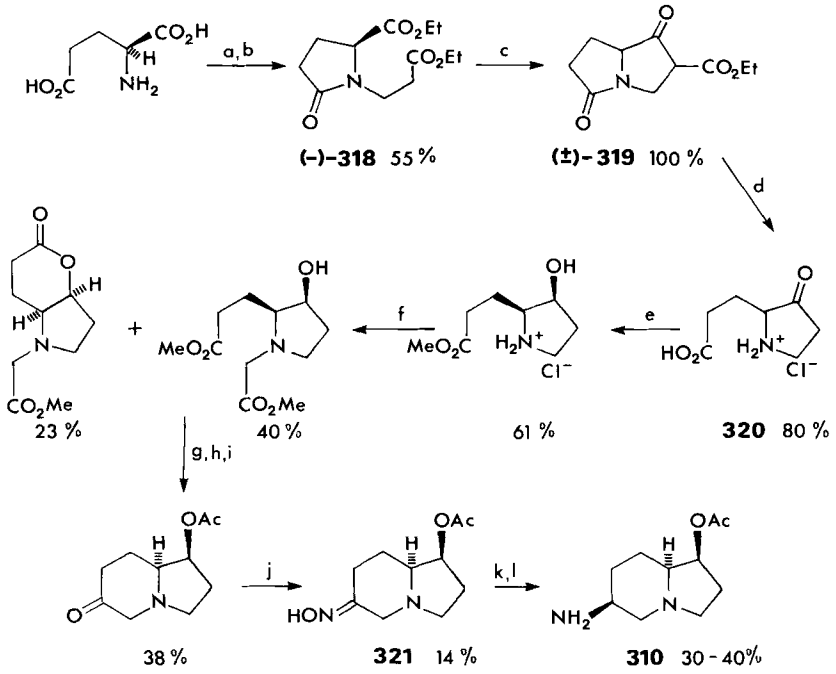
The earliest synthesis (Scheme 56), by Rinehart and co-workers (*295*), does not achieve any control over the stereochemistry. The product of Dieckmann cyclization, **316**, is an isomeric mixture, as is the important alcohol intermediate



SCHEME 56. Synthesis of slaframine by Cartwright, Gardiner, and Rinehart (*295*). Reagents: (a) H_2 (50 psi), PtO_2, EtOH–H_2O; (b) $H_2C{=}CHCO_2Et$, EtOH, Δ; (c) *t*-BuOK, $C_6H_5CH_3$, 0°C; (d) 8 *M* HCl, 100°C; (e) $NaBH_4$; (f) Ac_2O; (g) chromatography on alumina; (h) H_2NNH_2, H_2O, Δ; (i) $C_6H_5CH_2O_2CCl$; (j) 30% HBr–HOAc.

317, which results from hydrolysis, decarboxylation, and reduction of **316**. The synthesis requires chromatographic separation of the four diastereoisomeric pairs of products, a separation that is performed after acetylation of **317**, that is, on *N*-acetylslaframine and its epimers. For each of these isomers, the relative stereochemistries at C-1, C-6, and C-8a may be assigned by analyzing their PMR spectra. The composition of the isomeric mixture obtained indicates that some preference of hydride-ion delivery to the α face of the molecule occurs during borohydride reduction of the carbonyl group in the ketone precursor of alcohol **317**.

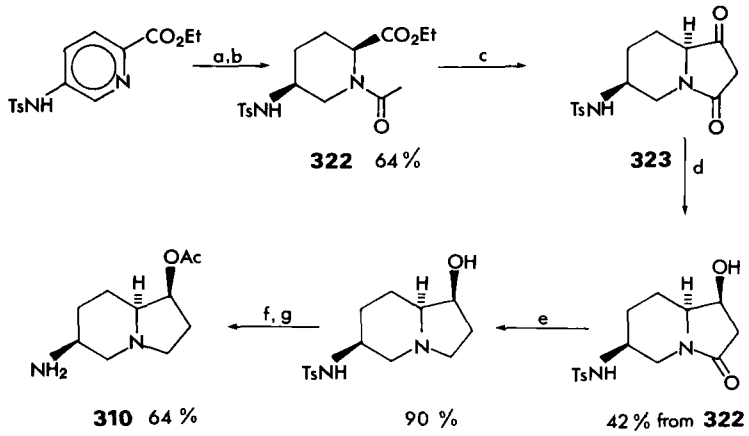
The synthesis of slaframine (**310**) by Gensler and Hu (*287*) starts with L-(+)-glutamic acid (Scheme 57). Unfortunately, any hope that the synthesis might provide support for the suggested absolute configuration of slaframine was dashed when it was found that the Dieckmann condensation, **318** to **319**, proceeded with complete racemization. From this point on, however, the synthesis proceeds with good stereoselectivity. Catalytic hydrogenation of the ketone group in intermediate **320** introduces the cis relationship of the hydrogens at the



SCHEME 57. Synthesis of slaframine by Gensler and Hu (*287*). Reagents: (a) $H_2C{=}CHCN$; (b) H_2SO_4, EtOH, Δ; (c) Na, EtOH; (d) 15% HCl, 75°C; (e) H_2 (1 atm), PtO_2, MeOH; (f) $BrCH_2CO_2Me$, Na_2CO_3, MeOH, 60°C; (g) NaH, C_6H_6, MeOH (cat.); (h) aq HCl, 85°C; (i) Ac_2O, py; (j) $NH_2OH{\cdot}HCl$, py, EtOH, Δ; (k) H_2 (40 psi), PtO_2, EtOH–H_2O–HCl; (l) Na_2CO_3, MeOH.

carbon atoms destined to become C-1 and C-8a in slaframine. In the final step, advantage is again taken of the preference for the delivery of hydrogen from the less-hindered face of the molecule when oxime **321** is catalytically hydrogenated to slaframine (**310**). Although slaframine is certainly the major product in this step, the degree of selectivity achieved is not explicitly stated.

Schneider and Harris published a further synthesis of this type in 1984 (*296*). In principle, this synthesis (Scheme 58) follows the same route as the Rinehart synthesis (*295*), but it achieves control of the stereochemistry by means of improved procedures in the key steps. First, the use of potassium hydride in the cyclocondensation of **322** gives ring formation without inducing epimerization α to the carbonyl group. This step thus retains the correct relative stereochemistry for positions 6 and 8a of the target alkaloid. Second, the stereoselective reduction of the ketone group in the bicyclic product **323** is achieved with the bulky reducing agent L-selectride at −107°C. An overall yield of slaframine (**310**) of 5% from the commercially available 2-chloro-5-nitropyridine is achieved by the Harris procedure.

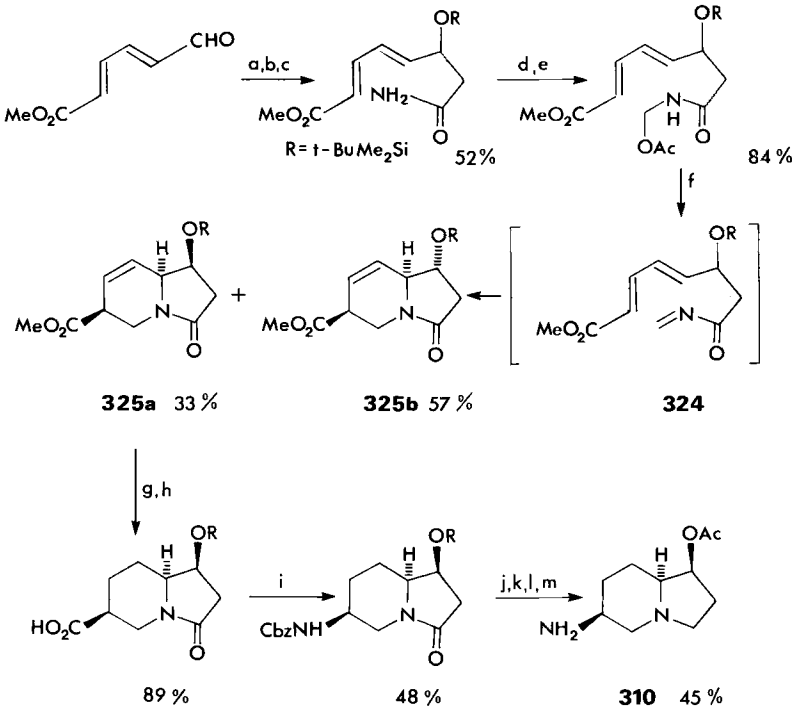


SCHEME 58. Synthesis of slaframine by Schneider and Harris (*296*). Reagents: (a) H_2 (4 atm), PtO_2, HOAc–Ac_2O; (b) Ac_2O; (c) KH, THF; (d) L-selectride, THF, −107–0°; (e) BH_3, THF, Δ; (f) Na, NH_3; (g) HCl, HOAc–MeOH, 75°C.

The final synthesis, quite different in concept from the others, is due to Weinreb and co-workers (*297*). In this synthesis (Scheme 59), the intramolecular imino Diels–Alder reaction **324** to **325**, is used to form both rings of the indolizidine skeleton simultaneously. The correct relative stereochemistry at C-6 and C-8a in the product is assured by the normal orbital requirements of the Diels–Alder reaction, although a readily separable but unequal mixture of products epimeric at C-1 is obtained. Scheme 60 shows the factors believed to be responsible for the formation of these products **325** in unequal amounts. The acylimine **324** involved in the cyclization may react via conformations **326a** or **326b**, leading to products **325a** and **325b**, respectively. That the desired isomer **325a** in the minor product may be ascribed to a nonbonded interaction in conformer **326a**, which is absent in conformer **326b**. The stereochemistry at C-1 in the two products follows from their conversion to slaframine (**310**) and epislaframine. The undesired product **325b** can, however, be epimerized at C-1 as shown in Scheme 60. The epimerization is accomplished by an oxidation–reduction sequence in which a completely stereoselective reduction of the ketone group in **327** comes about by using 9-BBN as the reductant.

D. Biological Activity

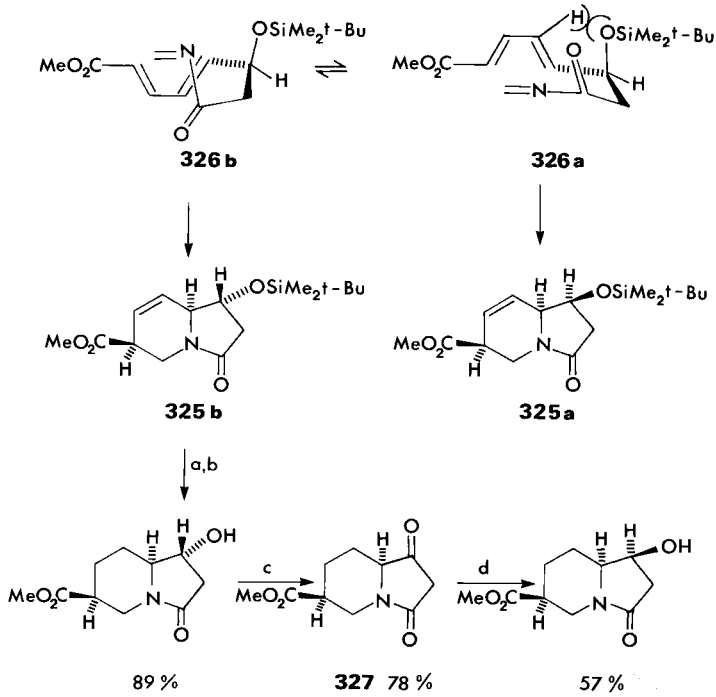
Slaframine toxicosis is a serious problem in veterinary practice, though fortunately its occurrence is limited (*298*). Veterinary case histories collected over a 10-year period in Missouri, summarized in the review by Broquist and Snyder (*277*), show a clear link between ingestion of red clover—the host for the toxin-



SCHEME 59. Synthesis of slaframine by Gobao, Bremmer, and Weinreb (*297*). Reagents: (a) TMEDA, *s*-BuLi, THF, −78°C; then bis(trimethylsilyl)acetamide; (b) 10% HCl; (c) *t*-$BuMe_2SiCl$, imidazole, DMF; (d) $(H_2CO)_n$, Cs_2CO_3, THF; (e) Ac_2O, py; (f) *o*-$Cl_2C_6H_4$, Δ; (g) H_2 (1 atm), 10% Pd–C, MeOH; (h) 5% aq KOH, MeOH; (i) Curtius sequence; EtO_2CCl, py, THF; NaN_3, H_2O; THF, Δ; $PhCH_2OH$; (j) BH_3, THF, Δ; (k) concd HCl, THF, Δ; (l) Ac_2O, py; (m) H_2 (1 atm), 10% Pd–C, MeOH–HOAc (1:1).

producing fungus—and excessive salivation in cattle, sheep, and horses. It is this excessive salivation that is so characteristic a feature of the disorder (hence its popular name, "the slobbers"). The salivate, which contains numerous air bubbles, tends to be thick and viscous (*299*); the thickness of the discharge is apparently indicative of the parasympathomimetic (cholinergic) effect of the toxin. Slobbering may be accompanied by reduced feed consumption, decrease in milk production, stiffness of joints, lacrimation, frequent urination, diarrhea, anorexia, bloating, abortion, and, occasionally, death (*277,298, 299*). Pathological changes, however, do not appear to occur; in fact, the most effective treatment for the disorder is simply to remove contaminated feedstocks, after which the symptoms slowly vanish once infected material passes through the alimentary canal. Antihistamines are also effective on laboratory animals (*299*).

Previous reviews (*277–279*) have dealt adequately with the earlier literature



SCHEME 60. Stereochemistry of intramolecular Diels–Alder reaction in Weinreb's slaframine synthesis and epimerization at C-1 of an epislaframine precursor. Reagents: (a) H_2, 10% Pd–C, MeOH; (b) aq HCl, THF; (c) CrO_3, py, CH_2Cl_2; (d) 9-BBN, THF.

on slobber syndrome among livestock and the involvement of *Rhizoctonia leguminicola* in toxicosis. Current understanding of the toxicology of slaframine is based on controlled studies with purified samples of the alkaloid, as well as on investigations using extracts of cultured *R. leguminicola* or merely infected feedstocks. Since the discovery that *R. leguminicola* also metabolizes the potent α-mannosidase inhibitor swainsonine (Section IX,A) (*300,301*), several authors have speculated on the possible contributory effect of swainsonine in moldy forage mycotoxicoses (*302,303*). One should thus be cautious in interpreting results of studies that use materials other than purified slaframine (*279*).

Controlled laboratory tests using the purified salivation factor are extensive. Slaframine is a powerful cholinergic stimulator of the exocrine glands, especially the salivary glands. For example, when administered intravenously (as the dicitrate salt) to anesthetized cats, it causes significant salivary activity after an appreciable induction period, and the effects remain in force, with gradual reduction, for as long as 6 hr. A subsequent dose of slaframine produces very little further response (*304,305*). In tests with mature cattle, the feeding over a period

of time of red clover deliberately contaminated with slaframine causes a pronounced increase of salivary flow (5–44%); subcutaneously introduced slaframine increases salivation during feeding by as much as 316% (*302*).

In guinea pigs, the response to slaframine can be blocked by the prior administration of atropine; once slaframine-induced salivation has started, however, it cannot be reversed by giving atropine (*299*). Both slaframine and atropine probably compete for the same cholinergic receptor; but slaframine must be capable of binding directly to the receptor rather than merely inhibiting cholinesterase since, if the latter were true, atropine should reverse the effects (*278*). Cholinergic activity is also suggested by the decrease in heart, respiration, and other metabolic rates in a number of animals treated with aqueous extracts of *R. leguminicola* mycelium (*279,306*). Pure slaframine, on the other hand, has been claimed to have no effect on respiration, blood pressure, or heart rate in cats and also seems not to affect neuromuscular transmission, peripheral blood flow, or ganglionic transmission (*304, 305*). These conflicting results may well implicate other metabolites of *R. leguminicola* in the observed physiological changes (*279*).

The effect of slaframine on the secretion of pancreatic juices is also substantial. Intraperitoneal injection into rats is accompanied by a decrease of up to 50% in the mass of the organ as well as a dramatic decrease in digestive enzyme levels (*304,307*). The effects are slow to develop, but are of prolonged duration. Enzyme levels recover more quickly than do pancreas weights, suggesting that the gland secretes all of the stored enzyme, after which the synthesis of new enzyme is stimulated. With goats, sheep, and calves, where cannulation of the pancreatic duct allows direct monitoring of pancreatic fluid production and composition, fluid volume increases substantially after an initial delay period, and activity may persist for a considerable time (up to 10 hr in the calf, for example) (*304,307*). While total protein levels remain virtually unchanged, mucoprotein levels drop by an amount consistent with simple dilution caused by the increased flow rates. The specific activity of digestive enzymes, on the other hand, increases significantly and remains high for several hours. The implication, once again, is that slaframine stimulates the synthesis of digestive enzymes. Support for the hypothesis comes from the noticeably increased incorporation of leucine-^{14}C into calf pancreatic proteins following the intravenous administration of slaframine.

Slaframine itself is not the active metabolite in causing parasympathomimetic effects in test animals. The frequently mentioned induction period before the onset of activity points to some sort of "bioactivation" of the alkaloid. Certain clinical tests support this hypothesis. For example, a longer delay in onset of salivation occurs when slaframine is injected intravenously rather than intraperitoneally into mice: the delay can be decreased by direct injection into the portal vein and increased by clamping the portal vein and hepatic artery (that is,

by isolating the liver) while simultaneously injecting slaframine into the vena cava (*304,305*). The implication is that slaframine must first be transported to the liver, where it is activated by drug-metabolizing enzymes in that organ. Support comes from experiments in which various inducers (e.g., phenobarbital) or inhibitors (e.g., 2-ethylaminoethyl 2,2-diphenylvalerate) of these enzymes, when used to pretreat mice prior to slaframine administration, respectively, either speed up or retard the onset of salivation. Inducers also bring about a reduction in the dose of slaframine needed to elicit a given degree of activity, whereas inhibitors require a greater dose to bring about the same effect. These results point to the involvement of the enzymes from the microsomes of liver endoplasmic reticulum, possibly the mixed-function oxidases, which are generally responsible for the metabolism of xenobiotics.

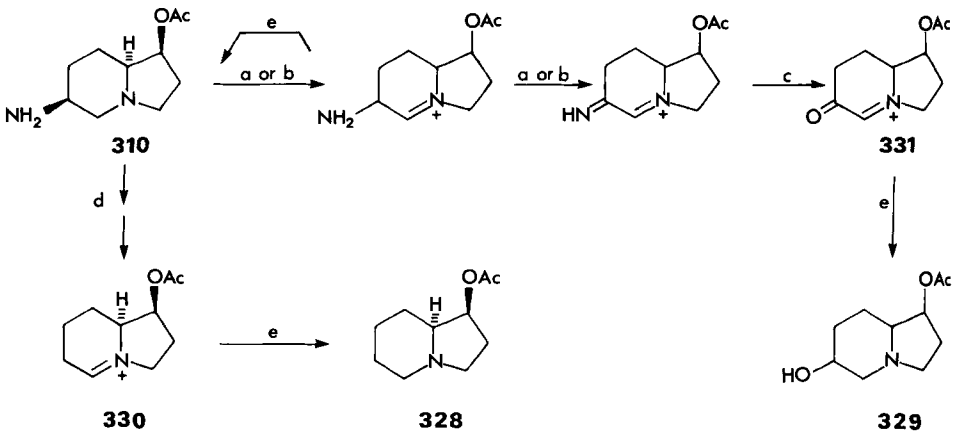
Slaframine is quite inactive in cholinergic *in vitro* tests (*308*), providing yet more evidence for the necessity of bioactivation. Such activation is, however, achievable under laboratory conditions: slaframine, when incubated with rat-liver homogenates (notably the microsomal fractions) in the presence of NADPH, induces *in vitro* contractions in sections of guinea-pig mid-ileum (*309*). The effects are of longer duration than those induced by acetylcholine; they are difficult to reverse by washing and can not be reversed by the addition of atropine. As in *in vivo* experiments, however, the action of the active metabolite can be blocked by prior treatment with atropine. The response is not inhibited by carrying out the incubations in the presence of carbon monoxide, and this probably rules out the involvement of cytochrome *P*-450. However, since liver homogenates from animals pretreated with phenobarbital cause increased activity, at least part of the microsomal oxidase system is implicated.

The same "active metabolite" of slaframine is apparently also produced nonenzymatically by the action of flavins, particularly flavin mononucleotide (FMN), on slaframine (*309*). Activation by flavins is independent of the addition of microsomes or of NADPH; it requires visible light, but can proceed anaerobically (another piece of evidence against the involvement of the complete mixed-oxidase system *in vivo*), though it is promoted by admitting oxygen to the system. The production of the bioactive slaframine metabolite (as measured in the guinea-pig ileum assay) occurs at the same rate as the photoreduction of flavin (as measured spectrophotometrically). Solutions of slaframine photooxidatively modified with FMN elicit an immediate salivation response in mice, the magnitude of which is comparable to that of 10 times the quantity of unactivated slaframine with an induction time of 15 min. It should be pointed out that the flavin results (implying an oxidative activation pathway) are in seeming conflict with the NADPH–microsome results (implying a reductive pathway). Later studies (*310*), however, have cast light on this point, as will be discussed in due course.

What is the active metabolite of slaframine? It appears to be a labile substance

whose activity is destroyed by heating or at high and low pH values (*309*). At least *in vivo* it appears to undergo ready conversion back to slaframine. Both deacetylslaframine (*307*) and deaminoslaframine (*309*) can be ruled out as candidates, since neither shows biological activity; so can an *N*-oxide of slaframine or a radical species arising from a one-electron oxidation, since the FMN reaction mixtures give no EPR signals (*310*). Attempts to isolate it from the blood or urine of animals injected with slaframine have failed (*309*). Guengerich and Aust have, however, managed to separate ionic products of photochemically oxidized slaframine by cation-exchange chromatography (*310*). While the metabolites themselves remain unisolable in pure form, they can be reduced to isolable products with sodium borohydride. The isolated compounds are slaframine itself, *cis*-1-acetoxyindolizidine (**328**), and 1-acetoxy-6-hydroxyindolizidine (**329**).

All three compounds incorporate a tritium label from tritiated sodium borohydride; with deuterated sodium borohydride, **328** incorporates one atom of deuterium, and **329** incorporates two. It seems reasonable to suggest that the bioactivated species are iminium ions like **330** and **331**. However, only the latter induces cholinergic responses; for example, when solutions of it were injected into rats, the animals salivated within 5 min, and two out of four animals died by apparently drowning in their saliva (*310*). Since it is exclusively compound **329** that is derived from the active metabolite on borohydride treatment, structure **331** seems reasonably secure (except perhaps for the position of the C=N bond). Neither **328** nor **329** shows biological activity. Scheme 61 summarizes the putative stages in the bioactivation of slaframine, together with the structures of



SCHEME 61. Bioactivation of slaframine and reductive interception of the oxidized species. Reagents: (a) FMN (− $FMNH_2$), light; (b) $flavoprotein^{ox}$ (− $flavoprotein^{red}$); (c) hydrolysis (− NH_3); (d) FMN (cat.), light; (e) $NaBH_4$.

the materials isolated from the borohydride reductions. The suggestion is that both iminium species **330** and **331** may be produced in the flavin-mediated reaction (and, indeed, in the microsomal system), though probably by slightly different pathways.

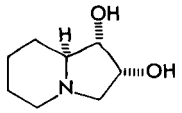
Supporting evidence for the intermediates and processes of Scheme 61 can be summarized briefly. Anaerobic production of both **330** and **331** is dependent on light and flavin but in ways suggestive of two different reactions. For **330**, the dependence is consistent with a catalytic role for flavin. It is uncertain how the unusual deamination proceeds, and several suggestions have been put forward (*310*). The production of the active metabolite **331**, in contrast, depends on FMN concentration over a wide range. Ammonia is a detectable product in both cases, and its formation is nearly stoichiometric with the formation of deaminated products. Under aerobic conditions, the yield of **331** increases at the expense of **330**. Moreover, **331** is a considerably more abundant product in enzymatically mediated processes than in the flavin-mediated reactions.

The remaining problem concerns the nature of the enzymes responsible for the bioactivation of slaframine in the endoplasmic reticulum of the liver. As indicated previously, there is evidence against mixed-function oxidation (that is, using reduced pyridine nucleotides) and against cytochrome *P*-450. However, since microsomal activation is rendered inoperative by boiling the microsomes before incubation with slaframine, the activation has to be ascribed to enzymes and not merely to free flavins. Slaframine does not support microsome-catalyzed reduction of cytochrome *c*, and this rules out NADH-cytochrome b_5 and NADPH-cytochrome *P*-450 reductase. The likeliest remaining candidate is a microsomal flavoprotein oxidase (*311*). Indeed, a preparation of this enzyme from porcine hepatic microsomes succeeds in oxidizing slaframine to the active metabolite **331** (*310*). Activity with this enzyme is stimulated by adding both reduced and oxidized pyridine nucleotides, a puzzling result, which is most likely due to the stabilization of the enzyme by these species (although slaframine-dependent oxidation of NADPH can not be ruled out directly). It has been shown that both NADPH and $NADP^+$ restore the activity of aged rat-liver microsomal preparations toward slaframine, whereas they have no effect on fresh preparations.

In view of slaframine's ability to stimulate exocrine glands, it has been suggested as a possible agent in cystic fibrosis therapy and other diseases involving cholinergic dysfunction (*304*). Its advantages would be prolonged activity, comparatively low toxicity, and apparent absence of pathological effects. The suggestion, however, seems never to have been followed through.

IX. Polyhydroxylated Indolizidines

The alkaloids to be considered in this section are the indolizidinediol **332**, swainsonine (**333**), swainsonine *N*-oxide (**334**), and castanospermine (**335**).



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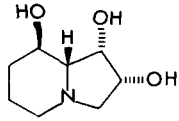

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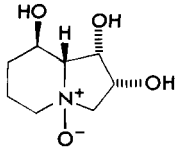

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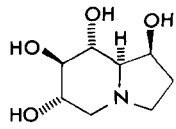

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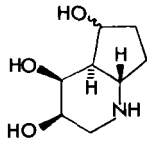
Both swainsonine and castanospermine are highly active glycosidase inhibitors, and a considerable volume of work has built up around these two compounds.

A. Isolation and Structures

The alkaloid swainsonine (**333**), first isolated in 1973 from the fungus *Rhizoctonia leguminicola* Gough et E.S. Elliott (*300*), has since been reported to occur in an interesting variety of higher plants, including *Swainsona canescens* (Benth.) A. Lee (*312*), *Astragalus lentiginosus* Dougl. ex G. Don (*313*), *Astragalus emoryanus* (Rydb.) Cory (*314*), and *Oxytropis sericea* Nutt. (*313*), as well as another fungus, *Metarhizium anisopliae* F3622 (*315*). In *R. leguminicola* it occurs along with slaframine (*300,301*) and very low concentrations of the diol **332** (*316*). At the time of its first isolation (*300*) from *R. leguminicola* (0.001% of the wet weight of mycelium), the alkaloid, which was not given a trivial name, was assigned the incorrect structure **336**, an error that was not corrected until some 10 years later (*301*).

In the meanwhile, the α-mannosidase inhibitor in the Darling pea, *Swainsona canescens*, had been isolated by Australian workers (0.001% of the dried plant material) and given the name swainsonine (*312*). A careful analysis of the spectra of the compound (mp 144–145°C) and of its di- and triacetates—in particular,



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the 90–MHz PMR spectra—led to the suggestion of structure **333** (*312*). The presence of strong Bohlmann bands in the IR spectra indicated the trans-fused nature of the rings. Structure **333**, with relative stereochemistry only, was confirmed by means of an X-ray analysis on a crystal of the diacetate (*317*).

In 1983 an improved procedure resulted in a larger quantity of the alkaloid being isolated from *Rhizoctonia leguminicola* (0.014% of the wet weight of mycelium), and it became obvious that the off-resonance ^{13}C-NMR spectrum of the compound was incompatible with structure **336** (*301*). A more careful analysis of the spectra led to the recognition that the compound had structure **333**. A comparison of optical rotations ($[\alpha]_D$ −87.2°, *c* 2.1, MeOH in this work, as compared with $[\alpha]_D$ −78.9°, *c* 1.14, MeOH for "authentic" swainsonine) showed that the compound isolated from the fungus was in fact swainsonine rather than its enantiomer. In addition, application of Horeau's procedure (*288*) to the 1,2-acetonide indicated an *R* absolute configuration at C-8 and hence the overall absolute configuration for (−)-swainsonine shown in **333**. In contrast to the case of slaframine (**310**) discussed earlier (Section VIII,A), this empirically based finding has been confirmed by several enantiospecific syntheses.

Quinolizidine alkaloids are of quite widespread occurrence in the Leguminosae (see Section VII), but the isolation of swainsonine from *Swainsona canescens* appears to be the first reported occurrence of a simple indolizidine alkaloid in this botanical family. Since then, however, species of two other genera of the Leguminosae, *Astragalus* and *Oxytropis*, have been reported to contain swainsonine (*313,314*). Ingestion by range animals of certain species of these genera has long been known to give rise to a chronic neurological disease called locoism (Section IX,D). The isolation of swainsonine (**333**) (0.003% of dried plant) and swainsonine *N*-oxide (**334**) (0.001%) from the spotted locoweed, *Astragalus lentiginosus* (*313*), of swainsonine (0.05–0.1% of dried plant) from the Texas locoweed, *Astragalus emoryanus* (*314*), and the detection of both swainsonine and its *N*-oxide in the white locoweed, *Oxytropis sericea* (*313*), has led to the suggestion that these alkaloids are the causative agents of locoism in range animals (*318*).

These and other recent reports suggest that the occurrence of indolizidine alkaloids in the Leguminosae may be more widespread than has been thought up to now. In addition to the examples mentioned above, there are the alkaloids of *Prosopis juliflora* (Section III,D), and the isolation of the indolizidine alkaloid castanospermine from the seeds of the Australian legume *Castanospermum australe* (*319*), the unripe seeds of which cause severe gastrointestinal irritation and sometimes even death when eaten by horses and cattle. This plant also contains 2(*R*),3(*S*)-2-hydroxymethyl-3-hydroxypyrrolidine (*320*). Castanospermine (mp 212–215°C dec; $[\alpha]_D$ +79.7°, *c* 0.93, H_2O) was assigned structure **335** on the basis of extensive NMR experiments, and this structure was confirmed by single-crystal X-ray analysis. These investigations defined only the relative ster-

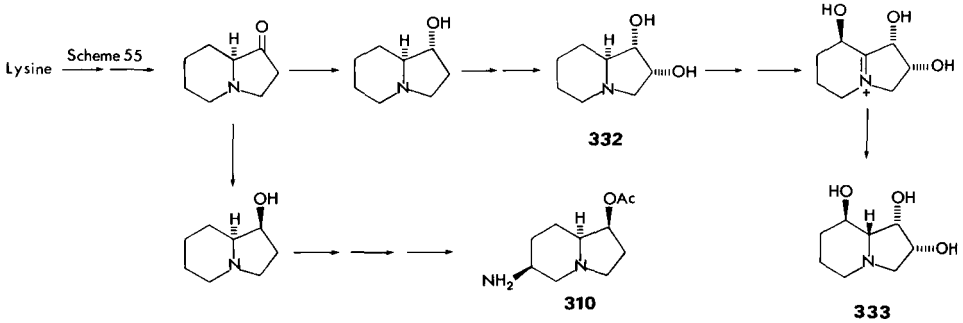
eochemistry, but the absolute configuration has been proved to be as shown in **335** by means of the enantioselective synthesis (*321*) to be described later.

B. Biosynthesis

Biosynthetic studies on swainsonine (**333**) have all related to its occurrence in *Rhizoctonia leguminicola,* and most of these studies have been carried out in parallel with studies on the biosynthesis of slaframine (**310**), which also occurs in the fungus (Section VIII,B). As was found for slaframine, the piperidine ring and C-1 of swainsonine are derived from lysine via pipecolic acid (*300*), while the remainder of the pyrrolidine ring comes from acetate via malonate (*292*). A common pathway appears to operate as far as (*S*)-1-oxoindolizidine (see Scheme 55), which is then reduced from the α face in the biosynthesis of slaframine, and from the β face in the biosynthesis of swainsonine (Scheme 62) (*294*).

Feeding experiments with pipecolic acid perdeuterated on the carbon atoms of the ring produce swainsonine minus deuterium at C-8 and C-8a (*294*). This result and the necessary epimerization of C-8a are best accommodated by postulating oxidation to an iminium compound, followed by reduction from the β face of the molecule. As indicated earlier, the diol **332** occurs in very low concentrations alongside swainsonine in *R. leguminicola,* and, in addition, feeding experiments show that **332**-*1*-*t* is incorporated very efficiently into swainsonine (*316*). The 8a epimer of **332**, on the other hand, has been shown not to be involved in normal metabolism. Consequently, hydroxylation at C-2 appears to precede the epimerization at C-8a, but the timing of the postulated oxidation–reduction process relative to hydroxylation at C-8 remains to be established.

The biosynthesis of castanospermine does not, at this stage, appear to have been investigated.



Scheme 62. Biosynthesis of swainsonine.

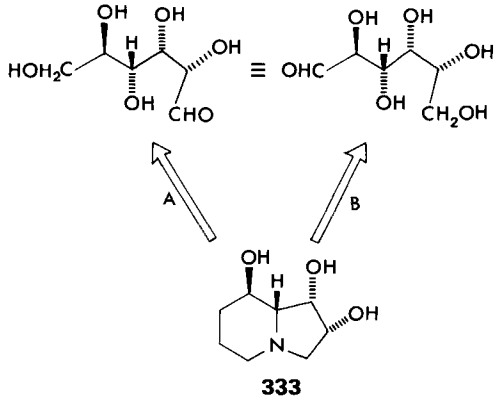
C. SYNTHESIS

1. (−)-Swainsonine

Swainsonine (**333**) is a potent toxin, and in some mammals it induces a condition similar to the genetic disease mannosidosis. It was initially expected to have great value in permitting controlled studies of this disease to be carried out. Unfortunately, as indicated above, it occurs naturally in rather low concentrations; hence the development of enantioselective syntheses has been an area of considerable activity, with five such syntheses submitted for publication in the period December 1983 to July 1984.

Retrosynthetic analysis clearly points to D-mannose, since each of the four contiguous chiral centers in this compound has the appropriate configuration for (−)-swainsonine. Two methods of utilizing D-mannose may be recognized and are indicated in general terms in Scheme 63. Syntheses following route A involve the introduction, with retention of configuration, of nitrogen at C-4, a two-carbon chain extension from C-6, and the necessary ring closures. Syntheses following route B involve introduction of nitrogen at C-3, again with retention of configuration, a two-carbon chain extension from C-1, and the appropriate ring closures. Examples of syntheses following each of these routes are discussed below.

To date, syntheses following route A have been carried out by the research groups of Fleet (*322*) and of Takaya (*315*). That due to Fleet is outlined in Scheme 64. The introduction of nitrogen at C-4 is carried out by a series of reactions involving two inversions of configuration. A suitably protected mannose derivative **337** is subjected to an oxidation–reduction sequence such that reduction occurs with hydrogen delivery from the less-hindered face of the



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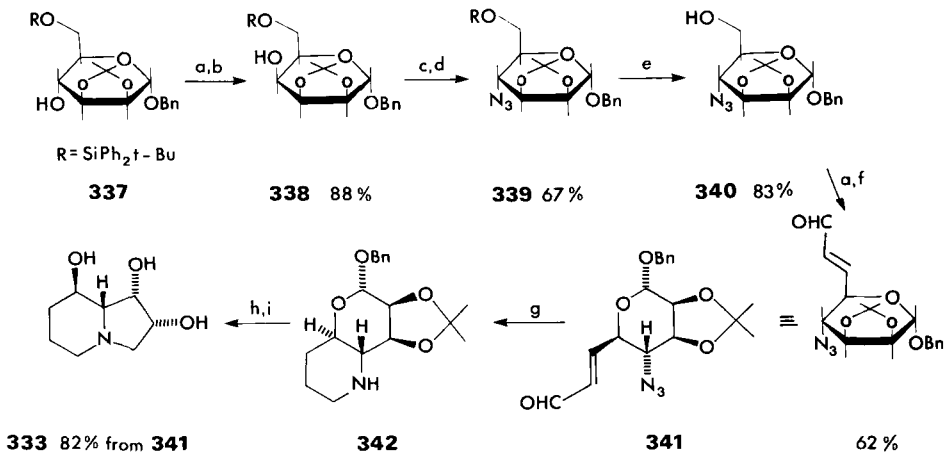
SCHEME 63. Structural relationship between (−)-swainsonine and D-mannose.



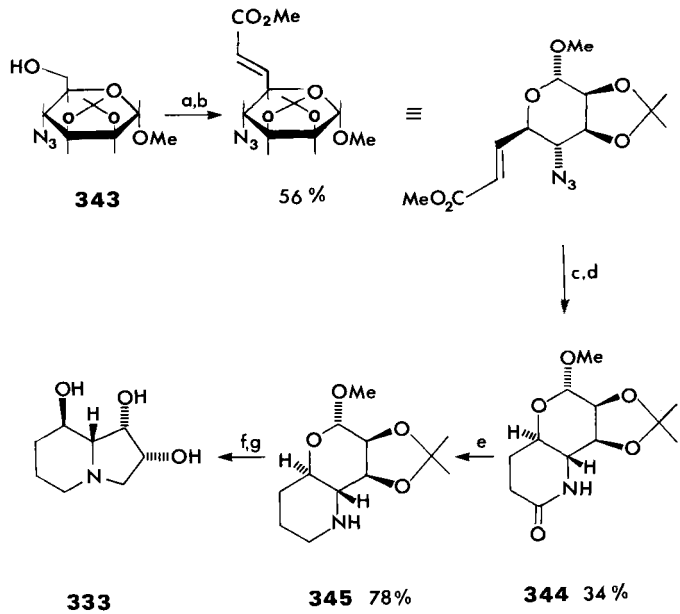
SCHEME 64. Synthesis of (−)-swainsonine by Fleet, Gough, and Smith (*322*). Reagents: (a) py·HCl–CrO_3, molecular sieve, CH_2Cl_2; (b) $NaBH_4$, EtOH; (c) $(CF_3SO_2)_2O$, py, CH_2Cl_2; (d) NaN_3, DMF; (e) Bu_4NF, THF; (f) $Ph_3P{=}CHCHO$; (g) H_2, 10% Pd–C, MeOH; (h) H_2, Pd black, AcOH; (i) 80% CF_3CO_2H–D_2O; H_2O workup.

molecule. Product **338**, a talose derivative, now has the inverted configuration at C-4. Conversion to the triflate, followed by S_N2 displacement with azide ion, produces the required C-4 azide substituted mannose derivative **339**. Two-carbon chain extension at C-6 is achieved by removal of the silyl protecting group, giving **340**, and oxidation to an aldehyde, which, without isolation, is used in a Wittig reaction to give **341**. This compound contains the complete skeleton of swainsonine with the appropriate stereochemistry at each chiral center. All that remains is to arrange for the necessary cyclizations. These are brought about by means of two multiple-step hydrogenations. In the first stage (hydrogenation with 10% Pd–C in methanol), both the azide and the C=C bond are reduced; intramolecular reductive amination of the amino aldehyde then takes place, and the piperidine ring of intermediate **342** results. Upon changing the catalyst and solvent (to palladium black and acetic acid, respectively), hydrogenation removes the anomeric benzyl ether, giving a lactol, which participates, via its open-chain tautomer, in a second reductive amination, this time with the nitrogen of the piperidine ring. The excellent yield (87%) obtained for this five-step sequence is a noteworthy feature of the synthesis and contrasts sharply with problems experienced with the cyclization steps in some of the other syntheses. Fleet's synthesis of (−)-swainsonine (**333**) is completed by removing the isopropylidene protecting group. Assuming that the starting benzyl α-D-mannopyranoside is obtainable in a yield comparable to that of the literature procedure cited, this synthesis accomplishes the conversion of D-mannose to (−)-

swainsonine in a remarkable 10% overall yield even without optimization of several of the steps. It should permit the efficient synthesis of the alkaloid in quantities of several grams.

The Takaya synthesis (*315*), the latter stages of which are shown in Scheme 65, is very similar in its broad design to the Fleet synthesis. Compound **343**, prepared in good yield from D-mannose by a similar series of reactions to those used by Fleet, differs from the Fleet intermediate **340** only in the nature of the anomeric alkoxy group. The oxidation of **343** and subsequent Wittig reaction achieve the two-carbon extension at C-6 in very similar yield to that obtained by the English group. However, the use of the ester in the Wittig reaction leads in significantly lower yield to the formation of piperidone **344** on cyclization, a compound that must then be reduced to the piperidine **345**. Somewhat surprisingly, the cleavage of the anomeric methyl ether in this intermediate could only be achieved with boron trichloride. The product appears to be unstable under the conditions of the reaction, with the result that the conversion of **345** to (−)-swainsonine (**333**) is achieved in only 2% yield.

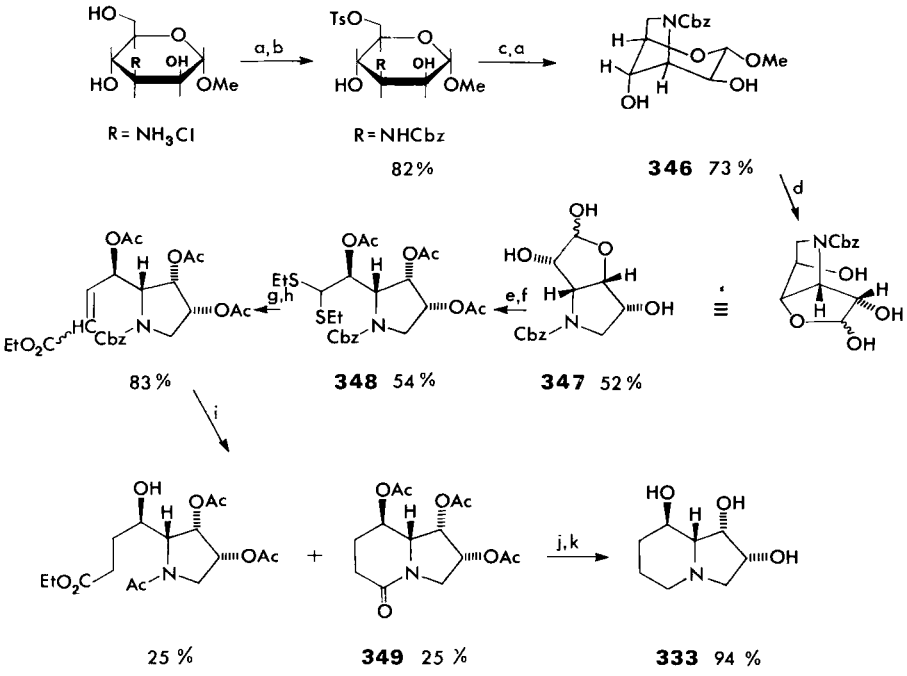
Syntheses following route B require the introduction, with retention of configuration, of nitrogen at C-3 of the mannose skeleton. This may be efficiently achieved from appropriately substituted glucose derivatives, and both of the



SCHEME 65. Late steps in the synthesis of (−)-swainsonine by Yasuda, Tsutsumi, and Takaya (*315*). Reagents: (a) py–SO_3, DMSO, NEt_3; (b) $Ph_3P{=}CHCO_2Me$, THF; (c) H_2, Pd black, MeOH; (d) MeOH, Δ; (e) BH_3, THF, 0°C; (f) BCl_3, CH_2Cl_2; (g) $NaBH_3CN$, H_2O–MeOH, pH 6–7.

reported syntheses using route B make use of documented procedures for converting glucose derivatives to the necessary C-3 aminomannose derivative. The syntheses from this point on are outline in Schemes 66 and 67.

In the case of the synthesis by Richardson and co-workers (*323,324*), the pyrrolidine ring of swainsonine is established first in the formation of the bridged bicyclic compound **346** by displacement of the C-6 tosyloxy group (Scheme 66). Treatment of **346** with acid induces a rearrangement to the fused bicyclic compound **347**. Attempts to carry out the necessary two-carbon chain extension by means of the Wittig reaction directly on **347**, or on its partially protected derivative, the di-*O*-methyl ether, fail because of subsequent Michael reactions. Consequently, the fully protected triacetate **348** has to be prepared. Cleavage of the dithioacetal and the Wittig reaction then proceed smoothly. The remaining task, formation of the six-membered ring after reduction of the alkene group and cleavage of the N-protecting group, is complicated by an O-to-N transacylation reaction, and the formation of **349** follows in only 25% yield. The conversion of

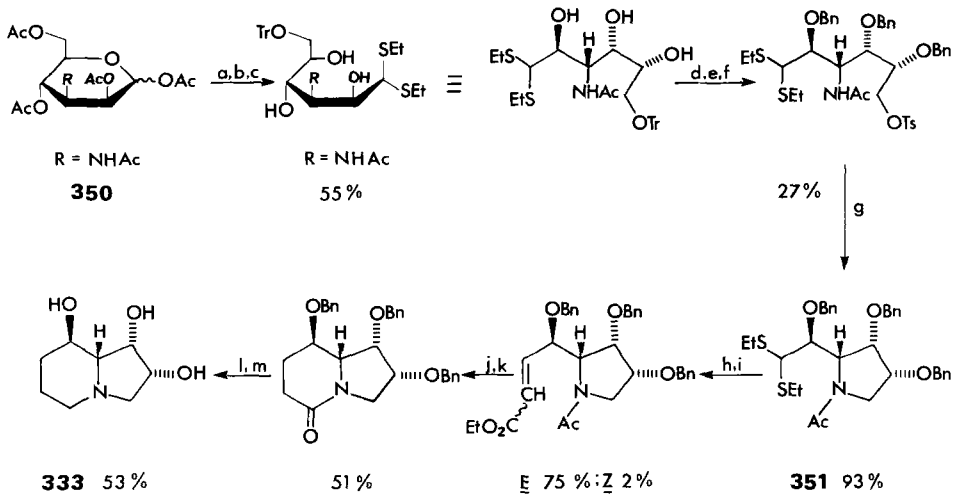


SCHEME 66. Synthesis of (−)-swainsonine by Ali, Hough, and Richardson (*323,324*). Reagents: (a) $NaHCO_3$, $PhCH_2OCOCl$, EtOH–H_2O; (b) *p*-TsCl, py; (c) H_2 (60 psi), 10% Pd–C, EtOH; then NaOAc; (d) 0.4 *M* HCl, 95–100°C; (e) CH_3CH_2SH, concd HCl; (f) Ac_2O, py; (g) $HgCl_2$, $CdCO_3$, Me_2CO–H_2O; (h) $Ph_3P{=}CHCO_2Et$, MeCN, Δ; (i) H_2 (60 psi), 10% Pd–C, EtOH–HOAc; (j) $BH_3{\cdot}Me_2S$, THF; (k) NaOMe, MeOH.

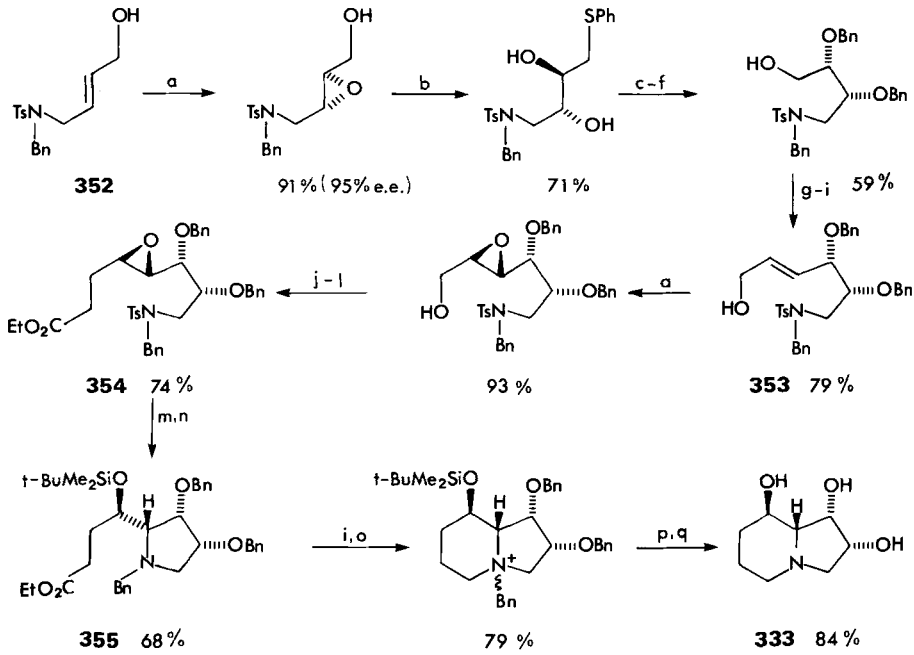
this compound to (−)-swainsonine (**333**) is carried out in high yield by routine procedures. The overall yield of swainsonine based on methyl α-D-glucopyranoside is about 0.7%.

In the synthesis by Suami and co-workers (*325,326*), the mannose derivative **350** is converted to a suitably protected open-chain compound before the pyrrolidine ring is formed, again by displacing a tosyloxy group from C-6 of the sugar (Scheme 67). The compound **351** so formed differs from compound **348** in the Richardson synthesis only in the nature of the O and N protecting groups. The elaboration of **351** to (−)-swainsonine follows a procedure similar to Richardson's, the difference being associated with the reagents required for cleavage of the different protecting groups. The choice of benzyl for protecting the hydroxyl groups is superior to Richardson's choice of acetates, since the competing transacylation mentioned earlier is avoided. On the other hand, the use of *N*-acetyl appears to be less satisfactory than the use of *N*-benzyloxycarbonyl, and, in the end, the yields obtained for the conversions of **351** and of **348** to (−)-swainsonine are very similar (21 and 19%, respectively), as indeed are the overall yields of the two syntheses.

The only other synthesis of (−)-swainsonine reported to date, that by Sharpless and co-workers (*327*), is shown in Scheme 68. It is totally different in concept from those described above in that it does not draw upon the chiral pool



SCHEME 67. Synthesis of (−)-swainsonine by Suami, Tadano, and Iimura (*325,326*). Reagents: (a) NaOMe, MeOH; (b) CH_3CH_2SH, HCl, −15°C; (c) Ph_3CCl, py, DMAP, 70°C; (d) $PhCH_2Br$, NaH, DMF; (e) *p*-TsOH, MeOH; (f) *p*-TsCl, py; (g) 1 *M* NaOH, dioxan, Δ; (h) $HgCl_2$, $CaCO_3$, MeCN–H_2O; (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (j) H_2 (1 atm), Raney Ni, EtOH; (k) KOH, EtOH–H_2O, 90°C; (l) $LiAlH_4$, THF, Δ; (m) 20% $Pd(OH)_2$, cyclohexene, EtOH, Δ.



SCHEME 68. Synthesis of (−)-swainsonine by Adams, Walker, and Sharpless (*327*). Reagents: (a) (−)-Diisopropyl tartrate, $(i\text{-PrO})_4Ti$, *t*-BuOOH, CH_2Cl_2, −20°C; (b) NaOH, PhSH, *t*-BuOH, 85°C; (c) $PhCH_2Br$, NaH, Bu_4NI, THF; (d) *m*-CPBA, CH_2Cl_2, −78°C; (e) Ac_2O, $(CF_3CO)_2O$, 2,6-lutidine; (f) $LiAlH_4$, THF, 0°C; (g) $(COCl)_2$, DMSO, DBU, CH_2Cl_2, −60°C; (h) $(EtO)_2POCH_2CO_2Et$, NaH, $C_6H_5CH_3$; (i) $i\text{-}Bu_2AlH$, $C_6H_5CH_3$, −78°C; (j) DCC, DMSO, $C_5H_5NH^+OTf^-$, 40°C; (k) $Ph_3P{=}CHCO_2Et$; (l) $KO_2CN{=}NCO_2K$, py, AcOH, 40°C; (m) Na/naphthalene, $(MeOCH_2)_2$, −60°C; (n) *t*-$BuMe_3SiOTf$, NEt_3, CH_2Cl_2, 0°C; (o) MsCl, NEt_3, CH_2Cl_2; (p) Pd black, 10% HCO_2H–MeOH; (q) Dowex 50W-X8, MeOH.

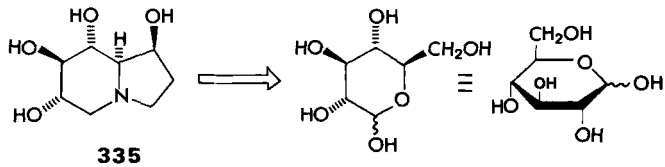
for a starting material. Instead, the four contiguous chiral centers are established by means of the familiar Sharpless asymmetric epoxidation, which is performed twice, on the allylic alcohols **352** and **353**. In the first case, the epoxide is obtained in 91% yield and an enantiomeric excess of 95%, while in the second case the desired diastereomer is obtained in 93% yield and a ratio of greater than 321:1. Once the four chiral centers are established, the necessary chain extension is carried out (as in the other four syntheses of swainsonine) by means of a Wittig reaction, followed by reduction of the resulting C=C bond. The ensuing product **354** contains all the skeletal atoms and stereochemistry for swainsonine and merely requires cyclization. The pyrrolidine ring is formed first by an intramolecular S_N2 displacement to yield **355**, a compound very similar to those formed in the Richardson and Suami syntheses. In contrast to those syntheses, however, the final cyclization in the Sharpless synthesis is not performed at the

acyl oxidation level; once the ester is reduced to an alcohol, which is in turn converted to its mesylate, ring closure occurs spontaneously.

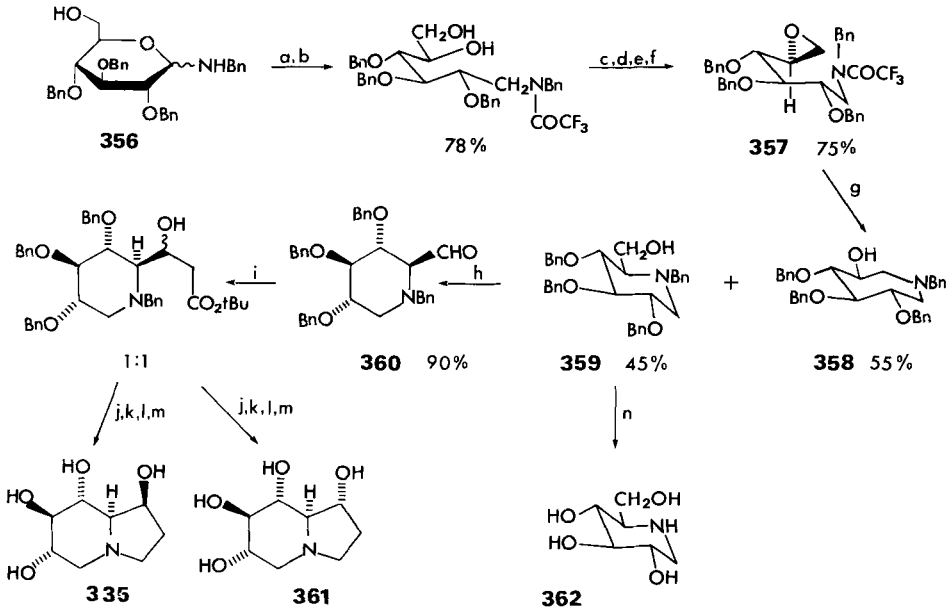
The Sharpless synthesis is a lengthy one (21 steps) and in addition is linear; but so efficient are the individual steps that swainsonine is obtained in an overall yield of 6.6%—an average yield per step of 88%. A further striking feature of this synthesis is the control that is possible over each of the four chiral centers. In principle, each of the 16 stereoisomers of swainsonine is attainable; in a footnote in Ref. 327, the completion of syntheses of compounds epimeric at C-2 and at both C-2 and C-8 is reported. It should also be mentioned here that the synthesis of the latter of these compounds, and also of a compound epimeric at C-8 only, has been reported by Takaya (*328*). In contrast to his synthesis of swainsonine, the syntheses of these two stereoisomers follow a "route B" approach. The biological activity of these stereoisomers is reportedly under investigation.

2. (+)-Castanospermine

The polyhydroxy nature of castanospermine (**335**) suggests that a synthesis based on a carbohydrate starting material is likely to be attractive. Indeed, as can be seen in Scheme 69, the configurations of the four chiral centers in the piperidine ring correlate exactly with the four chiral centers of D-glucose. The synthesis carried out by Bernotas and Ganem (*321*) and shown in Scheme 70 takes advantage of this fact. The nitrogen atom is introduced by the reaction of 2,3,4-tri-*O*-benzyl-D-glucopyranose and benzylamine, from which compound **356** results. After reductive opening of the ring and amide formation, synthesis of the substituted piperidine ring is achieved by forming the epoxide **357** with inversion of configuration at C-5, followed by opening the epoxide ring with a second inversion. Competitive reaction at C-6 leads to the azepane **358** along with the desired piperidine **359**. The extra two carbon atoms are introduced by oxidation to the aldehyde **360** and reaction with *t*-butyl lithioacetate. After separation of the diastereomeric material produced, the syntheses of (+)-castanospermine (**335**) and 1-epicastanospermine (**361**) ($[\alpha]_D$ +6°, *c* 0.45, H_2O) are completed by deprotection of nitrogen, cyclization to appropriate lactams, and reduction. As a bonus along the way, the deprotection of piperidine **359** leads to



SCHEME 69. Structural relationship between (+)-castanospermine and D-glucose.

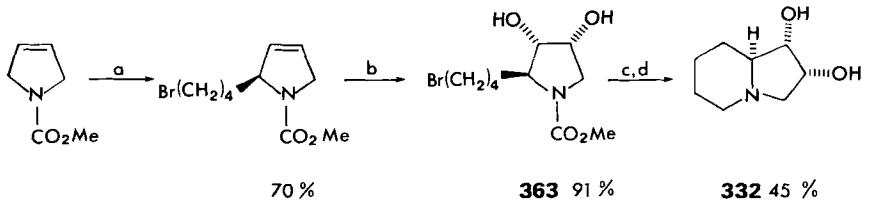


SCHEME 70. Synthesis of (+)-castanospermine and (+)-1-epicastanospermine by Bernotas and Ganem (*321*). Reagents: (a) $LiAlH_4$, THF, Δ; (b) trifluoroacetylation; (c) *t*-$BuMe_2SiCl$, imidazole; (d) mesylation; (e) Bu_4NF, THF; (f) NaOMe, MeOH; (g) $NaBH_4$, EtOH, 40°C; (h) DMSO, $(COCl)_2$; (i) $LiCH_2CO_2t$-Bu; (j) diastereomer separation; (k) hydrogenolysis; (l) CF_3CO_2H, H_2O, 60°; (m) *i*-Bu_2AlH; (n) hydrogenolysis.

the formation of the antibiotic (+)-deoxynojirimycin (**362**), which, like castanospermine, is a glucosidase inhibitor.

3. Indolizidinediol **332**

The racemate of indolizidinediol **332** was known as a synthetic material (*329*) some years before its detection as a metabolite of *Rhizoctonia leguminicola* (*316*). The Australian group, which first prepared the compound, was interested in pursuing the analogy between swainsonine and the mannosyl cation proposed as an intermediate in the enzymatic hydrolysis of mannopyranosides; they required **332** as a model for inhibition studies on glycosidases. Their synthesis, shown in Scheme 71, is very similar to that used by Macdonald for the synthesis of a diastereomer of monomorine I (see Section III,B). By coincidence, Harris and his group—the discoverers of **332** as a natural product—have used an almost identical route to prepare the racemic diol, the only difference being the cleavage of urethane **363** with methyllithium rather than with trimethylsilyl iodide (*316*). The yield by this procedure is very low, but it can be significantly improved by



SCHEME 71. Synthesis of indolizidinediol **332** by Colegate, Dorling, and Huxtable (*329*). Reagents: (a) LDA, $Br(CH_2)_4Br$, THF, −70°C; (b) OsO_4 (cat.), *t*-BuOOH, H_2O_2; (c) Me_3SiI, C_6H_6, 50°C; (d) Na_2CO_3, MeOH.

converting diol **363** to its acetonide before removal of the protecting group and cyclization.

D. BIOLOGICAL ACTIVITY

1. Introduction

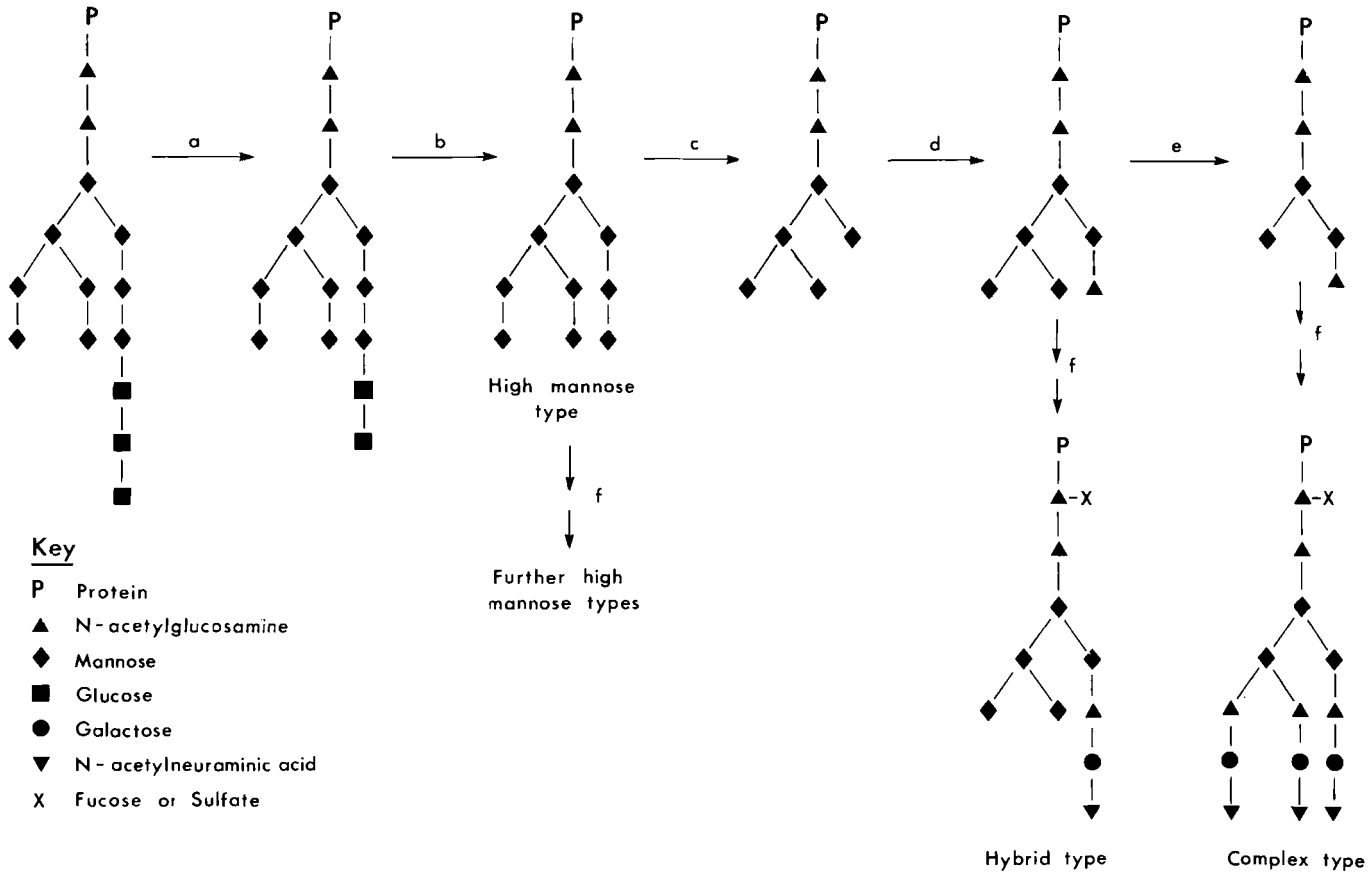
The most notable biological effect of both swainsonine (**333**) and castanospermine (**335**) can be stated in a nutshell: they are potent inhibitors of various glycosidases, both *in vivo* and *in vitro*. The former alkaloid is noteworthy as an inhibitor of α-D-mannosidases, while the latter is less specific in its mode of action, though best against glucosidases. Since the categorization of glycosidases (*330*) can be a confusing subject, some comment on the enzymes of relevance for this review is appropriate at this point.

Mammalian cells contain at least three distinct types of α-D-mannosidases, some of which occur in more than one form (*331*). The three distinct types are the acidic α-D-mannosidases (pH optimum around 4.0), which are found among the large number of lysosomal hydrolases; the intermediate or Golgi α-D-mannosidases (pH optimum 5.5–6.0), which are located in the Golgi apparatus: and the neutral or cytosolic α-D-mannosidase (pH optimum 6.5). In addition, an α-D-mannosidase has been found in the endoplasmic reticulum of rat liver (*332*); and it has been suggested that the cytosolic α-D-mannosidase, the function of which was not obvious, may in fact arise from the endoplasmic reticulum membrane α-D-mannosidase by proteolysis or disruption during extraction (*331*). Swainsonine is now known to inhibit examples of all three types of mammalian α-D-mannosidase with varying degrees of effectiveness (*331*). It can also inhibit plant mannosidases such as those from the jack bean (*Canavalia ensiformis*) (*301,314,333–335*), and from spinach (*Spinacia oleracea* L.) (*336*), as well as that from a primitive fish, the lamprey eel (*333*). It is, however, quite specific in its inhibition of mannosidases and has been shown to be without effect on mouse-liver α-glucosidase, β-galactosidase, hexosaminidase, and β-glucuronidase at

concentrations 10 times that required to inhibit mouse-liver α-D-mannosidase completely (*333*). The mechanisms whereby swainsonine inhibits the various mannosidases are different (*335*), and there are even some forms of mammalian mannosidase that are not inhibited by swainsonine (*331*). Swainsonine *N*-oxide, incidentally, is as potent an inhibitor of mouse-liver mannosidase and jack-bean mannosidase as swainsonine itself (*313*).

As is the case with the mannosidases, there exist a variety of glucosidases, including both acidic and neutral glucosidases. Castanospermine has been found to inhibit both the α- and the β-lysosomal glucosidases as well as the glucosidases I and II found in the endoplasmic reticulum (*337,338*). Since lysosomal α-glucosidase is known to be involved in glycogen metabolism, it is not surprising that rats treated with castanospermine show significantly altered patterns of glycogen distribution within the body (*339*). Castanospermine has also been found to inhibit the action of β-glucocerebrosidase and β-xylosidase (*337*). It is, however, without effect on yeast α-glucosidase, α- and β-galactosidase, α- and β-mannosidase, α- and β-L-fucosidase, β-*N*-acetylhexosaminidase, and β-glucuronidase (*337*). Laboratory rats given large doses of castanospermine develop diarrhea and high intestinal bacterial counts, a finding ascribed to the alkaloid's inhibition of intestinal maltase and sucrase (*339*). This finding is of interest in view of reports of severe gastrointestinal irritation suffered by horses and cattle after eating the unripe seeds of *Castanospermum australe* (*319*). A further intriguing aspect of the biological activity of castanospermine is provided by a recent report (*340*) of its insecticidal activity, a property that may also be linked to the inhibition of glycosidases.

The glycosidases of interest for the present discussion are all involved in the metabolism of glycoproteins, and specifically those widely occurring glycoproteins in which the oligosaccharide portion is covalently linked to protein through the amide nitrogen of asparagine (*341,342*). These macromolecules occur both as secreted proteins and as cell-surface proteins. The initial phase of the biosynthesis of the oligosaccharide portion, which takes place in the endoplasmic reticulum, involves lipid-linked saccharide intermediates and is known as the dolichol pathway. It leads ultimately to the formation of $Glc_3Man_9(GlcNAc)_2$-pyrophosphoryldolichol, the oligosaccharide portion of which is then transferred from its lipid carrier to the protein. Following this transfer, the oligosaccharide undergoes a number of processing or trimming reactions, which start in the endoplasmic reticulum and continue in the Golgi apparatus as the protein is transported through to its ultimate goal. The processing sequence has been extensively studied, and the basic pathway, outlined in Scheme 72, is known in considerable detail. As shown in this scheme, the oligosaccharide portion of the mature glycoprotein may be of the high mannose type, the complex type (a great variety of possible structures exists, of which only one is shown), or a hybrid type. A very profitable method for studying glycoprotein processing makes use



SCHEME 72. Significant steps in the processing of glycoproteins. (a) Glucosidase I (cleavage of α1-2 link); (b) glucosidase II (cleavage of α1-3 link); (c) Golgi mannosidase I (cleavage of α1-2 link); (d) UDP-GlcNAc or *N*-acetylglucosaminyltransferase II; (e) Golgi mannosidase II (cleavage of α1-3 and α1-6 links); (f) Appropriate sugar nucleotides.

of glycosidase inhibitors that block the pathway at specific steps (*343,344*), and both swainsonine and castanospermine are valuable tools in this respect.

Some of the glycosidases involved in glycoprotein processing, and the sites at which they cleave oligosaccharides, are shown in the caption to Scheme 72. The glycosidases involved in trimming are located in the endoplasmic reticulum and in the Golgi apparatus. By contrast, the lysosomal glycosidases are involved in the catabolism of mature glycoproteins (that is, the high mannose, hybrid or complex species of Scheme 72), sequentially degrading materials no longer required by the cell to monosaccharides, which are then returned to general cell metabolism. With these basic concepts in hand, we are now in a position to examine the inhibitory effects of our polyhydroxylated alkaloids.

2. Swainsonine Toxicosis and the Inhibition of Lysosomal Mannosidases

It has been known for many years that prolonged ingestion of various *Swainsona* species (Darling pea) in Australia or of certain *Oxytropis* and *Astragalus* species (locoweeds) in North America leads to significant stock losses (*345, 346*). In the United States, the resultant condition is known as locoism (*313*, and references therein, *347*) because affected animals seem to "go crazy," attempting to leap over imaginary objects or sometimes walking straight into obstructions. In general, the symptoms exhibited by animals after consumption of either Darling pea or locoweed are very similar (*348*); they include trembling, muscular incoordination and a staggering gait, depression, a tendency toward solitariness, partial blindness, and difficulty in eating or drinking resulting in emaciation. Abortion and birth defects occasionally occur, and affected animals may die from starvation or by misadventure. The condition is habit-forming, and poisoned animals will seek out the plant. If animals are prevented from obtaining the plant during the early stages of the disease, they will generally recover, though they may continue to show typical neurological symptoms when stressed (*347*). Postmortems usually do not reveal any gross lesions, though the disease is characterized by cellular vacuolation in most tissues (*346*). The microscopic lesion invariably present is the occurrence of numerous axonal spheroids in the central nervous system (*349*).

The first significant step in pinpointing swainsonine (**333**) as the toxic agent of both the Darling pea and the locoweeds was the recognition (*350*) of the similarity of *Swainsona* toxicosis to α-D-mannosidosis, a neurological disease in humans, cattle, and kittens (*351*). The disease is caused by a deficiency of lysosomal α-D-mannosidase arising from a defect in the genetic coding of individuals, and is manifested by the accumulation of mannose-rich oligosaccharides in the lysosomal system of cells (*352*)—hence its classification as a lysosomal storage disease. Once it had been shown that *Swainsona canescens* did in fact

contain a potent α-mannosidase inhibitor (*350*), this activity could be used in a bioassay, which eventually led to the isolation and purification of the active component, swainsonine (*312*). A clear, if circumstantial, case for swainsonine as the causative agent in *Swainsona* intoxication in livestock was rapidly established (*352*) and later substantiated (*353*). Evidence for the implication of swainsonine in locoweed intoxication also remained circumstantial until Touster and co-workers demonstrated the striking similarity of behavioral and biochemical effects in pigs fed either swainsonine or locoweed (*318*).

As mentioned earlier, the function of lysosomal hydrolases is the catabolism of the macromolecules that enter the lysosomal system. When lysosomal α-D-mannosidases are inhibited, activity is blocked whenever a sugar chain has a mannose residue at its nonreducing end. These undigested oligosaccharides then accumulate within the cell, forming foamy vacuolar inclusions, which eventually disrupt cellular function, particularly in neurones. In genetic mannosidosis, mannose-rich oligosaccharides may be detected in fibroblasts or in the urine (*354*). The composition of such oligosaccharides varies from species to species (*355*); $Man_2(GlcNAc)_2$ is dominant in bovine mannosidosis urine, which also contains appreciable amounts of $Man_3(GlcNAc)_2$, the major oligosaccharide of feline mannosidosis urine. By contrast, human mannosidosis urine is rich in $Man_2GlcNAc$, specifically Man(α1–3)Man(β1–4)GlcNAc.

The pK_a of swainsonine is 7.4 (*333*). It is likely that in the body it will tend to concentrate in the acidic environment of the lysosomes, and once there, it will inhibit the α-D-mannosidases. Its toxicity is thought to be due to this activity (*346,352*). It has, however, also been suggested (and disputed!) that other aspects of its activity—perhaps the abnormal processing of glycoproteins (see below)—may play a part (*335,356–358*). Certainly, oligosaccharides may be detected in the urine of animals intoxicated with locoweed or *Swainsona* (*358–362*), though the composition of these is generally more complex than, and rather difficult to correlate with, those obtained from subjects with genetic mannosidosis. *In vivo* studies with rats, sheep, and guinea pigs have shown that high mannose oligosaccharides are excreted in urine (*358,361*) rather than the expected low mannose compounds, probably indicative of a processing block being superimposed on the mannosidosis condition. Quantitative analysis of these high mannose oligosaccharides in the urine of sheep, however, provides a very valuable method for detecting the onset of locoism at a far earlier stage than was previously possible (*362*). For example, oligosaccharide levels in urine are significantly raised after 3 days of locoweed ingestion, whereas clinical symptoms of intoxication appear only after about 5 weeks. In view of the fact that swainsonine can be secreted in the milk of affected animals (*363*), early diagnosis is clearly important (*303,362*).

Oligosaccharides in the tissues of swainsonine-dosed animals, or in cells cultured in the presence of the alkaloid, have also been analyzed

(*318,350,361,364*), though once again the results do not allow unequivocal differentiation between the inhibition of lysosomal and of Golgi α-D-mannosidase activity. Two results stand out, however. First, identical oligosaccharides ($Man_4GlcNAc_2$, $Man_5GlcNAc_2$) accumulate in porcine kidney and brain tissue, irrespective of whether the animals are fed pure swainsonine or locoweed (*318*); this is a useful piece of evidence for swainsonine being the active principle in loco intoxication. Second (*361,364*), normal human fibroblasts cultured with swainsonine rapidly accumulate $Man_2GlcNAc$, which then dwindles as $Man_5GlcNAc$ and $Man_3GlcNAc$—probably Man(α1–3)[Man(α1–6)]Man(β1–4)GlcNAc—levels increase. Fibroblasts from a patient with genetic mannosidosis accumulate $Man_2GlcNAc$ as expected, but when these are incubated with swainsonine, $Man_2GlcNAc$ again gives way to $Man_5GlcNAc$ and $Man_3GlcNAc$. As with the results obtained from the analysis of the oligosaccharides excreted in the urine of affected animals, these results may in part be understood by recognizing the existence of a processing block. In addition, they support the existence of a minor form of acidic α-D-mannosidase [the M form (*331*)], which is unaffected in genetic mannosidosis, which has activity toward the core (α1–6)-mannoside linkage, and which can be inhibited by swainsonine.

The biochemical, morphological, and clinical similarities between swainsonine toxicosis and mannosidosis initially generated much excitement. With the isolation of swainsonine, it appeared that a valuable tool for inducing and terminating a phenocopy of genetic mannosidosis at will was available, thereby permitting controlled monitoring of a disease that could previously be studied only in animals that were chance carriers of mutant genes (*311,333*). Extensive investigations of various aspects of swainsonine-induced inhibition of lysosomal α-D-mannosidases were reported (*318,333,335,356,357,361,364–369*). However, the very diverse effects that swainsonine produces have led to the realization that it probably can not be used successfully to model a lysosomal storage disease resulting from the deficiency of a single enzyme (*365,366*). Indeed, it has been reported that the tissue levels of lysosomal α-D-mannosidase in rats and pigs are actually raised by the administration of swainsonine (*318, 356*). To add to the confusion, a recent investigation of the easy reversibility of swainsonine-induced inhibition of lysosomal α-D-mannosidase has now cast some doubt on the reliability of earlier measurements (*335*), particularly where results obtained by analyzing tissue extracts are extrapolated to organs *in vivo*.

The inhibition of lysosomal α-D-mannosidases by swainsonine has been used as a tool in investigating the possible role played by the oligosaccharide portion of glycoproteins in the stabilization of the protein toward proteases (*370–372*). Since lysosomes appear to lack endoglycosidases, the removal of sugar residues from glycoproteins must be achieved in a stepwise fashion; and the blocking of one of these steps—for example, removal of mannose—will result in the remainder of the carbohydrate chain being retained. Hence the finding that swain-

sonine does inhibit the proteolytic degradation of glycoprotein by cultured rat-liver cells (*371*) or isolated rat-liver lysosomes (*372*) but has no effect on the proteolytic degradation of nonglycoproteins by the same systems suggests that the removal of the oligosaccharide side chains of glycoproteins is indeed a prerequisite for their proteolysis in lysosomes.

3. Swainsonine, Castanospermine, and Glycoprotein Processing

The early investigators of the activity of swainsonine soon showed that it inhibited mannosidases other than lysosomal α-D-mannosidase (*333,373,374*) and underlined its potential value as a tool in the study of the biosynthesis of glycoproteins. Swainsonine has been shown to be a specific inhibitor of Golgi mannosidase II (*357*); that is, it inhibits step e in Scheme 72, a step that involves the cleavage of (α1–3)- and (α1–6)-mannoside linkages. It therefore suppresses the formation of the complex type of oligosaccharide, but permits the formation of high mannose or hybrid types. The detection of high mannose oligosaccharides in the urine of intoxicated test animals has already been mentioned (*358, 361, 362*). This type of alteration by swainsonine of the oligosaccharide portion of a glycoprotein has also been shown to occur in cell-free extracts of rat liver (*373,375*) and mouse liver (*333*); in cultured mammalian cells, such as Madin–Darby canine kidney cells (*373,376*), Chinese-hamster ovary cells (*373,376*), mouse melanoma B-16 cells (*376*), human-skin fibroblasts (*364,377,378*), and Daudi and Raji lymphoblastoid cell lines (*379*); in viruses such as influenza virus (*314,374*) and vesicular stomatitis virus (*380*); in cultured organs such as slices of the renal cortex of piglets (*381*); and in a cultured tissue of bovine cornea (*382*). By contrast, swainsonine is without effect on Golgi mannosidases IA and IB, the enzymes responsible for (α1–2)-mannoside cleavage in the degradation of $Man_9(GlcNAc)_2$-containing glycoproteins to $Man_5(GlcNAc)_2$ species (step c in Scheme 72) (*318,356,357*).

In a similar fashion to the above, studies using castanospermine have revealed the inhibition of glucosidase I; that is, the blocking of step a in Scheme 72. This has been established by using the NWS strain of influenza virus grown in MDCK cells (*383*), mouse lymphoma cells (*338*), cultured soybean cells (*384*), and the fungus *Aspergillus fumigatus* (*385*). In each case, the dominant oligosaccharide formed in the presence of castanospermine (and released by endoglucosaminidase digestion of the glycoprotein) is $Glc_3Man_7GlcNAc$, showing that trimming of some of the mannose residues does take place even without removal of the glucose residues. In a separate study using [Glc-^{3}H]$Glc_2Man_9GlcNAc$ as substrate, it has been shown that castanospermine also inhibits glucosidase II, although less effectively than it inhibits glucosidase I (*338*).

Substitution on to the chitobiose unit in the processing of glycoproteins has

been shown to be affected by castanospermine but not by swainsonine. For example, the fucosylation of fibronectin in human fibroblasts (*378*) or of membrane proteins in cultured soybean cells (*386*) is not impeded by swainsonine even though the glycoproteins produced are of the hybrid instead of the complex type. Similarly, the incorporation of sulfate into bovine cornea keratan is not suppressed by swainsonine, although once again the alkaloid causes incomplete processing of the mannose moieties of the oligosaccharide (*382*). In contrast, the incorporation of sulfate into the glycoprotein of NWS influenza virus grown in MDCK cells is suppressed by castanospermine, though not by swainsonine (*387*). The indication is that terminal glucose units need to be removed before sulfate residues can be added.

The above-mentioned effects exerted by castanospermine and swainsonine on the structures of glycoproteins suggest that they should be of value in studying the intracellular transport and secretion of glycoproteins. Available results are, however, somewhat contradictory. For example, it has been reported that, while swainsonine induces the synthesis of hybrid rather than complex forms of the glycoproteins fibronectin in human fibroblasts (*378*), α_1-antitrypsin in rat hepatocyte cultures (*375*), and a variety of glycoproteins, including α_1-antitrypsin, in human hepatoma Hep G2 cells (*338*), these abnormally processed species are secreted at normal rates. The results of a later study with Hep G2 cells, however, suggest that, while swainsonine indeed induces the formation of hybrid forms of the glycoproteins transferrin, α_1-antitrypsin, ceruloplasmin, and α_2-macroglobulin, these species are also secreted and transported through the Golgi at an accelerated rate (*389*). The suggestion is that the interaction between secretory glycoproteins and an endogenous carbohydrate-binding protein, or lectin, normally involved in the secretory pathway, does not take place with the abnormally processed macromolecules, thereby decreasing the lag time in the Golgi.

4. Mechanistic Aspects of Glycosidase Inhibition by Swainsonine and Castanospermine

Only one study on the mechanism of glycosidase inhibition by castanospermine has been published to date (*390*), and this study shows that inhibition of various glucosidases by castanospermine in the presence of *p*-nitrophenyl α-D-glucoside as substrate is markedly affected by the pH of the incubation mixture. While the alkaloid inhibits the enzymes studied both at pH 6 and 4.5, its effect is much more pronounced at the higher pH. Since the pK_a of castanospermine is 6.09, the implication is that the alkaloid is more active in its unprotonated form. This hypothesis ties in well with the previously mentioned finding that castanospermine is a good inhibitor of the neutral processing enzyme, glucosidase I, and that the *N*-oxide of the alkaloid is considerably less effective as an inhibitor

of glucosidases. As regards specific enzymes, castanospermine is a reversible competitive inhibitor of amyloglucosidase at both pH 4.5 and 6.0 (K_i 3.5 × 10^{-6} *M* and 1.5 × 10^{-6} *M*, respectively). It is a reversible competitive inhibitor of almond emulsin β-glucosidase at pH 6.5 (K_i 1 × 10^{-5} *M*), but at pH 4.5–5.0 the inhibition is of the mixed type (K_i about 2 × 10^{-5} *M*).

Much effort has been expended in attempts to discover just how swainsonine inhibits the action of mannosidases (*333–335,356, 365–369,377*). The first publication on the subject in 1980 tried to generalize results based on the inhibition of mannosidases from a variety of sources, and concluded that swainsonine is a specific, reversible, site-directed inhibitor of α-mannosidase (*333*). The position is now recognized to be more complex. It appears, hardly surprisingly, that the mechanism of inhibition varies according to the nature of the α-D-mannosidase. A recent mechanistic study (*335*) shows up clear differences in the mode of inhibition of rat-liver lysosomal α-D-mannosidase, rat-liver Golgi mannosidase II, and jack-bean α-D-mannosidase by swainsonine in the presence of *p*-nitrophenyl mannoside as substrate. The results may be summarized as follows.

Rat-liver lysosomal α-D-mannosidase is 50% inhibited by swainsonine concentrations as low as 2 × 10^{-7} *M*, and preincubation of the enzyme with swainsonine does not affect the extent of inhibition. Inhibition is competitive at swainsonine concentrations of below 5 × 10^{-7} *M* and is noncompetitive at higher swainsonine concentrations. Inhibition is largely (65–70%) reversible, as shown by dilution experiments and also in experiments using tritiated swainsonine. It would appear that there is a small irreversible component of inhibition, perhaps due to multiple forms being present in the enzyme used. It should be pointed out that there is some variation in reported values of K_i for lysosomal α-D-mannosidases: for example, K_i values of 6 × 10^{-10} *M* for human-placental acid α-D-mannosidase (*369*), 3 × 10^{-8} *M* for mouse-macrophage acid α-D-mannosidase (*366*), 5 × 10^{-8} *M* for mouse-liver α-mannosidase (*352*), and 8 × 10^{-8} *M* for lysosomal α-D-mannosidase in normal human fibroblasts (*368*) have been reported.

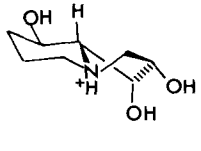
Rat-liver Golgi mannosidase II is also 50% inhibited by swainsonine concentrations of 2 × 10^{-7} *M* (*335*). The inhibition is unaffected by preincubation and is apparently noncompetitive. Only about 30% reversibility can be achieved, though this figure is influenced by swainsonine concentrations during the preincubation phase of the dilution experiments performed. The results obtained suggest two modes of binding for swainsonine, one rapid and irreversible, the other slower, with the extent of reversibility depending on the original swainsonine concentration and time of exposure of enzyme to inhibitor. Again, two forms of Golgi mannosidase II may be involved.

The inhibition of jack-bean α-D-mannosidase is substantially affected by preincubation with swainsonine (*335*). Without preincubation, 50% inhibition requires swainsonine concentrations of 2 × 10^{-6} *M*, but this figure drops to 4 ×

10^{-7} *M* with preincubation. Inhibition is competitive at swainsonine concentrations of 5×10^{-7} *M* or less and is noncompetitive at higher swainsonine concentrations. Inhibition is essentially irreversible; what little reversibility there is, as determined in experiments with tritiated swainsonine, depends on the concentration of swainsonine used during preincubation and on the preincubation time. In these studies, recovery of enzyme activity is inversely proportional to the amount of enzyme-bound inhibitor. Attempts to dissociate the enzyme–inhibitor complex by incubation with mannose or simple mannose derivatives fail [though slow dissociation in the presence of high substrate concentrations has been reported (*334*)], implying that swainsonine binds tightly to the active site. The complex can, however, be dissociated at pH 6 and in the presence of detergent, suggesting that the binding is not covalent. There is also a slight pH effect on inhibition: the alkaloid is a better inhibitor at pH 5.5–6.0 than at pH 4.0–4.5 (*390*). In other studies, K_i values of 5×10^{-8} *M* (*352*) and 5×10^{-7} *M* (*334*) for the enzyme, without and with swainsonine preincubation, respectively, have been reported.

The nature of the swainsonine–enzyme interaction requires some comment. The original proposal that the alkaloid is a specific substrate site-directed inhibitor (*333*) has been tacitly assumed in most later studies, and in fact seemed even more acceptable once the absolute configuration of the alkaloid had been established (*301*). Protonated swainsonine (**364**) has a configurational and conformational similarity to the putative half-chair mannosyl cation (**365**) resulting from enzyme-substrate reaction and would thus appear to meet geometrical requirements for recognition by the active site on the enzyme. In this regard, it is interesting that the synthetic optically active pyrrolidine **366**, deliberately designed as a swainsonine-like inhibitor (*391*), is even more potent than the alkaloid in inhibiting jack-bean α-D-mannosidase (50% inhibition at 5×10^{-7} *M*, versus 8×10^{-6} *M* for swainsonine). Racemic indolizidinediol **332**, effectively an 8-norhydroxyswainsonine, is, in sharp contrast, a very weak inhibitor of liver lysosomal α-D-mannosidase (50% inhibition at 7.5×10^{-3} *M*) (*329*).

A separate but related mechanistic question is that of the uptake and "internalization" of swainsonine by intact cells. Available evidence suggests that while swainsonine is rapidly internalized into human fibroblasts (*368*), the uptake is not mediated by a process that involves recognition of mannose-like



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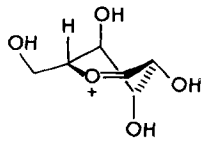
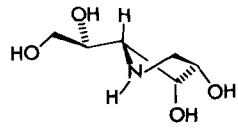


365



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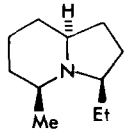
structural features. The rapidity and temperature sensitivity of the uptake, together with the finding that mannose and its 6-phosphate do not interfere with swainsonine uptake, suggest that the alkaloid enters the cells by permeation of plasma membranes rather than by endocytosis. Swainsonine is also rapidly returned to the medium from the intracellular pool when swainsonine-laden cells are washed with alkaloid-free solution. Similar effects have been found using mouse macrophages, although in this case swainsonine uptake and release is slower (*366*).

Finally, the effect of swainsonine and castanospermine on the uptake of glycoproteins has also been investigated. The results obtained depend on the nature of the system used. In rat-liver cells (*371*) and in isolated rat-liver lysosomes (*372*) uptake of glycoprotein appears not to be affected by swainsonine. By contrast, swainsonine in rat pulmonary macrophages (*367*) and both swainsonine and castanospermine in macrophages derived from rat bone marrow (*392*) cause a blockade of receptor-mediated uptake of mannose-terminated glycoproteins. In the latter case this blockade appears to be caused by mannose-terminated glycoproteins engaging mannose receptors, thereby preventing them from functioning further.

X. Addendum

Two new indolizidine alkaloids have recently been isolated (*393*) from two species of *Solenopsis*, a genus of ants in which only pyrrolidine, piperidine, and pyrrolizidine alkaloids had previously been detected (*65,66*). This is an important finding, since it means that the Pharaoh ant is not unique among the Arthropoda in producing indolizidine alkaloids (see Section III,B). Venom from workers of the thief ant *Solenopsis* (*Diplorhoptrum*) *conjurata* contains the new indolizidine **367** as well as five piperidine alkaloids, while indolizidine **368** is the sole alkaloidal component in the venom of queens of a different thief ant, *Solenopsis* (*Diplorhoptrum*) species AA. The relative configuration of **367** was deduced by gas chromatographic and mass spectrometric comparison with synthetic samples of the four diastereomers of 3-ethyl-5-methylindolizidine, the NMR spectra of which allowed unambiguous assignment of the relative stereo-



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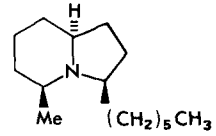

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chemistry. The relative configuration of **368** was also deduced by comparison with a synthetic sample of unequivocal stereochemistry.

A review which overlaps with some of the material in this chapter—specifically, with the synthesis of indolizidine and quinolizidine alkaloids of *Tylophora, Ipomoea,* and *Elaeocarpus* species—was published in 1985 (*394*).

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