DEVELOPMENTS IN THE CHEMISTRY OF DITERPENOID ALKALOIDS[1]

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ABSTRACT.—The occurrence of diterpenoid alkaloids in various plant genera is reviewed. Skeletal types occurring in C_{19}- and C_{20}-diterpenoid alkaloids, as well as characteristic structure features of alkaloids isolated to date, are discussed.

The observation that the normal-type oxazolidine ring-containing C_{20}-diterpenoid alkaloids, e.g. atisine, veatchine, and garryfoline, exist as a mixture of C(20)-epimers led to an investigation of the behavior of the carbinolamine ether linkage (N–C–O) in these alkaloids. Refluxing ajaconine in methanol afforded a new compound, 7α-hydroxyisoatisine. A mechanism for this unusual rearrangement of ajaconine into 7α-hydroxyisoatisine, via a "disfavored" 5-endo-trig ring closure, is proposed. Veatchine acetate in methanol at room temperature hydrolyzes to veatchine without using any external base. To clarify the nature of this unusual hydrolysis, a rearrangement of 7α-acetoxyatisine acetate in methanol was examined. 7α-Acetoxyatisine acetate in methanol at room temperature yielded a mixture of 7α-hydroxyisoatisine, ajaconine, and their C(15) acetates. A mechanism for this unusual rearrangement is discussed. Treatment of ethylene oxide, glycidol, and oxitane with various imine derivatives of C_{20}-diterpenoid alkaloids affords 5 and 6-membered cyclic carbinolamine ethers. These results and the earlier mentioned rearrangement of ajaconine are discussed in terms of Baldwin's cyclization rules and several apparent exceptions are noted.

The earlier assignments of stereochemistry of the C(16)-methyl group and the oxazolidine ring at C(20) in cuauchichicine have been revised on the basis of ^{13}C nmr spectral analysis. These assignments have been confirmed by a single crystal x-ray analysis of cuauchichicine. Cuauchichicine is the first normal-type oxazolidine ring-containing C_{20}-diterpenoid alkaloid which does not exist as a pair of epimers at C(20). The structure previously assigned to (−)-"β"-dihydrokaurene has been confirmed by X-ray crystallography. Consequently, during the correlation of cuauchichicine with (−)-"β"-dihydrokaurene, an unanticipated epimerization must have occurred in the first Wolff-Kishner reduction step.

The acid-catalyzed rearrangement of garryfoline to cuauchichicine has been studied by deuterium labeling to establish the mechanism of the reaction. Treatment of isogarryfoline with 10% DCl in D_2O at room temperature yielded a product with a C(16αD)-βCH$_2$D group, a fact which demonstrates that a 15→16 hydride shift mechanism is not involved in this rearrangement. A mechanism involving formation of an enol is suggested for this acid-catalyzed rearrangement of garryfoline to cuauchichicine.

A new one-step method for degradation of the oxazolidine ring of C_{20}-diterpenoid alkaloids to their corresponding imine derivatives is described. A new simple method using active manganese dioxide for converting the N-CH$_2$-CH$_2$OH group-containing alkaloids into their isooxazolidine ring-containing alkaloids is reported. This method has advantages over the old methods in that it is very simple and uses an inexpensive and non-toxic reagent.

The diterpenoid nitrogenous bases isolated from the plant families Compositae, Escalloniaceae, Garryaceae, Ranunculaceae, and Rosaceae have long been of interest because of their pharmacological properties, complex structures, and interesting chemistry. Most of the alkaloids have been isolated from species of *Aconitum* and *Delphinium* (Ranunculaceae), and *Garrya* (Garryaceae). Recently diterpenoid alkaloids have been isolated from *Spiraea* (Rosaceae) species and from two *Anopterus* (Escalloniaceae) species.

Many of the alkaloids isolated from these species are highly toxic. Extracts

[1]This paper was presented as a plenary lecture at the Twentieth Annual Meeting of the American Society of Pharmacognosy at Purdue University, West Lafayette, Indiana, July 30–August 3, 1979. Parts of this paper were also presented as a plenary lecture at the IUPAC 11th International Symposium on the Chemistry of Natural Products, Golden Sands, Bulgaria, September 17–23, 1978.

PLANT GENERA CONTAINING DITERPENOID ALKALOIDS

Compositae
Inula royleana

Escalloniaceae
Anopterus glandulosus
Anopterus macleayanus

Garryaceae
Garrya laurifolia
Garrya ovata var. lindheimeri
Garrya veatchii

Ranunculaceae
Aconitum species
Consolida ambigua
Delphinium species

Rosaceae
Spiraea species

PLATE 1

of *Aconitum* species were employed in ancient times as animal poisons, for treatment of neuralgia, hypertension, gout, rheumatism and even toothache. The extracts were also used in the mediaeval trials by ordeal and for tipping arrows to kill both men and beasts.

The diterpenoid alkaloids may be divided into two broad categories: those based on a hexacyclic C_{19}-skeleton (1), and those based on C_{20}-skeletons (2, 3). The three different C_{20}-skeletons isolated differ in the attachment of the C(15)–C(16) bridge at either C(11), C(12), or C(13). Biogenetically, these bases are probably derived from tetracyclic or pentacyclic diterpenes in which the nitrogen atom of methylamine, ethylamine, or β-aminoethanol is linked to C(17) and C(19) in the C_{19}-diterpenoid skeleton and to C(19) and C(20) in the C_{20}-diterpenoid skeleton to form a substituted piperidine ring.

DITERPENOID SKELETA

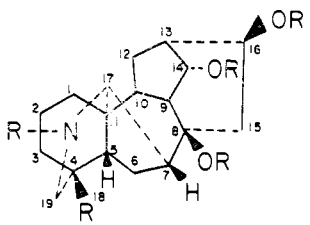
C_{19}-SKELETON C_{20}-SKELETON

PLATE 2

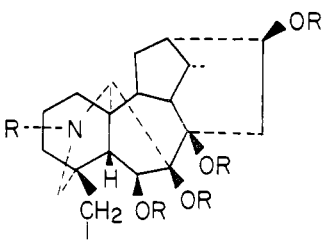
The C_{19}-diterpenoid alkaloids, commonly called *aconitines*, may be subdivided in four groups based on four different skeleta. These groups are defined as:

1. *Aconitum-type.* These alkaloids possess the skeleton of aconitine, in which position C(7) is not oxygenated or substituted by any other group except hydrogen.
2. *Lycoctonine-type.* These alkaloids possess the skeleton of lycoctonine, in which C(7) is always oxygenated.
3. *Pyrodelphinine-type.* These alkaloids possess a modified aconitine skeleton with a double bond between C(8) and C(15). The pyro-type derivatives have been known for many years as pyrolytic degradation products of the alkaloids. Within the last few years they have been isolated in our laboratory as naturally occurring alkaloids from the plant, *Aconitum falconeri.*
4. *Heteratisine-type.* These alkaloids possess the skeleton of heteratisine, in which a lactone moiety is present. The heteratisine skeleton obviously can be derived from the aconitine-type by some kind of an enzymatic oxidation of the Baeyer-Villiger type on a C(14)-ketone, with resultant expansion of the five-membered ring C to a six-membered lactone.

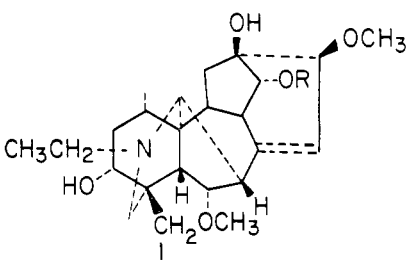
C_{19}-DITERPENOID SKELETA



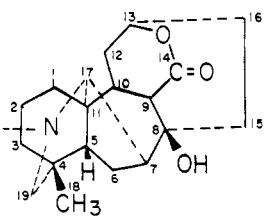
ACONITINE-TYPE
R = H, CH_3, CH_2OCH_3, OH



LYCOCTONINE-TYPE



PYRO-TYPE

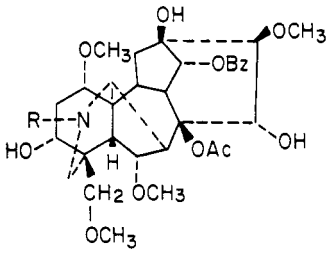


HETERATISINE

PLATE 3

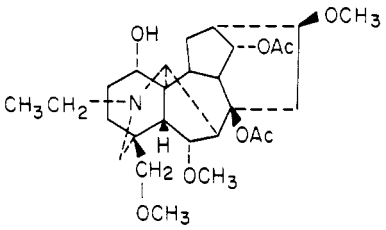
Typical aconitine-type alkaloids are aconitine, mesaconitine, delphisine, aconosine and talatizidine. All these compounds are modeled on the same skeleton and lack any substituent at C(7). The most highly substituted compounds, particularly those containing ester groups, manifest the highest toxicity. Indeed aconitine is among one of the most toxic compounds of plant origin known. Saponification of aconitine furnishes the alkamine, aconine, which is only 1/500 as toxic as aconitine itself.

ACONITINE-TYPE ALKALOIDS

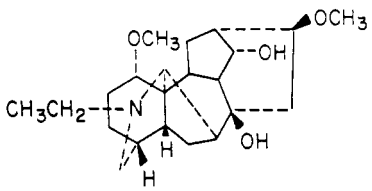


R = $-CH_2-CH_3$ ACONITINE

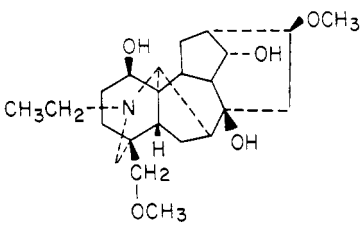
R = $-CH_3$ MESACONITINE



DELPHISINE



ACONOSINE



TALATIZIDINE

PLATE 4

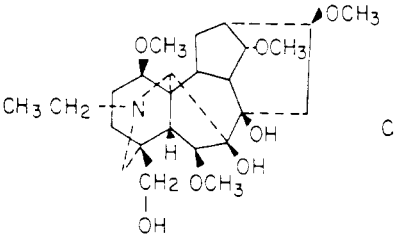
Lycoctonine-type alkaloids vary widely in the substitution patterns found. As mentioned previously, they are characterized by oxygen substitution at C(7). This substitution may be in the form of hydroxyl groups, methylenedioxy groups or methoxyl groups. A rather complicated type illustrated by avadharidine involves an anthranilic acid moiety attached to C(18). Both simple and substituted anthranilic acid derivatives occur in nature, e.g., inuline and ajacine.

The C_{20}-diterpenoid alkaloids consist of a series of aminoalcohols modeled on a C_{20}-skeleton. These compounds are usually not extensively oxygenated. Some occur in the plant as monoesters of benzoic or acetic acid. These relatively nontoxic alkamines are based on either an atisine skeleton, involving a 6,6,6,6-tetracyclic terpene, or on a veatchine or delnudine skeleton, involving a 6,6,6,5-tetracyclic terpene. Compounds based on the atisine model (which cannot be dissected in an isoprenoid fashion) appear in alkaloids isolated from *Aconitum*, *Delphinium*, and *Spiraea* species. A recently discovered C_{20}-diterpenoid skeleton occurs in delnudine, from *Delphinium denudatum*.

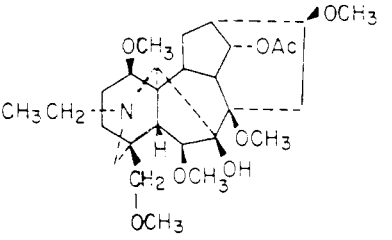
Typical atisine-type alkaloids are atisine, denudatine and ajaconine, all of which are characterized by a 2,2,2-bicyclooctane system. Denudatine is unusual in possessing an extra bond between C(7) and C(20). In ajaconine these two positions are bridged with an oxide ring.

In the case of hetidine and spiradine-D, an extra bridge exists between C(20) and C(14). The bases hetisine and kobusine are each characterized by a N–C(6) bond as well as a C(14)–C(20) bond. Further variations on this theme are found in spiradine-A and vakognavine. The case of vakognavine, is a very interesting one, for it is the first diterpenoid alkaloid in which the heterocyclic ring has been broken between N–C(19) to afford an aldehyde on C(4).

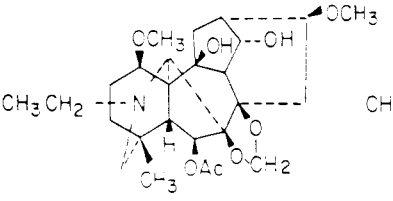
LYCOCTONINE-TYPE ALKALOIDS



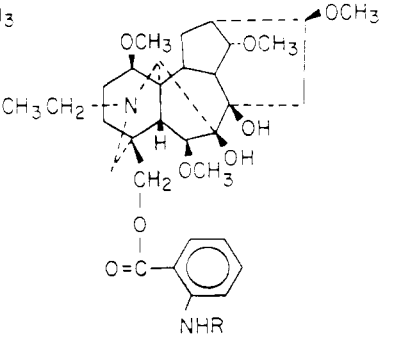
LYCOCTONINE



AMBIGUINE



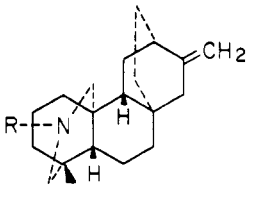
DICTYOCARPINE



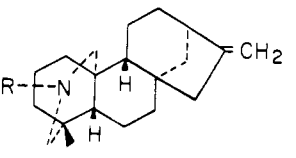
R = H	INULINE
R = $COCH_3$	AJACINE
R = $COCH_2CH_2CONH_2$	AVADHARIDINE

PLATE 5

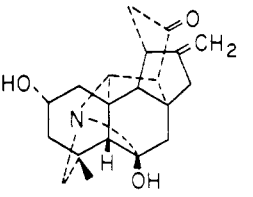
C_{20}-DITERPENOID SKELETA



ATISINE-TYPE



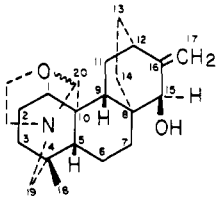
VEATCHINE-TYPE



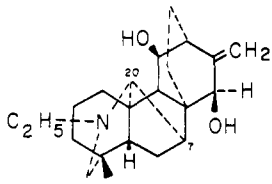
DELNUDINE

PLATE 6

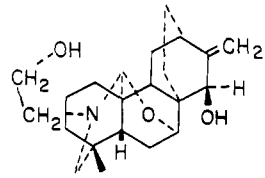
ATISINE-TYPE ALKALOIDS



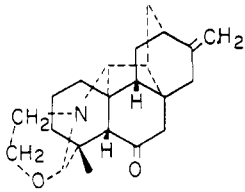
ATISINE



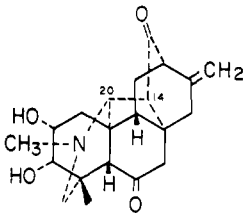
DENUDATINE



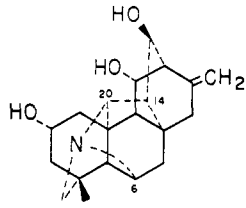
AJACONINE



SPIRADINE-D



HETIDINE



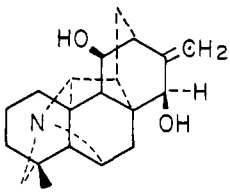
HETISINE

PLATE 7

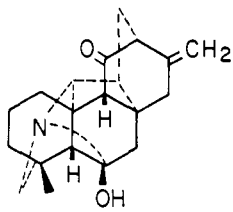
The number of the veatchine-type alkaloids with a 6,6,6,5-tetracyclic skeleton, is much smaller than the atisine-type. Representative alkaloids are veatchine, garryfoline, ovatine, songoramine, napelline and lucidusculine. The more complex members of this series contain bridging between C(7) and C(20). An unusual veatchine-type alkaloid is lindheimerine which contains an imine group.

The alkaloids anopterine and anopterimine are representative of a series of alkaloids recently isolated from two Australian *Anopterus* species. They are unusual because of the bridging between C(14) and C(20) as well as the presence of tiglic acid groups at C(11) and C(12).

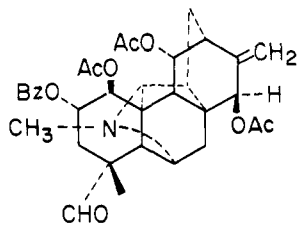
ATISINE-TYPE ALKALOIDS



KOBUSINE



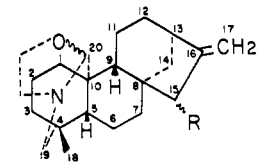
SPIRADINE-A



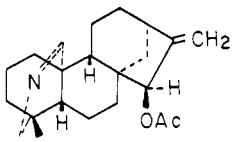
VAKOGNAVINE

PLATE 8

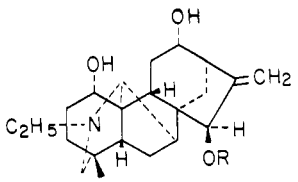
VEATCHINE-TYPE ALKALOIDS



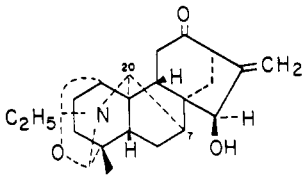
R = ---OH VEATCHINE
R = ▬ OH GARRYFOLINE
R = ▬ OAc OVATINE



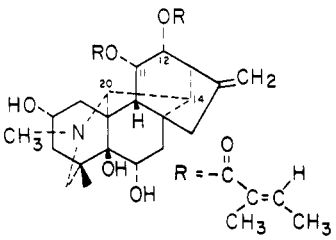
LINDHEIMERINE



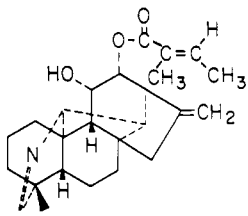
R=H NAPELLINE
R=Ac LUCIDUSCULINE



SONGORAMINE



ANOPTERINE

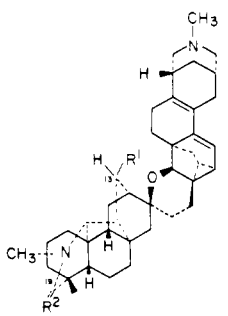


ANOPTERIMINE

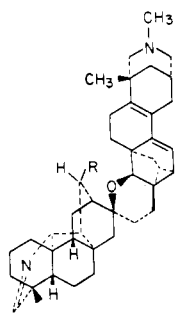
PLATE 9

The largest and most complicated "diterpenoid" alkaloids are the bis-diterpenoid alkaloids, which we have isolated from the mother liquors obtained from the seeds of *Delphinium staphisagria* (4). Eight compounds have been isolated with the structures shown here. The variations include an amide group at C(19) as in staphigine and staphirine, an imine group as in staphinine and staphimine, and finally, an oxazolidine ring as in staphisagnine and staphisagrine. It is interesting to note that these alkaloids occur as pairs of C(13)- demethoxy- and methoxy- derivatives.

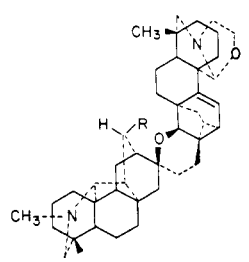
BIS-DITERPENOID ALKALOIDS



$R^1 = OCH_3$; $R^2 = H_2$ STAPHISINE
$R^1 = H$; $R^2 = H_2$ STAPHIDINE
$R^1 = OCH_3$; $R^2 = O$ STAPHIGINE
$R^1 = H$; $R^2 = O$ STAPHIRINE



R= OCH_3 STAPHININE
R= H STAPHIMINE

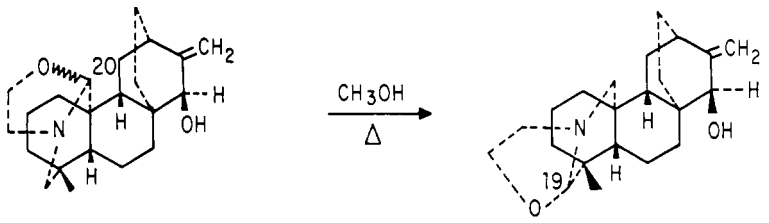


R= OCH_3 STAPHISAGNINE
R= H STAPHISAGRINE

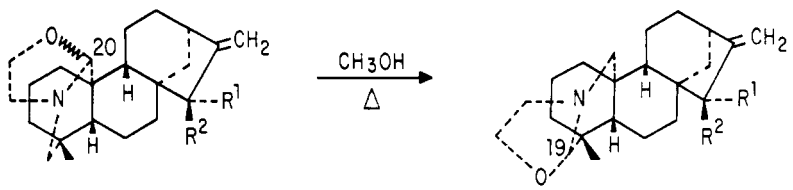
PLATE 10

The subject of the remainder of this paper will be recent developments in the chemistry of the C_{20}-diterpenoid alkaloids. The pioneering studies in this field were done by Walter Jacobs and his colleagues at the Rockefeller Institute and by Karel Wiesner and his group at the University of New Brunswick.

C_{20}-diterpenoid alkaloids (2, 3) containing the normal-type oxazolidine ring [attached at C(20)] are highly basic (pKa 11.5–12.5) and are known to rearrange to iso-type oxazolidine ring-containing [attached at C(19)] compounds by treatment with alcoholic base. Jacobs, who was the first to discover this isomerization, found that refluxing a solution of atisine (**1**) in methanolic NaOH afforded a high yield of isoatisine (**2**). We have found that the external base is unnecessary and that even simple refluxing in methanol will effect isomerization, e.g., veatchine (**3**)→garryine (**4**); garryfoline (**5**)→isogarryfoline (**6**). The very basic atisine is completely isomerized to isoatisine in methanol at room temperature in 24 hours. The rate of isomerization is dependent on the concentration of substrate and on the pKa. In contrast, the less basic veatchine and garryfoline are more stable in methanol at room temperature and require an extended time for isomerization.



1 ATISINE (pKa 12.5) 2 ISOATISINE (pKa 10.3)



3 R^1 = OH, R^2 = H VETACHINE (pKa 11.5) 4 R^1 = OH, R^2 = H GARRYINE (pKa 8.7)

5 R^1 = H, R^2 = OH GARRYFOLINE (pKa 11.8) 6 R^1 = H, R^2 = OH ISOGARRYFOLINE (pKa 8.6)

PLATE 11

The *normal*-type and *iso*-type oxazolidine ring-containing alkaloids form the corresponding ternary immonium salts (Schiff salts) by treatment with hydrochloric acid. For example, atisine (**1**)→atisinium chloride (**7**) and isoatisine (**2**)→isoatisinium chloride (**8**). The oxazolidine ring of these alkaloids can be regenerated from the corresponding immonium salts by treatment with cold base, e.g., atisinium chloride→atisine and isoatisinium chloride→isoatisine. The normal-type immonium salts (i.e., those with double bond between N and C(20)) are more stable in refluxing polar solvents than the iso-type salts. One can quantitatively

isomerize isoatisinium chloride to atisinium chloride by refluxing in polar solvents, such as DMSO, DMF, and high boiling alcohols. Thus, depending on conditions one can interconvert atisine and isoatisine or veatchine and garryine.

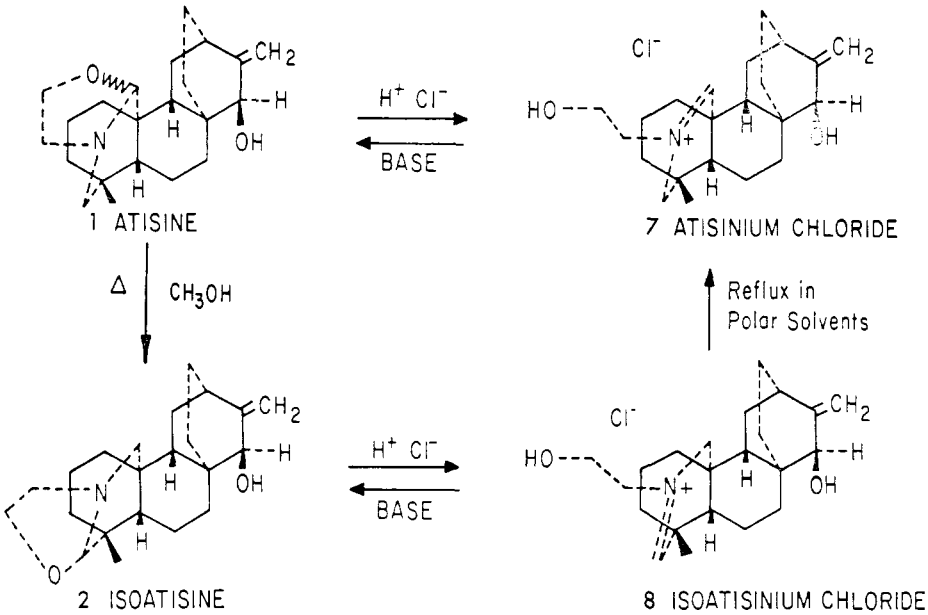
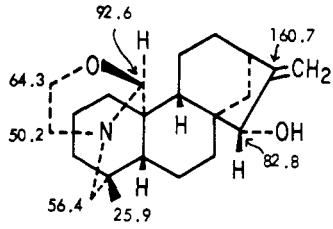


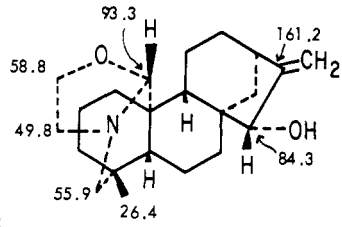
PLATE 12

Recently we observed with the aid of ^{13}C nmr spectroscopy that the normal-type oxazolidine ring-containing alkaloids exist as a mixture of C(20) epimers in solution (5, 6). The carbon-13 nmr spectrum of veatchine (**3A** major and **3B** minor) and of atisine (**1A** major and **1B** minor) in solution clearly demonstrates that these alkaloids consist of a mixture of C(20) epimers, for there is a doubling of certain ^{13}C nmr peaks of the oxazolidine and the piperidine rings. The X-ray analysis (7) of crystalline veatchine demonstrates the coexistence of both epimers (**3A** and **3B**) in the same crystal.

Several years ago Baldwin described a set of rules for predicting the facility of ring-forming reactions (8). In trigonal systems, 3- to 5-endo-trig closures are disfavored, while 6- and 7-endo-trig closures are favored as summarized below. In this paper we present the results of our studies on 5- and 6-endo-trig cyclizations involving nucleophilic attack of oxygen on immonium salts derived from C_{20}-diterpenoid alkaloids.

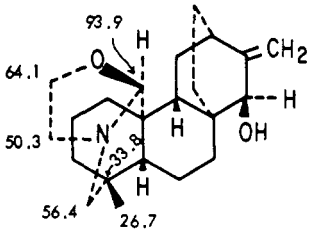
Atisine, an amorphous base (pKa 12.5), is isolated as the "hydrochloride," a compound which is really a ternary immonium salt. The structure and absolute configuration of this compound, atisinium chloride (**7**), has been established by X-ray crystallography (7). As mentioned previously, atisine can be regenerated from atisinium chloride by treatment with cold base. The fact that the oxazolidine ring closes in two different directions to afford a pair of epimers suggests the operation of unusual constraints on the mechanism of ring closure. Examination of a model of atisinium chloride reveals that closure of the oxazolidine ring on the pro-20R side of the plane is sterically hindered, especially by H(14), which is

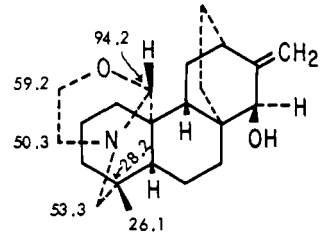




VEATCHINE EPIMERS

3A 3B





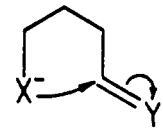
ATISINE EPIMERS

1A 1B

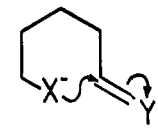
PLATE 13

situated almost directly over C(20). And access to the pro-20S side of the bond is almost equally restricted by H(2). It is interesting to note that cyclization of the ternary immonium salt to form the five-membered oxazolidine ring is an example of the "disfavored" 5-endo-trig ring closure. Yet this ring closure is a very facile one. Other examples of such "disfavored" 5-endo-trig closures are the conversion of isoatisinium chloride (**8**) to isoatisine (**2**), of veatchinium chloride to veatchine, and garryfoline hydrochloride to garryfoline. The structures of all

3- TO 7-EXO-TRIG RING CLOSURE-FAVORED PROCESS



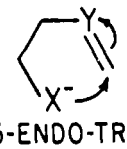
5-EXO-TRIG



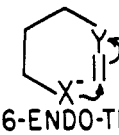
6-EXO-TRIG

3- TO 5-ENDO-TRIG RING CLOSURE-DISFAVORED PROCESS

6- TO 7-ENDO-TRIG RING CLOSURE-FAVORED PROCESS



5-ENDO-TRIG DISFAVORED



6-ENDO-TRIG FAVORED

PLATE 14

compounds mentioned have been established unambiguously by ^{13}C nmr spectroscopy and/or X-ray crystallography.

These 5-endo-trigonal cyclizations prompted us to examine the formation and behavior of 5- and 6-membered carbonolamine ethers (N–C–O) in various diterpenoid alkaloids. In 1957 Marion and his colleagues (9) reported the prepara-

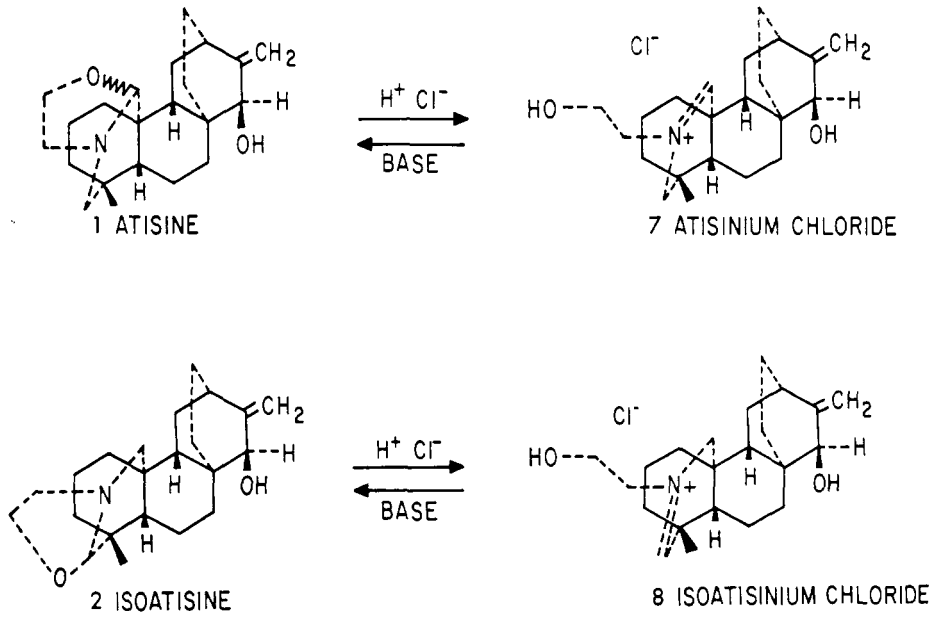


PLATE 15

tion of several 6-membered ring-containing carbinolamine ethers from C_{19}-diterpenoid alkaloid derivatives. Subsequently we prepared (10) dehydrocondelphine (**9**) from condelphine by treatment with aqueous potassium permanganate. Dehydrocondelphine is a weak base which protonates on the nitrogen to yield an $-\overset{\oplus}{N}H$-type salt (**10**) rather than the Schiff salt (**11**). This behavior is not because of a special stability of 6-membered carbinolamine ethers, but to the prohibitively high energy of the transition state for the opening of the ether (**9**) to the quaternary Schiff salt (**11**). Examination of the model for **11** indicates that this Schiff salt cannot close easily to the ether for steric and vectorial reasons. Application of the principle of microscopic reversibility suggests that the transition state for the O-protonation and opening of dehydrocondelphine to the Schiff salt would be very unfavorable.

The oxazolidine rings (**12**) of C_{20}-diterpenoid alkaloids in polar solvents are in equilibrium with the corresponding quaternary Schiff salts (**13**) and consequently are strong bases. Examination of a model of such a Schiff salt indicates that it is vectorially poorly arranged for ring closure. Though such a cyclization is "disfavored" according to Baldwin's rules, experimental evidence demonstrates (11) that an equilibrium does indeed exist between the oxazolidine (**12**) and the Schiff salt (**13**). It appears therefore that the Baldwin rules are less prohibitive for quarternary immonium salts bearing a full charge on the nitrogen. These salts

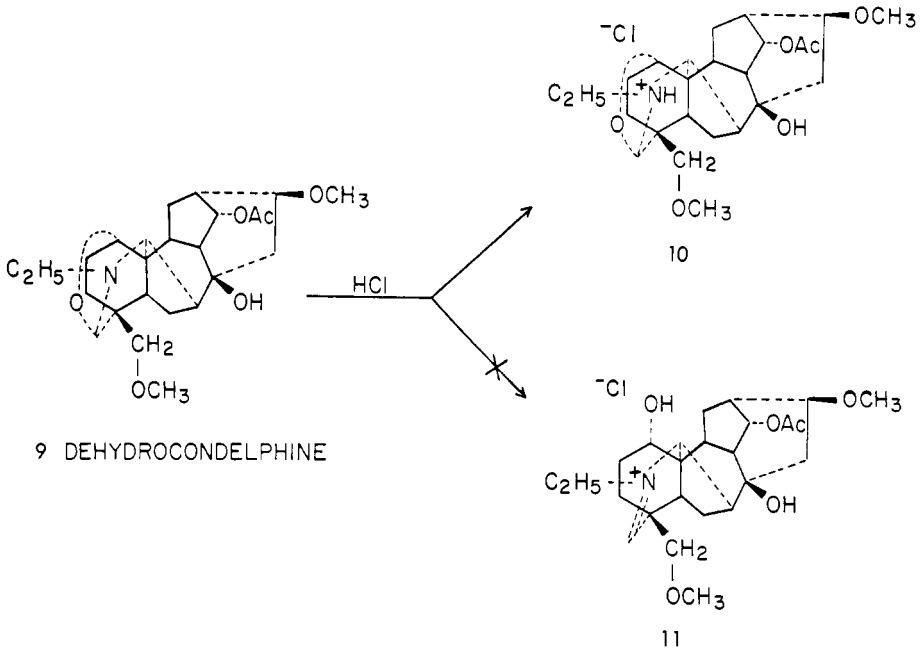


PLATE 16

resemble carbocations to a greater extent than uncharged groups. Clearly, an attack on a carbocation (**14**) will exhibit less vectorial specificity than an attack on, say, a carbonyl group (**15**). Because the quaternary immonium salts (**13**) are intermediate between an uncharged group and a carbocation, the equilibrium: oxazolidine (**12**)⇄Schiff salt (**13**) is probably slower than a ring closure which is not disfavored.

Ajaconine (**16**), the major alkaloid of the seeds of the garden larkspur (*Delphinium ajacus*=*Consolida ambigua*), was the first example of a C_{20}-diterpenoid alkaloid containing an internal carbinolamine ether linkage between C(7) and C(20). An attempt by Canadian workers to rearrange ajaconine in methanolic base resulted in a mixture which was not studied further (12). On the basis of chemical reactions and hydrogen-interaction theory, the Canadian workers concluded (12) that a driving force for rearrangement of the internal carinolamine ether is absent. They also mentioned that an entropy factor must favor the internal ether over the oxazolidine ring and thus the C(7)–C(20) ethers should be more stable than the oxazolidine ring derivatives.

Ajaconine (pKa 11.8) forms a ternary immonium salt (**17**) instead of a protonated ($-\overset{+}{N}H$) type salt by treatment with hydrochloric acid. The structure of ajaconium chloride (**17**) was confirmed by comparison of the ^{13}C nmr spectrum of ajaconium chloride with that of atisinium chloride. Treatment of the immonium salt (**17**) with base regenerates ajaconine (**16**) instead of 7α-hydroxyatisine (**18**) which would parallel the formation of atisine (**1**) from atisinium chloride (**7**).

The transformation of ajaconium chloride to ajaconine is an example of a 6-exo-trig ring closure, which is a "favored" process according to Baldwin's rule for ring closure. However, as already pointed out, ring closure of atisinium

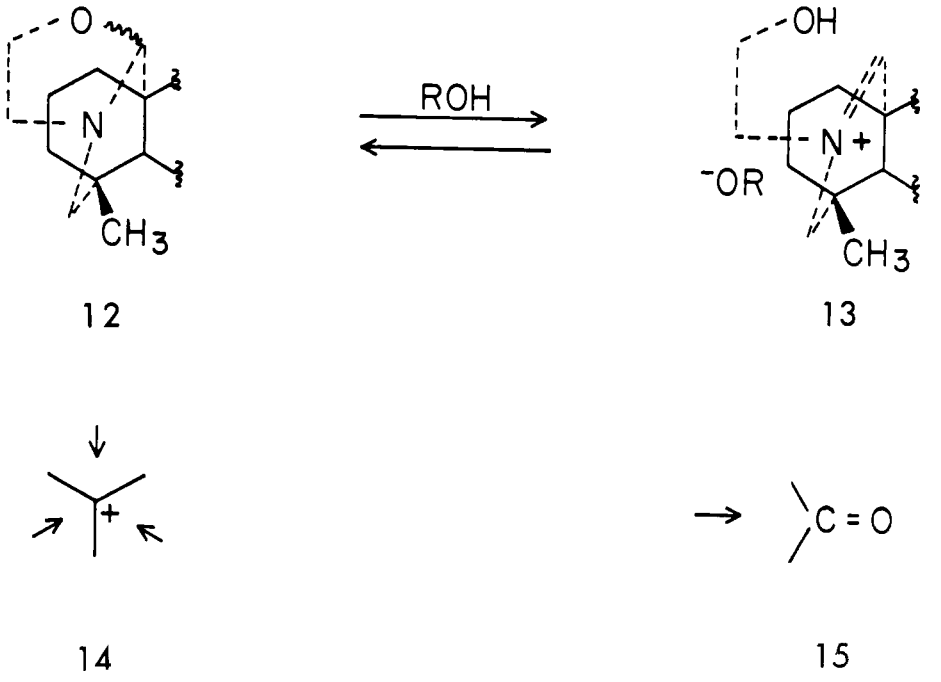


PLATE 17

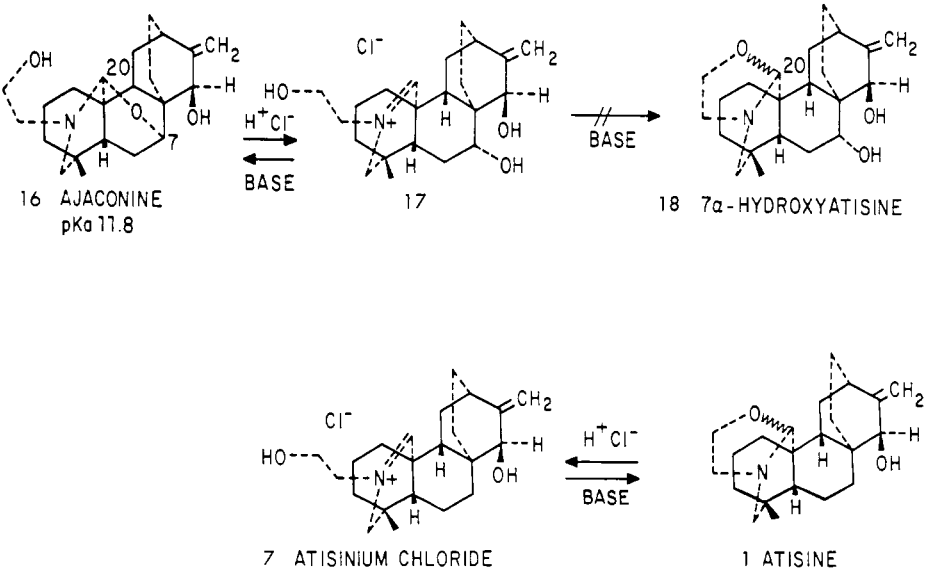
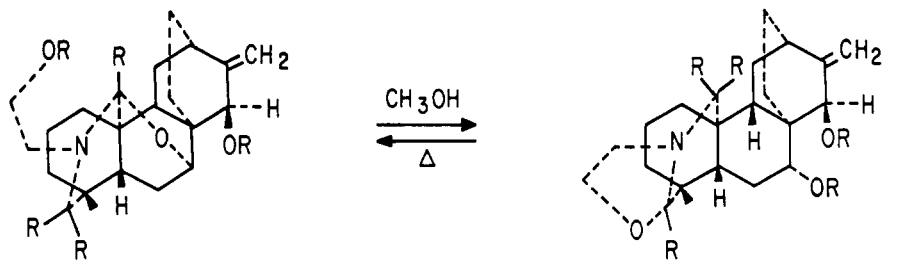


PLATE 18

chloride to atisine is a "disfavored" 5-endo-trig closure, and represents an apparent exception to Baldwin's rules.

The results obtained by the ^{13}C nmr study of ajaconine in non-ionic and ionic solvents indicate that in hydrogen-bonding type solvents the ether linkage of ajaconine ionizes and covalent solvation occurs (13). This observation accounts for the formation of the quaternary Schiff salt, with the resultant high pKa value (11.8) of ajaconine in aqueous solution—behavior which parallels that of atisine (pKa 12.5) and veatchine (pKa 11.5) (11). These results suggest that ajaconine may be rearranged by refluxing in an ionic solvent to a compound in which the C(7)–C(20) ether linkage is absent. This idea prompted us to investigate the rearrangement as well as the behavior of the carbinolamine ether linkage of ajaconine in ionic solvents.

Refluxing ajaconine in methanol or aqueous methanol afforded a mixture from which a new compound identified as 7α-hydroxyisoatisine (**19**) by proton and ^{13}C nmr spectra (13). When ajaconine was refluxed with deuterated methanol under nitrogen a mixture of C(19), (20)-deuterated ajaconine (**20**) and C(19), (20)-deuterated 7α-hydroxyisoatisine (**21**) was formed. Incorporation of deuterium in **20** and **21** indicates that ajaconine ionizes and rearranges to 7α-hydroxyisoatisine and that these two species are in equilibrium in refluxing methanol.



16 R=H AJACONINE
20 R=D

19 R=H 7α-HYDROXYISOATISINE
21 R=D

PLATE 19

A few comments on a mechanism for the rearrangement of ajaconine into 7α-hydroxyisoatisine in methanol are in order. In basic solution the normal-type immonium species **22** closes to ajaconine (**16**) and not to 7α-hydroxyatisine (**18**), because the latter closure, being a "disfavored" 5-endo-trig process, is much slower than the "favored" 6-endo-trig closure of the normal-type immonium species to ajaconine. However, species **22** undergoes an isomerization to the iso-immonium salt **23**, a reaction which is known in the case of atisine→isoatisine and veatchine→garryine. The intermediate **23** closes to 7α-hydroxyisoatisine (**19**), in spite of the closure being partially disfavored, because there is no faster process in competition with this ring closure. This rearrangement of ajaconine into 7α-hydroxyisoatisine is an unusual example of a "disfavored" 5-endo-trig process.

An interesting finding is that veatchine acetate (**24**) can be converted into veatchine (**3**) in methanol at room temperature *without using an external base.* This hydrolysis suggests participation of methoxide ion which is formed by opening of the oxazolidine ring by methanol. Diterpenoid alkaloid derivatives lacking the oxazolidine ring, such as dihydroatisine diacetate (pKa=7.3), and veatchine azomethine acetate, do not hydrolyze in methanol under these conditions.

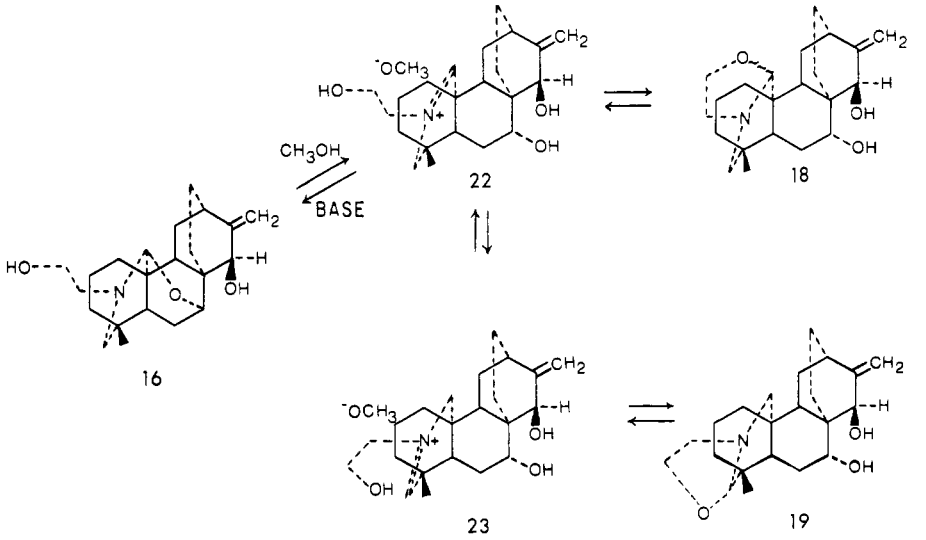


PLATE 20

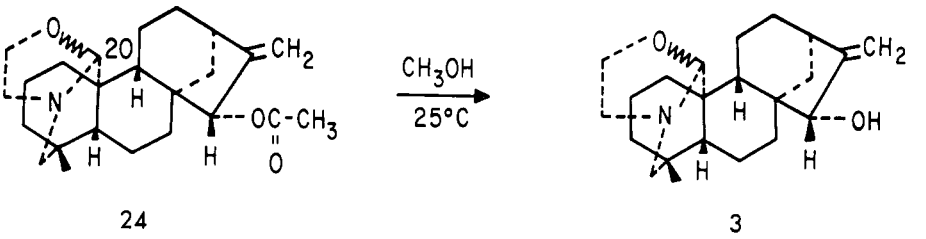


PLATE 21

This unexpected hydrolysis of veatchine acetate to veatchine suggested an investigation of the rearrangement of 7α-acetoxyatisine acetate (**25**). This compound was prepared from ajaconine (**16**) via the corresponding imine. Treatment of ajaconine with acetic anhydride and pyridine at 25° afforded the triacetate salt (**26**). A Hofmann-type degradation of the immonium salt was achieved by refluxing it in chloroform to give the imine (**27**) in a yield of 95%. The imine intermediate when stirred with ethylene oxide and acetic acid for sixty hours at room temperature, afforded 7α-acetoxyatisine acetate (**25**) in quantitative yield.

When 7α-acetoxyatisine acetate was stirred with methanol at room temperature, a mixture of 7α-hydroxyisoatisine (**19**), ajaconine, and their C(15) acetates (**28** and **29**) was formed. No starting material could be detected after 36 hours. The formation of these products can be explained on the basis of opening of the oxazolidine ring by methanol and formation of methoxide ion. The latter hydrolyzes the 7-acetate group of 7-acetoxyatisine acetate. The resulting 7-oxygen anion can close on the immonium species at C(20) to form ajaconine. And of course, as already mentioned, the normal-type oxazolidine ring derivatives isomerize readily in methanol to the iso-type oxazolidines.

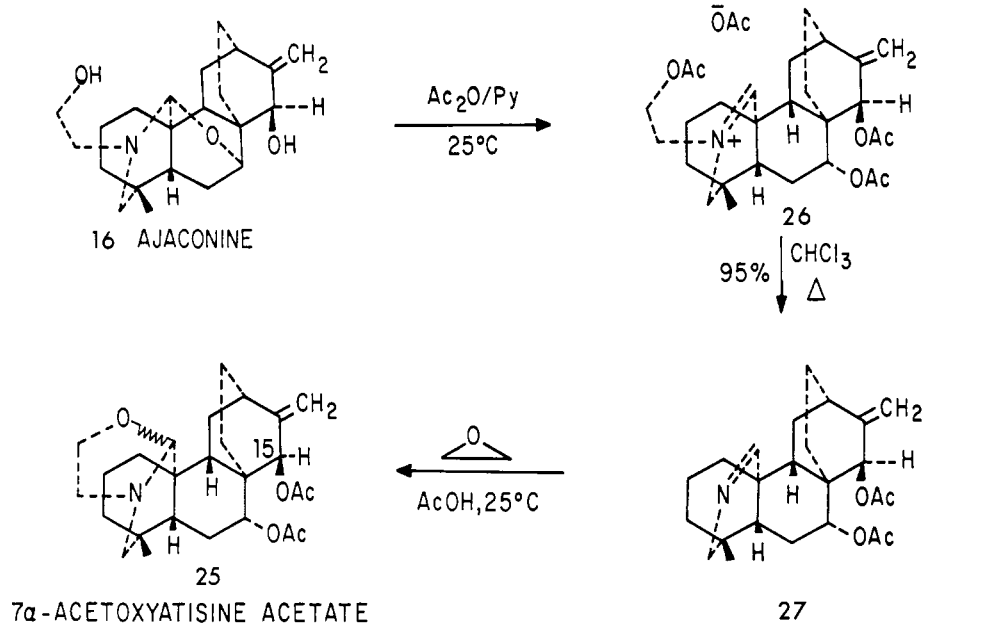


PLATE 22

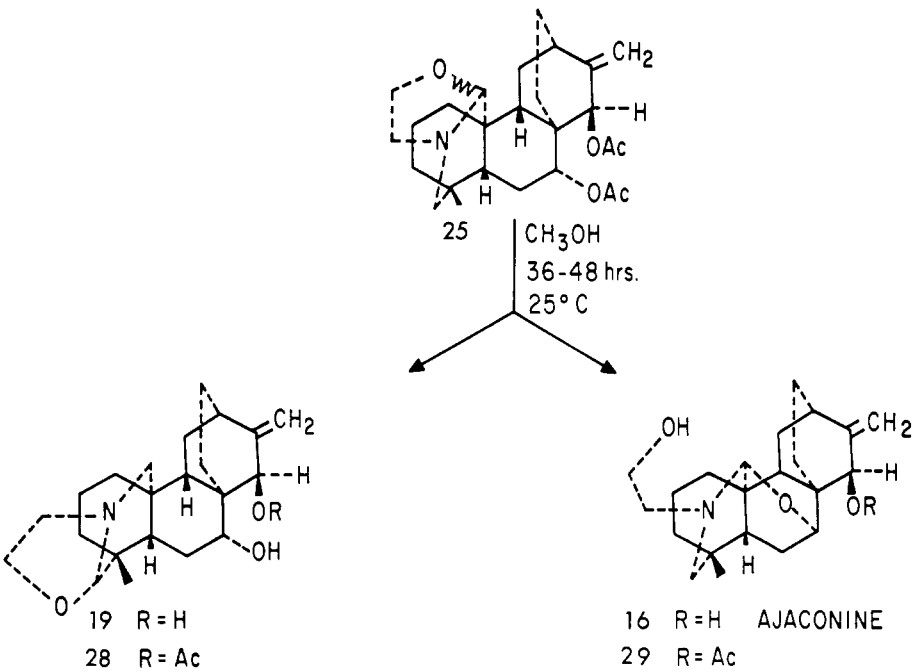


PLATE 23

An interesting reaction involves treatment of alkaloid imine derivatives with ethylene oxide in acetic acid or methanol to give the oxazolidine ring-containing alkaloids in almost quantitative yield (14). Treatment of lindheimerine (**30**) with ethylene oxide in acetic acid at room temperature afforded ovatine (**31**) in a yield of 98%. Similarly, the azomethine acetate (**32**) of veatchine upon treatment with ethylene oxide in acetic acid afforded veatchine acetate (**24**) in a yield of 97%. It is worth noting that formation of the oxazolidine ring in these compounds occurs via a "disfavored" 5-endo-trig process.

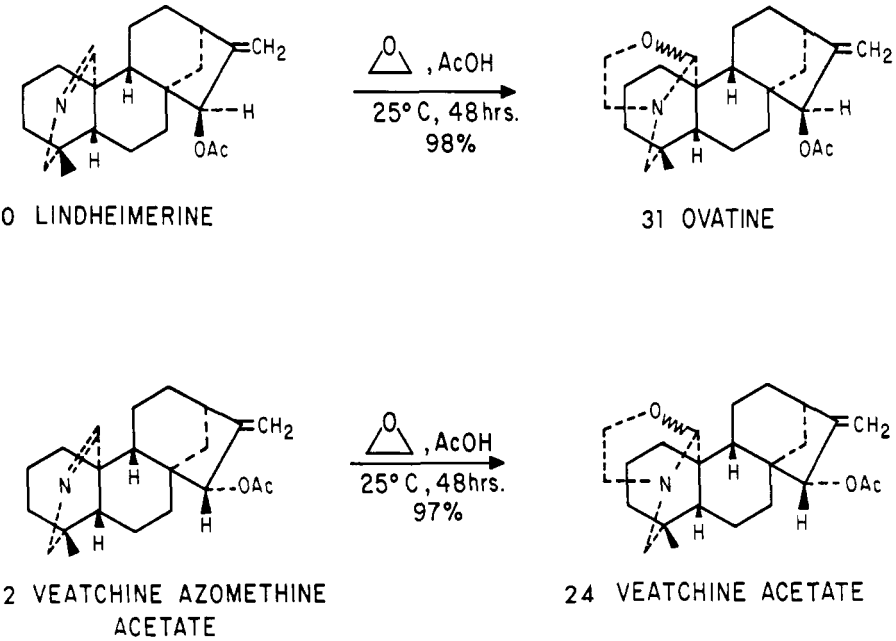


PLATE 24

When methanol was used instead of acetic acid as a solvent for the same reaction, lindheimerine (**30**), afforded ovatine (**31**) in 90% yield within 3 hours; under longer reaction times, lindheimerine afforded only garryfoline (**5**) (96% yield). Comparable results were obtained with veatchine azomethine acetate (**32**). Under short reaction times, veatchine acetate (**24**), was formed, and under long reaction times, veatchine (**3**) was produced.

When atisine azomethine acetate (**33**) was treated with ethylene oxide in methanol, either atisine acetate (**34**), atisine (**1**), or isoatisine (**2**) resulted, depending on the reaction time. Thus in 3 hours atisine acetate can be isolated; in 12 hours a mixture of atisine and isoatisine is produced; and in 24 hours only isoatisine is produced. Under the longer reaction times, hydrolysis of the C(15)-acetate as well as the isomerization of the oxazolidine ring takes place.

Unlike ethylene oxide, oxitane reacts very slowly with the alkaloid imine derivatives to give low yields of tetrahydro-1,3-oxazine derivatives. As an example, veatchine azomethine acetate (**32**) in acetic acid at 50° gives the 6-membered carbinolamine ether, homoveatchine acetate (**35**), in 25% yield. The latter was isolated as a mixture of C(20)-epimers. These results prompted the design of a

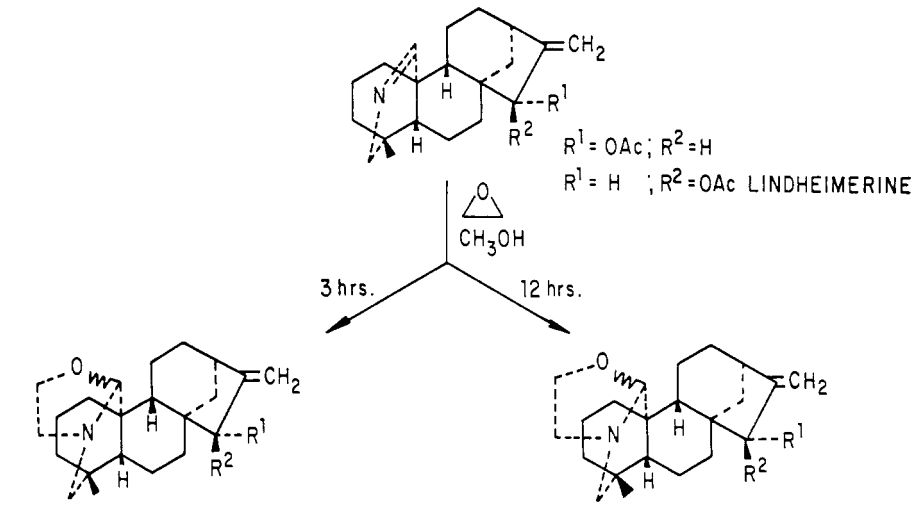


PLATE 25

reaction with imines which might proceed to form either a 5- or 6-membered heterocyclic ring. Treatment of veatchine azomethine acetate with glycidol afforded **36** as the major product. The presence of oxazolidine **37** was not detected in the reaction mixture. The structure of **36** was established by ^{13}C nmr spectroscopy and confirmed by X-ray crystallography. The minor products of the reaction consisted of a mixture of **38** and **39**, as indicated by ^{13}C nmr spectroscopy.

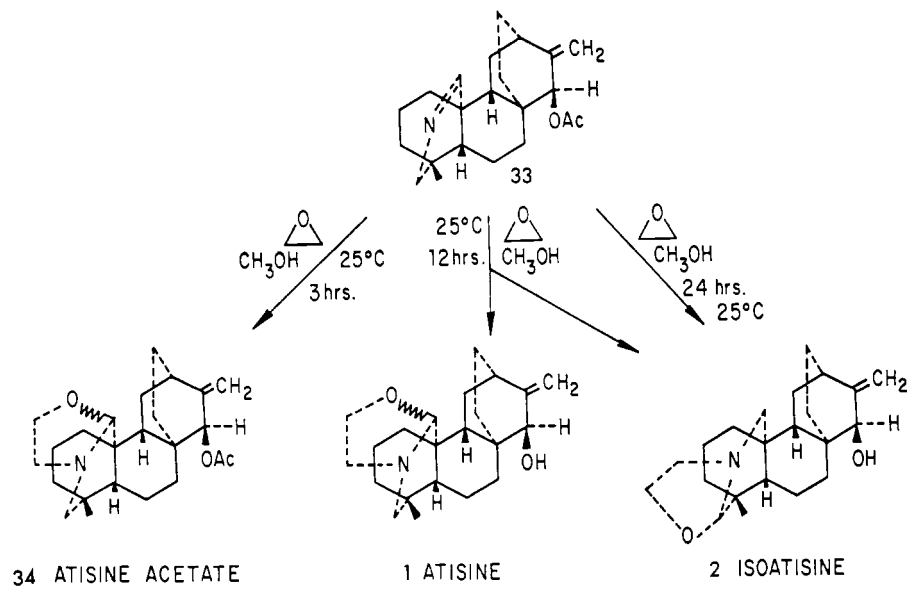
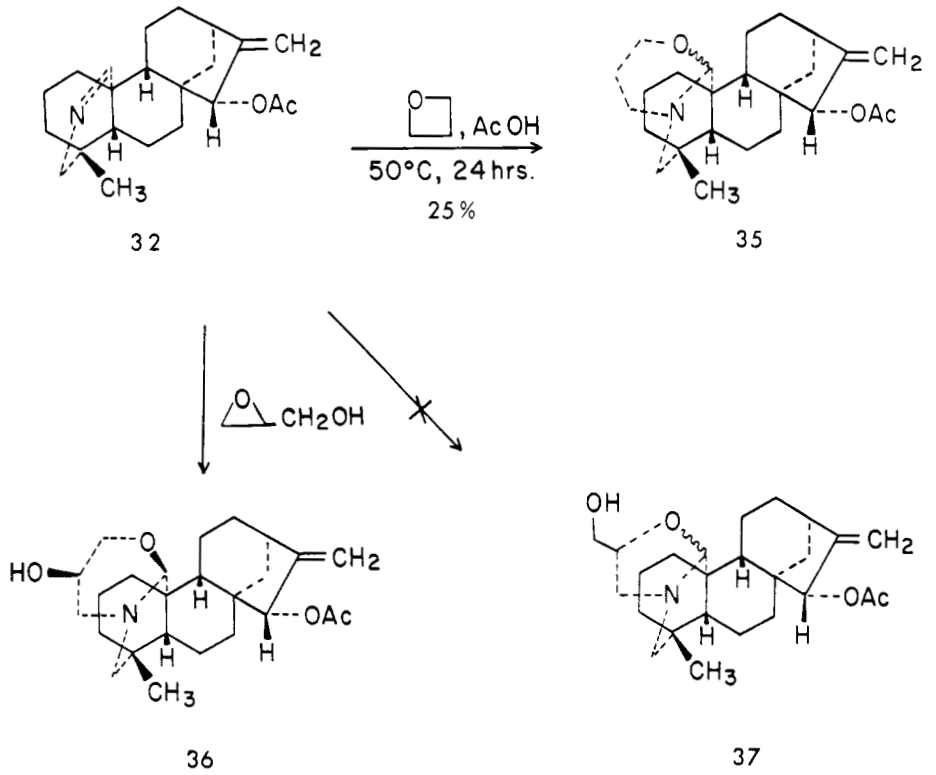


PLATE 26

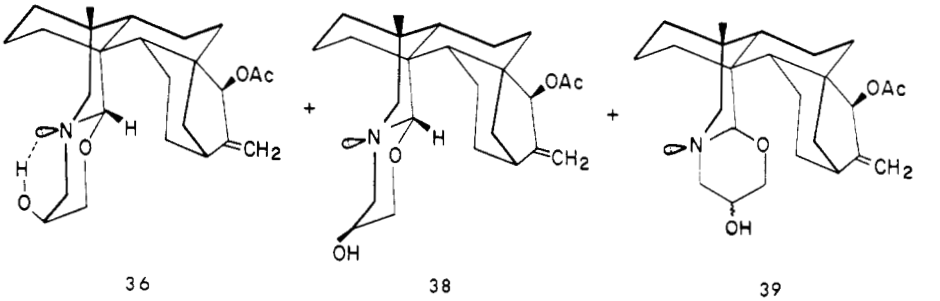


32 35 36 37

PLATE 27

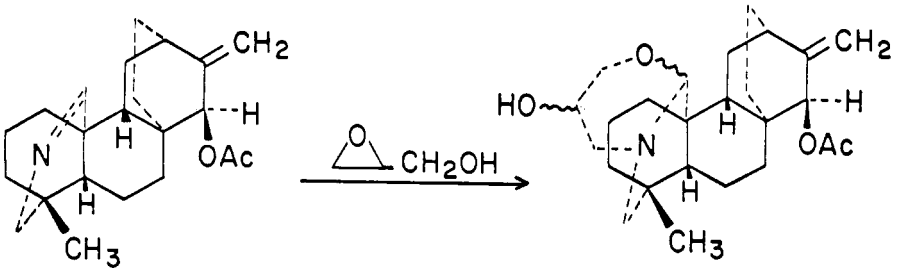
In a similar reaction, atisine azomethine acetate (**33**) reacted with glycidol to give a mixture of the C(20) epimers of compound **40**. Surprisingly, treatment of ajaconine azomethine acetate (**27**) with glycidol affords the single C(20) epimer (**41**). This behavior suggests that the 7α-acetoxy group in **27** exerts a profound influence on the direction of closure of the heterocyclic ring. It is noteworthy that none of the imines formed an oxazolidine ring derivative with glycidol.

The use of ethylene sulfide in the reaction affords excellent yields of thiazolidines (14). Thus, treatment of veatchine azomethine acetate (**32**) with ethylene sulphide afforded the thiazolidine (**42A**). Treatment of lindheimerine (**30**) under the

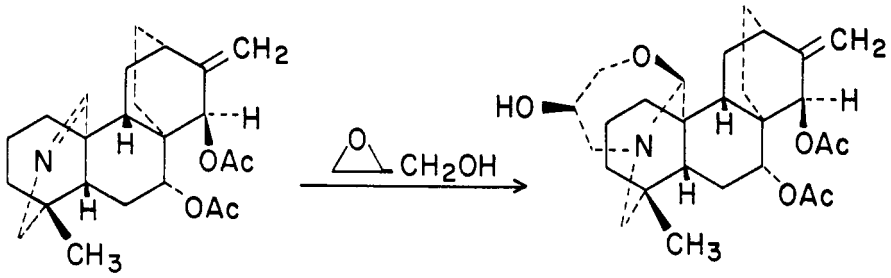


36 38 39

PLATE 28



33 40



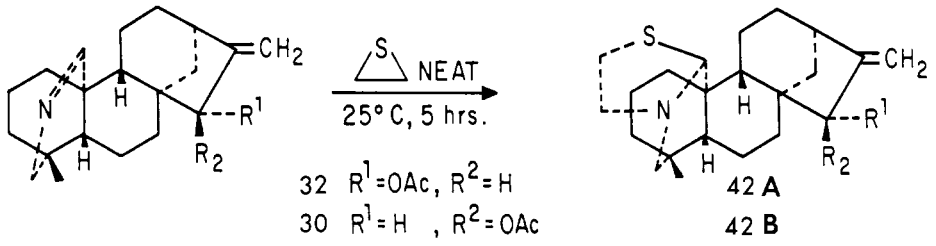
27 41

PLATE 29

same conditions gave the thiazolidine (**42B**). In a similar reaction, compound **33** afforded compound **43**. We have applied this method to various imine-containing compounds for preparation of the thiazolidines. Yields range from 90–95%. To our knowledge, this is the first use of ethylene sulfide for constructing a thiazolidine ring from an imine derivative. It is interesting to note that the thiazolidine ring-containing derivatives exist in one epimeric form at C(20), while the normal-type oxazolidine ring-containing alkaloids exist as a pair of epimers at C(20).

In summary, we have observed that certain reactions with diterpenoid alkaloid imines proceed by a "disfavored" 5-endo-trigonal process, while in other cases, such as the reactions with glycidol, a "favored" 6-endo-trigonal process is followed. Recently several other examples of the violation of the Baldwin cyclization rules have been reported (15, 16, 17).

During investigation of the constituents of *Garrya ovata* var. *lindheimeri*, we isolated (18) two new alkaloids, ovatine (**31**) and lindheimerine (**30**), as well as the known alkaloids, garryfoline (**5**) and cuauchichicine. The latter two alkaloids were isolated by Djerassi and coworkers (19) from the Mexican tree, *Garrya laurifolia*, and their gross structures established. We have recently determined by a ^{13}C nmr study that garryfoline (**5**) and ovatine (**31**) each exists as a mixture of C(20) epimers, paralleling the behavior of veatchine and atisine.



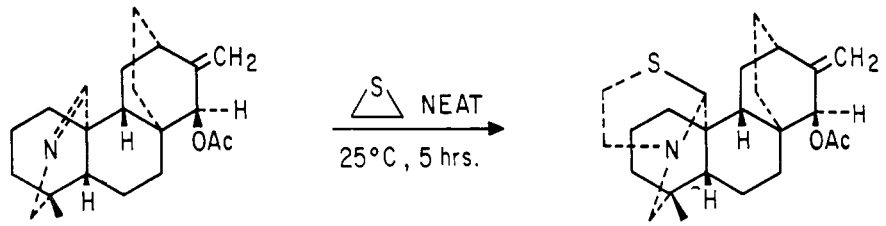


PLATE 30

The structure of ovatine was confirmed by basic hydrolysis to garryfoline. The structure of lindheimerine was confirmed by its preparation from either ovatine or garryfoline by a Hofmann-type degradation which will be discussed subsequently.

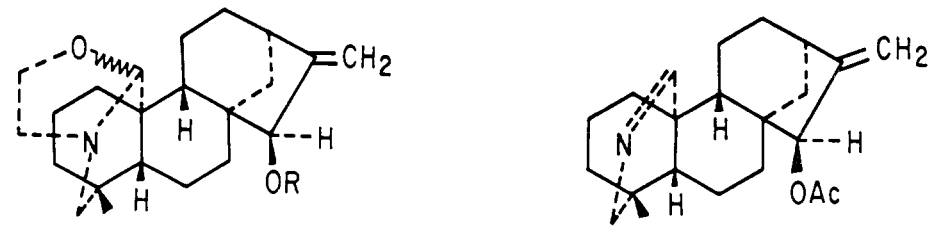


PLATE 31

Treatment of garryfoline with dilute mineral acid at room temperature results in rapid isomerization to cuauchichicine. The structure of cuauchichicine (**44**) was assigned in 1962 by Vorbrueggen and Djerassi (20). The stereochemistry of the C(16)-methyl group was assigned the α-configuration on the basis of chemical correlation of cuauchichicine azomethine (**45**) with (−)-"β"-dihydrokaurene (**46**). The structure of the latter, a minor hydrogenation product of *ent*-kaurene (**47**), was assigned on the behavior of ent-kaurene during catalytic hydrogenation. A β-configuration for the C(20)-hydrogen in cuauchichicine was assigned without any evidence (20b).

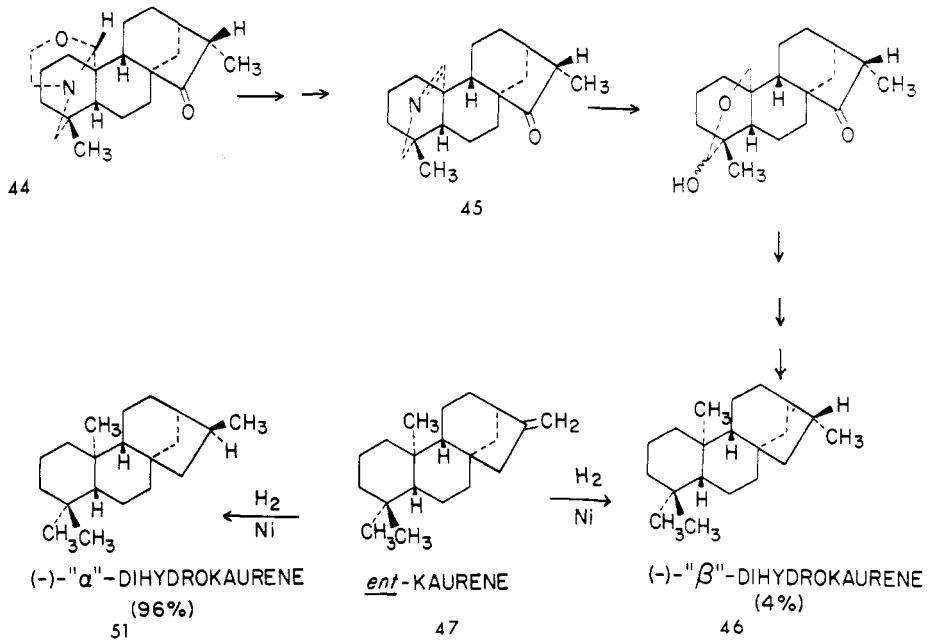


PLATE 32

A carbon-13 nmr study of cuauchichicine indicates that it exists as a *single* C(20) epimer, unlike other normal-type oxazolidine diterpenoid alkaloids such as veatchine, atisine, garryfoline, and ovatine. The configuration of hydrogen at C(20) was established as α on the basis of comparison of the ^{13}C nmr spectrum of cuauchichicine with those of atisine and veatchine C(20)-epimers.

Because alkaloids with the normal oxazolidine ring are unstable, we wanted a pair of stable C(16) epimers to simplify interpretation of the ^{13}C and ^{1}H nmr spectra and to establish the stereochemistry of the C(16) methyl group. Accordingly, we rearranged cuauchichicine into the more stable isocuauchichicine (**48**) by refluxing it in methanol. During this rearrangement the methyl group at the C(16) position does not epimerize. Cuauchichicine or isocuauchichicine was then refluxed in a solution of 2% sodium hydroxide in methanol to afford a mixture of C(16)-methyl epimers of isocuauchichicine. These epimers were separated by alumina column chromatography using hexane and benzene as the eluting system to give pure samples of isocuauchichicine (**48**) and 16-epi-isocuauchichicine (**49**). The C(16) deuterated epimers of isocuauchichicine were also prepared to allow assignment of the structure of cuauchichicine.

Comparison of molecular models of epimers **48** and **49** indicates that the β-methyl at C(16) is spacially crowded compared to the α-epimer. Steric compression would be expected to cause the β-methyl to appear at higher field in the ^{13}C nmr spectrum than the α-methyl group. Accordingly, we have assigned the signal at 10.1 ppm to the β-methyl group in **48** and the signal at 15.9 ppm to the α-methyl group in **49**. As a consequence, cuauchichicine with a signal at 10.1, may be assigned structure **50** with a C(16) β-methyl group. Subsequently this structure was confirmed by a single crystal X-ray analysis of cuauchichicine.

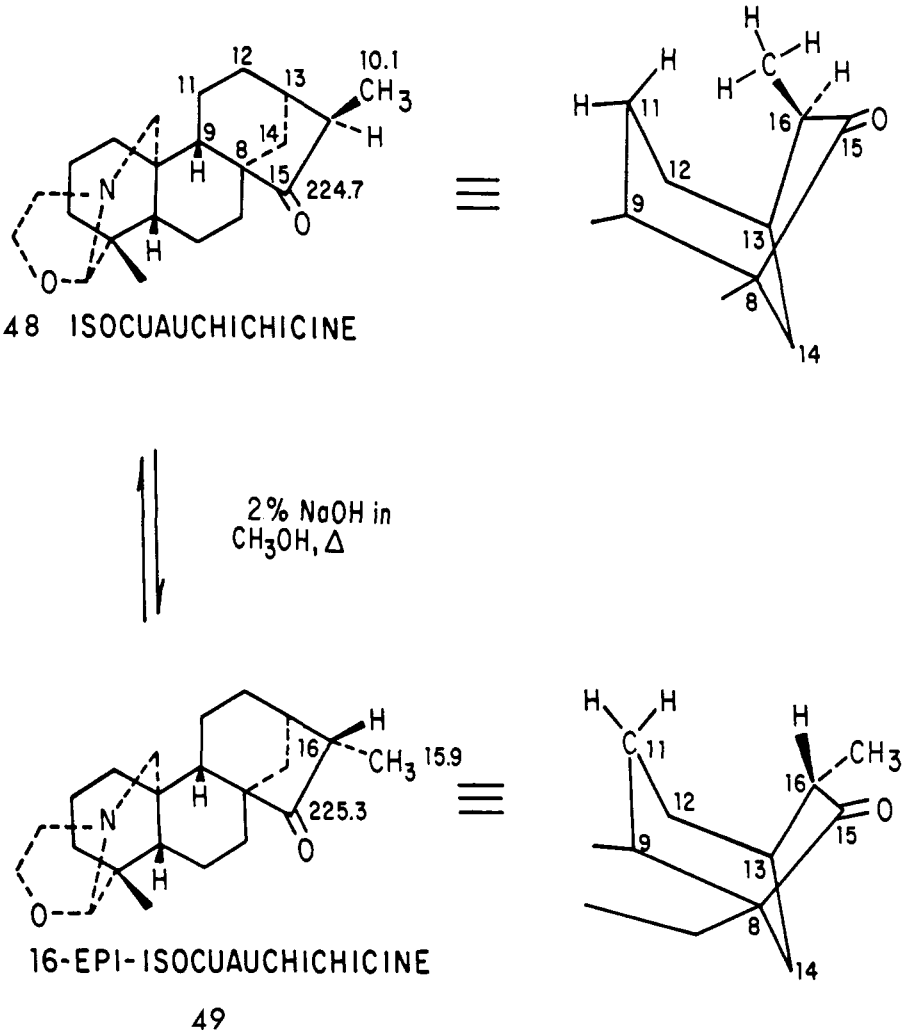


PLATE 33

The incorrect structure (**44**) originally assigned to cuauchichicine requires that either the structure of the final degradation product, (−)-"*β*"-dihydrokaurene (**46**), is incorrect, or that epimerization of the C(16)-CH_3 group occurred somewhere in the six-step correlation sequence. Because the structural assignments of almost one hundred natural products depend on (−)-"*β*"-dihydrokaurene, we have reinvestigated the structure of this key diterpene. Catalytic hydrogenation of a small sample of *ent*-kaurene, mp. 49–50°, gave a mixture of *ent*-kauranes consisting mainly of a compound, mp. 84.5–85.0°, identified as (−)-"*α*"-dihydrokaurene (Stevane A) (**51**). The "*β*"-epimer was produced in too small a yield to permit isolation in a pure state. A single crystal X-ray structure analysis of (−)-"*α*"-dihydrokaurene demonstrates the structure to be **51**, and therefore the structure of the epimeric, (−)-"*β*"-dihydrokaurene, must be as originally as-

signed, (20) i.e., structure **46** (21). These results indicate that epimerization at C(16) must have occurred during degradation of cuauchichicine azomethine to (−)-"β"-dihydrokaurene. This unanticipated epimerization most likely occurred during Wolff-Kishner reduction of the intermediate ketone **52**, and accounts for the error in the assignments of configuration of the C(16)-methyl in cuauchichicine azomethine acetate and therefore in cuauchichicine.

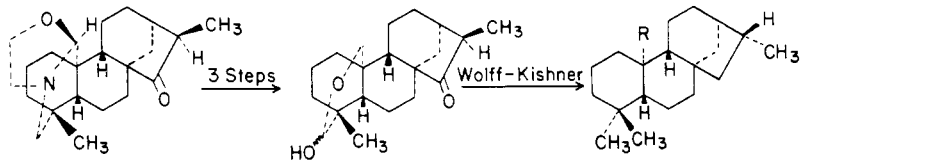


PLATE 34

In view of the fact that cuauchichicine exists as a single epimer at C(20), we were interested to learn whether 16-*epi*-cuauchichicine exists as one epimer or a pair of epimers at C(20). 16-*epi*-Isocuauchichicine (**49**) was converted to its immonium salt. This was converted to the normal-type immonium salt by thermal isomerization in refluxing DMSO. Treatment of this immonium salt with base effected ring closure to afford 16-*epi*-cuauchichicine (**53**). The ^{13}C nmr spectrum of 16-*epi*-cuauchichicine indicates that it exists as a pair of epimers at C(20).

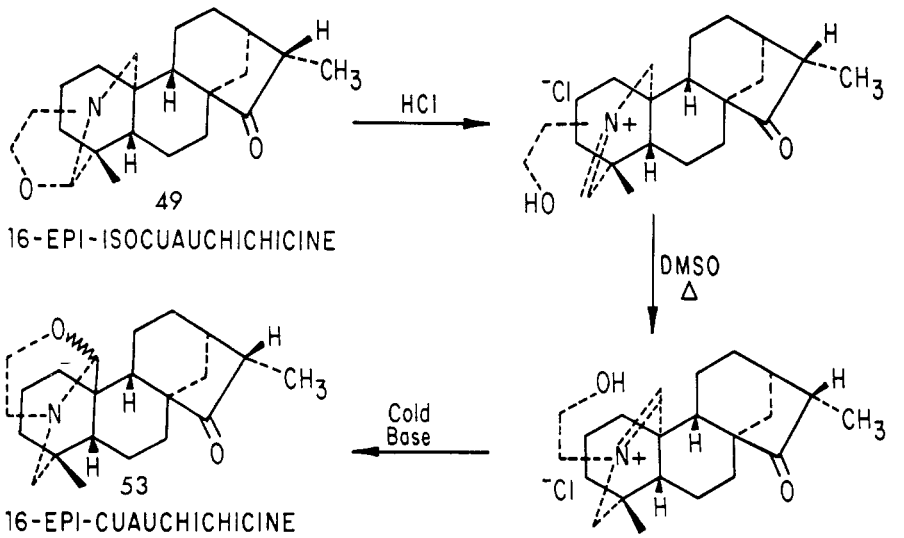


PLATE 35

With the structures of cuauchichicine (**50**) and garryfoline (**5**) now established with certainty, we investigated the mechanism of the acid-catalyzed rearrangement of garryfoline to cuauchichicine. A similar rearrangement has also been observed in the case of atisine, kobusine, and napelline. In contrast to the facile re-

arrangement of garryfoline, the C(15) epimer, veatchine (**3**), is stable even when heated in dilute hydrochloric acid. To account for the striking difference in the behavior of these two epimers under rearrangement conditions, a non-classical structure for the intermediate carbonium ion has been proposed (22).

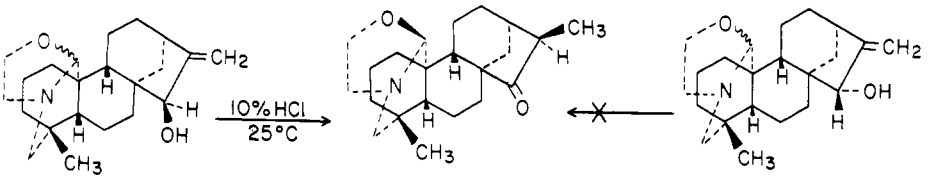


PLATE 36

In 1967 Barnes and McMillan (23) reported an investigation of this rearrangement using the epimeric (−)-kaur-16-en-15-ols. In mineral acid at room temperature the 15β-ol rearranged rapidly to 16(−)-kaur-15-one, while the 15α-ol was stable under these conditions. To establish a mechanism for this rearrangement, they prepared deuterated compound **54**. [15-^{2}H]-(−)-kaur-16-en-15β-ol (**54**) rearranged to 16R-[16-^{2}H]-(−)-kaur-15-one (**55**) in hydrochloric acid at 0°. The English authors proposed at 15⟶16 hydride shift to explain the rearrangement. Later work by the same group (24), however, demonstrated that compound **55** exchanges deuterium at C(16) with hydrogen in dilute acid at room temperature to afford **56**.

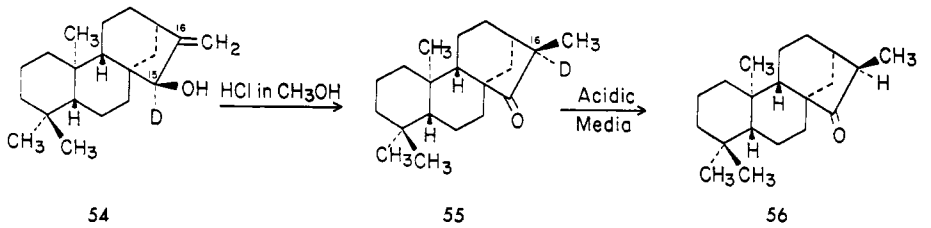
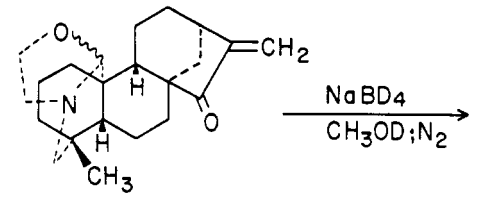


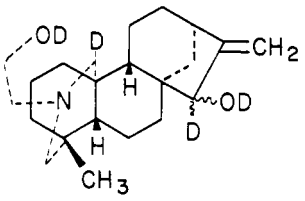
PLATE 37

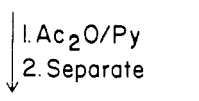
To study the rearrangement of garryfoline to cuauchichicine we prepared (25) C(15)-deuterated dihydrogarryfoline diacetate (**58**) from veatchinone (**57**). Compound **58** in 10% HCl rearranged to **60**, a compound which showed *no deuterium incorporation at C*(**16**) on the basis of ^{13}C nmr analysis.

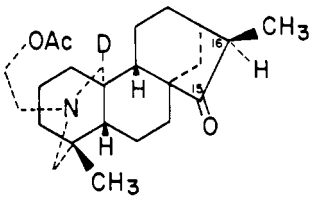
Treatment of isogarryfoline (**6**) with 10% DCl in D_2O at room temperature gave **61** in quantitative yield. Analysis of the ^{13}C nmr spectrum of **61** showed the presence of deuterium at C(16) and C(17). In dilute HCl no exchange of deuterium by hydrogen in compound **61** was observed in 24 hours, but after 96 hours, exchange was observed to give compound **62**. The mechanism outlined below, involving the enol (**63**), accounts for incoproration of deuterium at C(16) and C(17) and also explains formation of the C(16β)-CH_2D during rearrangement. During ketonization of enol (**63**), transfer of D^+ would be expected to occur from the less-hindered bottom side of the molecule to give compound **61** containing the C(16α)-D

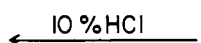


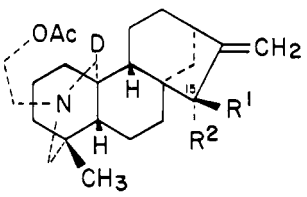
57











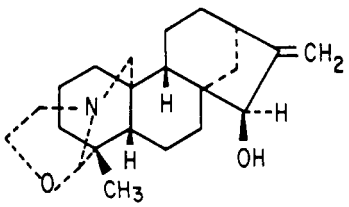
60

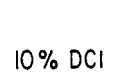
No deuterium incorporation at C(16)

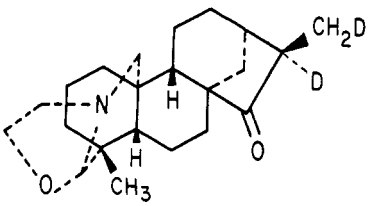
58 R^1 = OAc R^2 = D (major)

59 R^1 = D R^2 = OAc (minor)

PLATE 38

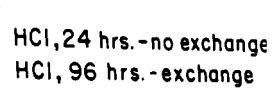


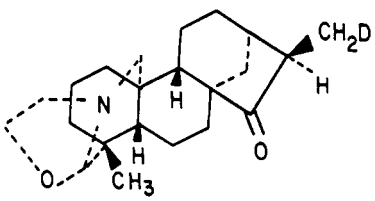




6 ISOGARRYFOLINE

61





62

PLATE 39

and C(16β)-CH_2D groups. These results demonstrate that a 15→16 hydride shift is not involved in the rearrangement of garryfoline to cuauchichicine.

We mentioned previously the isolation of ovatine (**31**) and lindheimerine (**30**) from *Garrya ovata*. Lindheimerine occurs in the plant in very small amounts and because we required this alkaloid and related compounds for preparing synthetic analogues, we sought a simple and efficient method for degrading the oxazolidine ring of ovatine (**31**) and related alkaloids to the corresponding imine derivatives.

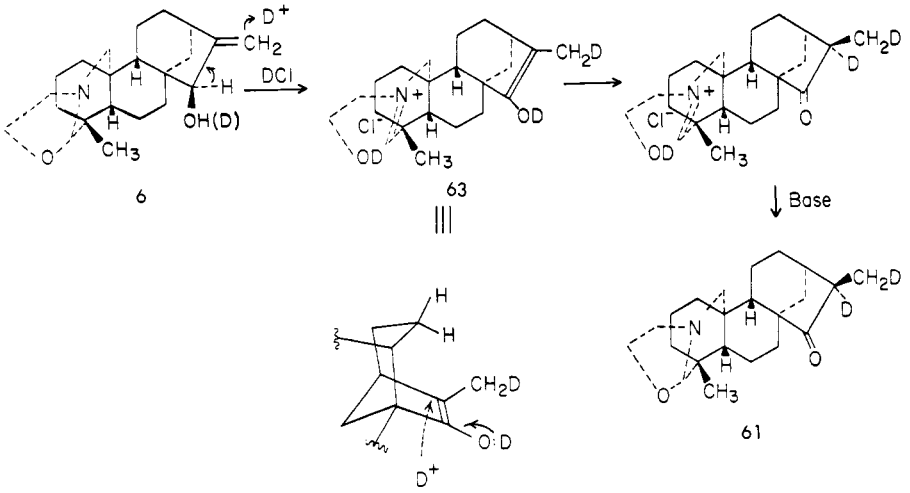


PLATE 40

An earlier method reported by Dvornik and Edwards (26) for this type of degradation involves four steps and in our hands proceeded with erratic yields. Thus, atisine (**1**) is converted to the immonium chloride (**7**) with HCl, and the latter to the immonium chloride diacetate (**64**) by treatment with Ac_2O and pyridine.

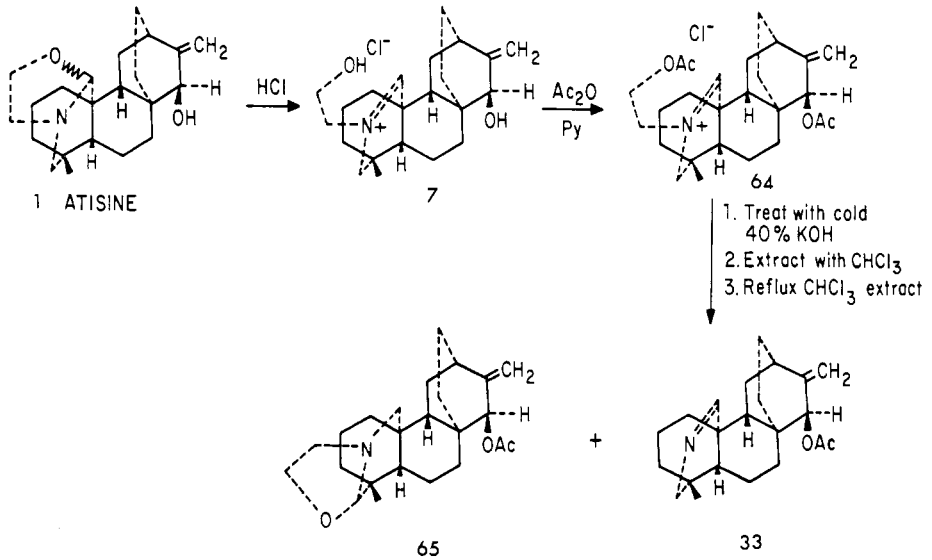


PLATE 41

Treatment of the diacetate with 40% KOH, extraction with chloroform, and decomposition in boiling chloroform gives a mixture of the desired imine (**33**) in low yield, as well as isoatisine acetate (**65**).

In our procedure (27), treatment of ovatine or garryfoline with acetic anhydride and pyridine at room temperature afforded a chloroform-soluble diacetate salt (**66**) in quantitative yield. A Hofmann-type degradation of the diacetate salt proceeded in refluxing chloroform to afford lindheimerine (**30**) in a yield of 90%. In practice the two steps can be combined into one. After acetylation, one evaporates the mixture to dryness *in vacuo*, adds $CHCl_3$, and then refluxes the mixture.

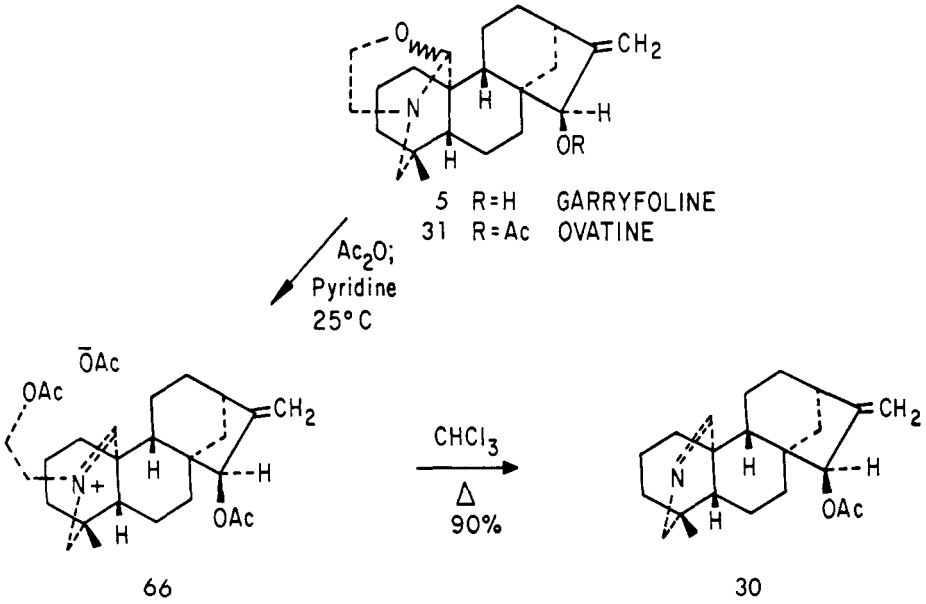


PLATE 42

The results of the degradation of various oxazolidine ring-containing alkaloids by this new method are summarized below. The normal oxazolidine ring-containing alkaloids gave higher yields than the iso-oxazolidine ring-containing alkaloids.

Because we required isogarryfoline (**6**) for a synthetic investigation, we wished to convert veatchine into isogarryfoline. To effect this transformation, we required a simple method for constructing the oxazolidine ring from the corresponding dihydro derivative. The earlier methods reported for this type of ring closure required the use of very toxic and expensive osmium tetroxide (28) or of mercuric acetate (29). In the case of osmium tetroxide, the ring closure proceeds in low yield and gives side products, e.g., glycols from the oxidation of the double bond. This method also requires a lengthy reaction time. In the case of mercuric acetate, slight over-oxidation produces an amide derivative which decreases the yield of the desired product.

We report (30) a simple method using active manganese dioxide for converting the N-CH_2-CH_2-OH containing alkaloids, e.g., dihydroveatchine, dihydroatisine, and dihydrogarryfoline, into their iso-oxazolidine ring-containing alkaloids, i.e.,

DEGRADATION OF OXAZOLIDINE-TYPE ALKALOIDS TO IMINES

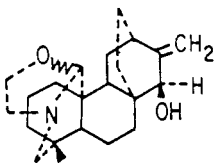
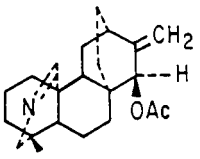
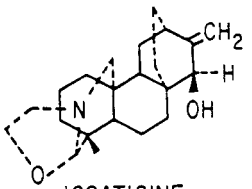
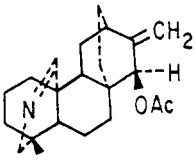
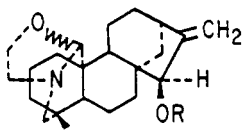
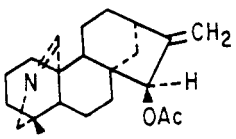
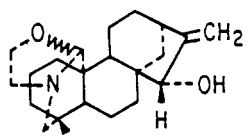
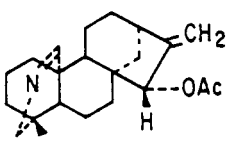
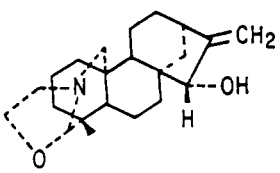
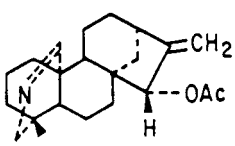
Substrate	Product	Yield, %
 ATISINE		91
 ISOATISINE		52
 R=H GARRYFOLINE R=Ac OVATINE	 LINDHEIMERINE	90 90
 VEATCHINE		89
 GARRYINE		49

PLATE 43

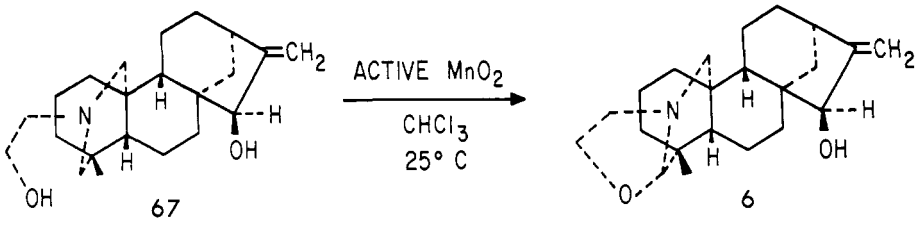


PLATE 44

garryine, isoatisine, isogarryfoline. A mixture of dihydrogarryfoline (**67**) and active manganese dioxide in chloroform was stirred at room temperature to afford isogarryfoline (**6**) in about 50% yield. This method has advantages over the old methods, in that it is very simple and uses an inexpensive and non-toxic reagent. The results obtained from manganese dioxide oxidation of dihydroderivatives to iso-oxazolidine ring containing compounds are summarized below.

ACKNOWLEDGMENTS

The results presented in this paper are derived from the work of Drs. Haridutt K. Desai, Janet Finer-Moore, Jacek Nowacki, and J. Bhattacharyya. We are greatly indebted to them for their efforts. We also thank Professor Karel Wiesner for very helpful correspondence regarding the Baldwin cyclization rules and their application to diterpenoid alkaloids.

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MnO_2 OXIDATION OF DIHYDRO DERIVATIVES

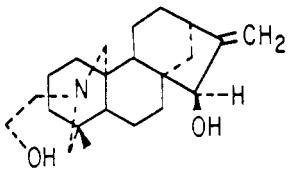
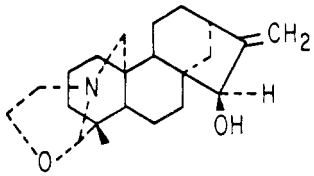
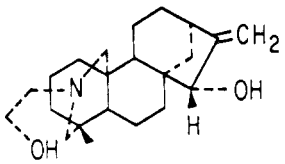
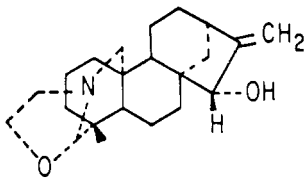
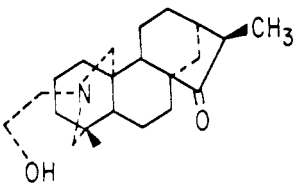
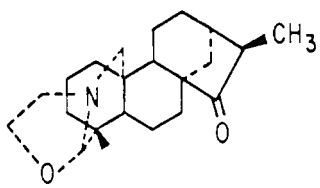
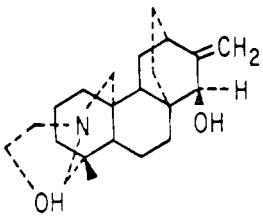
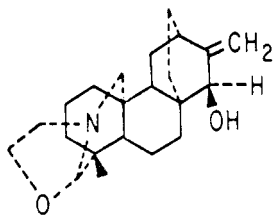
Substrate	Product	Yield,%
 DIHYDROGARRYFOLINE	 ISOGARRYFOLINE	45-50
 DIHYDROVEATCHINE	 GARRYINE	55-60
 DIHYDROCUAUCHICHICINE	 ISOCUAUCHICHICINE	60-64
 DIHYDROATISINE	 ISOATISINE	55-61

PLATE 45

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