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STUDIES IN THE CHEMISTRY OF NATURAL PRODUCTS: REARRANGEMENT REACTIONS OF DITERPENOID AND NORDITERPENOID ALKALOIDS[1]

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ABSTRACT.—The diterpenoid nitrogenous bases from the plant families Compositae, Escalloniaceae, Garryaceae, Ranunculaceae, and Rosaceae have long been of interest because of their pharmacological properties, complex molecular structures, and interesting chemistry. Most of these alkaloids have been isolated from species of *Aconitum* and *Delphinium* (Ranunculaceae) and *Garrya* (Garryaceae). With respect to the chemistry, several unusual acid-catalyzed and base-catalyzed rearrangements of diterpenoid and norditerpenoid alkaloids are discussed. Certain rearrangement products produced under solvolytic conditions are considered.

Diterpenoid nitrogenous bases occur in the plant families Compositae, Escalloniaceae, Garryaceae, Ranunculaceae, and Rosaceae and have long been of interest because of their pharmacological properties, complex molecular architecture, and interesting chemistry. Most of the alkaloids have been isolated from species of *Aconitum* and *Delphinium* (Ranunculaceae) and *Garrya* (Garryaceae). A few diterpenoid alkaloids have been also isolated from *Spiraea* (Rosaceae) species and from two *Anopterus* (Escalloniaceae) species (Table 1).

TABLE 1. Plant Genera Containing Diterpenoid Alkaloids.

COMPOSITAE	RANUNCULACEAE
Inula royleana	*Aconitum* sp.
ESCALLONIACEAE	*Consolida ambigua*
Anopterus gladulosus	*Delphinium* sp.
Anopterus macleayanus	ROSACEAE
GARRYACEAE	*Spiraea* sp.
Garrya laurifolia	
Garrya ovata var. *lindheimeri*	
Garrya veatchii	

Many of the alkaloids isolated from these plants are highly toxic. Extracts of *Aconitum* species were employed in ancient times for treatment of neuralgia, hypertension, gout, rheumatism, and even toothache. The crushed seeds of certain species were used as pediculicides. Aconite extracts were used also in the medieval trials by ordeal and for tipping arrows to kill both men and beasts.

Many of the norditerpenoid alkaloids exhibit neurotoxicity principally as a consequence of interacting with excitable membranes so as to hold open sodium channels following an action potential, with prolonged polarization resulting. In this respect they resemble the action of batrachotoxin, grayanotoxin, and veratridine.

The diterpenoid alkaloids may be divided into two broad categories: the norditer-

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penoid alkaloids that are based on a hexacyclic C_{19} skeleton and those based on C_{20} skeletons. Three different C_{20} skeletons exist and differ in the attachment of the C-15–C-16 bridge at either C-11, C-12, or C-13 (Figure 1). Biogenetically, all these alkaloids are probably derived from tetracyclic or pentacyclic diterpenes in which the nitrogen atom of methylamine, ethylamine, or β-aminoethanol is incorporated in the norditerpenoid skeleton and in the C_{20} diterpenoid skeleton to form a substituted piperidine ring.

C_{19}-skeleton C_{20}-skeleton

FIGURE 1. Diterpenoid skeleta.

The norditerpenoid alkaloids, commonly called aconitines, may be subdivided in four groups based on four different skeleta (Figure 2). These groups are defined as:

1. Aconitine-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. C-7 may be substituted with OH, OMe, or a methylenedioxy group bridging the oxygen at C-8.
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 aconitine-type alkaloids.
4. Heteratisine-type. These alkaloids possess the skeleton of heteratisine, in which a δ-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-

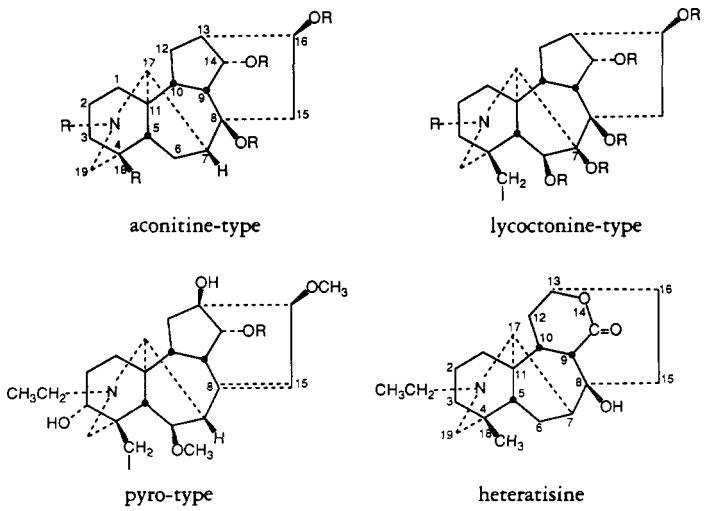
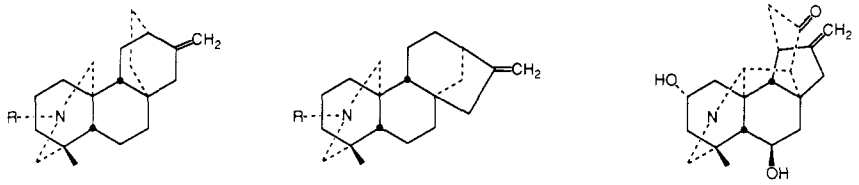


FIGURE 2. Norditerpenoid skeleta.

Villiger type on a C-14 carbonyl group, with resultant expansion of the five-membered ring C to a six-membered lactone.

The diterpenoid alkaloids consist of a series of amino alcohols 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 (Figure 3). 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, isolated from *Delphinium denudatum*.

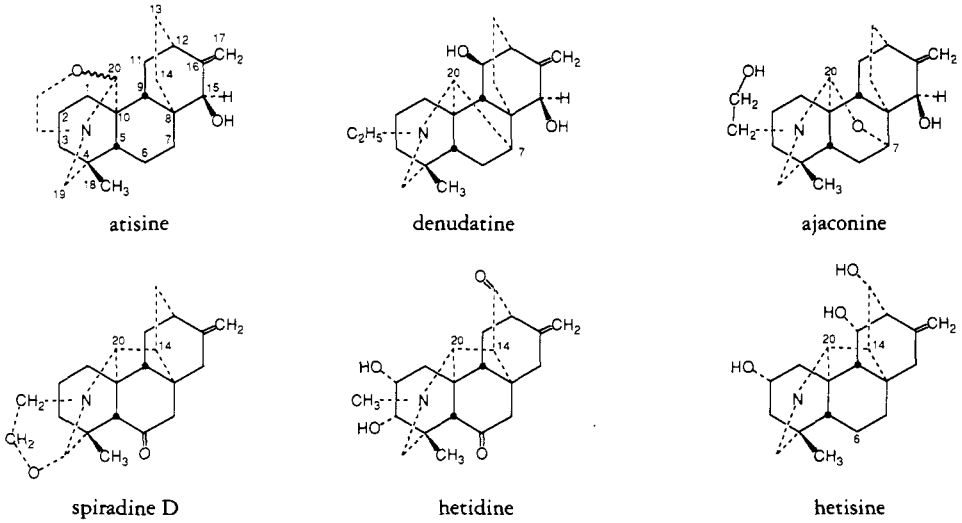


atisine-type veatchine-type delnudine

FIGURE 3. Diterpenoid skeleta.

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 oxygen atom (Figure 4).

In the case of spiradine D, hetidine, and hetisine, an extra bridge exists between C-20 and C-14. The alkaloid hetisine is characterized by an N–C-6 bond as well as a C-14–C-20 bond. It is this alkaloid and its derivatives that undergo a series of interesting rearrangements that constitute the first part of this paper.



atisine denudatine ajaconine

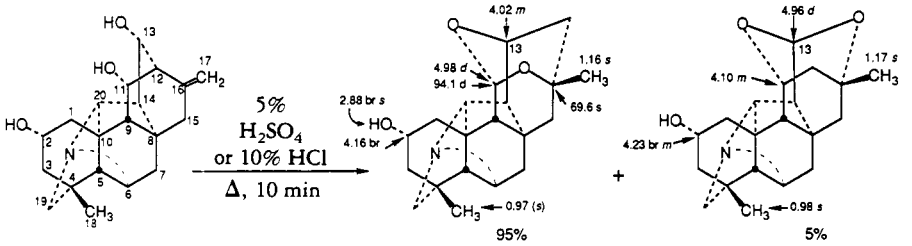
spiradine D hetidine hetisine

FIGURE 4. Atisine-type alkaloids.

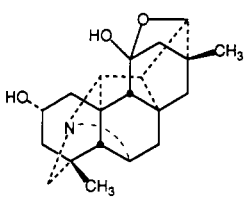
REARRANGEMENTS

In 1959 (1) we reported the rearrangement of hetisine [**1**] by treatment with aqueous H_2SO_4 to an alkaloid, mp 278.0–279.5°, that has also been isolated from *Aconitum heterophyllum* (2). After the structure of hetisine had been determined by an X-ray crystallographic study, Wiesner *et al.* (3) assigned structure **2** to this rearrangement product. However, as will appear later, the ^{1}H- and ^{13}C-nmr spectra of this compound are not compatible with structure **2**.

Recently we have returned to a study of this interesting rearrangement product. We find that treatment of hetisine with 5% aqueous H_2SO_4 or with 10% HCl at reflux temperature for 10 min affords the rearrangement products **3** and **4** in a yield of approximately 95% and 5%, respectively (Scheme 1). The major product **3** is identical with



1 hetisine, $C_{20}H_{27}NO_3$ **3** $C_{20}H_{27}NO_3$, mp 278.0–279.5°; ir 3150 (OH), 1100 (ether) cm^{-1} **4** $C_{20}H_{27}NO_3$, mp 288–290°; ir 3200 (OH), 1130 (ether) cm^{-1}



2

SCHEME 1

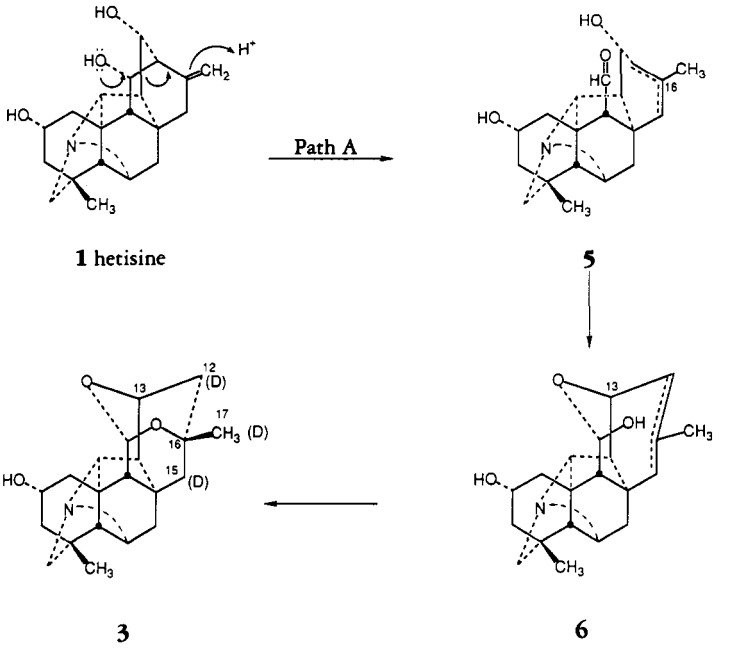
the alkaloid previously isolated from *A. heterophyllum* (2). Compound **3** showed ir absorption at 3150 (OH) and 1100 (ether) cm^{-1}. Its ^{1}H-nmr spectrum showed resonances at δ 0.97 (s, 4-Me), 1.16 (s, 16-Me), 2.88 br (s, 2α-OH), 4.02 (m, H-13), 4.16 br (H-2β) and 4.98 (d, C-11 acetal H). In the ^{13}C-nmr spectrum a doublet at 94.1 ppm and a singlet at 69.6 ppm (tertiary oxygenated C-16) cannot be accommodated by structure **2**, but do accord well with structure **3**. The structure of **3** was confirmed by a single crystal X-ray analysis ($R = 0.039$ and $R_w = 0.046$) (2). Interestingly, the C-10–C-20 bond is unusually long, 1.591 (4) Å, and is the only evidence for significant strain in the molecule. All other bond distances and angles have typical values.

The minor rearrangement product **4** showed ir absorption at 3200 (OH) and 1130 (ether) cm^{-1}. Its ^{1}H-nmr spectrum showed resonances at δ 0.98 (s, 4-Me), 1.17 (s, 16-Me), 4.10 (m, H-11), 4.23 br (m, H-2β), and 4.96 (d, C-13 acetal H).

This rearrangement of hetisine represents an unusual transformation of a dihydroxy[2.2.2.]bicyclo-octane system to an adamantane-type skeleton through a facile cleavage of the C-11–C-12 bond to give **3** and cleavage of the C-12–C-13 bond to give **4**.

The mechanism proposed for the transformation of hetisine [**1**] to **3** is shown in

path A (Scheme 2). Protonation of the exocyclic double bond and a retroaldol reaction involving the 11-OH group would lead to the aldehyde **5**. Hemiacetal formation between the aldehyde and the adjacent 13-OH would lead to **6** which could then cyclize to the acetal **3**. Intermediate **6** is believed to be involved rather than the dihydroxy aldehyde formed by hydration of **5** at C-16 because of the ease of formation of acetal **3**, and because hydration of **5** to a dihydroxy aldehyde would not be expected to proceed stereospecifically to form a single isomer which could subsequently cyclize to **3**.



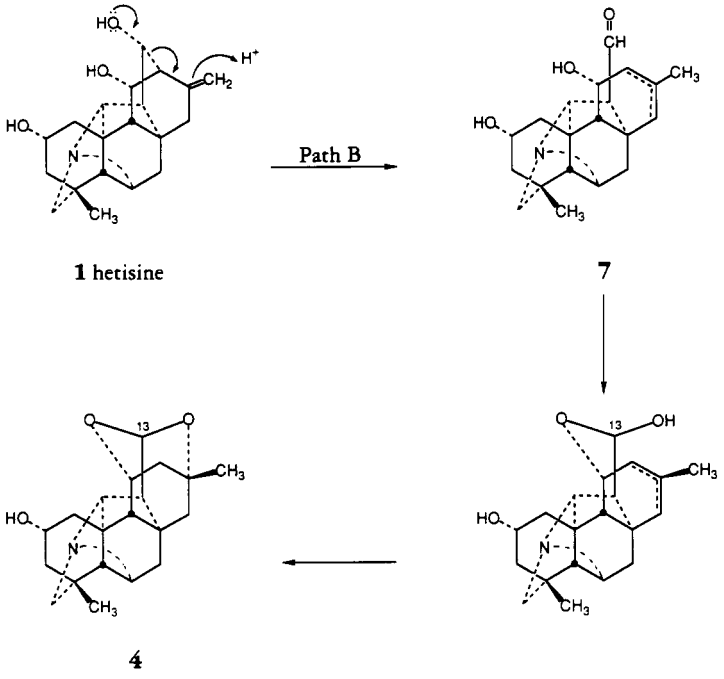
SCHEME 2

When hetisine was heated at reflux temperature with 10% DCl in D_2O under nitrogen, compound **3** deuterated at C-12, C-15, and C-17 was formed as the major product, a result that is in accord with the proposed mechanism.

Path B (Scheme 3) shows a mechanism for formation of compound **4** from hetisine [**1**] analogous to that proposed for formation of **3** and involves aldehyde **7** as an intermediate. In this case, cleavage of the C-12–C-13 bond occurs.

Treatment of 11-*epi*-hetisine [**8**] under the same conditions of rearrangement led to formation of compounds **3** and **4** (Scheme 4), but now in the ratio of 1:3 as determined by the ^{1}H-nmr spectrum (4). This ratio differs greatly from that given by hetisine [**1**], suggesting that changing the 11-OH configuration from α to β makes cleavage of the C-11–C-12 bond more difficult.

When the acid-catalyzed rearrangement of hetisine is carried out for a longer period, compounds **3** and **4** are not the only products (4). Chromatography of the product mixture over alumina afforded about 20% of a new product, mp 295–299° (Scheme 5). The ^{1}H-nmr and ^{13}C-nmr spectra indicate this product is a 1:1 mixture of the two isomeric compounds **9** and **10**, each possessing an endocyclic double bond. Further study of the nmr spectrum of the unresolved mixture was precluded because of overlapping of signals. When the perchlorate salt of the mixture of **9** and **10** was recrystallized several times from aqueous MeOH, a product enriched in **9** was obtained which was submitted for X-ray analysis. The electron density map revealed the coexistence of both C-13 epimers in the crystal (4) (Figure 5).

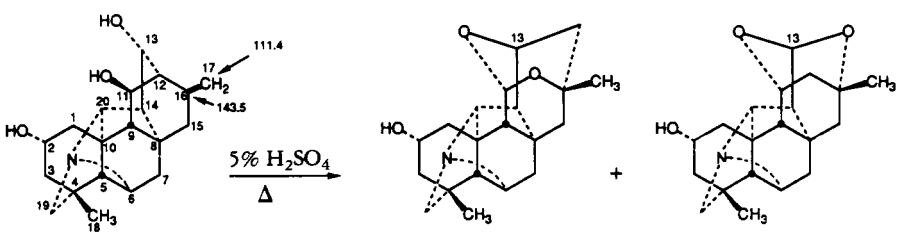


SCHEME 3

We have seen previously that cleavage of the C-11–C-12 bond in hetisine leads to the aldehyde intermediate **5**. Cleavage of the C-12–C-13 bond is less favorable, as demonstrated by the **3**-to-**4** ratio of 1:3. A mechanism that accounts for the origin of isomers **9** and **10** from intermediate **5** is shown in Scheme 6. The configuration of the 11β-OH bond in **9** and **10** is identical, whereas the configuration of the 13-OH bond may be α or β, as a result of the addition of H_2O taking place on either the α or β face of the well-stabilized allyl carbocation **11**.

That the reactions are reversible was shown by refluxing the mixture of **9** and **10** for 6 h in 5% H_2SO_4, resulting in formation of small quantities of **3** and **4**. Products of similar reactions of the intermediate **7** (Scheme 3) were not detected in the crystal by X-ray analysis. They may have been eliminated as minor products during the repeated crystallization of the perchlorate salt.

11-Dehydrohetisine [**15**] and 2,11-didehydrohetisine [**16**] undergo an interesting rearrangement in strong acid solution. These compounds were prepared by oxidation of



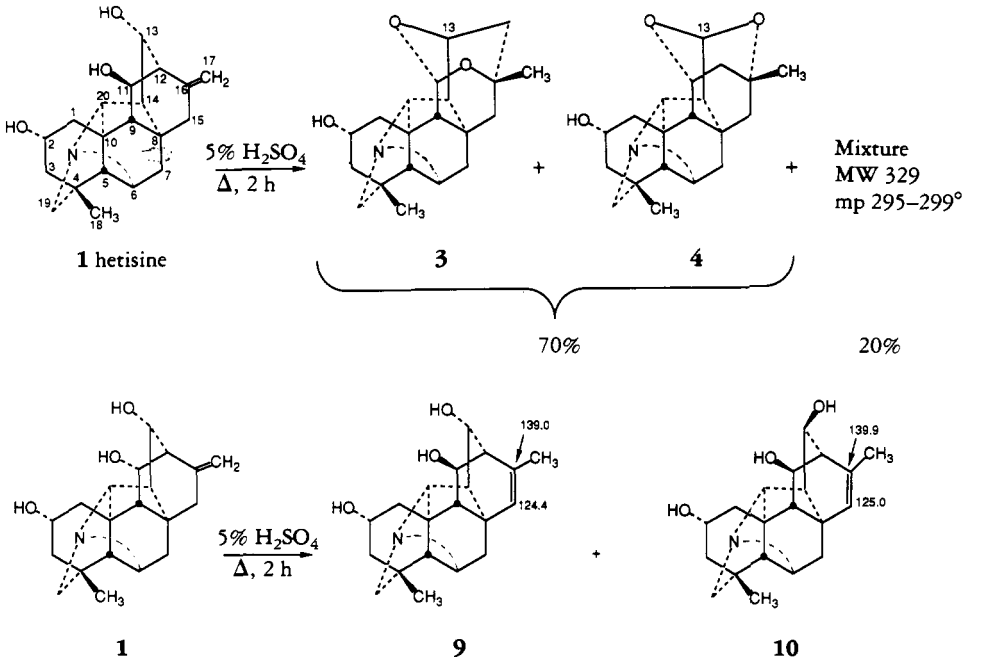
8 11-*epi*-hetisine mp 268–271°

3 mp 278.0–279.5°

4 mp 288–290°

Ratio **3**:**4** = 1:3

SCHEME 4



SCHEME 5

hetisine [**1**] with Sarett's reagent to furnish **15** as the major and **16** as the minor product (5) (Scheme 7).

Treating 11-dehydrohetisine [**15**] with 45% H_2SO_4 under reflux gave a rearrangement product, mp 202–203° (6) (Scheme 8). The mass spectrum, $[M]^+$ *m/z* 327, indicated that the product is isomeric with **15**. The ir spectrum indicated the presence of hydroxyl (3600 cm^{-1}) and carbonyl groups (1710 cm^{-1}). The ^{13}C-nmr spectrum indicated the presence of two carbonyl groups (208.7, 210.7 ppm). The ^1H-nmr spectrum showed the presence of a tertiary methyl group at δ 1.04 (3H, s) and the disappearance of the exocyclic methylene group that was present in **15**. These data suggested that the rearrangement product is of a new type, unrelated to the rearrangement products of hetisine earlier described. The structure of the rearrangement product **17** was solved by a single-crystal X-ray analysis of the perchlorate salt with R = 0.104 and R_w = 0.099 (6).

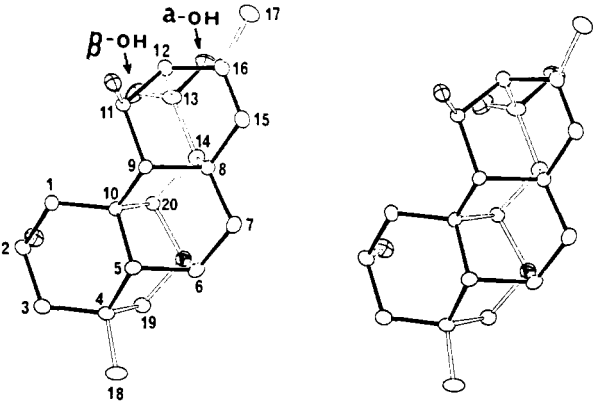
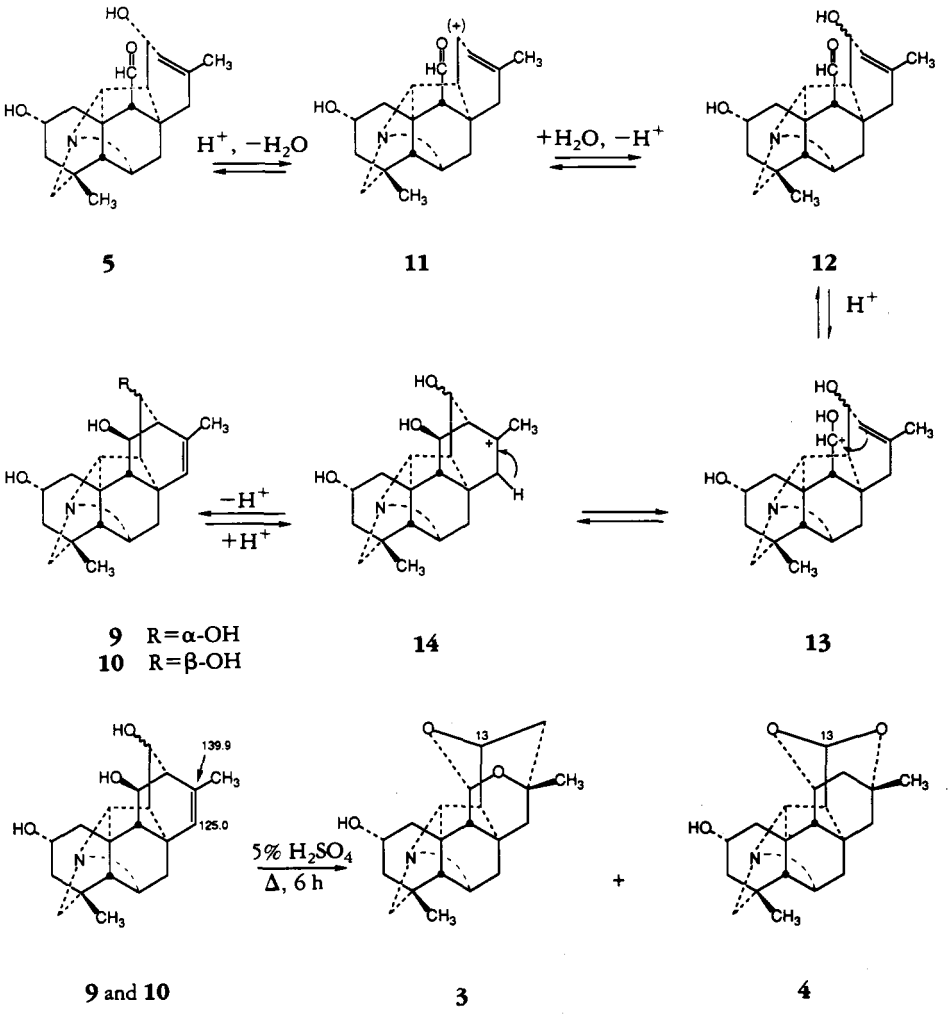


FIGURE 5. ORTEP drawing of the perchlorate salt of **9** and **10**.



5 **11** **12**

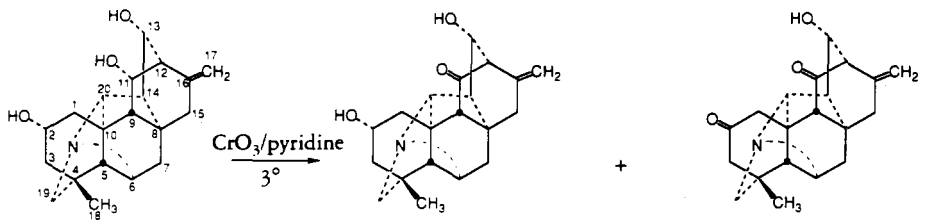
9 R=α-OH
10 R=β-OH

14 **13**

9 and **10** **3** **4**

SCHEME 6

The two carbonyl groups are clearly shown by O-11–C-11 and O-16–C-16 distances of 1.217 (5) Å and 1.203 (7) Å, respectively, and by the planarity of the bond meetings at C-11 and C-16. An interesting feature of this molecule is the formation of an additional carbonyl group and the formation of a new ring system incorporating the

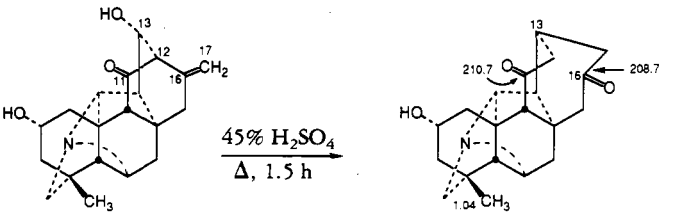


1 hetisine **15** **16**

mp 292–298°
Major

mp 237–240°
Minor

SCHEME 7



15

17 mp 202–203°;
ir 3600 (OH), 1710 (C=O) cm^{-1};
m/z 327

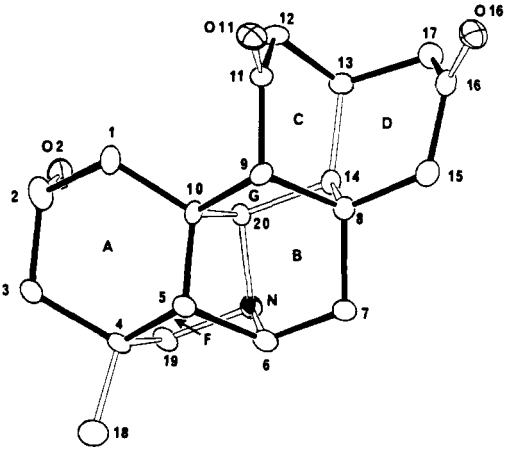
SCHEME 8

methylene carbon C-17. The molecule contains five six-membered rings and two five-membered rings fused together. All of the six-membered carbocyclic rings are in a chair conformation. The piperidine ring defined by C-6, C-7, C-8, C-14, C-20, and N is also a chair. The two five-membered rings F (C-4, C-5, C-6, N, C-19), and G (C-8, C-9, C-10, C-20, C-14) have a distorted half-chair conformation. The carbonyls at C-11 and C-16 of the eight-membered ring are almost parallel (6) (Figure 6).

For this interesting rearrangement we suggest the mechanism shown in Scheme 9. Hydration of the exocyclic methylene group followed by dehydration and enolization would lead to compound **18**. An internal Michael addition would then afford rearrangement product **17**.

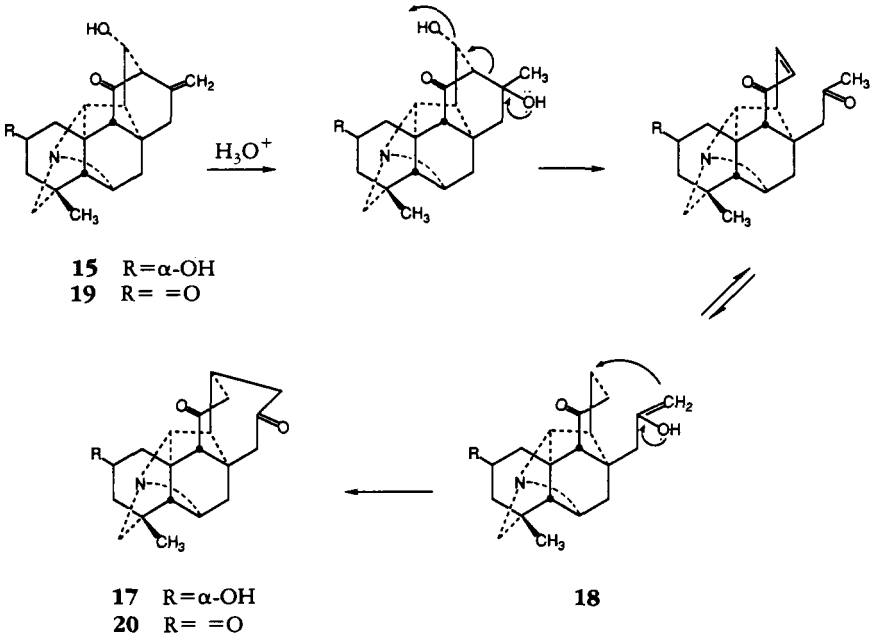
In a similar fashion we have found that refluxing 2,11-didehydrohetisine [**19**] with 45% H_2SO_4 gave the tricarbonyl compound **20**, mp 285–287°. The structure of **20** was deduced from its spectral data and confirmed by oxidation of **17** (the structure of which was established by X-ray analysis) with pyridinium chlorochromate to **20** (6).

11-Acetyl-2,13-didehydrohetisine [**22**] also undergoes an interesting rearrangement (7), and its preparation is as follows: 11-Acetylhetisine [**21**] was prepared by low temperature (−6°) or vigorous acetylation (5) of hetisine [**1**]. The product mixture, consisting of several acetates, was separated by chromatography over alumina. Oxida-



R =0.104
R_w=0.099

FIGURE 6. Projection view of the rearrangement product **17**.



15 R=α-OH
19 R= =O

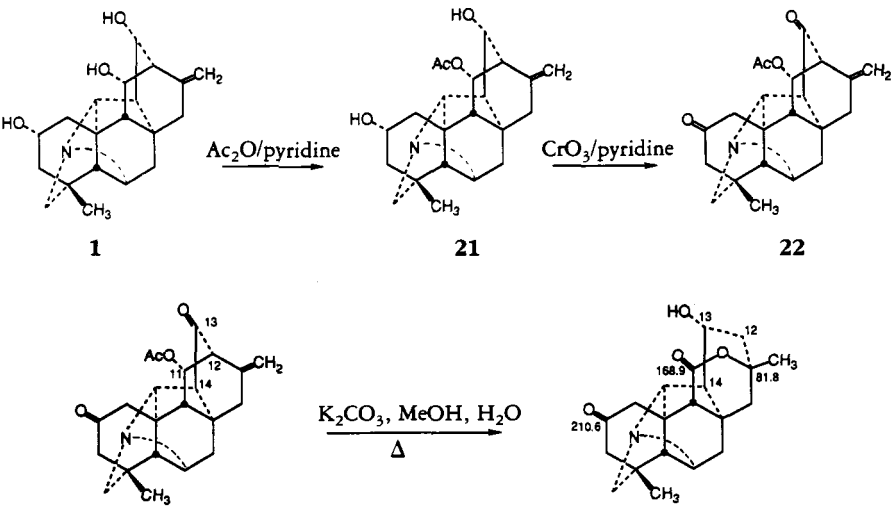
17 R=α-OH
20 R= =O

18

SCHEME 9

tion of 11-acetylhetisine with Sarett's reagent in methylene chloride afforded 11-acetyl-2,13-didehydrohetisine [**22**] in 48% yield (5) (Scheme 10).

When 11-acetyl-2,13-didehydrohetisine [**22**] was heated under reflux with aqueous K_2CO_3 in MeOH, a high-melting (mp 313–315°) product was obtained, ms *m/z* 343. The ir spectrum showed the presence of a hydroxyl group (3070 cm^{-1}), a carbonyl



1 **21** **22**

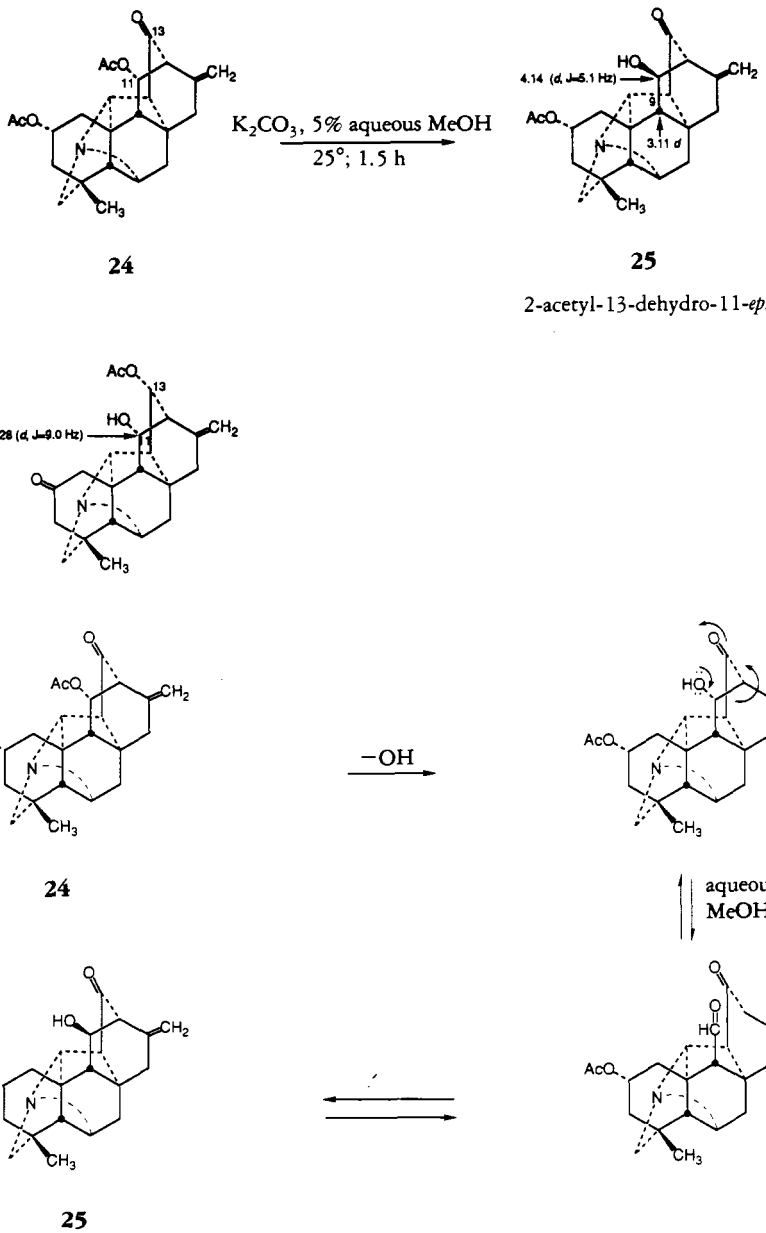
22

23 mp 313–315°; m/z 343;
ir 3070 (−OH), 1710 (>C=O), 1720 (δ-lactone) cm^{-1};
^{1}H nmr δ 1.15 (3H, s, 4-Me); 1.41 (3H, s, —C(=O)—Me),
No olefinic protons at δ 5.00

SCHEME 10

group (1710 cm^{-1}), and a δ-lactone moiety (1720 cm^{-1}). The ^1H-nmr spectrum indicated two three-proton singlets at δ 1.15 and 1.41 attributed to the tertiary 4-Me and a tertiary methyl group attached to oxygen, respectively. The absence of olefinic protons of the C-17 methylene group usually located at about δ 5.00 strongly suggested that this compound is a rearrangement product. The structure was shown to be **23** by a single-crystal X-ray analysis of the perchlorate salt (7). An interesting feature of the structure is the formation of the C-ring lactone under conditions of alkaline hydrolysis (Scheme 10).

13-Dehydro-2,11-diacetylhetisine [**24**] was prepared by oxidation of 2,11-diacetylhetisine with Sarett's reagent (5). Treatment of **24** with methanolic aqueous



24 **25**

2-acetyl-13-dehydro-11-*epi*-hetisine

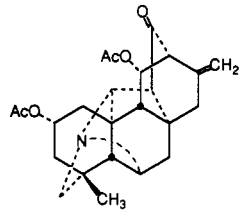
25

SCHEME 11

K_2CO_3 at 25° gave a mixture from which 2-acetyl-13-dehydro-11-*epi*-hetisine [**25**] was isolated (7). The structural assignment was based on its ^{1}H-nmr spectrum, which showed the H-11α as a doublet at δ 4.14 (J = 5.1 Hz). This small coupling constant is indicative of a β-hydroxyl at C-11. An α-hydroxyl group at C-11 would be expected to show a doublet with a large coupling (J = 9.0 Hz) owing to the H-11β. An example is 13-acetyl-2-dehydrohetisine, which shows H-11β at δ 4.28 (d, J = 9.0 Hz). A smaller coupling for H-11α is in agreement with a dihedral angle between the H-11α and H-9β of about 120°. The coupling relation between H-11α and H-9β in **25** was shown by irradiation of C-11α (δ 4.14), when the doublet for H-9β at δ 3.11 (J = 5.1 Hz) became a singlet (Scheme 11).

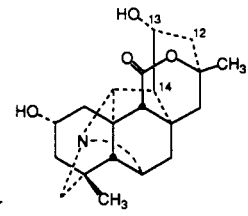
The epimerization of the 11-OH in **24** under the mild basic conditions apparently proceeds through hydrolysis of the C-11 acetate, followed by a retroaldol reaction to give an aldehyde which can then undergo an aldol condensation to give the 11β-OH epimer [**25**] (Scheme 11).

In contrast to the reaction of **24** with methanolic K_2CO_3 at room temperature, under refluxing conditions **24** gave the rearrangement product **26**. The structure assignment was proved by oxidation of **26** with CrO_3/pyridine to compound **23** whose structure had been determined previously by a single crystal X-ray analysis (Scheme 12).



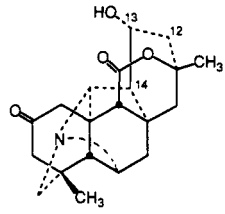
24

K_2CO_3, MeOH, H_2O
Δ



CrO_3/pyridine

26 *m/z* 345;
ir 3360, 3060, 1720 cm^{-1};
^{1}H nmr δ 0.97 (3H, s, 4-Me,
1.37 (3H, s, —C(=O)—Me),
No olefinic protons at δ 5.00

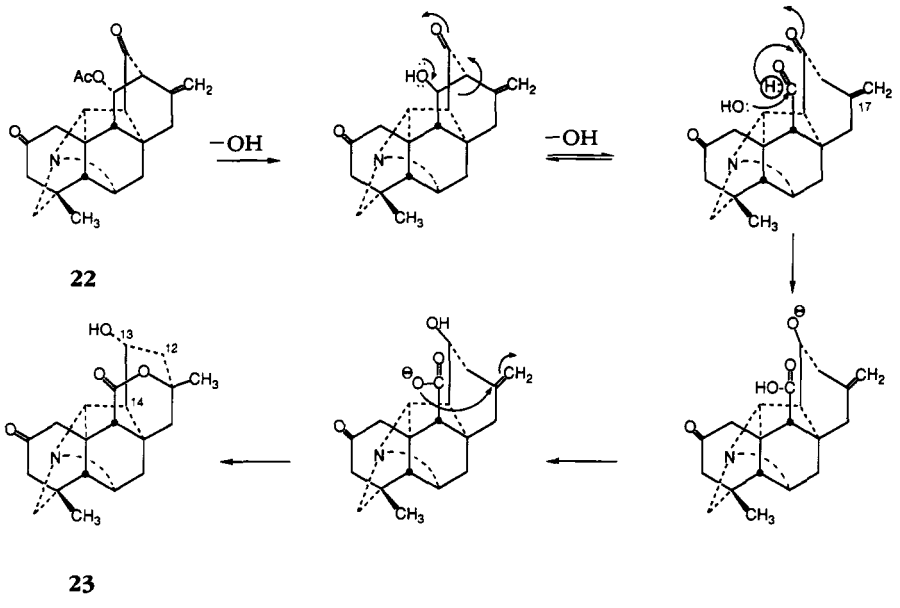


23

SCHEME 12

We suggest the following mechanism to account for the rearrangement of **22**↦**23** and **24**↦**26**. The first step appears to be the hydrolysis of the C-11 acetyl group under mild conditions (25°). The C-11 acetyl group is more susceptible to hydrolysis than the C-2 acetyl function in **24**. That the hydrolysis is accompanied by a reverse aldol condensation is suggested by the formation of the 11β-OH epimer **25** as mentioned above. Under conditions of reflux, a Cannizzaro-type process occurs, involving attack of hydroxide on the formyl moiety, accompanied by an intramolecular hydride transfer of the aldehydic hydrogen to the carbon of the C-13 carbonyl group (8–10). Then on workup under mildly alkaline conditions, the rearranged lactone **23** or **26** is obtained (Scheme 13).

Several years ago when the structure of kobusine [**27**] (11,12) was still uncertain we



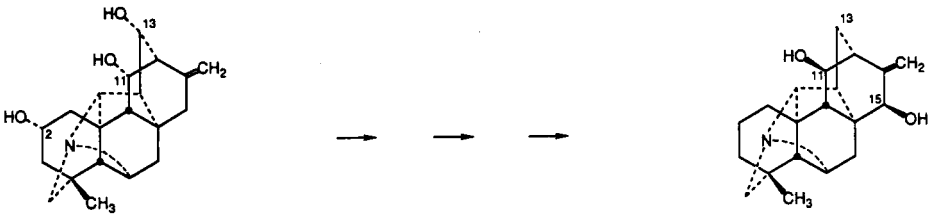
SCHEME 13

attempted a correlation with hetisine (13). Through several conventional reactions (14), hetisine was converted to 2-deoxy-11-dehydrohetisine [**28**]. Treatment with mesyl chloride afforded the mesylate **29**. Reduction of the mesylate with $LiAlH_4$, instead of removing the C-13 oxygen, furnished an interesting rearrangement product **30** containing a cyclopropyl group (13). The ^{1}H-nmr spectra of the product [δ 0.93 (s, C-CH_3), 1.18 ppm (s, CCH_3)] and of its acetate [δ 0.95 (s, CCH_3), 1.20 (s, CCH_3), 2.03 (s, $OCOCH_3$), 5.19 ppm (d, $J=8$ Hz, $CHOAc$] indicate that two tertiary methyl groups are present and that the vinyl protons of the exocyclic methylene group have disappeared. The new methyl signal at δ 1.18 ppm is considerably more deshielded than any of the tertiary methyl groups previously encountered in the hetisine series. The cyclopyropyl alcohol [**30**] was oxidized with chromic acid to a ketone **31**: mp 139–141°; ν max 1680 cm^{-1} (EtOH) 240 (ϵ 5400), 277.5 nm (ϵ 54); *m/z* 295, with spectral properties consistent with that of a ketone α to a cyclopropyl ring (Scheme 14).

The structure of the cyclopropyl derivative **30** was determined by single-crystal X-ray analysis of the methiodide (13). The formation of **30** can be rationalized in terms of an intermediate such as **32** in which some species of aluminium, such as hydride or oxide, coordinates with one of the mesylate oxygens providing at least partial ionization. Hydride attack on **32** could then occur at C-17 to afford the cyclopropyl derivative **30** (Scheme 15). This reaction represents the first reported example of this type of skeletal rearrangement among the diterpene alkaloids, though homoallylic carbocation rearrangements have ample precedents in other systems (14–16).

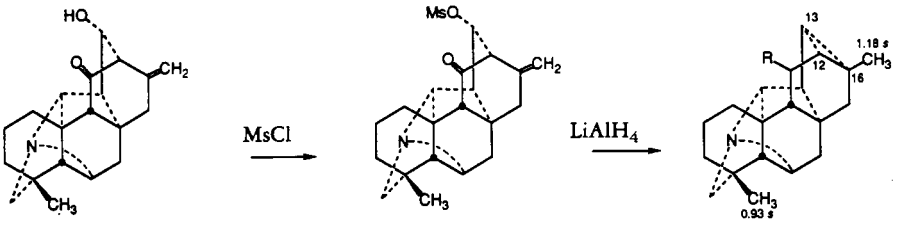
Dunstan and his colleagues (17) showed over 100 years ago that heating aconitine [**33**] with MeOH in a sealed tube at 120–130° led to replacement of an acetyl group with a methyl group to give a compound named "methylpikraconitine" [**34**] (Scheme 16). Schulze later confirmed these results (18). Of course the structure of aconitine was not known at that time. Later, Jacobs and Craig showed that delphinine behaved similarly (19). We know now that the change that occurs involves replacement of the 8-OAc group with an 8-OMe group.

Recently we have discovered that this reaction is very facile and that reaction in a sealed tube is unnecessary. The reaction occurs readily in refluxing MeOH to give a



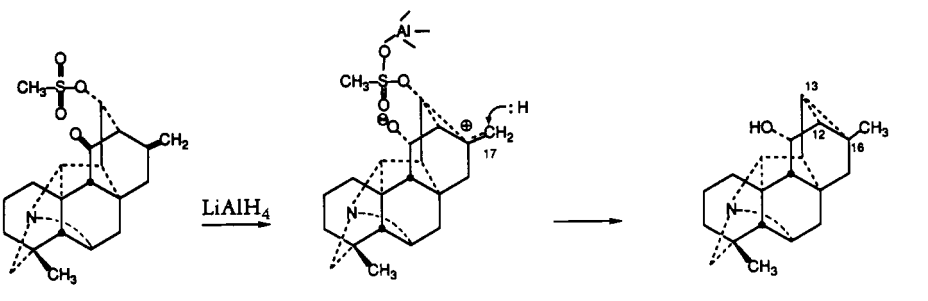
1 hetisine

27 kobusine



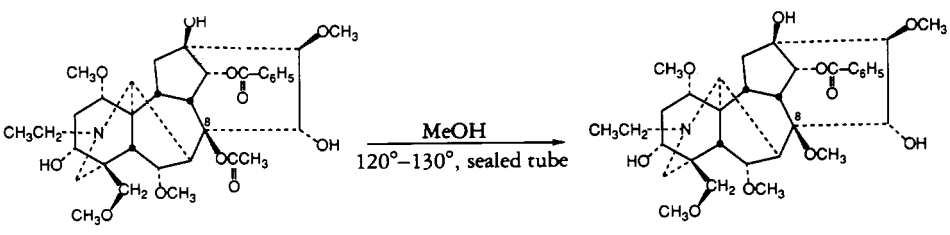
28 **29** **30** R=α-OH
31 R= =O

SCHEME 14



29 **32** **30**

SCHEME 15

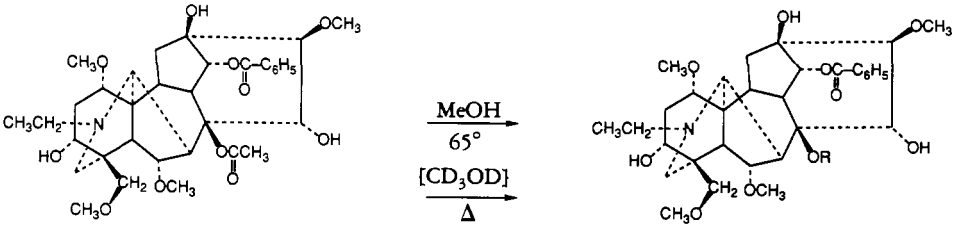


33 aconitine

34 methyl benzaconine
"methylpikraconitine"

SCHEME 16

quantitative yield of the 8-methoxy derivative **34** (20). Heating aconitine in CD_3OD under conditons of reflux afforded compound **35**. Since the 8-OMe group in **34** is shielded by the ring current of the C-14α benzoate, the methyl hydrogens of the 8-OMe group appear at δ 3.16. As expected, this methoxyl signal is absent in **35**. The reaction occurs so easily that crystallization of aconitine from MeOH is not recommended, for our experience shows that the crystallized product is invariably contaminated with substantial amounts of the 8-OMe derivative (Scheme 17).



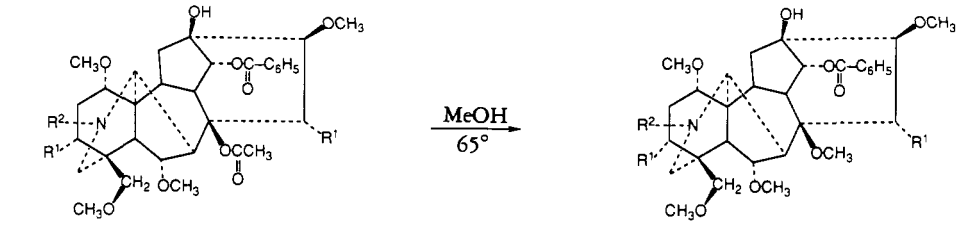
33 aconitine

34 R=Me δ 3.16
35 R=CD_3

SCHEME 17

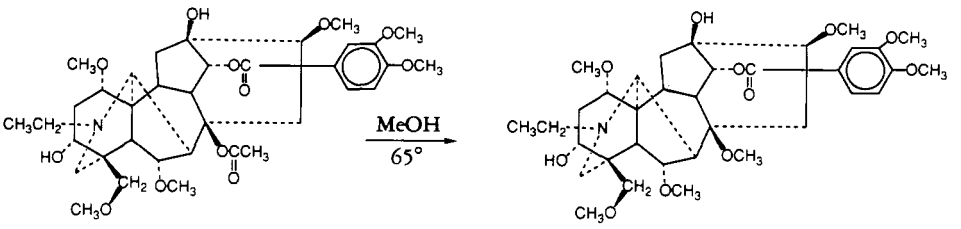
The reaction is a general one, for heating delphinine [**36**], 3-deoxyaconitine [**37**], and 8-*O*-acetylfalconerine [**38**] in refluxing MeOH gave the corresponding 8-OMe derivatives **39**, **40**, and **41**, respectively (20) (Scheme 18).

Also, using this reaction we have been able to effect a partial synthesis of the rare alkaloid hokbusine A [**43**] by heating mesaconitine [**42**] in MeOH (20) (Scheme 19). Comparison of the ^{13}C-nmr spectrum of hokbusine A, supplied by Dr. John Snyder (21), with that of our synthetic product **43** indicated identity. The ir spectrum of **43** in KBr was superimposable with that of an authentic sample of hokbusine A supplied by Dr. Yoshiteru Oshima. A comparison of the ^{13}C nmr spectra in $CDCl_3$ and in CD_3OD also showed identity.



36 R^1=H, R^2=Me delphinine
37 R^1=OH, R^2=Et 3-deoxyaconitine

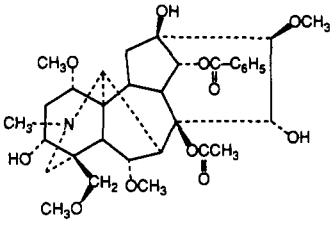
39 R^1=H, R^2=Me
40 R^1=OH, R^2=Et



38 8-*O*-acetylfalconerine

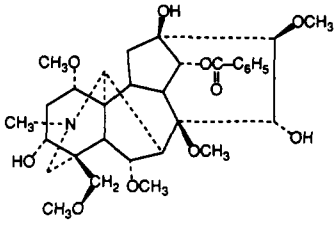
41

SCHEME 18



42 mesaconitine

MeOH
65°



43 hokbusine A
"*jianyouaconitine*"

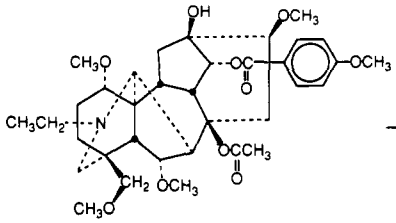
SCHEME 19

We have also been able to effect partial syntheses of the rare alkaloids acoforestine [**46**] and acoforestinine [**47**] by treating crassicauline A [**44**] and yunaconitine [**45**], respectively, with EtOH at reflux temperature (20). Of interest is the fact that an *n*-propyl group may be substituted at C-8 by refluxing yunaconitine with *n*-propyl alcohol (Scheme 20).

The mechanism of this facile replacement of the C-8 acetate group is of considerable interest. Edwards (22) interpreted this reaction in the case of bikhaconitine [**48**] as a rapid reversible formation of an ionic species **49** which, by attack of MeOH at C-8, gives the 8-OMe derivative **50** by reestablishment of the original skeleton (Scheme 21).

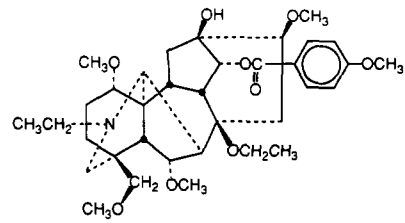
The facile conversion of the 8-OAc group proceeds via a synchronous fragmentation process involving cleavage of the C-7–C-17 bond of the type described by Grob *et al.* (23). The free electron pair of the nitrogen atom is oriented anti and parallel (anti-periplanar) with respect to the C-7–C-17 bond that undergoes cleavage, as is required for such a fragmentation (Figure 7).

An unusual epimerization of delphisine [**51**] takes place when it is solvolyzed in MeOH at reflux temperature (24) (Scheme 22). 8-OAc was replaced as expected with a methoxyl group, but the 1α-OH group was epimerized to a 1β-OH group. The evidence for the epimerization follows: The product **52**, mp 152–153°, showed an un-

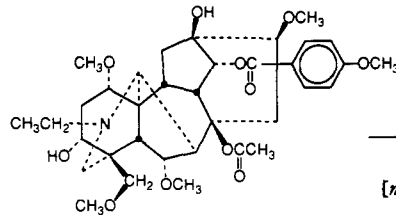


44 crassicauline A

EtOH
Δ

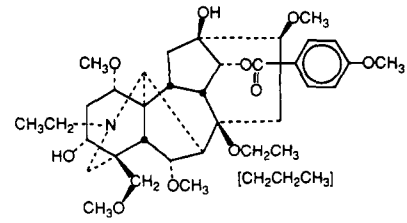


46 acoforestine



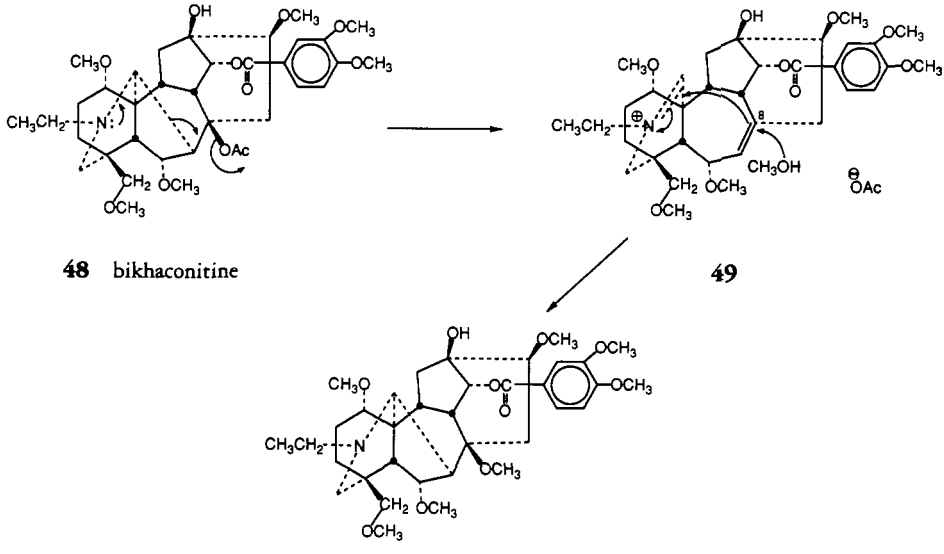
45 yunaconitine

EtOH
Δ
[*n*-PrOH]



47 acoforestinine

SCHEME 20



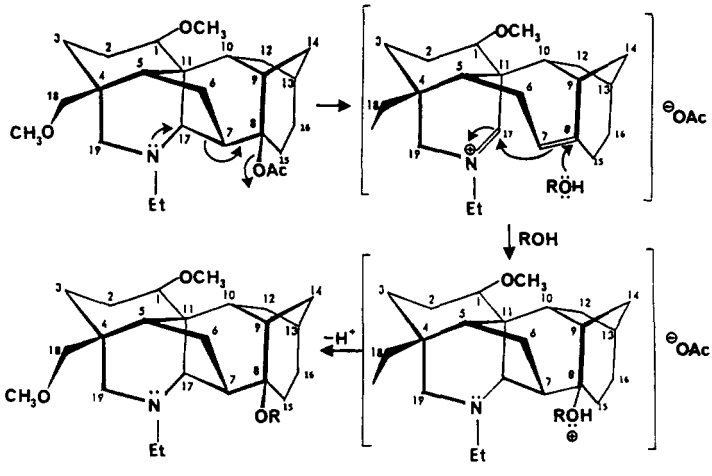
48 bikhaconitine **49**

50

SCHEME 21

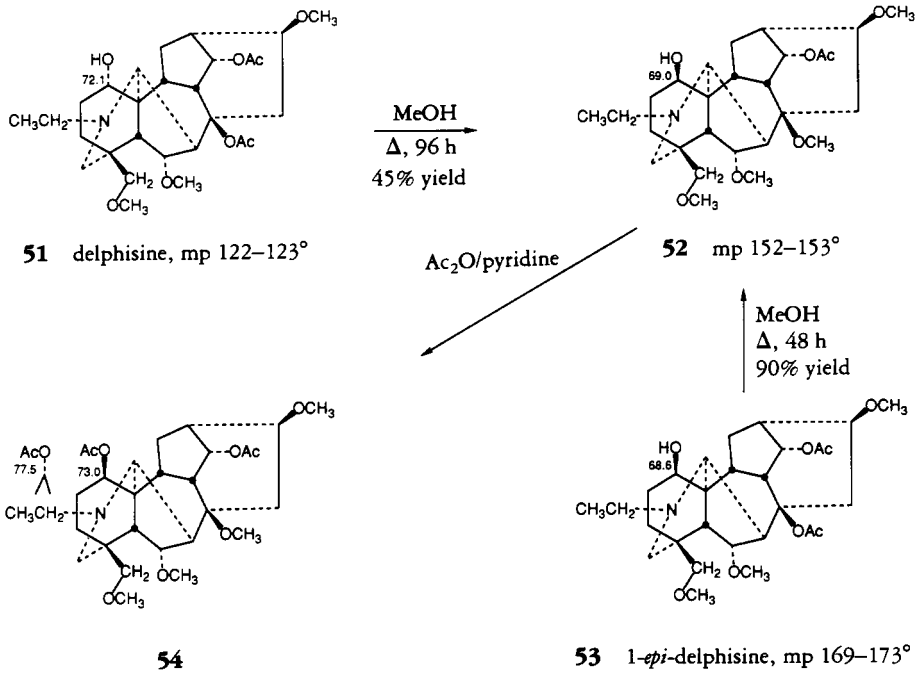
usual chemical shift (69.0 ppm) for C-1 compared with that for C-1 of delphisine [**51**] (72.1 ppm). By comparison, 1-*epi*-delphisine [**53**] with a 1β-OH shows a chemical shift at 68.6 ppm (25).

Methanolysis of 1-*epi*-delphisine [**53**] gave, in a yield of 90%, a product identified as 8-deacetyl-8-*O*-methyl-1-*epi*-delphisine [**52**] and possessing characteristics identical with those of the methanolysis product obtained from delphisine. The structure of **52** was also supported by the chemical shift of 73.0 ppm for its acetylation product **54**. This signal is assigned to C-1 bearing a β-OAc group, because alkaloids with a 1α-OAc show a signal at about 77.5 ppm (25). In summary, during solvolysis of delphisine, epimerization of the 1α-OH accompanies replacement of the 8-OAc group by a methoxyl function.



R=alkyl

FIGURE 7. Synchronous fragmentation mechanism.



51 delphisine, mp 122–123°

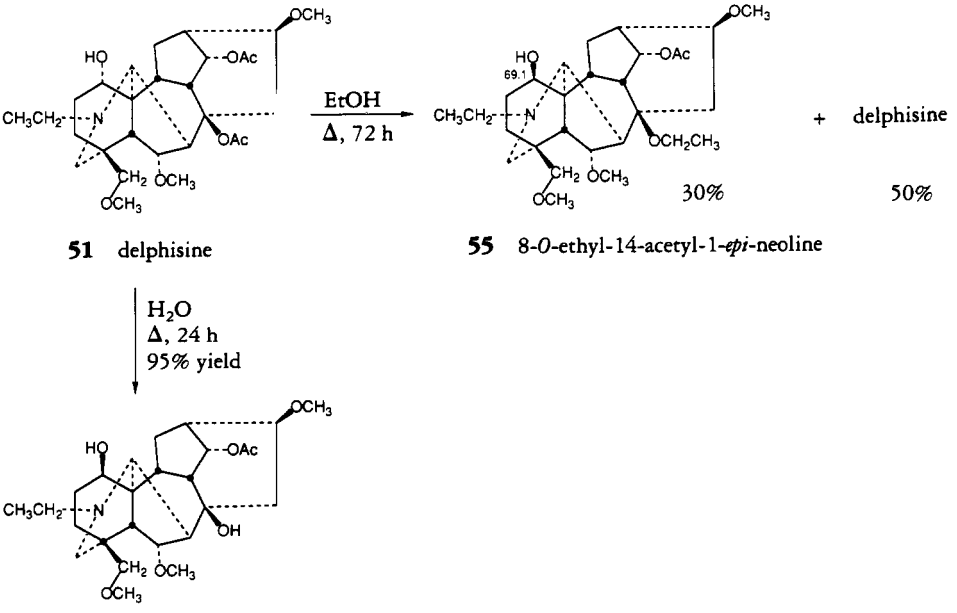
52 mp 152–153°

54

53 1-*epi*-delphisine, mp 169–173°

SCHEME 22

Refluxing a solution of delphisine [**51**] in EtOH for three days afforded 8-*O*-ethyl-14-acetyl-1-*epi*-neoline [**55**] in a yield of 30%. Refluxing a suspension of delphisine in H_2O for 24 h gave 14-*O*-acetyl-1-*epi*-neoline [**56**] (26) in a yield of 95% (Scheme 23). In both reactions epimerization occurred at C-1.



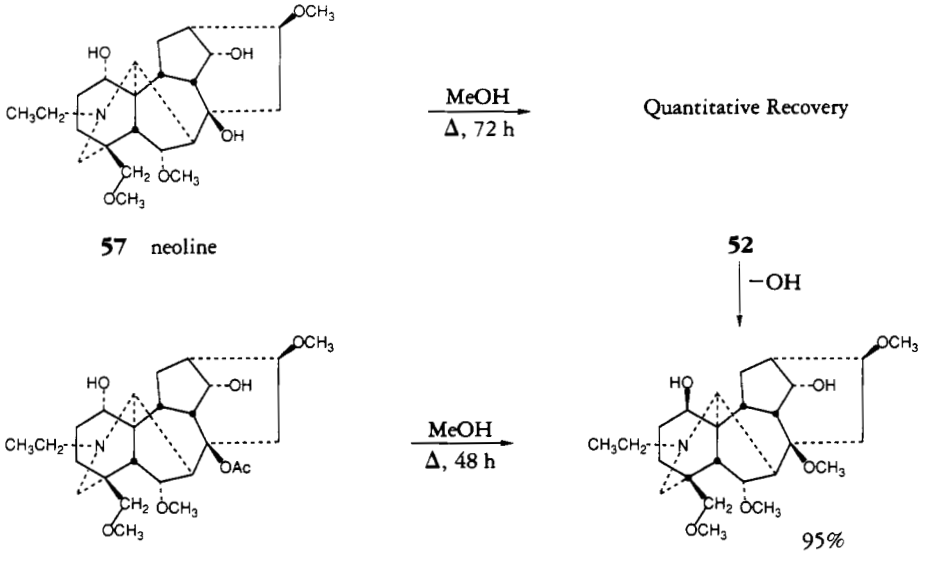
51 delphisine

55 8-*O*-ethyl-14-acetyl-1-*epi*-neoline

56 14-*O*-acetyl-1-*epi*-neoline

SCHEME 23

Treatment of other delphisine-related alkaloids under these solvolysis conditions gave interesting results. Heating a solution of neoline [**57**] in MeOH under reflux for four days led to a quantitative recovery of neoline. By contrast, 8-*O*-acetylneoline [**58**] under similar conditions gave 8-*O*-methyl-1-*epi*-neoline [**59**] (95% yield) which was identical with the product formed by alkaline hydrolysis of compound **52** prepared by solvolysis of delphisine in MeOH (Scheme 24).



57 neoline

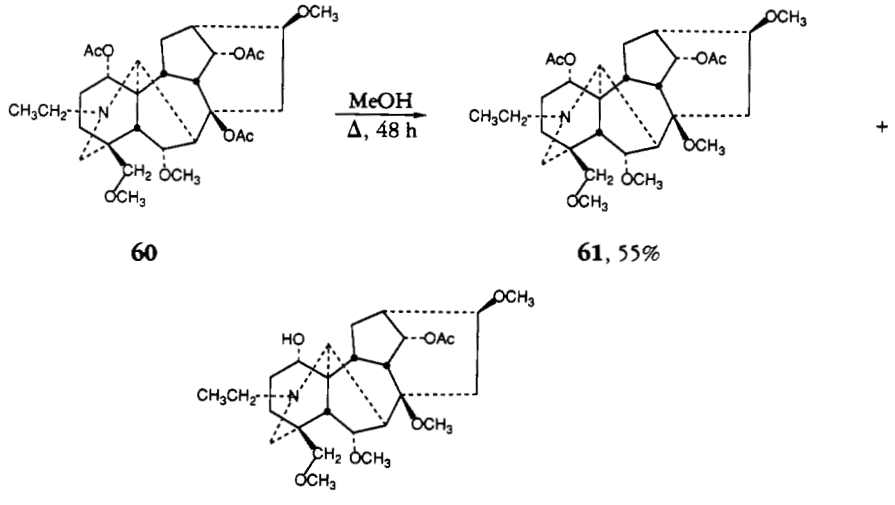
52

59 8-*O*-acetylneoline

58 8-*O*-methyl-1-*epi*-neoline

SCHEME 24

Treatment of 1-*O*-acetyldelphisine [**60**] in refluxing MeOH afforded two products: 1,14-di-*O*-acetyl-8-methoxyneoline [**61**] (55%) and 14-*O*-acetyl-8-methoxyneoline [**62**] (35%) (Scheme 25). In this case epimerization at C-1 did not occur and the yield of the two products was nearly quantitative.



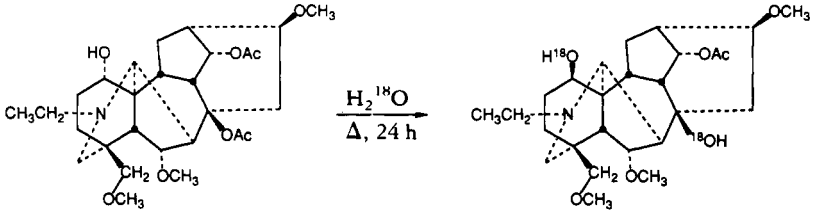
60

61, 55%

62, 35%

SCHEME 25

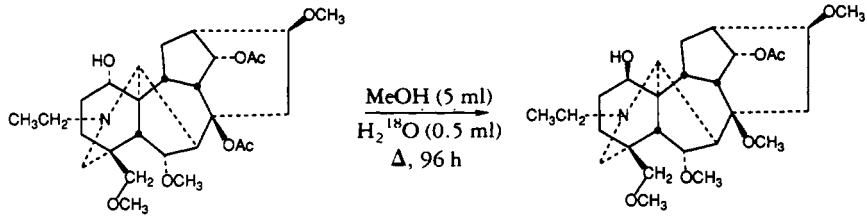
In an effort to gain some insight into the mechanism of this epimerization, we carried out the reaction in $H_2{}^{18}O$. Heating delphisine [**51**] under reflux in $H_2{}^{18}O$ gave the 1-*epi*-derivative **63** in a yield of 95%. The high resolution mass spectrum showed molecular ion peaks at *m/z* 483.2969 (1.80%, calcd 483.2968 for $C_{26}H_{41}NO_5{}^{18}O_2$) and *m/z* 481.2927 (2.95%, calcd 481.2926 for $C_{26}H_{41}NO_6{}^{18}O$). These results indicate that about 38% of the product is formed by addition of two molecules of $H_2{}^{18}O$ and 62% by addition of one molecule of $H_2{}^{18}O$ (Scheme 26).



51 delphisine

63, 95%

m/z 483.2969 (1.80%, calcd 483.2968 for $C_{26}H_{41}NO_5{}^{18}O_2$)
481.2927 (2.95%, calcd 481.2926 for $C_{26}H_{41}NO_6{}^{18}O$)



51 delphisine

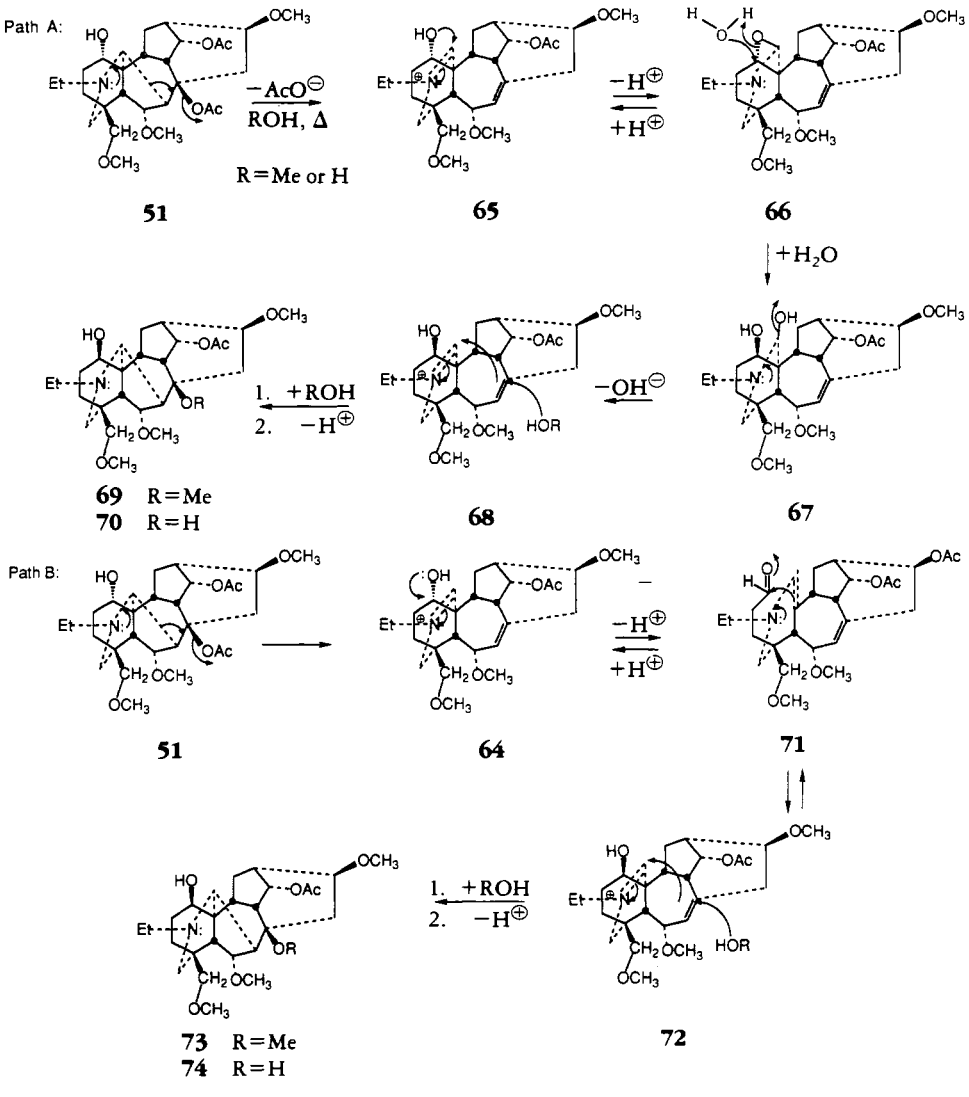
64, 13%

SCHEME 26

Repeating the reaction in 10% $H_2{}^{18}O$ in MeOH showed that 13% of the product **64**, as shown by the mass spectrum, was formed by addition of one molecule of $H_2{}^{18}O$. MM2 calculations (27) reveal that delphisine [**51**] has an energy 1.34 kcal·mole^{-1} higher than its rearrangement product **52**. The higher energy of delphisine [**51**] as compared with epimer **52** is also indicated by an examination of Dreiding models: delphisine shows strong 1,3-interaction between the 1α-OH and the C-10–C-12 bond.

Based on the above results, we have proposed two plausible mechanisms for this unusual epimerization (24). Formation of **65** from delphisine [**51**] is initiated by a synchronous fragmentation of the Grob type (23) mentioned previously, with the electron pair of nitrogen oriented anti and parallel to the C-7–C-17 bond that undergoes cleavage (20). Epimerization may then proceed by two pathways (Scheme 27). Path A proceeds through formation of an oxetane ring **66** which is opened by addition of H_2O to the β face (28) to give **67**. Because H_2O is regenerated by this mechanism, only a trace of H_2O is necessary for the epimerization to proceed. Loss of a hydroxyl group from C-17 leads to **68**. Attack of H_2O or ROH at C-8, followed by loss of a proton, affords the epimeric product **69** or **70**, respectively.

In path B, two epimeric intermediates, **64** and **72**, are equilibrated through the aldehyde intermediate **71**. In refluxing MeOH, the epimerization proceeds predominantly through path B, with formation of the more stable **73**. In boiling H_2O, an increasing amount of **74** forms through path A as indicated by the ^{18}O labelling experiments. It is important to note that each pathway requires both a 1α-OH and an 8-OAc



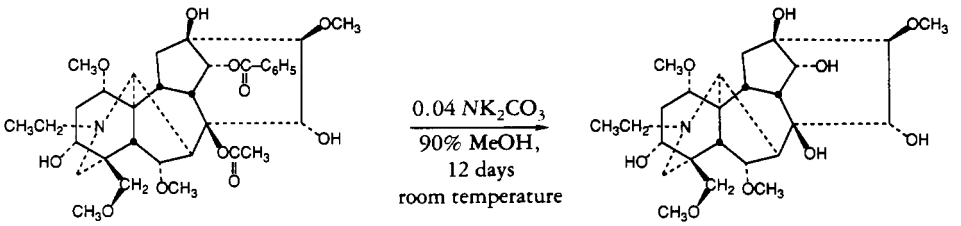
SCHEME 27

for the C-1 epimerization to occur. Consistent with the above mechanisms, neither 1-*epi*-delphisine [**53**], neoline [**57**], nor 1-*O*-acetyldelphisine [**60**] undergoes this epimerization.

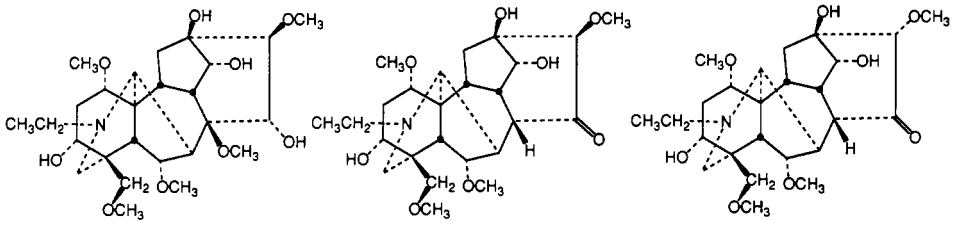
The last rearrangement to be discussed is one that Dr. Alex Katz and H. Rudin have reported for aconitine [**33**] (29). They observed that treatment of aconitine [**33**] with 0.04 *N*-K_2CO_3 in 90% MeOH at room temperature for twelve days produced not only the expected hydrolysis product, aconine [**75**], but also 8-*O*-methylaconine [**76**], 14-debenzoyl-pyroaconitine [**77**], and 16-*epi*-14-debenzoyl-pyroaconitine [**78**] (Scheme 28).

The formation of aconine [**75**] and 8-*O*-methylaconine [**76**] is easily accounted for via an ionic species **79** produced by the synchronous fragmentation reaction we have already discussed. Attack of H_2O or MeOH at C-8 on carbocation **79** produces aconine **75** and 8-*O*-methylaconine [**76**], respectively (Scheme 29).

Formation of the C-16 epimeric pyro-derivatives can be accounted for by the



33 aconitine **75** aconine

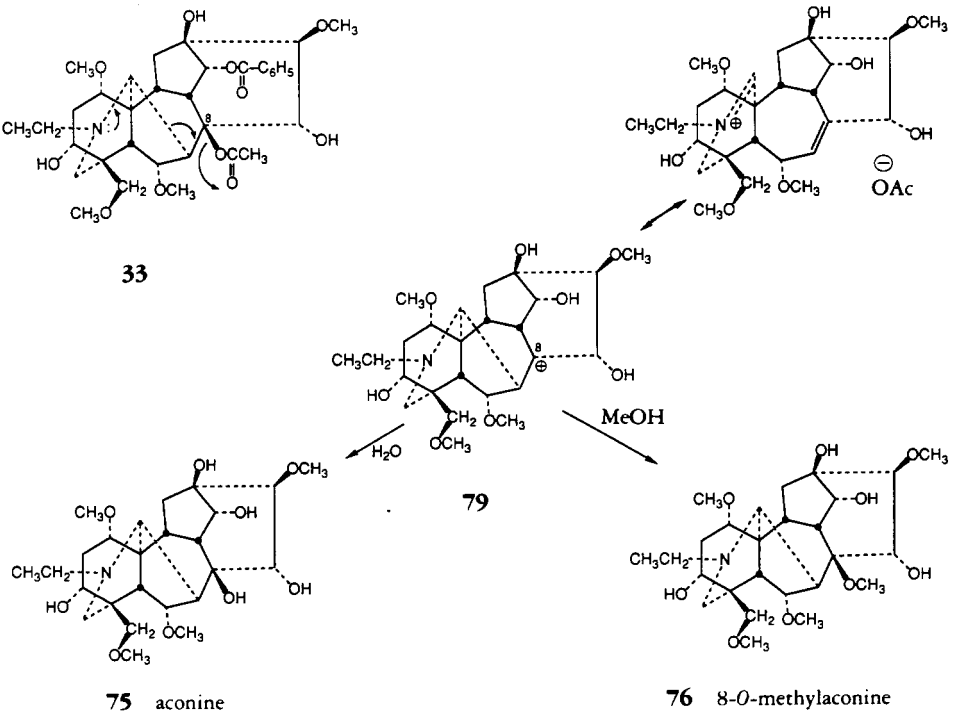


76 8-*O*-methylaconine **77** 14-debenzoyl-pyroaconitine **78** 16-*epi*-14-debenzoyl-pyroaconitine

SCHEME 28

mechanism shown in Scheme 30. Loss of a proton from **79** leads to enol **80** which can readily ketonize to **77**. Equilibration through enol **81** leads to 16-*epi*-14-desbenzoyl-pyroaconitine [**78**].

There is a passage in the Psalms (30) which says, "The Heavens declare the glory of

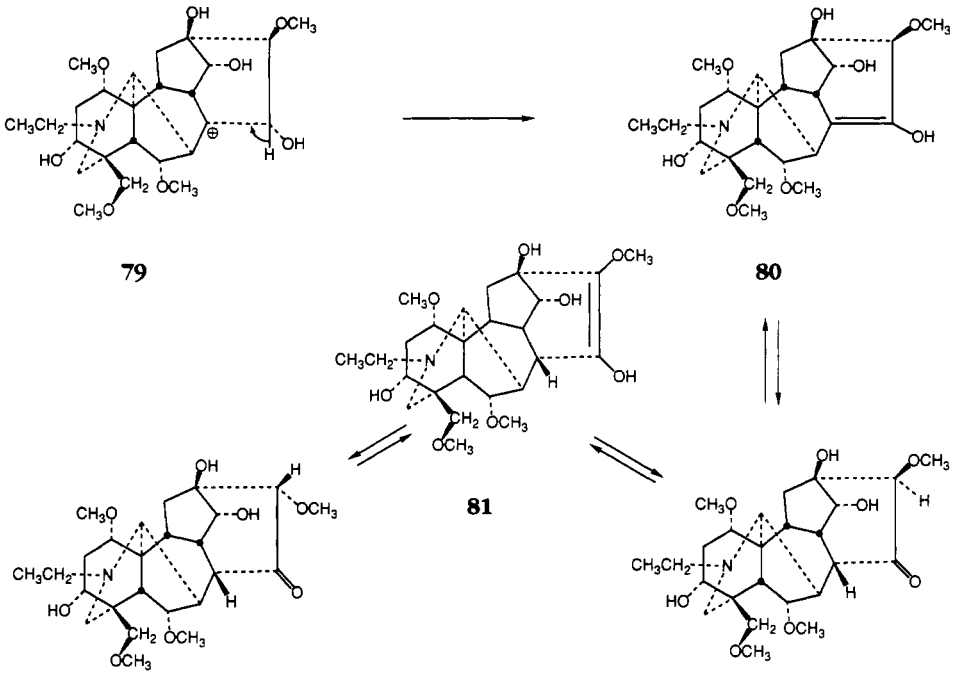


33

79

75 aconine **76** 8-*O*-methylaconine

SCHEME 29



79 **80** **81**

78 16-*epi*-14-debenzoyl-pyroaconitine **77** 14-debenozyl-pyroaconitine

SCHEME 30

God; the skies proclaim the work of His hands." I have been working in the field of natural products for forty years now. As we unravel the structures of complex natural products and illuminate their fascinating chemistry, I am impressed over and over with the marvellous design and handiwork of the Creator. In a certain real sense as I explore and discover new truth about the part of the universe that I work in, I feel that I am thinking God's thoughts after Him.

ACKNOWLEDGMENTS

The summary of rearrangements presented in this paper is based on work carried out in my laboratories by my colleagues, Abdel-Monem M. Ateya, Haridutt K. Desai, Joseph T. Etse, Jan A. Glinski, Qingping Jiang, Balawant S. Joshi, Joseph A. Maddry, Naresh V. Mody, Janet Finer-Moore, M. Gary Newton, Samir A. Ross, Lee C. Schramm, Kottayil I. Varughese, and Harold E. Wright. I express my thanks and appreciation to these individuals.

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