through the cooling coils. The sulfonium salt (ca. 0.3 mmol) was placed in a porcelain boat which was inserted in the entry tube at the end covered by the rubber septum. A steel wire through the septum permitted subsequent positioning of the boat. The aspirator was started and the system flushed for 15 min with oxygen at a rate of 15 ml/min. The traps were filled with liquid nitrogen and the sample boat pushed near and eventually into the furnace entrance. The water in the cooling coil was turned off to permit gradual heating of the sample. After 15 min the system was turned off and the sulfur dioxide trap removed.

Dimethyl sulfide was combusted in essentially the same way. The sample was contained in a liquid-nitrogen-cooled U-tube trap with a bypass which was inserted just after the Ascarite trap in the oxygen line. When the furnace reached operating temperature the liquid nitrogen was removed from the trap and the stopcocks turned so that the oxygen stream would pass through the trap and slowly carry the dimethyl sulfide into the furnace as the trap warmed up.

Isotope Ratio Determinations were performed on an Atlas CH-4 mass spectrometer equipped with dual Faraday cup collectors. The amplifier for the signal from the less-abundant isotope was a vibrating-reed electrometer. Samples from a given extent of reaction and from 100% reaction (in the case of sulfur dioxide, the 100% sample was from combustion of the original sulfonium salt) were introduced into the dual inlet system and the sample sizes adjusted to be the same within ±2%. In the earlier work (A. M. Katz) on the isotope effects with bromide, thiophenoxide, ethoxide, and phenoxide, the samples were measured as dimethyl sulfide (*m/e* 62 and 64). In the later work (R. Hargreaves) on the isotope effects with ethoxide in mixtures of ethanol and dimethyl sulfoxide, the samples were measured as sulfur dioxide (*m/e* 64 and 66). The 100% and *X*% samples were compared four or five times and the average taken for each isotope effect determination.

Control Experiments. In the reactions of trimethylsulfonium bromide with thiophenoxide and ethoxide <5% of the trimethylsulfonium ion reacted with bromide ion to give methyl bromide. In the reaction with phenoxide, however, methyl bromide constituted approximately 20% of the product. The observed isotope effect (IE_{obsd}) was then corrected by means of the relation $IE_{obsd} = 0.80\ (IE_{corr}) + 0.20\ (IE_{Br^- \text{ reaction}})$. Trimethylsulfonium bromide and thiophenol do not react under the conditions employed for reaction with thiophenoxide. The mass spectra of all samples were scanned and any samples containing significant impurities in the *m/e* 12–98 region were rejected.

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Alkaloids of *Delphinium staphisagria*. The Structure and Stereochemistry of Delphisine, Neoline, Chasmanine, and Homochasmanine

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Abstract: A new alkaloid, delphisine, has been isolated from the seeds of *Delphinium staphisagria* by a combination of pH extractions and chromatographic techniques. Chemical and spectral studies have suggested that it is a member of the aconitine-type alkaloids. An x-ray crystal structure determination of its hydrochloride confirmed it to be an aconitine-type alkaloid, with 1α-hydroxyl, 6α-methoxyl, 8β-acetate, 14α-acetate, 16β-methoxyl, 18-methoxyl, and *N*-ethyl substituents. The space group is $P2_12_12_1$, a = 13.866 (1), b = 22.27 (1), c = 9.098 (1) Å. The final agreement residuals are R = 0.0351 and R_w = 0.0400, based on 2875 observed reflections. The absolute configuration of delphisine is shown to be 1*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*R*, 9*R*, 10*R*, 11*S*, 13*R*, 14*S*, 16*S*, 17*R*. Ring A was found to exist in the boat conformation, stabilized by intramolecular hydrogen bonding. Spectral studies showed that this conformation exists in solution as well, and suggested that the previously published structure of neoline is in error. Neoline was prepared from delphisine by several routes. Comparison of both neoline and delphisine with their 1-epimers showed that neoline must have a 1α-hydroxyl group. On the basis of other well-established chemical correlations, the structures of chasmanine and homochasmanine must also be revised to show a 1α substituent.

The seeds of *Delphinium staphisagria L.* on extraction with ligroin yield a substantial alkaloid fraction of which delphinine (**1**) is the major component.[1] Accompanying delphinine are smaller amounts of the dimeric alkaloid staphisine (**2**).[2,3] A careful reexamination of the amorphous fraction accumulated during the isolation of a large quantity of delphinine led to the isolation of a new diterpene alkaloid named delphisine (**3**);[4] mp 122–123 °C, $[\alpha]^{26}D$ 7.1° (*c* 4.0, ethanol). In this paper we present the details of our chemical studies of this alkaloid[5] and its correlation with neoline.[6]

Isolation of Delphisine. The separation of the alkaloids present in the amorphous fraction depended primarily on differences in basicity. Staphisine (**2**), which is the major constituent of the amorphous fraction (~40%, after the removal of delphinine (**1**)), is very sensitive to heat and light. Long treatment (1 week or more) of staphisine on an active

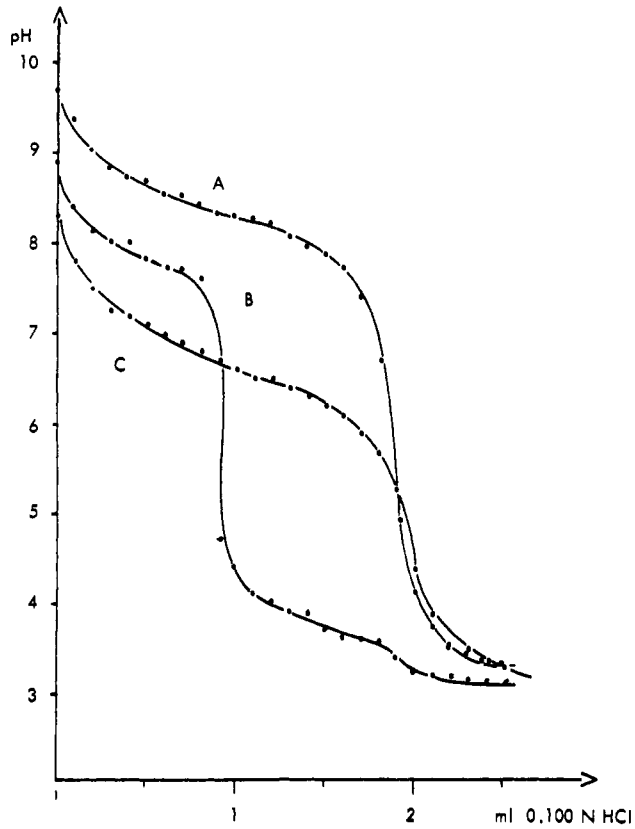
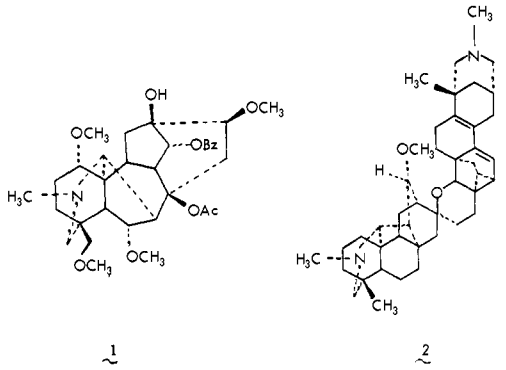


Figure 1. The neutralization curves for the alkaloids: (A) delphinine, (B) staphisine, and (C) delphisine.

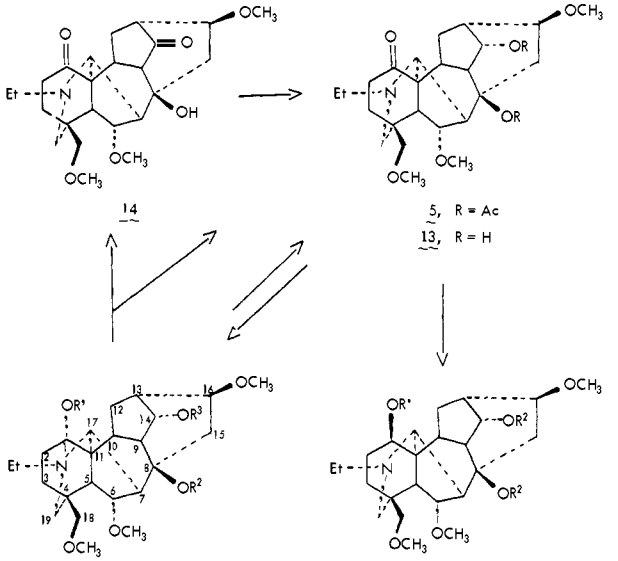


1 2

adsorbent, such as alumina, promotes decomposition to more polar derivatives, the separation of which is difficult. Figure 1 shows the results of an investigation of the ratio of free base to protonated base for the three principal components of the amorphous fraction. Delphinine (**1**, curve A, pK_a = 8.3),[7] staphisine (**2**, curve B, pK_a = 7.8 for the monoprotonated form), and delphisine (**3**, curve C, pK_a = 6.6) differ sufficiently in their basicity that separation of **3** can be accomplished by extraction at different pH values. *A posteriori*, it might be hypothesized that this behavior is related to the strong intramolecular hydrogen bonding between the 1α-hydroxyl and the basic nitrogen in delphisine (see the discussion of the crystal structure and NMR data below), which cannot occur in either **1** or **2**. Such hydrogen bonding is not favored in aconitine,[8] and its pK_a value of 7.6 gives support to this concept. However, delphisine 1-acetate (**4**, pK_a = 6.8) can only form an intramolecular hydrogen bond in the protonated form, yet its basicity is unexpectedly low. In addition, neoline (**6**, pK_a = 7.5) and 1-*epi*-neoline (**12**, pK_a = 6.7) have pK_a values which are the reverse of the order which would be predicted from the hydrogen bonding argument, since the 1α-hydroxyl in **6** can form a hydrogen bond, while the 1β-hydroxyl in **12** cannot. Although such bonding may be a factor in the basicity of some alkaloids, it clearly does not offer a complete explanation of the anomalous behavior of **4, 6,** and **12.**

Chromatographic separation over alumina (Merck, activity III) of the amorphous fraction accumulated during the isolation of delphinine[1] yields 12.8% of the crystalline alkaloid delphisine (**3**). Delphisine was isolated in a yield of 35% from the pH 4 fraction.[9] The chromatographic separation of the pH 5 extract yielded a mixture of **3** and **1** (9:1). The chromatogram of this crude oil showed two distinct spots (alumina, hexane:ethanol 19:1), the separation of which is difficult. Treatment of this mixture with acetic anhydride-pyridine yields delphisine acetate (**4**) and unchanged **1.** From this mixture the crystalline **4** was obtained by chromatographic separation over SiO_2 (60-200 mesh) in a yield of 42.7%. The remaining base fraction (pH >5) containing the bulk of the alkaloids was shown to consist mainly of staphisine (**2**). The investigation of this extract is still in progress. The low-basicity alkaloids from the mother liquor can be also separated by chromatography over acidic absorbents (e.g., SiO_2). The first fractions were shown to consist mainly of **3.** Rechromatography of these fractions on alumina proves to be a very successful method for the isolation of **3.** Even the relatively stable delphisine (**3**) during extended chromatography over alumina suffers some decomposition. In one experiment, an extended chromatography (2 months) of the amorphous fraction from the delphinine mother liquors furnished the monoacetoxy compound (**10**), but no delphisine. Chromatographic separation after preliminary pH separation (extraction, or chromatography over SiO_2) required not longer than 1-3 days and led to good yields of delphisine.

Chemistry of Delphisine (3). Microanalysis indicated the empirical formula for **3** to be $C_{28}H_{43}NO_8$. The NMR spectrum (Figure 2) showed signals characteristic of two acetate groups (3 H singlets each at δ 1.96 and 2.02), one methyl from *N*-ethyl (3 H triplet at δ 1.12, J = 7 Hz), three methoxyl groups (3 H singlets each at δ 3.25, 3.30, and 3.31), and one OH broad proton signal at δ 7.10 (disappearing on addition of D_2O).



14 5, R = Ac; 13, R = H

3, R' = H, $R^2 = R^3$ = Ac
4, R' = $R^2 = R^3$ = Ac
6, R' = $R^2 = R^3$ = H
7, R' = Ac, $R^2 = R^3$ = H
8, R' = R^2 = Ac, R^3 = H
9, R' = R^3 = Ac, R^2 = H
10, R' = R^3 = H, R^2 = Ac
17, R' = $R^2 = R^3 = CH_3$
18, R' = CH_3, $R^2 = R^3$ = H
19, R' = $R^2 = CH_3$, R^3 = H

11, R' = CH_3, R^2 = H
12, R' = R^2 = H
15, R' = R^2 = Ac
16, R' = H, R^2 = Ac

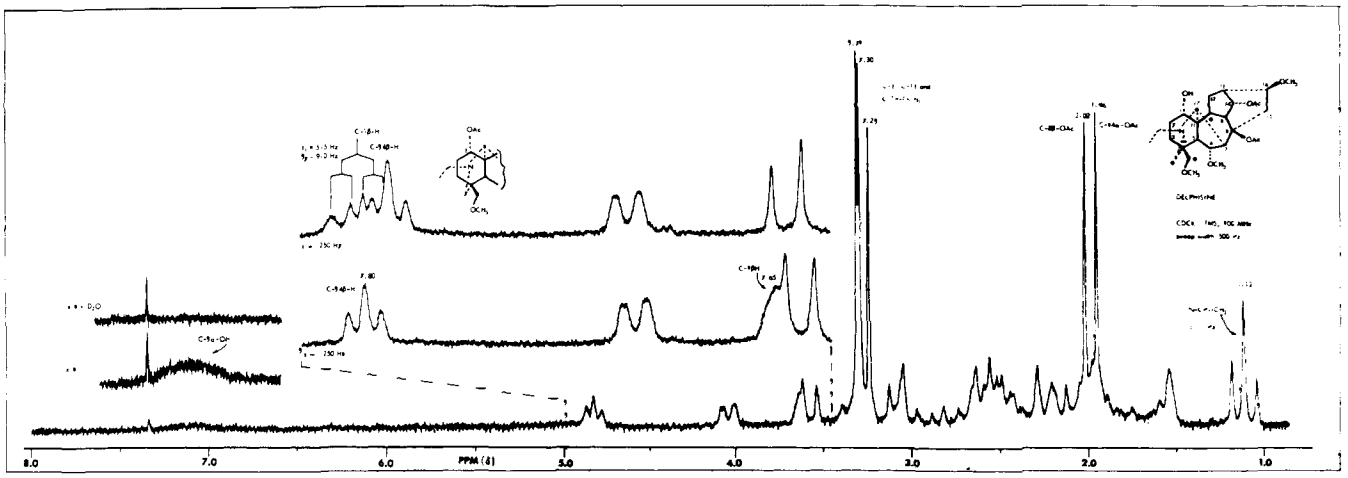


Figure 2.

Oxidation of delphisine (**3**) with Cornforth reagent (CrO_3-py-H_2O) gave 1-ketodelphisine (**5**), mp 170–171 °C, ν_{max} 1745, 1725 (OAc), and 1690 cm^{-1} (six-membered ketone), with no OH absorption. Delphisine was hydrolyzed with potassium carbonate in aqueous methanolic solution to the corresponding alkamine **6** which crystallized readily from ether or acetone–hexane, mp 159–161 °C. Under similar conditions of hydrolysis, delphisine acetate (**4**) has been converted mainly into monoacetate **7**. From the hydrolysis mixture two other compounds were isolated, the diacetate **8** (acetate groups in NMR 3 H singlets each at δ 1.98 and 2.02) and the alkamine **6** (no acetyl signal in NMR, no carbonyl absorption in ir). Treatment of **6** with acetic anhydride–pyridine mixture overnight at room temperature yielded diacetate **9** (acetate groups in NMR 6 H singlet at δ 2.02). Under more vigorous conditions of acetylation (acetic anhydride-*p*-toluenesulfonic acid at 100°) amino alcohol **6** formed a triacetate (NMR 6 H singlet at δ 2.02 and 3 H singlet at δ 1.97) which is identical with delphisine acetate (**4**). Diacetate **8** was obtained in very good yield when the **4** was treated in aqueous methanolic solution with potassium bicarbonate over 2 weeks at 35–40°. Under similar conditions, delphisine (**4**) has been converted into monoacetate **10.** Thus, the hydrolysis sequence of the three acetoxy groups in **4** is C-14, C-8, and C-1.

All simple derivatives of **3** were obtained under very mild experimental conditions. The spectral data in each case are consistent with the structure of **3** established by crystallographic analysis.

Molecular Structure and Stereochemistry of Delphisine (3). Treatment of delphisine in ethereal solution with HCl gas yielded a crystalline hydrochoride salt. On the basis of an x-ray crystal structure determination of delphisine hydrochloride, delphisine is established as a C_{19} diterpene alkaloid. The absence of an oxygenated functional group at C(7) shows that it is an aconitine-type alkaloid. Other substituents are 1α-hydroxyl, 6α-methoxyl, 8β-acetate, 14α-acetate, 16β-methoxyl, 18-methoxyl, and *N*-ethyl. The absolute configuration of delphisine is established as 1*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*R*, 9*R*, 10*R*, 11*S*, 13*R*, 14*S*, 16*S*, 17*R*. Ring A exists in the boat form in the solid state, presumably stabilized by an intramolecular N—H···O hydrogen bond. The hydroxyl hydrogen is hydrogen bonded to the Cl^- ion. Ring D also exists in the boat form, slightly flattened at C(15). Other aspects of the molecular structure are essentially as might be expected for such a system of fused and bridged rings. The numbering scheme used for the molecule is based on the conventional numbering of the aconitine-type alkaloids, and is shown in Figure 3. Significant interatomic distances and angles are listed in Table I.

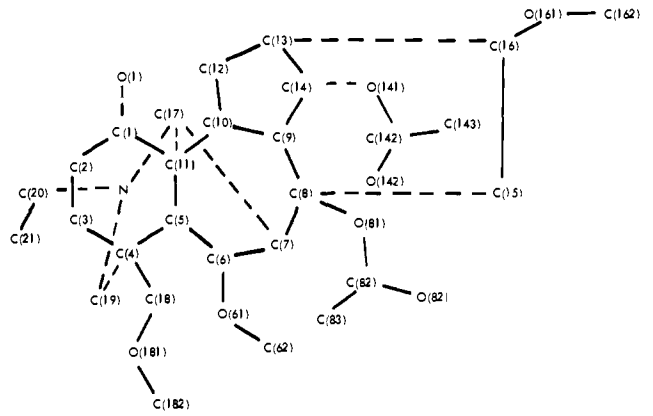


Figure 3. The numbering scheme used for the C, N, and O atoms in the molecule of delphisine hydrochloride. Hydrogen atoms are given the number of the nonhydrogen atom to which they are attached, with "A" or "B" appended where the hydrogen atom can be identified as belonging to the α or β side of the molecule; otherwise, an arbitrary integer is appended.

Influence of C-1 α-Substituent on Conformation of Ring A. A careful NMR study of **3** has shown that ring A retains the boat conformation in chloroform solution at room temperature. In the NMR spectrum of **3** (Figure 2) in lower field (between δ 3.5 and 5.0) there are four proton signals. The one proton intensity signal at δ 4.04 (doublet of doublets, J_1 = 1 and J_2 = 7 Hz) is assigned to C-6β H on the basis that the signal is invariable in the spectrum of demethoxyisopyrodelphinine in which the C-16α H (another alternative) is at much lower field. The signal centered at δ 4.80 (doublet of doublets, $J_1 = J_2$ = 4.5 Hz) which also appears in the NMR spectrum of condelphine[10] is assigned to the proton at C-14 which must be coupled with two nearly equivalent (C-9β and C-13β), adjacent protons. In the region between δ 3.5 and 3.7 there are two proton signals. One of these is a multiplet centered at δ 3.65 ($W_{H/2}$ = 6 Hz), and because the same signal is not seen in the spectrum of ketodelphisine (**5**) it can be assigned to C-1β H. The C-1β H signal in **4** is quite different, and suggests that the acetylation of the C-1α OH is accompanied by a conformation change in ring A. If ring A exists in the chair conformation, the dihedral angles between the geminal C-1 proton and the adjacent C-2 axial and equatorial protons are ~180 and ~60° and the signal should be split into a quartet with coupling constants of about 7 and 10 Hz. If ring A is in the boat conformation where the two dihedral

Table I. Significant Interatomic Distances and Angles in Delphisine Hydrochloride[a]

(a) Bonded Distances (Å) between Nonhydrogen Atoms

C(1)-O(1)	1.446 (3)	C(9)-C(10)	1.544 (3)
C(1)-C(2)	1.512 (3)	C(9)-C(14)	1.523 (3)
C(1)-C(11)	1.570 (3)	C(10)-C(11)	1.559 (3)
C(2)-C(3)	1.514 (4)	C(10)-C(12)	1.566 (3)
C(3)-C(4)	1.569 (4)	C(11)-C(17)	1.531 (3)
C(4)-C(5)	1.555 (3)	C(12)-C(13)	1.543 (3)
C(4)-C(18)	1.535 (4)	C(13-C(14)	1.529 (3)
C(4)-C(19)	1.538 (4)	C(13)-C(16)	1.533 (3)
C(5)-C(6)	1.555 (3)	C(14)-O(141)	1.458 (3)
C(5)-C(11)	1.566 (3)	O(141)-C(142)	1.315 (3)
C(6)-O(61)	1.426 (3)	C(142)-O(142)	1.186 (4)
C(6)-C(7)	1.556 (3)	C(142)-C(143)	1.499 (4)
O(61)-C(62)	1.423 (4)	C(15)-C(16)	1.533 (3)
C(7)-C(8)	1.545 (3)	C(16)-O(161)	1.437 (3)
C(7)-C(17)	1.522 (3)	O(161)-C(162)	1.426 (4)
C(8)-O(81)	1.468 (3)	C(17)-N	1.529 (3)
C(8-C(9)	1.548 (3)	C(18)-O(181)	1.425 (4)
C(8)-C(15)	1.546 (3)	O(181)-C(182)	1.393 (4)
O(81)-C(82)	1.340 (3)	C(19)-N	1.505 (3)
C(82)-O(82)	1.208 (3)	N-C(20)	1.503 (3)
C(82)-C(83)	1.495 (4)	C(20)-C(21)	1.503 (4)

(b) Bonded Distances Involving Hydrogen Atoms (Å)

O(1)-H(O1)	0.87 (4)	N-H(N)	0.93 (3)

For all C–H bonds (n = 42)
Range = 0.86 to 1.21, mean = 1.01, σ = 0.07

(c) Interatomic Distances between Atoms Involved in Hydrogen Bonding (Å)

O(1)···H(N)	1.83 (3)	Cl···H(O1)	2.15 (4)
O(1)···N	2.651 (3)	Cl···O(1)	2.988 (2)

(d) Other Close, Nonbonded Contacts with Cl (Å)

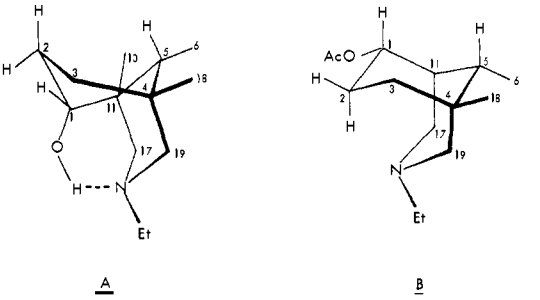
N···Cl	3.850 (2)	Cl···H(16A)	2.85 (3)
Cl···H(12A)	2.76 (3)	Cl···H(17A)	2.83 (3)

(e) Angles (Deg) between Bonded, Nonhydrogen Atoms

O(1)-C(1)-C(2)	106.8 (2)	C(1)-C(11)-C(10)	106.7 (2)
O(1)-C(1)-C(11)	113.6 (2)	C(1)-C(11)-C(17)	116.4 (2)
C(2)-C(1)-C(11)	109.8 (2)	C(5)-C(11)-C(10)	113.4 (2)
C(1)-C(2)-C(3)	110.4 (2)	C(5)-C(11)-C(17)	98.4 (2)
C(2)-C(3)-C(4)	113.9 (2)	C(10)-C(11)-C(17)	107.7 (2)
C(3)-C(4)-C(5)	110.5 (2)	C(10)-C(12)-C(13)	106.3 (2)
C(3)-C(4)-C(18)	106.5 (2)	C(12)-C(13)-C(14)	99.2 (2)
C(3)-C(4)-C(19)	112.0 (2)	C(12)-C(13)-C(16)	110.9 (2)
C(5)-C(4)-C(18)	114.4 (2)	C(14)-C(13)-C(16)	112.7 (2)
C(5)-C(4)-C(19)	107.4 (2)	C(9)-C(14)-C(13)	101.9 (2)
C(18)-C(4)-C(19)	106.1 (2)	C(9)-C(14)-O(141)	109.7 (2)
C(4)-C(5)-C(6)	113.9 (2)	C(13)-C(14)-O(141)	116.1 (2)
C(4)-C(5)-C(11)	108.7 (2)	C(14)-O(141)-C(142)	117.7 (2)
C(6)-C(5)-C(11)	103.1 (2)	O(141)-C(142)-O(142)	122.8 (3)
C(5)-C(6)-O(61)	113.0 (2)	O(141)-C(142)-C(143)	111.7 (2)
C(5)-C(6)-C(7)	104.8 (2)	O(142)-C(142)-C(143)	125.5 (3)
O(61)-C(6)-C(7)	112.7 (2)	C(8)-C(15)-C(16)	116.8 (2)
C(6)-O(61)-C(62)	113.3 (2)	C(13)-C(16)-C(15)	114.3 (2)
C(6)-C(7)-C(8)	109.9 (2)	C(13)-C(16)-O(161)	111.8 (2)
C(6)-C(7)-C(17)	104.3 (2)	C(15)-C(16)-O(161)	104.6 (2)
C(8)-C(7)-C(17)	108.8 (2)	C(16)-O(161)-C(162)	112.6 (2)
C(8)-O(81)-C(82)	122.6 (2)	C(7)-C(17)-C(11)	102.1 (2)
O(81)-C(82)-O(82)	124.8 (2)	C(7)-C(17)-N	113.9 (2)
O(81)-C(82)-C(83)	109.7 (2)	C(11)-C(17)-N	109.0 (2)
O(82)-C(82)-C(83)	125.6 (2)	C(4)-C(18)-O(181)	110.1 (2)
C(8)-C(9)-C(10)	113.1 (2)	C(18)-O(181)-C(182)	115.0 (3)
C(8)-C(9)-C(14)	111.2 (2)	C(4)-C(19)-N	113.4 (2)
C(10)-C(9)-C(14)	101.3 (2)	C(17)-N-C(19)	115.1 (2)
C(9)-C(10)-C(11)	117.3 (2)	C(17)-N-C(20)	111.4 (2)
C(9)-C(10)-C(12)	103.9 (2)	C(19)-N-C(20)	112.6 (2)
C(11)-C(10)-C(12)	113.8 (2)	N-C(20)-C(21)	112.7 (2)
C(1)-C(11)-C(5)	114.2 (2)		

[a] Esd's are shown in parentheses.

angles in question are nearly the same (~60°), the signal would be expected to be a triplet with coupling constant of about 3 Hz. In the case of C-1α OH (as in **3**) where the C-1β H signal was found to be a multiplet, $W_{H/2}$ = 6 Hz, the conformation of ring A is a boat (A). There are two reasons for this: the formation of an intramolecular hydrogen bond between N and C-1α OH, and the avoidance of the very close contact between C-1α OH and C-10–C-12 (syn-axial 1,3 interaction) which would be present if ring A were a chair. The infrared spectrum of delphisine (**3**) contained a broad absorption band (3640–3000 cm^{-1}) with a small peak at 3600 and two well-refined peaks at 3420 and 3235 cm^{-1}, indicative of a hydrogen-bonded hydroxyl group, and also the boat conformation for ring A.[8] If the C-1α OH is acetylated, the most important reason for the existence of ring A in boat form, the intramolecular hydrogen bond, is no longer possible and the conformation is found in chair B. The C-1β H signal in **4** at δ 4.86 is a quartet (J_{AX} = 9.0, J_{BX} = 5.5 Hz, X proton of an ABX-type quartet), but in this case the quartet signal is overlapped by the signal of the proton which is geminal to the acetate in the five-membered ring (C-14), and only three of the quartet peaks may be distinguished. In **7** the C-1β H signal can be clearly seen at δ 4.83 as a quartet (J_{AX} = 10, J_{BX} = 6 Hz). Removing the C-1β H signal from δ 3.65, by acetylation or oxidation of the C-1α OH group, left a one-proton intensity AB-type doublet, J = 9 Hz, centered at δ 3.58. This doublet is common to all aconitine-type alkaloids which are C-18- and C-6α-methoxyl substituted. In the alkaloid condelphine[10] the C-18 methylene signals appeared as two one-proton intensity doublets centered at δ 2.98 and 3.15 (J = 9 Hz). Because of the shielding effect of the C-6α OCH_3 group it is expected that the one of the two methylene protons in **3** will be found at lower field. Thus, the proton signal at δ 3.58 in the spectrum of **3** can be assigned to the lower field pair of C-18 methylene protons. The higher field C-18 methylene pair in the NMR spectrum of **3** can be seen only partially at δ 3.14 because the highest field part at δ 3.05 is overlapped with another proton signal. The connection between these two pairs was proved by NMR measurements under single irradiation decoupling of the centers at δ 3.05 and 3.14, respectively, in which case, the doublet at δ 3.58 looks quite different.



Correlation of Delphisine with Neoline. The hydrolysis product of delphisine, the amino alcohol **6**, is by exhaustive comparison *identical with neoline*, an alkaloid which was first isolated from amorphous aconitine by Freudenberg and Rogers.[11] Careful studies led Wiesner et al.[12] to assign structure **6** with a C-1α hydroxyl to the alkaloid. However, Marion et al.[13] subsequently correlated neoline with chasmanine, an alkaloid reported[14,15] to have structure **11** and, on this basis assigned structure **12**, with a C-1β hydroxyl, to neoline. Our study was undertaken to resolve this discrepancy. 1-Ketodelphisine (**5**) was hydrolyzed with alkali to the 1-keto-8,14-diol derivative (**13**), mp 150–152 °C. The latter also was prepared from **3** by the reverse procedure. Hydrolysis of **3** to the corresponding triol **6**, followed

by oxidation with Cornforth reagent, gave **13** as well as the 1,14-diketo derivative **14,** mp 170–171 °C, ν_{max} 1740 and 1690 cm^{-1}. The diketo derivative **14** was reduced with 1 equiv of sodium borohydride to a product which is identical with **13.** The stereospecifity of this reduction is anticipated, because the β side of the 14-keto group is less hindered,[16] thereby favoring an α-oriented 14-hydroxyl group. Similar arguments cannot be applied to the reduction of the 1-keto function. Reduction of **13** with sodium borohydride proceeded without stereospecifity, to afford a mixture of two epimeric triols **6** and **12** in a ratio of 1:3, respectively, which could be separated by preparative TLC over silica gel. The less polar triol **12** crystallized from chloroform as a chloroformate, mp 100–105°, $[\alpha]^{26}D$ +6.0° (*c* 5.3, ethanol). The more polar epimer was shown to be identical with the hydrolysis product of delphisine and, therefore, may be assigned structure **6.** The ir spectra of the epimeric triols **6** and **12** were different, especially in the hydroxyl region. The triol **6** showed broad absorption between 3620 and 3000 cm^{-1}, with a sharp peak at 3525 and a well-defined peak at 3290 cm^{-1}, indicative of a hydrogen-bonded hydroxyl group. In contrast triol **12** showed hydroxyl absorption between 3600 and 3210 cm^{-1} centered at 3430 cm^{-1}. The NMR spectra of the triols were also different. In **6** the methoxyl signals are at δ 3.35 (6 H singlet) and 3.32 (3 H singlet), and the methyl of the *N*-ethyl group at δ 1.12 (3 H triplet, J = 7 Hz). In **12** the methoxyl signals are at δ 3.32 (6 H singlet) and 3.29 (3 H singlet), and the methyl of the *N*-ethyl group at δ 1.03 (3 H triplet, J = 7 Hz). The NMR spectrum of the triol was different, especially the signals of the C-1 protons. Compound **6** displayed a multiplet at δ 3.66 ($W_{H/2}$ = 6 Hz); compound **12** showed a similar multiplet at δ 3.86. Similarly, when ketodelphisine (**5**) was subjected to reduction, delphisine (**3**) and 1-*epi*-delphisine (**15**) were obtained. On treatment with acetic anhydride and *p*-toluenesulfonic acid, triol **12** furnished triacetate **16** which was found to be different from triacetate **4** obtained from delphisine (**3**).

It will be noted that the structure of neoline, as proposed by Wiesner, et al.,[12] corresponds to epimer **6** while that proposed by Marion, et al.,[13] corresponds to epimer **12.** The epimer **6,** mp 159–160 °C, $[\alpha]^{26}D$ +21° (*c* 4.0, ethanol) *is identical* with natural neoline, mp 161 °C,[11] $[\alpha]^{26}D$ +22° (*c* 4.3, ethanol); thus a mixture of the two compounds produced a single spot in TLC and had an undepressed melting point (159 °C). The ir spectra, obtained in chloroform solution, KBr pellet, and Nujol mull, and the NMR spectra in $CDCl_3$ of both substances were respectively superimposable. Triol **6** and neoline also had identical ^{13}C NMR spectra (±0.05 ppm). Thus neoline must be assigned structure **6** and the revised structure **12** assigned by Marion, based on the correlation with chasmanine,[13] is in error.

The structure previously assigned to chasmanine from correlation of the alkaloid with browniine,[14] which in turn has been correlated with lycoctonine,[15] must now be considered. Chasmanine has been correlated[13] with neoline by treatment of each alkaloid with sodium hydride and methyl iodide in refluxing dioxane. The products **17,** designated as 1,8,14-tri-*O*-methylneoline and 8,14-di-*O*-methylchasmanine, respectively, were shown to be identical by mixture melting point, rotation, behavior on TLC, ir and nmr spectra, and by identical Debye-Scherrer diagrams. We have replicated this correlation, and there is no doubt about the identity of the two products. Consequently, on the basis of the correlation of chasmanine with neoline, chasmanine must have a 1α substituent and accordingly be assigned structure **18.** A ^{13}C NMR study of chasmanine, deoxyaconitine, delphinine, delphonine, and 1,8,14-tri-*O*-methylneoline[17] confirms this assignment. Because chasmanine diacetate has been converted to homochasmanine by treatment with methanol under pressure, followed by saponification,[18] homochasmanine may therefore be assigned structure **19.**

Experimental Section

General Experimental Procedures. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Rotations were taken in absolute ethanol. Infrared spectra were taken in KBr pellets (unless otherwise specified) on a Perkin-Elmer Model 137 Infracord and Model 237B spectrometers. NMR spectra were taken on a Varian HA-100 spectrometer, with tetramethylsilane as an internal standard.

Isolation of Delphisine (3). (A) Chromatographic Separation of the Amorphous Basic Fraction. The amorphous alkaloid mixture (16.0 g) which resulted from the concentration and desiccation of the mother liquors from the preparation of delphinine (**1**)[1] was dissolved in benzene (50 ml) and chromatographed over alumina (1400 g, Merck, neutral activity III). Elution of the column with hexane (1.5 l.) gave 5.0 g, which was shown to consist mainly of staphisine (**1**)[3] and crystallized readily from the concentrated acetone solution (mp 195–207 °C). The next fractions from the chromatograph yielded 3.5 g which was shown to consist mainly of staphisine.

Since elution of the column five times with 500 ml portions of hexane gave no product, the eluent was changed to 0.5% ethanol in hexane. With this solvent also, only a very small amount of substance totalling 0.7 g (from 5 × 500 ml portions) was eluted. Again the eluent was changed to 1% ethanol in hexane. The next two (500 ml each) fractions yielded 1.4 g of residue, which on TLC resembles the original basic fraction, except that the intensity of the spot corresponding to staphisine is diminished. The next fractions, 1.5, 1.8, 0.93, and 0.4 g (each from 500 ml of eluent), were shown to consist mainly of delphisine (**3**). The total amount of the crude **3** (4.55 g) was dissolved in acetone (25 ml) and diluted with hexane (200 ml). This solution was concentrated on the steam bath to about 50 ml of its volume (during the concentration the solution was filtered several times to keep it clear). The colorless crystals which were obtained (2.05 g) melted at 118–120 °C. Recrystallization of crude **3** from acetone–hexane mixture gave colorless crystals melting at 122–123 °C: $[\alpha]^{26}D$ +7.1° (*c* 4.0, ethanol); ν_{max} 3600, 3420, 3235 (hydrogen-bonded OH), 1745, 1725, 1235 (OAc), and 1065 (C–O) cm^{-1}; NMR δ 1.12 (3 H triplet, J = 7 Hz, NCH_2CH_3), 1.96 and 2.02 (3 H singlet each, C-14 and C-8 $OCOCH_3$), 3.25, 3.30, and 3.31 (3 H singlet each C-6, C-16, and C-18 OCH_3), 3.09 and 3.58 (1 H AB-type doublet each, J = 9 Hz, C-4 CH_2OCH_3), 3.65 (1 H multiplet, $W_{H/2}$ = 6 Hz, C-1β H), 4.04 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), 4.80 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H) and 7.10 (1 H broad, disappearing an addition of D_2O, C-1α OH).

Anal. Calcd for $C_{28}H_{43}NO_8$: C, 64.47; H, 8.30; N, 2.68. Found: C, 64.36; H, 8.36; N, 2.69.

Delphisine hydrochloride was prepared by treatment of an ethereal solution of the alkaloid with HCl gas. Clear tabular crystals were obtained from methanol–ether mixture (1:1), mp 206–210 °C dec.

(B) pH Separations. The amorphous alkaloid mixture (50 g)[1] accumulated during the isolation of a large quantity of delphinine (**1**) from the seeds of *Delphinium staphisagria* was dissolved in benzene (500 ml) and acidified with 2% H_2SO_4 to pH 1.0. The aqueous phase (~2 l.) was cooled and progressively basified (concentrated NH_4OH) and extracted with chloroform to give a pH 4 fraction[9] of 10.8 g, a pH 5 fraction of 8.2 g, and a pH >5 fraction of 25.8 g.

The pH 4 alkaloid fraction (10.0 g) was dissolved in benzene (100 ml) and chromatographed over alumina (1250 g). Elution of the column with hexane (2 l.) gave 0.4 g of residue which consisted of crude staphisine (**2**). The eluent was changed to 1% ethanol in hexane. The fractions after evaporation of the solvent were monitored by TLC (alumina, Merck, GF-254, Type E, hexane:ethanol 19:1) and were separated into two major groups. The first group consisted mainly of staphisine and related alkaloids, delphinine, and 50% delphisine (total amount 2.4 g), and the second consisted of crude delphisine (3.7 g). The latter fraction was used without further purifiction for the preparation of 1-ketodelphisine (see below).

The pH 5 alkaloid fraction (8.2 g) was chromatographed over alumina (1000 g) as above to yield fraction 1 (1.6 g) containing a mixture of the alkaloids, and fraction 2 (5.4 g) containing mainly **3** accompanied by ~10% of **1**, crystallization of which is difficult. Fraction 2 was dissolved in acetic anhydride–pyridine mixture (100 ml) (1:1), and the solution was allowed to stand at room temperature overnight. The mixture was poured over ice (500 g) and made basic with sodium carbonate, and the solution extracted with chloroform. Evaporation of the extract left an oily residue (6.8 g). Chromatographic separation of the products over silica gel (500 g, mesh 60–200) using hexane and hexane–ethanol mixture (up to 5%) as eluent yielded **4** (3.5 g). Recrystallization of crude **4** from boiling hexane gave colorless crystals melting at 149–151 °C, $[\alpha]^{26}D$ 0.0° (*c* 2.0, ethanol); ν_{max} 1745, 1728, 1250 (OAc), 1110 (C–O) cm^{-1}; NMR δ 1.09 (3 H triplet, J = 7 Hz, N–CH_2CH_3), 1.97 and 2.02 (3 H singlet and 6 H singlet, respectively, C-1, C-8, and C-14 $OCOCH_3$), 3.26, 3.28, and 3.31 (3 H singlet each, C-6, C-16, and C-18 OCH_3), 4.06 (doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), 4.73 (1 H doublet of doublets $J_1 = J_2$ = 4.5 Hz, C-14β H) and 4.86 (1 H ABX-type quartet, J_{AX} = 9, J_{BX} = 5.5 Hz).

Anal. Calcd for $C_{30}H_{45}NO_9$: C, 63.92; H, 8.05; N, 2.48. Found: C, 63.81; H, 8.27; N, 2.54.

Delphisine Acetate (4) from Neoline.[12] A mixture of neoline **6** (380 mg) and *p*-toluenesulfonic acid (500 mg) in acetic anhydride (15 ml) was heated on a steam bath for 1 h. After cooling, the mixture was poured over ice and made basic with sodium carbonate, and the solution extracted with chloroform. Evaporation of the solvent left a gum which was crystallized from boiling hexane to yield 270 mg, mp 148–150 °C, identical with a sample of **4** prepared by acetylation of delphisine.

Neoline 1-Acetate (7). To an aqueous methanolic (10% water) solution (25 ml) of potassium carbonate (500 mg) was added **4** (500 mg), and the solution was stirred at room temperature (25°) overnight. After removal of the solvent under vacuum, the residue was dissolved in water (50 ml) and extracted five times with chloroform. The extracts were combined and dried over sodium sulfate, and the solvent was removed under vacuum leaving a clear varnish. The latter was dissolved in chloroform (4 ml) and spread on a 3-mm thick 200 × 400 mm alumina (Merck, PF 254 + 366, Type T) plate. Development of the plate with hexane–ethanol mixture (19:1) and visualization by a uv lamp showed three bands. The least polar compound, the diacetate **8** (27 mg), was obtained as an oil: ν_{max} 3400 (OH), 1745, 1250 (OAc), and 1100 (C–O) cm^{-1}; NMR δ 1.15 (3 H triplet, J = 7 Hz, NCH_2CH_3), 1.98 and 2.02 (3 H singlet each, C-1 and C-8 $OCOCH_3$), 3.26, 3.28, and 3.31 (3 H singlet each, C-6, C-16, and C-18 OCH_3). The central band yielded the oily monoacetate **7** (270 mg): ν_{max} 3450 (OH), 1745, 1250 (OAc), 1100 (C–O) cm^{-1}; NMR δ 1.12 (3 H triplet, J = 7 Hz, NCH_2CH_3), 2.02 (3 H singlet C-1 $OCOCH_3$), 3.28, 3.31, and 3.34 (3 H singlet each, C-6, C-16, and C-18 OCH_3), 4.10 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H), 4.24 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), and 4.83 (1 H ABX-type quartet, J_{AX} = 10, J_{BX} = 6 Hz, C-1β H). The most polar compound, neoline (**6**) (90 mg), was obtained as a crystalline solid, mp 159–160 °C (hexane–ether).

Neoline 8-Acetate (10) and Neoline (6) by Hydrolysis of Delphisine. Delphisine (**3**) (500 mg) was treated with potassium carbonate (500 mg) in aqueous methanolic solution (25 ml) as above. The usual workup, followed by preparative TLC separation afforded the monoacetate **10** (26 mg) as an oil: ν_{max} 3600–3000 (OH), 1745, 1250 (OAc), 1100 (C–O) cm^{-1}; NMR δ 1.13 (3 H triplet, J = 7 Hz, NCH_2CH_3), 2.00 (3 H singlet, C-8 $OCOCH_3$), 3.26, 3.31, and 3.34 (3 H singlet each C-6, C-16, and C-18 OCH_3), and neoline (**6**) (380 mg), mp 159–160 °C; $[\alpha]^{26}D$ +21° (*c* 4.0, ethanol); ν_{max} 3550, 3525, 3290 (OH), and 1110 (C–O) cm^{-1}; NMR δ 1.12 (3 H triplet, J = 7 Hz, NCH_2CH_3), 3.32 and 3.35 (3 H singlet and 6 H singlet, respectively, C-6, C-16, and C-18 OCH_3).

Anal. Calcd for $C_{24}H_{39}NO_6$: C, 65.88; H, 8.98; N, 3.20. Found: C, 65.72; H, 9.14; N, 3.27.

Delphisine (200 mg) was treated with potassium bicarbonate (200 mg) in aqueous methanolic solution (10 ml) at 35–40° over 2 weeks. The usual workup followed by preparative TLC afforded the monoacetate (**10**) (112 mg) and neoline (**6**) (42 mg).

Neoline 1,14-Diacetate (9).[12] To a solution of neoline (**6**) (200 mg) in pyridine (2 ml) at room temperature acetic anhydride (2 ml) was added. After standing overnight, the mixture was poured onto ice and made basic with sodium carbonate. Extraction with chloroform and drying (Na_2SO_4) the chloroform extract, followed by evaporation to dryness under vacuum, yielded an oil: ν_{max} 3400 (OH), 1745, 1250 (OAc), 1110 (C–O) cm^{-1}; NMR δ 1.11 (3 H triplet, J = 7 Hz, NCH_2CH_3), 2.03 (6 H singlet, C-1 and C-14 $OCOCH_3$), 3.23, 3.28, and 3.33 (3 H singlet each, C-6, C-16, and C-18 OCH_3), 3.66 (1 H AB-type doublet, J = 9 Hz, C-4 CH_2OCH_3), 4.14 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), 4.75 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H), and 4.82 (1 H ABX-type quartet, J_{AX} = 9, J_{BX} = 6 Hz, C-1β H).

1-Ketodelphisine (5). Cornforth reagent (CrO_3–py–H_2O) was prepared by the gradual addition of a solution of 2 g of chromic anhydride in 2 ml of water to pyridine (20 ml) with stirring and ice cooling. This reagent (24 ml) was added to a solution of delphisine (**3**) (3700 mg) (see isolation of delphisine, part B) in pyridine (80 ml) with stirring and ice cooling. After 24 h the reaction mixture was directly filtered through a column of alumina (40 g, activity III) and eluted with benzene–ethyl acetate mixture (1:1). This yielded 2600 mg of an oil that crystallized from ether, mp 158–160°. After several recrystallizations from acetone–ether mixture the 1-ketodelphisine (**5**) consisted of colorless prisms, mp 170–171 °C: ν_{max} 1745, 1725 (OAc), 1690 (C=O), 1255 (OAc), 1120, and 1110 (C–O) cm^{-1}; NMR δ 1.10 (3 H triplet, J = 7 Hz, NCH_2CH_3), 1.97 and 2.02 (3 H singlet each, C-8 and C-14 $OCOCH_3$), 3.27 and 3.28 (6 H singlet and 3 H singlet, respectively, C-6, C-16, and C-18 OCH_3), 3.57 (1 H AB-type doublet J = 9 Hz, C-4 CH_2OCH_3), 4.00 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), 4.84 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H).

Anal. Calcd for $C_{28}H_{41}NO_8$: C, 64.72; H, 7.95; N, 2.70. Found: C, 65.01; H, 7.64; N, 2.79.

1-Ketoneoline (13).[12] A solution of **5** (2500 mg) in methanol (30 ml) was treated with a 50% solution of KOH in water (2 ml), and the mixture was stirred at room temperature for 12 h. Water was added (100 ml) and most of the methanol was evaporated under vacuum. The residue was acidified with 2 N sulfuric acid to pH 1 and extracted with chloroform. The aqueous layer was basified with sodium carbonate and extracted with chloroform. This extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue (2100 mg) was a colorless oil that crystallized from hexane. After several recrystallizations from ether–hexane mixture the keto diol **13** had mp 150–152 °C; ν_{max} 1690, 1680 (C=O), 1120, 1100, 1075 (C–O) cm^{-1}; NMR δ 1.11 (3 H triplet, J = 7 Hz, NCH_2CH_3), 3.27, 3.28, and 3.35 (3 H singlet each, C-6, C-16, and C-18 OCH_3).

Anal. Calcd for $C_{24}H_{37}NO_6$; C, 66.18; H, 8.56; N, 3.21. Found: C, 66.23; H, 8.60; N, 3.26.

1,14-Diketoneoline (14).[12] Cornforth reagent (12 ml) was added to a solution of **6** (1000 mg) in pyridine (20 ml) with stirring and ice cooling. After 24 h the reaction mixture when worked-up in the usual manner (see above) furnished a mixture of diketo alcohol **14** and keto diol **13** in the ratio of roughly 3:2. Separation of these two compounds on 3 mm thick, 200 × 400 mm silica gel (Merck, H:HF) plates eluted with a mixture of chloroform:hexane:acetone (2:1:1) gave **14** (510 mg) (less polar): mp 170–172 °C; ν_{max} 1740, 1690 (C=O), 1125, 1100 (C–O) cm^{-1}; NMR δ 1.15 (3 H triplet, J = 7 Hz, NCH_2CH_3), 3.25, 3.27, and 3.35 (3 H singlet each, C-6, C-16, and C-18 OCH_3).

Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.14; N, 3.23. Found: C, 66.42; H, 8.24; N, 3.19.

The more polar compound was obtained in yield of 260 mg, and it was identical with the hydrolysis product of 1-ketodelphisine, viz. keto diol **13**.

1-Ketoneoline (13) by Reduction of 14.[12] Sodium borohydride (10 mg) was added to a stirred solution of the diketo alcohol **14** (100 mg) in 2-propanol (5 ml) at 20°, and the mixture was stirred overnight. Acetone was added (10 ml) and the mixture evaporated to dryness (under vacuum). The residue, dissolved in chloroform, was washed with five portions of 2 N sulfuric acid. The combined acid washings were neutralized with concentrated NH_4OH and extracted with chloroform. This extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue (80 mg), when purified on 2 mm thick 200 × 100 mm silica gel plates, afforded keto diol **13** (62 mg).

1-*epi*-Neoline (12). Sodium borohydride (300 mg) was added to a stirred solution of the keto diol **13** (700 mg) in methanol (30 ml) at room temperature over a period of 2 h. After 6 h of stirring, acetone was added and workup in the usual manner (see above) resulted in an oily mixture of two epimeric triols which was dissolved in 4 ml of chloroform and spread on two 3-mm thick 200 × 400 mm silica gel plates. Development of the plates with acetone–ethyl acetate (1:1) mixture and visualization by uv lamp showed two main bands. The less polar triol **12** was obtained as an oil that crystallized from chloroform (320 mg), mp 100–105 °C; $[\alpha]^{26}D$ +6.0° (*c* 5.3, ethanol); ν_{max} 3430 (OH), 1125, 1100 (C–N) cm^{-1}; nmr δ 1.03 (3 H triplet, J = 7 Hz, NCH_2CH_3), 3.29 and 3.32 (3 H singlet and 6 H singlet, respectively, C-6, C-16, and C-18 OCH_3), 3.60 (1 H AB-type doublet, J = 9 Hz, C-4 CH_2OCH_3), 3.86 (1 H multiplet, $W_{H/2}$ = 6 Hz, C-1α H), 4.15 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), and 4.23 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H).

Anal. Calcd for $C_{24}H_{39}NO_6 \cdot CHCl_3$: C, 53.91; H, 7.24; N, 2.51. Found: C, 53.76; H, 7.28; N, 2.59.

The more polar triol was obtained in yield of 110 mg and was identical with the hydrolysis product of delphisine, neoline (**6**).

1-*epi*-Delphisine Acetate (15). A mixture of triol **12** (500 mg) and *p*-toluenesulfonic acid (800 mg) in acetic anhydric (5 ml) was heated on a steam bath for 1 h. After cooling, the mixture was poured on ice and made basic with sodium carbonate; the solution was extracted with chloroform. Evaporation of the extract left a gum (490 mg) which was dissolved in 4 ml of chloroform and spread on a 3-mm thick silica gel plate. Development of the plate with a chloroform–ethyl acetate (7:3) mixture and visualization by uv lamp showed one main band (and a few less polar bands of small intensity). The triacetate (**15**) (320 mg) was obtained as an oil: ν_{max} 1745, 1725, 1250 (OAc), 1105 (C–O) cm^{-1}; NMR δ 1.07 (3 H triplet, J = 7 Hz, NCH_2CH_3), 1.96, 2.00, 2.03 (3 H singlet each, C-1, C-8, and C-14 $OCOCH_3$), 3.26 and 3.30 (3 H singlet and 6 H singlet, respectively, C-6, C-16, and C-18 OCH_3), 3.58 (1 H AB-type doublet, J = 9 Hz, C-4 CH_2OCH_3), 4.04 (1 H doublet of doublets, $J_1 \sim 1$, J_2 = 7 Hz, C-6β H), 4.80 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz), and 5.16 (1 H, multiplet, $W_{H/2}$ = 6 Hz, C-1α H).

1-*epi*-Delphisine (16). Sodium borohydride was added to a stirred solution of ketodelphisine (**5**) (500 mg) in methanol (25 ml) until no more starting material was detected by TLC. Acetone was added and workup in the usual manner (see above) resulted in an oily mixture of two epimeric acetoxy alcohols which was dissolved in 4 ml of chloroform and spread on two 3-mm thick 200 × 400 mm silica gel plates. Development of the plates with chloroform–ethyl acetate (6:4) mixture (twice) and visualization by uv lamp showed two bands. The less polar compound **16** was obtained as an oil (320 mg); ν_{max} 3460 (OH), 1750, 1730, 1250 (OAc), 1110 (C–O) cm^{-1}; NMR δ 1.08 (3 H triplet, J = 7 Hz, NCH_2CH_3), 1.96 and 2.02 (3 H singlet each, C-8 and C-14 $OCOCH_3$), 3.25, 3.27, and 3.30 (3 H singlet each, C-6, C-16, and C-18 OCH_3), 3.52 (1 H AB-type doublet J = 9 Hz, C-4 CH_2OCH_3), 3.96 (1 H multiplet, $W_{H/2}$ = 6 Hz, C-1α H), 4.03 (1 H doublet of doublets, J_1 = 1, J_2 = 7 Hz, C-6β H), and 4.86 (1 H doublet of doublets, $J_1 = J_2$ = 4.5 Hz, C-14β H).

The more polar compound was obtained in a yield of 94 mg and was identical with the alkaloid delphisine (**3**).

X-Ray Structure Determination. Delphisine (3) was recrystallized from acetone–hexane, forming clear, nearly equidimensional tabular crystals. Preliminary examination of these crystals on a diffractometer established that they were orthorhombic. Least-squares refinement of 2θ values for 15 accurately centered reflections in the range 12–77° 2θ established the unit cell dimensions as a = 14.849 (1), b = 20.62 (1), c = 9.111 (1) Å. Examination of the diffracted intensity for all axial reflections to a limit of 2θ = 150° revealed no systematically absent spectra, thus establishing the space group as $P222$. Since the solution of a crystal structure in a noncentrosymmetric space group without translational symmetry is very difficult without the presence of a heavy atom, further work on delphisine as the free base was abandoned.

Crystals of delphisine hydrochloride were obtained from methanol–ether as described above. The crystals were found to be orthorhombic, space group $P2_12_12_1$. The unit cell dimensions were determined by least-squares refinement of 2θ values for 15 accurately centered reflections in the range 23–84° 2θ. The density was measured by flotation in benzene–CCl_4. The crystal data for delphisine hydrochloride are summarized in Table II. Integrated intensity measurements were made using Cu Kα (graphite monochromator) radiation on an Enraf-Nonius CAD-4 diffractometer. A total of 3288 reflections were measured to a maximum 2θ of 150.83°, of which 2889 (87.9%) were observed at the 3σ level of significance, based on counting statistics only. The data were reduced to relative structure amplitudes; corrections were applied for Lorentz and polarization factors, but no absorption correction was included. Normalized structure amplitudes (E's) were calculated and found to correspond closely to the statistical distribution expected for a noncentrosymmetric structure.

Table II. Crystal Data for Delphisine Hydrochloride

$C_{28}H_{44}NO_8Cl$, MW 558.12, mp 206–210 °C dec, clear tabular crystals from MeOH–Et_2O.
Orthorhombic, space group $P2_12_12_1$; a = 13.866 (1), b = 22.27 (1), c = 9.098 (1) Å, absent spectra, $h00$ for $h \neq 2n$, $0k0$ for $k \neq 2n$, $00l$ for $l \neq 2n$.
V = 2809.4 Å^3, Z = 4, d_m = 1.320 (1) g/cm^3 (flotation in C_6H_6–CCl_4), d_x = 1.319 g/cm^3.
$F(000)$ = 1200 e, μ for Cu Kα (λ 1.5418 Å) = 12.17 cm^{-1}

Phases were determined for the 605 E's > 1.3 using MULTAN.[19] The absolute figure of merit for the best starting set of phases was 1.29, with the next highest value being 0.94. The best starting set of phases was extended with the TANGEN link of the XRAY system, using the weighted tangent formula. An E-map based on the 603 resulting phases clearly indicated the positions of the chloride ion and 25 other nonhydrogen atoms. The missing atoms were those comprising the five-member ring C, the 14α-acetate group, C(16), the methoxyl group bonded to it, and the terminal methyl of the 6α-methoxyl group. One of the atoms of the initial model was subsequently found to be an artifact. Least-squares refinement of this initial partial model gave an R factor of 0.37 and resulted in a difference map which revealed all of the missing atoms except for C(182), as well as several additional peaks which were subsequently shown to be spurious. Further least-squares refinement reduced R to 0.18 and clearly indicated (by excessively large shifts in temperature factors) which atoms were artifacts. Initially the largest peak from the E-map was identified as Cl, and all other peaks were identified as carbon atoms in the structure factor calculations. Nitrogen and oxygen atoms were unambiguously identified from a consideration of bond lengths and isotropic temperature factors. The refinement of the isotropic model converged at R = 0.106, and the anisotropic model at R = 0.073, with all observed reflections given unit weights. Hydrogen atoms were located from difference maps and included in the final refinement with individual isotropic temperature factors. The function minimized was $\Sigma w|\Delta F|^2$, with the weights established empirically from the equation $w = 1/(1 + ((F_o - 14)/10)^2)$ which resulted in a distribution of $w|\Delta F|^2$ which was essentially independent of both $|F_{obs}|$ and sin θ/λ. Eight of the strongest reflections showed evidence of being affected by secondary extinction and were removed from the least-squares refinement. Six of the weaker reflections calculated to small $|F_c|$ values; examination of the raw data suggested that the background measurements had been underestimated, and these reflections were reclassified to an unobserved status. The refinement converged to final values of R = 0.0351 and R_w = 0.0400, based on 2875 observed reflections. Of the 405 unobserved reflections, only 29 calculated greater than the 3σ threshold value. The final atomic positional and thermal parameters are given in Table III, and a comparison of observed and calculated structure factors is shown in Table IV.[20] A difference electron density map based on these parameters revealed no peaks or holes greater than 0.3 e/Å^3.

Structure factor calculations based on both enantiomorphs established the absolute configuration to a certainty in excess of 99.5%, according to Hamilton's test. In addition, 56 reflections which were particularly sensitive to a change in enantiomorph ($|F_c(hkl)| > 20$, $|F_c(hkl)|/|F_c(\bar{h}\bar{k}\bar{l})|$ either >1.05 or <0.95) were remeasured, with both reflections of the Friedel pair being examined. In all cases, the ratio of uncorrected integrated intensities confirmed the assignment of the absolute configuration.[20]

Except as noted, all calculations were carried out on a CDC

Table III. Atomic Positional ($\times 10^4$) and Thermal ($\times 10^3$) Parameters for Delphisine Hydrochloride[a]

Atom	X/a	Y/b	Z/c	U_{11} or U_{iso}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl	3811.7 (5)	0737.6 (3)	9597.3 (7)	57.3 (4)	65.3 (4)	37.5 (3)	−0.3 (4)	−5.9 (3)	−6.3 (3)
C(1)	2143 (2)	0792 (1)	6175 (3)	28 (1)	41 (1)	37 (1)	−2 (1)	3 (1)	0 (1)
O(1)	2213 (1)	1095 (1)	7576 (2)	36 (1)	55 (1)	35 (1)	2 (1)	6 (1)	−2 (1)
C(2)	1234 (2)	1017 (1)	5443 (3)	24 (1)	62 (2)	51 (1)	−1 (1)	1 (1)	2 (1)
C(3)	1305 (2)	1685 (1)	5153 (3)	32 (1)	63 (2)	52 (2)	13 (1)	2 (1)	3 (1)
C(4)	2250 (2)	1877 (1)	4328 (3)	31 (1)	39 (1)	43 (1)	7 (1)	−5 (1)	−3 (1)
C(5)	2811 (2)	1315 (1)	3788 (3)	30 (1)	31 (1)	34 (1)	0 (1)	−4 (1)	−2 (1)
C(6)	3830 (2)	1457 (1)	3168 (2)	33 (1)	26 (1)	34 (1)	0 (1)	1 (1)	2 (1)
O(61)	3906 (1)	2050 (1)	2587 (2)	44 (1)	30 (1)	52 (1)	3 (1)	5 (1)	10 (1)
C(62)	4720 (2)	2130 (1)	1656 (4)	54 (2)	45 (1)	63 (2)	−1 (1)	14 (2)	20 (1)
C(7)	4529 (1)	1345 (1)	4478 (2)	27 (1)	24 (1)	30 (1)	−3 (1)	1 (1)	−2 (1)
C(8)	5093 (1)	0756 (1)	4231 (2)	26 (1)	26 (1)	30 (1)	−1 (1)	2 (1)	−2 (1)
O(81)	5653 (1)	0819 (1)	2871 (2)	30 (1)	32 (1)	35 (1)	−4 (1)	7 (1)	−3 (1)
C(82)	6427 (2)	1177 (1)	2768 (3)	33 (1)	33 (1)	51 (1)	−4 (1)	8 (1)	0 (1)
O(82)	6723 (1)	1496 (1)	3744 (2)	45 (1)	47 (1)	59 (1)	−18 (1)	9 (1)	−10 (1)
C(83)	6858 (2)	1125 (1)	1267 (3)	51 (2)	64 (2)	53 (2)	−14 (1)	18 (1)	−1 (1)
C(9)	4372 (1)	0255 (1)	3803 (2)	28 (1)	25 (1)	30 (1)	−2 (1)	−1 (1)	−2 (1)
C(10)	3431 (2)	0274 (1)	4710 (2)	28 (1)	25 (1)	34 (1)	−6 (1)	−1 (1)	−1 (1)
C(11)	3032 (1)	0903 (1)	5143 (2)	25 (1)	28 (1)	33 (1)	−1 (1)	−2 (1)	−2 (1)
C(12)	3647 (2)	−0143 (1)	6057 (3)	32 (1)	31 (1)	36 (1)	−4 (1)	2 (1)	4 (1)
C(13)	4701 (2)	−0353 (1)	5883 (3)	36 (1)	28 (1)	38 (1)	0 (1)	−1 (1)	5 (1)
C(14)	4763 (2)	−0363 (1)	4204 (3)	30 (1)	26 (1)	40 (1)	0 (1)	3 (1)	−2 (1)
O(141)	5724 (1)	−0439 (1)	3583 (2)	36 (1)	29 (1)	53 (1)	2 (1)	9 (1)	−4 (1)
C(142)	6050 (2)	−0990 (1)	3426 (3)	50 (1)	28 (1)	60 (2)	7 (1)	2 (1)	2 (1)
O(142)	5642 (2)	−1415 (1)	3903 (4)	88 (2)	34 (1)	161 (3)	11 (1)	50 (2)	17 (2)
C(143)	6997 (2)	−1001 (1)	2629 (4)	57 (2)	58 (2)	76 (2)	22 (1)	17 (2)	0 (2)
C(15)	5768 (2)	0582 (1)	5516 (3)	29 (1)	30 (1)	40 (1)	−1 (1)	−7 (1)	−3 (1)
C(16)	5399 (2)	0100 (1)	6577 (3)	31 (1)	38 (1)	38 (1)	5 (1)	−5 (1)	1 (1)
O(161)	6256 (1)	−0188 (1)	7118 (2)	34 (1)	55 (1)	52 (1)	9 (1)	−7 (1)	12 (1)
C(162)	6124 (3)	−0447 (2)	8537 (4)	63 (2)	86 (2)	63 (2)	12 (2)	−11 (2)	32 (2)
C(17)	3866 (2)	1266 (1)	5798 (2)	26 (1)	27 (1)	30 (1)	0 (1)	−2 (1)	−3 (1)
C(18)	1938 (2)	2307 (1)	3097 (3)	41 (1)	44 (1)	56 (2)	8 (1)	−10 (1)	3 (1)
O(181)	1293 (1)	2009 (1)	2118 (2)	44 (1)	88 (2)	50 (1)	−5 (1)	−13 (1)	7 (1)
C(182)	1599 (3)	1985 (2)	0660 (4)	79 (2)	104 (3)	52 (2)	−14 (2)	−4 (2)	1 (2)
C(19)	2933 (2)	2238 (1)	5324 (3)	42 (1)	33 (1)	45 (1)	11 (1)	−8 (1)	−7 (1)
N	3471 (1)	1856 (1)	6412 (2)	29 (1)	30 (1)	36 (1)	1 (1)	−1 (1)	−5 (1)
C(20)	4237 (2)	2200 (1)	7223 (3)	36 (1)	37 (1)	47 (1)	−1 (1)	−7 (1)	−14 (1)
C(21)	3837 (2)	2726 (1)	8058 (4)	57 (2)	52 (2)	64 (2)	4 (1)	−8 (2)	27 (1)
H(O1)	2626 (29)	0921 (18)	8148 (49)	106 (14)					
H(1B)	2118 (15)	0333 (9)	6340 (23)	20 (5)					
H(2A)	0701 (27)	0917 (17)	6145 (43)	80 (12)					
H(2B)	1157 (23)	0730 (14)	4440 (35)	59 (9)					
H(3A)	1278 (25)	1906 (15)	6083 (39)	68 (10)					
H(3B)	0757 (23)	1811 (15)	4534 (38)	65 (9)					
H(5B)	2422 (19)	1090 (12)	2968 (32)	48 (7)					
H(6B)	3990 (18)	1182 (11)	2360 (28)	33 (6)					
H(621)	4827 (36)	1812 (21)	0892 (52)	101 (15)					
H(622)	5422 (30)	2076 (19)	2336 (49)	92 (13)					
H(623)	4623 (31)	2580 (20)	1175 (48)	110 (14)					
H(7B)	4938 (18)	1690 (10)	4556 (28)	26 (6)					
H(831)	6419 (29)	1090 (18)	0592 (45)	94 (12)					
H(832)	7320 (35)	1466 (21)	1025 (49)	111 (15)					
H(833)	7207 (37)	0749 (24)	1084 (52)	117 (17)					
H(9B)	4243 (18)	0271 (12)	2706 (30)	34 (7)					
H(10B)	2942 (18)	0079 (11)	4158 (29)	39 (7)					
H(12A)	3593 (18)	0077 (11)	7050 (30)	39 (7)					
H(12B)	3224 (17)	−0484 (10)	5978 (26)	29 (6)					
H(13B)	4789 (17)	−0770 (11)	6293 (26)	31 (6)					
H(14B)	4415 (18)	−0723 (12)	3751 (27)	33 (6)					
H(1431)	7297 (30)	−0632 (19)	2667 (45)	86 (13)					
H(1432)	6818 (55)	−1040 (37)	1673 (93)	207 (32)					
H(1433)	7265 (32)	−1343 (20)	2806 (49)	114 (15)					
H(15A)	5909 (19)	0929 (11)	6015 (30)	39 (7)					
H(15B)	6413 (18)	0419 (11)	5016 (30)	33 (7)					
H(16A)	5086 (21)	0278 (12)	7410 (32)	45 (7)					
H(1621)	6826 (58)	−0629 (35)	9051 (81)	190 (32)					
H(1622)	5692 (29)	−0835 (19)	8421 (47)	97 (14)					
H(1623)	5892 (42)	0007 (25)	9185 (69)	157 (21)					
H(17B)	4127 (18)	1110 (11)	6660 (29)	31 (6)					
H(181)	1579 (23)	2676 (14)	3476 (36)	52 (9)					
H(182)	2523 (25)	2453 (14)	2561 (36)	60 (9)					

Table III (*Continued*)

Atom	*X/a*	*Y/b*	*Z/c*	U_{11} or U_{iso}
H(1821)	1067 (35)	1785 (21)	0044 (60)	115 (16)
H(1822)	1504 (31)	2470 (20)	0591 (47)	103 (14)
H(1823)	2268 (42)	1724 (24)	0618 (60)	141 (20)
H(19A)	2572 (22)	2534 (12)	5970 (32)	45 (8)
H(19B)	3480 (22)	2420 (14)	4832 (36)	53 (8)
H(N)	3038 (23)	1706 (14)	7104 (35)	57 (9)
H(201)	4552 (22)	1904 (14)	7905 (36)	59 (9)
H(202)	4704 (23)	2347 (14)	6433 (36)	57 (9)
H(211)	3337 (33)	2578 (20)	8784 (48)	100 (14)
H(212)	3618 (32)	3076 (20)	7370 (52)	106 (15)
H(213)	4395 (28)	2873 (17)	8599 (44)	87 (12)

[a] $T = \exp[-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12} + \ldots)]$. The esd in the last digit shown is given in parentheses.

6400 computer using the programs of the XRAY system.[21] Atomic scattering factors for Cl, C, N, and O were derived from analytic approximations,[22] while those for H were taken from exact Hartree–Fock wave functions.[23] The scattering factors for Cl and O were corrected for anomalous dispersion (Cl: $\Delta f' = 0.3$, $\Delta f'' = 0.7$; O: $\Delta f' = 0.0$, $\Delta f'' = 0.037$).[24,25]

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Supplementary Material Available: A comparison of observed and calculated structure factors for delphisine hydrochloride (Table IV) (27 pages). Ordering information is given on any current masthead page.

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