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THE SYNTHESIS OF 1-*epi*-DELPHISINE AND 1-*epi*-NEOLINE ANALOGUES

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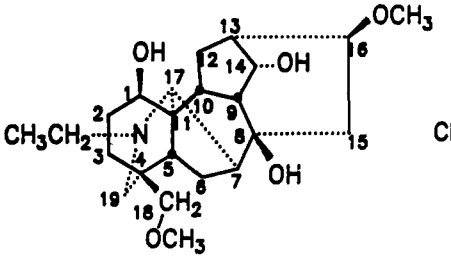
ABSTRACT.—Four new 1-β-hydroxy and 1-β-methoxy C_{19}-diterpene alkaloids have been prepared: 1-*epi*-1-*O*-methyldelphisine [**7**], 1-*epi*-1-*O*-methylneoline [**10**], 1-*epi*-14-acetylneoline [**13**], and 1-*epi*-1,14-diacetylneoline [**15**], as well as the new compounds, 1-*O*-methyldelphisine [**8**] and 14-acetyl-1-dehydroneoline [**12**]. The structures of these compounds were established on the basis of spectral data and correlation with compounds of established structure. ^{1}H- and ^{13}C-nmr data are reported for each compound.

A total of some 220 naturally occurring C_{19}-diterpenoid alkaloids have been reported, but only three, talatizidine [**1**] (1), delphirine [**2**] (1-*epi*-neoline) (2,3), and puberanine [**3**] (4), possess 1β-OH or 1β-OMe substituents. As part of a continuing systematic study of the ^{1}H- and ^{13}C-nmr spectral characteristics of C_{19}-diterpenoid alkaloids (5,6), we report here the preparation of 1β-OH and/or 1β-OMe derivatives of delphisine [**4**] and neoline and their ^{1}H- and ^{13}C-nmr spectral characteristics.

In the course of this study, we observed that alkylation of acetoxy-bearing substrates with MeI and NaH or KH yielded a mixture of products in which replacement of the acetoxy groups by either OH and/or OMe substituents had occurred. However, *O*-alkylation proceeded without cleavage of the acetoxy functionalities with trialkyloxonium salts in the presence of a strong non-nucleophilic base.



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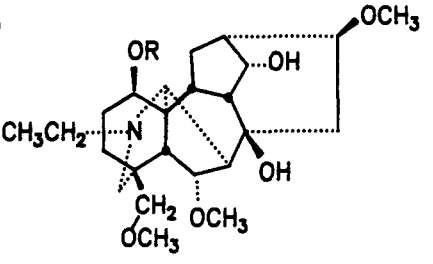
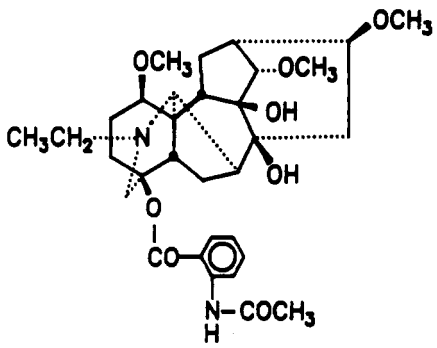


2 R=H
10 R=Me

RESULTS AND DISCUSSION

Delphisine [**4**], from *Delphinium staphisagria* (7), was treated with pyridinium chlorochromate (8) to afford 1-dehydrodelphisine [**5**] in 70% yield. Reduction of **5** with $NaBH_4$ in MeOH-absolute EtOH (1:1) gave 1-*epi*-delphisine [**6**] and delphisine [**4**] in a ratio of about 2:1.

Treatment of **6** with trimethyloxonium tetrafluoroborate in the presence of bis-1,8-(dimethylamino)-naphthalene (proton sponge) at room temperature (9,10) furnished 1-*epi*-1-*O*-methyldelphisine [**7**] in 80% yield. The starting compound **6** was recovered from the reaction in about 19% yield. Several previous attempts to convert **6** into **7**, with either MeI and NaH in dioxane or MeI and KH in DMSO, resulted in a mixture of products from which the hydrolyzed compound, 1-*epi*-neoline [**2**], was isolated as the major component. The structure of 1-*epi*-1-*O*-methyldelphisine [**7**] was confirmed by comparing its tlc behavior and mass, ^{1}H-, and ^{13}C-nmr spectral data with those of **6**.



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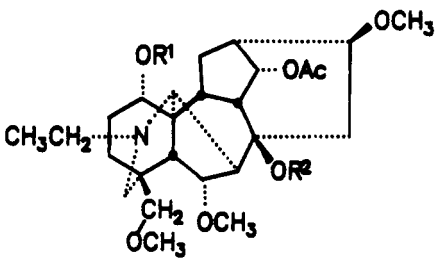


4 R^1=H, R^2=Ac
8 R^1=Me, R^2=Ac
9 R^1=R^2=Ac
14 R^1=R^2=H

The ^{1}H spectrum showed signals for the NCH_2CH_3 methyl as a triplet centered at δ 1.01, two singlets at δ 1.93 and 2.00 for the two acetoxy substituents, and four methoxyl methyl singlets at δ 3.17, 3.20, 3.24, and 3.27. The methoxyl carbons were observed in the decoupled ^{13}C nmr as quartets at 56.0, 56.4, 57.8, and 59.1 ppm. The placement of the fourth methoxyl substituent at C-1 was inferred from a comparison of its ^{13}C-nmr data with **6** (see Table 1). Typically, the C-1 carbon resonates as a doublet between 68.0 and 69.0 ppm if a 1β-OH group is present (6). Thus, the deshielding of this carbon signal at 78.4 ppm in **7**, coupled with the observed shielding of C-2 by about 7.2 ppm to 22.9 ppm, is consistent with the assignment of the 1β-OMe substituent in **7**.

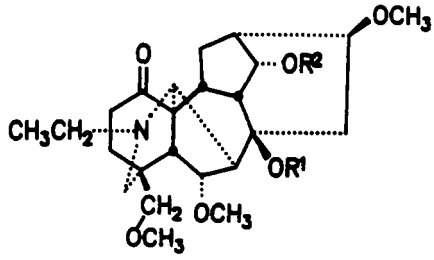
In a parallel study, similar treatment of delphisine [**4**] with either MeI and NaH in dioxane or MeI and KH in DMSO also resulted in a mixture of products from which neoline (2,11) was isolated as the major compound. Alternatively, treatment of delphisine [**4**] with trimethyloxonium tetrafluoroborate and proton sponge gave the expected 1-*O*-methyl derivative **8** in a yield of 60%. Confirmatory evidence in support of the deduced structure of **8** was obtained by comparing its mass, ^{1}H-, and ^{13}C-nmr spectral data with those of **4** and 1-acetyldelphisine [**9**] (2,6,11).

The observed molecular ion at *m/z* 535, being 14 amu greater than that of **4** (2,6,11), was compatible with the structure assigned for **8**. The pattern of the ^{1}H-nmr spectrum was also consistent with structure **8** in that four methoxyl methyl signals were observed as a 6H singlet at δ 3.20 and two singlets, each integrating for 3H, at δ 3.26 and 3.28. These four methoxy groups were further confirmed by the noise-decoupled ^{13}C-nmr spectrum, which showed four methyl carbon quartets at 55.9, 56.5, 57.8, and 59.0 ppm together with three methine carbon doublets at 82.6, 83.6, and 84.9 ppm, as well as a methylene carbon triplet at 80.3 ppm. The triplet at 80.3 ppm was assigned to C-18 while the three doublets at 82.6, 83.6, and 84.9 were attributed to C-16, C-6, and C-1, respectively, by comparison with **4** and **9** (see Table 1). The observed shielding of C-2 from 29.4 ppm in **4** to 26.3 ppm in **8** is in agreement with the placement of the fourth methoxy group at C-1 (6).

Alkaline hydrolysis of **7** with 50% alcoholic KOH gave **10**, the ^{1}H-nmr spectrum of which showed the anticipated collapse of the acetoxy methyl singlets observed in the proton spectrum of **7**. In the ^{13}C-nmr noise-decoupled spectrum, the resonances for the C-8 and C-14 acetoxy substituted carbon that typically appear as a singlet at 85.0 to 86.0 ppm and as a doublet at 74.5 to 77.0 ppm (6), respectively, were replaced by a singlet at 73.9 ppm (for C-8) and a doublet at 75.9 ppm (for C-14).

TABLE 1. ^{13}C-nmr Chemical Shifts and Assignments for 1-*epi*-neoline [**2**], delphisine [**4**], 1-*epi*-delphisine [**6**], 1-*epi*-1-*O*-methyldelphisine [**7**], 1-*O*-methyldelphisine [**8**], 1-acetyldelphisine [**9**], 1-*epi*-1-*O*-methylneoline [**10**], 14-acetyl-1-dehydroneoline [**12**], 1-*epi*-14-acetylneoline [**13**], 14-acetylneoline [**14**], and 1-*epi*-1,14-diacetylneoline [**15**].

Carbon	2	4	6	7	8	9	10	12	13	14	15
C-1	69.0	72.0	68.6	78.4	84.9	77.5	78.5	213.4	68.8	72.0	73.1
C-2	30.3	29.4	30.1	22.9	26.3	27.5	22.9	41.4	30.1	29.5	27.4
C-3	31.2	30.0	31.1	31.5	34.8	34.6	31.4	39.0	31.0	30.0	32.0
C-4	40.1	38.1	39.2	39.2	39.0	39.0	39.2	39.4	39.2	38.0	39.1
C-5	39.7	44.0	39.0	39.0	48.9	49.3	40.1	53.3	39.0	44.5	39.4
C-6	82.8	84.1	83.7	83.9	83.6	83.5	82.8	82.3	82.8	83.3	83.2
C-7	51.7	48.2	47.8	47.9	48.9	49.4	51.6	46.1	52.1	52.6	52.2
C-8	73.9	85.8	86.0	86.0	85.9	85.6	73.9	74.3	74.8	74.6	74.3
C-9	48.4	43.2	43.5	43.7	44.2	44.3	48.4	48.4	46.3	46.4	46.4
C-10	39.4	38.5	38.3	38.5	38.7	38.5	39.6	36.6	36.4	36.6	36.6
C-11	50.5	49.8	50.7	50.7	50.4	49.4	50.3	60.9	50.6	49.7	49.2
C-12	28.9	29.4	29.2	29.7	29.1	29.5	28.9	34.0	29.2	29.3	29.4
C-13	45.5	43.2	44.6	45.6	44.8	44.1	46.3	39.0	45.0	43.3	46.0
C-14	75.7	75.5	75.4	75.6	75.4	75.0	75.9	75.0	77.1	77.1	77.1
C-15	42.1	38.5	38.1	38.2	37.6	37.7	42.2	42.4	42.2	42.6	42.4
C-16	82.4	82.6	83.2	83.3	82.6	83.1	82.5	81.9	82.4	81.9	82.4
C-17	63.3	62.7	62.1	62.7	61.3	60.1	63.7	63.4	62.6	63.3	62.8
C-18	80.4	79.8	80.0	80.2	80.3	80.1	80.6	79.3	80.3	80.1	80.4
C-19	53.8	56.7	53.5	53.8	53.8	54.3	53.9	54.7	53.7	57.9	53.8
N-CH_2	48.8	48.0	48.5	48.7	48.9	48.6	48.8	48.4	48.8	48.2	48.7
CH_3	13.5	12.9	13.2	13.4	13.3	13.5	13.5	13.3	13.3	13.0	13.4
1′	—	—	—	56.0	55.9	—	56.1	—	—	—	—
6′	57.5	57.9	57.8	57.8	57.8	58.1	57.6	57.8	57.5	57.9	57.8
16′	56.2	56.5	56.3	56.4	56.5	56.5	56.3	55.8	56.0	56.1	56.1
18′	59.2	59.0	58.9	59.1	59.0	59.1	59.2	59.1	59.1	59.1	59.3
C=O	—	169.3, 170.4	169.5, 170.6	169.5, 170.6	169.4, 170.9	169.3, 170.1, 170.5	—	170.2	170.4	170.4	170.2, 170.4
CH_3	—	21.2, 22.2	21.1, 22.2	22.2, 21.1	21.2, 22.4	21.2, 22.0, 22.4	—	21.1	21.3	21.3	21.1, 21.3



5 $R^1=R^2=Ac$
11 $R^1=R^2=H$
12 $R^1=H$, $R^2=Ac$

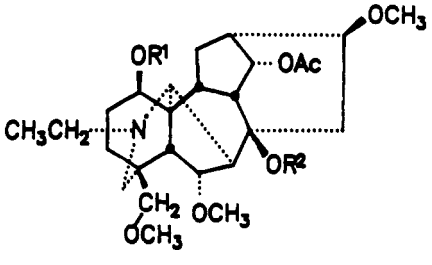
Treatment of 1-dehydrodelphisine [**5**] with 50% alcoholic KOH yielded 1-dehydroneoline [**11**] is almost quantitative yield, identified by its tlc behavior, mp, mmp, ir, ^{1}H-, and ^{13}C-nmr spectra (2,11).

Treatment of 1-dehydroneoline [**11**] with Ac_2O-pyridine (2:1) at room temperature furnished 14-acetyl-1-dehydroneoline [**12**] in 90% yield. The structure of **12**, amorphous, $C_{26}H_{39}NO_7$ (eims [M]$^+$ 477.1), was deduced from the analysis of its ^{1}H- and ^{13}C-nmr spectral data. The salient features of the ^{1}H-nmr spectrum were an acetoxy methyl singlet at δ 2.02 and a downfield methine doublet of doublets centered at δ 4.84 ($J=4.5$ Hz). In general, in the aconitine type of C_{19}-diterpenoid alkaloids, the *CH* doublet of doublets at δ 4.84 together with the absence from the ^{13}C nmr of a carbon singlet in the range of 85.0 to 86.0 ppm is diagnostic of esterification at C-14 but not at C-8 (7).

Acetylation of **12** with acetyl chloride afforded 1-dehydrodelphisine [**5**], which was identical with an authentic sample by its tlc behavior, mp, mmp, and its ir, ^{1}H-, and ^{13}C-nmr spectra (2,11).

Reduction of **12** with $NaBH_4$ in MeOH-absolute EtOH (1:1) furnished 1-*epi*-14-acetylneoline [**13**] in 80% yield and 14-acetylneoline [**14**] (6) in less than 5% yield.

The structure of 1-*epi*-14-acetylneoline [**13**] was established by comparison of its spectral data with data of members of the neoline series of alkaloids. Characteristically, the C-1 carbon resonance in the ^{13}C-nmr spectrum of a 1β-OH substituted C_{19}-diterpenoid alkaloid occurs as a doublet in the region of 68.0 to 69.0 ppm (Table 1). On the contrary, for C-1 carrying an α-substituted hydroxy group, the carbon signal usually appears as a doublet in the region of 71.0 to 72.0 ppm (6) as in **14**. Treatment of **13** with Ac_2O/pyridine furnished the diacetyl derivative **15**, in which the acetoxy groups must be located at C-1 and C-14, not at C-8 and C-14. A 8,14-diacetyl derivative



6 $R^1=H$, $R^2=Ac$
7 $R^1=Me$, $R^2=Ac$
13 $R^1=H$, $R^2=H$
15 $R^1=Ac$, $R^2=H$

would be identical with 1-*epi*-delphisine [**6**]. However, in the ^{13}C-nmr spectrum of **15**, the C-1 doublet is deshielded to 73.4 ppm, whereas in **6**, it is at 68.6 ppm. Thus, the deshielding of the C-1 doublet in **15** can only be possible if the second acetoxy function is at C-1. This conclusion was also corroborated by the observed shielding of the C-2 signal by about 2.9 ppm to 27.4 ppm (see Table 1, cf. 30.1 ppm for **6**). Furthermore, support for the deduced structure of **15** could also be based on the 1H broad singlet at δ 5.18 in its ^{1}H-nmr spectrum. This signal must be due to the H-1α that is geminal to the β-substituted acetoxy group, since this signal was completely absent from the proton spectrum of **6**.

EXPERIMENTAL

Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Ir spectra were taken on a Perkin-Elmer model 1420 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded on JEOL FT models FX-60 and FX-90Q spectrometers in $CDCl_3$. Mass spectra were determined on a Finnegan Quadrupole 4023 instrument. For chromatographic separations on a Chromatotron (12,13), unless otherwise indicated, rotors were coated with a 1-mm-thick layer of Si gel PF254+365 (EM Art. 7741); for vlc (14), Si gel HR (EM Art. 7744). 50% Methanolic KOH solution was prepared from 50 g of KOH made up to 100 ml in MeOH.

FRACTIONATION OF MOTHER LIQUORS OF *D. STAPHISAGRIA*.—The dried mother liquors of *D. staphisagria* (98.0 g) (7,15) were fractionated into six groups by a gradient pH extraction technique (16): group 1 (neutral fraction A, 9.50 g), group 2 (neutral fraction B, 26.90 g), group 3 (pH 4.5, 44.99 g), group 4 (pH 8.0, 21.32 g), group 5 (pH 10.0, 12.45 g), group 6 (pH 12.0, 0.16 g).

ISOLATION OF DELPHISINE [**4**].—A fraction of 26.90 g of group 3 (pH 4.5) was chromatographed (vlc) over Si gel. Elution was performed with hexane-$CHCl_3$ in a manner of increasing polarity. Fractions eluted with hexane/$CHCl_3$ (80:20) and hexane-$CHCl_3$ (85:15) were similar on tlc plates and so were combined (15.04 g). The combined fraction was crystallized from Me_2CO/hexane mixture several times to give 10.2 g of delphisine [**4**], mp 122–123°, which was identical with an authentic sample of delphisine as judged by co-tlc behavior, mmp, and ir, ^{1}H- and ^{13}C-nmr spectra (2,11).

OXIDATION OF DELPHISINE [**4**] TO 1-DEHYDRODELPHISINE [**5**].—A solution of **4** (600 mg) in CH_2Cl_2 (50 ml) was added rapidly in one portion to a stirred suspension of pyridinium chlorochromate (8) (pcc, 80 mg) in CH_2Cl_2 (5.0 ml) in a round-bottom flask fitted with a condenser. The reaction mixture was stirred continuously for 8 h at room temperature, diluted with anhydrous Et_2O (50 ml) and the supernatant decanted to leave a black gummy precipitate. The latter was washed repeatedly with anhydrous Et_2O (10 × 100 ml) till the Et_2O washings became clear. These were combined, filtered through a short pad of florisil, and distilled under vacuum to give 560 mg of residue. This residue was crystallized from Me_2CO/Et_2O mixture several times to afford 458 mg (76% yield) of 1-dehydrodelphisine [**5**], mp 170–172°, which was identical with an authentic sample (11) by co-tlc behavior, mmp, and ^{1}H- and ^{13}C-nmr spectra.

REDUCTION OF 1-DEHYDRODELPHISINE [**5**].—Compound **5** (310 mg), dissolved in MeOH-absolute EtOH (1:1) (20 ml), was treated with $NaBH_4$ (20 mg) under anhydrous conditions. The resulting solution was stirred continuously at room temperature for 5 h. H_2O (50 ml) was added, and the mixture was extracted with 5 × 25 ml of $CHCl_3$. The combined extracts were washed with H_2O (2 × 25 ml), dried over anhydrous Na_2SO_4, and evaporated in vacuo to give 300 mg of residue which was separated on a silica rotor of a Chromatotron with hexane with increasing amounts of $CHCl_3$ to give delphisine [**4**] [71 mg with $CHCl_3$-hexane (9:1)], 1-*epi*-delphisine [**6**] (220 mg with 2% MeOH in $CHCl_3$), and a mixture of **4** and **6** (4 mg with $CHCl_3$).

1-*epi*-Delphisine [**6**] (220 mg) was crystallized from Me_2CO/hexane mixture to afford 200 mg of crystalline material, mp 168.5–170.5°, $[\alpha]^{25}D$ −7.9° (c = 0.75, 95% EtOH). Ir (Nujol) ν max 3545 (OH), 1720 (C=O), 1460, 1450, 1365, 1250, 1110 cm^{-1}; its ^{1}H- and ^{13}C-nmr spectra were identical with reported values (11).

CONVERSION OF 1-*epi*-DELPHISINE [**6**] TO 1-*epi*-1-*O*-METHYLDELPHISINE [**7**].—A solution of 1-*epi*-delphisine [**6**] (284 mg) in dry CH_2Cl_2 (50 ml) was treated with trimethyloxonium tetrafluoroborate (180 mg) and bis-1,8-(dimethylamino)-naphthalene (250 mg). After the reaction mixture had stirred continuously at room temperature for 5 days, it was quenched with H_2O (50 ml) and was extracted with 10 × 50 ml Et_2O. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure, leaving a residue (282 mg) that was separated on a silica rotor of a Chromatotron

(hexane followed by 1% MeOH in $CHCl_3$) to furnish 55 mg of recovered **6** and 228 mg of pure **7**: amorphous, $[\alpha]^{25}D$ −6.8° (c = 0.18, absolute EtOH). Ir (Nujol) ν max 1740, 1730, 1455, 1370, 1250, 1080, 1020, 980, 960, 910 cm^{-1}; ^1H nmr δ 1.01 (3H, t, J = 7.2 Hz, N-CH_2CH_3), 1.93, 2.00 (2 × 3H, 2 × s, 2 × OAc), 3.17, 3.20, 3.24, 3.27 (4 × 3H, 4 × s, 4 × OMe), 3.95 (1H, dd, $J_1 = J_2$ = 6.6 Hz, H-6β), 4.83 (1H, t, J = 5 Hz, H-14β); ^{13}C nmr see Table 1; ms m/z (% rel. int.) $[M]^+$ ($C_{29}H_{45}NO_8$) 535.4 (2), $[M-Me]^+$ 520 (16), $[M-OMe]^+$ 504 (6), 476 (2), 460 (4), 75 (2), 71 (5), 58 (5), 44 (12), 43 (100).

HYDROLYSIS OF 1-*epi*-1-*O*-METHYLDELPHISINE [**7**].—To a stirred solution of **7** (55 mg) in MeOH (10 ml) at room temperature was added 2 ml of 50% methanolic KOH solution. The mixture was left overnight, ice-H_2O (30 ml) was added and the reaction mixture extracted with 8 × 25 ml of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 50 mg of residue. This residue was purified on a Si gel rotor of a Chromatotron (2% MeOH in $CHCl_3$) to give 47 mg of pure 1-*epi*-1-*O*-methylneoline [**10**]: amorphous, $[\alpha]^{25}D$ −8.6° (c = 0.17, absolute EtOH); ir (Nujol) ν max 3440 (OH), 1450, 1350, 1300, 1220, 1200, 1120, 1100, 975 cm^{-1}; ^1H nmr δ1.04 (3H, t, J = 7 Hz, N-CH_2CH_3), 3.20, 3.29, 3.32, 3.33 (4 × 3H, 4 × s, 4 × OMe); ^{13}C nmr see Table 1. The mass spectrum showed a molecular ion m/z 451 $[M]^+$ ($C_{25}H_{41}NO_6$) (7%), $[M-Me]^+$ 436 (78), $[M-OMe]^+$ 420 (25), 122 (5), 108 (5), 96 (10), 85 (18), 71 (35), 58 (44), 45 (100).

CONVERSION OF 1-*epi*-DELPHISINE [**6**] TO 1-*epi*-NEOLINE [**2**].—To a solution of 1-*epi*-delphisine [**6**] (60 mg) in MeOH (10 ml) was added 2 ml of 50% methanolic KOH solution at room temperature. After 12 h, workup of the reaction mixture in the usual manner (see above) gave a residue (55 mg) which was purified on a silica rotor of a Chromatotron (2% MeOH in $CHCl_3$) to afford pure **2** (53 mg), identified by tlc behavior and comparison of its ir, ^1H-, and ^{13}C-nmr spectral data with those of an authentic sample (2,11).

HYDROLYSIS OF 1-DEHYDRODELPHISINE [**5**] TO 1-DEHYDRONEOLINE [**11**].—To 200 mg of **5** in 20 ml MeOH was added 6 ml of 50% methanolic KOH solution. After 18 h, MeOH was distilled and 80 ml of H_2O was added. The solution was extracted with 10 × 50 ml $CHCl_3$. This process was repeated with 120-mg and 300-mg samples of 1-dehydrodelphisine. The $CHCl_3$ extracts from the three reactions were combined, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo to give 630 mg of residue. Recrystallization from hexane/Et_2O mixtures several times afforded 1-dehydroneoline [**11**], mp 151–153°. The latter was identical with an authentic sample by tlc behavior, mp, mmp, ir, mass, ^1H- and ^{13}C-nmr spectra (2,11).

CONVERSION OF 1-DEHYDRONEOLINE [**11**] TO 14-ACETYL-1-DEHYDRONEOLINE [**12**].—Ac_2O-pyridine (8:5) (13 ml) was added to 220 mg of **11** and left overnight. Ice-H_2O (50 ml) was added, and the reaction mixture was extracted with Et_2O (5 × 50 ml). The aqueous layer was made alkaline (pH 10.0) with $NaHCO_3$ and then extracted with 5 × 50 ml $CHCl_3$. The combined $CHCl_3$ and Et_2O extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to furnish 200 mg of residue. This residue was purified on a Si gel rotor of a Chromatotron, eluting with $CHCl_3$-hexane (80:20) to afford 190 mg of pure **12**, amorphous. Ir (Nujol) ν max 3460 (OH), 1740 (OAc), 1680 (C=O), 1450, 1370, 1230, 1150, 1100, 1050, 980 cm^{-1}; ^1H nmr δ 1.06 (3H, t, J = 7 Hz, NCH_2CH_3), 2.02 (3H, s, OAc), 3.19, 3.25, 3.32 (3 × 3H, 3 × s, 3 × OMe), 4.04 (1H, dd, $J_1 = J_2$ = 7.3 Hz, H-6β), 4.84 (1H, t, J = 4.5 Hz, H-14β); ^{13}C nmr see Table 1; ms m/z $[M]^+$ ($C_{26}H_{39}NO_7$) 477.1 (2%), $[M-Me]^+$ 446 (3), $[M-OMe]^+$ 434 (0.1), 228 (3), 202 (2), 176 (9), 128 (11), 121 (4), 108 (6), 96 (35), 85 (16), 71 (20), 58 (28), 55 (21), 43 (100).

REDUCTION OF 14-ACETYL-1-DEHYDRONEOLINE [**12**] TO 1-*epi*-14-ACETYLNEOLINE [**13**].—$NaBH_4$ (20 mg) was added to the stirred solution of **12** (100 mg) in 20 ml of MeOH-absolute EtOH (1:1) mixture at room temperature. After 6 h, 25 ml of H_2O was added. Workup of the reaction mixture in the usual manner (see above) resulted in an oily residue (102 mg), which was separated on a silica rotor of a Chromatotron (1% MeOH in $CHCl_3$) to give 1-*epi*-14-acetylneoline [**13**] (83 mg) and 14-acetylneoline [**14**] (6) in trace amounts (1.5 mg). Compound **13**: amorphous, $[\alpha]^{25}D$ +4.8 (c = 0.20, 95% EtOH); ir (Nujol) ν max 3440 (OH), 1740 (CO), 1460, 1450, 1370, 1240, 1160, 1050, 970 cm^{-1}; ^1H nmr δ 1.03 (3H, t, J = 7 Hz, N-CH_2CH_3), 2.04 (3H, s, OAC), 3.24, 3.29, 3.32 (3 × 3H, 3 × s, 3 × OMe), 4.06 (1H, dd, J = 7.3 Hz, H-6β), 4.87 (1H, t, J = 5 Hz, H-14β); ^{13}C nmr see Table 1; ms m/z $[M]^+$ ($C_{26}H_{41}NO_7$) 479.1 (4%), $[M-Me]^+$ 464 (8), 462 (5), $[M-OMe]^+$ 448 (1), 246 (1), 180 (5), 128 (13), 122 (31), 108 (6), 96 (24), 85 (14), 75 (6), 71 (18), 58 (54), 43 (100).

CONVERSION OF 14-ACETYL-1-DEHYDRONEOLINE [**12**] TO 1-DEHYDRODELPHISINE [**5**].—Compound **12** (25 mg) was treated with acetyl chloride (10 ml), and the solution was left to stand 48 h. Ice-H_2O (25 ml) was added, and the mixture was then extracted with 5 × 25 ml of ice-cold $CHCl_3$. The aqueous layer was rendered alkaline (pH 10.0) with $NaHCO_3$ and extracted with 5 × 20 ml $CHCl_3$. The $CHCl_3$ extracts were combined, dried over anhydrous Na_2SO_4, and evaporated in vacuo to leave a residue (20 mg).

The latter was recrystallized several times from Me_2CO/hexane mixtures to afford **5** (15 mg), mp 170–172°, which was identical with an authentic sample (8) by co-tlc, mmp, ir, ^1H and ^{13}C nmr.

CONVERSION OF 1-*epi*-14-ACETYLNEOLINE [**13**] TO 1-*epi*-1,14-DIACETYLNEOLINE [**15**].—Compound **13** (10 mg), dissolved in pyridine (2 ml), was treated with Ac_2O (3 ml) at room temperature. After 12 h, workup of the reaction mixture in the usual manner gave an oily residue which was purified on a silica rotor of a Chromatotron (gradient, 2% MeOH in $CHCl_3$) to afford **15** as an oil (7 mg). Ir (Nujol) ν max 3500 (OH), 1740 (C=O), 1450, 1375, 1240, 1160, 1120, 1020 cm^{-1}; ^1H nmr δ 1.05 (3H, t, $J=7$ Hz, N-CH_2CH_3), 2.01 (3H, s, OAc), 2.06 (3H, s, OAc), 3.24, 3.32, 3.35 (3 × 3H, 3 × s, 3 × OMe), 4.11 (1H, dd, $J_1=J_2=6.2$ Hz, H-6β), 4.87 (1H, t, $J=5$ Hz, H-14β), 5.14 (1H, t, H-1α); ^{13}C nmr see Table 1.

CONVERSION OF DELPHISINE [**4**] TO 1-*O*-METHYLDELPHISINE [**8**].—A solution of delphisine [**4**] (100 mg) in dry CH_2Cl_2 (10 ml) was treated with trimethyloxonium tetrafluoroborate (60 mg) and bis-1,8-(dimethylamino)-naphthalene (90 mg) at room temperature for 3 days. Workup of the reaction mixture as described above furnished a residue (110 mg) that was purified on an alumina rotor (Alumina 60 PF254 + 366; Art. 1104) of a Chromatotron, eluting with Et_2O-hexane (3:7) to afford pure **8** (60 mg) and recovered **4** (33 mg). 1-O-Methyldelphisine [**8**]: mp 137.8–138.9°, $[\alpha]^{25}D$ +5.1° ($c=0.11$, absolute EtOH); ir (Nujol) ν max 1745 (CO), 1460, 1375, 1250, 1165, 1100 cm^{-1}; ^1H nmr δ 1.04 (3H, t, $J=7.0$ Hz, N-CH_2CH_3), 1.94, 2.01 (2 × 3H, 2 × s, 2 × OAc), 3.20 (6H, s, 2 × OMe), 3.26, 3.28 (2 × 3H, 2 × s, 2 × OMe), 4.03 (1H, dd, $J_1=J_2=6.3$ Hz, H-6β), 4.76 (1H, t, $J=5.0$ Hz, H-14β); ^{13}C nmr see Table 1; ms *m/z* (% rel. int.) $[M]^+$ ($C_{29}H_{45}NO_8$) 535.4 (1), $[M-Me]^+$ 520 (2), 505 (28), $[M-OMe]^+$ 504 (93), 476 (15), 460 (6), 444 (34), 416 (9), 404 (2), 384 (6), 344 (3), 91 (5), 85 (4), 75 (9), 71 (19), 58 (22), 44 (40), 43 (100).

ATTEMPTED METHYLATION OF 1-*epi*-DELPHISINE [**6**] WITH MeI AND KH.—A suspension of KH (15 mg) in mineral oil, containing about 10 mg of KH, was placed in a 3-neck round-bottom flask. The KH was washed repeatedly with dry hexane (4 × 20 ml) under argon. After removing all residual traces of hexane with a stream of argon, dry DMSO (13 ml) was added to the dry KH at 0°. 1-*epi*-Delphisine [**6**] (30 mg) dissolved in dry DMSO (10 ml) was added 30 min later as the suspension warmed to room temperature. The reaction mixture was then cooled in an ice bath for 10 min, after which MeI (2 ml) was added. After this addition, the reaction mixture was allowed to warm slowly to room temperature. Finally, the reaction was quenched by adding $CHCl_3$ (20 ml) (17,18). The $CHCl_3$ layer was washed with H_2O (5 × 20 ml), dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo, to leave a residue (25 mg). The latter was purified on a silica rotor of a Chromatotron, eluting with $CHCl_3$-hexane (4:1), to furnish 1-*epi*-neoline [**2**] (18 mg) which was identical with an authentic sample by co-tlc behavior and ^1H- and ^{13}C-nmr spectra (2,3).

ATTEMPTED METHYLATION OF 1-*epi*-DELPHISINE [**6**] WITH MeI AND NaH.—A 50% dispersion of NaH in mineral oil containing about 20 mg of NaH was placed in a 3-neck round-bottom flask. The NaH was washed with dioxane (3 × 10 ml) which had been dried over sodium wire. The washed NaH was resuspended in 10 ml dry dioxane and then stirred constantly under a stream of N_2. To this stirred suspension, 1-*epi*-delphisine [**6**] (30 mg) dissolved in dry dioxane (5 ml) and MeI (5 ml) were added under anhydrous conditions at room temperature. Monitoring the progress of the reaction by Si gel tlc [solvent system $CHCl_3$-MeOH (96:4)] showed only the presence of starting material after 4 days.

In a second experiment, the recovered material [**6**] (30 mg), dissolved in dioxane (5 ml) as before, was added to a fresh, stirred suspension of NaH (60 mg) in dioxane (10 ml). MeI (5 ml) was then added, and the reaction mixture was heated under reflux under a stream of N_2 on an oil bath maintained at 62°. After 12 h, the reaction mixture was filtered through a short column of neutral alumina (Alumina Woelm TSC, Act III/20 nm, Woelm Cat. 04511), washing the column repeatedly with $CHCl_3$ (5 × 20 ml). The filtrate was evaporated to dryness in vacuo to afford a residue (28 mg), which was purified on a 1 mm alumina rotor (Alumina 150 PF254, Type T; Art 1064) of a Chromatotron, eluting with Et_2O containing increasing amounts of MeOH in a gradient fashion. This process furnished 1-*epi*-neoline [**2**] (2% MeOH in Et_2O) as the major compound, its identity being established by comparing its tlc behavior and ^1H- and ^{13}C-nmr characteristics with those of an authentic sample (2,3).

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