

DEMETHYLATION OF NORDITERPENOID ALKALOIDS

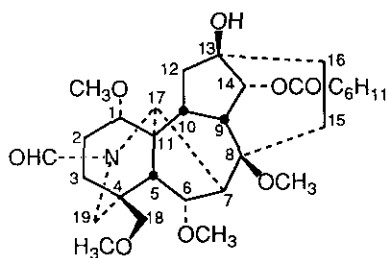
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Abstract – *The reaction of the aconitine-type alkaloids delphinine and delphisine, and the lycoctonine-type alkaloids delsoline, ajacine, and deltaline has been carried out with HBr-AcOH in glacial acetic acid. These reactions proceed by partial demethylation and acetylation of the hydroxyl groups formed during the demethylation.*

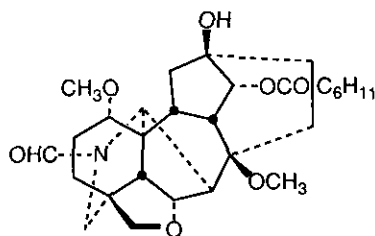
The norditerpenoid alkaloids are highly toxic bases which are substituted by a number of acetoxy, hydroxyl or methoxyl groups.¹ To date, well over 300 alkaloids of this class have been isolated from *Aconitum*, *Consolida* and *Delphinium* species and their structures have been established. Most of the naturally occurring aconitine- and lycoctonine-type alkaloids appear to have a tertiary nitrogen substituted by a methyl or an ethyl group. Also, most of them possess an oxygen function at C(1), C(8), C(14) and C(16). Some of the alkaloids bear oxygen functions at C(3), C(6), C(7), C(9), C(10), C(13), C(15), C(18) and rarely at the C(5) position. The oxygen function in the naturally-occurring alkaloids at C(3), C(5), C(7), C(9), C(10), C(13) or C(15) is always a hydroxyl group; however, C(1) and C(6) are substituted by an acetoxy, hydroxyl or methoxyl group. The only exceptions are polyschistine C and 1-deoxydelsoline which do not possess an oxygen function at C(1). The carbon atoms at C(8) and C(14) are substituted by a hydroxyl, methoxyl or an ester function. Franchetine and 8-deoxy-14-dehydroaconosine are the only examples lacking an oxygen function at the C(8) position. The majority of norditerpenoid alkaloids bear a methoxyl group at C(16),² Delbiterine³ and delstaphisine,⁴ however, have a hydroxyl at C(16). Cardiopetaline and cardiopetalidine lack the oxygen function at C(16). The heteratisine-type alkaloids containing a δ -lactone in the ring C are devoid of an oxygen function at this position. The primary oxygen function at C(18) is usually a hydroxyl, methoxyl or an aromatic ester group.

Selective demethylation reactions would be useful in facilitating the structure determination of newly isolated naturally-occurring norditerpenoid alkaloids. Unsuccessful attempts were made by Jacobs and co-workers to demethylate norditerpenoid alkaloids and their derivatives with HI-P and with $AlCl_3$. Partial demethylation occurred with hydrochloric acid and in a few cases with nitric acid.⁵ Treatment of octahydroisopyro- α -oxodelphinine (**1**) with aqueous $ZnCl_2$ in 5% HCl afforded the dimethoxy ether (**2**); this reagent gave closely analogous desmethylhydro derivatives.⁶ Similar demethylation to form cyclic ethers was carried out on neoline⁷ and *N*-acetyl-*N*-deethylisopyrochasma⁸. Several attempts were made in our laboratory to demethylate delphinine with BF_3 -ether, BF_3 -ethanedithiol, BCl_3 , BBr_3 , iodotrimethylsilane, chlorotrimethylsilane and 9-borabicyclo(3.3.1)nonane; no identifiable products were isolated from these experiments.

Treatment of the aconitine-type alkaloid delphisine (**3**) with 48% aq. HBr at 20°C gave two compounds, identified as delphidine (**4**) and neoline (**5**). A saturated solution of HBr in glacial acetic acid is a well

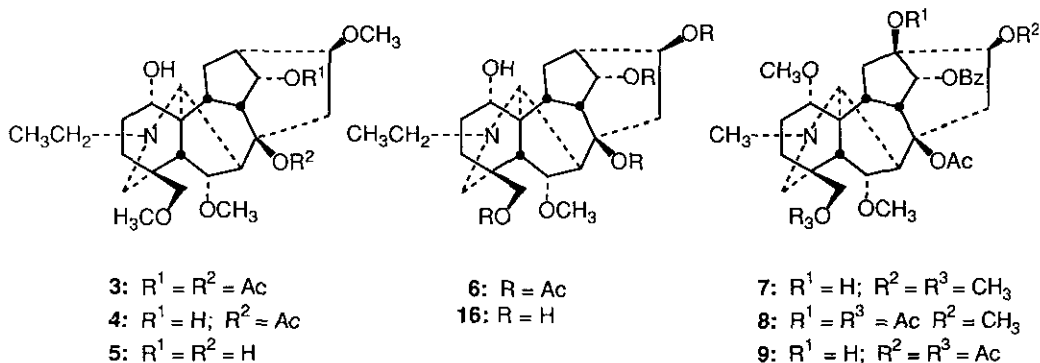


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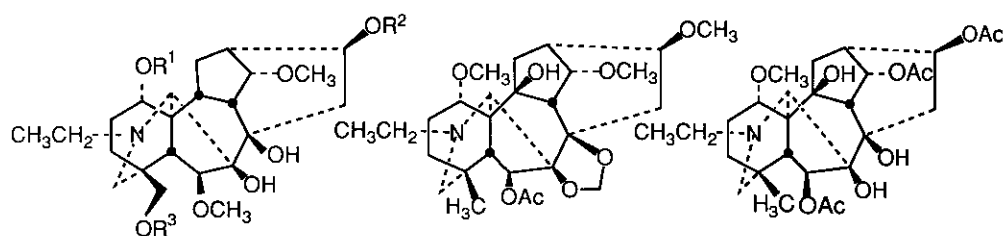
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known reagent in carbohydrate chemistry for the preparation of glycosyl bromides.⁹ The reagent is also employed in cleaving benzoylcarbamates used as protective groups for aminoacids.¹⁰ *t*-Butyl ethers of primary hydroxyl groups¹¹ and aromatic ethers¹² can be cleaved with HBr-AcOH at 20°C. When **3** was treated with 30% HBr-AcOH in glacial acetic acid, an amorphous compound C₃₀H₄₃NO₁₀ was isolated in 48% yield. This alkaloid, containing a C-6 methoxyl group (δ 3.18, s, 3H; 58.1 ppm) has been assigned structure (**6**) essentially on the basis of its ¹H and ¹³C nmr spectral data (Table 1). Alkaline hydrolysis of **6** afforded **16** by deacetylation of the acetoxy groups at C-8, C-14, C-16 and C-18. A similar reaction of delphinine (**7**) with HBr-AcOH afforded two compounds **8** and **9**, the structures of which are consistent with their spectral data. In both the cases, the primary methoxyl group at C(18) has been demethylated. In delphinine (**7**), the yield of **9**, C₃₅H₄₅NO₁₁, mp 191.5–193.5°C, formed by demethylation of the C-16 methoxyl group predominates (48%) compared to **8** (11%) in which the methoxyl group at C(16) is unaffected.



In the case of the lycoctonine-type alkaloid delsofine (**10**), treatment with HBr-AcOH gave **11** in 24% yield by demethylation of only the C(16) methoxyl group. Similarly ajacine (**12**) and deltaline (**13**) afforded **14** and **15**, respectively. The structures of these alkaloids are consistent with their spectral data (Table 1). In the case of deltaline (**13**) both the C(14) and C(16) methoxyl groups are demethylated and acetylated and the methylenedioxy group is cleaved to give the diol (**15**).

Although there is little specificity in the demethylation of norditerpenoid alkaloids with HBr-AcOH, the C-16 methoxyl group is demethylated in all cases; the C-18 methoxyl is demethylated in the two aconitine-type alkaloids which possess an α -methoxyl group at the C-6 position; the C-18 methoxyl is not demethylated in delsofine (**10**), a lycoctonine-type alkaloid which has a β -methoxyl group at C-6. In all the alkaloids, the C-1 and C-6 methoxyl groups do not appear to undergo demethylation with this reagent.



10: $R^1=H$; $R^2=R^3=CH_3$

11: $R^1=H$; $R^2=Ac$; $R^3=CH_3$

12: $R^1=R^2=CH_3$; $R^3=CO-C_6H_4-NHAc$

14: $R^1=CH_3$; $R^2=Ac$; $R^3=CO-C_6H_4-NHAc$

13

15

EXPERIMENTAL

General: – Melting points are corrected and were determined 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 recorded on a Perkin-Elmer model 1420 spectrophotometer. 1H Nmr spectra were determined on a Bruker WM 300 spectrometer in $CDCl_3$ solution. ^{13}C Nmr spectra were recorded on JEOL FX-60 and FX-270 spectrometers in $CDCl_3$; the chemical shift assignments for all compounds were determined from DEPT spectra and are reported in Table 1. Mass spectra were recorded on a Finnegan Quadrupole 4023 mass spectrometer.

General Procedure for Demethylation Reactions with HBr-AcOH: – To a solution of the substrate in glacial acetic acid, hydrogen bromide (30 wt.% solution in acetic acid, Aldrich) was added and the solution was stirred at room temperature for three to four days in a glass-stoppered flask. The progress of the reaction was monitored by tlc. The tlc plates were first exposed to aq. NH_4OH (~ 3 min.) in a separate chamber and then developed in an appropriate solvent along with the starting material. When the spot corresponding to the starting material disappeared, the reaction was worked-up in the following manner:

The reaction mixture was diluted with water (2–3 fold) and cooled in an ice bath. It was then basified to pH 10 (at 0–5°) with saturated $NaHCO_3$ and Na_2CO_3 solutions. The basic reaction mixture was then repeatedly extracted with $CHCl_3$. The major homogeneous product(s) were obtained by fractionation on an alumina or a silica gel rotor of a Chromatotron.^{13,14}

Action of aq. HBr on Delphinine (3): – A solution of delphinine (3, 100 mg) in aq. HBr (5 ml, 48% HBr in water, Eastman) was stirred at room temperature for four days. The reaction mixture was basified to pH 10 with aq. Na_2CO_3 solution and the basic solution was extracted with $CHCl_3$ (30 ml x 5), washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The mixture was separated on an alumina rotor (1 mm, EM 1104-3). The products were identified as delphidine (4, 20.3 mg) and neoline (5, 48.5 mg) having identical mixture mp, tlc behavior, 1H and ^{13}C nmr spectra with those of authentic delphidine and neoline, respectively.

Action of HBr-AcOH on Delphinine (3): – To a solution of delphinine (3, 90 mg) in acetic acid (2 ml) a solution of HBr in AcOH (0.3 ml) was added and the mixture was stirred for three days at room temperature.

Usual work-up and purification on an alumina rotor gave **6** as a homogeneous amorphous compound (48.0 mg, 48%) besides traces of some minor compounds, $[\alpha]^{19} +20.8^\circ$ (c, 0.25; CHCl_3); eims m/z (%), 577.1 (M^+ for $\text{C}_{30}\text{H}_{43}\text{NO}_{10}$, 1.2), 560 $[\text{M}-\text{OH}]^+$ (10.5), 518 $[\text{M}-\text{OAc}]^+$ (4.5); ir (nujol) ν_{max} : 1735(br), 1370, 1255 and 1235 cm^{-1} ; ^1H nmr: δ 1.16 (3H, t , $J = 7.1$ Hz, NCH_2CH_3), 1.97, 2.01, 2.04, 2.06 (each 3H, s , 4 x OAc), 2.20 (1H, d , $J = 6$ Hz, C(5)- β -H), 2.33, 2.64 (each 1 H, AB q , $J = 12$ Hz, C(19)-H), 3.04 (1H, s , C(17)-H), 3.18 (3H, s , OCH_3), 3.65 (1H, br s , C(1)- β -H), 4.03 (1H, d , $J = 6.5$ Hz, C(6)- β -H), 4.07, 4.20 (2H, AB q , $J = 10.3$ Hz, C(18)-H), 4.83 (1H, t , $J = 4.7$ Hz, C(14)- β -H). For ^{13}C nmr values see Table 1.

Action of HBr-AcOH on Delphinine (7): – To a solution of delphinine (**7**, 150 mg) in acetic acid (3.5 ml) a solution of HBr-AcOH (0.5 ml) was added and the mixture was stirred for four days at room temperature. Usual work-up and purification on an alumina rotor gave two homogeneous products: **8** (19.1 mg, 11.3%) and **9** (80.2 mg, 48.8 %). Compound **8** was amorphous, $[\alpha]^{24} +18^\circ$ (c, 0.25; CHCl_3); eims m/z (%), 669 (M^+ for $\text{C}_{36}\text{H}_{47}\text{NO}_{11}$, 0.1), 652 $[\text{M}-\text{OH}]^+$ (0.5), 638 $[\text{M}-\text{OCH}_3]^+$ (35.1); ir (nujol) ν_{max} : 1730 (br), 1460, 1375, 1250 cm^{-1} ; ^1H nmr δ 1.23 (3H, s , C(8)-OAc), 2.06 (6H, s , 2 x OAc), 2.34 (3H, s , N- CH_3), 3.10, 3.28, 3.40 (each 3H, s , 3 x OCH_3), 3.97 (1H, d , $J = 6.5$ Hz, C(6)- β -H), 4.04 (1H, dd , $J_1 = 5.6$, $J_2 = 8.9$ Hz, C(16)- α -H), 4.11, 4.25 (2H, AB q , $J = 10.4$ Hz, C(18)-H), 5.12 (1H, d , $J = 5.2$ Hz, C(14)- β -H), 7.40–8.10 (5H, aromatic protons). For ^{13}C nmr values see Table 1.

Compound **9** crystallized from CH_2Cl_2 -hexane, mp 191.5–193.5 $^\circ\text{C}$, $[\alpha]^{24} + 17.8^\circ$ (c, 0.275, CHCl_3); eims m/z (%), 655 (M^+ for $\text{C}_{35}\text{H}_{45}\text{NO}_{11}$, 2), 624 $[\text{M}-\text{OCH}_3]^+$ (32.7); ir (nujol) ν_{max} : 1730, 1460, 1450, 1380 cm^{-1} ; ^1H nmr δ 1.36 (3H, s , C(8)- β -OAc), 2.02, 2.07 (each 3H, s , 2 x OAc), 2.31 (3H, s , N- CH_3), 3.08, 3.24 (each 3H, s , 2 x OCH_3), 3.95 (1H, d , $J = 6.5$ Hz, C(6)- β -H), 4.08, 4.22 (2H, AB q , $J = 10.4$ Hz, C(18)-H), 4.98 (1H, d , $J = 4.7$ Hz, C(14)- β -H), 7.40–8.10 (5H, aromatic protons). For ^{13}C nmr values see Table 1.

Action of HBr-AcOH on Delsoline (10): – To a solution of delsoline (**10**, 50 mg) in acetic acid (2 ml) a solution of HBr-AcOH (0.25 ml) was added and the mixture was stirred for three days at room temperature. Work-up and fractionation of the product on an alumina rotor gave **11** as a homogeneous amorphous product (12.1 mg, 22.6 %), $[\alpha]^{26} +16.8^\circ$ (c, 0.125; CHCl_3); eims m/z (%), 495 (M^+ for $\text{C}_{26}\text{H}_{41}\text{NO}_8$, 2.3), 480 $[\text{M}-\text{CH}_3]^+$ (14.8), 478 $[\text{M}-\text{OH}]^+$ (9.4), 464 $[\text{M}-\text{OCH}_3]^+$ (5.6); ir (nujol) ν_{max} : 3450, 1730, 1250 cm^{-1} ; ^1H nmr δ 1.13 (3H, t , 7.2 Hz, NCH_2CH_3), 2.06 (3H, s , OAc), 3.34, 3.36, 3.44 (each 3H, s , 3 x OCH_3), 3.29, 4.06 (each 1H, s , 2 x OH exchanges with D_2O), 3.65 (1H, t , $J = 4.5$ Hz, (14)- β -H), 3.68 (1H, br s , C(1)- β -H), 4.01 (1H, s , C(6)- α -H), 4.82 (1H, t , $J = 8.5$ Hz, C(16)- α -H). For ^{13}C nmr values see Table 1.

Action of HBr-AcOH on Ajacine (12): – To a solution of ajacine (**12**, 100 mg) in acetic acid (3 ml) a solution of HBr-AcOH (0.5 ml) was added at room temperature and the mixture was stirred for three days. Usual work-up and purification on an alumina rotor gave **14** as an amorphous homogeneous compound (18.1 mg, 17.2 %), $[\alpha]^{28} +51^\circ$ (c, 0.2; CHCl_3); eims m/z (%), 656 (M^+ for $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_{10}$, 0.2), 641 $[\text{M}-\text{CH}_3]^+$ (1.8), 625 $[\text{M}-\text{OCH}_3]^+$ (36.1); ir (nujol) ν_{max} : 3450, 1730, 1690, 1590, 1525, 760 cm^{-1} ; ^1H nmr δ 1.08 (3H, t , $J = 7.1$ Hz, NCH_2CH_3), 2.06 (3H, s , OAc), 2.24 (3H, s , NAc), 3.25, 3.39, 3.43 (each 3H, s , 3 x OCH_3), 3.63 (1H, t , $J = 4.5$ Hz, C(14)- β -H), 4.18 (1H, s , C(6)- α -H), 4.79 (1H, dd , $J_1 = 5.7$, $J_2 = 9.2$ Hz, C(16)- α -H), 7.11 (1H, t , $J = 7.8$ Hz, H-5'), 7.57 (1H, t , $J = 7.8$ Hz, H-4'), 7.98 (1H, d , $J = 8.0$ Hz, H-3'), 8.72 (1H, d , $J = 8.0$ Hz, H-6'), 10.99 (1H, br s , -NH -Ac). For ^{13}C nmr values see Table 1.

Action of HBr-AcOH on Deltaline (13): – To a solution of deltaline (**13**, 150 mg) in acetic acid (5 ml) a solution of HBr-AcOH (0.5 ml) was added at room temperature and the mixture was stirred for three days. Usual work-up and separation of the products on an alumina rotor and purification by ptlc on silica gave a

Table 1. ^{13}C Nmr (CDCl_3) spectra of 3, and 6 to 15.

Carbon	3	6	7	8	9	10	11	12	14	13	15
1	72.1	77.7 d	84.9	84.6 d	84.7 d	72.6	72.6	83.9	83.9 ^a	79.2	82.1 d
2	29.5 ^a	28.9 ^a t	26.3	26.2 t	25.9 t	27.2	27.3	26.1	26.0	27.1	26.1 t
3	30.1 ^a	29.6 ^a t	34.7	34.1 t	34.1 t	29.3	29.4	32.2	32.3	39.4	38.2 t
4	38.1	37.1 s	39.3	38.5 s	38.4 s	37.4	37.6 s	38.2 s	37.7 s	33.7	34.4 s
5	44.1	44.9 d	48.8	49.3 d	49.4 d	43.9	43.7	43.3	43.6	50.4	51.4 d
6	84.2	83.6 d	83.0 ^a	82.8 d	82.5 d	90.4	90.4	91.0	90.1	77.3	77.0 d
7	48.3	47.8 d	48.2	47.9 d	48.0 d	87.8	87.7 s	88.6	88.6 s	91.6	88.3 s
8	85.8	85.4 s	85.4	85.4 s	84.7 s	78.5	78.4 s	77.5	77.1 s	83.8	77.1 s
9	43.3	43.0 d	45.1	43.6 d	45.5 d	44.9	45.0	50.5	50.4	50.4	51.4 d
10	43.3 [*]	43.0 d	41.0	41.8 d	41.2 d	43.3 [*]	43.7	46.1 [*]	45.8	81.6	79.9 s
11	49.8	49.6 s	50.2	50.3 s	50.1 s	49.3	49.3 s	49.1	49.0 s	56.0	51.4 s
12	29.5 ^a	29.0 ^a t	35.7	35.2 t	36.1 t	30.5	30.0	28.6	28.9	36.5	36.4 ^{at}
13	38.5 [*]	39.6 d	74.8	82.1 s	74.9 s	37.7 [*]	38.3	37.6 [*]	37.9	38.5	37.7 d
14	75.5	75.1 ^b d	78.9	77.6 d	78.8 d	84.5	84.1	83.9	82.3 ^a	81.7 ^a	75.5 d
15	38.5	37.2 t	39.3	39.4 t	38.5 t	33.5	32.6	33.8	33.2	34.8	37.6 ^{ad}
16	82.7	74.5 ^b d	83.7 ^a	80.0 d	75.4 d	82.9	75.3	82.6	74.9	81.5 ^a	73.1 d
17	62.7	62.8 d	63.3	63.3 d	63.2 d	66.0	66.1	64.5	64.5	63.5	66.3 d
18	79.8	71.5 t	80.2	71.7 t	71.6 t	77.3	77.4	69.8	68.8	25.7	25.7 q
19	56.8	56.5 t	56.1	55.6 t	55.6 t	57.2	57.4	52.5	52.4	56.9	56.3 t
N-CH ₂ (CH ₃)	48.0	48.3 t	42.3	42.5 q	42.3 q	50.3	50.4	51.0	51.1	50.2	51.1 t
CH ₃	12.9	12.8 q	-	-	-	13.5	13.5	14.0	14.1	13.8	14.2 q
1'	-	-	56.1	56.4 q	56.3 q	-	-	55.8	55.8	55.3	55.4 q
6'	58.0	58.1 q	57.6	57.8 q	57.6 q	57.2	57.4	57.8	57.8	-	-
14'	-	-	-	-	-	57.9	57.7	58.1	58.2	57.7	-
16'	56.5	-	58.6	58.3 q	-	56.3	-	56.3	-	56.2	-
18'	59.0	-	58.9	-	-	59.1	59.1	-	-	-	-
CO	170.4	171.3 s	169.4	172.2 s	171.1 s	-	170.5 s	-	170.8 s	169.9	172.8 s
CH ₃	169.3	170.3(2C)	-	170.4 s	170.4 s	-	-	-	-	-	170.5 s
	-	169.6 s	-	169.9 s	169.7 s	-	-	-	-	-	170.2 s
	22.2	22.4	21.4	21.6 q	21.8 q	-	21.4	-	21.5	21.8	21.6 q
	21.2	21.0(3C)	-	21.4 q	21.1 q	-	-	-	-	-	21.4 q
	-	-	-	21.1 q	20.9 q	-	-	-	-	-	21.3 q
	-	-	166.0	166.5 s	166.6 s	-	-	168.1	168.1 s	-	-
	-	1'	130.4	130.1 s	129.9 s	-	-	114.5	114.5 s	-	-
	-	2'	129.6	130.0 d	129.6 d	-	-	141.9	142.0 s	-	-
	-	3'	128.4	128.6 d	128.5 d	-	-	120.6	120.7	-	-
	-	4'	132.8	133.3 d	133.4 d	-	-	135.0	135.0	-	-
	-	5'	128.4	128.6 d	128.5 d	-	-	122.5	122.5	-	-
	-	6'	129.6	130.0 d	129.6 d	-	-	130.3	130.3	-	-
NHCO	-	-	-	-	-	-	-	169.0	169.1 s	-	-
CH ₃	-	-	-	-	-	-	-	25.5	25.5	-	-
C-7-O	-	-	-	-	-	-	-	-	-	93.9	-
CH ₂	-	-	-	-	-	-	-	-	-	-	-
C-8-O	-	-	-	-	-	-	-	-	-	-	-

a,b These assignments may be interchanged in any vertical column.

* The literature values have been reversed.

homogeneous amorphous compound (**15**) (15.0 mg, 9.2 %); $[\alpha]_D^{28} +13.6^\circ$ (c, 0.25; CHCl₃); eims m/z (%), 551 (M⁺ for C₂₈H₄₁NO₁₀, 0.3), 536 [M-CH₃]⁺ (0.5), 520 [M-OCH₃]⁺ (24); ir (nujol) ν_{\max} : 3410, 1730, 1250 cm⁻¹; ¹H nmr δ 0.88 (3H, s, C(4)-CH₃), 1.05 (3H, s, NCH₂CH₃), 1.99, 2.04, 2.10 (each 3H, s, 3 x OAc), 3.24 (3H, s, OCH₃), 5.24 (1H, br s, C(6)- α -H), 5.34 (1H, t, J = 5.1 Hz, C(14)- β -H). For ¹³C nmr values see Table 1.

Alkaline Hydrolysis of 6: – A solution of (**6**; 18 mg) in 5% methanolic potassium hydroxide (5 ml) was stirred at room temperature for 10 h and evaporated *in vacuo*. The residue was dissolved in water (15 ml), saturated with NaCl and extracted with CHCl₃ (10 ml x 10). The organic layer was dried (Na₂SO₄) and evaporated to give a residue (13 mg) which was passed through a short column of silica gel and eluted with CHCl₃, and increasing amounts of MeOH. The fraction obtained by elution with CHCl₃:10% MeOH gave a residue which crystallized from acetone to afford **16** as colorless cubes (3.5 mg), mp 235–237°C; eims m/z (%), 409 (M⁺ for C₂₂H₃₅NO₆, 15), 392(100), 376(8). Ir (nujol) ν_{\max} : 3350, 1451, 1378, 1300, 1230, 1190, 1160, 1100, 1050, 1028, 1000, 990, 970, 950 cm⁻¹. ¹H Nmr: δ 1.13 (3H, t, J = 7.2 Hz, NCH₂CH₃), 2.33, 2.72 (each 1H, ABq, J = 12.6 Hz, C(19)-H), 3.33 (3H, s, OCH₃), 3.51, 3.79 (each 1H, ABq, J = 10.2 Hz, C(18)-H), 3.72 (1H, br t, J = 7 Hz, C(1)- β -H), 4.18 (1H, dd, J = 6.5 Hz, C(6)- β -H). ¹³C Nmr: δ 76.8 d (C-1), 30.5^a t (C-2), 31.4^a t (C-3), 40.2 s (C-4), 46.0^b d (C-5), 84.6 d (C-6), 54.1 d (C-7), 75.5 s (C-8), 48.5 d (C-9), 45.9^b d (C-10), 50.8 s (C-11), 29.7 t (C-12), 45.4^b d (C-13), 74.2 d (C-14), 45.4 t (C-15), 73.7 d (C-16), 64.2 d (C-17), 70.1 t (C-18), 58.5 t (C-19), 49.1 t (NCH₂), 13.3 q (NCH₂CH₃), 58.3 q (C-6 OCH₃). (^{a,b}These assignments may be interchanged).

ACKNOWLEDGEMENT

We thank Mr. Courtney Pape for recording the mass spectra.

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Received, 15th August, 1990