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METHANOLYSIS OF THE C-8 ACETOXYL GROUP IN ACONITINE-TYPE ALKALOIDS: A PARTIAL SYNTHESIS OF HOKBUSINE A

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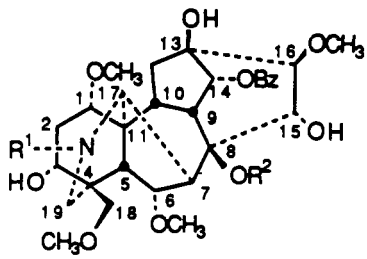
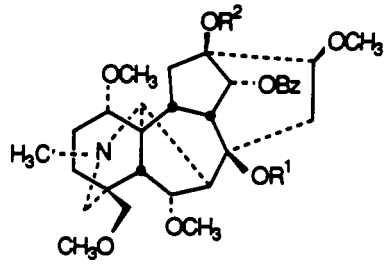
ABSTRACT.—The C-8 acetoxyl group of aconitine-type norditerpenoid alkaloids can be readily replaced by a methoxyl group by heating the appropriate alkaloid in MeOH. Thus, aconitine [**1**], delphinine [**2**], 3-deoxyaconitine [**12**], and falconerine-8-*O*-acetate [**13**] afforded the corresponding 8-deacetyl-8-*O*-methyl derivatives. Hokbusine A [**8**] was synthesized from mesaconitine [**9**] by replacement of the 8-OAc group by 8-OMe.

Replacement of the C-8 acetoxyl group by a methoxyl function in the norditerpenoid alkaloids has been employed for the introduction of a methoxyl group at C-8 in aconitine [**1**] (1,2), delphinine [**2**] (3) and bikhaconitine [**3**] (4) to give compounds **4**, **5**, and **6** respectively. The C-1 methoxyl is equatorial in accordance with later findings (5,6) that aconitine, pseudaconitine, and bikhaconitine, which have been interrelated, have this group in an α-configuration. Edwards (4) interpreted this reaction as a rapid reversible formation of an ionic species, which by the attack of MeOH at the C-8 position in **3** gives **6** by reestablishment of the original skeleton. This facile conversion of the C-8 acetoxyl group thus proceeds via a synchronous fragmentation process involving cleavage at the C-7–C-17 bond of the type described by Grob *et al.* (7). The free electron pair of the nitrogen atom is oriented anti and parallel (anti-periplanar) with respect to the bond which undergoes cleavage as required for such a pathway. Utilizing this reaction, we prepared acoforestine and acoforestinine from crassicauline A and yunaconitine, respectively (8). In these alkaloids, the 8-acetoxyl group was replaced by an ethoxyl group. Yunaconitine was also transformed to give 8-deacetyl-8-*O*-propylyunaconitine by heating with *n*-PrOH (8).

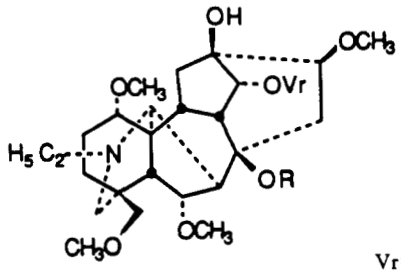
Recent communications on the isolation of "jianyouaconitine" (9,10) (8-deacetyl-8-*O*-methylmesaconitine) [**8**] from the tubers of *Aconitum carmichaeli* Debx. (Chinese medicine: Jianyou Fu Zi) prompted us to carry out a partial synthesis of compound **8** from mesaconitine [**9**]. Hikino *et al.* (11) have previously reported the isolation of an alkaloid designated as hokbusine A from *A. carmichaeli* and *Aconitum napellus* for which the same structure **8** was assigned. They derived the structure of hokbusine A from spectroscopic data and correlation with trimethylbenzoylmesaconine (11). Snyder and



1 R^1=Et, R^2=Ac
4 R^1=Et, R^2=Me
7 R^1=Et, R^2=CD_3
8 R^1=R^2=Me
9 R^1=Me, R^2=Ac
10 R^1=R^2=Me; 3-OAc



2 R^1=Ac, R^2=H
5 R^1=Me, R^2=H
16 R^1=Me, R^2=Ac



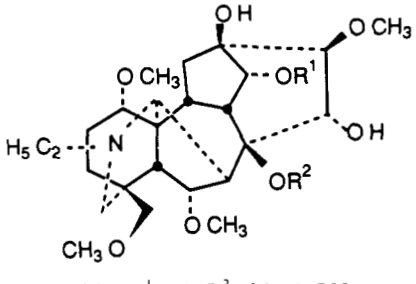
3 R=Ac
6 R=Me

co-workers (10) based their structural assignment of "jianyouaconitine" on nmr spectroscopic evidence, particularly homo and heteronuclear nOe's and selective INEPT studies; they noted that the structure of hokbusine A needed re-evaluation. In a recent paper, Hang *et al.* (12) have concluded that hokbusine A and the compound isolated by them ("jianyouaconitine") are idential; they have also corrected some of the previously reported (11) ^{13}C-nmr data for hokbusine A.

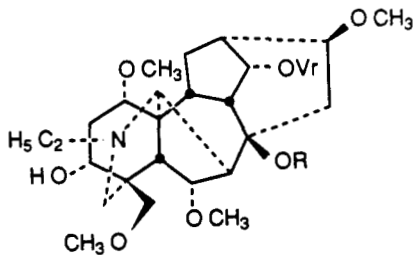
The partial synthesis of hokbusine A was effected by heating mesaconitine [**9**] under reflux with MeOH. The amorphous product had spectral properties in agreement with structure **8**. It gave a crystalline hydrochloride salt, mp 193–195°, $[\alpha]_D$ −17.8°, and a monoacetate **10** resulting from acetylation of the 3-hydroxyl group.

A comparison of the ^{13}C-nmr spectra of hokbusine A supplied by Dr. John Snyder with that of the synthetic product [**8**] (Table 1) indicated close agreement of ^{13}C-nmr signals of thse compounds. Also, a comparison of the ^{13}C-nmr spectrum of Dr. Snyder's "jianyouaconitine" with that of our synthetic hokbusine A indicated agreement. A direct comparison of synthetic **8** with hokbusine A also established identity (see Experimental).

Heating crude aconitine with MeOH in a sealed tube at 120–130° gives methyl benzaconine ($C_{32}H_{45}NO_{11}$) (1), mp 210–211°, also named methylpikraconitine ($C_{33}H_{47}NO_{10}$) (2). We failed to obtain a crystalline compound even after repeated attempts of heating pure aconitine (13) with MeOH at 120–130° or under refluxing conditions. The amorphous compound obtained by methanolysis was formulated as 14-*O*-benzoyl-8-*O*-methylaconine [**4**] from its spectral behavior. When the reaction product was worked up without basification, the crystalline acetate salt of **4**, mp 150–153°, was obtained. Heating aconitine [**1**] in CD_3OD afforded **7**. In compound **4**, since the 8-methoxyl group is shielded by the ring current of the C-14-α-benzoate, the methyl protons of the C-8-methoxyl appear highly shielded at δ 3.16. As expected, this methoxyl



11 R^1=H, R^2=Me, 3-OH
12 R^1=Bz, R^2=Ac
14 R^1=Bz, R^2=Me



13 R=Ac
15 R=Me

TABLE 1. ^{13}C chemical Shifts[a] and Assignments for 14-*O*-Benzoyl-8-*O*-methylmesaconine (Hokbusine A) [**8**], **8** HCl, 3-*O*-Acetyl-14-*O*-benzoyl-8-*O*-methylmesaconine [**10**], 14-*O*-Benzoyl-8-*O*-methylaconine [**4**], 8-*O*-Methylaconine [**11**], 8-Deacetyl-8-*O*-methyldelphinine [**5**], 13-*O*-Acetyl-8-deacetyl-8-*O*-methyldelphinine [**16**], 8-Deacetyl-3-deoxy-8-*O*-methylaconitine [**14**], and 8-*O*-Methylfalconerine [**15**].

Carbons	Hokbusine A[b] [8]	8[c]	8[d]	8 HCl	10	4	11	5	16	14	15
C-1	82.1 d	82.6 d	82.3	80.1	83.2 d	82.6 d	82.6	85.2	84.9	85.8 d	83.4 d
C-2	33.0 t	33.9 t	33.1	29.7	32.0 t	33.4 t	33.5	26.2	26.2	26.5 t	33.3 t
C-3	71.1 d	71.5 d	71.1	69.7	71.5 d	71.7 d	71.7	34.6	34.4	35.2 t	71.8 d
C-4	43.4 s	43.3 s	43.5 s	43.5 s	42.4 s	43.1 s	43.1 s	39.2 s	39.2 s	39.1 s	43.0 s
C-5	44.9 d	45.8 d	45.0	44.3	45.5 d	46.1 d	48.1	48.3	48.5	49.7 d	48.0 d
C-6	82.8 d	83.0 d	82.8	82.1	82.1 d	83.4 d	83.8	82.6	82.9	83.3 d	82.7 d
C-7	41.7 d	41.4 d	41.9	41.5	41.8 d	42.5 d	42.4	46.3	44.8	42.9 d	45.0 d
C-8	82.3 s	82.1 s	82.1 s	83.2 s	82.1 s	82.4 s	83.2 s	78.2 s	78.2 s	82.3 s	78.6 s
C-9	44.9 d	45.1 d	45.0	43.3	44.6 d	45.2 d	46.0	47.4	47.5	45.7 d	45.9 d
C-10	41.2 d	41.3 d	41.2	40.6	41.0 d	41.5 d	41.6	41.5	42.2	41.6 d	45.0 d
C-11	50.5 s	50.4 s	50.5 s	50.6 s	50.0 s	50.5 s	50.5 s	50.6 s	50.9 s	50.5 s	50.9 s
C-12	35.9 t	36.1 t	35.9	35.2	36.6 t	36.2 t	36.9	36.1	35.8	37.2 t	28.7 t
C-13	74.7 s	74.7 s	74.7 s	74.6 s	74.8 s	74.9 s	76.5 s	75.4 s	82.6 s	75.0 s	38.4 d
C-14	79.2 d	79.4 d	79.2	78.7	79.3 d	79.5 d	78.3	79.3	77.4	79.7 d	75.9 d
C-15	77.3 d	77.2 d	77.3	77.0	77.5 d	77.6 d	77.6	36.3	36.5	78.0 d	35.6 t
C-16	93.1 d	93.3 d	93.1	92.3	93.6 d	93.4 d	93.3	83.8	80.1	93.7 d	83.0 d
C-17	63.2 d	62.5 d	63.2	67.0	62.0 d	60.9 d	62.3	62.8	63.0	61.5 d	60.8 d
C-18	76.6 t	76.6 t	77.0	76.3	71.5 t	77.0 t	76.9	80.0	80.1	80.4 t	77.1 t
C-19	50.1 t	49.6 t	50.1	52.0	50.0 t	48.8 t	48.8	56.4	56.3	53.5 t	47.8 t
N-$CH_2(CH_3)$	42.4 q	42.5 q	42.4	42.1	42.4 q	47.3 t	47.4	42.3	42.4	49.3 t	48.5 t
Me	—	—	—	—	—	13.3 q	13.4	—	—	13.6 q	13.3 q
C-1′	56.2 q	56.3 q	56.2	55.7	56.5 q	55.8 q	55.8	56.1	56.3	56.3 q	55.6 q
C-6′	58.6 q	58.5 q	58.6	58.9	58.6 q	59.1 q	58.7	58.5	58.1	58.5 q	58.5 q
C-8′	50.0 q	49.7 q	50.0	50.6	49.5 q	49.8 q	50.3	47.8	47.5	48.6 q	48.6 q
C-16′	62.3 q	62.4 q	62.3	61.7	62.4 q	62.4 q	60.9	58.6	58.7	62.2 q	56.2 q
C-18′	59.1 q	59.1 q	59.1	59.1	58.6 q	58.5 q	59.1	58.9	59.1	59.1 q	59.1 q
C=O	—	—	—	—	170.2 s	—	—	—	170.4 s	—	—
Me	—	—	—	—	21.1 q	—	—	—	21.4	—	—
CO	166.3 s	166.2 s	166.3 s	166.3 s	166.2 s	166.3 s	—	166.5 s	166.6 s	166.4 s	166.1 s
1′	130.0 s	130.1 s	130.0 s	129.9 s	130.2 s	130.3 s	—	130.7 s	130.7 s	130.5 s	123.4 s
2′,6′	129.7 d	129.6 d	129.7	129.9	129.6 d	129.7 d	—	129.7	130.8	129.8 d	110.3 d, 112.3 d
3′,5′	128.4 d	128.3 d	128.4	128.5	128.2 d	128.3 d	—	128.1	128.2	128.4 d	148.5 s, 123.7 d
4′	133.9 d	132.8 d	132.9	133.1	132.7 d	132.8 d	—	132.4	132.5	132.9 s	152.7 s
OMe	—	—	—	—	—	—	—	—	—	—	55.9, 55.9

[a]Spectra were taken in $CDCl_3$; multiplicities were assigned in **4**, **8**, **10**, **14** and **15** by SFORD and DEPT experiments.
[b]These values were taken from a spectrum of hokbusine A in $CDCl_3$ provided by Dr. John Snyder.
[c]These values were taken from a spectrum of synthetic hokbusine A [**8**] provided by Dr. John Snyder.
[d]These values were taken from a spectrum of jianyouaconitine provided by Dr. John Snyder.

signal is absent in **7**. Alkaline hydrolysis of **4** gave 8-*O*-methylaconine [**11**] as an amorphous compound with spectral data identical with those of a sample of 8-*O*-methylaconine prepared by Katz and Rudin (14).

Heating delphinine [**2**], 3-deoxyaconitine [**12**], and falconerine-8-*O*-acetate [**13**] (15) with MeOH gave the corresponding C-8-methoxy derivatives **5**, **14**, and **15**, respectively. Acetylation of **5** gave 13-*O*-acetyl-8-deacetyl-8-*O*-methyldelphinine [**16**].

Although the reaction product obtained by heating aconitine under drastic conditions (sealed tube at ca. 130°) has been known for some time (1,2), the ease of replacement of the 8-OAc group with -OMe under mild conditions (refluxing at 65°) is described here for the first time. This facile replacement of the 8-OAc with 8-OMe or 8-OEt suggests that artifacts bearing a methoxyl or an ethoxyl group at C-8 may be formed during the isolation of norditerpenoid alkaloids. Some of these compounds may result by reaction with solvent under the experimental conditions used for extraction and isolation of the alkaloids.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—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. ^{1}H-nmr spectra were determined on Varian EM-390 and JEOL FX-90Q spectrometers in $CDCl_3$ solution with TMS as an internal reference. ^{13}C-nmr spectra were recorded on JEOL FX-60 and FX-90Q spectrometers in $CDCl_3$; the chemical shift assignments for all compounds are reported in Table 1. Mass spectra were recorded on a Finnegan Quadrupole 4023 mass spectrometer. Chromatotron separations were carried out on 1-mm Al_2O_3 (EM 1104-3) rotors.

SYNTHESIS OF HOKBUSINE A (8-DEACETYL-8-*O*-METHYLMESACONITINE) [**8**].—A solution of mesaconitine [**9**] (51.5 mg) in MeOH (7 ml) was refluxed on a steam bath for 26 h. The reaction product was purified on a Chromatotron to afford **8** as an amorphous compound (50.7 mg), $[\alpha]^{21}D$ +9.6° (c = 0.28, EtOH), fabms *m/z* $[M+1]^+$ 604 (calcd for $C_{32}H_{45}NO_{10}$, 603); ir (Nujol) ν max 3450, 1715, 1600, 1275, 1095, 701 cm^{-1}; ^{1}H nmr δ 2.36 (3H, s, N-Me), 3.08, 3.29, 3.29, 3.32, 3.74 (each 3H, s, OMe), 4.07 (1H, br d, J = 7 Hz, H-6β), 4.57 (1H, dd, J = 4.5, 2.5 Hz, H-15β), 4.87 (1H, d, J = 6 Hz, H-14β), 7.52 (3H, m, aromatic protons), 8.06 (2H, dd, J = 8, 2 Hz, aromatic protons). The ir spectrum of this sample in KBr was superimposable with that of an authentic sample of hokbusine A provided by Dr. Yoshiteru Oshima. A comparison of the ^{13}C-nmr spectra in $CDCl_3$ and CD_3OD also showed identity.

The alkaloid **8** (20.3 mg) was dissolved in dry Et_2O, and to the cooled solution a small drop of methanolic HCl was added. The crystalline hydrochloride salt of **8** which separated was washed with dry Et_2O, mp 193–195°, $[\alpha]^{20}D$ −17.8° (c = 0.4, EtOH). Attempts to recrystallize the hydrochloride from various solvents were unsuccessful.

3-*O*-ACETYL-8-DEACETYL-8-*O*-METHYLMESACONITINE (3-*O*-ACETYLHOKBUSINE A) [**10**].—A solution of **8** (130 mg) in pyridine (3 ml) and Ac_2O (3 ml) was kept at 20° for 24 h. Usual workup and purification on a Chromatotron afforded **10** (99.7 mg) as an amorphous compound; fabms *m/z* $[M+1]^+$ 646 (calcd for $C_{34}H_{47}NO_{11}$, 645); $[\alpha]^{21}D$ +6.05° (c = 0.31, $CHCl_3$); ir (Nujol) ν max 3500, 1724, 1276, 1242, 1090, 710 cm^{-1}; ^{1}H nmr δ 2.05 (3H, s, OAc), 2.35 (3H, s, N-Me), 3.11, 3.19, 3.25, 3.28, 3.69 (each 3H, s, OMe), 4.07 (1H, br d, J = 7 Hz, H-6β), 4.53 (1H, d, H-15β), 4.83 (1H, d, J = 6 Hz, H-14β), 7.47 (3H, m, aromatic protons), 8.02 (2H, dd, J = 8, 2 Hz, aromatic protons).

14-*O*-BENZOYL-8-*O*-METHYLACONINE [**4**].—A solution of pure aconitine [**1**] (100 mg) in MeOH (7 ml) was refluxed on a steam bath for 20 h. After removal of the MeOH, the residue was basified with 10% $NaHCO_3$, extracted with Et_2O and dried over anhydrous Na_2SO_4, and the solvent was removed. Purification of the crude product on a Chromatotron afforded **4** as an amorphous compound (62.5 mg). All attempts to crystallize the compound were unsuccessful; $[\alpha]^{24}D$ +4.4° (c = 1.13, $CHCl_3$) fabms *m/z* $[M+1]^+$ 618 (calcd for $C_{33}H_{47}NO_{10}$, 617); eims *m/z* $[M]^+$ 617 (0.3%), $[M-Me]^+$ 602 (1.7), $[M-OMe]^+$ 586 (49), 105 (100); ir (Nujol) ν max 3460, 1720, 1600, 1327, 1095, 710 cm^{-1}; ^{1}H nmr δ 1.12 (3H, t, J = 7 Hz, N-CH_2CH_3), 3.16, 3.28, 3.31, 3.34, 3.76 (each 3H, s, OMe), 4.07 (1H, br d, J = 6 Hz, H-6β), 4.57 (1H, d, J = 7 Hz, H-15β), 4.88 (1H, d, J = 5 Hz, H-14β), 7.53 (3H, m, aromatic protons), 8.07 (2H, dd, J = 8, 2 Hz, aromatic protons). When the reaction product was worked up without basification, a crystalline compound, mp 150–153° (Et_2O), was obtained. This compound was identified as an acetate salt of **4**: $[\alpha]^{20}D$ −9.2° (c = 0.282, EtOH); eims *m/z* $[M-60]^+$ 617; ^{1}H nmr δ 2.03 (3H, s, OAc); ^{13}C nmr 166.3 (CO), 22.6 ($COCH_3$) ppm.

14-*O*-BENZOYL-8-*O*-DEUTEROMETHYLACONINE [**7**].—A solution of aconitine [**1**] (14 mg) in CD_3OD (95%) (0.85 ml) was refluxed for 18 h in a N_2 atmosphere. The solvent was removed in vacuo; the residue was chromatographed on a small column of Al_2O_3 (activity III, basic) and eluted with $CHCl_3$ to give **7** as an amorphous compound (11.7 mg): eims *m/z* $[M]^+$ 620 ($C_{33}H_{44}D_3NO_{10}$), $[M-Me]^+$ 605, $[M-OMe]^+$ 589; ^1H nmr δ 1.09 (3H, t, $J=7.5$ Hz, N-CH_2-CH_3), 3.26, 3.28, 3.31, 3.73 (each 3H, s, OMe), 4.05 (1H, br d, H-6β), 4.57 (1H, d, $J=6$ Hz, H-15β), 4.85 (1H, d, $J=5$ Hz, H-14β), 7.48 (3H, m, aromatic protons), 8.05 (2H, dd, $J=8$, 2 Hz, aromatic protons).

8-*O*-METHYLACONINE [**11**].—14-*O*-Benzoyl-8-*O*-methylaconine [**4**] (60 mg) was stirred at 20° with 5% KOH in MeOH (7 ml) for 24 h. Usual workup and purification on an Al_2O_3 rotor (1 mm, EM 1064) of a Chromatotron gave 8-*O*-methylaconine [**11**] whose tlc behavior, ir, ^1H-nmr, and ^{13}C-nmr spectra were identical with those of an authentic sample (14).

8-DEACETYL-8-*O*-METHYLDELPHININE [**5**].—A solution of delphinine [**2**] (100 mg) in MeOH (7 ml) was heated in a sealed tube at 130° for 24 h. The residue was purified on a Chromatotron to afford compound **5** (86.7 mg): mp 173.5–175.5° (MeOH/H_2O); $[\alpha]^{28}D$ +31.9° ($c=0.53$, $CHCl_3$) [lit. (3) mp 173–175°]; $[\alpha]^{25}D$ +27° (EtOH)]; ir (Nujol) ν max 3500, 1718 cm^{-1}; eims *m/z* $[M]^+$ 571 ($C_{32}H_{45}NO_8$) (0.1%), $[M-OMe]^+$ 540 (13), 105 (55), 40 (100); ^1H nmr δ 2.28 (3H, s, N-Me), 2.93, 3.22, 3.22, 3.24, 3.47 (each 3H, s, OMe), 4.86 (1H, d, $J=4.5$ Hz, H-14β), 7.39 (3H, m, aromatic protons), 8.03 (2H, dd, $J=8$, 2 Hz, aromatic protons).

13-*O*-ACETYL-8-DEACETYL-8-*O*-METHYLDELPHININE [**16**].—The alkaloid **5** (14.5 mg) was kept at room temperature with acetyl chloride (2 ml) for 3 days. Acetyl chloride was removed in vacuo, 10% Na_2CO_3 (10 ml) was added, and the mixture was extracted with $CHCl_3$ (3 × 10 ml). Usual workup afforded the acetyl derivative **16** (15 mg) as an amorphous compound: $[\alpha]^{24}D$ +16.0° ($c=0.15$, $CHCl_3$); ir (Nujol) ν max 1740, 1726 cm^{-1}; eims *m/z* $[M]^+$ 613 ($C_{34}H_{47}NO_9$) (1%), 585 (7), 584 (26), $[M-Me]^+$ 582 (100), 105 (68); ^1H nmr δ 2.03 (3H, s, OAc), 2.37 (3H, s, N-Me), 2.98, 3.27, 3.27, 3.30, 3.39 (each 3H, s, OMe), 5.12 (1H, d, $J=6$ Hz, H-14β), 7.41–8.13 (5H, m, aromatic protons).

8-DEACETYL-3-DEOXY-8-*O*-METHYLACONITINE [**14**].—A solution of 3-deoxyaconitine [**12**] (32.0 mg) in MeOH was refluxed for 2 days. The solvent was removed in vacuo and the residue was purified on a small column of alumina. The amorphous solid **14** (28.5 mg) thus obtained was homogeneous by tlc: $[\alpha]^{24}D$ +9.1° ($c=0.30$, $CHCl_3$); ir (Nujol) ν max 3495, 1720, 1600, 1275, 1090, 705 cm^{-1}; eims *m/z* $[M]^+$ 601 ($C_{33}H_{47}NO_9$) (0.3%), $[M-OMe]^+$ 570 (66); ^1H nmr δ 1.06 (3H, t, $J=7$ Hz, N-CH_2-CH_3), 3.09, 3.27, 3.69 (each 3H, s, OMe), 3.24 (6H, s, OMe), 4.53 (1H, t, $J=5$ Hz, H-6β), 4.83 (1H, d, $J=5$ Hz, H-14β), 7.39–8.09 (aromatic protons).

8-*O*-METHYLFALCONERINE [**15**].—A solution of falconerine-8-*O*-acetate [**13**] (70.0 mg) in MeOH was refluxed for 2 days. The solvent was evaporated in vacuo, and the residue was purified on a small column of alumina to give **15** (62.5 mg) as an amorphous solid: $[\alpha]^{24}D$ +19.6° ($c=0.55$, $CHCl_3$); ir (Nujol) ν max 3490, 1712, 1598, 1512, 760 cm^{-1}; eims *m/z* $[M]^+$ 645 ($C_{35}H_{51}NO_{10}$) (0.03%), $[M-OMe]^+$ 614 (86); ^1H nmr δ 1.02 (3H, t, $J=7$ Hz, N-CH_2-CH_3), 3.08, 3.19, 3.27 (each 3H, s, OMe), 3.25 (6H, s, OMe), 3.87, 3.88 (each 3H, s, aromatic OMe), 4.93 (1H, t, $J=4.5$ Hz, H-14β), 6.78–7.72 (veratroyl protons).

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