Journal of Natural Products
Vol. 58, No. 6, pp. 929-933, June 1995

N-OXIDES OF SOME NORDITERPENOID ALKALOIDS

YILI BAI, HARIDUTT K. DESAI, and S. WILLIAM PELLETIER*

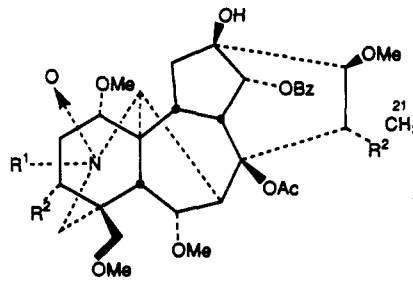
Institute for Natural Products Research and Department of Chemistry, University of Georgia, Athens, Georgia 30602-2556

ABSTRACT.—Eight new *N*-oxides [**1–8**] of the norditerpenoid alkaloids aconitine, ajacine, delphinine, delphisine, deltaline, heteratisine, lappaconitine, and *N*-deacetyllappaconitine have been prepared with *m*-chloroperbenzoic acid. The structures of these compounds were established on the basis of their spectroscopic data (^{1}H, ^{13}C, DEPT, COSY, HETCOR, and selective INEPT nmr experiments). The complete nmr chemical shift assignments for all eight *N*-oxides are reported. Table 2 shows the differences between the ^{13}C-nmr shifts of the *N*-oxides compared with those of the parent alkaloids.

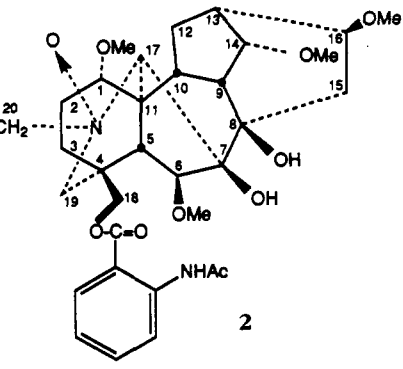
In 1989, we reported the preparation of the *N*-oxides of yunaconitine, crassicauline-A, and some of their derivatives (1). No naturally occurring *N*-oxides of the diterpenoid alkaloids have been reported. In continuation of our pharmacological studies of the diterpenoid alkaloids (2) we report here the preparation and complete nmr assignments for the *N*-oxides of aconitine, ajacine, delphinine, delphisine, deltaline, heteratisine, lappaconitine, and *N*-deacetyllappaconitine [**1–8**]. Previously, the *N*-oxides were prepared (1) by refluxing a $CHCl_3$ solution of the alkaloid and *m*-CPBA (excess). Now we report the preparation of the *N*-oxides **1–8** by carrying out the reactions at room temperature and in fairly good yields.

All the *N*-oxides reported in this work were easily formed (see Experimental) and were found to be stable under the conditions used in their handling. They were all found to be more polar on tlc plates (Al_2O_3, EM-1103 and 1104) compared with their starting materials and were soluble in $CHCl_3$ except for the low solubility of heteratisine-*N*-oxide [**6**].

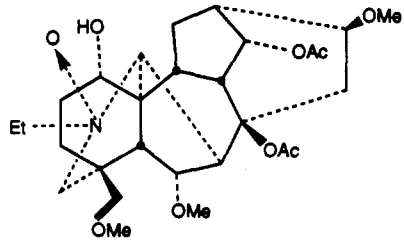
The differences between the ^{1}H- and ^{13}C-nmr chemical shifts of **1–8** compared with those of their parent alkaloids are remarkable. These changes in the chemical shifts are due to the bonding of the lone electron pair of the *N*-atom (see Table 2). Table 2 shows that the ^{13}C-nmr chemical shifts of all the carbons (i.e., C-17, C-19, and C-20) directly attached to the *N*-atom are shifted downfield by 12–20 ppm, while C-21 (*N*-CH_2CH_3) moves 5–6 ppm upfield. In the ^{1}H-nmr spectrum, H_3-21, which generally appears as a triplet around 1–1.2 ppm suffers a deshielding effect and moves to about 1.4–1.5 ppm. The nmr chemical shift assignments for the *N*-oxides **1–8** are based on the study of their ^{1}H-, ^{13}C-, DEPT, COSY, HETCOR, and selective INEPT nmr spectra. (For ^{13}C-nmr assignments, see Table 1, and for ^{1}H-nmr assignments, see the Experimental.) The unambiguous ^{13}C-nmr assignments for C-17 (methine), C-19 (methylene), and C-20 (methylene) are based on the study of DEPT, 2D, and selective INEPT nmr experiments. Thus, in the case of deltaline *N*-oxide [**5**], when H_3-21 (Me of the *N*-Et, δ 1.42) was selectively pulsed, a signal at δ 69.6 (t) showed a response; this signal can be assigned to C-20, two bonds away. When H_3-18 (δ 0.92) was selectively pulsed, the responses shown were for the carbon signals at δ 75.3 (t), 48.5 (d), 35.9 (s), and 35.6 (t) and these signals could be assigned to C-19, C-5, C-4, and C-3, respectively. Only C-4 is two bonds away and the other three carbons are three bonds away from H_3-18. C-17 was assigned the value of δ 77.5 (methine) which responded when H-1, overlapped under a signal at δ 3.28 (3H, s, OMe-1), was selectively pulsed. The spectral data obtained for each *N*-oxide support their respective structures. The pharmacological properties of these *N*-oxides, along



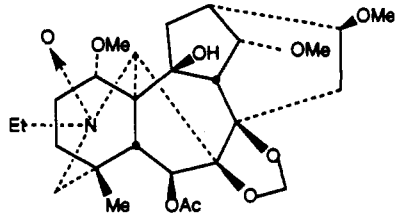
1 R^1=Et, R^2=OH
3 R^1=Me, R^2=H



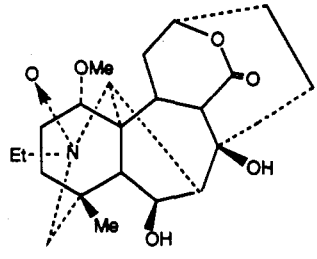
2



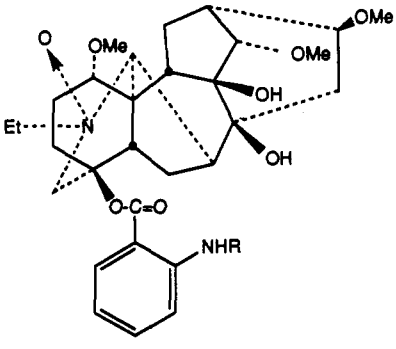
4



5



6



7 R=Ac
8 R=H

with other diterpenoid alkaloids, will be reported elsewhere.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were measured on a Perkin-Elmer model 141 polarimeter in $CHCl_3$. Ir spectra were taken on a Perkin-Elmer model 1420 spectrophotometer in nujol. ^{1}H-, ^{13}C- (including DEPT), and 2D nmr spectra were recorded in $CDCl_3$ on Bruker AC-250 and AC-300 instruments equipped with the standard Bruker software. The pulse sequence employed for selective INEPT data was as given in Desai and Pelletier (3). Ms were recorded on a Finnigan Quadrupole 4023 instrument at 70 eV. Isolation of the reaction products was carried out by separation on an Al_2O_3 rotor (1 mm, EM-1104) of a Chromatotron (4).

GENERAL PROCEDURES FOR PREPARING *N*-OXIDES.—To a $CHCl_3$ solution of *m*-CPBA (7–10 ml), a $CHCl_3$ solution of the norditerpenoid alkaloid was added at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction solution was then passed through a small column of basic Al_2O_3 (Woelm, activity-III) and the column was eluted with more $CHCl_3$. This step eliminated the residual excess of *m*-CPBA and benzoic acid from the reaction mixture. The $CHCl_3$ eluate was then evaporated to dryness *in vacuo* and the residue was fractionated on an Al_2O_3 rotor of a

TABLE 1. ^{13}C-Nmr Chemical Shifts and Assignments for *N*-Oxides **1–8**.

Carbon	Compound							
	1	**2**	**3**	**4**	**5**	**6**[a]	**7**	**8**
C-1	83.7	83.8	85.2	72.2	77.5	87.1	85.7	86.0
C-2	33.6	20.3	23.8	27.8	24.1	25.6	23.0	23.1
C-3	68.1	31.2	34.0	28.2	35.6	37.1	31.0	31.2
C-4	44.1	39.3	40.9	38.2	35.9	38.5	84.9	83.1
C-5	43.7	50.4	47.6	42.7	48.8	57.6	47.1	47.4
C-6	82.1	88.2	81.5	82.9	78.1	71.7	22.3	22.3
C-7	49.2	86.8	53.9	52.4	87.9	54.0	52.4	52.4
C-8	90.7	77.5	84.0	84.7	82.1	77.8	74.7	74.8
C-9	44.9	42.0	44.4	43.0	49.8	51.0	77.9	77.9
C-10	43.7	45.8	43.2	46.5	83.7	45.7	50.8	50.9
C-11	51.2	51.7	51.2	54.7	56.5	51.1	51.4	51.4
C-12	36.3	30.2	36.1	30.5	40.7	29.8	27.0	27.2
C-13	73.6	38.6	74.5	38.1	36.6	76.7	35.4	35.5
C-14	78.3	83.8	78.1	75.1	81.2	175.5	89.0	89.1
C-15	78.5	34.4	38.5	37.5	34.1	33.9	43.6	43.7
C-16	89.3	82.8	82.6	81.7	80.7	31.1	81.9	82.0
C-17	77.9	77.2	79.4	77.4	77.5	78.9	76.5	76.4
C-18	73.7	71.4	79.6	79.1	25.9	26.4	—	—
C-19	60.3	69.8	73.9	68.6	75.3	77.7	74.8	75.4
C-20	65.6	67.3	62.6	65.4	69.6	67.5	66.6	66.6
C-21	7.6	8.1	—	7.3	8.7	8.2	7.8	7.8
OCH_3-1	56.6	56.3	56.1	—	56.2	56.7	57.0	57.1
OCH_3-6	58.6	57.9	58.0	58.5	—	—	—	—
OCH_3-14	—	59.7	—	—	57.7	—	57.7	57.8
OCH_3-16	61.3	56.3	58.8	56.6	56.2	—	56.0	56.0
OCH_3-18	58.7	—	59.0	59.2	—	—	—	—
O-CH_2-O	—	—	—	—	93.8	—	—	—
OAc-6	—	—	—	—	169.8	—	—	—
	—	—	—	—	21.4	—	—	—
OAc-8	172.4	—	169.9	169.9	—	—	—	—
	21.1	—	21.3	22.1	—	—	—	—
OAc-14	—	—	—	170.5	—	—	—	—
	—	—	—	21.1	—	—	—	—
NHAc	—	169.2	—	—	—	—	169.1	—
	—	25.5	—	—	—	—	25.4	—
C=O (aromatic)	165.9	167.8	166.2	—	—	—	167.1	166.9
1′	129.4	114.4	129.8	—	—	—	114.7	110.5
2′	129.4	141.8	129.6	—	—	—	141.7	150.8
3′	128.6	120.6	128.4	—	—	—	120.3	116.7
4′	133.3	135.0	133.1	—	—	—	134.8	134.2
5′	128.6	122.4	128.4	—	—	—	122.2	116.0
6′	129.4	130.3	129.6	—	—	—	130.7	131.1

[a]In CD_3OD.

Chromatotron. The tlc homogeneous fractions were combined and the purity of the combined fraction was determined by examining its nmr spectra (^{1}H and ^{13}C) and the tlc behavior in different solvent systems. In all the reactions the major compounds isolated were the *N*-oxides of the starting material except for the lycoctonine-type alkaloids ajacine and *N*-deacetyllappaconitine. All the *N*-oxides reported here are amorphous white solids. The samples of all the alkaloids used for this work were authentic samples from our alkaloid collection.

Aconitine-N-*oxide* [**1**].—Aconitine (150 mg) was treated with *m*-CPBA (250 mg) as described above to give compound **1** ($C_{34}H_{47}NO_{12}$, 67 mg, 40%); $[\alpha]_D$ −6.0° (*c*=0.35); ir ν max 3490, 1725, 1715, 1280, 1095 cm^{-1}; eims *m/z* 554 (0.6), 115 (0.5), 105 (54), 86 (48), 84 (100); ^{1}H nmr δ 1.42 (3H, t, *J*=7.2 Hz, NCH_2Me), 1.43 (3H, s, OAc-8), 2.38 (1H, d, *J*=6.5 Hz, H-5), 2.77 (1H, d, H-12), 2.90 (1H, t, H-9), 3.21 (3H, s, OMe-6), 3.24 (3H, s, OMe-1), 3.26 (3H, s, OMe-18), 3.43 (1H, br s, H-17), 3.68 (3H, s, OMe-16), 3.73 (1H, m, H-3β), 4.08 (1H, d, *J*=6.5 Hz, H-6β), 4.37 (1H, d, *J*=2.6 Hz, OH-15), 4.46 (1H, dd, *J*=5.3 and 2.6 Hz, H-15β), 4.86 (1H, d, *J*=5.0 Hz, H-14β), 7.43 (2H, t, *J*=7.5 Hz, H-3′, -5′), 7.56 (1H, t,

TABLE 2. ^{13}C-Nmr Data Differences[a] Between *N*-Oxides and Their Parent Alkaloids.

Carbon	Compound							
	1	**2**	**3**	**4**	**5**	**6**[b]	**7**	**8**
C-1	+1.3	−0.1	+0.3	+0.2	+0.2	+3.6	+1.5	+2.9
C-2	−0.3	−5.8	−2.5	−2.2	−3.1	−1.3	−3.2	−3.2
C-3	−2.9	−0.9	−0.6	−1.2	−0.9	+0.3	−0.9	−0.9
C-4	+0.9	+1.1	+1.7	+0.2	+2.2	+3.8	+0.2	−1.4
C-5	−3.2	−0.1	−1.0	−1.1	−1.6	−0.7	−1.5	−2.6
C-6	−1.3	−2.8	−1.4	−1.1	−1.1	−1.2	−4.5	−4.6
C-7	+4.4	−1.8	+5.9	+4.6	−3.7	+3.3	+4.8	+4.7
C-8	−1.4	0	−1.4	−1.1	+0.7	+2.4	−0.9	−1.0
C-9	+0.7	−1.3	−0.6	−0.1	−0.6	+1.6	−0.7	−0.8
C-10	+2.8	−0.3	+2.2	+3.4	−0.1	+2.9	+1.8	+2.2
C-11	+1.2	+2.6	+1.0	+5.0	+0.5	+1.8	+0.4	+0.4
C-12	+0.4	+1.6	+0.7	+1.1	+1.3	+0.6	+2.8	+3.1
C-13	−0.4	+1.0	−0.3	−0.3	−1.9	+0.9	−1.0	−1.0
C-14	−0.6	−0.1	−0.6	−0.4	−0.5	−0.5	−1.2	−1.3
C-15	−0.3	+0.6	−0.7	−0.8	−0.7	−0.8	−1.3	−1.2
C-16	−0.8	+0.2	−0.9	−0.9	−0.8	+2.1	−1.0	−1.1
C-17	+17.0	+12.7	+16.1	+14.8	+14.0	+16.7	+15.0	+14.7
C-18	−2.5	+1.6	−0.6	−0.6	+0.2	+0.4	—	—
C-19	+13.3	+17.3	+17.9	+12.0	+18.4	+19.9	+19.3	+19.6
C-20	+16.7	+16.3	+20.1	+17.2	+19.4	+18.5	+16.7	+17.6
C-21	−5.8	−5.9	—	−5.6	−5.1	−5.3	−5.7	−5.8
OCH_3-1	+0.7	+0.5	0	—	+0.9	+1.5	+0.5	+0.9
OCH_3-6	+0.6	+0.1	+0.4	+0.5	—	—	—	—
OCH_3-14	—	+1.7	—	—	0	—	−0.2	−0.2
OCH_3-16	+0.2	0	+0.2	0	0	—	−0.1	−0.5
OCH_3-18	−0.4	—	0	+0.1	—	—	—	—
O-CH_2-O	—	—	—	—	−0.1	—	—	—
OAc-6	—	—	—	—	0	—	—	—
	—	—	—	—	−0.3	—	—	—
OAc-8	+0.1	—	+0.5	+0.4	—	—	—	—
	−0.3	—	−0.2	−0.1	—	—	—	—
OAc-14	—	—	—	−0.1	—	—	—	—
	—	—	—	−0.1	—	—	—	—
NHAc	—	+0.2	—	—	—	—	−0.4	—
	—	0	—	—	—	—	−0.2	—
C=O (aromatic)	0	−0.3	+0.3	—	—	—	−0.6	−0.8
1′	−0.4	−0.1	+0.1	—	—	—	−1.8	−1.7
2′	−0.2	−0.1	+0.3	—	—	—	−0.1	+0.1
3′	0	0	+0.3	—	—	—	−0.1	−0.1
4′	+0.1	0	+0.4	—	—	—	+0.2	+0.2
5′	0	−0.1	+0.3	—	—	—	−0.4	−0.4
6′	−0.2	0	+0.3	—	—	—	−0.6	−0.7

[a](+) Indicates a downfield shift and (−) an upfield shift.
[b]Solvents are different ($CDCl_3$ for heteratisine, and CD_3OD for its *N*-oxide).

J=7.5 Hz, H-4′), 8.02 (2H, d, J=7.5 Hz, H-2′, -6′). For ^{13}C-nmr chemical shift assignments, see Table 1.

Ajacine-N-*oxide* [**2**].—Ajacine (150 mg) was treated with *m*-CPBA (250 mg) as described above to give compound **2** ($C_{34}H_{48}N_2O_{10}$, 23 mg, 20%); $[\alpha]_D$ +29.3° (c=0.195); ir ν max 3400, 1690, 1251, 1082, 665 cm^{-1}; ^{1}H nmr δ 1.43 (3H, t, J=7.2 Hz, NCH_2Me), 2.24 (3H, s, $NHAc$), 3.30, 3.36, 3.44 (3H each, s, 3×OMe), 3.63 (1H, t, J=4.5 Hz, H-14β), 4.16, 4.33 (1H each, d, J=13.0 Hz, H_2-18), 4.62 (2H, dd, H_2-19), 4.73 (1H, br s, H-6α), 7.09 (1H, t, J=7.6 Hz, H-5′), 7.56 (1H, t, J=7.8 Hz, H-4′), 7.97 (1H, d, J=8.1 Hz, H-6′), 8.70 (1H, d, J=8.0 Hz, H-3′), 10.98 (1H, br s, *N*HAc). For ^{13}C-nmr chemical shift assignments, see Table 1.

Delphinine-N-*oxide* [**3**].—Delphinine (200 mg) was treated with *m*-CPBA (350 mg) as described above to give compound **3** ($C_{33}H_{45}NO_{10}$, 167 mg, 81.3%); $[\alpha]_D$ +3.85° (c=0.53); ir ν max 1725, 1715 cm^{-1}; eims m/z 584 $[M-31]^+$ (8), 508 (12), 105 (100); ^{1}H nmr δ 1.25 (3H, s, OAc-8), 1.65 (1H, m, H-3), 2.40 (1H, br d, J=4.2 Hz, H-10β), 2.44, 2.95 (1H each, dd, J=16.1 Hz, H_2-15), 2.81 (1H, br t, H-9), 3.12 (3H, s, OMe-6),

3.20 (3H, s, OMe-18), 3.22 (3H, s, OMe-1), 3.28 (1H, br s, H-7), 3.31 (3H, s, *N*-Me), 3.45 (3H, s, OMe-16), 3.35, 3.73 (1H each, d, J=11 Hz, H_2-19), 7.42 (2H, t, J=7.6 Hz, H-3′, -5′), 7.52 (1H, t, J=7.5 Hz, H-4′), 8.02 (2H, d, J=7.7 Hz, H-2′, -6′). For ^{13}C-nmr chemical shift assignments, see Table 1.

Delphisine-N-*oxide* [**4**].—Delphisine (100 mg) was treated with *m*-CPBA (200 mg) as described above to yield compound **4** ($C_{28}H_{43}NO_9$, 62 mg, 59%); $[\alpha]_D$ −2.47° (c=0.35); ir ν max 3490, 1725, 1715, 1280, 1095 cm^{-1}; eims *m/z* 520 $[M-17]^+$ (0.03), 504 $[M-16-17]^+$ (4), 488 (1), 476 (1), 462 (2), 444 (2), 432 (1), 417 (5), 71 (13), 43 (100); ^{1}H nmr δ 1.44 (3H, t, J=7.1 Hz, NCH_2Me), 1.55 (m, H-3), 1.84, 1.90 (2H, 2×m, H_2-12), 1.97 (3H, s, OAc-8), 2.04 (3H, s, OAc-14), 2.08, 2.15 (2H, 2×m, H_2-15), 2.31 (1H, s, H-5), 2.42 (1H, m, H-13), 2.52 (1H, m, H-9), 3.18 (1H, br s, H-17), 3.28 (3H, s, OMe-6), 3.28 (3H, s, OMe-18), 3.31 (3H, s, OMe-16), 3.62 (1H, m, H-1β), 4.09 (1H, d, J=6.5 Hz, H-6β), 4.80 (1H, t, J=4.7 Hz, H-14β). For ^{13}C-nmr chemical shift assignments, see Table 1.

Deltaline-N-*oxide* [**5**].—Deltaline (175 mg) was treated with *m*-CPBA (250 mg) to furnish compound **5** after the usual protocol mentioned in the general procedure. Compound **5** ($C_{27}H_{41}NO_9$, 173 mg, 95.8%); $[\alpha]_D$ −33.5° (c=0.39); ir ν max 3400, 1740, 1245, 1085, 800 cm^{-1}; eims *m/z* 476 $[M-O-OMe]^-$ (5), 465 $[M+1-OAc]^+$ (16), 448 $[M-O-OAc]^+$ (27), 434 [*m/z* 465 −OMe]$^-$ (7), 43 (100); ^{1}H nmr δ 0.92 (3H, s, Me-18), 1.42 (3H, t, *N*-CH_2Me), 2.07 (1H, s, OAc), 3.26 (3H, s, OMe-1), 3.27 (3H, s, OMe-16), 3.40 (3H, s, OMe-14), 3.51 (1H, br s, H-17), 4.16 (1H, t, J=4.8 Hz, H-14β), 4.93 (2H, s, O-CH_2-O), 5.34 (1H, s, H-6). For ^{13}C-nmr chemical shift assignments, see Table 1.

Heteratisine-N-*oxide* [**6**].—Heteratisine (110 mg) was treated with *m*-CPBA (200 mg) to provide compound **6** after following the general procedure. Compound **6** ($C_{22}H_{33}NO_6$, 64 mg, 55.8%); $[\alpha]_D$ +19.9° (c=0.21); ir ν max 3490, 1730 cm^{-1}; eims *m/z* 377 $[M-30]^+$ (0.75), 360 $[M-30-17]^+$ (16), 344 (18), 330 (31), 272 (14); ^{1}H nmr δ 0.94 (3H, s, Me-4), 1.25 (3H, t, J=7.0 Hz, NCH_2Me), 1.48 (1H, br s, H-5), 3.16 (3H, s, OMe-1), 3.63 (1H, d, J=7.2 Hz, H-9), 3.72 (1H, br s, H-17), 4.38 (1H, d, J=7.4 Hz, H-6β), 4.62 (1H, t, J=6.8 Hz, H-13). For ^{13}C-nmr chemical shift assignments, see Table 1.

Lappaconitine-N-*oxide* [**7**].—Lappaconitine (100 mg) was treated with *m*-CPBA (190 mg) to furnish compound **7** after following the usual protocol. Compound **7** ($C_{32}H_{44}N_2O_9$, 87 mg, 84.7%); $[\alpha]_D$ +26.8° (c=0.38); eims *m/z* 504 (6), 417 (2), 376 (4), 83 (100), 43 (90); ^{1}H nmr δ 1.48 (3H, t, J=6.8 Hz, NCH_2Me), 2.16 (3H, s, NHAc), 3.25 (3H, s, OMe-1), 3.27 (3H, s, OMe-16), 3.35 (3H, s, OMe-14), 3.65, 4.26 (1H each, d, J=14.0 Hz, H_2-19), 6.97 (1H, t, J=7.5 Hz, H-5′), 7.47 (1H, t, J=7.9 Hz, H-4′), 7.82 (1H, d, J=7.9 Hz, H-6′), 8.61 (1H, d, J=8.4 Hz, H-3′), 10.86 (1H, br s, NH). For ^{13}C-nmr chemical shift assignments, see Table 1.

N-*deacetyllappaconitine*-N-*oxide* [**8**].—An aliquot (100 mg) of compound **7** was dissolved in 13 ml of 2% HCl (aqueous) and the solution was refluxed for 2 h. The reaction solution was worked up and purified to give compound **8** ($C_{30}H_{42}N_2O_8$, 50 mg, 48.5%); $[\alpha]_D$ +15.3° (c=0.37); ir ν max 3350, 3450, 1680 cm^{-1}; eims *m/z* 393 (15), 376 (48), 342 (11), 84 (100); ^{1}H nmr δ 1.49 (3H, t, J=6.8 Hz, NCH_2Me), 3.27 (3H, s, OMe-16), 3.29 (3H, s, OMe-1), 3.39 (3H, s, OMe-14), 3.51 (1H, br s, H-17), 3.63, 4.34 (1H, each, d, J=14.3 Hz, H_2-19), 6.61 (1H, d, J=8.0 Hz, H-3′), 7.21 (1H, t, J=8.0 Hz, H-4′), 7.67 (1H, d, J=8.0 Hz, H-6′). For ^{13}C-nmr chemical shift assignments, see Table 1.

ACKNOWLEDGMENTS

This work was supported by Grant HL 32562 from the National Institutes of Health. We thank Mr. Courtney Pape for the mass spectra.

LITERATURE CITED

1. F.P. Wang and S.W. Pelletier, *West China J. Pharm. Sci.*, **4**, 193 (1989).
2. Y. Bai, H.K. Desai, and S.W. Pelletier, *J. Nat. Prod.*, **57**, 963 (1994).
3. H.K. Desai and S.W. Pelletier, *J. Nat. Prod.*, **56**, 1140 (1993).
4. H.K. Desai, E.R. Trumbull, and S.W. Pelletier, *J. Chromatogr.*, **366**, 439 (1986).

Received 31 October 1994