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Novel Product and Its Derivatives from the Reaction of Lappaconitine with HIO_4

Qiao Hong CHEN[1], Feng Peng WANG[1]*, Kai Bai YU[2]

[1]*Department of Chemistry of Medicinal Natural Products, School of Pharmacy, West China University of Medical Sciences, Chengdu 610041*
[2]*Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041*

Abstract: Treatment of lappaconitine **1** with HIO_4 at room temperature afforded **2** in 41% yield, to which Br_2-HOAc solution was added and allowed to stand at room temperature for 2 days to give **3** (13 %) and **4** (31%).

Keywords: Norditerpenoid alkaloid, lappaconitine, oxidation.

Lappaconitine **1**, a bisnorditerpenoid alkaloid, was isolated from many plants of *Aconitum* and *Delphinium* species such as *A. barbatum* var. puberulum, *A. sinomontanum*[1, 2]. It is now used in the clinical practice as an analgesic in China[3], and antiarrhythmic drugs in Uzbekistan[4, 5]. In our attempts to prepare the 10-oxygenated derivatives by treating lappaconitine **1** with HIO_4 followed by bromination, unexpected by-products were obtained in modest yields. This communication described the isolation and characterization of these novel compounds **2**, **3** and **4**.

Lappaconitine **1** (237 mg, 0.40 mmol) was allowed to react with HIO_4 (2.0 mmol). After workup, the mixture of crude products was chromatographed on Si gel column eluting with cyclohexane-acetone (5:1) to give compound **2**[6] (98 mg, 41% yield) and the starting material (44 mg) (**Scheme 1**). Compound **2**, $C_{32}H_{42}N_2O_8$, mp. 215~216℃, had a ^{13}C NMR spectrum (**Table 1**) that was in agreement with the finally established structure. The NMR and IR spectra of **2** exhibited three methoxyl groups (δ_H 3.21, 3.32, 3.57, each 3H, s; δ_C 55.4 q, 57.1 q, 59.8 q), one ketone group (δ_C 210.5 s; 1747 cm^{-1}) and an anthronyl group (δ_H 8.65, 1H, d, *J*=8.0 Hz, H-3"; 7.48, 1H, t, *J*=8.0 Hz, H-4"; 7.02, 1H, t, *J*=8.0 Hz, H-5"; 7.97, 1H, d, *J*=8.0 Hz, H-6"; 2.21, 3H, s, CO*CH*$_3$; 11.03, 1H, s, NH); δ_C 167.5 s, 115.9 s, 141.8 s, 120.4 d, 134.6 d, 122.6 d, 131.3 d, 168.9 s, 25.5q). Comparison of lappaconitine **1**[7, 8] with **2** showed that the ^{13}C NMR data of the two alkaloids were very different, especially in the signals derived from the rings C and D, indicating that **2** was probably a novel skeletal alkaloid. Finally, its structure was established as **2** by single crystal X-ray analysis (**Figure 1**), and all of the ^1H- and ^{13}C-NMR data (**Table 1**) were unambiguously assigned based on 2D-NMR (HMQC, ^1H-^1H COSY, HMBC).

By treating **2** with Br_2-HOAc at room temperature for 2 days, compounds **3**[9] (13%) and **4**[10] (31%) were obtained (**Scheme 1**). Compound **3**, $C_{31}H_{40}N_2O_8$, had an additional

hydroxyl group but lost one methoxyl group when compared with **2**. Their ^{13}C NMR spectra were very similar except for some signals attributable to C-5, C-7, C-8, C-9, C-10, C-13, C-14 and C-15 (**Table 1**), thus leading to the elucidation of the structure of compound **3**. Assignments of its ^{1}H- and ^{13}C NMR data (**Table 1**) were carried out mainly by comparison with those of **2**. Compound **4**, $C_{31}H_{38}N_2O_8$, was isolated as a white amorphous powder. Its ^{13}C NMR spectrum showed distinctive signals at δ_C 213.7 s, for a ketone group and δ_C 203.6 s, 144.8 s and 148.9 s for an α, β-unsaturated ketone group, suggesting that it had a double bond $\Delta^{13(14)}$. Thus, its structure might be assigned as **4**. The formation of **4** can be explained apparently by bromination, elimination and a retroaldol process. All of the ^{13}C NMR data (**Table 1**) of compound **4** were assigned by comparing with those of lappaconitine **1**, especially in 2D-NMR (^{1}H-

Scheme 1

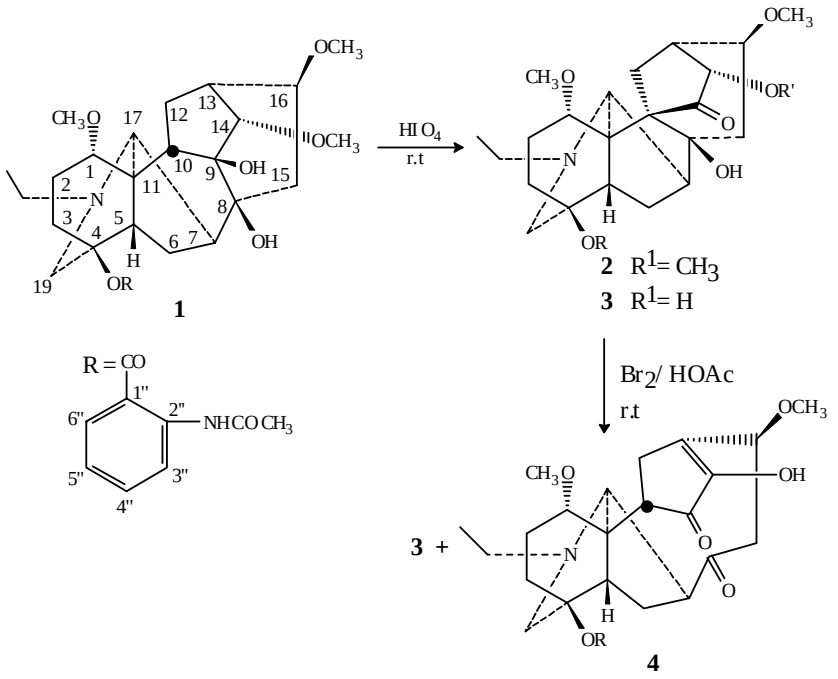

Figure 1. ORTEP drawing of Compound **2**

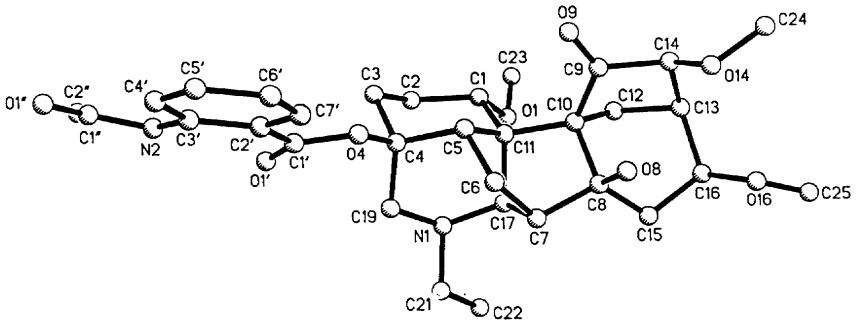

Table 1. ^{13}C NMR data of compoumds **1**[6, 7], **2**, **3** and **4**

carbon	**1**	**2**	**3**	**4**
1	84.0	77.7d	76.3 d	81.0 d
2	26.0	25.4 t	25.5 t	25.8 t
3	31.7	31.9 t	31.9 t	31.8 t
4	84.5	84.0 s	84.0 s	81.5 s
5	48.3	48.0 d	46.9 d	47.6 d
6	26.6	19.8 t	20.3 t	25.5 t
7	47.4	42.1d	43.7 d	51.2 d
8	75.3	77.7 s	82.0 s	213.7 s
9	78.4	210.5s	215.0s	203.6 s
10	49.7	60.3 s	54.4 s	47.0 d
11	50.8	54.7 s	54.6 s	54.4 s
12	24.0	29.6 t	30.0 t	28.5 t
13	36.1	32.6 d	44.3 d	148.9 s*
14	89.9	85.9 d	80.2 d	144.8 s*
15	44.6	34.5 t	37.8 t	37.6 t
16	82.7	79.5 d	79.8 d	81.0 d
17	61.3	63.8 d	64.4 d	72. 8
19	55.3	55.1 t	55.2 t	54.1
NCH_2CH_3	48.9	50.5 t	50.6 t	48.7
NCH_2CH_3	13.4	13.2 q	13.4 q	12.6
1’	56.4	55.4 q	55.7 q	57.3
14’	57.7	59.8 q	---	---
16’	55.9	57.1 q	57.8 q	56.8
C=O	167.2	167.5 s	167.6 s	167.3
1”	115.6	115.9 s	115.6 s	115.4
2”	141.4	141.8 s	141.5 s	141.6
3”	120.2	120.4 d	120.2 d	120.3
4”	134.2	134.6 d	134.4 d	134.5
5"	122.2	122.6 d	122.4 d	122.3
6”	130.9	131.3 d	131.2 d	130.9
$NHCOCH_3$	168.9	168.9 s	169.0 s	169.0
$NHCOCH_3$	25.4	25.5 q	25.6 q	25.4

*exchangable.

^1H COSY, HMQC, HMBC). But, it should be pointed out that assignments for C-13 and C-14 in ^{13}C NMR spectrum of **4** are still not unequivocal without observation of the conclusive correlated peaks and lack of the comparable analogues.

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6. **2**: colorless rhombic crystals, mp. 215-216℃ (CH_3OH); IR (KBr) cm^{-1}: 3467 (OH), 3278 (NH), 1747 (five-membered cyclic ketone), 1703 (COO), 1681. ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (1H, dd, *J*=10.8, 6.8 Hz, H-1β), 2.20 (2H, m, overlapped, H_2-2), 1.76, 2.76 (each 1H, m, overlapped, H-3a, H-3e), 2.22 (1H, m, overlapped, H-5), 1.54 (1H, dd, *J*=14.4, 5.6 Hz, H-6a), 2.56 (1H, m, overlapped, H-6e), 3.64 (1H, m, overlapped, H-7), 1.38 (1H, dd, *J*=11.4, 4.2 Hz, H-12 a), 1.92 (1H, dd, *J*=11.4, 5.2 Hz, H-12e), 3.04 (1H, m, overlapped, H-13), 3.65 (1H, d, *J*=8.0 Hz, H-14), 1.75 (1H, m, overlapped, H-15a), 1.93 (1H, dd, H, *J*=11.4, 5.2 Hz, H-15e), 4.09 (1H, dd, *J*=8.0, 6.4 Hz, H-16α), 3.09 (1H, s, H-17), 2.75, 3.73 (each 1H, ABq, *J*=9.6 Hz, H_2-19), 2.53 (2H, m, overlapped, *NCH*$_2$), 1.08 (3H, t, *J*=7.2 Hz, *N*CH_2*CH*$_3$), 2.21 (3H, s, NHC*OCH*$_3$), 8.65 (1H, d, *J*=8.0 Hz, H- 3"), 7.48 (1H, t, *J*=8.0 Hz, H-4"), 7.02 (1H, t, *J*=8.0 Hz, H-5"), 7.97 (1H, d, *J*= 8.0 Hz, H-6"), 3.21 (3H, s, 1α–OCH_3), 3.57 (3H, s, 14α–OCH_3), 3.32 (3H, s, 16β–OCH_3), 11.03 (1H, s, NH, exchangeable), 4.05 (1H, s, 8-OH, exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$): see **Table 1**; EIMS *m/z* 582 $[M]^+$ (14), 551 $[M-31]^+$ (62), 404 (78), 403 (100), 388 (38), 372 (28), 178 (20), 162 (26), 137 (29), 119 (45); HREIMS *m/z* 582.2931 (cald for $C_{32}H_{42}N_2O_8$ 582.2941); Crystal structure for **2**: a colorless orthorhombic crystal from CH_3OH was mounted on P_4 four circle diffractmeter and exposed to graphite-monochromated MoKα irradiation. The unit cell parameters are a=12.061 (2) Å, b=12.799 (2) Å, c=13.867 (2) Å in space group $P2_12_12_1$. Of the 4303 measured with $1.91^0<\theta<25.99^0$ scan, 3929 were independently observed at the level of $F>4\sigma$ *(F)*. The structure was solved by the direct method using the program SHELXTL and the atomic parameters were refined by the full-matrix least squares on F^2 method. The final R indexes [I<2σ(I)] was R^1=0.0386, WR^2= 0.0697.
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9. **3**: white amorphous powder. IR (KBr) cm^{-1}: 3442 (OH), 3318 (NH), 1749 (five-membered cyclic ketone); ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (3H, t, *J*=7.1 Hz, *N*CH_2*CH*$_3$), 2.21 (3H, s, *N*CHO*CH*$_3$), 3.33, 3.45 (each 3H, s, 2×OCH_3), 8.65 (1H, d, *J*=8.2 Hz, H-3"), 7.50 (1H, t, *J*=8.2 Hz, H-4"), 7.04 (1H, t, *J*=8.2 Hz, H-5"), 7.95 (1H, d, *J*=8.0 Hz, H-6"), 11.02 (1H, br.s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): see **Table 1**; EIMS *m/z* 568 $[M]^+$ (5), 551 (10), 390 (59), 389 (100), 360 (73), 330 (73), 179 (49), 162 (34), 137 (64), 119 (86); HREIMS *m/z* 568.2765 (cald for $C_{31}H_{40}N_2O_8$ 568.2784).
10. **4**: white amorphous powder. ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (1H, dd, *J*=10.8, 6.8 Hz, H-1β), 2.10, 2.60 (each 1H, m, overlapped, H_2-2), 1.98 (1H, m, overlapped, H-3a), 2.80 (1H, m, overlapped, H-3e), 3.17 (1H, d, *J*=5.6 Hz, H-5), 2.10 (2H, m, overlapped, H_2-6), 2.76 (1H, overlapped, H-7), 3.06 (1H, t, *J*=4.8 Hz, H-10), 1.80 (1H, d, *J*=16.8 Hz, H-12a), 2.53 (1H, dd, *J*=16.8, 7.2 Hz, H-12e), 2.01 (1H, dd, *J*=12.4, 2.8 Hz, H-15a), 2.88 (1H, t, *J*=12.4 Hz, H-15e), 4.08 (1H, m, W1/2=9.4 Hz, H-16α), 3.78 (1H, s, H-17), 2.16, 3.80 (each 1H, ABq, *J*=11.2 Hz, H_2-19), 2.44 (2H, q, *J*=6.8 Hz, *NCH*$_2$), 1.05 (3H, t, *J*=6.8 Hz, *N*CH_2*CH*$_3$), 2.25 (3H, s, NHCO*CH*$_3$), 8.66 (1H d, *J*=8.0 Hz, H-3"), 7.55 (1H, t, *J*=7.1 Hz, H-4"), 7.06 (1H, t, *J*=7.1 Hz, H-5"), 7.96 (1H, d, *J*=8.0 Hz, H-6"), 3.47 (3H, s, 1α-OCH_3), 3.30 (3H, s, 16β-OCH_3), 11.04 (1H, s, NH, exchangeable), 6.65 (1H, br.s, 14-OH, exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$): see **Table 1**; EIMS *m/z* 566 $[M]^+$ (65), 551 $[M-15]^+$ (35), 480 (21), 119 (30), 58 (100); HREIMS *m/z* 566.2634 (cald for $C_{31}H_{38}N_2O_8$ 566.2628).

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