New Products from the Reaction of Acetyllycoctonine with *N*-Bromosuccinimide (NBS)

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Six new artificial products 11—16 were obtained from the reaction of acetyllycoctonine (10) with *N*-bromosuccinimide (NBS). The structures of these compounds were established on the basis of spectral data. It is emphasized that the varieties and yields of the products in this reaction depended greatly upon reaction conditions and the types of substrate.

Key words C_{19}-diterpenoid alkaloid; acetyllycoctonine; oxidation; *N*-deethylation; imine

Although many papers on oxidation involving the nitrogen atom of the C_{19}-diterpenoid alkaloids with various oxidizers such as $KMnO_4$, OsO_4, CrO_3, Ag_2O, *m*-CPBA, *etc.* have been reported,[1] there have been no prior reports on preparation of the imines starting from these alkaloids with NBS. In the previous works on modification of C_{19}-diterpenoid alkaloids, we reported the reaction of the aconitine-type alkaloids 3-acetylpseudaconine (**1**),[2,3] 3,13-diacetylyunaconitine (**2**),[3] 3-acetylyunaconitine (**3**),[4,5] (**4**),[6] (**5**), and (**6**),[7] with *N*-bromosuccinimide (NBS) to give the *N*-deethyl and/or the imine derivatives. In addition, it was found that the varieties and yields of the resultants were greatly depended upon reaction conditions.[3] Only a paper reported by Marion and colleagues described that the lycoctonine-type alkaloid delcosine (**7**) exposed to NBS (80 °C, 68 h) afforded the lactam (**8**).[8] To observe application of this method, we turned our attention to the lycoctonine-type C_{19}-diterpenoid alkaloids which differ from the aconitine-type ones by an oxygenated group at C-7. After NBS oxidation of lycoctonine (**9**) to give the complex products, its acetyl derivative acetyllycoctonine (**10**) was used for this oxidation reaction. Meanwhile, we have tried hard to isolate others by-products than the major ones to clearly understand the reaction process. In this paper, we wish to report the isolation and identification of the new products produced by the NBS oxidation of **10**.

Results and Discussion

Treatment of acetyllycoctonine (**10**) derived from lycoctonine (**9**) from the roots of *Delphinium potaninii*[9] in *t*-BuOH with NBS at 50 °C for 2 h followed by a general work-up gave a residue which was chromatographed on silica gel column repeatedly to afford the major product **11** (33.5%), in addition to the minor ones **12** (2.9%), **13** (10.1%), **14** (2.5%), **15** (2.4%), and **16** (1.5%). They were obtained as amorphous powder and their molecular formulae were also established based on HR-MS and ^{13}C-NMR data. A comparison to the ^{1}H- and ^{13}C-NMR spectra of **11** (Table 1 and Experimental) with those of acetyllycoctonine (**10**) showed that the additional signals at δ_H 9.19 (s) and δ_C 174.8 (d) for an iminium moiety and an obvious downfield shift effect from δ 1.02 to δ 1.53 belong to the *N*-ethyl group. Another chemical shift of the carbons attached to the nitrogen atoms C-17, C-19, C-21 also shifted downfield. Thus, surprisingly, its structure was assigned as **11**, which is very stable to the acid such as 5% HCl or base (25% NH_4OH). Compound **12** as a hydrolyzed derivative of **11** was established easily on the basis of comparison of their ^{1}H- (^{13}C)-NMR spectra.

The ^{1}H- (^{13}C)-NMR spectra of compounds **13**, **14**, and **15** showed absence of the *N*-ethyl group and presence of the characteristic signals at δ_H 7.72 (br s), δ_C 167.5 (d); δ_H 4.04 (br s); δ_H 6.25 (d, J=4.4 Hz), δ_C 173.7 (s) for an imine group, an NH group and a lactam moiety, respectively. From these observations, their structures were determined. Finally, the exhibition of an amide group (δ_C 171.3 s, 22.2 t) in the ^{13}C-NMR spectrum of **16** led to establishment of its structure.

The formation of compounds **11**—**16** can be explained by

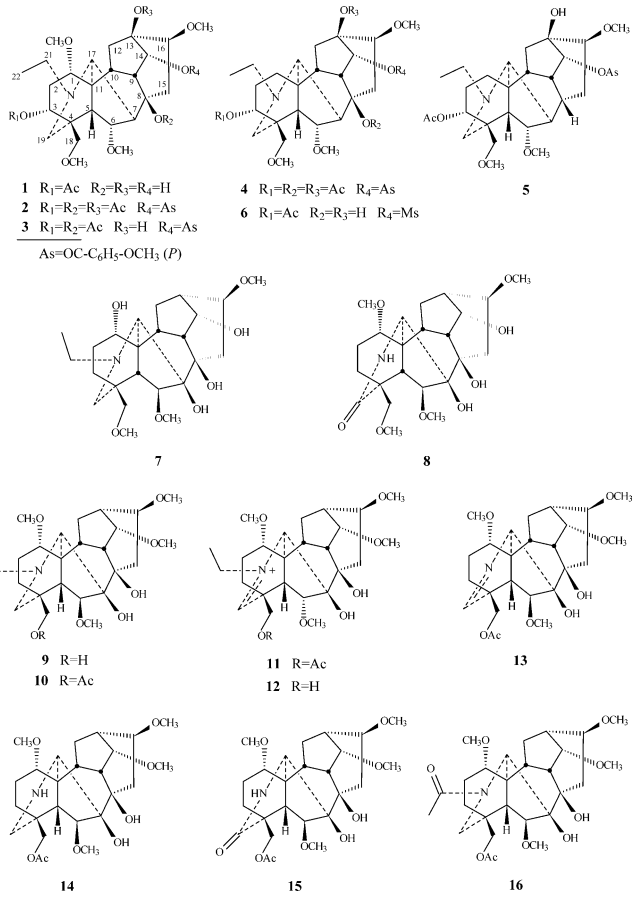

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Table 1. ^{13}C-NMR Data of Compounds **10**,[11] **11**, **12**, **13**, **14**, **15**, and **16**

Carbon	**10**	**11**	**12**	**13**	**14**	**15**	**16**
1	84.0	79.1	80.1	81.9	82.5	83.6	81.0
2	26.1	17.7	18.2	20.0	25.0	25.1	25.0
3	31.9	23.4	24.3	24.5	28.8	28.5	30.8
4	37.2	45.4	48.1	46.1	37.0	47.1	36.1
5	43.3	40.8	41.7	42.9	48.3	49.2	50.1
6	90.9	86.2	82.3	90.6	91.0	91.7	90.6
7	88.5	86.8	86.8	86.5	84.0	85.3	83.8
8	77.5	76.1	77.1	77.0	Missed	76.2	77.4
9	50.4	41.6	42.3	42.9	43.6	42.8	43.3
10	38.1	42.6	44.5	45.3	45.1	44.6	45.7
11	49.0	50.6	51.6	50.5	48.5	48.5	47.9
12	28.7	29.7	30.7	30.4	29.4	28.6	27.9
13	46.1	36.4	37.2	38.0	38.5	37.7	38.2
14	84.0	82.7	83.4	83.9	84.2	81.7	83.8
15	33.7	32.5	32.8	33.1	33.4	33.1	33.6
16	82.6	81.6	82.3	80.7	82.9	81.4	82.5
17	64.6	69.7	69.7	64.2	60.4	59.2	61.7
18	69.1	64.1	64.7	65.7	69.0	65.6	68.7
19	52.4	174.8	178.6	167.5	48.1	173.3	45.1
21	51.0	57.4	57.5	—	—	—	171.3
22	14.1	12.3	13.1	—	—	—	22.2
1-OCH_3	55.7	55.3	56.0	56.3	55.7	55.7	55.2
6-OCH_3	57.8	56.7	57.6	57.7	57.7	57.8	58.3
14-OCH_3	58.0	57.8	58.6	58.6	57.9	58.5	56.3
16-OCH_3	56.3	55.4	56.2	56.4	56.2	56.4	57.8
18-OAc	170.9	169.3	—	170.4	170.8	170.2	170.7
	20.8	19.9	—	20.6	20.7	20.7	20.7

the mechanism depicted in Fig. 1. Compound **14** was produced by the intermediate A from **10** through a one-step process (route a) with loss of ethylene and HBr. **14** was subjected first in a nucleophilic addition followed by the α-elimination of HBr to form **13**. Another elimination of the intermediate A (route b) afforded two iso-imminium salts **11** or **12**, and C; the former gave **13** by an Cope elimination, and the latter was attacked by OH^- to form the *N*,*O*-mixed acetal D followed by further oxidation to give **16**. Similarly, the lactam **15** could be formed through the intermediate E from **14** *via* F and G.

It is worthy to note that the major product is the iminium salt (**11**) instead of the imine or *N*-deethyl derivative, as compounds **1**—**6** belong to the aconitine-type alkaloids when treatment of acetyllycoctonine (**10**) under optimized conditions (6 mmol NBS, 50 °C, 2 h).[10] This indicated these reactions involving the nitrogen atom were greatly affected by not only the 7-oxygenated substituents such as OH group but also the substituent at C-3[3] or C-18 in addition to the reaction conditions.[3] This is also a new method for preparation the imines of lycoctonine-type alkaloids, but, it is still necessary to promote the yield of the desired products. The results described here should also prove helpful in further research on scope and limitation of the NBS oxidation using various analogues of lycoctonine.

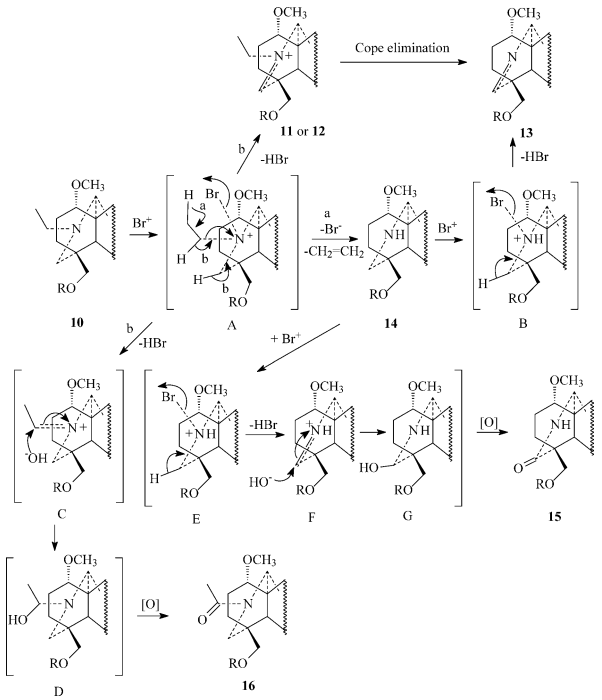

Fig. 1. A Plausible Mechanism from **10** to Compounds **11**, **12**, **13**, **14**, **15**, and **16**

Experimental

General Experimental Procedures ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian INOVA 400/54 or a Bruker AC-E 200 spectrometer, in $CDCl_3$ with TMS as internal standard. MS were measured on Finnigan LCQ and a Micromass Auto Spec Ultima-Tof spectrometer.

Reaction of Acetyllycoctonine (10) with NBS To a solution of acetyllycoctonine (**10**) (970 mg, 1.90 mmol) in *t*-BuOH (170 ml), which was derived from lycoctonine (**9**) isolated from the roots of *Delphinium potaninii*,[7] NBS (1063 mg, 6.00 mmol) was added and the solution was heated at 50 °C for 2 h. Evaporation, basifying (25% NH_4OH, 50 ml), extraction ($CHCl_3$, 40 ml×3), drying (anhydrous Na_2SO_4), removal of solvent and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98 : 2—75 : 25) afforded the pure compounds **13** (98 mg, 10.1%), **15** (23 mg, 2.4%), and fractions A, B, and C. Fraction A was subjected column chromatography (silica gel H, petroleum ether–acetone/5 : 2) to afford compound **16** (15 mg, 1.5%). Similarly, separa-

tions using silica gel column chromatography of fraction B (silica gel H, $CHCl_3$–CH_3OH/97 : 3) and fraction C [silica gel H, $CHCl_3$–CH_3OH/9 : 1 (saturated by 25% NH_4OH)] afforded the compounds **14** (25 mg, 2.5%), **11** (325 mg, 33.5%), and **12** (28 mg, 2.9%), respectively.

Compound **11**: White amorphous powder. $C_{27}H_{42}NO_8$, HR-EI-MS *m/z* 508.2784 (Calcd for $C_{27}H_{42}NO_8$, 508.2832); mp 129—130.5 °C; $[\alpha]_D^{20}$ +48.3° (*c*=0.785, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.53 (3H, t, *J*=7.2 Hz, *N*-$CH_2\underline{CH_3}$), 2.16 (3H, s, OAc), 3.18, 3.38, 3.43, 3.46 (each 3H, s, $OCH_3\times4$), 3.70 (1H, t, *J*=4.4 Hz, H-14β), 4.72, 4.86 (each 1H, ABq, *J*=11.6 Hz, H_2-18), 9.19 (1H, s, H-19); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; ESI-MS: *m/z* 509 (M+1, 100).

Compound **12**: White amorphous powder. $C_{25}H_{40}NO_7$, HR-EI-MS *m/z* 466.2743 (Calcd for $C_{25}H_{40}NO_7$, 466.2726); mp 132—133 °C; $[\alpha]_D^{20}$ +62.1° (*c*=0.580, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.51 (3H, t, *J*=7.2 Hz, *N*-$CH_2\underline{CH_3}$), 3.15, 3.38, 3.43, 3.49 (each 3H, s, $OCH_3\times4$), 3.70 (1H, t, *J*=4.4 Hz, H-14β), 9.42 (1H, s, H-19); ^{13}C-NMR (100 MHz, $CDCl_3$): see Table 1; EI-MS: *m/z* 466 (M^+, 5), 436 (M-30, 55), 406 (M-60, 100).

Compound **13**: White amorphous powder. $C_{25}H_{37}NO_8$, HR-EI-MS *m/z* 479.2501 (Calcd for $C_{25}H_{37}NO_8$, 479.2519); mp 136—137 °C; $[\alpha]_D^{20}$ +103.8° (*c*=0.530, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.09 (3H, s, OAc), 3.13, 3.33, 3.34, 3.39 (each 3H, s, $OCH_3\times4$), 3.64 (1H, t, *J*=4.4 Hz, H-14β), 4.21, 4.31 (each 1H, ABq, *J*=11.4 Hz, H_2-18), 7.72 (1H, br s, H-19); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m/z* 479 (M^+, 100), 464 (M-15, 95), 448 (M-31, 90).

Compound **14**: White amorphous powder. $C_{25}H_{39}NO_8$, HR-EI-MS *m/z* 481.2688 (Calcd for $C_{25}H_{39}NO_8$, 481.2676); mp 63—64.5 °C; $[\alpha]_D^{20}$ +55.7° (*c*=0.415, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.07 (3H, s, OAc), 3.28, 3.32, 3.37, 3.42 (each 3H, s, $OCH_3\times4$), 3.60 (1H, t, *J*=4.6 Hz, H-14β), 3.88 (2H, s, H_2-18); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m/z* 481 (M^+, 5), 466 (M-15, 65), 450 (M-31, 100).

Compound **15**: White amorphous powder. $C_{25}H_{37}NO_9$, HR-EI-MS *m/z* 495.2471 (Calcd for $C_{25}H_{37}NO_9$, 495.2468); mp 97—98.5 °C; $[\alpha]_D^{20}$ +64.9° (*c*=0.535, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.08 (3H, s, OAc), 3.26, 3.34, 3.40, 3.43 (each 3H, s, $OCH_3\times4$), 3.65 (1H, t, *J*=4.4 Hz, H-14β), 4.29, 4.58 (each 1H, ABq, *J*=12.0 Hz, H_2-18), 6.25 (1H, d, *J*=4.4 Hz, NH); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m/z* 495 (M^+, 15), 480 (M-15, 85), 464 (M-31, 20).

Compound **16**: White amorphous powder. $C_{27}H_{41}NO_9$, HR-EI-MS *m/z* 523.2757 (Calcd for $C_{27}H_{41}NO_9$, 523.2781); mp 89—91 °C; $[\alpha]_D^{20}$ +33.2° (*c*=0.845, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.05 (3H, s, *N*-$COCH_3$), 2.14 (3H, s, OAc), 3.20, 3.32, 3.37, 3.39 (each 3H, s, $OCH_3\times4$), 3.61 (1H, t, *J*=4.6 Hz, H-14β), 3.93, 4.02 (each 1H, ABq, *J*=11.2 Hz, H_2-18); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m/z* 523 (M^+, 10), 505 (M-18, 10), 476 (M-47, 100).

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