Chinese Chemical Letters Vol. 10, No. 5, pp. 375–378, 1999

Modifications of Norditerpenoid Alkaloids: I. *N*-Deethylation Reactions

Feng Peng WANG[1]*, Ju Zheng FAN[1], Zheng Bang LI[1], Jin Song YANG[1], Bo Gang LI[2]

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

Abstract: Using oxidation with $KMnO_4$, $KMnO_4$/acetone-H_2O, NBS, followed by Polonovsky reaction and imine formation, the N-deethylation of six norditerpenoid alkaloids 6-epi-forsticine, yunnaconitine, 3,13-diacetylyunnaconitine, 13-dehydroxy-indaconitine, indaconitine and 3-acetylpseudaconine are reported in 36-60% yields.

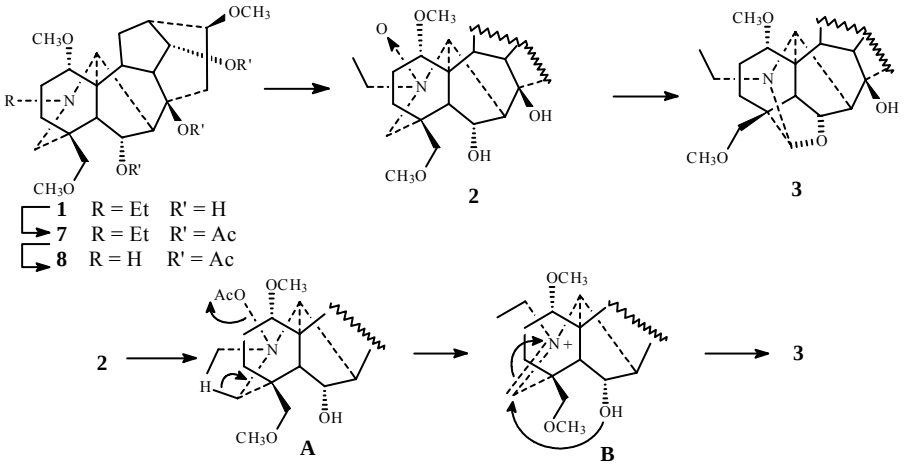
Keywords: Norditerpenpid alkaloids; N-deethylation.

The norditerpenoid and diterpenoid alkaloids are a group of highly oxygenated and complex natural products. They not only have important pharmacological activities such as analgesic, local anesthetic, anti-inflammatory and antiarrhythmetic[1], but also may set off a lot of interesting chemical reactions[2]. In order to search for high activity, low-toxicity compounds and conversion of the skeletons, we are carrying out the structure modifications of the aconitine-type norditerpenoid alkaloids. In this case, the *N*-deethylation is one of the most common reactions. Reference [1c] gave a systematic summing–up of the *N*-deethylation for the norditerpenoid alkaloids. Most common oxidizing reagents such as $KMnO_4$, Ag_2O, NBS, $Hg(OAc)_2$, CrO_3/pyridine were used for this purpose. In addition, an *N*-deethylation of the norditerpenoid alkaloid *N*-oxides *via* Polonovsky reaction also was reported. But, oxydation of the norditerpenoid alkaloids with $KMnO_4$/acetone-H_2O as reported in Ref. [1c] gave complecated resultants with low yields depending upon the reaction conditions. In this paper, the *N*-deethylations of six norditerpenoid alkaloids 6-epi-forsticine **1**[4], yunnaconitine **9**, 3,13-diacetylyunnaconitine **11**, 13-dehydroxyind-aconitine **13**, indaconitine **16** and 3-acetylind-aconitine **18** were reported by using different oxidizing reagents ($KMnO_4$, $KMnO_4$/acetone-H_2O, NBS), Polonovsky reaction and imine formation methods.

Reaction of 6-epi-forsticine **1** with m-CPBA gave the *N*-oxide **2**[5], **2** in DMF-H_2O solution was irradiated using microwave for 2 min to afford a main product (64%). Its mass spectrum showed the molecular ion peak at m/z 435 (9%). The ^{1}H- and ^{13}C-nmr spectra indicated the presence of an *O, N*-mixed acetyl moiety [$_H$ 4.36 (1H,s); $_c$ 92.0d], resulting in establishing the structure as **3**[6]. **Figure 1** showed the possible process of formation for **3**. When **1** was kept in DMF-Ac_2O solution in refrigerator for

48 h, or oxidized with $KMnO_4$ or $K_3Fe(CN)_6$ at room temperature for 15 min (or 4 h), the main product was still **3** rather than the desired one. Oxidation of **4** with $KMnO_4$ at (pH 8) at room temperature for 30 min gave the desired products **5**[7] (17%) and the by-product **6**[8] (22%). Similarly, oxidation of **7** with $KMnO_4$ gave **8**[9] in 62% yield. Under the same

Figure 1

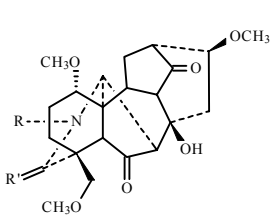


conditions, the *N*-deethylation of **9** and **11** occurred and gave the desired products **10**[10] and **12**[11] in 38% and 39% yields, respectively. When **13** was oxidized with m-CPBA, only **14** in low yield were afforded. But, reaction of **13** with $KMnO_4$ 50% acetone water[12] at room temperature for 6.5 h leads to the main product **14**[13] (36.7%). Polonovsky reaction of 13-dehydroxy-indaconitine N-oxide **15** with Ac_2O at 70℃ for 3 h, in addition to **14** (28%), one more polar minor unidentified compound was isolated.

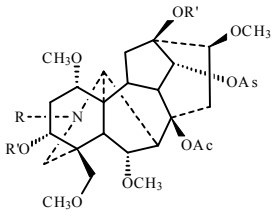
According to Ref. [12], oxidation of indaconitine **16** with $KMnO_4$ in 50% acetone water solution afforded the desired compound **17**[14] (19.3%). The experiments indicated that the yield of the *N*-deethyl products starting from the norditerpenoid alkaloids *via* oxidation with $KMnO_4$ was greatly affected by the reaction conditions. As exemplified by yunnaconitine **9**, our research showed that the *N*-deethyl products in more than 50% yield could be given when the reaction proceeded under the following conditions : substrate **9** / $KMnO_4$ (Mol / Mol)=1:1.15, reaction time 1.5 h, temperature 15℃ in 50% acetone water solution.

To our surprise, attempt to prepare 14-dehydro derivative starting from 3-acetylpseudaconine **18** using NBS leads to the *N*-deethyl **19**[15] (59.0%) and imine **20**[16] (30.0%). Catalytic hydrogenation of **20** resulted in at least over 80% yield of **19**. This seems to be a useful method for the *N*-deethylation of the norditeropenoid alkaloids.

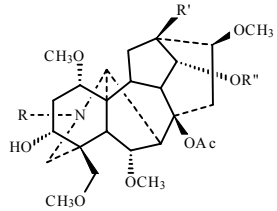
In summary, we find that in the *N*-deethylation of the norditerpenoid alkaloids, the yields of the resulting products being greatly dependent upon the used reagents, reaction conditions and methods, especially in the $KMnO_4$ oxidation and Polonovsky reaction. In addition, the *N*-deethylation using NBS oxidation-catalytic hydrogenation under very mild conditions leads to the desired products at least in over 80% yields.



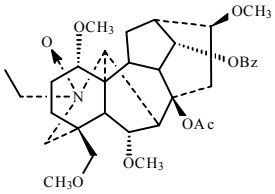
4 R = Et R' = H_2
5 R = H R' = H_2
6 R = Et R' =O



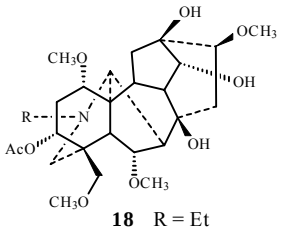
9 R = Et R' = H
10 R = R' = H
11 R = Et R' =Ac
12 R = H R' = Ac



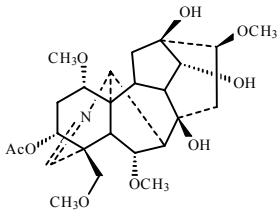
13 R = Et R' = H R" = Bz
14 R = R' = H R" = Bz
16 R = Et R' = OH R" = Bz
17 R = H R' = OH R" = Bz



15



18 R = Et
19 R = H



20

Acknowledgments

We thank the National Natural Science Foundation of China (No.39370807) and the Chengdu Diao Pharmaceutical Company for support of this work. We also thank Professor Xiao Tian LIANG for helpful discussion on the subject.

References and Notes

1. a). M. H. Benn and J .M. Jacyno, The toxicology and pharmacology of diterpenoid alkaloids, in "*The Alkaloids*: *Chemical* and *Biological Perspectives*" (S. W. Pelletier, ed.), vol.1, pp.153-210, John Wiley & Sons, New York, 1983; b). F. N. Dzhakhangirov, M. N. Sultankhodzhaev, B. Tashkhodzhaev, and B. T. Silimov, *Khim. Prir. Soedin*, **1997**, *33*, 254-270.
2. a). F. P. Wang and X. T. Liang, Chemistry of the diterpenoid alkaloids, in "*The Alkaloids*: *Chemistry* and *Pharmacology*" (G. A. Cordell, ed.), vol. 42, Academic Press, pp.152-247; b). S. W. *Pelletier, J. Nat. Prod*, **1992**, **55**, 1-24; c). Feng Peng WANG, *Youji Huaxue*, **1994**, *14*, 359-369.
3. F. P. Wang and S. W. Pelletier, *West China J. Pharm. Sci*, **1989**, *4*, 193.
4. F. P. Wang, C. S. Peng, Z. B. Li, *Phytochemistry*, submitted.
5. **2**: white amorphous powder, $C_{24}H_{39}NO_7$ (EIMS+^{13}C NMR). IR(cm^{-1}): 3513(OH). ^{1}H NMR (200MHz, $CDCl_3$)δ: 1.47 (3H, t, J=6.8Hz, NCH_2CH_3), 3.27, 3.33 (each 3H, s, 2×OCH_3), 4.87 (1H, d, J=6.6Hz, 6β-H). ^{13}C NMR (50MHz)δ: 85.3 (1), 22.6 (2), 32.6 (3), 40.2 (4), 47.1 (5), 69.8 (6), 55.8 (7), 73.0 (8), 48.1 (9), 48.1 (10), 51.1 (11), 28.1 (12), 36.9 (13), 78.2 (14), 37.1 (15), 81.1 (16), 59.4 (17), 79.7 (18), 74.2 (19), 55.8 (1'), 56.3 (16'), 58.9 (18'), 66.3 (21), 7.5 (22). EIMS m/z: 435 $(M-H_2O)^+$, 13), 406 (88), 390 (49), 378 (100).
6. **3**: white amorphous powder. $C_{24}H_{37}NO_6$ (EIMS+^{13}C NMR). IR(cm^{-1}): 3521 (OH). ^{1}H NMR (200MHz, $CDCl_3$)δ: 1.04 (3H, t, J=7.2Hz, NCH_2CH_3), 3.26, 3.28, 3.34 (each 3H, s, 3×OCH_3), 3.74 (1H, s, 8-OH), 4.05 (1H, t, J=4.8Hz, 14β-H), 4.36 (1H, s, 19-H), 4.72 (1H, dd, J=5.0, 2.5Hz, 6β-H), 5.35 (1H, d, J=5.0Hz, 14-OH). ^{13}C NMR (50MHz) δ: 86.7 (1), 24.7 (2), 27.3 (3),

45.5 (4), 51.3 (5), 78.8 (6), 52.9 (7), 70.1 (8), 45.4 (9), 46.5 (10), 47.2 (11), 25.8 (12), 36.8 (13), 75.0 (14), 34.3 (15), 82.0 (16), 63.7 (17), 79.9 (18), 92.0 (19), 56.3 (1'), 56.6 (16'), 59.2 (18'), 45.6 (21), 14.3 (22). EIMS m/z(%): 435 (M^+, 9), 420 (19), 404 (100), 376 (34).

7. **5**: white amorphous powder. IR (cm^{-1}): 1742 (C=O). ^{1}H NMR (200MHz, $CDCl_3$) δ: 3.32, 3.33, 3.36 (each 3H, s, 3×OCH_3). ^{13}C NMR (50MHz) δ: 84.5 (1), 24.2 (2), 27.5 (3), 46.3 (4), 55.2 (5), 215.3 (6), 61.4 (7), 81.3 (8), 56.0 (9), 45.9 (10), 48.7 (11), 25.8 (12), 44.9 (13), 211.8 (14), 34.9 (15), 82.8 (16), 66.4 (17), 73.9 (18), 165.5 (19), 55.9 (1'), 56.2 (16'), 59.3 (18').
8. **6:** white amorphous powder. $C_{24}H_{33}NO_7$ (EIMS+^{13}C NMR). IR (KBr) cm^{-1}): 1639 (O=C-N), 1758 (C=O). ^{1}H NMR (200MHz, $CDCl_3$): 1.19 (3H, t, J=7.2Hz, NCH_2CH_3), 3.32, 3.32, 3.35 (each 3H, s, 3×OCH_3). ^{13}C NMR (50MHz) δ: 84.1 (1), 24.1 (2), 31.0 (3), 46.6 (4), 54.9 (5), 213.8 (6), 60.0 (7), 81.3 (8), 56.5 (9), 45.7 (10), 47.4 (11), 25.8 (12), 43.9 (13), 210.9 (14), 34.5 (15), 81.6 (16), 65.5 (17), 72.6 (18), 169.0 (19), 55.8 (1'), 56.2 (16'), 59.0 (18'), 41.3 (21), 12.7 (22). EIMS m/z (%): 447 (M^+, 10), 71 (100).
9. **8:** white amorphous powder. $C_{28}H_{41}NO_9$ (EIMS+^{13}C NMR). IR (KBr) cm^{-1}: 1750, 1250 (COO). ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.88 (3H, s, 8-OAc), 2.00, 2.03 (each 3H, s, 2×OAc), 3.22, 3.22, 3.29 (each, s, 3×OCH_3), 4.82 (1H, t, J=4.5Hz, 14β-H), 5.77 (1H, d, J=6.6Hz, 6β-H). ^{13}C NMR (50MHz) δ: 82.1 (1), 23.0 (2), 28.7 (3), 38.5 (4), 43.9 (5), 73.8 (6), 52.8 (7), 84.8 (8), 43.5 (9), 43.0 (10), 51.0 (11), 28.4 (12), 38.6 (13), 75.0 (14), 37.2 (15), 81.9 (16), 56.8 (17), 79.3 (18), 49.2 (19), 55.2 (1'), 56.3 (16'), 59.0 (18'), 169.4, 169.4, 170.4; 21.0, 21.1, 21.9 (3×OAc). EIMS m/z(%): 535 (M^+, 6), 504 (M-31, 100), 444 (38).
10. **10:** white amorphous powder. $C_{33}H_{45}NO_{11}$ (EIMS+^{13}C NMR). IR (KBr) cm^{-1}: 1729, 1250 (COO). ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.30 (3H, s, 8-OAc), 3.12, 3.27, 3.30, 3.51, 3.84 (each 3H, s, 5×OCH_3), 4.86 (1H, d, J=5.0Hz, 14β-H), 6.90, 7.98 (each 2H, AA'BB' system, Ar-H). ^{13}C NMR (50MHz) δ: 83.1 (1), 34.2 (2), 71.0 (3), 40.7 (4), 43.6 (5), 81.1 (6), 43.7 (7), 85.1 (8), 47.4 (9), 40.5 (10), 49.5 (11), 34.5 (12), 74.6 (13), 78.3 (14), 39.0 (15), 82.8 (16), 58.7 (17), 76.3 (18), 54.8 (19), 55.6 (1'), 57.4 (6'), 56.5 (16'), 59.1 (18'), 169.6, 21.5 (OAc), 165.9 (COO), 122.3 (1"), 131.6 (2", 6"), 113.7 (3", 5"), 163.4 (4"), 55.3 (4"-OCH_3). EIMS m/z(%): 600 $(M-31)^+$, 10), 415 (72), 135 (100).
11. **12:** white amorphous powder. IR (KBr) cm^{-1}: 1750, 1250 (COO). ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.30 (3H, s, 8-OAc), 2.03, 2.05 (each 3H, s, 2×OAc), 3.18, 3.21, 3.25, 3.36, 3.95 (each 3H, s, 5×OCH_3), 5.07 (1H, d, J=6.0Hz, 14β-H), 6.90, 8.01 (each 2H, AA'BB' system, Ar-H). ^{13}C NMR (50MHz) δ: 80.5 (1), 31.4 (2), 72.0 (3), 42.8 (4), 42.6 (5), 79.8 (6), 56.4 (7), 85.1 (8), 45.0 (9), 41.1 (10), 49.5 (11), 34.2 (12), 81.6 (13), 76.9 (14), 39.4 (15), 83.4 (16), 58.8 (17), 73.6 (18), 41.4 (19), 55.4 (1'), 57.9 (6'), 55.6 (16'), 58.2 (18'), 169.6, 170.3, 170.4, 21.1, 21.2, 21.5 (3×OAc), 165.8 (O=C-OR), 122.3 (1"), 131.8 (2", 6"), 113.7 (3", 5"), 163.4 (4"), 54.8 (4"-OCH_3).
12. O. Achmatowicz, JR., Y. Tsuda, and L. Marion, *Can. J. Chem*, **1965**, *43*, 2336.
13. **14**: white amorphous powder. ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.31 (3H, s, 8-OAc), 3.16, 3.27, 3.30, 3.36 (each 3H, s, 4×OCH_3), 4.12 (1H, d, J=6.6Hz, 6β-H), 5.05 (1H, t, J=4.7Hz, 14β-H), 7.36~8.05 (5H, m, Ar-H). ^{13}C NMR (50MHz) δ: 79.9 (1), 29.7 (2), 69.5 (3), 42.6 (4), 42.4 (5), 81.6 (6), 50.9 (7), 84.2 (8), 43.1 (9), 39.0 (10), 49.7 (11), 28.0 (12), 43.3 (13), 75.1 (14), 37.4 (15), 82.4 (16), 59.1 (17), 76.8 (18), 41.1 (19), 55.2 (1'), 57.5 (6'), 56.8 (16'), 58.3 (18').
14. **17**: white amorphous powder. ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.31 (3H, s, 8-OAc), 3.16, 3.27, 3.30, 3.36 (each 3H, s, 4×OCH_3), 4.10 (1H, d, J=6.6Hz, 6β-H), 5.05 (1H, t, J=4.7Hz, 14β-H), 7.37~8.05 (5H, m, Ar-H). ^{13}C NMR (50MHz) δ: 80.0 (1), 34.9 (2), 71.0 (3), 43.8 (4), 51.4 (5), 83.4 (6), 43.6 (7), 84.3 (8), 47.3 (9), 41.0 (10), 49.4 (11), 34.9 (12), 74.1 (13), 78.9 (14), 37.4 (15), 82.4 (16), 61.0 (17), 77.6 (18), 40.7 (19), 55.7 (1'), 57.6 (6'), 56.8 (16'), 59.1 (18'), 168.9, 21.3 (OAc), 166.0 (O=C-O), 129.8 (1"), 129.5 (2", 6"), 128.6 (3", 5"), 133.4 (4").
15. **19**: white amorphous powder. $C_{25}H_{39}NO_9$ (EIMS+^{13}C NMR). ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.06 (3H, s, OAc), 3.21, 3.24, 3.34, 3.42 (each 3H, s, 4×OCH_3), 4.00 (1H, d, J=4.8Hz, 14β-H), 4.24 (1H, d, J=6.8Hz, 6β-H), 5.16 (1H, br s, 3β-H). ^{13}C NMR (100MHz) δ: 80.6 (1), 30.3 (2), 71.8 (3), 42.5 (4), 57.2 (5), 81.9 (6), 49.0 (7), 73.3 (8), 45.1 (9), 41.1 (10), 49.1 (11), 35.0 (12), 76.3 (13), 78.9 (14), 40.9 (15), 83.1 (16), 58.9 (17), 74.2 (18), 41.3 (19), 55.6 (1'), 57.7 (6'), 58.0 (16'), 59.0 (18'), 170.0, 21.1 (OAc). FABMS m/z(%): 498 ((M+1), 100).
16. F. P. Wang, Z. B. Li, J. S. Yang and B. G. Li, *Chin. Chem. Lett*, submitted

Received 23 November 1998

Revised 31 March 1999