Chinese Chemical Letters Vol. 11, No. 5, pp. 421–424, 2000

Oxidation of the Norditerpenoid Alkaloids Isotalatizidine and 6-Epiforsticine

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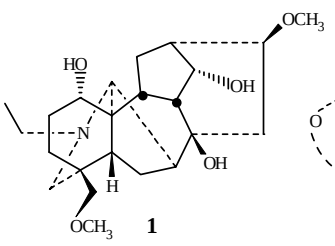
Abstract: Oxidation of **1** with $KMnO_4$ in acetone-H_2O (1:1) for 1h gave nevadenine **2** (38%). But, **3** was formed in 98% yield when prolonging time and raising temperature (40℃). Reaction of **1** and **10** with Conforth reagent afforded the ketones **11** (55%), **12** (30%), and **13** (13%), **14** (20%), respectively. While oxidation of **7** and **15** with a variety of the oxidizing agents gave **17** only in low 20% of yield besides the minor **16**. In addition, **1** was converted to **2** by the fungi *Curvularia lunata.*

Keywords: Norditerpenoid alkaloid, oxidation, isotalatizidine, 6-epiforsticine, *Curvularia lunata.*

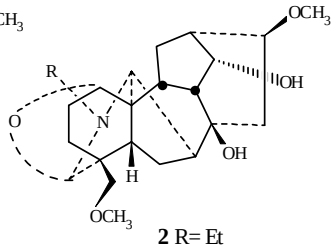
In previous works on modifications of norditerpenoid alkaloids, we reported some important reactions such as *N*-deethylation and preparations of the imines and 7, 17-*seco* derivatives[1]. Now we wish to report oxidation of the norditerpenoid alkaloids isotalatizidine and 6-epiforsticine.

Oxidation of norditerpenoid alkaloids having an 1α-hydroxyl group with reagents such as $KMnO_4$ $K_3Fe(CN)_6$, OsO_4, Ag_2O and NBS afforded compounds with an *O*, *N*-mixed acetal systems[2]. Thus, treatment of isotalatizidine **1** with $KMnO_4$ in acetone-H_2O (5:1) for 1 h gave the known compound nevadenine **2**[3] in 38% yield, the products greatly depended upon reaction condition. Compound **3**[4] was formed in 98% yield when prolonging the reaction time and raising the temperature (40℃). The NMR spectrum of **3** showed signals at δ_H 4.07 (1H, s); δ_C 82.8 (d) for an *O*, *N*-mixed acetal moiety but absence of an *N*-ethyl group. K. Wiesner, *et al*[5] reported a method for preparation of **6** starting from **4** by CrO_3/pyridine oxidation *via* an acyloin rearrangement of product **5**. This led us to obtain **9** starting from **7** through oxidation followed by bromation of **8**. Model reaction of **1** and **10**[6] with Conforth reagent/ pyridine[7] yielded the ketones **11**[8] (55%), **12**[9] (30%), and **13**[10] (13%), **14**[11] (20%), respectively. But, oxidation of pseudaconine **7** and 3-acetyl pseudaconine **15** with a variety of reagents such as CrO_3/pyridine, Jone's or Conforth reagents, PDC/CH_2Cl_2, afforded the desired product **17**[12] in low yield (20%), besides the minor compound **16**[13], probably due to hindrance of the 13-hydroxyl group. Treatment of the diketone **17** with 1% NaOH in methanol at

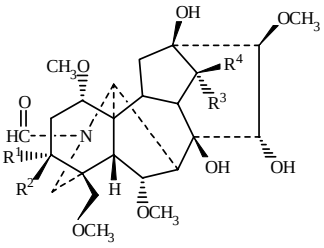
room temperature for 1 day yielded the complex products instead of the desired compound **8**.



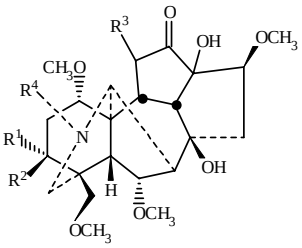
1



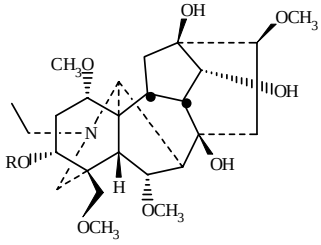
2 R= Et
3 R= H



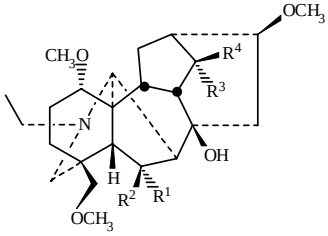
4 R^1 =R^3= OH R^2+R^4= H
5 R^1+R^2= R^3+R^4= O



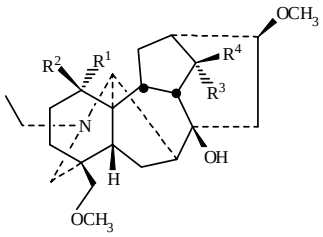
6 R^1= OH R^2= R^3= H R^4= CHO
8 R^1+R^2= O R^3= H R^4=Et
9 R^1+R^2= O R^3= Br R^4= Et



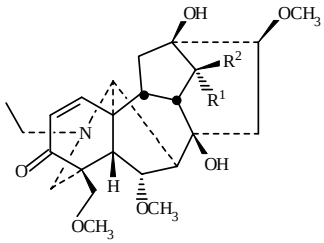
7 R= H
15 R= Ac



10 R^1= R^3=OH R^2=R^4=H
13 R^1+R^2= O R^3=OH R^4= H
14 R^1+R^2= R^3+R^4= O



11 R^1+R^2= O R^3= OH R^4=H
12 R^1+R^2= R^3+R^4=O



16 R^1= OH R^2= H
17 R^1+R^2= O

In addition, we have found that isotalatizidine **1** was converted to nevadenine **2** by the fungi *Curvularia lunata*.

Acknowledgment

We thank the National Natural Science Foundation of China (No. 393707) 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

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4. **3**: colorless rhombic crystals, mp. 283-285℃ (acetone- n-hexane). $C_{21}H_{31}NO_5$ (EIMS+ ^{13}C-NMR). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.31, 3.33 (each 3H, s, 2×OCH_3), 4.07 (1H, s, H-19), 4.20 (1H, t, *J*=4.8 Hz, H-14β). ^{13}C NMR (50 MHz) δ: 69.1 (1), 23.0 (2), 22.3 (3), 42.8 (4), 36.9 (5), 25.9 (6), 43.8 (7), 72.0 (8), 45.5 (9), 53.5 (10), 46.5 (11), 26.9 (12), 38.5 (13), 75.2 (14), 39.5 (15), 81.6 (16), 55.6 (17), 74.0 (18), 82.8 (19), 56.3 (16'), 59.2 (18'). EIMS *m/z* (%): 377 (M^+, 32), 346 (M-31, 100).
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8. **11**: white amorphous powder, $C_{23}H_{35}NO_5$ (EIMS+^{13}C NMR). ^{1}H NMR (200 MHz , $CDCl_3$) δ: 1.04 (3H, t, *J*=7.0 Hz, NCH_2CH_3), 2.93 (1H, s, H-17), 3.29, 3.31 (each 3H, s, 2×OCH_3), 3.85 (1H, br.s, disappeared with D_2O, HO-14α), 4.21 (1H, t, *J*=4.4 Hz, H-14β). ^{13}C NMR (50 MHz) δ: 215.0 (1), 40.8 (2), 35.4 (3), 38.4 (4), 49.6 (5), 25.3 (6), 45.8 (7), 73.5 (8), 46.3 (9), 39.5 (10), 59.9 (11), 31.2 (12), 39.0 (13), 75.2 (14), 41.0 (15), 81.7 (16), 64.8 (17), 78.2 (18), 53.9 (19), 48.7 (NCH_2-), 13.2 (NCH_2CH_3), 56.1 (16'), 59.3 (18'). EIMS *m/z* (%): 405 (M^+, 12), 390 (100), 374 (M-31, 75), 349 (43).
9. **12**: white amorphous powder, $C_{23}H_{33}NO_5$ (EIMS+^{13}C NMR). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.06, 3.13 (each 1H, ABq, *J*=9.0 MHz, H_2-18), 3.29 (6H, s, 2×OCH_3), 3.67 (1H, m, W1/2=17.6 Hz, H-16α). ^{13}C NMR (50 MHz) δ: 214.4 (1), 40.8 (2), 35.2 (3), 38.5 (4), 49.2 (5), 25.4 (6), 46.1 (7), 81.3 (8), 53.8 (9), 37.6 (10), 59.7 (11), 28.7 (12), 46.4 (13), 216.3 (14), 39.7 (15), 86.0 (16), 65.6 (17), 78.2 (18), 53.7 (19), 48.8 (NCH_2-), 13.3 (NCH_2CH_3), 56.0 (16'), 59.3 (18'). EIMS *m/z* (%): 403 (M^+, 78), 388 (100), 372 (11).
10. **13**: white amorphous powder, $C_{24}H_{37}NO_6$ (^{1}H- and ^{13}C-NMR). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06 (3H, t, *J*=7.0 Hz, NCH_2CH_3), 3.29, 3.32, 3.34 (each 3H, s, 3×OCH_3), 4.03 (1H, t, *J*=5.0 Hz, H-14β). ^{13}C NMR (50 MHz) δ: 84.3 (1), 25.7 (2), 32.4 (3), 37.9 (4), 55.9 (5), 217.7 (6), 58.3 (7), 73.1 (8), 47.7 (9), 45.8 (10), 46.7 (11), 27.1 (12), 37.0 (13), 74.6 (14), 36.2 (15), 81.4 (16), 62.5 (17), 76.9 (18), 53.5 (19), 49.1 (NCH_2-), 13.3 (NCH_2CH_3), 56.2 (1'), 56.6 (16'), 59.2 (18').
11. **14**: white amorphous powder, $C_{24}H_{35}NO_6$ (^{1}H- and ^{13}C-NMR). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.32, 3.32, 3.33 (each 3H, s, 3×OCH_3). ^{13}C NMR (50 MHz) δ: 84.7 (1), 25.6 (2), 32.1 (3), 38.0 (4), 55.7 (5), 218.6 (6), 58.2 (7), 81.8 (8), 55.7 (9), 43.7 (10), 47.2 (11), 24.8 (12), 46.0 (13), 212.3 (14), 34.8 (15), 84.0 (16), 62.9 (17), 76.6 (18), 53.5 (19), 49.0 (NCH_2-), 13.2 (NCH_2CH_3), 56.2 (1'), 56.2 (16'), 59.2 (18').
12. **17**: white amorphous powder, $C_{24}H_{33}NO_7$ (^{1}H- and ^{13}C-NMR). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, t, *J*=7.0 Hz, NCH_2CH_3), 3.29, 3.42, 3.50 (each 3H, s, 3×OCH_3), 4.28 (1H, d, *J*=6.2 Hz, H-6β). 6.45, 6.28 (each 1H, ABq, *J*=10.2 Hz, H-1 and H-2). ^{13}C NMR (50 MHz) δ:147.3 (1), 132.5 (2), 200.2 (3), 50.1 (4), 48.6 (5), 83.6 (6), 50.7 (7), 86.1 (8), 57.4 (9), 40.1 (10), 51.2 (11), 41.1 (12), 87.9 (13), 215.7 (14), 39.7 (15), 86.8 (16), 60.1 (17), 71.8 (18), 48.8 (19), 48.7 (NCH_2-), 12.8 (NCH_2CH_3), 58.1 (6'), 58.4 (16'), 59.0 (18').
13. **16**: white amorphous powder, $C_{24}H_{31}NO_7$ (^{1}H- and ^{13}C-NMR). ^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.00 (3H, t, *J*=7.0 Hz, NCH_2CH_3), 3.23, 3.42, 3.50 (each 3H, s, 3×OCH_3), 4.10 (1H, t, *J*=4.6

Hz, 14β-H), 6.28, 6.45 (ABq, J=10.2 Hz, H-2, H-1). ^{13}CNMR (50 MHz) δ: 147.7 (1), 131.7 (2), 200.6 (3), 49.1 (4), 48,6 (5), 81.5 (6), 52.9 (7), 74.6 (8), 48.7 (9), 37.8 (10), 50.9 (11), 38.1 (12), 76.1 (13), 79.2 (14), 43.3 (15), 82.8 (16), 61.3 (17), 72.0 (18), 51.3 (19), 48.7 (NCH_2-), 12.9 (NCH_2CH_3), 57.9 (6'), 58.1 (16'), 59.0 (18')

Received 26 November 1999
Revised 7 March 2000