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Demethoxylation and *O*-Demethylation of Pseudaconine and Isotalatizidine

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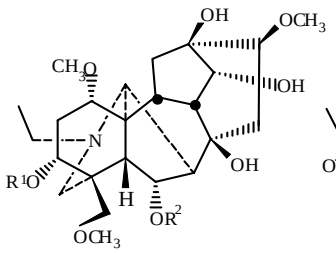
Abstract: Demethoxylation and *O*-demethylation of the norditerpenoid alkaloids pseudaconine and isolatatizidine were described.

Keywords: Norditerpenoid alkaloid, demethoxylation, *O*-demethylation, oxidation, pseudaconine, isotalatizidine.

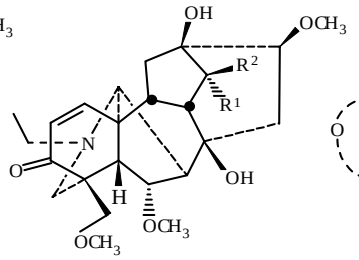
The norditerpenoid alkaloids not only have important pharmacological activities, but also may set off a lot of interesting chemical reactions[1, 2]. In the course of our studies on search for high activity, low toxicity compounds and conversion of the skeletons, a series of modifications of these alkaloids have been reported[3]. In the present paper, we report some chemical reactions including the demethoxylation, *O*-demethylation and oxidation, of the norditerpenoid alkaloids pseudaconine **1** and isotalatizidine **7**.

Treatment of the norditerpenoid alkaloids containing methoxyl groups with CrO_3/acids generally led to the demethoxylation at C-1 or C-16[2a]. Reaction of pseudaconine **1** with pyridium dichromate (PDC)[4] gave **2**[5] (4.8%). Its NMR spectra showed distinctive signals at δ_H 6.45, 6.28, ABq, J=10.2 Hz; δ_C 131.7 d, 147.7 d, 200.6 s for an α,β-unsaturated ketone, at δ_H 3.23, 3.42, 3.50, each 3H, s, for three methoxyl groups. An attempt to hydrolysis the *N*, *O*-mixed acetal **3** with 0.5% HCl under reflux for 16 h afforded **4**[6] (51%). The presence of one methoxyl group and two olefin protons at δ_H 5.74, 1H, d, J=9.4 Hz; 5.92, 1H, dd, J=9.4, 6.8 Hz in the ^{1}H NMR spectrum of **4** indicated a demethoxylation at C-16. *O*-Demethylation of the norditerpenoid alkaloids with reagents are very useful for modifications or chemical correlations. For example, reaction of crassicauline A **5** with HBr-AcOH gave compound **6**[7]. Under similar condition, aconitine **7** afforded compounds **8**, **9** and **10**[8], while treatment of aconitine **7** producd selectively *O*-demethyl products **10**, **11** and **12**[8]. The reaction products depend upon the substrates, the general, the order of increasing difficulty is 16-OCH_3>18-OCH_3>6-OCH_3>1-OCH_3[6,7]. Attempt to prepare **13** starting

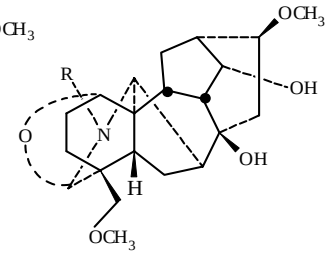
from **1** under 50% H_2SO_4 as catalyst *via* like-Pinacol rearrangement [2a] gave the *O*-6-demethyl product **14**[9] (96%). The NMR spectrum of **14** showed signals at δ_H 3.27, 3.27, 3.40, each 3H, s; δ_C 57.5 q, 58.0 q, 58.0 q, for three methoxyl groups, and at δ_H 4.66, 1H, d, *J*=6.6 Hz for H-6β, but absence of signals for olefinic protons, indicating an



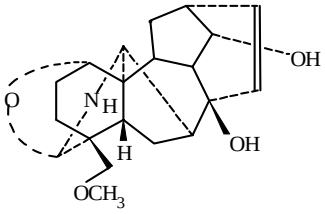
1 R^1= H R^2= CH_3
14 R^1= R^2= H



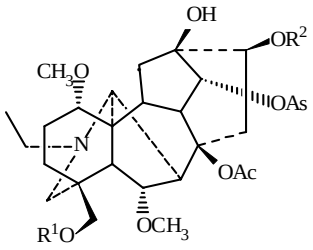
2 R^1= OH R^2= H



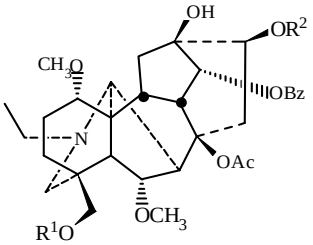
3 R= H



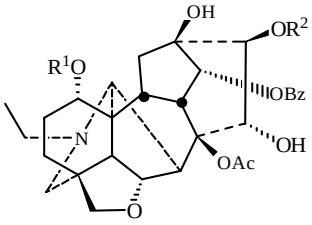
4



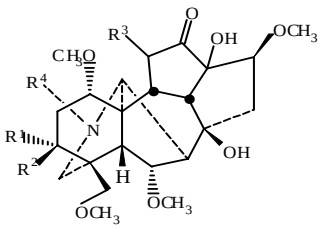
5 R^1 = R^2 = Me
6 R^1 = R^2 = Ac



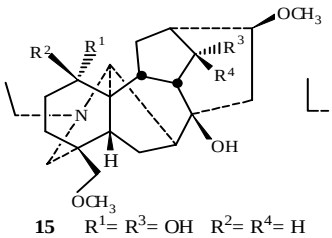
7 R^1 = R^2 = Me
10 R^1 = R^2 = H
11 R^1 = H R^2 = Me
12 R^1 = Me R^2 =H



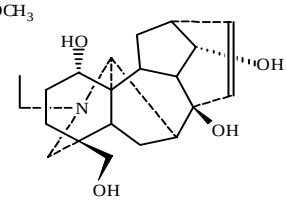
8 R^1 = Me R^2 = Ac
9 R^1 = R^2 = Ac



13 R^1= OH R^2= R^3= H R^4= Et



15 R^1= R^3= OH R^2= R^4= H



16

O-demethylation at C-16 in **1**. Comparison with **1**, the shift effects [α-effect: C-6 (-5.2 ppm), β-effects: C-5 (+4.9 ppm), C-7 (+4.6 ppm)] caused by $OCH_3 \rightarrow OH$ are in accordance with that in Ref[10]. Isotalatizidine **15** under similar condition gave **16**[11] (17%). Its ^1H NMR spectrum revealed no signals for methoxyl groups while the signals of two olefinic protons (δ_H 5.71, d, *J*=9.5 Hz; δ_H 5.90, dd, *J*=9.5, 7.0 Hz) attributable to H-15 and H-16, respectively, were observed.

Acknowledgments

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References and Notes

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5. **2**: white amorphous powder, $C_{24}H_{35}NO_7$ (^1H- and ^{13}C-NMR), ^1H NMR (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, H-14β), 6.28, 6.45 (each 1H, ABq, *J*=10.0 Hz, H-2 and H-1). ^{13}C NMR (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').
6. **4**: white amorphous powder, $C_{21}H_{31}NO_5$ (^1H- and ^{13}C-NMR), ^1H NMR (200 MHz , $CDCl_3$) δ: 3.33 (3H, s, OCH_3), 4.09 (1H, br.s, H-14β), 4.14 (1H, s, H-19), 5.74 (1H, d, *J*=9.4 Hz, H-15), 5.92 (1H, dd, *J*=9.4, 6.8 Hz, H-16). ^{13}C NMR (50 MHz) δ: 69.5 (1), 22.3 (2), 21.6 (3), 42.8 (4), 37.1 (5), 26.1 (6), 43.5 (7), 73.2 (8), (9), (10), (11), (12), (13), (14), 132.5 (15), 129.0 (16), 54.2 (17), 74.1 (18), 82.9 (19), 59.3 (18').
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9. **14**: white amorphous powder, $C_{24}H_{37}NO_8$ (EIMS+^{13}C NMR), ^1H NMR (200 MHz , $CDCl_3$) δ: 1.08 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.27, 3.27, 3.40 (each 1H, s, 3×OCH_3), 4.00 (1H, br.s,

H-14 β), 4.62 (1H, d, *J*=6.6 Hz, H-6 β). ^{13}C NMR (50 MHz) δ : 83.0 (1), 35.5 (2), 70.4 (3), 46.8 (4), 53.3 (5), 77.7 (6), 56.6 (7), 72.8 (8), 48.7 (9), 40.3 (10), 49.7 (11), 36.9 (12), 77.3 (13), 78.9 (14), 43.5 (15), 84.9 (16), 62.9 (17), 75.5 (18), 50.6 (19), 49.7 (*N*CH_2-), 13.0 (*N*CH_2*CH_3*), 57.5 (1'), 58.0 (16'), 58.0 (18'). EIMS *m/z*: 468 (M-1, 5), 437 (32), 406 (100).

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11. **16**: white amorphous powder, ^{1}H NMR (200 MHz, $CDCl_3$) δ : 1.06 (3H, t, *J*=7.2 Hz, *N*CH_2*CH_3*), 3.28, 3.47 (each 1H, ABq, *J*=10.4 Hz, H_2-18), 4.09 (1H, t, *J*=5.0 Hz, H-1 β), 5.71 (1H, d, *J*=9.5 Hz, H-15), 5.90 (1H, dd, *J*=9.5, 7.0 Hz, H-16).

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