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# 1-*EPI*-DEACETYLACONITINE, A NEW NORDITERPENOID ALKALOID FROM *ACONITUM NEMORUM*

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**Abstract:** A new norditerpenoid alkaloid, 1-*epi*-deacetylaconitine (**1**), along with three known compounds, neoline, songorine and 12-*epi*-napelline, was isolated from the roots of *Aconitum nemorum*. The structure of the new compound was elucidated on the basis of 1D and 2D NMR, EIMS and FABMS experiments. The structure of 1-*epi*-deacetylaconitine is unusual because it is the only aconitine series norditerpenoid alkaloid in which the 1-methoxyl group exists in the β-configuration and an intramolecular hydrogen bond is present between the nitrogen atom and the hydrogen of 3α-hydroxyl group.

*Aconitum nemorum* M. Pop.[1] (Ranunculaceae) is endemic to Xinjiang of China and the middle Asia area. Its roots are used in folk Chinese medicine as an anti-inflammatory and analgesic drug. The occurrence of three norditerpenoid alkaloids, 14-benzoyltalatizamine, 14-acetyltalatizamine and talatizamine, from this species growing in Kyrgyzstan has been previously reported.[2] Under a program of studies on the bioactive constituents of some Chinese medicinal plants, we investigated this plant growing in Xinjiang of China. A new norditerpenoid alkaloid, 1-*epi*-deacetylaconitine (**1**), was isolated along with three known alkaloids, neoline, songorine and 12-*epi*-napelline.[3] Its structure was established based on 1D and 2D NMR, EIMS and FABMS experiments. In this note, we report the isolation and characterization of this new compound.

1-*epi*-Deacetylaconitine (**1**), $C_{32}H_{45}NO_{10}$ (combined analysis of FABMS, EIMS, $^{13}C$ NMR and DEPT

data), mp 215—217°C (uncorrected), $[\alpha]^{25}_{D}$ – 21.2° (c 0.25, MeOH) was isolated from the crude alkaloids of the roots by repeated column chromatography on silica gel and crystallization methods. The IR spectrum in KBr indicated the presence of hydroxyl groups (3600—3200 $cm^{-1}$) and a benzoyl group (1720, 1605, 1470, 1280, 730 $cm^{-1}$). FABMS spectrum (positive ion mode, *m*-nitrobenzyl alcohol as a matrix) gave a base ion peak at *m/z* 604 ($[M + H]^+$). EIMS showed ion peaks at *m/z* 603 ($[M]^+$, 2), 588 ($[M – CH_3]^+$, 5), 572 ($[M – OCH_3]^+$, 84), 554 ($[M – OCH_3 – H_2O]^+$, 37), 122 (28), 105 (100).

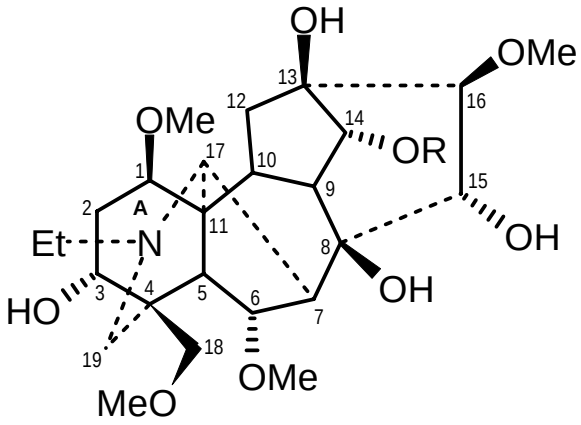
The $^1H$ NMR spectrum (400 MHz, $CDCl_3$) of **1** (see Table 1) showed signals at δ 3.24, 3.30, 3.35 and 3.70 (each 3H, s, $OCH_3$), 8.03 (2H, d, J = 7.2 Hz, H-2' and H-6'), 7.53 (1H, t, *J* = 7.2 Hz, H-4'), 7.43 (2H, t, *J* = 7.2 Hz, H-3' and H-5'), 4.93 (1H, d, *J* = 4.5 Hz, H-14β) and 4.76 (1H, d, *J* = 5.2 Hz, H-15β). By careful examination of $^1H$-$^1H$ COSY spectrum, the signal for an N-$CH_2$-$CH_3$ methyl group was found as a triplet at δ 1.34 (3H, *J* = 6.5 Hz) and the signal for H-3 as a broad singlet overlapping with that for H-6 at δ 4.21. The spectral evidences above indicated that **1** had a basic structure of deacetylaconitine.

Table 1. $^1H$ NMR Shifts and Assignments for **1**

| H | δ (ppm) | *J* (Hz) | H | δ (ppm) | *J* (Hz) |
|---|---|---|---|---|---|
| 1 | 3.44 | br s | 18a | 3.55 | d (8.4) |
| 2α | 1.37 | m | 18b | 3.53 | d (8.4) |
| 2β | 2.30 | br d (11.6) | 19a | 3.52 | d (12.4), |
| 3 | 4.21 | br s | 19b | 3.26 | d (12.4) |
| 5 | 2.95 | br d (5.6) | N-C*H*$_2$CH$_3$ | 3.26, 2.98 | m |
| 6 | 4.21 | br d (5.6) | N-CH$_2$C*H*$_3$ | 1.34 | t (6.5) |
| 7 | 2.25 | br s | 1-$OCH_3$ | 3.30 | s |
| 9 | 2.54 | t (4.2) | 6-$OCH_3$ | 3.35 | s |
| 10 | 2.22 | dd (9.6, 4.2) | 16-$OCH_3$ | 3.70 | s |
| 12α | 1.77 | br d (9.6) | 18-$OCH_3$ | 3.24 | s |
| 12β | 2.22 | t (9.6) | H-2'/ H-6' | 8.03 | d (7.2) |
| 14 | 4.93 | d (4.5) | H-3'/H-5' | 7.43 | t (7.2) |
| 15 | 4.76 | d (5.2) | H-4' | 7.53 | t (7.2) |
| 16 | 3.10 | br d (5.2) | 3-OH | 7.82 | br s |
| 17 | 3.33 | br s | | | |

The $^{13}C$ NMR spectrum (100 MHz, $CDCl_3$) of **1** showed 30 signals for 32 carbons. By HMQC and HMBC spectra, all carbon signals could be assigned (see Table 2). The chemical shifts of C-1 and C-2 in the $^{13}C$ NMR spectrum of **1** were significantly upfield by 2—4 and 4—6 ppm, respectively, in comparison with those of aconitine and aconine.[4, 5] These differences suggested that 1-methoxyl group in **1** was in β orientation according to Pelletier and Etse's discovery (1989).[6]

Furthermore, in the $^{1}H$ NMR spectrum of **1**, a broad singlet at δ 7.82 ($D_2O$ exchangeable), assignable to the proton of 3-hydroxyl group by HMBC, showing the presence of an intramolecular N…H—O hydrogen bond[7] between nitrogen atom and the hydrogen of 3-hydroxyl group, and the coupling pattern (broad singlet) of the proton at C-3 in **1** suggested that the conformation of ring A in **1** was in the boat form [8] as shown in Figure 1 and that the 1β-methoxyl group was in equatorial conformation and 3-hydroxyl group was in α orientation and in axial conformation.



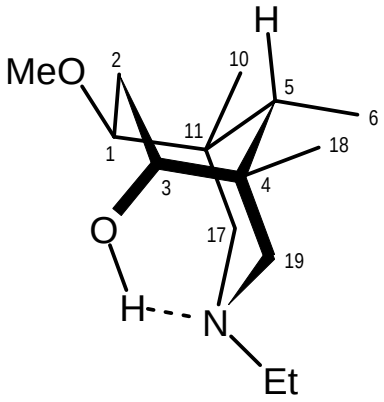
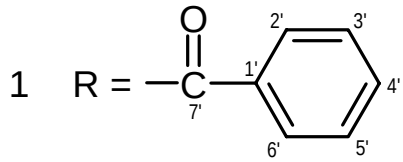




Figure 1. The conformation of ring A in 1-*epi*-deacetylaconitine




1a R = H

The stereochemistry of the ring A in **1** was finally confirmed by the NOESY experiment. In the NOESY of 1 (Table 3), H-1 revealed NOEs with H-2α and H-12α while no NOE with H-2β and H-3 revealed NOEs with both H-2α and H-2β while no NOE with H-5, showing that H-1 was α orientation and in axial conformation and that H-3 was β and in equatorial conformation. Further, it was shown that the ring A was in the boat form.[8] In addition, the lack of an NOE between H-2α and N-ethyl protons supported the

hydrogen bonding between 3-OH proton and nitrogen.[8] In conclusion, 1-*epi*-deacetylaconitine was elucidated as depicted.

Table 2. $^{13}$C NMR Chemical Shifts and Assignments for **1** and **1a**

| Carbon | **1** | **1a** | Carbon | **1** | **1a** | Carbon | **1** | **1a** |
|---|---|---|---|---|---|---|---|---|
| 1 | 80.0 | 82.1 | 12 | 35.3 | 36.9 | 6-$OCH_3$ | 58.2 | 57.9 |
| 2 | 29.1 | 29.7 | 13 | 74.2 | 78.9 | 16-$OCH_3$ | 60.9 | 61.3 |
| 3 | 69.5 | 71.6 | 14 | 78.7 | 81.4 | 18-$OCH_3$ | 59.1 | 59.1 |
| 4 | 43.3 | 43.1 | 15 | 81.1 | 78.6 | 1' | 129.8 | |
| 5 | 47.9 | 46.1 | 16 | 90.0 | 90.7 | 2' | 128.5 | |
| 6 | 81.4 | 82.9 | 17 | 64.3 | 61.7 | 3' | 129.9 | |
| 7 | 43.2 | 48.3[a] | 18 | 76.9 | 77.6 | 4' | 133.0 | |
| 8 | 78.3 | 76.2 | 19 | 50.6 | 49.1 | 5' | 129.9 | |
| 9 | 43.6 | 47.5[a] | $N-CH_2$ | 49.9 | 48.1 | 6' | 128.5 | |
| 10 | 40.6 | 41.5 | $CH_3$ | 11.1 | 12.9 | 7' | 166.3 | |
| 11 | 50.0 | 50.1 | 1-$OCH_3$ | 55.1 | 55.6 | | | |

[a] These assignments may be interchanged.

Table 3. Significant NOEs from NOESY of **1**

| Observed H | Show NOEs to | Observed H | Show NOEs to |
|---|---|---|---|
| H-1 | H-2α, H-12α, 1-OC*H*$_3$ | H-12α | H-12β, H-9, H-1, H-16, H-17 |
| H-2α | H-2β, H-1, H-3 | H-14 | H-9 |
| H-2β | H-2α, H-3, 1-OC*H*$_3$ | H-15 | 16-OC*H*$_3$ |
| H-3 | H-2α, H-2β, H-18a, H-18b | H-16 | H-12α, H-17, 16-OC*H*$_3$ |
| H-5 | H-6, H-10 | H-17 | H-12α, H-16, N-$CH_2$C*H*$_3$ |
| H-6 | H-5, H-9, H-7, 6-OC*H*$_3$ | H-19a | H-19b |
| H-9 | H-10, H-6, H-14 | H-19b | H-19a, N-$CH_2$C*H*$_3$ |
| H-10 | H-5, H-9 | N-$CH_2$C*H*$_3$ | H-19b, H-17 |

Hydrolysis (4% methanolic KOH, 48 hours at room temperature) of 1-*epi*-deacetylaconitine afforded a

new aminoalcohol (**1a**), $C_{25}H_{41}NO_9$, amorphous, $[\alpha]^{25}_D$ – 26.4° (c 0.1, MeOH). The EIMS spectrum of **1a** showed fragment ion peaks at *m/z* 499 ($[M]^+$, 4), 484 ($[M - CH_3]^+$, 7), 468 ($[M - OCH_3]^+$, 100), 450 ($[M - OCH_3 - H_2O]^+$, 31). The $^1$H NMR (400 MHz, $CDCl_3$) of **1a** showed proton signals at δ 1.15 (3H, t, *J* = 6.5 Hz, N-$CH_2CH_3$), 3.24, 3.29, 3.33 and 3.63 (each 3H, s, $OCH_3$), 3.90 (1H, d, *J* = 4.4 Hz, H-14β), 4.03 (1H, br s, H-3β), 4.15 (1H, br d, *J* = 6.4 Hz, H-6β), 4.54 (1H, d, *J* = 4.8 Hz, H-15β). The $^{13}$C NMR (400 MHz, $CDCl_3$) data of **1a** were shown in Table 1. It is interesting that the intramolecular hydrogen bond seemed absent in **1a**, as the proton signal for 3-hydroxyl group at δ 7.82 in **1** was not found in the same and nearby region of $^1$H NMR spectrum of **1a**.

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