THE STRUCTURES OF TWO NEW DITERPENOID ALKALOIDS FROM ACONITUM NAPELLUS L. S. STR.

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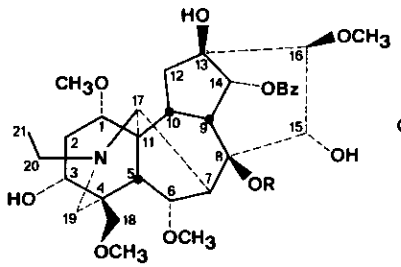
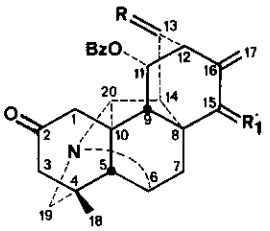
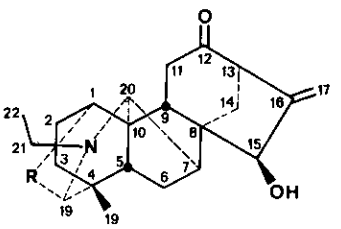
Abstract - From aerial parts of Aconitum napellus L. s. str. (syn. A. anglicum Stapf) were isolated two new diterpenoid alkaloids, 8-O-ethylbenzoylaconine (1) and 15-acetyl-13-dehydrocardiopetamine (3), besides cardiopetamine (5), 15-acetylcardiopetamine (4), songoramine (6), and songorine (7). The structures were established by ^{1}H- and ^{13}C-nmr and confirmed by partial synthesis.

From aerial parts of plants[1] of Aconitum napellus L. s. str., syn. A. anglicum Stapf we were able to isolate six diterpenoid alkaloids: 8-O-ethylbenzoylaconine (1), a new base of the aconitine type, the new alkaloid 15-acetyl-13-dehydrocardiopetamine (3), 15-acetylcardiopetamine (4), cardiopetamine (5) of the hetisine subtype, and songoramine (6) and songorine (7) of the veatchine type.

8-O-Ethylbenzoylaconine (1) had mp 139-141°C and its molecular formula $C_{34}H_{49}NO_{10}$ was settled by hrms and ^{13}C-nmr. The ^{1}H-nmr spectrum was similar to those of the aconitine-group bases, aconitine[2], polyschistine A[3], N-deacetylaconitine[4], and hokbusine A[5,6], and disclosed the presence of an N-ethyl group in the molecule, three methoxy groups at C-1α, C-6α, and C-18, two hydroxy groups at C-3α and C-15α, and a benzoate group at C-14α. The high-field triplet at 0.60 ppm indicated that an ethoxy group was at the C-8 position, in the shielding region of the aromatic nucleus. Furthermore, the ^{13}C-nmr chemical shifts were very close to those of hokbusine A[6] and polyschistine A[3] except for a few changes, in accordance with the ascribed structure (1). The partial synthesis of 1, by solvolysis of aconitine (2) in ethanol, confirmed its structure.







1 R = Et
2 R = Ac

3 R = O; R_1 = βOAc, α H
4 R = βOH, α H; R_2 = βOAc, α H
5 R = R_1 = βOH, α H

6 R = O
7 R = C-1 α OH, C-19 α H

As far as we know, other aconitine-type alkaloids with a C-8 ethoxy group which have been isolated are: aljesaconitine B[7], polyschistine A[3], columbidine[8], acoforine, acoforestine, and acoforestinine[9]. The authors have suggested that these compounds are artifacts formed from the corresponding base having a good leaving group at C-8, during the treatment of the vegetable material with ethanol. The participation of nitrogen lone-pair electrons favours the solvolytic process[9,10].

The molecular formula of 15-acetyl-13-dehydrocardiopetamine (3), mp 253-255°C, was also determined by hrms and ^{13}C-nmr. The ^{1}H- and ^{13}C-nmr spectra were characteristic of a hetisine-type alkaloid[11-15] giving signals for a methyl group, an exocyclic methylene, a tertiary amine, two carbonyl groups, an acetate and benzoate. Signals owing to methoxy, N-methyl, or N-ethyl groups, frequent in C-19 diterpenoid alkaloids, were not observed. For the ^{13}C-nmr data it was clear that the new alkaloid was 15-acetyl-13-dehydrocardiopetamine[12].

Treatment of 15-acetylcardiopetamine (4) with Cornforth's reagent yielded 15-acetyl-13-dehydrocardiopetamine (3), and therefore its structure was confirmed.

EXPERIMENTAL

Melting points were determined on a Reichard Thermovar apparatus. Optical rotations (EtOH) were measured with a Perkin-Elmer 137 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer. Exact mass measurements and eims were obtained on a VG Micromass ZAB-2F instrument. Nmr spectra ($CDCl_3$) were taken on a Bruker WP-2000 SY spectrimeter. The ^{1}H couplings were verified by double resonance experiments. Alumina Merck, Art. 1077, 5581, and 1092, was used for cc, tlc, and ptlc, respectively. The isolated alkaloids were identified by comparison with authentic samples (mp, ir, ms, and ^{1}H- and ^{13}C-nmr). Mixtures

of hexane-EtOAc were used as crystallization solvent.

Isolation of alkaloids. Dried plants[1] (0.25 kg) were extracted with 80% EtOH (3 l) at room temperature, the solvent was removed, and the residue (19.5 g) was treated with 0.5 N H_2SO_4 (250 ml). The acid solution was basified with NH_4OH to pH 7.5-8 and extracted with $CHCl_3$ to give 0.72 g of crude alkaloid material. This was chromatographed over alumina with hexane, hexane containing increasing amounts of EtOAc, and EtOAc. Alkaloid mixtures from the column were further separated by cc and ptlc, when necessary. The following alkaloids, in order of elution, were obtained:

Songoramine (6)[16] — 10 mg, mp 212-214°C, $[\alpha]_D$-57° (c 0.07). ^{1}H-Nmr, δ 0.85 (3H, s, H-18), 1.03 (3H, t, J-7.2 Hz, H-22), 2.68 and 2.71 (1H, each, q, J=7.2 Hz, H-21), 2.84 (1H, s, H-20), 3.15 (1H, d, J=4.1 Hz, H-13), 3.71 (1H, s, H-19), 3.98 (1H, d, J=5.2 Hz, H-1), 4.40 (1H, t, J=2.1 Hz, H-15), 5.20 and 5.31 (1H each, s, H-17). For ms and ^{13}C-nmr see references 16 and 17, respectively.

8-O-Ethylbenzoylaconine (1) — 17 mg, mp 139-141°C, $[\alpha]_D$-3.0° (c 0.10). M^+, m/z 631.3319 for $C_{34}H_{49}NO_{10}$, Δ -3.7 mmu. Ir (KBr), 3460 (br), 1720, 1595, 1445, 1270, 1090, 975, and 710 cm^{-1}. ^{1}H-Nmr, δ 0.60 (3H, t, J=7 Hz, H-8"), 1.09 (3H, t, J=7 Hz, H-21), 1.90 (1H, dt, J_1=13 Hz, J_2=5.1 Hz, H-2β), 2.06 (1H, d, J-6.5 Hz, H-5), 2.68 (1H, s, H-7), 2.87 (1H, s, H-17), 2.90 (1H, d, J=11.3 Hz, H-19α), 3.13 (1H, dd, J_1=7.5 Hz, J_2=5.8 Hz, H-1), 3.25, 3.26, 3.30 and 3.73 (3H each, s, OCH_3), 3.48 and 3.61 (1H each, d, J=8.5 Hz, H-18), 3.63 (1H, s, 15-OH, disappearing when D_2O was added), 3.79 (1H, dd, J_1=9.1 Hz, J_2=4.8 Hz, H-3), 4.07 (1H, d, J=6.6 Hz, H-6), 4.54 (1H, br s, $W_{\frac{1}{2}}$=12 Hz; d, J=6.1 Hz, when D_2O was added, H-15), 4.82 (1H, d, J=5.1 Hz, H-14), and 7.42-8.05 (5H, m, aromatic protons). Ms, m/z (relative intensity), 631(1) M^+, 600(100), 586(6), 584(6), 554(18), 478(31), 460(8), 432(9), 122(14), 105(59), 77(21), and 45(19). ^{13}C-Nmr, δ 13.4 (q, C-21), 15.4 (q, C-8"), 33.4 (t, C-2), 36.3 (t, C-12), 41.5 (d, C-10), 43.1 (d and s, C-4 and C-9), 45.3 (d, C-7), 45.7 (d, C-5), 47.4 (t, C-20), 48.8 (t, C-19), 50.6 (s, C-11), 55.9 (q, C-1'), 57.1 (t, C-8'), 58.6 (q, C-6'), 59.1 (q, C-18'), 61.0 (d, C-17), 62.3 (q, C-16'), 71.6 (d, C-3), 74.8 (s, C-13), 76.8 (t, C-18), 78.3 (d, C-14), 79.7 (d, C-15), 82.4 (s, C-8), 82.7 (d, C-6), 83.6 (d, C-1), 93.5 (d, C-16), and 128.4 (d), 129.7 (d), 130.4 (s), 132.9 (d), and 166.4 (s) for benzoate carbons.

15-Acetyl-13-dehydrocardiopetamine (3)[11] — 15 mg, mp 253-255°C, $[\alpha]_D$-46° (c 0.03). M^+, m/z 487.2007 for $C_{29}H_{29}NO_6$, Δ -1.2 mmu. Ir (KBr), 1725, 1705, 1240, 1225, 1090, 1020, and 710 cm^{-1}. ^{1}H-Nmr, δ 1.12 (3H, s, H-18), 1.87 and 1.93 (1H each),

dd, J_1=10 Hz, J_2=2.2 Hz, H-7), 2.08 (1H, s, H-5), 2.17 (3H, s, OAc), 2.21 (1H, d, J=13.7 Hz, H-19β), 2.41 (1H, d, J=14 Hz, H-1β), 2.56 (1H, d, J=1.8 Hz, H-14), 2.71 (1H, d, J=13.2 Hz, H-19α), 2.75 (1H, d, J=14 Hz, H-1α), 2.80 (1H, s, H-12), 2.91 (1H, dd, J_1=8.5 Hz, J_2=2.1 Hz, H-9), 3.16 (1H, s, H-20), 3.40 (1H, br s, $W\frac{1}{2}$=7 Hz, H-6), 5.34 and 5.52 (1H each, s, H-17), 5.50 (1H, s, H-15), 5.68 (1H, d, J=8.4 Hz, H-11), and 7.48-7.95 (5H, m, aromatic protons). Ms, m/z (relative intensity), 487(24) M^+, 366(12), 338(7), 278(6), 233(8), 105(100), 77(35), and 43(35). For ^{13}C-nmr data see reference 12.

Songorine (7)[18] — 8 mg, mp 198-200°C, $\{\alpha\}_D$-42° (c 0.1). ^{1}H-Nmr, δ 0.77 (3H, s, H-18), 1.15 (3H, t, J=7 Hz, H-22), 2.26 and 2.83 (1H each, d, J=12.1 Hz, H-19β and H-19α, respectively), 2.70 (2H, q, J=7.2 Hz, H-21), 3.06 (1H, d, J=3.9 Hz, H-13), 3.68 (1H, s, H-20), 3.78 (1H, dd, J_1=10.1 Hz, J_2=7.1 Hz, H-1), 4.34 (1H, t, J=2.3 Hz, H-15), 5.16 and 5.26 (1H each, s, H-17). For ms and ^{13}C-nmr see references 16 and 19, respectively.

15-Acetylcardiopetamine (4)[11] — 22 mg, mp 236-238°C, $\{\alpha\}_D$+16° (c 0.2). ^{1}H-Nmr, δ 1.10 (3H, s, H-18), 1.82 (2H, m, H-7), 2.02 (1H, s, H-5), 2.10 (3H, s, OAc), 2.22 (1H, d, J=12 Hz, H-19β), 2.28 (1H, d, J=13.3 Hz, H-1β), 2.29 (1H, d, J=10 Hz, H-14), 2.58 (1H, d, J=2.5 Hz, H-12), 2.71 (1H, d, J=12 Hz, H-19α), 2.71 (1H, d, J=9 Hz, H-9), 3.11 (1H, s, H-20), 3.37 (1H, br s, $W\frac{1}{2}$=8 Hz, H-6), 3.48 (1H, d, J=13.2 Hz, H-1α), 4.18 (1H, br d, J=9.7 Hz, $W\frac{1}{2}$=6 Hz, H-13), 5.15 (1H, s, H-15), 5.26 and 5.34 (1H each, s, H-17), 5.57 (1H, d, J=9 Hz, H-11), and 7.42-8.08 (5H, m, aromatic protons). Ms, m/z (relative intensity), 489(100) M^+, 430(11), 385(10), 384(41), 369(13), 368(53), 340(18), 308(14), 105(100), 77(52), and 43(25). For ^{13}C-nmr see reference 12.

Cardiopetamine (5)[11] — 40 mg, mp 302°C (decomp.), $\{\alpha\}_D$+45° (c 0.02). ^{1}H-Nmr, δ 1.13 (3H, s, H-18), 2.04 (1H, s, H-5), 2.31 (1H, d, J=13 Hz, H-1β), 2.62 (1H, d, J=2.5 Hz, H-12), 2.70 (1H, d, J=13 Hz, H-19β), 2.75 (1H, dd, J_1=8.3 Hz, J_2=2 Hz, H-9), 3.07 (1H, s, H-20), 3.37 (1H, br s, $W\frac{1}{2}$=7 Hz, H-6), 3.50 (1H, d, J=13 Hz, H-1α), 3.94 (1H, s, H-15), 4.15 (1H, br d, J=10.8 Hz, $W\frac{1}{2}$=6.5 Hz, H-13), 5.18 (2H, s, H-17), 5.61 (1H, d, J=8.5 Hz, H-11), and 7.42-8.08 (5H, m, aromatic protons). Ms, m/z (relative intensity) 447(100) M^+, 419(4), 342(33), 326(46), 298(15), 296(12), 105(72), and 77(31). For ^{13}C-nmr see reference 12.

8-O-Ethylbenzoylaconine (1) from aconitine (2)[9] — Aconitine (20 mg) was heated with absolute ethanol (5 ml), in a PARR reactor at 130°C for 24 h, the solvent

removed, and the reaction mixture was chromatographed over alumina with EtOAc to afford 8-O-ethylbenzoylaconitine (10 mg), aconitine (6 mg), and two other minor compounds.

15-Acetyl-13-dehydrocardiopetamine (3) from 15-acetylcardiopetamine (4)— 15-Acetylcardiopetamine (10 mg) in pyridine (0.3 ml) was treated with Cornforth's reagent (0.1 ml) at 0°C for 72 h. Water was added and the EtOAc extract was percolated over alumina to yield 15-acetyl-13-dehydrocardiopetamine (8 mg).

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REFERENCES AND NOTES

1. The plant material was supplied by Dr. P. Poyser, ICI Pharmaceutical Division, Manchester, England.
2. A. Katz and H. Rudin, *Helv. Chim. Acta*, 1984, 67, 2017.
3. H. Wang, A. Lao, Y. Fujimoto, and T. Tatsuno, *Heterocycles*, 1985, 23, 803.
4. E. Arlandini, M. Ballabio, B. Cicha, C. Bugatti, M.L. Colombo, and F. Tome, *J. Nat. Prod.*, 1987, 50, 937.
5. G.Y. Hang, P. Cai, J.Z. Wang, and J.K. Snyder, *J. Nat. Prod.*, 1988, 51, 364.
6. H. Hikino, Y. Kuroina, and C. Konno, *J. Nat. Prod.*, 1983, 46, 178.
7. H. Bando, K. Wada, M. Watanabe, T. Mori, and T. Amiya, *Chem. Pharm. Bull.*, 1985, 33, 4717.
8. S.W. Pelletier, S.K. Srivastava, B.S. Joshi, and J.D. Olsen, *Heterocycles*, 1985, 23, 331.
9. S.W. Pelletier, B.S. Joshi, J.A. Glinski, H.P. Chokshi, S. Chen, K. Bhandary, and K. Go, *Heterocycles*, 1987, 25, 365.
10. S. Sakai, I. Yamamoto, K. Hotoda, K. Yamaguchi, N. Aimi, E. Yamanaka, J. Haginiwa, and T. Okamoto, *Yakugaku Zasshi*, 1984, 104, 222.
11. A.G. González, G. de la Fuente, M. Reina, P.G. Jones, and P.R. Raithby, *Tetrahedron Lett.*, 1983, 24, 3765.
12. A.G. González, G. de la Fuente, M. Reina, R. Díaz, and I. Timón, *Phytochemistry*, 1986, 25, 1971.
13. J.A. Grina, D.R. Schroeder, E.T. Wydallis, and F.R. Stermitz, *J. Org. Chem.*, 1986, 51, 390.
14. F. Sun, X.T. Liang, and D.Q. Yu, *J. Nat. Prod.*, 1988, 51, 50.
15. J.A. Glinski, B.S. Joshi, Q.P.Jiang, and S.W. Pelletier, *Heterocycles*, 1988,

27, 185.

16. M.S. Yunusov, Ya.V. Raskes, S.Yu. Yunusov, and A.S. Samatov, *Khim. Prir. Soedin.*, 1970, 6, 101.

17. G. de la Fuente, M. Reina, E. Valencia, and A. Rodríguez-Ojeda, *Heterocycles*, 1988, 27, 1109.

18. S.Yu. Yunusov and I.G. Sorokina, *J. Gen. Chem.*, 1948, 18, 515.

19. H. Takayama, A. Tokita, M. Ito, S. Sakai, F. Kurosaki, and T. Okamoto, *Yakugaku Zasshi*, 1982, 102, 245.

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