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Cardionidine, an Unusual C-20 Diterpenoid Alkaloid from Delphinium Cardiopetalum DC

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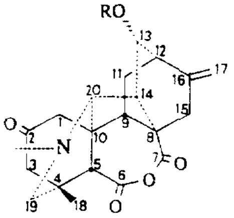
Abstract: The structure of cardionidine (1), a new hetisine-type C-20 diterpenoid alkaloid bearing an anhydride function, was inferred from spectroscopic and chemical data, and X-ray analysis.

In earlier communications we have described the structure determination of several diterpenoid alkaloids from *Delphinium cardiopetalum*[1]. We now wish to report on the structure elucidation of cardionidine (1), the first hetisine-type C-20 diterpenoid alkaloid with an anhydride function, isolated in a very small amount (3 mg. $6 \cdot 10^{-5}$% yield) from the same species[2].

Cardionidine (1) had m.p. 310-315° (decomp), $[\alpha]_D = -50°$ (c 0.03, EtOH), and its HRMS presented the molecular ion at m/z 371.1737, $C_{21}H_{25}NO_5$ (calcd. 371.1742).

The ^{13}C NMR spectrum[3] suggested the presence of a carbonyl group (210.1 ppm) and oxygenated carbon (69.2 ppm) and an exocyclic methylene group (146.1 and 107.3 ppm) in cardionidine (1). Its IR absorptions at 1760, 1720, 1170 and 1087 cm^{-1}, the loss of carbon dioxide from the MS[4] ions at m/z 371, 354 and 343 amu, and the carbon resonances at 167.6 and 170.9 ppm pointed to the existence of an anhydride function in the molecule. The ^1H NMR spectrum (200 MHz, $CDCl_3$) displayed characteristic signals of a diterpenoid alkaloid with a hetisine-type skeleton[1,5-7] at δ 1.25 (3H, s, H-18), 2.03 (3H, s, N-Me), 2.07 and 3.07 (1H each, d, J= 14.0 Hz, H-1β and H-1α), 2.10 and 2.70 (1H each, d, J= 11.4 Hz, H-19α and H-19β), 2.37 (1H dd, J= 7.0, 2.4 Hz, H-9), 2.70 and 2.85 (1H each, dt, J= 17.0, 2.0 Hz, H-15β and H-15α), 3.0 (1H, dd, J= 9.8, 2.4 Hz, H-14), 3.29 (1H, s, H-20), 4.25 (1H, dd, J= 9.8, 2.4 Hz, H-13β)[8], 4.76 and 4.89 (1H each, br s H-17e and H-17z), and the distinctive signal of H-6 (br s) was not observed[7]. Treated with Ac_2O-Py cardionidine (1) yielded an acetate (2), M^+ 413 (6%), whose ^1H-NMR spectrum gave signals at 2.20 (3H, s) and 5.03 (1H, br d, J= 9.8 Hz, H-13β) strengthening the existence of a secondary hydroxy group in 1.

The above spectroscopic and chemical evidence led to structure **1**, among others, being tentatively assigned to cardionidine, considering the oxygenation pattern usually found in the hetisine-type alkaloids[9]. In order to determine an unambiguous structure for cadionidine, an X-ray analysis was performed, from which its absolute configuration was established as 4S (Fig. 1)[10].



1: R = H

2: R = Ac

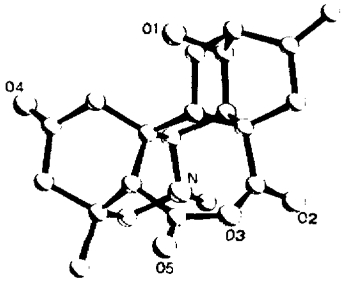


Fig. 1. X-Ray cristal structure of 1

Acknowledgements

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References and Notes

1. De la Fuente, G.; Gavín, J.A.; Reina, M.; Acosta, R.D. J.Org.Chem. **1990**, 55, 342 , and references therein.
2. The plants were collected in the Cadí-Moixeró Natural Park, Lerida Province, Spain, growing on a calcareous and clayey soil,and authenticated by Professors J.Molero and C.Blanché, Botany Department, University of Barcelona.
3. H^{13}C NMR ($CDCl_3$: CD_3OD (1:3), 100 MHz) δ 22.7 (C-18), 29.3, 29.6, 33.4, 36.5, 40.9, 41.8 (N-Me), 45.6, 45,8, 56.3, 57.6, 62.3, 64.2, 67.9, 69.2 (C-13), 107.3 (C-17), 146.1 (C-16), 167.6 (C-6), 170.9 (C-7) and 210.1 (C-2).
4. EIMS m/z 371 (100%, M^+), 354 (42%, M^+-OH), 343 (12%, M^+-CO), 327 (24%, M^+-CO_2), 326 (16%, M^+-CO_2H), 315 (28%), 314 (19%), 313 (16%), 313 (16%), 310 (4%, M^+-OH-CO_2), 299 (57%, M^+-CO-CO_2),282 (12%), 242 (56%), 241 (45%), 236 (43%), 190 (51%), 119 (79%) and 91 (67%).
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10. The compound crystallized in the monoclinic system, space group $P2_1$, Z = 2, a = 8.499(1), b = 9.494(2), c = 10.918(2) Å, β = 101.38(2)°, V = 863.7(3) $Å^3$. All unique diffraction maxima with $3 \leq 2\theta < 121°$ were collected on a computer-controlled four-cicle diffractometer, using graphite monochromatized CuK_α (λ = 1.5418 Å) radiation and ω :θ scan mode. After correction for Lp effects, 1180 reflections with $I > 3\sigma(I)$ were considered as observed. Structure solved by direct methods (SHELXS86), refined by full-matrix least squares. Final refinement converged to R = 0.047, R_w = 0.050. The absolute configuration was determined by comparison of 23 Bijvoet pairs with $Fo \geq 10\sigma(Fo)$, which are in the range $5.0 \leq Fo \leq 50.0$ and $0.15 \leq \sin\theta/\lambda \leq 0.40$ $Å^{-1}$. The average Bijvoet differences are 0.237 for the correct enantiomer vs 0.297 for the wrong one.

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