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THE STRUCTURE OF BARBELINE, AN UNUSUAL C_{19}-DITERPENOID ALKALOID FROM *DELPHINIUM BARBEYI* HUTH

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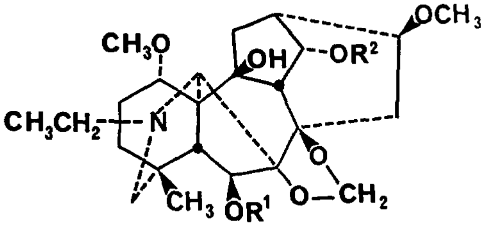
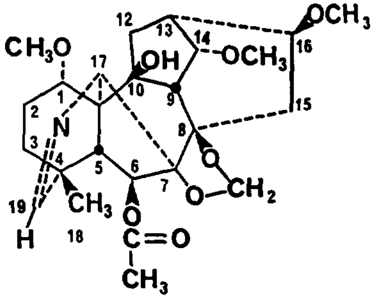
Summary: From the ethanolic extract of Delphinium barbeyi Huth, a novel C_{19}-Diterpenoid alkaloid barbeline (4) has been isolated and its structure determined by spectroscopic data and an X-ray crystal diffraction study. Barbeline is the only example of an alkaloid containing a C(19)=N- azomethine group among the 230 naturally occurring C_{19}-diterpenoid alkaloids. Two other new alkaloids, 6-acetyldelpheline and 6-deoxydelpheline, as well as the known alkaloids browniine, delphatine and glaucenine have also been isolated from this plant.

The occurrence of anthranoyllycoctonine, delpheline, deltaline (1), delcosine, deltamine (2), dictyocarpine (3) and lycoctonine, from *Delphinium barbeyi* Huth (*D. glaucum* S. Watts) has been reported earlier.[1] We report here the isolation of a novel alkaloid *barbeline* (4), from the mother liquors of the alkaloidal fraction (pH 8.5) obtained from the ethanolic extract of *D. barbeyi*, m.p. 265.5-267.5°C; $C_{25}H_{35}NO_8$; (FAB-MS): m/z 478 (M^+ + 1); Found: C, 63.10; H, 7.48; N, 2.83; Calc. for $C_{25}H_{35}NO_8$: C, 62.88; H, 7.39 N, 2.93%; $[\alpha]^{22}_{D}$ +45.03° (c, 0.31 $CHCl_3$); IR (nujol) νmax 3190 (broad, OH), 1738 (acetate), 1650 (C = N)cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (3H, s, tert. methyl), 2.07 (3H, s, OAc), 3.22, 3.34, 3.47 (each 3H, s, OMe), 4.19 (1H, dd, J = 6Hz, C(14)-β-H), 4.96, 4.98 (each 1H, s, O-CH_2-O), 5.32 (1H, brs, C(6)-α-H), 7.44 (1H, brs, N = CH; not exchanged on D_2O addition). Biogenetic considerations and the presence of one methyl, one acetoxyl and three methoxyl groups in the molecule suggest that barbeline is a new C_{19}-diterpenoid alkaloid.[2] The significant absence of an N-Me (δ 2.4) or an N-Et group (triplet ~δ 1.1) suggested that the nitrogen is unsubstituted. The absence of an NH group was seen from the D_2O exchange studies. The proton-noise decoupled ^{13}C NMR spectrum of barbeline showed 24 lines due to 25 carbon atoms. The multiplicities determined by DEPT studies showed six singlets: 169.3, 90.8, 83.6, 81.5, 55.9, 42.9, nine doublets: 169.3, 81.7, 81.5, 80.4, 77.9, 62.6, 49.6, 45.6, 38.1, five triplets: 94.1, 40.8, 34.5, 30.6, 24.1 and five quartets: 57.5, 56.1, 55.5, 22.7 and 21.4 ppm. Five of the quaternary carbon signals at 169.3, 90.8, 83.6, 81.5 and 55.9 ppm can be readily ascribed to the acetate carbonyl, and C(7), C(8), C(10) and C(11), respectively.[2] The downfield signal at 42.9 ppm (value for 1-3 ~ 33.5 ppm) can be assigned to C(4) possessing an adjacent double bond as in an amide[3] or N = C(19). The medium strength band in the IR at 1650 cm^{-1} is more characteristic of -N = C than of an amide.[4] The overlapping signal at 169.3

ppm should be assigned to C(19).[5] The broadened singlet at δ 7.44 is due to the C(19)-H of the azomethine and shows a long range coupling with C(17)-H as in the case of anopterimine.[6] One of the methoxyl group is located at C(1) as seen by the loss of 31 mass units (OMe) (m/z 446) from the molecular ion peak.[7] The remaining signals for the methine, methylene and the methyl carbons closely resemble those for deltaline.[8] On the basis of these data, the unique structure (**4**) seemed likely for barbeline. An X-ray crystal diffraction study of barbeline established structure **4**. An ORTEP plot of the structure appears in figure 1.





1 R^1 = Ac; R^2 = CH_3

2 R^1 = H; R^2 = CH_3

3 R^1 = Ac; R^2 = H

4 **Barbeline**

A crystal of **4**, was mounted on a Syntex P3 automated diffractometer. Unit cell dimensions were determined by least squares refinement of the best angular positions for fifteen independent reflections (2 >15°) during normal alignment procedures using molybdenum radiation (λ = 0.71069Å) and yielded: $\underline{a}$ = 16.767(8), $\underline{b}$ = 16.767, $\underline{c}$ = 15.747(8)Å; $\alpha = \beta$ = 90.0°, γ = 120.0°, and V = 3859(4)Å^3. For Z = 6 the computed density was 1.233 g/cm^3. The space group was $P6_1$. Data, (1749 points) were collected at room temperature using a variable scan rate, a θ-2θ scan mode and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 45.0°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections and as the intensities of these reflections showed less than 6% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization and background effects. After removal of space-group forbidden and redundant data, observed data, (1116 points) ($I > 3.0\sigma(I)$) were used for solution and refinement. The structure was solved for carbon, nitrogen and oxygen positions using direct methods.[9] Least squares refinement[10] converged with anisotropic thermal parameters. Hydrogen atom positions were calculated using appropriate geometry and a C-H distance of 0.97Å. Hydrogen positions were included in the final refinement with isotropic thermal parameters but held invariant. A difference Fourier revealed no electron density of interpretable level. Scattering factors were taken from Cromer and Mann.[11] The final cycle of refinement-function minimized $\Sigma(|F_o|-$

$|F_c|)^2$, led to final agreement factor, R = 7.0%; R = ($\Sigma/|F_o|-|F_c||/\Sigma|F_o|$) x 100. Unit weights were used until the final cycles of refinement when weights equal to $1/\sigma F$ were introduced. R_w = 9.6%. The molecule was refined in the absolute configuration of other members of the family.[12]

Barbeline is the only alkaloid containing a C(19)=N azomethine function among the 230 naturally occurring C_{19}-diterpenoid alkaloids. The likely biogenetic precursor would be of the HN$<$ type. But there are only three such alkaloids known (flavaconitine, hokbusine B, and polyschistine C) and none of these is of the required lycoctonine type. Our attempts to convert the closely related deltaline (1) to (4) were unsuccessful. It is highly unlikely, therefore, that barbeline is an artifact of isolation.

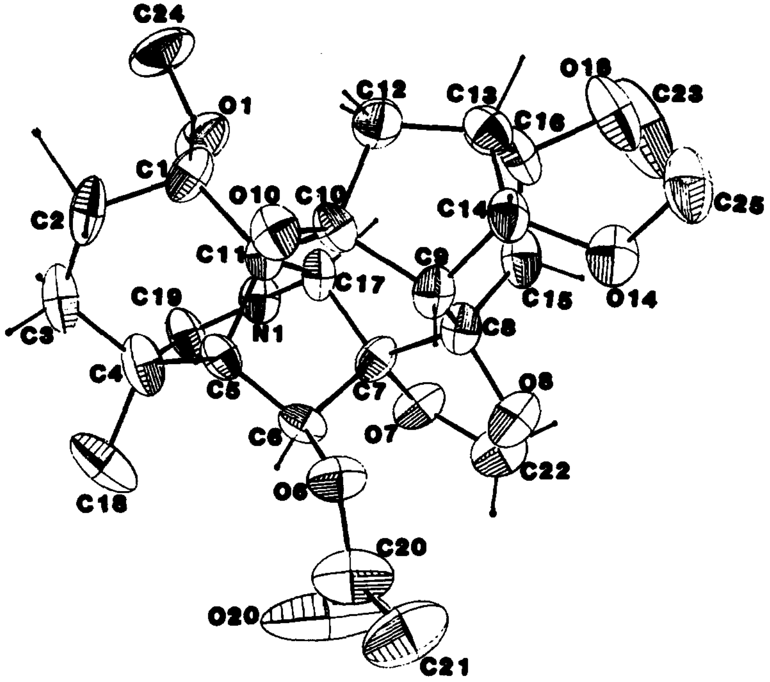


Figure 1. An ORTEP plot of barbeline (4)

We have also isolated from the alkaloidal fractions two new alkaloids that have been identified from their spectral data[2,13] as *6-acetyldelpheline* and *6-deoxydelpheline* and the known alkaloids browniine, delphatine, and glaucenine.

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