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# THE STRUCTURE AND ABSOLUTE CONFIGURATION OF HETEROPHYLLOIDINE

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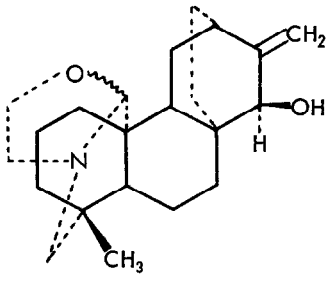
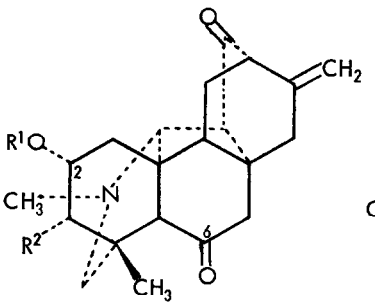
*The structure and absolute configuration of heterophylloidine, a new $C_{20}$-diterpenoid alkaloid isolated from Aconitum heterophylloides Stapf, have been determined with the aid of $^{13}C$ NMR spectral data and single-crystal X-ray analysis of the product obtained by treatment of heterophylloidine with aqueous hydrobromic acid.*

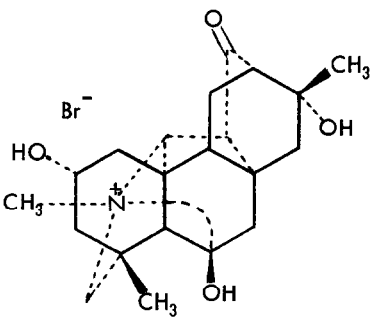
Our search for new diterpenoid alkaloids from the genus Aconitum led us to investigate the basic constituents of Aconitum heterophylloides Stapf, a very rare plant native to the Himalaya mountains in India. 120 grams of the roots of A. heterophylloides were extracted and fractionated into a weak-base and a strong-base fraction according to the previously described procedure.[1] Investigation of the strong-base fraction yielded atisine (1) as the major alkaloid. We report here the isolation and structure elucidation of a new $C_{20}$-diterpenoid alkaloid, heterophylloidine (2), from the weak-base fraction of A. heterophylloides.



1 Atisine



2 $R^1$ = Ac, $R^2$ = H
3 $R^1$ = $R^2$ = H
5 $R^1$ = H, $R^2$ = OH



4

Heterophylloidine, $C_{23}H_{29}NO_4$, $[\alpha]_D^{24}$ - 82.0°(c 1.5, $CHCl_3$), was isolated in an amorphous form (70 mg) as a minor constituent. The IR spectrum in nujol exhibited absorption at 1730 and 1250 (acetate), 1720 and 1695 (cyclohexanones), and 1640 (double bond) $cm^{-1}$. The 90 MHz $^1H$ NMR spectrum in $CDCl_3$ indicated the presence of a C(4) methyl (3H, s) at δ 1.5, an acetyl group (3H, s) at δ 2.06, an N-methyl (3H, s) at δ 2.4, an exocyclic methylene (each 1H, 2bs) at δ 4.84 and 5.0, and an undefined one-proton multiplet at δ 5.16 ppm for a C(2) α-proton. The $^{13}C$ NMR spectrum of 2 in $CDCl_3$ exhibited the following signals: 211.7, 203.4, 169.4, 142.2, 110.6, 70.9, 68.5, 63.0, 60.4, 59.1, 52.8, 50.3, 49.9, 44.4, 43.8, 43.3, 41.7, 36.8, 35.7, 34.8, 31.2,

22.6, and 21.6 ppm which revealed the presence of a C(4)-methyl group, two ketone groups, an exocyclic methylene , an N-methyl group, an acetoxyl group, and other characteristic features for the atisine-type skeleton. Hydrolysis of 2 in 5% KOH in methanol at room temperature afforded the aminoalcohol 3, mp. 154-158°C.

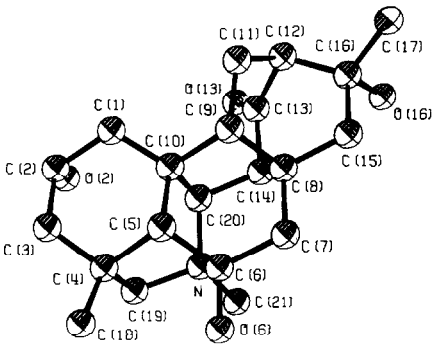



Figure 1. ORTEP Drawing of 4.

Because of the very small amount of heterophylloidine available, the heavy atom derivative 4, prepared by treatment of a methanolic solution of 2 with 49% HBr in water, was subjected to X-ray analysis (Figure 1). Crystals of compound 4 belonged to the orthorhombic space group $P2_12_12_1$ with $Z = 4$, $a = 11.738$ (3), $b = 12.155$ (4), and $c = 13.548$ (3)Å. Data collected out to $2\theta = 50^\circ$ with Mo Kα radiation ($\lambda = .71069$Å) and $\omega - 2\theta$ scans included 767 observed reflections ($I \geq 2\sigma(I)$). The structure was solved by the heavy atom method.[2] Anisotropic refinement of the nonhydrogens, with anomalous dispersion corrections for the bromine converged at $R = 0.063$ and 0.072 for the two enantiomers.[3] On the basis of Hamilton's test[4] the structure was assigned the absolute configuration shown in figure 1, which matches the absolute configuration assigned to other $C_{20}$-diterpenoid alkaloids.[5]

The X-ray analysis of 4 revealed the substitution pattern and the basic skeleton of heterophylloidine. Finally, the structure of heterophylloidine as 2 was established by relating 2 and its hydrolysis product 3 to hetidine (5)[6] through a study of their $^{13}C$ NMR spectra.[7] It is of interest that hydration of the exocyclic double bond, hydrolysis of the C(2) acetoxyl group, and formation of the carbinolamine linkage occurred during preparation of the heavy atom derivative. In this case, both $^{13}C$ NMR data and X-ray analysis were necessary to establish the structure of heterophylloidine.

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## REFERENCES AND NOTES

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