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THE STRUCTURE OF HABRANTHINE

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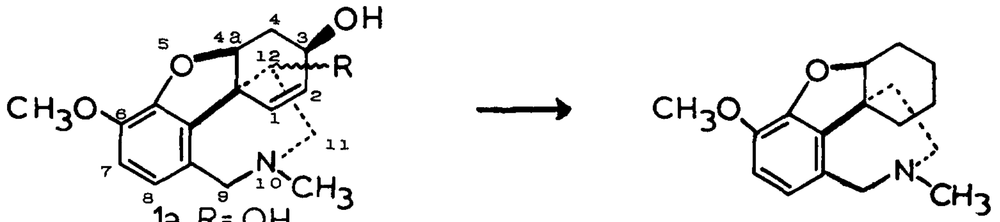
We wish to report the structure of a novel Amaryllidaceae alkaloid, habranthine (1a, m.p. 198-99°, $[\alpha]_D^{25} = -320°$) isolated from Habranthus brachyandrus[1] in 0.006% yield. Habranthine ($C_{17}H_{21}NO_4$) formed dihydro and O,O-diacetyl derivatives.* The basic ring system of habranthine was established to be that of galanthamine (1b) when the successive treatment of dihydrohabranthine with thionyl chloride and lithium aluminum hydride afforded deoxylycoramine[2] (2)** The identity of this degradation product with authentic 2 was proven by tlc, gpc and mass spectral criteria. Other chemical degradations, e.g., HBr rearrangement and MnO_2 oxidation, which were successful in the galanthamine-type alkaloids, led to no useful characterizable products when applied to habranthine. The major evidence for our assignment of structure 1a for habranthine rests on spectroscopic data.



1a, R= OH
1b R= H

2

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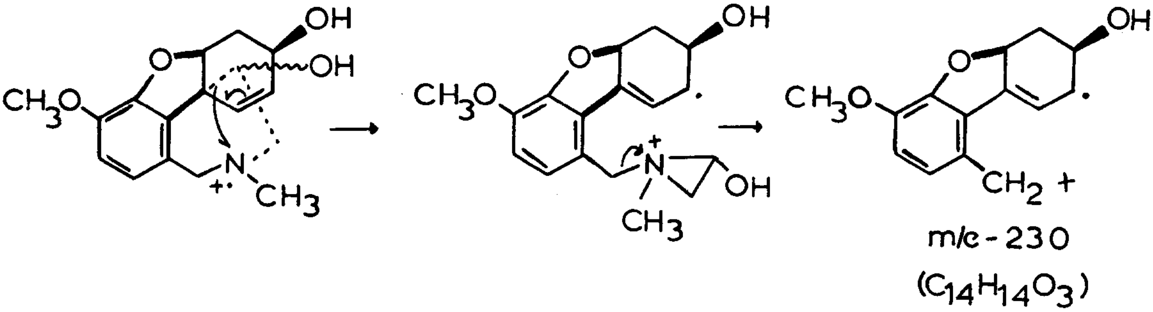
*Satisfactory combustion analyses or high resolution mass spectral measurements have been obtained on all derivatives and ions whose composition are discussed.

**The absolute stereochemistry of 2 can be inferred from the known absolute configuration of galanthamine (1b)[3].

The nmr spectrum of D_2-habranthine in deuteriochloroform[4] showed two hydroxyl protons between 2.4 and 3.0 ppm. The spectrum shows the presence of two adjacent aromatic protons (6.63 ppm, J_{AB} = 8 Hz.). The olefinic protons appear as a rather complex multiplet between 6.24 and 5.60 ppm. The presence of the aromatic methoxyl and N-methyl groups are indicated by the 3 proton singlets at 3.83 and 2.56 ppm respectively. The two benzylic protons at C_9 in the spectrum appear as a doublet (partially collapsed AB) at 3.67 ppm. In the nmr spectrum of O,O-diacetylhabranthine the two benzylic protons appear as a well defined AB quartet (J_{AB} =16 Hz.). A doublet at 3.05 ppm was assigned to the two C_{11} protons. The protons at C_3 and C_{12} appear as triplets at 4.10 and 3.43 ppm, respectively. In the spectrum of the O,O-diacetylhabranthine these two triplets shift to 5.30 ppm (C_3) and 4.88 ppm (C_{12}). The C_3 and C_{12} protons in habranthine were distinguished by decoupling experiments. The triplet representing the C_{12}-hydrogen collapsed to a singlet on irradiation at the frequency of the C_{11} proton at 3.05 ppm. The two C_4 protons are quite different in chemical shift and show a geminal coupling of 16 Hz. One of these protons is centered at 2.0 ppm and the other at ~2.7 ppm. Half of the latter proton is hidden beneath the N-methyl peak. The C_{4a} proton appears as a triplet at 5.33 ppm. In the spectrum of O,O-diacetylhabranthine this triplet shifts upfield to 4.70 ppm which approximates the chemical shift observed for this proton in galanthamine (4.58 ppm). This suggests that the unusually low chemical shift of the C_{4a} proton of habranthine is due to an anisotropic deshielding effect of the C_{12} hydroxyl group which is absent in the O,O-diacetate.

The mass spectrum of habranthine is characteristic of alkaloids having the galanthamine-type ring system. An ion at m/e 230 ($C_{14}H_{14}O_3$) is the base peak in the spectrum. A metastable peak in the spectrum at m/e 174.4

(m^*_c = 174.6) showed that this ion is formed directly from the molecular ion at m/e 303 ($C_{17}H_{21}NO_4$). Our investigations of the mass spectra of galanthamine, N-demethylgalanthamine and other galanthamine-type derivatives have shown that the m/e 230 ion results from a loss of the -C_{11}-C_{12}-N- fragment including any substituents attached to these atoms. A proposed mechanism for this cleavage is shown below for habranthine:



This fragmentation confirmed the presence of a hydroxyl group at either C_{11} or C_{12}. The alkaloid is recovered unchanged when treated with lithium aluminum hydride and shows no reactions characteristic of an α-hydroxy amine. The chemical shift of the two C_{11} protons in the nmr spectrum (3.05 ppm) provides additional support for assignment of a hydroxyl group to the C_{12} position in the alkaloid.

In very dilute carbon tetrachloride solution, habranthine shows two intramolecularly hydrogen-bonded hydroxyl groups (3570 and 3457 cm^{-1}). The former absorption is comparable to that observed for the OH-O bonding in galanthamine (1b, 3575 cm^{-1}).[5] The C_3-OH could be distinguished from the C_{12}-OH by evidence that the C_{12}-OH (3457 cm^{-1}) was very strongly hydrogen-bonded to the lone pair of the nitrogen atom. The addition of a trace of mineral acid to the solution removed the 3457 cm^{-1} absorption and a free hydroxyl group was observed at 3623 cm^{-1}. The 3570 cm^{-1} absorption of the C_3 hydroxyl remained.

ORD and CD data further substantiated the stereochemical assignment for the C_3-hydroxyl group as well as the basic ring system of 1a. The curves of habranthine closely parallel those of galanthamine and differ from the C_3 epimer of 1b, *epi*galanthamine.

Although a number of alkaloids having the crinine-type nucleus have been shown to have a hydroxyl group at the position analogous to C_{12} in galanthamine, habranthine is the first of the galanthamine-type alkaloids to have a hydroxyl group at this position.

Acknowledgement

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REFERENCES

(1) For an earlier isolation of *H. brachyandrus* (syn. *Hippeastrum brachyandrum*) see H. G. Boit and W. Dopke, *Chem. Ber.*, 2582 (1959); they report no new alkaloid having the same physical constants or composition as habranthine.

(2) S. Uyeo and J. Koizumi, *Pharm. Bull.* (Tokyo) 1, 202 (1953).

(3) D. J. Williams and D. Rogers, *Proc. Chem. Soc.*, p. 357 (1964).

(4) The NMR spectrum was obtained in deuterochloroform on a Varian A-60 spectrometer and a time-averaging computer.

(5) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, p. 806 (1962).