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THE CRYSTAL AND MOLECULAR STRUCTURE OF THE HYDROBROMIDE OF LEPISTINE, A FUNGAL ALKALOID

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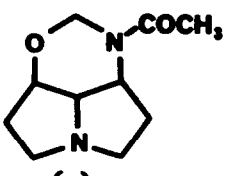
The agaric Lepista caespitosa (Bresadola) Singer - now[1] described as Clitocybe fasciculata Bigelow - is an Asiatic species growing commonly in the northern part of New Zealand. Fruiting bodies of the fungus gave 0.4% of alkaloid, the major component being lepistine, $C_{10}H_{16}N_2O_2$, a hygroscopic liquid b.p. 140 - 150°C (0.01 mm Hg), $n_D^{20°}$ 1.5270. It gave a hydrochloride B.HCl m.p. 242°, a hydroiodide B.HI m.p. 250 - 253° and a methiodide B.CH_3I m.p. 198 - 199°.

Chemical and spectroscopic studies suggested that the molecule was a three-ring system containing a tertiary amine, an acetyl of a secondary amine and an isolated methylene group. A tentative structure (I) was assigned; however, the reactions of the deacetylated product could not be explained on this basis. For this reason, a crystallographic structure determination was undertaken.

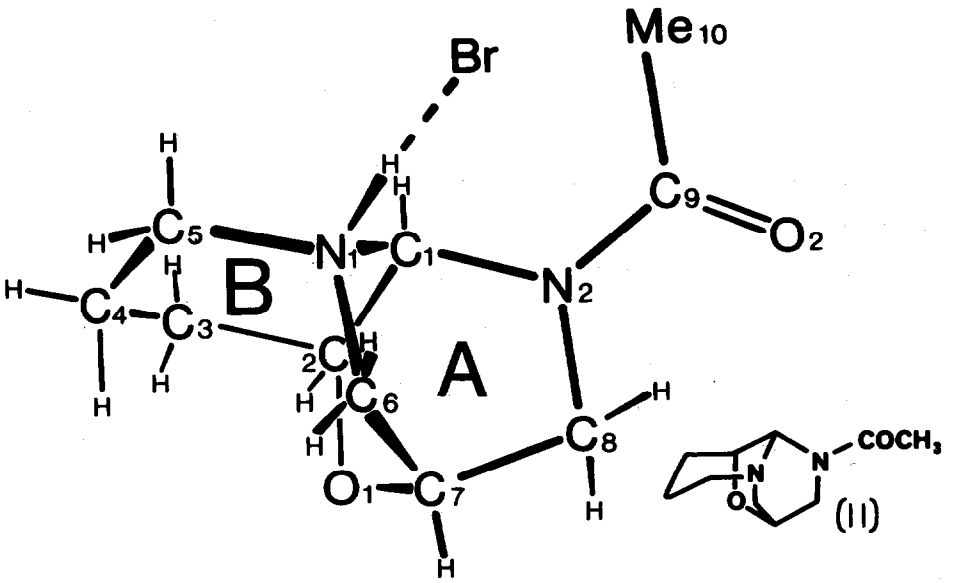


(I)

Suitable crystals of the hydrobromide [$C_{10}H_{16}N_2O_2$.HBr; found: C, 43.6; H, 6.2; N, 10.1; required: C, 43.3; H, 6.1; N, 10.1%], m.p. (decomp) 262 - 264°, were obtained from ethanol. They were orthorhombic, space group $P2_12_12_1$, $\underline{a}$ = 16.214, $\underline{b}$ = 10.516, $\underline{c}$ = 6.973 (± 0.005) Å, Vol = 1188.9 Å^3, d_{obs} = 1.51, d_{calc} = 1.52 gcm^{-3}, Z = 4.

Three-dimensional intensity data were collected on a Philips 4-circle diffractometer with graphite-monochromated Mo-Kα radiation to θ = 22°. The position of the bromide ion was deduced from a temperature-sharpened Patterson map and the lighter atoms were located in the subsequent Fourier maps. The structure was refined isotropically by block diagonal least squares to R = 0.066 (bromide ion anisotropic) for 790 observed data. At this stage a difference Fourier map clearly showed the hydrogen atom contributions. The absolute configuration was determined by including the anomalous contribution of the bromide ion (Δf" = 2.55) in the structure factor calculations. Further refinement is continuing.

A projection of the structure down the $\underline{c}$ axis, giving the absolute configuration, shows that lepistine (II) is tricyclic, as was deduced from the chemical work, but the ring system is (6,6,6) and not (5,5,6).



The eight-atom arrangement, A, is a typical [2.2.2] bicyclo-octane system. The six-membered ring, B, is an almost perfect chair: N(1), C(5), C(2) and C(3) are co-planar within 0.01 Å. The molecular cation has an approximate plane of symmetry defined by atoms C(1), C(4), C(7), C(8), N(2), C(9), O(2) and C(10). (The identities of atoms O(1) and N(1) were determined by comparing their electron densities in the Fourier maps with those of their pseudo-mirror images, C(6) and C(2) respectively; the identity of N(1) is independently established by its being hydrogen bonded to the bromide ion, N···Br 3.10 Å).

The bond lengths in the molecule are quite normal: mean $(sp^3)C-C(sp^3)$ 1.52, $(sp^3)C-O$ 1.44, $(sp^3)C-N(sp^3)$ 1.50 Å; e.s.d.'s 0.01 Å.

The atoms of the N-acetyl system C(1), C(8), N(2), C(9), O(2) and C(10) are co-planar within 0.03 Å, indicating considerable electron delocalization and stabilization within this six-atom system. This is supported by the observed bond angles and lengths: C(1)-N(2)-C(8) 114°, C(1)-N(2)-C(9) 125°, C(8)-N(2)-C(9) 121°; C(1)-N(2) 1.45, C(8)-N(2) 1.48, N(2)-C(9) 1.36, O(2)-C(9) 1.23, C(10)-C(9) 1.51 Å. On deacetylation of the neutral alkaloid, a potentially reactive[2] $R-NH-CHR-NR_2$ system will be produced, with the nitrogen atom of the NH group (N(2) in the molecule) now sp^3 hybridised.

Lepistine is an isomer of the oxygen-bridged pyrrolizidine alkaloids lolinene (N-acetyltestucine) and decorticasine[3], and is in some respects structurally similar to porantherine and porantheridine[4]. Except for oxygen O(1), the tricyclic framework is topologically identical with a major part of the skeleton of Base R, a Lycopodium alkaloid related to fawcettidine[5].

Previously, important small differences between the n.m.r. spectra of lepistine and deacetyllepistine could not be fully interpreted:
lepistine τ 5.9(2H,bs), 6.2-6.7(2H,t?), 6.7-7.2(4H,m);
deacetyllepistine τ 5.85(1H,d), 6.25(1H,t), 6.75(1H,s), 6.8-7.0(2H,d), 7.0-7.4(4H,m).
The broad two-hydrogen singlet at τ 5.9 in lepistine (suggesting the presence of an isolated methylene group) is actually due to the chance overlap of the signals from the hydrogens on C(2) and C(7). These atoms give rise to the signals at τ 5.85 and 6.25 in the deactylated product. The observed torsion angles between the various hydrogen atoms are consistent with the coupling constants derived from the n.m.r. spectrum. Details of the chemical work will be published shortly[6].

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