The Crystal Structure of (−)-(*S*)-Hyoscine Hydrobromide

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Summary The structure of (−)-(*S*)-hyoscine hydrobromide (scopolamine hydrobromide) has been determined.

CRYSTALS of the potent antagonist of acetylcholine at the autonomic parasympathetic post-ganglionic (muscarinic) junction, (−)-(*S*)-hyoscine hydrobromide $C_{17}H_{21}NO_4$,HBr (alternatively known as scopolamine hydrobromide), as supplied by B.D.H. Ltd., are colourless needles elongated along *c*, Laue group *P4/mmm*, space-group D_4^6—$P4_12_12$, $a = 1196{\cdot}5 \pm 0{\cdot}7$, $c = 2652 \pm 2$ pm, $Z = 8$. One octant of the three-dimensional *X*-ray diffraction data in the range $2\theta = 0$—90° was measured on a computer-controlled four-circle diffractometer employing Cu-*K* radiation, and gave 2138 observations reducing to 614 unique observed [$I \geqslant 3\sigma(I)$] diffraction maxima. The data were corrected for Lorentz and polarisation effects in the usual manner, and for long-term variation in the intensity of the incident radiation by periodic measurement of a standard diffraction maximum. The structure was solved by the heavy-atom method, phased on the bromine atom, and refined by multiple cycles of least-squares to a present value of $R = 0{\cdot}09$. One half molecule of water per molecule of hyoscine has been found crystallographically.

The structure of (−)-(*S*)-hyoscine hydrobromide is shown in the Figure. The conformation of the tropine residue is that expected, with the six-membered ring in the chair conformation. The epoxide oxygen atom on the methylene bridge is in the boat configuration with respect to the nitrogen atom, and the methyl group C(1) attached to the nitrogen atom is in the *axial* position with respect to the six-membered ring. The equatorial configuration of this methyl group, as found, for example, in 1-cocaine hydrochloride,[1] tropine,[2] and pseudotropine,[3] is unfavourable in this compound because of the close (247 pm) approach of the nitrogen atom and O(1). The ester group attached to C(13) is in the axial (α) position of the six-membered ring.

If one defines a mirror plane of the tropine residue as the plane in which lie N, C(1), O(1), and C(13), and by which C(11)–C(17)–C(12) and C(15)–C(16)–C(14) are related, the plane of the ester group C(13)–O(2)–C(2)–O(3)–C(3) makes an angle of 44·5° with this mirror plane, and the plane of the benzene ring makes an angle of 79·4° with this plane.

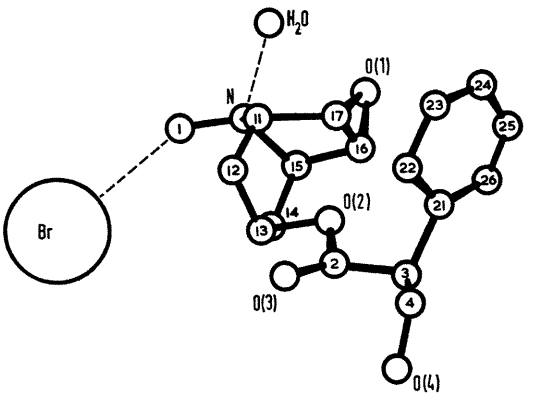

FIGURE. *The molecule of* (−)-(*S*)-*hyoscine hydrobromide projected down* (100).

The plane of the benzene ring also makes an angle of 87·4° with the plane of the ester group. The distances of the nitrogen atom from the various oxygen atoms of the molecule are N–O(1) 247, N–O(2) 388, N–O(3) 541, and N–O(4) 804pm. These nitrogen–oxygen distances compare with those found in muscarinic agonists such as muscarine itself[4] of $N–O_{ring}$ 307, and $N–O_{hydroxy}$565 pm, and in L-(+)-*S*-acetyl-β-methylcholine[5] of $N–O_{ester}$ 319, and $N–O_{carbonyl}$ 440 pm.

The absolute configuration of (−)-hyoscine has not been

determined by the effects of anomolous dispersion in this investigation, but is known to have the (*S*)-configuration by relationship with (−)-tropic acid whose absolute configuration has been determined by chemical means by Fodor and Csepreghy.[6] The Figure shows the (−)-(*S*)-enantiomer. The antagonistic potency of the naturally occurring (*S*)-enantiomer to acetylcholine in the autonomic post-ganglionic nervous system is approximately 20 times that of the (*R*)-enantiomer[7] which has a structure the mirror image of that shown in the Figure.

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