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THE CONFIGURATION OF THE SUBSTITUENTS AT THE NITROGEN ATOM OF TROPINE ETHOBROMIDE

P.Benci, C.H.Stam and C.H.MacGillavry

Laboratory for Crystallography, University of Amsterdam

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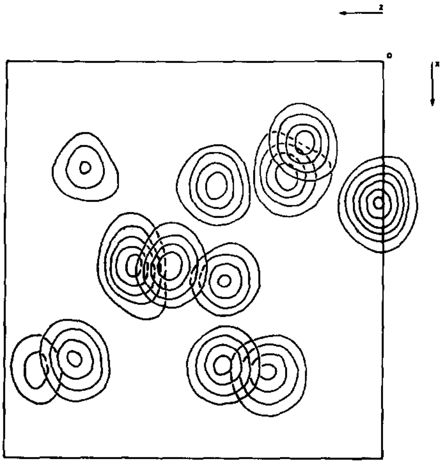
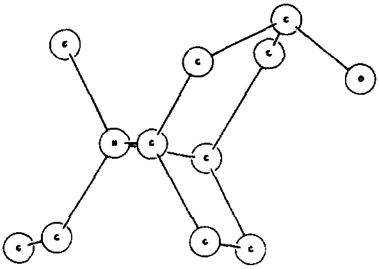
Fodor (1) has formulated a rule stating that when two different groups are attached successively to the nitrogen atom of nortropane derivatives, the group entering last is fixed in the equatorial position with respect to the piperidine ring.

According to this rule N-ethylnortropine methobromide (NENTMB), which is obtained by quaternisation of N-ethyltropine with methylbromide, should have the methyl group in an equatorial position, whilst in tropine ethobromide (TEB), which is formed by adding ethylbromide to tropine, it is the ethyl group which should be equatorially attached.

The configuration of NENTMB, as found from a crystal structure determination undertaken some years ago (2), was in agreement with the above mentioned rule. It was then stated that TEB did not lend itself to a crystal structure determination, the reason for this being the rapid conversion of the orthorhombic crystals to a disordered cubic modification. In the meantime it has been possible to obtain reasonable intensity data from orthorhombic crystals of TEB using a purer sample and cooling the crystals to -150°C during the exposures in order to retard the conversion. Although conversion still took place, as a result of which the intensity data are not of very high quality, it has been possible to solve the crystal structure and to establish beyond doubt the equatorial attachment of the ethyl group, in accordance with Fodor's rule.

The orthorhombic crystals of TEB have cell constants: $a=19.81$, $b=10.04$ and $c=11.08$ Å at -150°C. The space group is Pbca and there are 8 molecules in the unit cell. 1135 independent reflections were obtained visually from Weissenberg diagrams taken at -150°C. The bromine positions were derived directly from the Weissenberg diagrams and refined by least squares methods using the reflections with $\theta > 55^{\circ}$ only. An eightfold minimum function was then calculated by centring an E^2-Patterson at the 8 equivalent bromine positions in the unit cell. This yielded the complete structure except for an uncertainty in the position of the second carbon atom of the ethyl group. A subsequent fourier synthesis, based on all the non-hydrogen atoms except the uncertain one, unambiguously established the configuration around the nitrogen atom. A composite picture of this three-dimensional fourier synthesis is given in the figure, from which the equatorial attachment of the ethyl group is clear. The structure was refined by least squares methods with isotropic temperature parameters for the lighter atoms and anisotropic ones for bromine. This converged to an R-factor of 10.3%.





It is perhaps interesting to indicate the structural relation between the orthorhombic modification of TEB and the disordered cubic one, which has a unit cell edge of about 10.8 Å and rocksalt-like structure (2). The bromine atoms in the orthorhombic structure occupy a general position: x=0.119, y=0.038, z=0.259, which in the space group Pbca amounts to an approximately all face centred configuration with cell constants a'=a/2, b'=b, c'=c (an exact face centred configuration obtains for x=1/8, y=0, z=1/4). Similarly the centres of the N-ethyltropinium ions also occupy an approximate F-lattice at x=1/8, y=1/2, z=1/4. When the orthorhombic structure is exposed to x-rays apparently a rotational disordering of the more or less spherically shaped N-ethyltropinium ions sets in, and with relatively small displacements of the bromine atoms, a cubic rocksalt-like structure is formed, the cell edge of which is about half the original a and about equal to the original b and c.

Our thanks are due to Professor G.Fodor for drawing our attention to the problem and providing us with a purer sample of tropine ethobromide.

1. G.Fodor, Experientia **11**, 129 (1955); Tetrahedron **1**, 86 (1957).
2. C.H.MacGillavry and G.Fodor, J. Chem. Soc. **1964**, 597.