120. *The Stereochemistry of the Tropane Alkaloids. Part XVI.* The Configuration of the* N-*Epimeric Ethylmethylnortropinium Salts.*

By CAROLINE H. MACGILLAVRY and GÁBOR FODOR.

Tropine ethobromide and ethiodide, and their *N*-epimers (*N*-ethylnortropine methiodide and methobromide), have been investigated by *X*-ray diffraction methods. All four substances have a more or less deformed, rocksalt-type structure, with frequent pseudocubic twinning. In *N*-ethylnortropine methobromide the methyl group is equatorial and the ethyl group axial with respect to the piperidine ring. Thus the earlier rule is confirmed, that the group entering last assumes the equatorial position.

IN studies of the configuration of tropane derivatives, a marked specificity was found when two different groups were successively attached[1] to the nitrogen atom of nortropanes. The position of methoxycarbonyl groups on the nitrogen could be established by attempts to form lactones with an adjacent hydroxyl group. In this way it was found that the group entering last is attached to the nitrogen in the equatorial position with respect to the piperidine ring. This stereospecificity was interpreted[1c,d,f] in terms of Pitzer strain in the five-membered ring of the tropane skeleton. This concept has been criticised on the basis of nuclear magnetic resonance (n.m.r.) spectra,[2] but the problem is still unresolved;[3] the n.m.r. spectra are now being studied by one of us (G. F.) and will be discussed elsewhere.

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* Part XIV, *J.*, 1961, 3222; Part XV, *Arch. Pharm.*, 1962, **295**, 91.

[1] (*a*) Fodor, Koczka, and Lestyán, *Magyar Kém. Folyóirat*, 1953, **59**, 243; (*b*) Fodor, Koczka, and Lestyán, *J.*, 1956, 1411; (*c*) Fodor, *Experientia*, 1955, **11**, 129; (*d*) Fodor, Tóth, and Vincze, *J.*, 1955, 3504; (*e*) Fodor, Kovács, and Halmos, *J.*, 1956, 873; (*f*) Fodor, *Bull. Soc. Chim. France*, 1956, 1032.

[2] Closs, *J. Amer. Chem. Soc.*, 1959, **81**, 5456.

[3] Fodor, *Chem. and Ind.*, 1961, 1500.

In order to determine the scope of this stereospecificity, our investigations have been extended to simple alkyl derivatives of tropine and to the corresponding quaternary salts.[1b] Since in this case no chemical method such as ring closure could be used, *X*-ray determination of the crystal structures seemed desirable. It had already been found[4] that tropine ethiodide and *N*-ethylnortropine methiodide have different crystal forms and give different Debye–Scherrer diagrams. On further single-crystal investigation, it was found that these iodides are not suitable for a detailed structure determination. Therefore, the corresponding bromides were prepared by ion-exchange. The crystal structure of *N*-ethylnortropine methobromide could be solved and it was found that the ethyl group in this compound occupies the axial position while the methyl is equatorial with respect to the piperidine ring. Since the compound was prepared by quaternisation of *N*-ethylnortropine, the group which entered last is again bound equatorially. It is to be expected that in tropine ethobromide the ethyl group has the equatorial and the methyl group the axial position. Unfortunately, this substance did not lend itself to a structure determination.

CRYSTALLOGRAPHIC INVESTIGATIONS.

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Tropine Ethiodide.—Powder and Weissenberg diagrams show that the crystals are cubic with cell edge $a = 10{\cdot}8$ Å. The lattice is face-centred and there are four molecules per unit cell. The diagrams are interpreted as produced by a rocksalt-type of structure in which the ethyltropinium ion assumes a number of different orientations such as to conform statistically to the cubic symmetry. The compound is therefore unsuitable for the purpose of determining the configuration of the *N*-ethyltropinium group. No ordering could be obtained by cooling to −150°.

N-*Ethylnortropine Methiodide.*—The unit cell is orthogonal with $a = 11{\cdot}2$, $b = 10{\cdot}2$, $c = 10{\cdot}2$ Å. The symmetry is lower than orthorhombic, probably that of space group *Aa*. The crystals show frequent, partly polysynthetic, pseudocubic twinning. The iodine positions could be determined and it was clear from the intensity distribution that the packing is of a deformed sodium chloride type. Although several methods of growing single crystals were tried, a completely untwinned crystal could not be obtained. This, combined with the preponderance of iodine scattering, prevented a complete structure determination.

Tropine Ethobromide.—Several crystals have a cubic habit {001}. They show no birefringence except in small regions. A Weissenberg diagram of such a crystal shows spots and short streaks arranged in clusters, simulating a diagram of sodium chloride type. Other crystals are more pronouncedly birefringent. A fragment of one of these was rotated about an axis of about 20·2 Å. Odd layers are weak so that there is a pseudoperiod of 10·1 Å. The crystal is orthorhombic with cell edges 11·2, 10·1, and the above-mentioned 20·2 Å. During the exposures the crystal transformed into the sodium chloride-type multiple twin, and so again proved unsuitable for further investigation.

N-*Ethylnortropine Methobromide.*—$C_{10}H_{20}BrNO$, orthorhombic, $a = 12{\cdot}04 \pm 0{\cdot}05$, $b = 13{\cdot}78 \pm 0{\cdot}06$, $c = 6{\cdot}88 \pm 0{\cdot}01$ Å, $U = 1141$Å^3, $D_m = 1{\cdot}4$, $Z = 4$, $D_c = 1{\cdot}46$.

From systematic absences the space group is either *Pmnb* or $P2_1nb$. From Patterson projections and intensity considerations the bromine atom was placed in either space group on $x = 1/4$, $y = 1/12$, $z = 1/4$. Although the quaternary base could have a mirror plane, it is clear from the vector maps that no use is made in the crystal structure of this possible molecular symmetry. The space group is accordingly $P2_1nb$. From the three-dimensional Patterson function, calculated from the intensities *hk*, $l = 0$ through 5, the positions of the bromine atoms were confirmed. The positions of the oxygen atoms were determined by identification of the Br–O vectors, and, with the help of a molecular model, possible positions for all other atoms were then found. This model was derived from the structure of tropine hydrobromide,

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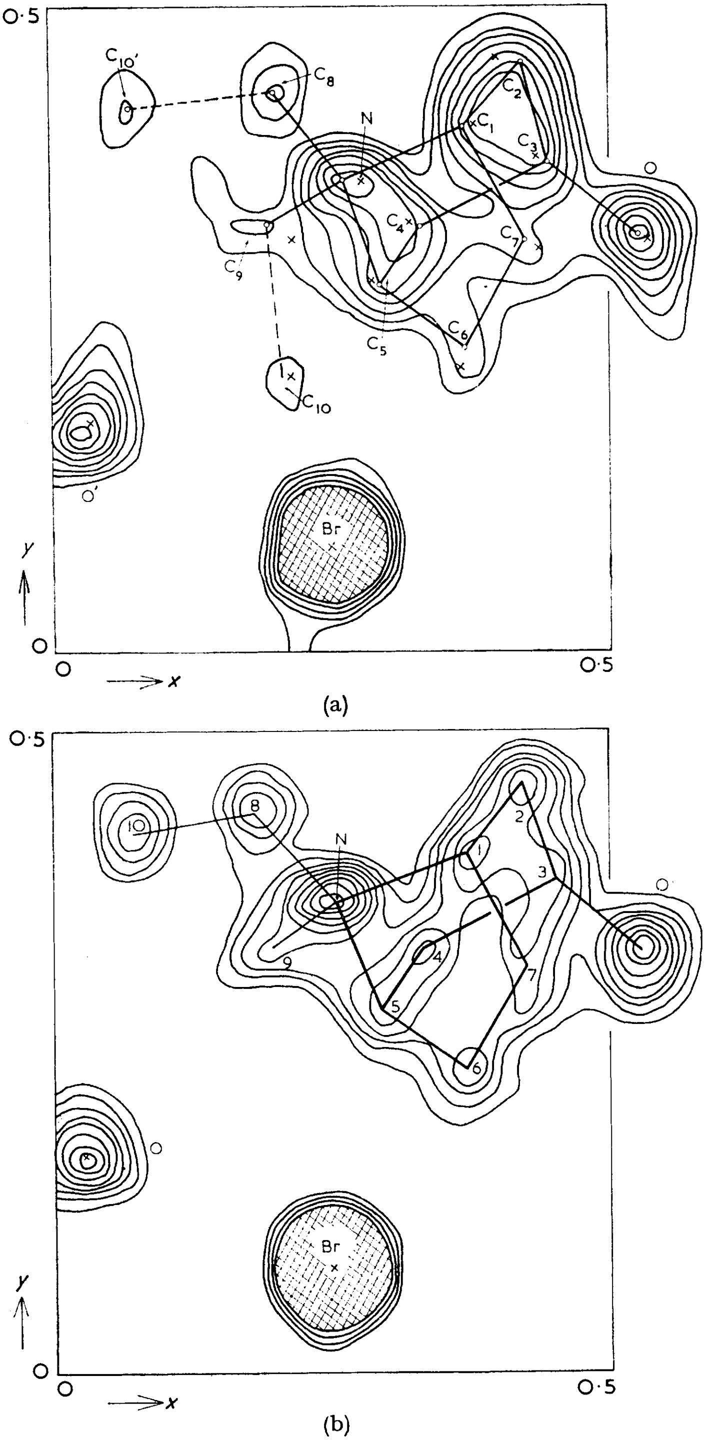
[4] Fodor, *Acta Chim. Acad. Sci. Hung.*, 1955, **5**, 380.

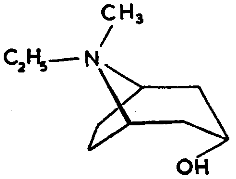


(a)

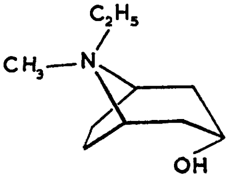
(b)

Electron density maps of N-ethylnortropinemethobromide, projected along the c-axis: (a) phased on Br and structure (I), input positions marked ×, output marked ○; (b) phased on Br and structure (II). The map (b) shows no false maxima and is evidently correctly phased.

determined in the Amsterdam laboratory 9 years ago.[5] The *N*-methyl group, which was found there in the equatorial position, was substituted in our trial model by the ethyl group, the quaternary methyl group then occupying the axial position on the nitrogen atom (structure I). An electron-density projection along the *c*-axis confirmed the assumed position of all the atoms except that of the terminal CH_3 of the ethyl group, which showed at half the expected height (Fig. a). On the other hand, a maximum appeared which could be interpreted only as a methyl group attached to the axial carbon atom on the nitrogen atom. In other words, the electron-density map showed that the ethyl and the methyl group on the nitrogen atom should be interchanged, thus leading to structure (II). The new model led to an electron density map without spurious maxima (Fig. b). The model (II) was confirmed by a three-dimensional electron-density map. At this stage, the discrepancy index *R* for the 95 reflections *hk*0 is 10·9%. For the 575 reflections *hk*, *l* = 1—5, *R* is at present about 16%.



(I)



(II)

Although the space group and cell dimensions of *N*-ethylnortropine methobromide differ from those of the corresponding iodide, the packing is again roughly of the sodium chloride type. This is seen by transforming to the axes $a' = a$, $b' = b/2 + c$, $c' = b/2 - c$. The bromine atoms are placed in this pseudocell on an *A*-centred orthogonal lattice with $a' = 12{\cdot}0$, $b' = c' = 9{\cdot}7$ Å, these cell constants being very similar to those of the corresponding iodide. Moreover, with $y_{Br} = 1/8$ instead of 1/12, the bromine arrangement would be face-centred. This bromine-occupied lattice is approximately centred by the *N*-ethyl-*N*-methylnortropinium groups. All four compounds described here thus have roughly the same sort of packing. All show pseudocubic twinning with various degree of frequency. It is remarkable that the iodides twin more frequently than the bromides, and the *N*-ethyltropine salts much more than their *N*-epimers. This would seem to indicate that the *N*-ethyltropine ion can assume a more closely knit and isometric configuration.

In contrast to the present result, the position of the methyl group in tropine hydrobromide was formerly found to be equatorial,[5] as already remarked. Therefore, it seems desirable to check the structure of the tropine and pseudotropine bases themselves, in which the nitrogen carries a free electron pair. This investigation has been started.

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[5] Visser, Manassen, and de Vries, *Acta Cryst.*, 1954, **7**, 288.