

Crystal and Molecular Structure of Pseudotropine

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Pseudotropine crystallizes in the space group $Pnam$, $a=8.023 \pm 6$, $b=10.555 \pm 4$, $c=9.391 \pm 4$ Å. The molecular symmetry is m . The N-CH₃ group is equatorially attached with respect to the piperidine ring, which is in a deformed chair form. The deformation can be ascribed to the formation of the ethylene bridge, and to steric hindrance of the atoms of this bridge with the carbon atom 3, and also slightly with the *N*-methyl group. The molecules are bound by OH-N bridges to form chains along the X axis.

The conformation of tropine [Fig. 1(a)] and pseudotropine [Fig. 1(b)] and their compounds has been studied by several authors using various techniques, *e.g.* nuclear magnetic resonance (n.m.r.) and dipole-moment measurements. We refer to papers by Closs (1959) and Bishop, Fodor, Katritzky, Soti, Sutton & Swinbourne (1966) for details and further references.

An X-ray crystal-structure determination of tropine hydrobromide (Visser, Manassen & De Vries, 1954) showed the piperidine ring to be in the chair form, with the OH group attached in axial position to the C(3) atom and the CH₃ group on the nitrogen atom in equatorial position with respect to this ring. Although the axial (α) position for the OH group in tropine, β in pseudotropine, has long been considered as well-established, the conformation at the nitrogen atom is more open to speculation. Closs (1959) showed that in acid solution the CH₃ group in pseudotropine, tropine and tropane is predominantly in the equatorial position as shown in Fig. 1, in accordance with the crystallographic result of Visser *et al.* At pH 6 the two n.m.r. signals coalesce showing that the two forms interconvert rapidly. On the other hand, the crystal structure of *N*-ethylnortropine methobromide (MacGillavry & Fodor, 1964) shows the last CH₃ group introduced to be equatorially attached, in agreement with Fodor's prediction (Fodor, Tóth & Vincze, 1955). Apparently, the addition reaction shifts the originally attached ethyl group towards the axial position.

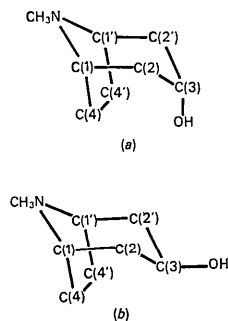


Fig. 1. Chemical formulae of (a) tropine and (b) pseudotropine, with the numbering of atoms.

It seemed to be of interest to determine the crystal structure of unsubstituted tropine and/or pseudotropine, in order to establish the situation of the methyl group at the ternary nitrogen atom, where the quaternary substituent is replaced by a lone electron pair. Also, a more accurate determination of the conformation of the piperidine ring would permit the checking of conclusions drawn by Bishop *et al.* from n.m.r. fine structure of the H(3) signal in tropine.

A preliminary investigation of the crystals of tropine and pseudotropine showed that the former has some undesirable crystallographic properties, like twinning and polymorphism. On the other hand, pseudotropine crystallizes reasonably well, and was accordingly chosen for structure determination.

Pseudotropine crystallizes in orthorhombic needles; the needle axis was chosen to be the a axis, in order to conform with the standard space group denomination. The prominent habit is {011}; cleavage parallel to the a axis occurs in several azimuths, including {011} and {001}. Cell constants b and c were computed by least squares from data of a Weissenberg diagram $0kl$ with Cu K radiation calibrated with Al powder lines. θ values of $h00$ reflexions for Cu $K\alpha$ radiation were measured on a single-crystal diffractometer, and a again found by least squares. $a=8.023 \pm 0.006$; $b=10.555 \pm 0.004$; $c=9.391 \pm 0.004$ Å. Density by flotation, 1.177 g.cm^{-3} ; X-ray density, with four molecules per cell, 1.179 g.cm^{-3} .

Reciprocal planes hkl , with l from 0 to 6, were registered with Cu K radiation on Weissenberg diagrams. Intensities were estimated visually and scaled with the help of intensities $0kl$, measured on a manually operated single-crystal diffractometer. Some doubtful intensities from the films were also measured with the counter and scaled to the others.

Extinctions $h0l$ and $hk0$ indicate the space group $Pna2_1$ or $Pnam$. In the first space group, the pseudotropine molecule would be in general position; in the centrosymmetric group, the molecular symmetry must be m . The three-dimensional Patterson function shows a large concentration of peaks in the planes $w=0$ and $w=\frac{1}{2}$, which is a strong indication for the space group $Pnam$. The approximate orientation of the molecule in

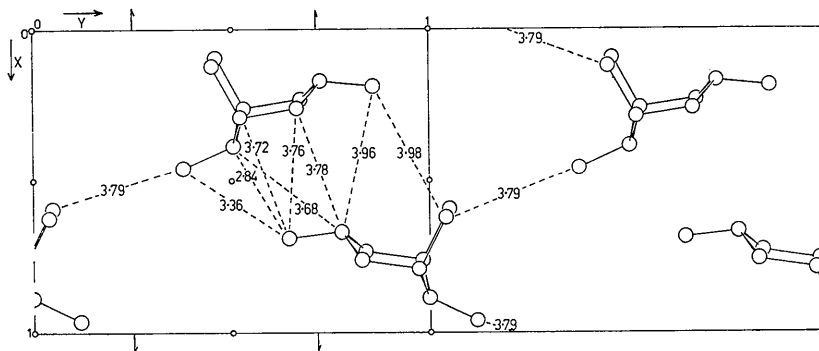


Fig. 2. Projection of one half of the cell nearly parallel to the z axis, from $z = \frac{1}{2}$ to $z = 1$. Intermolecular distances smaller than 4 Å are indicated.

temperature factors. After two cycles, a three-dimensional difference synthesis showed clear indications for several of the hydrogen atoms in plausible positions. The remaining hydrogen atoms were located with the

help of a program written for the X1 by W. Rutten and H. Geise, which introduces the valency angles with respect to bonds already located.

After one least-squares cycle a difference map was again computed which on the whole confirmed the input hydrogen positions. A final least-square cycle gave all shifts smaller than the estimated standard deviations. The final R is 11.4%. Atomic positions and thermal parameters are given in Table 1, structure factors in Table 2.

Discussion

The structure is shown in Fig. 2 in a projection of one half of the cell nearly parallel to the z axis. The two molecules in the mirror plane $z = \frac{3}{4}$ are drawn as shown, and the positions of the molecules in the other mirror plane are generated by the centres of symmetry, indicated in the figure. Strings of molecules along [100], generated by screw axes $x, \frac{3}{4}, \frac{3}{4}$ and $x, \frac{1}{4}, \frac{1}{4}$, are bound by $\text{OH} \cdots \text{N}$ hydrogen bonds of length 2.84 Å. Moreover, most of the van der Waals contacts occur between these molecules, as seen from Fig. 2 and Table 3. Habit and cleavage parallel to the a -axis are completely consistent with this structure.

Table 3. Intermolecular distances smaller than 4 Å between a molecule in the layer $z = \frac{3}{4}$ and the molecules in the layer $z = \frac{1}{4}$

Atom of molecule in $z = \frac{3}{4}$	Atom of molecule in $z = \frac{1}{4}$	Distance
O	C(1)	3.99 Å
C(4)	C(4')	3.72

For the other intermolecular distances see Fig. 2.

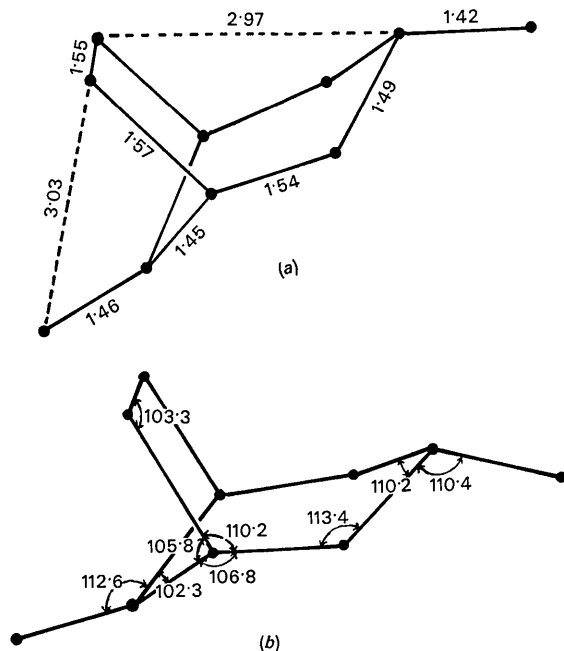


Fig. 3. (a) Bond distances and some interatomic distances smaller than 3.1 Å. (b) Interbond angles.

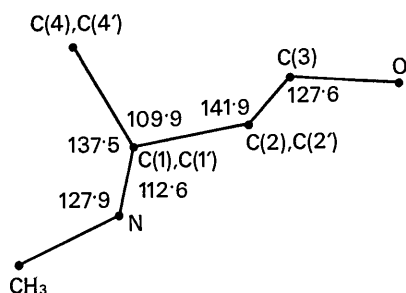


Fig. 4. Angles between planes in the molecule perpendicular to the mirror plane.

The molecular geometry (Fig. 3) shows that the 'bridge' C(4)–C(4') deforms the chair-type piperidine ring, in particular by bringing the atoms C(1) and C(1') closer together than normally: the valence angle C(1)NC(1') is only 102°30'. Interatomic distances are fairly normal. On the other hand, the valency angles at C(1) and C(2) appear to be such that a minimum distance of 3 Å between the ethylene bridge atoms and on one side C(3), on the other side CH₃, is achieved. This same minimum distance between carbon atoms

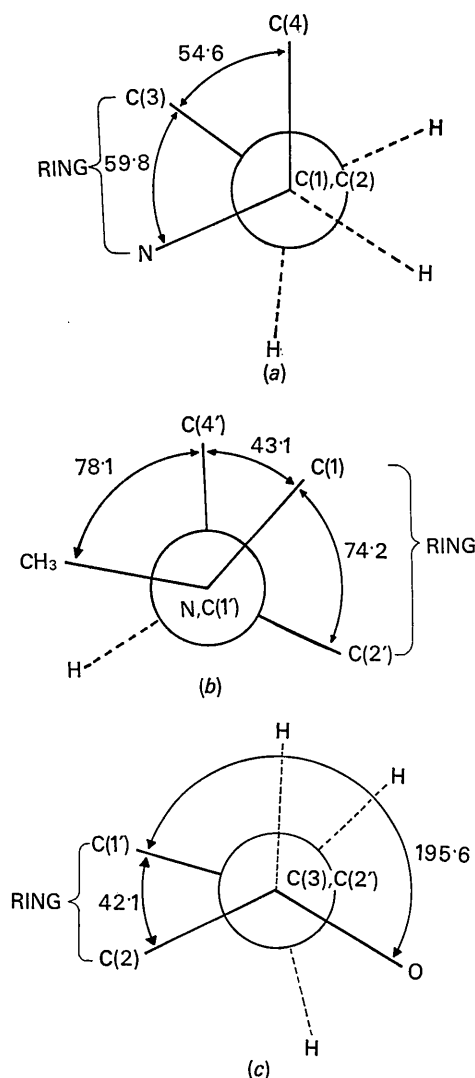


Fig. 5. Dihedral angles of pseudotropine (a) viewed along C(1)–C(2), (b) viewed along N–C(1'), (c) viewed along C(3)–C(2'). The approximate positions of the H atoms are marked by dotted lines.

further removed than next-nearest neighbours has been noted before in molecules with steric hindrance (Stam & MacGillavry, 1963). In particular the small angle between the planes N.C(1).C(1') and C(1).C(2).C(2'). C(1'), and the large angle between the latter plane and C(2).C(3).C(2'), appear to be effective in bending the outer parts of the piperidine ring away from the ethylene bridge (Fig. 4).

It is interesting to compare some dihedral angles with those assumed for tropine by Bishop *et al.* (1966) in order to account for their n.m.r. results. Viewed along C(1)–C(2), the conformation is not far from ideally staggered [Fig. 5(a)]; viewed along N–C(1') and C(3)–C(2') however, the dihedral angles deviate appreciably from the 'ideal' value of 60° [Fig. 5(b) and (c)]. In particular the angles in Fig. 5(c) are very similar to

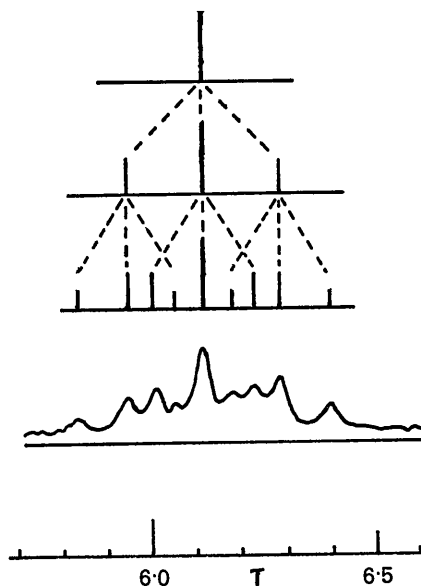


Fig. 6. N.M.R. spectrum of the proton at C(3) and (above) splitting pattern of this spectrum.

those assigned by Bishop *et al.* to the same bond in tropine.

The n.m.r. spectrum* of pseudotropine (recorded on a Varian A 60 spectrometer) gives a multiplet at $\tau = 6.12$ ppm (Fig. 6). This multiplet can be ascribed to the C(3) proton. First order analysis is possible, because the coupling constants are small compared with the differences of the chemical shifts. Coupling constants $J_1 = 10.2$ cps and $J_2 = 6.6$ cps are found. The value of J_1 is in good agreement with the J value of Karplus (1959) for an azimuth value of 160° . The Karplus rule does not give the value found for J_2 .

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