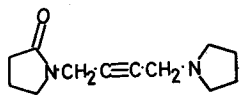
The crystal and molecular structure of oxotremorine sesquioxalate

Oxotremorine, *N*-(4-pyrrolidino-2-butynyl)-2-pyrrolidone, I, is a muscarinic agent of great potency with a chemical structure which differs considerably from other muscarinic stimulants (Cho, Haslett & Jenden, 1962). It is a tertiary amine, whereas all powerful muscarinic agonists possess a trimethylammonium group, and it contains an acetylenic bond at the position in the molecule where strong muscarinic agents usually have an oxygen atom.



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Its mode of action is not yet fully understood. It has been suggested by Bebbington, Brimblecombe & Shakeshaft (1966) that it is able to assume a conformation in which the distances between the pyrrolidine nitrogen, the carbonyl oxygen and the acetylenic bond are about the same as the distances between the trimethylammonium nitrogen, the hydroxyl group and the furan oxygen in muscarine, which would make it possible for oxotremorine to interact directly with the muscarinic receptor.

On the other hand, Holmstedt (1967), in attempting to explain the observed increase in brain acetylcholine after administration of oxotremorine, advanced the hypothesis that oxotremorine acts either by stimulation of the synthesis of acetylcholine or by release of acetylcholine from an inactive and otherwise undetected precursor.

The preferred conformations of several muscarinic agonists have been established by X-ray structure determinations in the crystalline state, nmr studies in solution and molecular orbital calculations (for a review see Baker, Chothia & others, 1971). The calculations for muscarine and acetylcholine made by Kier (1967) using extended Hückel theory molecular orbital calculations showed a fairly good agreement with the X-ray values reported in the literature. Kier (1970) also undertook calculations on the oxotremorine molecule and concluded that it is able to assume a conformation compatible with that of the muscarinic receptor. We found it of interest, therefore, to perform an X-ray determination of the crystal and molecular structure of oxotremorine, and compare it with the calculated conformation and also with the structure of a related quaternary compound, trimethyl-[4-(2-oxopyrrolidino)-2-butynyl]-ammonium iodide, the crystal structure of which has recently been reported (Baker & Pauling, 1973).

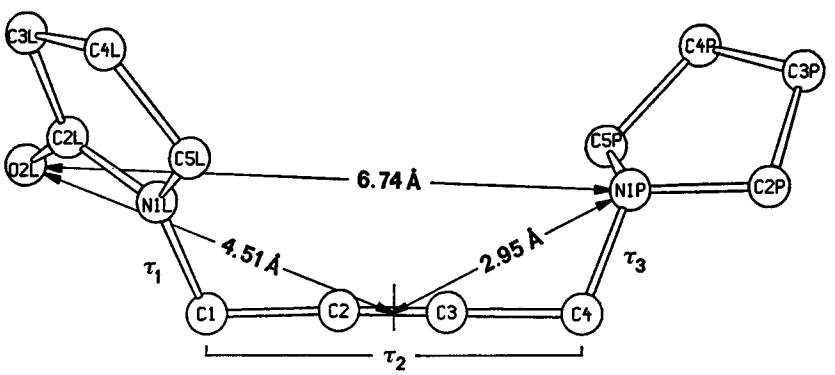

FIG. 1. Perspective drawing of the oxotremorine molecule giving the atomic numbering and the distances thought to be relevant to the muscarinic receptor.

Crystals of oxotremorine sesquioxalate, $C_{12}H_{18}N_2O \cdot 1{\cdot}5\ H_2C_2O_4$, were grown at room temperature from an ethanol solution. The crystals are triclinic, space group P_1, with two formula units in a unit cell of dimensions $a = 8{\cdot}872$ Å, $b = 11{\cdot}839$ Å, $c = 8{\cdot}184$ Å, $\alpha = 99{\cdot}60(5)^0$, $\beta = 90{\cdot}67(7)^0$, $\gamma = 92{\cdot}66(5)^0$. X-ray intensity data were collected on an automated four-circle diffractometer, the $\theta - 2\theta$ scan technique and Mo $K\alpha$ radiation were used. A total of 2979 independent reflections for 2θ values up to 50^0 were recorded. Of these, 1627 with intensities greater than three times their standard deviations were used in the structure analysis. The structure was solved by direct methods and refined by Fourier and least-squares calculations. At the present stage of the refinement, the conventional R value (agreement between observed and calculated structure factors) is 0·115 with anisotropic thermal parameters for all the non-hydrogen atoms.

The unit cell contains two oxotremorine molecules, protonated at the pyrrolidine nitrogen, an oxalate ion placed on a centre of symmetry and two oxalic acid molecules. The oxalate ion is connected to the oxalic acid molecules by short hydrogen bonds (O · · · O distance 2·46 Å). The oxotremorine molecule participates in two hydrogen bonds: the lactam oxygen is acceptor in an O–H · · · O bond donated by an oxalic acid molecule and the pyrrolidine nitrogen is joined to an oxalate ion by an N–H · · O bond.

The oxotremorine molecule is illustrated in Fig. 1. The bond lengths and angles are in agreement with expected values and those of the lactam ring and the carbon chain compare well with the corresponding values in trimethyl-[4-(2-oxopyrrolidino-2-butynyl] ammonium iodide (Baker & Pauling, 1973) except that the Cl to C4 chain appears to be linear within experimental error.

The conformation of the oxotremorine molecule can be described in terms of three torsion angles: τ_1 = C2–Cl–N1L–C2L, τ_2 = N1L–Cl–C4–N1P and τ_3 = C3–C4–N1P–C2P. (Fig. 1). We have then assumed C1–C2–C3–C4 to be linear and neglected conformational variations in the two rings. The conformation found in the present study is illustrated in Fig. 2 as viewed along the three relevant bond directions.

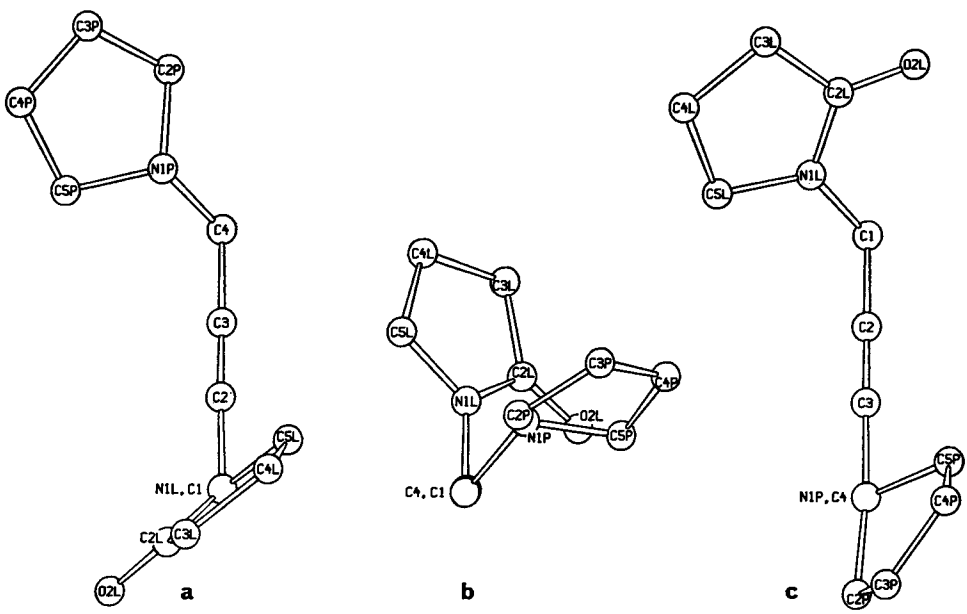

FIG. 2. The conformation of the oxotremorine molecule: (*a*) viewed down the N1L-C1 bond, (*b*) viewed down the C4-C7 direction, (*c*) viewed down the N1P-C4 bond.

The numerical values for the torsion angles are $\tau_1 = 132°$, $\tau_2 = -40°$ and $\tau_3 = 174°$. The corresponding values found by Baker & Pauling (1973) in the trimethyl-[4-(2-oxopyrrolidino)-2-butynyl]ammonium ion are $\tau_1 = 99°$, $\tau_2 = 143°$ and $\tau_3 = -179°$. This ion differs from oxotremorine only in that the pyrrolidine group is replaced by a trimethylammonium group. The conformation at C4–N1P is close to antiplanar in both cases despite the different groups attached to C4. This is in contrast to the calculations on oxotremorine by Kier (1970) which showed the pyrrolidine ring to be symmetrically disposed relative to the triple bond ($\tau_3 \sim 120°$). Kier's calculations for τ_2 showed that the two rings were able to assume any values outside the range $-60°$ to $+60°$. The lactam ring was predicted to be able to assume two zones of conformational preference, with τ_1 values in the ranges 60 to 120° and -60 to $-120°$. The values for τ_1 and τ_2 found in the present study are both slightly outside the predicted ranges. However, the conformation of oxotremorine in the solid state is not incompatible with the geometry of the muscarinic receptor as delineated by Beckett, Harper & Clitherow (1963) and Kier (1967). It must also be kept in mind that the conformation in the solid state may not reflect exactly the conformation of the drug at the receptor.

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