Molecular Conformation of (+)-Tubocurarine Chloride, a Mono-quaternary Curare Alkaloid

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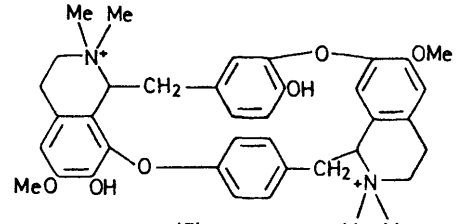
Summary *X*-Ray crystallographic analysis of the molecular structure of (+)-tubocurarine chloride confirms that it is a mono-quaternary nitrogeneous alkaloid; comparison of the conformation of the molecule in this study with that of *OO'N*-trimethyl-(+)-tubocurarine iodide indicates a considerable degree of flexibility of the molecule.

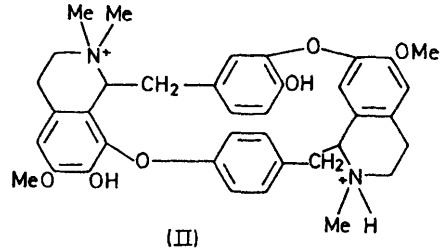
RECENTLY, it was shown[1] that the accepted structure (I) of (+)-tubocurarine chloride was incorrect and that the compound is a mono-quaternary salt with the structure shown in formula (II). This finding changes the interpretation of the mechanism of action of certain neuromuscular blocking agents, of which (+)-tubocurarine is one of the original members, because present theories assume that a bisonium structure is the major requisite for activity. Since the structure of this compound is important to the understanding of neuromuscular blockade, a crystallographic analysis was undertaken not only to corroborate the n.m.r. results but also to extend the present knowledge regarding the conformation of this molecule and to obtain relevant structural parameters for this compound.

The space group is $P2_1$ with 2 molecules of $(C_{37}H_{42}N_2O_6)^{2+}2Cl^-\cdot 5H_2O$ per unit cell and with $a = 21{\cdot}053(3)$ Å, $b = 10{\cdot}267(3)$ Å, $c = 9{\cdot}184(2)$ Å, and $\beta = 103{\cdot}23(3)°$. Three-dimensional intensity data were collected on a Picker FACS-1 diffractometer to a maximum 2θ of 50° using graphite monochromatized Mo-K_α radiation. The atomic parameters (isotropic thermal parameters for the solvent atoms, anisotropic thermal ellipsiods for all other non-hydrogen atoms, and positional parameters for all atoms) were refined by block-diagonal least-squares to a final R value of 9·5%.

The structure determined from the *X*-ray analysis and shown in the Figure has only one quaternary nitrogen atom [N(20)] which is in the phenolic tetrahydroisoquinoline ring thus confirming the n.m.r. results[1]. The tubocurarine molecule assumes a folded conformation with the two tetrahydroisoquinoline rings turned towards the centre of the molecule so that the distance between the nitrogen atoms is 8·97 Å. This N^+–N^+ distance is comparable to that found in other curare alkaloids;[2,3] and is shorter than the assumed intercharge separation of 13—15 Å which was used in several explanations of neuromuscular blockade.[5] Also there is a short intramolecular contact of 4·82 Å between the quaternary nitrogen atom and the oxygen atom of the methoxy-substituent on the other tetrahydroisoquinoline ring, [N(20)–O(37) in the Figure]. Protruding from the compact bulk of the molecule is the phenol ring which forms a hydrogen bond with one of the ordered chloride ions in the crystal.



(I)



(II)

This compact structure has a degree of flexibility which is evident in the differences in conformation between (+)-tubocurarine and its more potent methylated derivative, *OO'N*-trimethyl-(+)-tubocurarine.[3] A comparison of the

crystal structures shows that the relative orientations of the phenolic tetrahydroisoquinoline ring with the quaternary nitrogen N(20), the benzene ring, and the phenol ring are similar in the two structures; however, the other tetrahydroisoquinoline ring is rotated out from the centre of the molecule in the methylated compound forming a more open conformation. In the methylated derivative the separation between positive charges is 10·7 Å and, for comparison, the N^+–O separation which is 4·82 Å in (+)-tubocurarine is 8·48 Å in the methylated species. In both of these structures the 2 positive centres are on opposite sides of the body of the molecule making the simultaneous attachment of the 2 onium functions to the receptor a remote possibility.

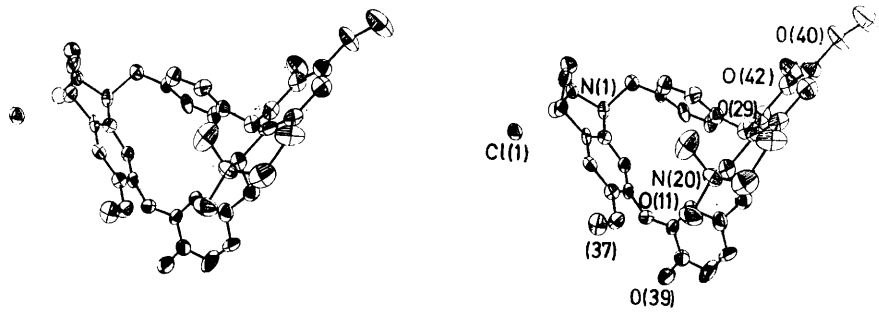


FIGURE. *A stereodrawing of (+)-tubocurarine chloride showing the molecule and the chloride ion hydrogen bonded to* N(1). *This drawing was done using the program ORTEP.*[4]

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