Solution Conformation of (+)-Tubocurarine Chloride

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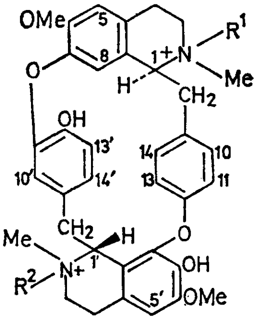
N.m.r. studies have determined the solution conformation of (+)-tubocurarine chloride (2). The conformation is not rigid and variable temperature n.m.r. spectra have disclosed hindered phenyl rotation.

UNTIL recently the widely accepted structure of (+)-turbocurarine chloride, a member of the bisbenzylisoquinoline family of alkaloids,[1-3] was that of a tetra-*N*-methyl diquaternary salt (1). Workers at the Wellcome Research Laboratories revised this structure[4] and suggested that (+)-tubocurarine chloride is the tri-*N*-methyl quaternary hydrochloride (2). They further showed that (+)-chondrocurarine chloride is the tetra-*N*-methyl diquaternary compound (1) and not a positional isomer of (+)-tubocurarine chloride differing in the location of a methyl ether residue. These studies profited from the isolation of the di-*N*-methyl dihydrochloride, (+)-tubocurine dihydrochloride (3).



(1) $R^1 = R^2 = Me$
(2) $R^1 = H, R^2 = Me$
(3) $R^1 = R^2 = H$

In order to obtain additional evidence for the structure of (+)-tubocurarine chloride the [$^2H_6$]dimethyl sulphoxide solution n.m.r. spectrum was carefully scrutinized. At ambient temperature the resonances are broad and ill defined; however, one unusual feature can be observed in the low field portion of the spectrum (Figure 1a). A singlet appears at δ 4·80 which can only be assigned to an aromatic proton of either of the two tetrahydroisoquinoline groups (*i.e.* 5-H, 8-H, or 5′-H †). The doublet to slightly lower field was shown to arise from either 1-H or 1′-H by spin-decoupling experiments.

Interestingly when the solution was heated to 90 and then to 125°, the chemical shift of the doublet remained unaffected while the singlet shifted downfield until it reached δ 5·08 (Figure 1b and c). A number of changes in the position of other aromatic proton resonances are also observed when the temperature is increased. The doublets centred at δ 6·10 and 6·52 in the ambient temperature spectrum as well as resonances in the δ 6·8—7·2 region broaden and coalesce to a single broad resonance at δ 6·66 at 125°.

The resonances unaffected by heating consist of two additional singlets (δ 6·79 and 6·86) and an ABX pattern [δ 7·04, 6·89, and 6·54 (J_{AX} 2, J_{BX} 0, J_{AB} 8 Hz)]. The two singlet resonances arise from the remaining tetrahydroisoquinoline aromatic protons and the ABX pattern from 14′-, 13′-, and 10′-H of the trisubstituted aromatic ring. Therefore, by a process of elimination the aromatic resonances which broaden and coalesce can be attributed to 10-, 11-, 13-, and 14-H of the disubstituted aromatic ring.

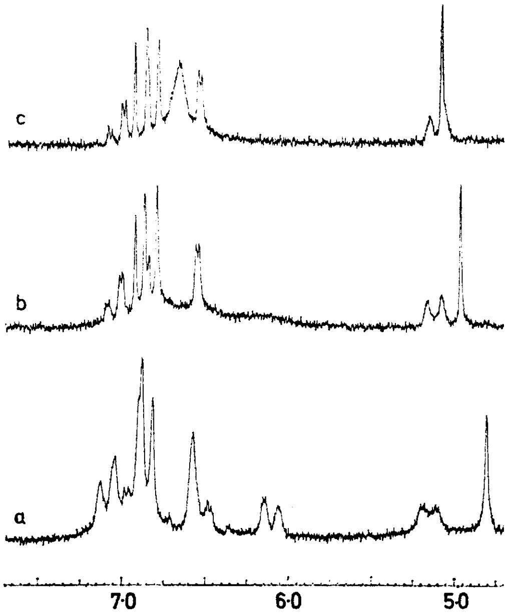


FIGURE 1 Downfield region of the n.m.r. spectrum of (+)-tubocurarine chloride in [$^2H_6$]dimethyl sulphoxide solution at various temperatures: a, ambient; b, 90°; c, 125°

These observations can be explained when the solution conformation of (+)-tubocurarine chloride is considered to be that shown in Figure 2. This conformation incorporates the configurations determined by Tomita[5] for the two asymmetric centres.

The bulk of the aromatic rings requires that they be oriented perpendicular to the planes of the tetrahydroisoquinoline rings. This relationship places 8-H of the

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† The numbering system is that of *Chem. Abs.*, 1970, **72**, 3922s.

[1] M. Kulka, in 'The Alkaloids, Chemistry and Physiology,' eds. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1954, vol. IV, pp. 199—243.

[2] Ref. 1, 1960, vol. III, pp. 439—470.

[3] Ref. 1, 1967, vol. IX, pp. 134—170.

[4] A. J. Everett, L. A. Lowe, and S. Wilkinson, *Chem. Comm.*, 1970, 1020.

[5] M. Tomita and J. Kutitomo, *Yakugaku Zasshi*, 1962, **82**, 741 (*Chem. Abs.*, 1963, **58**, 4613).

tetrahydroisoquinoline hydrochloride ring over the centre of the disubstituted aromatic ring. Because of the nature of the magnetic anisotropy of the aromatic ring, this arrangement results in the anomalously high field chemical shift of the singlet resonance at δ 4·80. The proton on the asymmetric carbon of the quaternary tetrahydroisoquinoline ring, 1′-H, is oriented at the periphery of three aromatic rings and therefore deshielded relative to 1-H which is affected by only two aromatic rings.

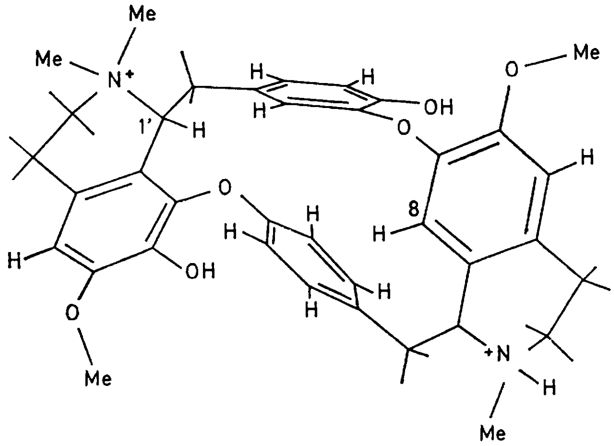

FIGURE 2 The solution conformation of (+)-tubocurarine chloride

Dreiding models of this conformation reveal that the disubstituted aromatic ring can rotate along the axis between the *para*-substituents although steric factors are likely to cause this rotation to be hindered. The n.m.r. spectra confirm that at ambient temperature the rotation is hindered and the four protons of this ring are non-equivalent (ABCD system) and give rise to four doublet of doublets. At elevated temperature the rate of rotation increases and the four resonances begin to coalesce to an AA′BB′ pattern. Increased rotation of the aromatic ring also affects the chemical shift of 8-H. A shift to lower field is observed since the shielding by the disubstituted aromatic ring decreases as the rotation rate increases due to a change in the time-averaged orientation of the two rings.

The trisubstituted aromatic ring does not rotate even at elevated temperature because of its *meta*-attachment to the tetrahydroisoquinoline rings. Therefore the resonances of 10′-, 13′-, and 14′-H are unaffected by elevated temperature.

The conformation and associated dynamic characteristics are thought to be general for the bisbenzylisoquinoline alkaloids of the curine type since totally analogous spectral results have been obtained with (1) and (3).

The data as presented do not rigorously rule out an alternate conformation in which the trisubstituted aromatic ring has been rotated 180° also placing 8-H over the plane of the disubstituted ring. Ambiguities regarding the chemical shift of 8-H in the absence of the aromatic rings and the exact time-averaged position of the disubstituted aromatic ring make attempts to distinguish between these conformations unreliable. Molecular models reveal the alternate conformation to be more crowded particularly in the very close approach of 1′-H to the protons of the disubstituted aromatic ring thereby destabilizing this second conformation.

Note added in proof: Since this paper was submitted, two communications have appeared detailing the *X*-ray crystallography of (+)-tubocurarine chloride[6] and *OO′N*-trimethyl-(+)-tubocurarine di-iodide.[7] The suggested solution conformation is in excellent agreement with these studies. The solid state studies have more accurately determined the relative orientations of the planes of the aromatic rings; however, the solution studies have disclosed a conformational flexibility not obvious from the *X*-ray structures.

EXPERIMENTAL

All experimental work on (+)-tubocurarine chloride (2), was performed on the USP reference standard (packaged June 1967). The (+)-tubocurine dihydrochloride (3) was obtained from a chloroform extraction of crude (+)-tubocurarine chloride in an alkaline solution. (+)-Chondrocurarine iodide (1) was prepared by the addition of methyl iodide to a chloroform solution of (+)-tubocurine. The chondrocurarine iodide precipitated out of solution and was recrystallized from methanol containing some methyl iodide.

[2/2190 *Received*, 19*th September*, 1972]

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[6] P. W. Codding and M. N. G. James, *J.C.S. Chem. Comm.*, 1972, 1174.

[7] H. M. Sobell, T. D. Sakore, S. S. Tavale, F. G. Canepa, P. Pauling, and T. J. Petcher, *Proc. Nat. Acad. Sci. U.S.A.*, 1972, **69**, 2213.