Revision of the Structures of (+)-Tubocurarine Chloride and (+)-Chondrocurine

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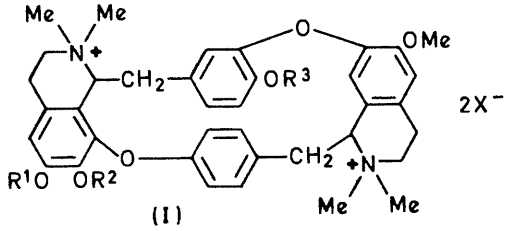
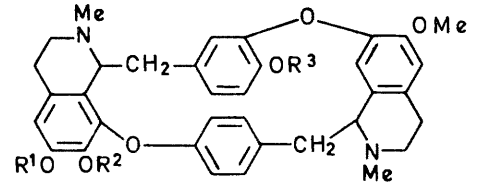
Summary The hitherto accepted structures for (+)-tubocurarine chloride and (+)-chondrocurine have been found to be incorrect; the former is a mono- not a di-quaternary salt, the latter being the related tertiary base.

RECENT work in these laboratories has shown that the hitherto accepted structures at (+)-tubocurarine chloride (I; R^1 = Me, R^2 = R^3 = H, X = Cl), (+)-chondrocurine (II; R^1 = R^3 = H, R^2 = Me) and (+)-chondrocurarine chloride (I; R^1 = R^3 = H, R^2 = Me, X = Cl) are incorrect.



(I)



(II)

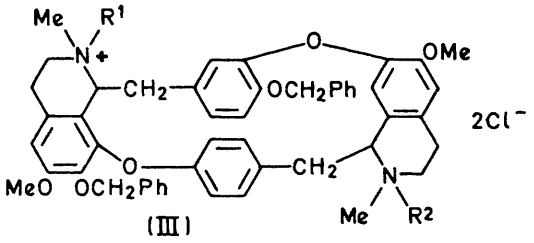
Until recently, when Shamma *et al.*[1] successfully dequaternised (+)-tubercurarine chloride with sodium thiophenoxide, the tertiary base (+)-tubocurine had not been described. These authors however did not report the requaternisation of their tertiary base. In an attempt to prepare ^{14}C-labelled (+)-tubocurarine iodide, we observed that quaternisation of the tertiary base prepared by the above procedure did not give the expected (+)-tubocurarine iodide. The physical constants of the product corresponded to those cited for (+)-chondrocurarine iodide [(+)-chondrocurine dimethiodide].[2]

Further examination of the tertiary base showed (a) that permethylation with methyl iodide and sodium methoxide gave the known *OO*-dimethyl-(+)-tubocurine dimethiodide (I; R^1 = R^2 = R^3 = Me, X = I) and hence the optical configuration and the skeletal structure had remained undisturbed during dequaternisation; (b) that the physical constants corresponded to those described for (+)-chondrocurine;[3] (c) that the i.r. spectrum and behaviour on t.l.c. were identical with those found with a sample of (+)-chondrocurine kindly provided by the Squib Institute for Medical Research and (d) that the quaternary iodide obtained by its reaction with methyl iodide in methanol was indistinguishable from (+)-chondrocurine dimethiodide likewise prepared from the authentic natural (+)-chondrocurine.

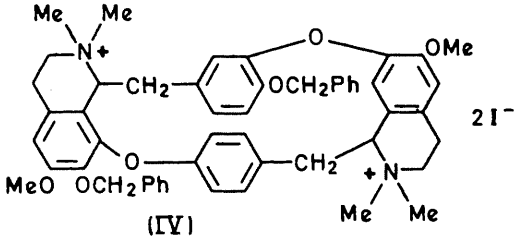
To account for the conversion of (+)-tubocurarine chloride into (+)-chondrocurine on the basis of the accepted structures, the transposition of the methyl group [R^1 in (I)] and hydrogen [R^2 in (I)] during dequaternisation had to be envisaged. To block such a migration, protection of the phenolic groups by benzylation seemed a feasible approach. Benzylation of (+)-tubocurarine chloride in the presence of sodium methoxide did not give the expected *OO*-dibenzyl (+)-tubocurarine chloride [(+)-tubocurine dibenzyl ether dimethochloride] (I; R^1 = Me, R^2 = R^3 = $PhCH_2$, X = Cl). The product of the reaction was *OO*-dibenzyl-(+)-tubocurine benzochloride methochloride (III; R^1 = Me-, R^2 = $PhCH_2$ or R^1 = $PhCH_2$, R^2 = Me), an amorphous salt, but readily converted into a crystalline iodide.

On dequaternisation of the chloride with sodium thiophenoxide, an *N*-methyl and the *N*-benzyl residue were eliminated [re-quaternisation with methyl iodide gave the dimethiodide (IV)], and the resulting tertiary base on hydrogenolysis was debenzylated to a product again identical with (+)-chondrocurine. To explain this transformation, the replacement of methyl by benzyl at a quaternary site during the reaction of (+)-tubocurarine chloride with benzyl chloride and the dual migration of methyl and benzyl residues present as phenolic ethers had to be accommodated.

At this juncture, the accepted structures of (+)-chondrocurarine chloride and (+)-tubocurarine chloride became suspect and a more tolerable explanation became apparent as a result of spectroscopic analysis.



(III)

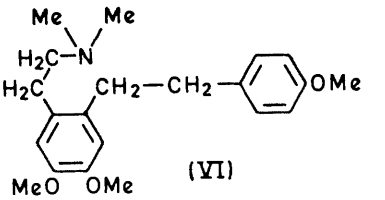


(IV)

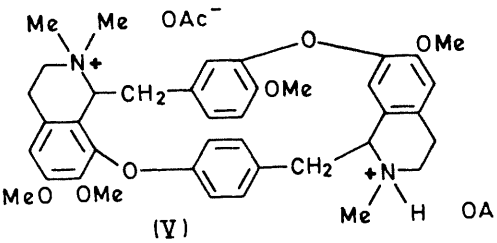
N.m.r. spectroscopy showed the presence in (+)-tubocurarine chloride of only three N-CH_3 groups instead of four. On addition of NaOD one of the N-CH_3 signals moved to high field (56 Hz), giving conclusive proof that one basic centre was not quaternary. In contrast, with (+)-tubocurine dimethiodide and *OO*-dimethyl-(+)-tubocurarine dimethiodide, signals corresponding to four N-CH_3 functions were clearly observed. Confirmation of the presence of a tertiary basic nitrogen in (+)-tubocurarine chloride was provided by the i.r. spectrum which showed a strong N^+–H stretching frequency in the range 2300—2700 cm^{-1} which was replaced by N^+–D absorption at approximately 1800 cm^{-1} after recrystallising (+)-tubocurarine chloride from D_2O. The relationship between the mass spectra of (+)-tubocurarine iodide and (+)-chondrocurarine iodide is consistent with the suggested structures.

Consequently (+)-tubocurarine chloride must possess both a tertiary and a quaternary basic function and the alkaloid is not a diquaternary salt as hitherto described. Furthermore, as our reaction sequences have shown, (+)-tubocurarine chloride on dequaternisation yields the tertiary base (+)-tubocurine (II; R^1 = Me, R^2 = R^3 = H) identical with (+)-chondrocurine. (+)-Chondrocurine and (+)-tubocurine are synonymous and their structures do not differ as previously described[2,4] in the relative positions of methoxy- and phenolic groups. (+)-Chondrocurarine chloride is the dimethochloride of (+)-tubocurine, differing from (+)-tubocurarine chloride in the degree of quaternisation and not in the location of a methyl ether residue.

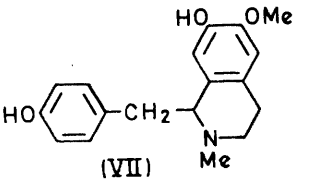
The respective sites of the quaternary and tertiary functions in (+)-tubocurarine chloride were established by cleaving the diphenyl ether bonds in *OO*-dimethyl-(+) tubocurarine acetate (V) [obtained from (+)-tubocurarine acetate with diazomethane] with sodium and liquid ammonia, a procedure previously used in establishing the structure and configuration of *OO*-dimethyl-(+)-chondrocurine.[3] Of the two fragments (VI) and (VII) which were



(VI)

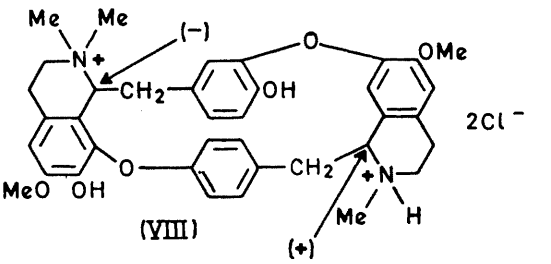


(V)



(VII)

isolated and characterised, the non-phenolic optically inactive compound (VI) must necessarily be derived from the quaternary half of the molecule by Emde-type degradation. The phenolic fragment (VII) was identified by conversion to the known (+)-*O*-methylarmepavine methiodide.



(VIII)

The correct structure of (+)-tubocurarine chloride, taking into account the established optical configuration,[3,4] is therefore shown in the formula (VIII). The quaternary nitrogen is located in the tetrahydroisoquinoline ring bearing the free phenolic group and whose asymmetric centre is *laevo*rotatory. The tertiary nitrogen is associated with the *dextro*rotatory centre of asymmetry.

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[1] M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Letters*, 1966, 1375.
[2] J. D. Dutcher, *J. Amer. Chem. Soc.*, 1946, **68**, 419; 1952, **74**, 2221.
[3] I. R. C. Bick and P. S. Clezy, *J. Chem. Soc.*, 1953, 3893.
[4] H. King, *J. Chem. Soc.*, 1935, 1481; 1936, 1276; 1937, 1472; 1939, 1157; 1940, 737; 1947, 936; 1948, 265, 1945.