X-Ray Studies on Potent New Curariform Agents. Part 3.† Crystal and Molecular Structure of 1-Methyl-2-phenyl-3-hydroxymethylimidazo[1,2-a]pyridinium Chloride ‡

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The structure of the title compound, representative of a new series of powerful, selective, monoquaternary neuromuscular blocking agents, has been determined by a three-dimensional *X*-ray analysis. Monoclinic crystals in space group $P2_1/n$ have lattice parameters a = 7.692(1), b = 10.493(1), c = 16.821(4) Å, β = 90.82(2)°, and Z = 4. The structure was solved by the heavy-atom method and refined by full-matrix least-squares calculations to R = 0.076 for 1 658 observed reflections. The molecule is an acetylcholine antagonist with N–C–C–O torsion angle 78.2(5)° and N···O distance 3.17(1) Å, with the two planar ring systems inclined at 51.4(5)°.

Neuromuscular drugs act by associating with nicotinic cholinergic receptors at the post-synaptic cleft of the neuromuscular junction and thereby block the action on muscle of the neurotransmitter acetylcholine.[1] The basic problem of designing novel structures having the desired activity is the absence of information about the receptor; hence it may be that the only approach is *via* the pharmacophore concept.[2] When the possible three-dimensional arrangements of features common to a set of active compounds have been determined, each of these arrangements becomes a candidate pharmacophore. Such features traditionally include heteroatoms, charges, lipophilic groups, hydrogen bonding, dipoles, *etc.*, and a further consideration must be the receptor-bound conformation, although this is not necessarily the same as that adopted in the crystal. Any structure–activity study can usually identify certain recognition features in a molecule which are necessary for the activity, but given the multifaceted nature of receptor sites, such an approach must be an oversimplification.

The title compound, representative of a series of specially synthesised monoquaternary compounds known§ to be competitive antagonists, is here compared with acetylcholine. There is evidence of a hydrogen bond to the chloride anion.

Experimental

Colourless crystals of the title compound obtained by recrystallisation from propan-2-ol–ethyl ethanoate had m.p. 249—250 °C (decomp.) (Found: C, 65.7; H, 5.3; N, 10.2. $C_{15}H_{15}ClN_2O$ requires C, 65.6; H, 5.5; N, 10.2%).

Crystal data. Monoclinic, M 274.7, a = 7.692(1), b = 10.493(1), c = 16.821(4) Å, β = 90.82(2)°, U = 1 357.5 Å^3, space group $P2_1/n$, Z = 4, D_c = 1.343 g cm^{-3}, D_m = 1.346 g cm^{-3} (by flotation), $F(000)$ = 576, λ = 1.5418 Å, μ(Cu-K_α) = 24.1 cm^{-1}.

Data collection. Unit-cell parameters were determined and intensity data collected at room temperature with an Enraf-Nonius CAD 4 diffractometer using nickel-filtered Cu-K_α radiation and an ω—2θ scan procedure.[3] 2 911 reflections

Table 1. Fractional atomic co-ordinates (× 10^4) for $[C_{15}H_{15}N_2O]^+Cl^-$

	x/a	*y/b*	*z/c*
Cl	2 688(2)	−3 645(2)	10 978(1)
O(1)	1 214(6)	−1 786(5)	9 754(3)
N(1)	2 862(6)	658(5)	10 571(3)
N(2)	2 607(7)	2 318(5)	9 795(3)
C(1)	2 753(8)	206(6)	9 793(3)
C(2)	2 827(8)	−1 180(6)	9 608(4)
C(3)	3 113(8)	−8(7)	11 277(4)
C(4)	3 260(9)	676(7)	11 966(4)
C(5)	3 154(9)	2 011(7)	11 965(4)
C(6)	2 902(9)	2 665(7)	11 284(4)
C(7)	2 775(8)	1 971(5)	10 564(4)
C(8)	2 363(9)	3 641(6)	9 539(4)
C(9)	2 585(7)	1 234(5)	9 320(3)
C(10)	2 431(8)	1 268(6)	8 456(3)
C(11)	3 521(9)	2 014(6)	8 001(4)
C(12)	3 394(9)	1 965(7)	7 175(4)
C(13)	2 198(9)	1 189(6)	6 803(4)
C(14)	1 091(10)	451(7)	7 257(4)
C(15)	1 211(8)	491(6)	8 076(4)

Table 2. Bond lengths (Å) for $[C_{15}H_{15}N_2O]^+Cl^-$

H(1)–O(1)	1.005(11)	C(2)–O(1)	1.419(8)
C(1)–N(1)	1.394(8)	C(3)–N(1)	1.391(9)
C(7)–N(1)	1.379(8)	C(7)–N(2)	1.349(8)
C(8)–N(2)	1.465(9)	C(9)–N(2)	1.389(8)
C(2)–C(1)	1.488(9)	C(9)–C(1)	1.345(9)
C(4)–C(3)	1.366(10)	C(5)–C(4)	1.404(10)
C(6)–C(5)	1.347(10)	C(7)–C(6)	1.415(9)
C(10)–C(9)	1.457(9)	C(11)–C(10)	1.385(9)
C(15)–C(10)	1.392(9)	C(12)–C(11)	1.393(10)
C(13)–C(12)	1.372(10)	C(14)–C(13)	1.388(10)
C(15)–C(14)	1.379(10)		

† Part 2, D. J. Pointer, J. B. Wilford, and J. D. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1075.

‡ *Supplementary data available* (SUP 56391, 3 pp.): thermal parameters, H-atom co-ordinates. For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, Issue no. 1, 1986. Structure factor tables are available on request from the editorial office.

§ Allen and Hanbury Research Limited (now Glaxo Operations, U.K., Plc., Ware, Herts.), compound no. AH 10599B: 4.0 mg produces 59% block, duration 1.8 min (cat tibialis).

Table 3. Bond angles (deg.) for $[C_{15}H_{15}N_2O]^+Cl^-$

C(2)–O(1)–H(1)	116.2(49)	C(3)–N(1)–C(1)	129.6(6)
C(7)–N(1)–C(1)	109.3(6)	C(7)–N(1)–C(3)	121.0(6)
C(8)–N(2)–C(7)	123.2(6)	C(9)–N(2)–C(7)	109.3(6)
C(9)–N(2)–C(8)	127.3(6)	C(2)–C(1)–N(1)	121.8(6)
C(9)–C(1)–N(1)	106.6(6)	C(9)–C(1)–C(2)	131.7(5)
C(1)–C(2)–O(1)	111.5(6)	H(2A)–C(2)–O(1)	109.5(4)
H(2A)–C(2)–C(1)	109.0(4)	H(2B)–C(2)–O(1)	108.5(4)
H(2B)–C(2)–C(1)	108.9(4)	H(3)–C(3)–N(1)	121.0(4)
C(4)–C(3)–N(1)	118.0(7)	C(4)–C(3)–H(3)	121.0(5)
H(4)–C(4)–C(3)	119.2(5)	C(5)–C(4)–C(3)	121.3(8)
C(5)–C(4)–H(4)	119.5(5)	H(5)–C(5)–C(4)	119.3(5)
C(6)–C(5)–C(4)	121.1(8)	C(6)–C(5)–H(5)	119.6(5)
H(6)–C(6)–C(5)	120.9(5)	C(7)–C(6)–C(5)	118.2(8)
C(7)–C(6)–H(6)	120.8(5)	N(2)–C(7)–N(1)	106.3(6)
C(6)–C(7)–N(1)	120.3(7)	C(6)–C(7)–N(2)	133.3(6)
H(8A)–C(8)–N(2)	107.7(4)	H(8B)–C(8)–N(2)	106.2(5)
H(8C)–C(8)–N(2)	114.4(4)	C(1)–C(9)–N(2)	108.5(6)
C(10)–C(9)–N(2)	123.6(6)	C(10)–C(9)–C(1)	127.9(6)
C(11)–C(10)–C(9)	121.6(7)	C(15)–C(10)–C(9)	119.3(6)
C(15)–C(10)–C(11)	119.1(7)	H(11)–C(11)–C(10)	120.2(5)
C(12)–C(11)–C(10)	119.7(7)	C(12)–C(11)–H(11)	120.1(5)
H(12)–C(12)–C(11)	119.6(5)	C(13)–C(12)–C(11)	120.9(7)
C(13)–C(12)–H(12)	119.5(5)	H(13)–C(13)–C(12)	120.2(5)
C(14)–C(13)–C(12)	119.5(7)	C(14)–C(13)–H(13)	120.3(5)
H(14)–C(14)–C(13)	120.0(5)	C(15)–C(14)–C(13)	119.9(8)
C(15)–C(14)–H(14)	120.1(5)	C(14)–C(15)–C(10)	120.8(7)
H(15)–C(15)–C(10)	119.6(5)	H(15)–C(15)–C(14)	119.6(5)
O(1)–H(1)–Cl	149.0(67)		

Table 4. Selected non-bonded distances (Å) for $[C_{15}H_{15}N_2O]^+Cl^-$

Intramolecular:

C(2)–Cl	3.467	H(2A)–Cl	2.868
C(3)–Cl	3.863	H(3)–Cl	2.811
N(1)–O(1)	3.166	C(1)–O(1)	2.403
H(2A)–O(1)	2.049	H(2B)–O(1)	2.037
H(15)–O(1)	2.928	C(2)–N(1)	2.069
H(2A)–H(1)	2.225	N(2)–N(1)	2.183
C(2)–N(1)	2.517	H(2A)–N(1)	2.699
H(3)–N(1)	2.156	C(4)–N(1)	2.363
C(5)–N(1)	2.749	C(6)–N(1)	2.423
C(9)–N(1)	2.195	C(1)–N(2)	2.219
C(6)–N(2)	2.538	H(6)–N(2)	2.896
H(8A)–N(2)	2.068	H(8B)–N(2)	2.048
H(8C)–N(2)	2.149	C(10)–N(2)	2.508
C(11)–N(2)	3.124	H(11)–N(2)	2.949
H(2A)–C(1)	2.103	H(2B)–C(1)	2.103
C(3)–C(1)	2.519	H(3)–C(1)	2.840
C(7)–C(1)	2.261	C(10)–C(1)	2.518
C(15)–C(1)	3.121	H(15)–C(1)	2.946
C(3)–C(2)	3.070	H(3)–C(2)	2.829
C(9)–C(2)	2.585	C(10)–C(2)	3.229
C(15)–C(2)	3.343	H(15)–C(2)	2.966
H(2B)–H(2A)	1.764	C(3)–H(2A)	2.830
H(3)–H(2A)	2.346	C(9)–H(2B)	2.750
C(10)–H(2B)	2.886	C(15)–H(2B)	2.828
H(15)–H(2B)	2.652	H(4)–C(3)	2.115
C(5)–C(3)	2.415	C(6)–C(3)	2.810
C(7)–C(3)	2.410	C(4)–H(3)	2.134
H(4)–H(3)	2.450	H(5)–C(4)	2.149
C(6)–C(4)	2.396	C(7)–C(4)	2.742
C(5)–H(4)	2.152	H(5)–H(4)	2.463
H(6)–C(5)	2.116	C(7)–C(5)	2.371
C(6)–H(5)	2.102	H(6)–H(5)	2.436
C(8)–C(6)	3.131	H(8C)–C(6)	2.939
C(7)–H(6)	2.176	C(8)–H(6)	2.955
H(8C)–H(6)	2.482	C(8)–C(7)	2.476
H(8B)–C(7)	2.920	H(8C)–C(7)	2.722
C(9)–C(7)	2.233	C(9)–C(8)	2.558
C(10)–C(8)	3.085	C(11)–C(8)	3.234

Table 4. (*continued*)

Intramolecular:

H(11)–C(8)	2.876	H(8B)–H(8A)	1.764
H(8C)–H(8A)	1.764	C(9)–H(8A)	2.663
C(10)–H(8A)	2.678	C(11)–H(8A)	2.735
H(11)–H(8A)	2.632	H(8C)–H(8B)	1.764
C(9)–H(8B)	3.064	H(11)–H(8B)	2.575
C(11)–C(9)	2.482	H(11)–C(9)	2.710
C(15)–C(9)	2.459	H(15)–C(9)	2.659
H(11)–C(10)	2.142	C(12)–C(10)	2.403
C(13)–C(10)	2.785	C(14)–C(10)	2.410
H(15)–C(10)	2.142	H(12)–C(11)	2.143
C(13)–C(11)	2.405	C(14)–C(11)	2.772
C(15)–C(11)	2.394	C(12)–H(11)	2.149
H(12)–H(11)	2.468	H(13)–C(12)	2.130
C(14)–C(12)	2.385	C(15)–C(12)	2.753
C(13)–H(12)	2.124	H(13)–H(12)	2.447
H(14)–C(13)	2.142	C(15)–C(13)	2.396
C(14)–H(13)	2.146	H(14)–H(13)	2.472
H(15)–C(14)	2.131	C(15)–H(14)	2.136
H(15)–H(14)	2.455		

Intermolecular:

C(6)–Cl(a)	3.909	H(6)–Cl(a)	2.843
C(8)–Cl(a)	3.744	H(8B)–Cl(a)	3.588
H(8C)–Cl(a)	2.945	C(8)–Cl(b)	3.917
H(8A)–Cl(c)	3.390	H(8B)–Cl(b)	2.959
H(8C)–Cl(c)	3.691	C(11)–Cl(b)	3.774
H(11)–Cl(b)	2.718	C(4)–Cl(d)	3.615
H(4)–Cl(d)	2.955	C(5)–Cl(d)	3.596
H(5)–Cl(d)	2.913	H(13)–Cl(e)	3.611
C(14)–Cl(f)	3.862	H(14)–Cl(f)	2.797
N(2)–O(1c)	3.097	C(7)–O(1c)	3.114
C(9)–O(1c)	3.381	H(12)–O(1e)	2.760
H(13)–O(1e)	2.958	N(2)–H(1c)	2.967
C(8)–H(1c)	3.069	C(2)–N(1b)	3.379
H(2A)–N(1b)	2.893	H(2A)–N(2b)	2.858
H(2A)–C(1b)	3.035	C(7)–C(2b)	3.499
C(7)–H(2Ab)	2.798	C(9)–H(2Ab)	3.014
C(12)–H(2Be)	2.908	H(12)–H(2Be)	2.569
C(13)–H(2Be)	2.962	H(15)–C(3c)	2.718
C(11)–H(3b)	2.968	H(11)–H(3b)	2.558
H(15)–C(4c)	2.910	H(12)–C(5g)	3.047
C(14)–H(5h)	3.070	H(12)–C(6g)	2.974
H(14)–H(6h)	2.615	H(13)–C(8i)	2.916
H(13)–H(8Bi)	2.534	H(14)–H(11i)	2.385
H(15)–H(12i)	2.539		

Key to symmetry operations relating designated atoms to reference atoms at (x,y,z): (a) x, $1.0 + y$, z; (b) $1.0 - x$, $-y$, $2.0 - z$; (c) $-x$, $-y$, $2.0 - z$; (d) $0.5 - x$, $0.5 + y$, $2.5 - z$; (e) $0.5 - x$, $0.5 + y$, $1.5 - z$; (f) $-0.5 + x$, $-0.5 - y$, $-0.5 + z$; (g) $0.5 + x$, $0.5 - y$, $-0.5 + z$; (h) $-0.5 + x$, $0.5 - y$, $-0.5 + z$; (i) $0.5 - x$, $-0.5 + y$, $1.5 - z$

($1.5° \leqslant \theta \leqslant 70°$) were measured, of which 2 569 were unique and 1 658 considered observed [$I \geqslant 1.5\sigma(I)$]. Three intensity-control reflections measured every hour during data collection showed no reduction in diffracted intensity. Lorentz, polarisation, and a semi-empirical absorption correction,[4] using normalised and averaged transmission curves measured from four reflections (minimum transmission 88.6%), were applied to the data.

The structure was solved by the heavy-atom method, and after least-squares refinement with isotropic temperature factors for all non-hydrogen atoms, the DIFABS empirical absorption correction[5] was applied. Following refinement using anisotropic thermal parameters for all atoms, a difference-Fourier map revealed the location of all hydrogen atoms, which were then included in the structure refinement with constraints to maintain idealised geometry, except the hydroxylic hydrogen atom for which only the O–H bond length was restrained. The final full-matrix least-squares refinement was carried out with

Table 5. Comparison of torsion angles $N(1)^+$–C(1)–C(2)–O(1) and $N(1)^+ \cdots O(1)$ distances in the title compound and in salts of acetylcholine

	Torsion angle	$N^+ \cdots O$ distance (Å)	Ref.
Title compound	78.2(5)°	3.17(1)	
Acetylcholine chloride	84.64°	3.26	*a*
Acetylcholine bromide	78.43°	3.2	*b*
Acetylcholine perchlorate	73.66°	3.13	*c*

[a] J. L. Herdklotz and R. L. Sass, *Biochem. Biophys. Res. Commun.*, 1970, **40**, 583. [b] T. Svinning and H. Sørum, *Acta Crystallogr., Sect. B*, 1975, **31**, 1581. [c] V. Mahajan and R. L. Sass, *J. Cryst. Mol. Struct.*, 1974, **4**, 15.

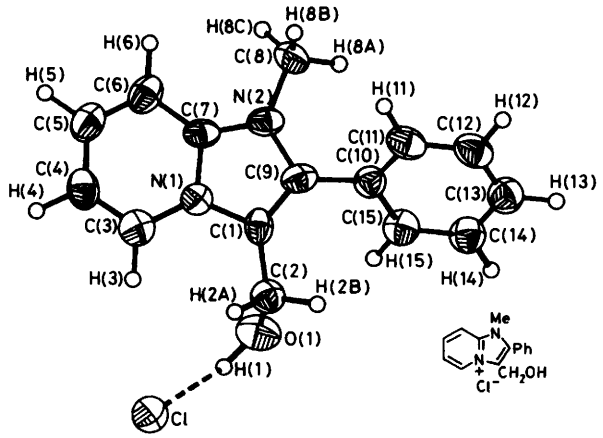

Figure 1. Molecular structure of the title compound showing the atom-numbering system used in the analysis. The dotted line represents atoms within hydrogen-bonding distance. The thermal ellipsoids are drawn to include 50% probability (E. K. Davies, SNOOPI program for drawing crystal structures, University of Oxford, 1983)

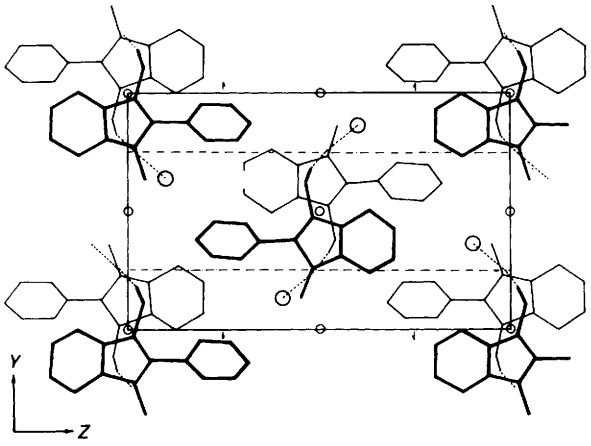

Figure 2. The molecular packing viewed along the *a* axis. Dotted lines represent atoms within hydrogen-bonding distance.

unit weights and omitted eleven low-angle weak reflections which were found to be over-estimated. The final *R*-factors were $R = \Sigma|\Delta F|/\Sigma|F_o| = 0.076$ and $R_w = [\Sigma|F|^2/\Sigma|F_o|^2]^{\frac{1}{2}} = 0.074$. Scattering factors for neutral atoms were used in all cases except Cl, for which that of the chloride anion was used.[6]

All computations were made using SHELX-76,[7] on a DEC VAX-11/750 computer.

Table 6. Least-squares planes given in the form $lX' + mY' + nZ' = d$ where X', Y', and Z' are co-ordinates in Å; deviations (Å) of atoms from the planes are also given.

Plane 1: methylimidazo[1,2-*a*]pyridinium ring system

$0.9940X + 0.0548Y - 0.0945Z = 0.3239$

Ring atoms

N(1) −0.030, C(3) −0.006, C(4) 0.020, C(5) 0.016, C(6) −0.015, C(7) −0.020, N(2) 0.012, C(9) 0.020

Other atoms

C(8) −0.052, C(10) 0.062, C(2) 0.013, O(1) −1.281

Plane 2: phenyl ring

$0.6673X - 0.7447Y - 0.0112Z = -0.0430$

Ring atoms

C(10) 0.004, C(11) −0.003, C(12) −0.001, C(13) 0.004, C(14) −0.003, C(15) 0.001

Other atoms

C(9) 0.080, O(1) 1.721

Results and Discussion

Table 1 lists the fractional atomic co-ordinates. The atomic numbering system is given in Figure 1, and Tables 2 and 3 list the bonded distances and interbond angles. A selection of intermolecular non-bonded distances is given in Table 4.

Bond lengths and angles are close to those found in the comparable compound 1,1′-azo-2-phenylimidazo[1,2-*a*]pyridinium dibromide,[8] with C(3)–C(4) and C(5)–C(6) significantly short, representing double bonds in both the major contributing canonical forms of an imidazo[1,2-*a*]pyridinium ring system. Conformationally the molecule can resemble acetylcholine and comparisons of the torsion angle and $N^+ \cdots O$ distance between the present structure and several salts of acetylcholine show close agreement (Table 5). The atoms of the methylimidazo[1,2-*a*]pyridinium ring system and of the phenyl ring lie close to their least-squares mean planes (Table 6). The oxygen atom is remote from both planes.

The molecular packing is shown in Figure 2. The molecules lie in layers very close to the [400] planes with the imidazo[1,2-*a*]pyridinium ring least-squares planes deviating by only 6.3°. The phenyl ring mean plane deviates by 51.4° from coplanarity with the heterocycle (sign convention as defined by Klyne and Prelog[9]). Although the oxygen atoms lie outside these planes, there is no evidence of any O–H ··· N hydrogen bonds between the layers and, surprisingly for a salt, there are no short ion–dipole interactions to hold the layers together.

The hydroxy group and the chloride ion are sufficiently close [H(1) ··· Cl is 2.14(4) and O–H(1) ··· Cl is 3.043(9) Å] to form a hydrogen bond. The latter distance represents a contraction of 0.16 Å on the sum of their covalent radii. Such a contraction may be taken as evidence[10] for a hydrogen bond, and closely parallels the results reported[11] by us for the structure of diammonium 2-oxopropane-1,3-disulphonate. The

atoms involved are not collinear, and the bond angle O–H • • • Cl is close to 149° (Figure 2). Very similar results are reported for hydroxylamine hydrochloride,[12] notably the non-linear bond angle.

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