Crystal and Molecular Structure of Adiphenine Hydrochloride, a Muscarinic Antagonist of Acetylcholine

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The crystal and molecular structure of the title compound has been determined by single-crystal *X*-ray analysis from three-dimensional counter data. Crystals are monoclinic, space group $P2_1/c$, with $Z = 4$ in a cell of dimensions $a = 15{\cdot}79, b = 7{\cdot}28, c = 17{\cdot}34$ Å (all ±0·01 Å), and $\beta = 108{\cdot}3° \pm 0{\cdot}05°$. The structure was established by Fourier and least-squares methods and the final R is 6·3% for 2580 structure amplitudes. The molecular geometry is compared with those of certain related anticholinergic and cholinergic molecules. A possible model for the blocking action of adiphenine and related anticholinergic agents is suggested.

CERTAIN esters of amino-alcohols, closely related to acetylcholine (I), act as atropine-like antagonists of acetylcholine at the parasympathetic post-ganglionic (muscarinic) receptor.[1] In general, these antagonists differ from acetylcholine in possessing larger substituents in the acyl group and on the nitrogen atom. 2-Diethylaminoethyl diphenylacetate hydrochloride (II) (adiphenine hydrochloride),[2] though not as potent as atropine in its anticholinergic activity, has found clinical applications as an antispasmodic,† since doses which

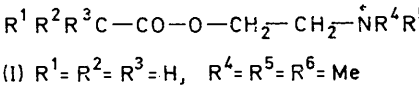
† The antispasmodic action of adiphenine stems also from a direct papaverine-like relaxant action on smooth muscle.

[1] D. J. Triggle, ' Chemical Aspects of the Autonomic Nervous System,' Academic Press, New York, **1965**.

[2] R. Meier, *Klin. Wochschr.*, **1936**, **15**, 1403.

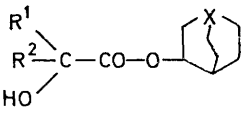
affect the intestine have little action on the eye, heart, or salivary glands.[3]

This antagonism to acetylcholine is competitive in nature [1,4] but it is not clear whether the anticholinergic agents interact with the same receptor area as acetylcholine. Recent theories of receptor–ligand interaction have included suggestions that antagonists interact mainly with neighbouring accessory receptor areas,[5] or that antagonists interact at sites topographically distinct from those involved in agonist binding, and that even for agonists a number of distinct but overlapping binding sites are involved.[6] However, correlation of structural features observed in the crystal structures of the anticholinergic agents quinuclidinyl benzilate hydrobromide (III),[7] atropine hydrobromide,[8]

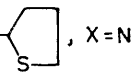


(I) $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = R^6 = Me$

(II) $R^1 = R^2 = Ph$, $R^3 = R^4 = H$, $R^5 = R^6 = Et$



(III) $R^1 = R^2 = Ph$, $X = \overset{+}{N}-H$

(IV) $R^1 = R^2 =$  , $X = N$

and (−)-(*S*)-hyoscine hydrobromide [9] with the structure of acetylcholine in the conformation suggested [10] as relevant to interaction with the muscarinic receptor, led Pauling and Petcher [8] to suggest that both atropine and acetylcholine interact with the receptor in similar ways and at the same site. Structural information for antagonists such as adiphenine hydrochloride which are closely related to acetylcholine itself, should be of value in obtaining a fuller understanding of structure-activity relationships both for antagonists and agonists.

EXPERIMENTAL

Crystallographic Measurements.—Adiphenine hydrochloride (K and K Laboratories), was recrystallised from benzene as rod-like crystals. Approximate cell dimensions were determined from oscillation and Weissenberg photographs. The final cell dimensions and intensity data were measured with a Stoe two-circle computer-controlled diffractometer by use of graphite monochromated Mo-K_α radiation and a scintillation counter. The crystal used had dimensions 0·1 × 0·5 × 0·1 mm and was set up about the needle axis (*b*). From 4222 reflections scanned within the range of $\sin\theta/\lambda \leqslant 0{\cdot}65$, 2580, for which $I > 3\sigma(I)$, were considered to be observed and were used in the structure analysis. The ω scan mode was employed, and for each reflection, 120 counts of 1 s at intervals of 0·01° were taken. For reflections on the 3rd and higher layer-lines for which $2\theta' < 18°$, a variable scan-range technique was employed, $\Delta\omega$ being calculated by the expression $A + B \sin\mu/\tan\theta'$, with $A = 0{\cdot}9$ and $B = 0{\cdot}5$. Backgrounds were measured for 25 s at each end of the scan. In the conversion of intensities to structure amplitudes, the polarisation factor appropriate to monochromated radiation was used. Absorption corrections were not applied.

Crystal Data.—$C_{20}H_{25}NO_2,HCl$, $M = 347{\cdot}9$. Monoclinic, $a = 15{\cdot}79 \pm 0{\cdot}01$, $b = 7{\cdot}28 \pm 0{\cdot}01$, $c = 17{\cdot}34 \pm 0{\cdot}01$ Å, $\beta = 108{\cdot}3 \pm 0{\cdot}05°$, $U = 1892{\cdot}1$ Å^3, $D_m = 1{\cdot}228$, $Z = 4$, $D_c = 1{\cdot}221$, $F(000) = 744$. Systematic absences: $h0l$ when l is odd, $0k0$ when k is odd, space group $P2_1/c$ (C_{2h}^5). Mo-K_α radiation, $\lambda = 0{\cdot}71069$ Å; μ(Mo-K_α) = 2·2 cm^{-1}.

Structure Analysis.—The co-ordinates of the chloride ion were obtained from the three-dimensional Patterson synthesis. Structure factors were calculated (R 57%) and the phase angles were then used with the observed amplitudes to evaluate a three-dimensional electron-density distribution, from which the positions of all atoms in the asymmetric unit (except for hydrogen atoms) could be determined.

Refinement of atomic parameters was carried out by the method of least-squares. Initially, positional and isotropic thermal parameters were adjusted and R was reduced to 13·5%. Finally, the atoms were allowed to vibrate anisotropically and the refinement was terminated when the calculated shifts in the parameters were all $< 0{\cdot}1\ \sigma$. Hydrogen atoms were located from a Fourier difference synthesis and were included in the calculations in their theoretical positions [assuming C(sp^3)–H 1·10, C(sp^2)–H 1·08, and N–H 1·04 Å], but their parameters were not refined. The final value of R is 6·3% for the 2580 observed structure amplitudes.*

The weighting scheme used in the final cycles of refinement was: $w^{\frac{1}{2}} = 1{\cdot}0$ if $|F_o| \leqslant 17{\cdot}5$ and $w^{\frac{1}{2}} = 17{\cdot}5/|F_o|$ if $|F_o| > 17{\cdot}5$, chosen so as to give approximately constant values for the average of $\Sigma w(|F_o| - |F_c|)^2$ when taken in groups of increasing $|F_o|$ and increasing $\sin\theta/\lambda$. Two reflections, $20\bar{4}$ and $40\bar{2}$ which seemed to be affected by extinction, were assigned zero weight. Atomic scattering factors were taken from ref. 11, except for hydrogen atoms, for which those of ref. 12 were used.

Computations were performed on the Birmingham University KDF 9 computer and we thank the staff of the Computer Centre for their assistance. Local versions of FORDAP, the Zalkin Fourier program, and ORFLS and ORFFE the Busing, Martin, and Levy full-matrix least-squares and function-and-error programs were employed;

* Observed and calculated structure factors are published in Supplementary Publication No. 20661 (18 pp., 1 microfiche). See Notice to Authors No. 7, in *J.C.S. Dalton*, 1972, Index issue.

[3] U. Salow, *Klin. Wochschr.*, 1936, **15**, 1405; H. Rakatansky and J. B. Kirsner in 'Drugs of Choice, 1972—1973,' ed. W. Modell, Mosby, St. Louis, 1972.
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[5] E. J. Ariens and A. M. Simonis, *Ann. N.Y. Acad. Sci.*, 1967, **144**, 842.
[6] J. F. Moran and D. J. Triggle, in 'Cholinergic Ligand Interactions,' eds. D. J. Triggle, J. F. Moran, and E. A. Barnard, Academic Press, New York, 1971.
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[11] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.
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RESULTS AND DISCUSSION

The stereochemistry of adiphenine is illustrated in Figure 1, which shows a view of the cation as seen along the *b* axis of the unit cell and also the atomic numbering scheme used. The final atomic co-ordinates are in Table 1 and the thermal parameters in Table 2. Molecular dimensions calculated from the parameters in Table 1 are in Table 3. Standard deviations are 0·004—0·008 Å for lengths, *ca.* 0·3° for bond angles, and *ca.* 0·5° for torsion angles.

TABLE 1

Atomic co-ordinates (× 10⁴) with estimated standard deviations in parentheses. Hydrogen atom co-ordinates derived from the known positions of the heavier atoms

	x/a	*y/b*	*z/c*
C(1)	−3091(2)	3303(6)	1030(2)
C(2)	−2978(3)	2838(6)	296(3)
C(3)	−3323(3)	3954(8)	−389(3)
C(4)	−3767(3)	5541(8)	−335(3)
C(5)	−3872(3)	6041(7)	402(3)
C(6)	−3535(3)	4928(6)	1084(3)
C(7)	−3520(3)	690(6)	1823(2)
C(8)	−3312(3)	−668(6)	2420(2)
C(9)	−3962(4)	−1841(7)	2515(3)
C(10)	−4832(4)	−1690(8)	2028(3)
C(11)	−5056(3)	−350(8)	1418(4)
C(12)	−4393(3)	836(7)	1318(3)
C(13)	−2774(2)	1956(6)	1737(2)
C(14)	−2349(3)	2887(6)	2556(2)
C(15)	−1082(2)	2918(6)	3731(2)
C(16)	−266(2)	1781(6)	4147(2)
C(17)	520(3)	1686(6)	3102(2)
C(18)	1241(3)	2533(7)	2816(3)
C(19)	1386(2)	1563(6)	4578(2)
C(20)	1598(3)	2571(7)	5386(2)
N	561(2)	2328(4)	3944(2)
O(1)	−1520(2)	2235(4)	2917(2)
O(2)	−2691(2)	3991(6)	2873(2)
Cl	626(1)	6582(1)	4021(1)
H[C(2)]	−2622	1580	256
H[C(3)]	−3231	3518	−978
H[C(4)]	−4026	6431	−873
H[C(5)]	−4229	7300	429
H[C(6)]	−3636	5318	1678
H[C(8)]	−2616	−816	2820
H[C(9)]	−3788	−2893	2988
H[C(10)]	−5342	−2616	2114
H[C(11)]	−5761	−228	1021
H[C(12)]	−4571	1890	826
H[C(13)]	−2243	1082	1644
H¹[C(15)]	−886	4369	3720
H²[C(15)]	−1561	2844	4096
H¹[C(16)]	−413	326	3977
H²[C(16)]	−117	1880	4824
H¹[C(17)]	−146	2018	2653
H²[C(17)]	595	164	3103
H¹[C(18)]	1100	2500	2200
H²[C(18)]	1900	2300	3200
H³[C(18)]	1300	3800	3000
H¹[C(19)]	1977	1662	4352
H²[C(19)]	1289	79	4683
H¹[C(20)]	1100	2300	5600
H²[C(20)]	2200	2000	5800
H³[C(20)]	1800	3700	5200
H[N]	592	3770	3960

The most obvious structural difference between adiphenine and acetylcholine is in the two phenyl substituents on C(13) in adiphenine. Ring substituents at similar sites relative to the ester group, are present in atropine, hyoscine, the quinuclidinyl derivative (III), and the related cholinergic antagonist quinuclidinyl di-α-α′-thienylglycollate (IV), whose crystal structure has also been determined,[13] and in certain other synthetic anticholinergic agents. A comparison of the orientations of the rings in these structures indicates certain common features. In the crystal structure of atropine hydrobromide the phenyl ring makes an angle

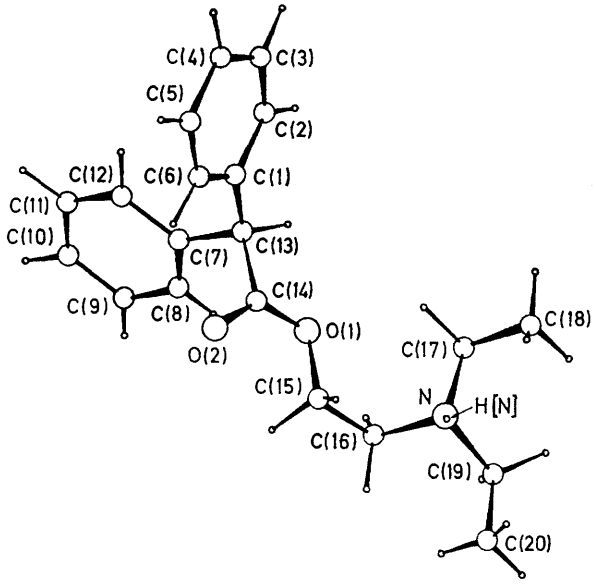

FIGURE 1 Drawing of the adiphenine cation as viewed along the *b* axis (the positive direction of the *b* axis is towards the viewer, *a* and *c* axes as in Figure 2)

TABLE 2

Anisotropic thermal parameters (× 10⁴) for the heavier atoms

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	267	517	382	−2	38	−14
C(2)	390	580	460	−20	84	−38
C(3)	450	804	432	−77	68	−6
C(4)	462	781	547	−41	44	173
C(5)	575	618	702	114	113	95
C(6)	490	513	502	93	106	19
C(7)	387	480	375	45	72	−69
C(8)	534	579	361	46	100	−15
C(9)	730	575	546	−33	240	−19
C(10)	643	649	711	−152	265	−102
C(11)	406	687	822	−74	82	−110
C(12)	439	526	606	14	35	5
C(13)	300	492	370	51	12	−61
C(14)	374	478	380	46	72	−19
C(15)	321	566	334	12	21	−93
C(16)	341	489	331	−22	50	56
C(17)	431	489	306	−73	81	−84
C(18)	502	672	371	−105	159	−11
C(19)	367	531	351	80	−11	4
C(20)	450	673	376	29	−7	10
N	281	363	271	15	26	1
O(1)	314	600	376	49	28	−71
O(2)	614	895	553	323	−44	−293
Cl	471	388	395	48	115	22

Temperature factors are in the form:
$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{12}hka^*b^* + \ldots)]$.

[13] A. Meyerhöffer, *Acta Cryst.*, 1970, *B*, **26**, 341.

TABLE 3

Molecular dimensions

(*a*) Bonded distances (Å) with standard deviations ($\times 10^3$) in parentheses

C(1)–C(2)	1·381(6)	C(1)–C(13)	1·527(6)
C(2)–C(3)	1·400(6)	C(7)–C(13)	1·539(6)
C(3)–C(4)	1·370(8)	C(13)–C(14)	1·525(5)
C(4)–C(5)	1·387(8)	C(14)–O(1)	1·347(5)
C(5)–C(6)	1·394(7)	C(14)–O(2)	1·194(5)
C(6)–C(1)	1·393(6)	C(15)–O(1)	1·451(4)
C(7)–C(8)	1·394(6)	C(15)–C(16)	1·511(5)
C(8)–C(9)	1·384(7)	C(17)–C(18)	1·508(6)
C(9)–C(10)	1·372(7)	C(19)–C(20)	1·522(6)
C(10)–C(11)	1·400(8)	C(16)–N	1·509(5)
C(11)–C(12)	1·408(7)	C(17)–N	1·514(5)
C(12)–C(7)	1·386(6)	C(19)–N	1·522(5)

(*b*) Bond angles (deg.); mean standard deviation 0·3°

C(6)–C(1)–C(2)	118·9	C(2)–C(1)–C(13)	118·5
C(1)–C(2)–C(3)	120·7	C(6)–C(1)–C(13)	122·4
C(2)–C(3)–C(4)	120·1	C(8)–C(7)–C(13)	119·2
C(3)–C(4)–C(5)	119·7	C(12)–C(7)–C(13)	122·2
C(4)–C(5)–C(6)	120·3	C(13)–C(14)–O(1)	110·8
C(5)–C(6)–C(1)	120·1	C(13)–C(14)–O(2)	126·7
C(12)–C(7)–C(8)	118·6	O(1)–C(14)–O(2)	122·5
C(7)–C(8)–C(9)	121·0	C(14)–O(1)–C(15)	115·4
C(8)–C(9)–C(10)	120·9	O(1)–C(15)–C(16)	110·6
C(9)–C(10)–C(11)	119·2	C(15)–C(16)–N	114·5
C(10)–C(11)–C(12)	119·9	C(16)–N–C(17)	111·5
C(11)–C(12)–C(7)	120·3	C(16)–N–C(19)	110·0
C(1)–C(13)–C(14)	113·5	C(17)–N–C(19)	110·6
C(7)–C(13)–C(14)	107·6	N–C(17)–C(18)	112·5
C(1)–C(13)–C(7)	113·2	N–C(19)–C(20)	112·3

(*c*) Torsion angles (deg.);* mean standard deviation for angles not involving hydrogen 0·5°.

C(2)–C(1)–C(13)–C(14)	141·4
C(6)–C(1)–C(13)–C(14)	−42·5
C(8)–C(7)–C(13)–C(14)	−56·8
C(12)–C(7)–C(13)–C(14)	124·1
C(2)–C(1)–C(13)–C(7)	−95·5
C(6)–C(1)–C(13)–C(7)	80·6
C(8)–C(7)–C(13)–C(1)	176·9
C(12)–C(7)–C(13)–C(1)	−2·2
C(1)–C(13)–C(14)–O(1)	−124·3
C(1)–C(13)–C(14)–O(2)	58·7
C(7)–C(13)–C(14)–O(1)	109·5
C(7)–C(13)–C(14)–O(2)	−67·4
C(13)–C(14)–O(1)–C(15)	−175·1
O(2)–C(14)–O(1)–C(15)	2·0
C(14)–O(1)–C(15)–C(16)	166·6
O(1)–C(15)–C(16)–N	83·3
C(15)–C(16)–N–C(17)	−75·3
C(15)–C(16)–N–C(19)	161·7
C(16)–N–C(17)–C(18)	168·3
C(16)–N–C(19)–C(20)	−72·5
C(20)–C(19)–N–C(17)	163·9
C(18)–C(17)–N–C(19)	−69·0
H¹[C(18)]–C(18)–C(17)–N	−159
H²[C(18)]–C(18)–C(17)–N	57
H³[C(18)]–C(18)–C(17)–N	−39
H¹[C(20)]–C(20)–C(19)–N	66
H²[C(20)]–C(20)–C(19)–N	−178
H³[C(20)]–C(20)–C(19)–N	−71

* Sign convention as defined by W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

of 86° with the plane of the ester group and in the (−)-(*S*)-hyoscine structure the corresponding angle is 89°.[8] In the crystal structure of (III) the two phenyl rings make angles † of 107 and 106° with the ester group and in (IV) the angles between the thiophen rings and the ester group are 93 and 119°. In adiphenine hydrochloride the angles are 44 and 89° for rings C(1), C(2)—(6) and C(7), C(8)—(12), respectively (Table 4). Each of these molecules thus has at least one ring substituent nearly perpendicular to the plane of the ester group. The inter-ring angles in the structures (III) and (IV) and in adiphenine are also similar (102, 96, and 98°). However, the orientation of the rings in these structures differ with respect to the atomic arrangement of the ester group. If these orientations are described in terms of the angle between the C=O bond direction and the projection of the ring normal on the plane of the ester group, and considering the ring which is most nearly perpendicular to the ester group, then in adiphenine this angle is 16° while in (IV) the angle is 83°. Examination of the published[8,9] drawings of the atropine and hyoscine cations indicates that in these structures the angle is also close to 90°. The corresponding angle for the other ring substituent in adiphenine is 87°, while in (IV) it is 0·5°. In the crystal structure of (III) the two phenyl rings are oriented approximately symmetrically with respect to the C=O bond direction, at angles of 55 and −43°.

† Angles here and in the Discussion which follows are calculated from co-ordinates given in ref. 7 [for (III)] and 13 [for (IV)].

TABLE 4

(i) Equations of least-squares planes in the form $lx + my + nz = p$ where x, y, and z are fractional co-ordinates relative to the cell axes. Deviations (Å) of atoms from least-square planes are given in square brackets.

Plane (*a*): C(1)—(6) $-13{\cdot}096x - 3{\cdot}660y + 0{\cdot}508z = 2{\cdot}884$

[C(1) −0·007, C(2) 0·007, C(3) −0·001, C(4) −0·004, C(5) 0·004, C(6) 0·002, C(13) −0·121]

Plane (*b*): C(7)—(12) $-6{\cdot}521x + 4{\cdot}694y + 12{\cdot}837z = 4{\cdot}954$

[C(7) −0·006, C(8) 0·000, C(9) 0·006, C(10) −0·007, C(11) 0·001, C(12) 0·005, C(13) −0·003]

Plane (*c*): C(13)—(15), O(1), O(2) $-8{\cdot}592x - 5{\cdot}291y + 9{\cdot}861z = 3{\cdot}034$

[C(13) −0·028, C(14) 0·023, C(15) −0·031, O(1) 0·034, O(2) 0·001, C(16) −0·342]

(ii) Dihedral angles (deg.)

(*a*)–(*b*)	97·9
(*b*)–(*c*)	88·5
(*a*)–(*c*)	44·4

The underlying reason for this difference in the orientation of the ring substituents in adiphenine hydrochloride is to be found in the conformation about the C(13)–C(14) bond. The ring atoms C(1) and C(7) are respectively plus and minus *synclinal* to the carbonyl oxygen atom, O(2), with hydrogen atom, H[C(13)], *antiplanar* to it [torsion angle H–C(13)–C(14)–O(2) 178°]. In the crystal structures of (III) and (IV), however, the ring atom substituents are plus and minus *anticlinal* and the hydroxylic oxygen atom *synplanar* to the carbonyl oxygen atom [torsion angle HO–C–C=O −7 in (III) and 15° in (IV)]. The conformation about the corresponding bond in acetylcholine is believed to be such that one of the hydrogen atoms of the acetoxy methyl group is *synplanar* to the carbonyl oxygen atom.[10]

The bond lengths, C(1)–C(13) (1·53), C(7)–C(13) (1·54), and C(14)–C(13) (1·53 Å) are significantly longer

than the accepted [14] value for the C(sp^2)–C(sp^3) single-bond length (1·505 Å) and this may be indicative of repulsive forces involving the phenyl rings and the ester group. A significant distortion of the valency angles at C(13) is also indicative of this. Short contact distances C(1) · · · C(12) and O(2) · · · C(6) (2·89 and 3·04 Å) occur. C–H · · · O hydrogen bonding does not appear to be involved in the latter contact since the pertinent hydrogen atom, H[C(6)], in its calculated position, does not lie close to the C(6) · · · O(2) line [angle H–C(6) · · · O(2) 43°] and the H · · · O(2) distance (2·35 Å) is greater than those observed in cases where C–H · · · O hydrogen bonding has been postulated (2·07—2·27 Å).[15]

The ester group C(13), C(14), O(1), C(15), O(2) is planar to within 0·03 Å (Table 4) and adopts the *antiplanar* conformation [torsion angle C(13)–C(14)–O(1)–C(15) —175°], typical of esters. This conformation is also adopted by the ester groups in the crystal structures of all acetylcholine derivatives listed by Shefter [16] and Baker *et al.*,[10] in surveys of the structures of cholinergic molecules. Bond lengths and angles also agree with those generally found in esters. The C(14)–O(1) length (1·35 Å) indicates some double-bond character for this bond, while C(15)–O(1) (1·45 Å) is close to the accepted [14] value for the C(sp^3)–O single bond length. These values may be compared with those (1·36 and 1·46 Å) quoted by Mathieson and Welsh [17] as being typical for these bonds in esters and with mean lengths of 1·33 and 1·43 Å for the equivalent bonds in cholinergic molecules.[16] The C(14)–O(2) length (1·19 Å) is also in good agreement with the value quoted by Mathieson and Welsh (1·21 Å), and with that (1·18 Å) observed [18] in the crystal structure of acetylcholine chloride. The pattern of bond-angle variation at C(14) follows the trend normally found in esters, as does the large (115·4°) angle at O(1). The conformation about the O(1)–C(15) bond is *antiplanar* [torsion angle C(14)–O(1)–C(15)–C(16) 167°], the generally preferred [19] conformation of primary esters, and also the conformation adopted by acetylcholine chloride in the solid state [18] and in D_2O solution.[20] In the crystal structure of acetylcholine bromide,[21] however, the arrangement is *synclinal*, as is the arrangement about the corresponding bonds in (III) and (IV).

The torsion angle O(1)–C(15)–C(16)–N^+ is 83°, very similar to the corresponding angles in acetylcholine chloride and bromide (85 and 77°). A similar conformation is observed in the crystal structures of most cholinergic agents containing the O–C–C–N^+ grouping.[10,16,20] However, in the quinuclidinyl derivatives (III) and (IV), because of the geometry of the rigid quinuclidine ring system, the torsion angles are constrained to be close to 120°. The arrangement about the C(16)–N^+ bond is normal, such that the substituents on the nitrogen atom are staggered relative to the C(16) substituents, with torsion angles C(15)–C(16)–N^+–C(19) 162° and C(15)–C(16)–N^+–H 44°. The mean C–N^+ bond length is 1·515 Å, considerably longer than the accepted [14] value for the C(sp^3)–N^+ single bond (1·48 Å). They are, however, in good agreement with the lengths of the C–N^+ bonds in acetylcholine chloride and with the lengths of similar bonds in alkaloid structures.[22] In this context, it is of interest that in the cationic species (III) the C–N bond mean is 1·51 Å whereas in the neutral molecule (IV) it is 1·47 Å.

Bond angles are generally normal, except C(15)–C(16)–N^+, 114·5°, which is significantly greater than the angles commonly found at sp^3-hybridised carbon atoms. Large values for this angle have also been observed in the crystal structures of acetylcholine bromide and chloride. The effect of this is to increase slightly intramolecular contact distances between the cationic head and the remainder of the molecule. The close contact C(17) · · · O(1) of 3·16 Å is very similar to the corresponding distance in acetylcholine chloride (3·17 Å). The distance H^1[C(17)] · · · O(1) is *ca.* 2·36 Å and angle H^1[C(17)]–C(17) · · · O(1) *ca.* 37° so that C–H · · · O hydrogen bonding is probably not involved.

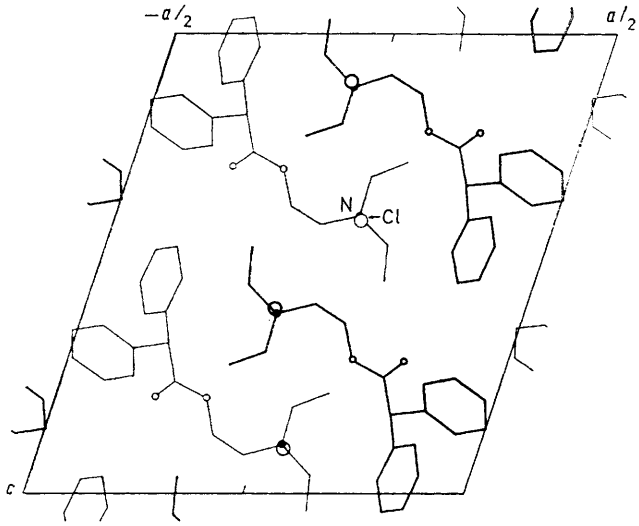

FIGURE 2 The crystal structure as viewed along the *b* axis

The crystal structure is illustrated in Figure 2 and shorter intermolecular distances are listed in Table 5. Adiphenine cations stacked along the *b* axis are interleaved with chloride ions which are separated by the *b* unit-cell translation (7·28 Å). The N^+ · · · Cl^- vectors

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are very nearly parallel to the *b* axis with angle $Cl \cdots N^+ \cdots Cl^{IV}$ 175·5° and distances $N^+ \cdots Cl^{IV}$ 4·18 and $N^+ \cdots Cl$ 3·10 Å. The shorter distance implies a strong hydrogen bond and hydrogen atom H[N], in its calculated position, is in fact close to the $N^+ \cdots Cl$ line (angle $H\text{–}N^+ \cdots Cl$ 1·4°). All other intermolecular contact distances correspond to normal van der Waals interactions.

Perhaps the most striking result to emerge from this analysis is the close similarity of the acetylcholine-like moiety of adiphenine hydrochloride to the conformation postulated [10] for acetylcholine as being relevant to muscarinic activity and to interaction with the receptor. For the four torsion angles which define the conformation of acetylcholine, which in our system are C(13)–C(14)–O(1)–C(15), C(14)–O(1)–C(15)–C(16), O(1)–C(15)–C(16)–N^+, and C(15)–C(16)–N^+–C(19), values of 180, 150, 85, and 180° were suggested, and for the non-bonded distances $N^+ \cdots O(1)$, $N^+ \cdots C(14)$, and $N^+ \cdots C(13)$, 3·2, 4·5, and 5·4 Å.[10] The conformation adopted by adiphenine hydrochloride is such that the corresponding torsion angles are −175, 167, 83, and 162° and the distances, 3·21, 4·49, and 5·46 Å. The conformations of the acetylcholine-like moieties of the quinuclidinyl anticholinergics (III) and (IV) are somewhat different from that of adiphenine hydrochloride (see earlier), yet the corresponding non-bonded distances are also quite similar [3·55, 4·37, and 5·66 in (III), and 3·45, 4·42, and 5·60 Å in (IV) (calc. from refs. 7 and 13)].

TABLE 5

Shorter intermolecular contacts (Å) excluding hydrogen atoms

$N \cdots Cl$	3·10	$C(9) \cdots C(6^{IV})$	3·63
$C(17) \cdots Cl^{I}$	3·56	$C(4) \cdots C(19^{III})$	3·65
$C(16) \cdots Cl^{II}$	3·60	$C(2) \cdots C(19^{III})$	3·66
$C(2) \cdots Cl^{I}$	3·64	$C(18) \cdots C(8^{III})$	3·66
$C(18) \cdots Cl^{I}$	3·66	$C(3) \cdots C(11^{V})$	3·71
$C(15) \cdots Cl$	3·71	$C(18) \cdots O(1^{III})$	3·73
$C(15) \cdots Cl^{II}$	3·75	$C(3) \cdots C(10^{V})$	3·75
$C(20) \cdots Cl$	3·77	$C(4) \cdots C(20^{III})$	3·76
$C(16) \cdots Cl$	3·80	$C(11) \cdots C(9^{VI})$	3·76
$C(3) \cdots C(19^{III})$	3·50	$C(4) \cdots C(9^{VII})$	3·76
$C(9) \cdots O(2^{IV})$	3·58	$C(3) \cdots C(20^{III})$	3·79

Superscripts refer to the following equivalent positions:

I $-x, -\frac{1}{2}+y, \frac{1}{2}-z$	V $-1-x, -y, -z$
II $-x, 1-y, 1-z$	VI $-1-x, \frac{1}{2}+y, \frac{1}{2}-z$
III $-x, \frac{1}{2}+y, \frac{1}{2}-z$	VII $x, \frac{1}{2}-y, -\frac{1}{2}+z$
IV $x, -1+y, z$	

The extent to which results obtained in the solid state or in solution can be extrapolated to predict the conformation of flexible molecules interacting with receptors in biological systems is open to question (*cf.* ref. 23). Nevertheless, our results are consistent with the view [5] that anticholinergic agents compete with acetylcholine for the same receptors but that the critical interaction is mainly between the terminal substituents and neighbouring accessory receptor areas. The effect of this interaction with the accessory receptor areas is then believed to be transmitted in some way to the part of the receptor area relevant to cholinergic stimulation, causing some change in its properties which prevents it from interacting with acetylcholine.[5]

An alternative mechanism, which follows naturally from the structural results, is that the stereochemistry of the interaction of the terminal groups of the anticholinergic agent with the accessory receptor areas is such that the acetylcholine-like moiety straddles the receptor area proper, but that the whole, or a critical part of it is prevented from coming into sufficiently close proximity for stimulatory interaction to occur. In this way the anticholinergic agent occupies the cholinergic receptor site but interacts with it in a non-functional manner.

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