Stereochemistry of Anticholinergic Agents. Part VI.[1] Crystal and Molecular Structure of Hexasonium Iodide

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Hexasonium iodide {2-[cyclohexyl(phenyl)acetoxy]ethyldimethylsulphonium iodide} crystallises in the monoclinic space group $P2_1/c$ with $a = 16{\cdot}04(2)$, $b = 11{\cdot}36(1)$, $c = 11{\cdot}12(1)$ Å, $\beta = 92{\cdot}58(5)°$, and $Z = 4$. The structure was established by the heavy-atom method from three-dimensional *X*-ray counter data and refined by least-squares to *R* 6·3% for 2443 observed structure amplitudes. The cyclohexyl ring is in the chair conformation with the acetoxy-group in the equatorial orientation. In the C(:O)·O·C·C·S$^+$ chain the C(:O)·O·C·C grouping is (−)-*synclinal* and the O·C·C·S$^+$ grouping (+)-*synclinal*. The cyclohexyl and phenyl rings are oriented (+)- and (−)-*anticlinal* with respect to the ester oxygen atom. The overall shape of the cation resembles in some respects that of atropine and also that of a number of potent synthetic anticholinergic agents related structurally to acetylcholine. Mean σ for bond lengths, bond angles and torsion angles: 0·018 Å, 1·0, and 1·5°.

HEXASONIUM IODIDE {2-[cyclohexyl(phenyl)acetoxy]-ethyldimethylsulphonium iodide} is a synthetic anticholinergic drug,[2] differing from a number of other anticholinergic drugs structurally related to acetylcholine whose solid-state structures have been described,[3,4] in that it contains a sulphonium group in place of the nitrogen-containing cationic head. The activity of hexasonium is extremely high in inhibiting acetylcholine-induced spasms of isolated guinea-pig intestine, and is similar to that of atropine in *in vivo* tests on rabbits.[5] It also has a papaverine-like effect in inhibiting spasms induced by barium ions. We now report the crystal structure analysis of hexasonium iodide as part of our programme of studies of the stereochemistry of competitive antagonists of acetylcholine at the parasympathetic post-ganglionic (muscarinic) receptor.

EXPERIMENTAL

Crystallographic Measurements.—Cell dimensions were measured initially from oscillation and Weissenberg photographs, final cell dimensions being measured with a Stoe two-circle computer-controlled diffractometer by use of graphite monochromated Mo-K_α radiation and a scintillation counter. Three-dimensional counter data were collected with a crystal of dimensions 0·65 × 0·50 × 0·15 mm set about the unique (*b*) axis. Of the 3465 reflections scanned within the range $0{\cdot}08 \leqslant \sin\theta/\lambda \leqslant 0{\cdot}60$, 2443, having $I > 2{\cdot}5\sigma(I)$, were considered observed and were used in the structure analysis. The ω-scan technique was employed, backgrounds being measured for 30s at each end of the scan, with 140 counts of 1s at intervals of 0·01° defining the peak. For reflections on the fifth and higher layers, a variable-scan technique was used,[1] designed to increase the scan range at low values of the azimuth angle and high values of the equi-inclination angle. A yellowing of the crystal during data collection did not seem to affect the intensities of the 4 standard reflections on the zero layer which were monitored at the end of each layer. In the conversion of intensities to structure amplitudes, the polarisation factor appropriate to monochromated radiation was used, but absorption corrections were not applied.

[1] Part V, J. J. Guy and T. A. Hamor, *Acta Cryst.*, 1974, **B30**, 2277.
[2] M. Protiva and O. Exner, *Coll. Czech. Chem. Comm.*, 1954, **19**, 524.
[3] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1974, 1126, and refs. therein.
[4] A. Meyerhöffer, *FOA Reports*, 1972, **6**, 1, and refs. therein.
[5] M. Protiva and E. Adlerova, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1066; Z. Votava and J. Sramkova, *Cesk. farm.*, 1954, **3**, 238.

Crystal Data.—$C_{18}H_{27}IO_2S$, $M = 434{\cdot}4$. Monoclinic, $a = 16{\cdot}04 \pm 0{\cdot}02$, $b = 11{\cdot}36 \pm 0{\cdot}01$, $c = 11{\cdot}12 \pm 0{\cdot}01$ Å, $\beta = 92{\cdot}58 \pm 0{\cdot}05°$. $U = 2022{\cdot}8$, $Z = 4$, $D_c = 1{\cdot}426$, $F(000) = 880$. 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) = 17·1 cm^{-1}.

Structure Analysis.—The co-ordinates of the iodide ion were obtained from a three-dimensional Patterson synthesis, and structure factors calculated. The observed structure amplitudes were used with the calculated phase angles to evaluate a three-dimensional electron-density distribution from which the positions of all non-hydrogen atoms, except those of the two cyclic systems, were found. Least-squares refinement of these parameters with isotropic thermal parameters reduced R to 19% and a second electron-density distribution revealed the co-ordinates of all non-hydrogen atoms. Further least-squares refinement of positional and isotropic thermal parameters reduced R to 11% when the atoms were allowed to vibrate anisotropically. A Fourier difference synthesis was used to locate the hydrogen atoms which were included in the parameter list in their calculated positions [assuming C(sp^3)–H 1·10 and C(sp^2)–H 1·08 Å] but their parameters were not refined. Refinement was terminated when all shifts were $<0{\cdot}1\sigma$, and R 6·3% for the 2443 independent reflections.

The weighting scheme used in the final cycles of refinement was $w^{\frac{1}{2}} = 1{\cdot}0$ if $|F_o| \leqslant 38{\cdot}0$ and $w^{\frac{1}{2}} = 38{\cdot}0/|F_o|$ if $|F_o| > 38{\cdot}0$, chosen 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 $\sin\theta/\lambda$. Atomic scattering factors were taken from ref. 6, except for those of hydrogen which were taken from ref. 7.

Computations were carried out on the Birmingham University 1906A computer. The major computer programs used in the analysis have been listed and acknowledged in ref. 8.

RESULTS AND DISCUSSION

A stereoscopic view of the hexasonium cation along the c axis of the unit cell is shown in Figure 1, which also shows the atomic numbering scheme used. Molecular dimensions are listed in Tables 1 and 2, and the crystal structure is illustrated in Figure 2. Atomic and thermal parameters, shorter intermolecular distances (none of which is shorter than the sum of the relevant van der Waals radii) and final observed and calculated structure factors are listed in Supplementary Publication No. SUP 21203 (16 pp., 1 microfiche).*

The sample of hexasonium iodide used in the analysis was racemic. The atomic co-ordinates and torsion angles and the drawing in Figure 1 refer to the enantiomer with the *S*-configuration at the chiral centre, the acetoxy-carbon atom [C(13)], this enantiomer having a configuration analogous to that used in the description of the structure of penthienate bromide.[3] For penthienate, the enantiomer was chosen on the basis of results [9] on related anticholinergic molecules which

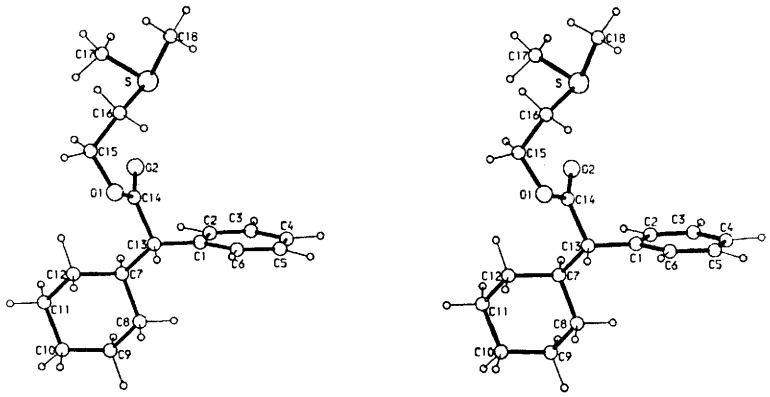

FIGURE 1 Stereoscopic view of the hexasonium cation along the c axis

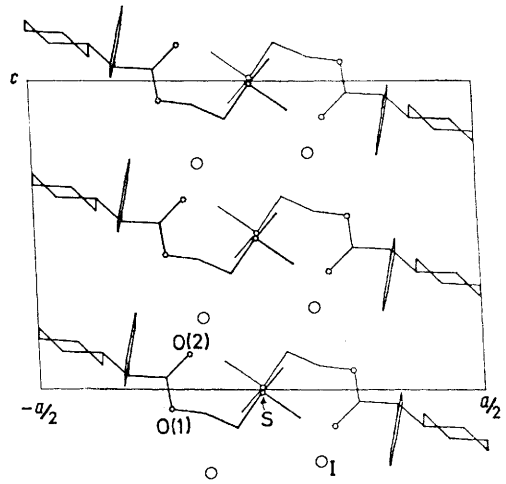

FIGURE 2 The crystal structure projected along the b axis

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

[6] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

[7] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

[8] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 942.

[9] B. W. J. Ellenbroek, R. J. F. Nivard, J. M. van Rossum, and E. J. Ariens, *J. Pharm. Pharmacol.*, 1965, **17**, 393; R. W. Brimblecombe, D. M. Green, T. D. Inch, and B. J. Thompson, *ibid.*, 1971, **23**, 745.

indicated that this enantiomer might be pharmacologically the more active form. Studies [9] of the anticholinergic activity of optical isomers have, however, involved only compounds with a hydroxy-substituent at the acetoxy-carbon atom, so that extrapolation of results to predict the more active enantiomer of hexasonium would not be justifiable.

The ester group, C(13), C(14), O(1), C(15), O(2), is planar to within 0·052 Å [Table 2(*d*)] and adopts the *antiplanar* conformation typical of esters; [torsion angle C(13)–C(14)–O(1)–C(15) −174°].

The conformation of the central chain of the hexasonium cation, which is related to acetylcholine by substitution of S^+Me_2 for N^+Me_3, is determined by the geometry of the ester group and by the arrangements about bonds O(1)–C(15) and C(15)–C(16). The conformations about these bonds, however, differ from those found in the crystal structures of acetylcholine salts [10] and from those of various anticholinergic molecules containing an acetylcholine moiety.[3] The result of this is that the position of the positive sulphonium head relative to the ester group is not analogous to that of the cationic head in the acetylcholine salts and in the anticholinergics based on acetylcholine. This is illustrated in Figure 3 which shows the hexasonium cation as viewed in a direction perpendicular to the mean plane of the ester group. Similar views of acetylcholine chloride, (−)-hyoscyamine (atropine) hydrobromide,[11] and certain

TABLE 1

Molecular dimensions

(*a*) Bonded distances (Å), with standard deviations (×10³) in parentheses

C(1)–C(2)	1·391(15)	C(12)–C(7)	1·558(17)
C(2)–C(3)	1·334(21)	C(1)–C(13)	1·496(15)
C(3)–C(4)	1·386(26)	C(7)–C(13)	1·539(14)
C(4)–C(5)	1·360(26)	C(13)–C(14)	1·516(13)
C(5)–C(6)	1·388(23)	C(14)–O(1)	1·320(11)
C(6)–C(1)	1·402(17)	C(14)–O(2)	1·228(11)
C(7)–C(8)	1·529(15)	O(1)–C(15)	1·457(11)
C(8)–C(9)	1·501(19)	C(15)–C(16)	1·523(12)
C(9)–C(10)	1·514(24)	S–C(16)	1·811(9)
C(10)–C(11)	1·519(22)	S–C(17)	1·789(10)
C(11)–C(12)	1·492(17)	S–C(18)	1·784(9)

(*b*) Selected non-bonded distances (Å)

S · · · O(1)	3·48	S · · · H[C(13)]	5·60
S · · · O(2)	2·96	S · · · Centre of ring C(1)—(6)	5·97
S · · · C(14)	3·52	S · · · Centre of ring C(7)—(12)	7·36
S · · · C(13)	4·89		

(*c*) Bond angles (deg.); mean σ 1·0°, for angles involving S 0·5°

C(6)–C(1)–C(2)	116·1	C(12)–C(7)–C(13)	113·6
C(1)–C(2)–C(3)	124·0	C(8)–C(7)–C(13)	110·9
C(2)–C(3)–C(4)	118·5	C(1)–C(13)–C(7)	114·0
C(3)–C(4)–C(5)	121·1	C(1)–C(13)–C(14)	111·8
C(4)–C(5)–C(6)	119·5	C(7)–C(13)–C(14)	109·2
C(5)–C(6)–C(1)	120·7	C(13)–C(14)–O(1)	111·9
C(12)–C(7)–C(8)	110·4	C(13)–C(14)–O(2)	125·4
C(7)–C(8)–C(9)	112·1	O(1)–C(14)–O(2)	122·6
C(8)–C(9)–C(10)	111·9	C(14)–O(1)–C(15)	118·1
C(9)–C(10)–C(11)	112·7	O(1)–C(15)–C(16)	113·0
C(10)–C(11)–C(12)	112·9	C(15)–C(16)–S	113·9
C(11)–C(12)–C(7)	110·4	C(16)–S–C(17)	101·0
C(2)–C(1)–C(13)	124·5	C(16)–S–C(18)	99·6
C(6)–C(1)–C(13)	119·4	C(17)–S–C(18)	101·6

(*d*) Torsion angles (deg.); mean σ 1·5°

C(7)–C(8)–C(9)–C(10)	−53·7
C(8)–C(9)–C(10)–C(11)	51·5
C(9)–C(10)–C(11)–C(12)	−52·8
C(10)–C(11)–C(12)–C(7)	54·3
C(11)–C(12)–C(7)–C(8)	−55·6
C(12)–C(7)–C(8)–C(9)	55·7
C(13)–C(7)–C(8)–C(9)	−176·9
C(13)–C(7)–C(12)–C(11)	178·8
C(2)–C(1)–C(13)–C(14)	−75·0
C(6)–C(1)–C(13)–C(14)	104·7
C(8)–C(7)–C(13)–C(14)	−177·0
C(12)–C(7)–C(13)–C(14)	−51·6
C(2)–C(1)–C(13)–C(7)	49·2
C(6)–C(1)–C(13)–C(7)	−131·1
C(8)–C(7)–C(13)–C(1)	57·4
C(12)–C(7)–C(13)–C(1)	−177·2
C(1)–C(13)–C(14)–O(1)	−134·7
C(1)–C(13)–C(14)–O(2)	45·3
C(7)–C(13)–C(14)–O(1)	98·7
C(7)–C(13)–C(14)–O(2)	−81·3
C(13)–C(14)–O(1)–C(15)	−174·0
O(2)–C(14)–O(1)–C(15)	6·0
C(14)–O(1)–C(15)–C(16)	−86·1
O(1)–C(15)–C(16)–S	84·4
C(15)–C(16)–S–C(17)	67·4
C(15)–C(16)–S–C(18)	171·2
H[C(13)]–C(13)–C(14)–O(1)	−17
H[C(13)]–C(13)–C(14)–O(2)	−163

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

TABLE 2

Mean plane calculations

(*a*) Deviations (Å) of atoms from least-squares planes. In the equations of the planes, *x*, *y*, and *z* are fractional co-ordinates relative to the cell axes

Plane (*a*): C(1)—(6)

$$-15{\cdot}779x - 0{\cdot}324y + 2{\cdot}378z = 4{\cdot}768$$

C(1) −0·000, C(2) −0·008, C(3) 0·006, C(4) −0·012, C(5) 0·004, C(6) 0·010, C(13) 0·004

Plane (*b*): C(7)—(12)

$$-5{\cdot}900x - 0{\cdot}326y - 10{\cdot}137z = 1{\cdot}059$$

C(7) −0·243, C(8) 0·233, C(9) −0·208, C(10) 0·199, C(11) −0·218, C(12) 0·237

Plane (*c*): C(8), C(9), C(11), C(12)

$$-9{\cdot}163x - 2{\cdot}366y - 8{\cdot}529z = 2{\cdot}316$$

C(8) −0·004, C(9) 0·004, C(11) −0·004, C(12) 0·004, C(7) −0·678, C(10) 0·613

Plane (*d*): C(13)—(15), O(1), O(2)

$$5{\cdot}915x + 9{\cdot}304y - 5{\cdot}061z = 1{\cdot}211$$

C(13) −0·031, C(14) 0·011, C(15) −0·040, O(1) 0·052, O(2) 0·008, S 1·807, C(1) 0·919, C(2) 0·707, C(3) 1·567, C(4) 3·009, C(5) 2·738, C(6) 2·118, C(7) −1·484, C(17) 0·592, C(18) 3·240

(*b*) Dihedral angles (deg.)

(*a*)–(*b*)	101·9	(*b*)–(*d*)	75·6
(*a*)–(*d*)	62·5		

[10] F. G. Canepa, P. J. Pauling, and H. Sörum, *Nature*, 1966, **210**, 907; J. K. Herdklotz and R. L. Sass, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 583; V. Mahajan and R. L. Sass, *J. Cryst. Mol. Structure*, 1974, **4**, 15.

[11] E. Kussäther and J. Haase, *Acta Cryst.*, 1972, **B28**, 2896.

anticholinergic cations containing an acetylcholine moiety have been presented elsewhere.[1,3] In hexasonium, the sulphonium head is positioned on the side of the ester group containing the carbonyl oxygen atom, whereas in atropine and in anticholinergics based on acetylcholine, whose crystal structures have been determined, at least part of the cationic head is positioned on the opposite side of the ester group, the side containing the ester oxygen atom and the acetoxy-methyl group of the acetylcholine moiety.[3]

The S^+–C bond lengths (1·811, 1·789, 1·784 Å, mean 1·795 Å) are shorter than the accepted value for the S–C bond length (1·817 Å).[12] This is different from the situation with carbon–nitrogen bonds, where N^+–C lengths are *ca.* 0·02—0·04 Å longer than N–C lengths. The $S^+ \cdots O(2)$ distance (2·96 Å) is *ca.* 0·3 Å shorter

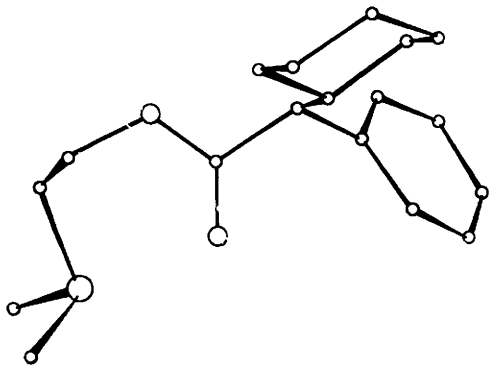

FIGURE 3 The hexasonium cation viewed in a direction perpendicular to the mean plane of the ester group

than the sum of the accepted van der Waals radii of sulphur and oxygen but is similar to S · · · O non-bonded distances in a number of other molecules,[3,13] and seems to represent an attractive interaction.

The cyclohexyl ring adopts the chair conformation, with the acetoxy-group substituted equatorially. The cyclohexyl and phenyl rings are oriented respectively (+)- and (−)-*anticlinal* to the ester oxygen atom as defined by torsion angles C(7)–C(13)–C(14)–O(1) and C(1)–C(13)–C(14)–O(1). Hydrogen atom H[C(13)] is oriented *synplanar* with respect to O(1). The orientation of the rings about the C(13)–C(14) bond is thus similar to the situation in adiphenine hydrochloride,[3,8] and is related to the orientations in penthienate,[3] benactyzine,[14] and piperidolate [3] by a rotation of *ca.* 60°. The orientations about C(13)–C(1) and C(13)–C(7) are also roughly comparable with the situation in adiphenine.

It does not, however, seem possible to explain anticholinergic activity solely in terms of the conformations of the acyl or alcohol moieties. Thus the conformations of the acyl moieties of penthienate, glycopyrronium,[15] and hexasonium are all different, as are the conformations of the C(:O)·O·C·C(N,S)$^+$ groupings of the alcohol moiety, yet their activities are similar. Of greater importance appears to be the overall shape and size of the molecule, in particular the relative positions and orientations of the cationic head and one ring substituent of the acyl group. In all potent anticholinergics derived from acetylcholine by the introduction of ring substituents into the acyl group, whose crystal structures have been determined, and also in atropine, the cationic head and one ring substituent form a claw-like arrangement with the ester group acting as connector between the extremities of the 'claw.' The cationic head and the ring substituent forming the 'claw' are both on the same side of the ester plane. The ring may be either aromatic (*e.g.* thienyl in penthienate, phenyl in atropine) or saturated (*e.g.* cyclopentyl in glycopyrronium). The ring plane is generally steeply inclined with respect to the ester plane.[3] The distances between the extremities of the 'claw,' expressed as the nitrogen to centre-of-ring distance, range from 5·1 in benactyzine to 6·1 Å in atropine. Similar N^+ to centre-of-ring distances of *ca.* 6 Å have also been observed in the crystal structures of the anticholinergics trimethyl-β-diphenylaminoethylammonium iodide and 3,3-diphenylpropyltrimethylammonium iodide.[16]

The hexasonium cation also adopts a claw-like shape (Figure 3), with the distance between the sulphur atom and the centre of the phenyl ring 5·97 Å, and the angle between the mean planes of the ester group and the phenyl ring 62·5°. It differs, however, in that the cationic head and the phenyl ring, the extremities of the 'claw,' extend in a quite different direction relative to the atomic arrangement of the ester group [*cf.* hexasonium (Figure 3) with penthienate and glycopyrronium (ref. 3) and atropine (ref. 1)].

We had previously suggested [3] that the antagonist molecule may approach the muscarinic receptor with the acetylcholine-like moiety oriented in the same way as was proposed [17] for the interaction of acetylcholine with the receptor, *i.e.* with the side containing the acetoxymethyl group and the ester-oxygen atom directed towards the receptor. Interaction would then occur primarily *via* the cationic head and the ring substituent,[3,18] the extremities of the 'claw' which extend in this general direction. Clearly, if hexasonium adopts the conformation observed in the solid state when interacting with the receptor, and if the interaction takes place analogously, it would have to approach the receptor with the ester group oriented quite differently. Even for the acetylcholine-based anticholinergics discussed [3] previously, it does not seem possible to define a particular orientation of the ester group relative to the receptor for optimum binding. The function of the

[12] *Chem. Soc. Special Publ.*, No. 18, 1965.
[13] M. Nardelli, G. Fava, and G. Giraldi, *Acta Cryst.*, 1962, **15**, 737.
[14] T. J. Petcher, *J.C.S. Perkin II*, 1974, 1151.
[15] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 1875.
[16] A. Del Pra, M. Mammi, G. Valle, P. Pratesi, and L. Villa, *Il Farmaco, Ed. Sci.*, 1973, **28**, 675.
[17] C. Chothia, *Nature*, 1970, **225**, 36.
[18] P. J. Pauling and T. J. Petcher, *Nature*, 1970, **228**, 673.

central C·C(:O)·O·C·C chain appears to be merely to provide a suitable connector between the binding groups, and, in fact, in many anticholinergic substances, *e.g.* those described in ref. 16, the chain connecting the cationic head and the ring substituents does not contain an ester group.

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