Stereochemistry of Anticholinergic Agents. Part II.[1] Crystal and Molecular Structure of Glycopyrronium Bromide

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Crystals of the title compound are orthorhombic, space group *Pbca*, with $Z = 8$ in a cell of dimensions $a = 12{\cdot}06 \pm 0{\cdot}01$, $b = 33{\cdot}27 \pm 0{\cdot}02$, $c = 9{\cdot}63 \pm 0{\cdot}01$ Å. The structure was determined by Patterson and Fourier methods by use of three-dimensional *X*-ray counter-data, and refined by least squares to R 8·0% for 1783 structure amplitudes. Estimated standard deviations for bond lengths, bond angles and torsion angles average 0·016 Å, 0·8°, and 1·0°. In the glycopyrronium cation the two five-membered rings each adopt the envelope conformation, and the acetylcholine-like moiety adopts a conformation similar to that of acetylcholine in crystals of the bromide salt.

GLYCOPYRRONIUM BROMIDE,† a synthetic anticholinergic drug,[2] closely related to acetylcholine, exhibits atropine-like activity at the parasympathetic postganglionic (muscarinic) receptor. It has been used clinically in the treatment of gastrointestinal disorders since doses which cause useful reductions in gastric secretion and motility do not have the undesirable side-effects of atropine.[3] The antagonism to the action of acetylcholine at the muscarinic receptor is competitive in type, but the nature of the receptor–ligand interaction is not fully understood.[4] Comparisons [1,5] of the crystal structures of a number of anticholinergic agents showed close stereochemical similarities among these molecules, and with acetylcholine in the conformation suggested [6] as corresponding to muscarinic activity. We now report the crystal structure of glycopyrronium bromide in the course of continuing studies of the stereochemistry of anticholinergic agents.

Atomic parameters and molecular dimensions based on three-dimensional *X*-ray counter-data are listed in Tables 1—4. Intermolecular contact distances are in Table 5. A view of the glycopyrronium cation is shown in Figure 1, which also shows the atomic numbering scheme used, and the crystal structure is illustrated in Figure 2.

The sample of glycopyrronium bromide used was racemic. The atomic co-ordinates of Table 1 and the drawing in Figure 1 refer to the enantiomer with a positive torsion angle for the O–C–C–N^+ group [*cf.* Table 3(*c*)], corresponding to the conformation of acetylcholine suggested [6] as relevant to interaction with the muscarinic receptor. Our discussion of stereochemistry is based on this enantiomer. There is, however, evidence that for some anticholinergic molecules which, like glycopyrronium, have chiral centres both in the acyl and choline-like moieties, anticholinergic activity is influenced to a much greater extent by the absolute configuration of the acyl group than by that of the

† 3-(α-Cyclopentylmandeloyloxy)-1,1-dimethylpyrrolidinium bromide.

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

[2] B. V. Franko, R. S. Alphin, J. W. Ward, and C. D. Lunsford, *Ann. N.Y. Acad. Sci.*, 1962, **99**, 131.

[3] P. E. Baume, J. H. Hunt, and D. W. Piper, *Gastroenterology*, 1972, **63**, 399.

[4] 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; E. J. Ariens and A. M. Simonis, *Ann. N.Y. Acad. Sci.*, 1967, **144**, 842.

[5] P. J. Pauling and T. J. Petcher, *Nature*, 1970, **228**, 673.

[6] R. W. Baker, C. H. Chothia, P. Pauling, and T. J. Petcher, *Nature*, 1971, **230**, 439.

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

	x	*y*	*z*
C(1)	5703(9)	1547(3)	3385(11)
C(2)	4973(10)	1487(4)	2248(12)
C(3)	5245(12)	1645(4)	944(13)
C(4)	6197(14)	1857(4)	742(14)
C(5)	6933(13)	1913(4)	1851(15)
C(6)	6679(12)	1765(4)	3140(13)
C(7)	4573(9)	1708(3)	5502(11)
C(8)	4238(11)	1619(3)	7037(12)
C(9)	3695(14)	2004(4)	7533(16)
C(10)	4158(16)	2337(4)	6614(17)
C(11)	4973(11)	2150(3)	5584(13)
C(12)	5403(9)	1413(3)	4852(10)
C(13)	4899(9)	982(3)	4816(11)
C(14)	3299(9)	594(3)	4227(10)
C(15)	2951(8)	406(3)	5600(12)
C(16)	1304(9)	468(3)	4278(11)
C(17)	2236(10)	663(3)	3393(10)
C(18)	1574(10)	937(3)	6264(11)
C(19)	1131(11)	237(4)	6742(13)
N	1736(8)	513(2)	5762(9)
O(1)	3823(6)	982(2)	4420(8)
O(2)	5405(7)	680(3)	5046(11)
O(3)	6350(6)	1397(2)	5719(7)
Br	8376(1)	691(0)	5471(1)
H[C(2)]	4209	1316	2391
H[C(3)]	4665	1618	66
H[C(4)]	6417	1973	−270
H[C(5)]	7691	2080	1676
H[C(6)]	7259	1810	3993
H[C(7)]	3820	1680	4820
H^1[C(8)]	3654	1365	7105
H^2[C(8)]	4981	1547	7676
H^1[C(9)]	2793	1985	7471
H^2[C(9)]	3938	2072	8625
H^1[C(10)]	3434	2471	5980
H^2[C(10)]	4522	2582	7195
H^1[C(11)]	4973	2295	4554
H^2[C(11)]	5830	2165	6013
H[C(14)]	3841	380	3654
H^1[C(15)]	3079	83	5621
H^2[C(15)]	3436	547	6464
H^1[C(16)]	1180	150	4008
H^2[C(16)]	516	631	4139
H^1[C(17)]	2298	512	2377
H^2[C(17)]	2096	982	3256
H^1[C(18)]	690	1010	6250
H^2[C(18)]	1900	970	7300
H^3[C(18)]	1810	1150	5450
H^1[C(19)]	1500	250	7800
H^2[C(19)]	230	300	6750
H^3[C(19)]	1150	−60	6250
H[O(3)]	6800	1200	5200

choline moiety.[4] A tentative assignment [4] of configuration to the four stereoisomers of the α-cyclohexylmandelic acid ester of β-methylcholine if extrapolated to glycopyrronium, would indicate (but with a high degree of uncertainty) that in the more active isomers the acyl group has the opposite configuration to that

TABLE 2

Anisotropic thermal parameters ($\times 10^4$) for the heavier atoms

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	429	219	408	−15	60	−90
C(2)	539	538	343	−56	−11	52
C(3)	711	420	400	27	90	8
C(4)	941	474	432	102	321	91
C(5)	745	699	480	−139	256	88
C(6)	553	493	525	12	24	−2
C(7)	518	290	256	2	41	82
C(8)	659	406	322	−89	179	122
C(9)	898	665	456	98	189	−15
C(10)	1216	445	698	40	285	−182
C(11)	767	241	413	−77	25	−14
C(12)	431	333	214	−21	−47	20
C(13)	397	359	323	24	33	−108
C(14)	446	357	243	−55	41	−63
C(15)	369	334	387	−42	−51	−96
C(16)	451	419	260	11	−132	−46
C(17)	583	448	210	−179	−36	−4
C(18)	535	403	248	143	90	27
C(19)	545	516	457	−114	−5	75
N	447	312	313	−31	80	22
O(1)	390	321	465	−68	−5	24
O(2)	542	449	987	116	−7	91
O(3)	481	505	304	−3	−14	56
Br	440	505	428	69	23	−70

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

TABLE 3

Molecular dimensions

(*a*) Bond distances (Å) with standard deviations in parentheses

C(1)–C(2)	1·419(16)	C(12)–C(13)	1·556(15)
C(2)–C(3)	1·399(17)	C(12)–O(3)	1·416(13)
C(3)–C(4)	1·362(20)	C(13)–O(2)	1·197(13)
C(4)–C(5)	1·401(21)	C(13)–O(1)	1·352(13)
C(5)–C(6)	1·370(18)	C(14)–O(1)	1·449(12)
C(6)–C(1)	1·403(17)	C(14)–C(15)	1·521(15)
C(7)–C(8)	1·560(15)	C(14)–C(17)	1·530(16)
C(8)–C(9)	1·516(18)	C(16)–C(17)	1·553(16)
C(9)–C(10)	1·524(20)	C(15)–N	1·516(14)
C(10)–C(11)	1·529(20)	C(16)–N	1·528(13)
C(11)–C(7)	1·551(14)	C(18)–N	1·506(13)
C(1)–C(12)	1·525(15)	C(19)–N	1·504(14)
C(7)–C(12)	1·535(15)		

(*b*) Bond angles (deg.); mean standard deviation 0·8°

C(6)–C(1)–C(2)	117·6	C(7)–C(12)–O(3)	108·0
C(1)–C(2)–C(3)	119·6	O(3)–C(12)–C(13)	107·1
C(2)–C(3)–C(4)	121·3	C(12)–C(13)–O(2)	124·7
C(3)–C(4)–C(5)	119·7	C(12)–C(13)–O(1)	112·3
C(4)–C(5)–C(6)	120·0	O(2)–C(13)–O(1)	122·9
C(5)–C(6)–C(1)	121·7	C(13)–O(1)–C(14)	117·0
C(11)–C(7)–C(8)	102·2	O(1)–C(14)–C(15)	112·0
C(7)–C(8)–C(9)	104·5	O(1)–C(14)–C(17)	107·4
C(8)–C(9)–C(10)	105·8	C(14)–C(17)–C(16)	104·9
C(9)–C(10)–C(11)	108·5	C(15)–C(14)–C(17)	106·6
C(10)–C(11)–C(7)	102·6	C(14)–C(15)–N	105·1
C(2)–C(1)–C(12)	121·7	C(17)–C(16)–N	103·0
C(6)–C(1)–C(12)	120·4	C(15)–N–C(16)	102·2
C(8)–C(7)–C(12)	115·7	C(15)–N–C(18)	112·2
C(11)–C(7)–C(12)	115·1	C(15)–N–C(19)	113·0
C(1)–C(12)–C(7)	110·2	C(16)–N–C(18)	110·3
C(1)–C(12)–C(13)	110·0	C(16)–N–C(19)	111·2
C(1)–C(12)–O(3)	111·4	C(18)–N–C(19)	107·9
C(7)–C(12)–C(13)	110·1	H[O(3)]–O(3)–C(12)	99·8

TABLE 3 (*Continued*)

(*c*) Torsion angles (deg.);* mean standard deviation for angles not involving hydrogen atoms 1·0°

C(2)–C(1)–C(12)–C(13)	44·8
C(6)–C(1)–C(12)–C(13)	−140·7
C(8)–C(7)–C(12)–C(13)	61·6
C(11)–C(7)–C(12)–C(13)	−179·4
C(2)–C(1)–C(12)–O(3)	163·4
C(6)–C(1)–C(12)–O(3)	−22·1
C(8)–C(7)–C(12)–O(3)	−55·1
C(11)–C(7)–C(12)–O(3)	64·0
C(2)–C(1)–C(12)–C(7)	−76·8
C(6)–C(1)–C(12)–C(7)	97·7
C(1)–C(12)–C(7)–C(8)	−176·9
C(1)–C(12)–C(7)–C(11)	−57·9
C(1)–C(12)–C(13)–O(2)	97·5
C(1)–C(12)–C(13)–O(1)	−79·2
C(7)–C(12)–C(13)–O(2)	−140·9
C(7)–C(12)–C(13)–O(1)	42·4
C(7)–C(8)–C(9)–C(10)	−24·0
C(8)–C(9)–C(10)–C(11)	−0·2
C(9)–C(10)–C(11)–C(7)	24·3
C(10)–C(11)–C(7)–C(8)	−38·1
C(11)–C(7)–C(8)–C(9)	38·9
O(3)–C(12)–C(13)–O(2)	−23·7
O(3)–C(12)–C(13)–O(1)	159·6
C(12)–C(13)–O(1)–C(14)	174·5
O(2)–C(13)–O(1)–C(14)	−2·4
C(13)–O(1)–C(14)–C(15)	79·5
C(13)–O(1)–C(14)–C(17)	−163·7
O(1)–C(14)–C(15)–N	96·6
O(1)–C(14)–C(17)–C(16)	−125·9
C(14)–C(15)–N–C(16)	39·0
C(14)–C(17)–C(16)–N	29·5
C(15)–N–C(16)–C(17)	−42·1
C(16)–C(17)–C(14)–C(15)	−5·7
C(17)–C(14)–C(15)–N	−20·6
C(14)–C(15)–N–C(18)	−79·1
C(14)–C(15)–N–C(19)	158·6
C(18)–N–C(16)–C(17)	77·3
C(19)–N–C(16)–C(17)	−163·0
H[O(3)]–O(3)–C(12)–C(13)	60·9

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

TABLE 4

(*a*) Deviations (Å) of atoms from least squares planes

Plane (*a*): C(1)—(6)
C(1) — 0·000, C(2) 0·002, C(3) 0·003, C(4) — 0·008, C(5) 0·009, C(6) — 0·005

Plane (*b*): C(7)—(11)
C(7) 0·255, C(8) — 0·205, C(9) 0·076, C(10) 0·079, C(11) −0·204, C(12) — 0·238

Plane (*c*): C(8)—(11)
C(8) 0·001, C(9) — 0·001, C(10) 0·001, C(11) — 0·001, C(7) 0·618, C(12) 0·416

Plane (*d*): C(14)—(17), N
C(14) — 0·042, C(15) 0·187, C(16) 0·232, C(17) −0·111, N — 0·267, O(1) — 1·303

Plane (*e*): C(14)—(17)
C(14) 0·034, C(15) — 0·022, C(16) 0·021, C(17) — 0·033, N — 0·628, O(1) — 1·104

Plane (*f*): C(12)—(14), O(1), O(2)
C(12) 0·030, C(13) — 0·026, C(14) 0·034, O(1) — 0·038, O(2) — 0·001, C(15) — 1·312, C(17) 0·416

(*b*) Equations of planes

(*a*) $-5{\cdot}725x + 28{\cdot}258y + 2{\cdot}218z = 1{\cdot}856$
(*b*) $10{\cdot}129x + 0{\cdot}254y + 5{\cdot}225z = 7{\cdot}805$
(*c*) $9{\cdot}005x + 4{\cdot}683y + 6{\cdot}258z = 8{\cdot}979$
(*d*) $-0{\cdot}589x + 32{\cdot}020y + 2{\cdot}567z = 2{\cdot}752$
(*e*) $-1{\cdot}845x + 29{\cdot}801y + 4{\cdot}016z = 2{\cdot}894$
(*f*) $-3{\cdot}490x + 1{\cdot}999y + 9{\cdot}196z = 2{\cdot}889$

x, y and z are fractional co-ordinates relative to the cell axes

TABLE 4 (*Continued*)

(*c*) Dihedral angles (deg.)

(*a*)–(*b*)	105·5	(*b*)–(*e*)	84·0
(*a*)–(*c*)	94·9	(*b*)–(*f*)	74·0
(*a*)–(*d*)	25·5	(*c*)–(*d*)	74·2
(*a*)–(*e*)	21·6	(*c*)–(*e*)	73·6
(*a*)–(*f*)	65·9	(*c*)–(*f*)	65·6
(*b*)–(*d*)	83·6	(*d*)–(*f*)	70·9
		(*e*)–(*f*)	60·2

TABLE 5

Shorter intermolecular contacts (Å) excluding hydrogen atoms

O(3) · · · Br	3·40	C(10 · · · C(3^{II})	3·69
C(3) · · · C(18^{I})	3·55	C(19) · · · C(4^{III})	3·72
O(2) · · · Br	3·61	C(10) · · · C(6^{II})	3·73
C(11) · · · C(4)	3·62	C(16) · · · Br^{IV}	3·79
C(4) · · · C(18^{I})	3·65		

Roman numeral superscripts refer to the following equivalent positions relative to the reference molecule at x, y, z: I $\frac{1}{2}+x, y, \frac{1}{2}-z$, II $x, \frac{1}{2}-y, \frac{1}{2}+z$, III $\frac{1}{2}-x, -y, \frac{1}{2}+z$, IV $-1+x, y, z$

shown in Figure 1. Our general conclusions, however, do not depend on the choice of enantiomer.

Bond lengths (mean standard deviation 0·016 Å), generally are quite normal. Aromatic C–C bonds range from 1·36—1·42 Å (mean 1·392 Å), and C(sp^3)–C(sp^3) bonds from 1·52—1·56 Å (mean 1·536 Å). The C(sp^3)–N$^+$ bonds average 1·514 Å, also in good agreement with

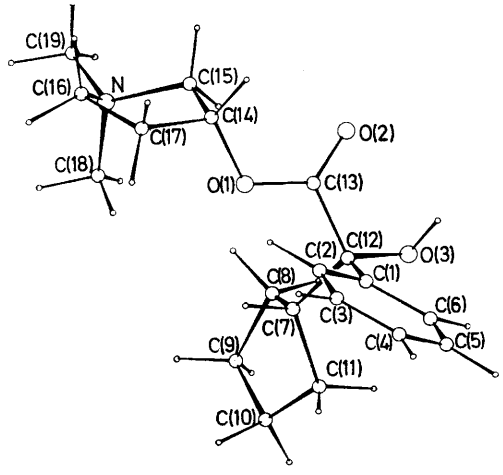

FIGURE 1 One enantiomer of the glycopyrronium cation viewed along the *c* axis (positive *c* is away from the viewer, *a* and *b* axes as in Figure 2)

previous results,[1] and the C(12)–O(3) bond length of 1·42 Å is close to the accepted [7] value for the C(sp^3)–O single-bond length (1·43 Å). Bond lengths within the ester group are all in good agreement with the values quoted by Mathieson and Welsh [8] as being typical for esters, apart from the C(12)–C(13) bond which is somewhat long (1·556 Å). The bond angles at C(13) and O(1) also follow the trends normally observed in esters.

The phenyl ring is planar to within 0·009 Å. The two five-membered rings each adopt the envelope conformation. In the cyclopentyl ring, atoms C(8)—(11) are accurately coplanar, with C(7) displaced from this plane by 0·62 Å. The pyrrolidinium ring has the four carbon atoms coplanar to within 0·03 Å and the nitrogen atom displaced by 0·63 Å.

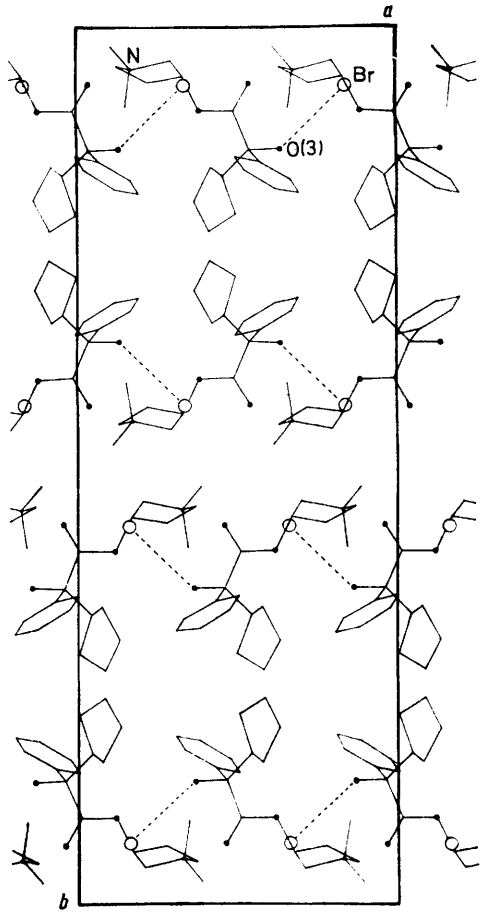

FIGURE 2 The contents of the unit cell projected along the *c* axis

The ester group, C(12)—(14), O(1), O(2), is planar to within 0·04 Å and has the antiplanar conformation [torsion angle C(12)–C(13)–O(1)–C(14) 174°], typical of esters.[8] The conformation about the C(12)–C(13) bond is such that the hydroxylic oxygen atom, O(3), is synplanar to the carbonyl oxygen atom [torsion angle O(3)–C(12)–C(13)–O(2) −24°] and the ring-atom substituents, C(1) and C(7), respectively + and − anticlinal to it. The conformation about this bond is therefore similar to that observed for the corresponding bonds in the crystal structures of the related cholinergic antagonists quinuclidinyl benzilate (I) hydrobromide [9] and quinuclidinyl di-α-thienylglycollate (II),[10] but differs

$R_2C(OH)CO_2C_7H_{12}N$

(I) R = Ph

(II) R = 2-C_4H_3S

from that observed for the corresponding bond in the crystal structure [1] of adiphenine hydrochloride. Here

[7] *Chem. Soc. Special Publ.*, No. 18, 1965.

[8] A. McL. Mathieson and H. K. Welsh, *Acta Cryst.*, 1965, **18**, 953.

[9] A. Meyerhoffer and D. Carlstrom, *Acta Cryst.*, 1969, *B*, **25**, 1119.

[10] A. Meyerhoffer, *Acta Cryst.*, 1970, *B*, **26**, 341.

there is a hydrogen atom in place of the hydroxy-group and this is oriented antiplanar to the carbonyl oxygen atom with the ring atom substituents + and — synclinal. Pharmacologically, replacing hydrogen by hydroxy at this site generally increases the anticholinergic activity of molecules of this type. Previously this has been attributed to hydrogen-bond formation between the hydroxy-group and a receptor group.[11] If, however, the conformation about the (in our numbering system) C(12)–C(13) bond is determined by whether C(12) carries a hydrogen atom or a hydroxy-group,* this effect and the concomitant effect it has on the orientations of the ring substituents would also have to be considered in any explanation of the change in anticholinergic activity. Angles between the mean planes of these ring substituents and the ester group are listed in Table 4. As in the crystal structures of (I) and (II), both rings are quite steeply inclined with respect to the plane of the ester group. The inter-ring angle of 105° is similar to those observed in these structures and in adiphenine hydrochloride where they range from 96—102°. The O(3) · · · O(2) distance is 2·72 Å, but hydrogen bonding does not occur, the pertinent hydrogen atom H[O(3)] being situated favourably rather for hydrogen-bond formation to the bromide ion, the angle H–O(3) · · · Br^- being *ca.* 27°. The distances O(3) · · · Br^- and H[O(3)] · · · Br^- are 3·40 and *ca.* 2·56 Å, respectively, corresponding to a rather weak interaction. The conformation about C(1)–C(12) is such that C(6) is synplanar to O(3), so that there is also a short C(6) · · · O(3) distance of 2·80 Å but the position of the hydrogen atom, H[C(6)], is not favourable for C–H · · · O hydrogen bonding. The phenyl ring also makes a short contact with O(1). The distances C(2) · · · O(1) and H[C(2)] · · · O(1) are 3·02 and *ca.* 2·29 Å, and angle H–C(2) · · · O(1) is 40°, so that a weak C–H · · · O interaction might be involved (*cf.* ref. 12).

The overall shape of the acetylcholine-like moiety of the glycopyrronium cation is governed by the conformations about the bonds C(13)–O(1), O(1)–C(14), C(14)–C(15), and C(15)–N^+. The conformation about C(13)–O(1), discussed earlier, appears to be the same in all esters for which structural information is available with torsion angle C(12)–C(13)–O(1)–C(14) *ca.* 180°.

Torsion angle C(13)–O(1)–C(14)–C(15) is 80°, similar to the corresponding angles in (I)[9] and (II)[10] and in acetylcholine in crystals of the bromide salt.[13] In the crystal structure of acetylcholine chloride,[14] however, the corresponding angle is —167° and this antiplanar conformation typical[15] of primary esters is also adopted by adiphenine hydrochloride[1] and by the anticholinergic drug parpanit whose crystal structure has recently been determined.[16] The value of torsion angle O(1)–C(14)–C(15)–N^+ is determined by the geometry of the pyrrolidinium ring. In a planar five-membered ring this angle would be ±120° and N^+ · · · O(1) *ca.* 3·4 Å. In the actual structure however, the ring adopts the envelope conformation, with the nitrogen atom displaced from the plane of the other four atoms so that it lies on the same side of the plane as O(1). The result is that the O(1)–C(14)–C(15)–N^+ torsion angle is reduced to 97° and the N^+ · · · O(1) distance to 3·23 Å, the conformation now being similar to that generally observed for O–C–C–N^+ groups.[1,6] The out-of-plane position of the nitrogen atom affects the conformation about the C(15)–N^+ bond to an even greater extent. In a planar ring the substituents on the nitrogen atom would eclipse those on C(15) with torsion angles 0 or ±120°, whereas in fact the torsion angle C(14)–C(15)–N^+–C(19) is 159°, corresponding to a rotation of *ca.* 39° about the C(15)–N^+ bond from the energetically unfavourable eclipsed orientation. In the crystal structure of acetylcholine chloride the corresponding torsion angle is 171 in acetylcholine bromide —176, and in adiphenine hydrochloride 162°.

The conformation of the acetylcholine-like moiety of the glycopyrronium cation is thus similar to that of acetylcholine bromide but differs from acetylcholine chloride with respect to the arrangement about the O(1)–C(14) bond. Pauling and co-workers,[6] have suggested that the conformation of acetylcholine relevant to interaction with the muscarinic receptor is similar to that observed in crystals of the chloride, which is also the conformation adopted by acetylcholine in solution.[17] Theoretical calculations,[18] although giving conflicting results, seem to indicate that the energies of the two conformations are quite similar. Inspection of a model of the glycopyrronium cation provides no obvious reason why the torsion angle C(13)–O(1)–C(14)–C(15) should be 80° rather than —167° as it is in acetylcholine chloride and presumably it could take up this conformation in solution or when interacting with the receptor. However, the acetylcholine moieties of (I) and (II) and of 3-acetoxyquinuclidine methiodide,[19] which, like glycopyrronium bromide, are secondary esters and have the ester oxygen atom linked to a nitrogen-containing ring system, adopt a similar conformation with the C–O–C–CN^+ torsion angles 65, 85, and 77°. Yet, despite the difference in this torsion angle, the non-bonded distances N^+ · · · O(1) 3·23, N^+ · · · C(13) 4·22, and N^+ · · · C(12) 5·41 Å in the glycopyrronium cation agree quite well with the distances postulated[6] for the active conformation of acetylcholine (3·3, 4·5, and 5·4 Å,

* Further *X*-ray crystallographic analyses of anticholinergic agents containing the grouping $R^1R^2CH{\cdot}CO{\cdot}O{\cdot}$ are in progress, and are expected to provide structural data relevant to this discussion.

[11] R. B. Barlow, 'Introduction to Chemical Pharmacology,' Methuen, London, 1964.
[12] W. C. Hamilton and J. A. Ibers, 'Hydrogen Bonding in Solids,' Benjamin, New York, 1968.
[13] F. G. Canepa, P. J. Pauling, and H. Sorum, *Nature*, 1966, **210**, 907.
[14] J. K. Herdklotz and R. L. Sass, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 583.
[15] A. McL. Mathieson, *Tetrahedron Letters*, 1965, **46**, 4137.
[16] E. A. H. Griffith and B. E. Robertson, *Acta Cryst.*, 1972, *B*, **28**, 3377.
[17] C. C. J. Culvenor and N. S. Ham, *Chem. Comm.*, 1966, 537.
[18] B. Pullman and P. Courriere, *Mol. Pharmacol.*, 1972, **8**, 612, and refs. therein.
[19] R. W. Baker and P. J. Pauling, *J.C.S. Perkin II*, 1972, 2340.

respectively). The structural results for glycopyrronium bromide are therefore consistent with the model for the blocking action of anticholinergic agents related to acetylcholine, suggested [1] in our earlier paper.

EXPERIMENTAL

Crystallographic Measurements.—Colourless crystals of glycopyrronium bromide suitable for *X*-ray analysis were obtained from butan-2-one. Unit-cell dimensions were initially measured from oscillation and Weissenberg photographs, the final cell dimensions and intensity data being measured with a Stoe two-circle computer-controlled diffractometer by use of graphite-monochromated Mo-K_α radiation and a scintillation counter. The crystal, of dimensions $0{\cdot}5 \times 0{\cdot}2 \times 0{\cdot}04$ mm, was mounted about the direction of elongation (a). The ω scan mode was employed and 120 counts of 1 s at intervals of 0·01° were taken for each reflection. For reflections on the fifth and higher layers ($\mu > 8{\cdot}47°$) for which $2\theta' < 14°$, the peak scan was defined 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. Reflections were scanned within the range $0{\cdot}1 \leqslant \sin\theta/\lambda \leqslant 0{\cdot}59$, and of these, 1783, for which $I > 3\sigma(I)$, were considered observed and were included in the structure analysis. In the conversion of intensities to structure amplitudes the polarization factor appropriate to monochromated radiation was used. Absorption corrections were not applied.

Crystal Data.—$C_{19}H_{28}BrNO_3$, $M = 398{\cdot}3$. Orthorhombic, $a = 12{\cdot}06 \pm 0{\cdot}01$, $b = 33{\cdot}27 \pm 0{\cdot}02$, $c = 9{\cdot}63 \pm 0{\cdot}01$ Å, $U = 3864$ Å^3, $Z = 8$, $D_c = 1{\cdot}369$, $F(000) = 1664$. Systematic absences: $hk0$ when h is odd, $h0l$ when l is odd, $0kl$ when k is odd; space group $Pbca$ (D_{2h}^{15}). Mo-K_α radiation, $\lambda = 0{\cdot}71069$ Å; μ(Mo-K_α) = 22·75 cm^{-1}.

Structure Analysis.—The co-ordinates of the bromide ion were obtained from a Patterson synthesis. Structure factors were calculated (R 39%) and a three-dimensional electron-density distribution was computed by use of the calculated phase angles and the observed structure amplitudes. From this, the positions of all non-hydrogen atoms were found.

Positional and isotropic thermal parameters were then refined by the method of least-squares and after four cycles, R was reduced to 10·1%. The hydrogen atom positions were obtained from a Fourier difference synthesis and further refinement of the positional and anisotropic thermal parameters of the non-hydrogen atoms was terminated when the calculated shifts were all $< 0{\cdot}2\sigma$. The final value of R is 8·0% for the 1783 reflections used in the analysis.* Calculated structure amplitudes for the remaining reflections are generally small ($< 10{\cdot}0$).

The weighting scheme used in the least-squares calculations was $w^{\frac{1}{2}} = 1{\cdot}0$ if $|F_o| \leqslant 60{\cdot}0$ and $w^{\frac{1}{2}} = 60{\cdot}0/|F_o|$ if $|F_o| > 60{\cdot}0$, giving 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 obtained from ref. 20 except for those for hydrogen atoms which were taken from ref. 21.

All computations were performed on the Birmingham University KDF 9 computer; the major computer programs used in the analysis have been listed and acknowledged in ref. 1.

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[20] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.
[21] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.