Stereochemistry of Anticholinergic Agents. Part IV.[1] Crystal and Molecular Structure of Penthienate Bromide [Diethyl-(2-hydroxyethyl)-methylammonium Bromide α-Cyclopentyl-2-thienylglycolate]: Some Stereochemical Correlations

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Crystals of the title compound are triclinic, space group $P\bar{1}$ with $Z = 2$ in a unit cell of dimensions $a = 7{\cdot}14 \pm 0{\cdot}01$, $b = 8{\cdot}32 \pm 0{\cdot}01$, $c = 17{\cdot}31 \pm 0{\cdot}01$ Å, $\alpha = 90{\cdot}7 \pm 0{\cdot}05$, $\beta = 83{\cdot}9 \pm 0{\cdot}05$, $\gamma = 97{\cdot}5 \pm 0{\cdot}05°$. 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* 7·1% for 2219 structure amplitudes. The thienyl ring is planar and is oriented nearly perpendicular to the mean plane of the ester group. The cyclopentyl ring is in the envelope conformation. The acetylcholine-like system adopts a conformation similar to that of acetylcholine in crystals of the chloride salt. The molecular geometry is compared with those of certain related anticholinergic cations as determined in the solid state by *X*-ray crystallography. A common feature is that the previously defined ' methyl side ' of the acetylcholine system is partially blocked by ring substituents in the acyl group and by a large cationic head.

PENTHIENATE BROMIDE [2] (1) belongs to a class of synthetic anticholinergic agents which differ from acetylcholine itself in possessing larger substituents on the nitrogen atom and in the acyl group. Its activity at the parasympathetic post-ganglionic (muscarinic) receptor as measured [2] by the inhibition of the effects of acetylcholine stimulation of isolated rabbit ileum is approximately twice that of atropine sulphate. A comparison of the crystal structure of penthienate bromide, which is herein reported, with the structures of related anticholinergic molecules previously determined [1,3-9] should lead to a better understanding of the nature of the receptor–antagonist interaction.

EXPERIMENTAL

Crystallographic Measurements.—Penthienate bromide was recrystallised from acetone as rod-like crystals suitable for diffraction studies. A crystal, dimensions 0·6 × 0·2 × 0·2 mm, was mounted about the direction of elongation (*b*) and the cell dimensions were determined by oscillation, Weissenberg, and precession photography. Final cell dimensions and intensities were measured using a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo-K_α radiation and a scintillation counter. Of 3417 reflections scanned within the range $0{\cdot}1 \leqslant \sin\theta/\lambda \leqslant 0{\cdot}6$, 2219, for which $I > 2{\cdot}5\sigma(I)$, were considered to be observed and were used in the structure analysis. The ω scan mode was employed with a variable scan width, as described [1] previously. The polarisation factor appropriate to monochromated radiation was used when converting the intensities into structure amplitudes, but absorption corrections were not applied.

Crystal Data.—$C_{18}H_{30}BrNO_3S$, $M = 420{\cdot}4$. Triclinic, $a = 7{\cdot}14 \pm 0{\cdot}01$, $b = 8{\cdot}32 \pm 0{\cdot}01$, $c = 17{\cdot}31 \pm 0{\cdot}01$ Å, $\alpha = 90{\cdot}7 \pm 0{\cdot}05$, $\beta = 83{\cdot}9 \pm 0{\cdot}05$, $\gamma = 97{\cdot}5 \pm 0{\cdot}05°$, $U = 1016{\cdot}8$ Å^3, $Z = 2$, $D_c = 1{\cdot}373$, $F(000) = 440$. Space group $P1$ or $P\bar{1}$; $P\bar{1}$ established by the analysis. Mo-K_α radiation, $\lambda = 0{\cdot}71069$ Å; μ(Mo-K_α) = 22·5 cm^{-1}.

Structure Analysis.—The co-ordinates of the bromide ion and the sulphur atom were obtained from a three-dimensional Patterson synthesis, and structure factors were calculated (*R* 40%). The phase angles were used with the observed structure amplitudes to evaluate a three-dimensional electron density distribution from which the positions of all non-hydrogen atoms were located. Least-squares refinement of positional and isotropic thermal parameters reduced *R* to 13·2%, when the atoms were allowed to vibrate anisotropically. Hydrogen atom positions were located from a Fourier difference synthesis and were included in the calculations in their theoretical positions [assuming C(sp^3)–H 1·10, and C(sp^2)–H 1·08 Å] but their parameters were not refined. Refinement was continued until all shifts were $< 0{\cdot}1\sigma$, and *R* 7·1% for the 2219 observed structure amplitudes. Bond lengths calculated from these parameters were generally normal apart from certain anomalies in the thienyl ring. Thus the formal double bonds C(6)–C(7) 1·44 ± 0·01 and C(8)–C(9) 1·32 ± 0·016 Å differed significantly, the latter length being smaller than might be expected even for a pure double bond, and the formal single bond C(7)–C(8) of 1·412 Å was shorter than double bond C(6)–C(7). A Fourier difference map computed in the mean plane of the more or less flat (maximum deviation 0·008 Å) thienyl ring also showed some anomalies, especially a positive region of 0·54 e Å^{-3} in the vicinity of C(7).

These effects were explained by assuming disorder in the orientations of the thienyl rings, with *ca.* 10% of the rings, statistically distributed in the crystal, rotated about the C(10)–C(6) bond through an angle of 180°. It was further assumed that the ' reversed ' rings were rotated 10° about an axis through C(6), perpendicular to the ring plane, so as to simulate the orientation of the ' normal ' rings relative to the remainder of the molecule as determined by the initial least-squares refinement. Further least-squares refinement was then carried out, the parameters (positional and thermal) of the atoms of the normal ring and the positional parameters of the reversed ring being adjusted in alternate cycles. Bond lengths in the thienyl ring were now much more reasonable and a Fourier difference synthesis indicated a more even electron density distri-

[1] Part III, J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1974, 101.
[2] F. P. Luduena and A. M. Lands, *J. Pharmacol.*, 1954, **110**, 282; R. B. Barlow, ' Introduction to Chemical Pharmacology,' Methuen, London, 1964.
[3] E. A. H. Griffith and B. E. Robertson, *Acta Cryst.*, 1972, **B28**, 3377.
[4] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 942.
[5] A. Meyerhöffer and D. Carlström, *Acta Cryst.*, 1969, **B25**, 1119.
[6] A. Meyerhöffer, *Acta Cryst.*, 1970, **B26**, 341.
[7] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 1875.
[8] E. Kussäther and J. Haase, *Acta Cryst.*, 1972, **B28**, 2896.
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bution. The overall R factor, however, remained the same. A similar procedure has been used by Visser *et al.*[10] in treating disorder in the crystal structure of 3,3′-dithienyl. Only data for the normal ring are listed in the Tables. Estimated standard deviations are not quoted for the thienyl ring parameters, because of the additional uncertainty introduced by the disorder.

TABLE 1

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

	x	y	z
C(1)	−2444(12)	−1625(11)	3591(5)
C(2)	−3273(14)	−3200(12)	3193(5)
C(3)	−4824(18)	−3930(16)	3812(8)
C(4)	−5454(16)	−2561(15)	4314(7)
C(5)	−4133(14)	−1012(13)	4061(6)
C(6)	−562(11)	1135(10)	3489(4)
C(7)	570	1316	4083
C(8)	1013	2935	4333
C(9)	174	3968	3933
C(10)	−1255(11)	−374(10)	3048(4)
C(11)	551(11)	−1016(9)	2667(4)
C(12)	3163(12)	−482(12)	1716(5)
C(13)	3881(12)	653(9)	1067(5)
C(14)	2375(11)	3193(10)	1232(5)
C(15)	2418(14)	4931(11)	1508(7)
C(16)	5705(13)	3283(11)	643(6)
C(17)	7670(14)	2890(13)	664(7)
C(18)	4865(14)	2757(11)	2078(5)
S(19)	−1110	2986	3240
N(20)	4210(9)	2461(7)	1275(4)
O(21)	1356(8)	−95(7)	2073(3)
O(22)	1243(9)	−2129(9)	2901(4)
O(23)	−2325(8)	111(7)	2462(3)
Br	−2319(1)	−2276(1)	962(1)
H[C(1)]	−1470	−1975	3986
H¹[C(2)]	−3914	−2911	2665
H²[C(2)]	−2183	−4019	3049
H¹[C(3)]	−5974	−4562	3488
H²[C(3)]	−4204	−4883	4119
H¹[C(4)]	−6946	−2356	4243
H²[C(4)]	−5401	−2855	4939
H¹[C(5)]	−4774	−136	3740
H²[C(5)]	−3587	−338	4593
H[C(7)]	1132	365	4389
H[C(8)]	1896	3360	4798
H[C(9)]	209	5133	4025
H¹[C(12)]	2967	−1695	1466
H²[C(12)]	4164	−422	2141
H¹[C(13)]	2936	529	617
H²[C(13)]	5297	271	829
H¹[C(14)]	2129	3241	609
H²[C(14)]	1230	2455	1553
H¹[C(15)]	1230	5360	1340
H²[C(15)]	2410	4850	2190
H³[C(15)]	3850	5530	1380
H¹[C(16)]	5331	2917	60
H²[C(16)]	5777	4596	698
H¹[C(17)]	7620	1580	800
H²[C(17)]	8280	3360	1160
H³[C(17)]	8640	3270	180
H¹[C(18)]	5730	1790	2220
H²[C(18)]	3690	2230	2500
H³[C(18)]	5270	4030	1950
H[O(23)]	−2430	−1300	2100

The weighting scheme used in the least-squares was $w^{\frac{1}{2}} = 1{\cdot}0$ if $|F_0| \leqslant 17{\cdot}0$ and $w^{\frac{1}{2}} = 17{\cdot}0/|F_0|$ if $|F_0| > 17{\cdot}0$. Atomic scattering factors were taken from ref. 11, except for those of hydrogen, which were taken from ref. 12. Crystallographic programs used in the analysis are listed in ref. 4. Computations were performed on the Birmingham University 1906A computer. Final observed and calculated structure factors are listed in Supplementary Publication No. 21022 (16 pp., 1 microfiche).*

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index Issue.

[10] G. J. Visser, G. J. Heeres, J. Wolters, and A. Vos, *Acta Cryst.*, 1968, **B24**, 467.

RESULTS AND DISCUSSION

The stereochemistry of the penthienate cation is illustrated in Figure 1, and atomic and molecular parameters are listed in Tables 1—4. The sample of penthienate bromide used in the analysis was racemic and the enantiomer depicted in the Figures has the *S*-configuration at the chiral centre, C(10). On the basis of extrapolation of results [13] on related anticholinergic molecules this enantiomer would be expected to be pharmacologically the more active form. The O–C–C–N torsion angle is then positive synclinal [*cf.* Table 3(*c*)], corresponding to the choice of enantiomer used [1] previously in discussing the crystal structures of anticholinergics.

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)	391	409	425	43	60	−2
C(2)	559	505	471	−119	60	16
C(3)	674	699	976	−306	201	−77
C(4)	527	726	767	−106	99	41
C(5)	431	609	615	28	122	18
C(6)	341	422	330	67	−25	−5
C(7)	562	422	465	−124	−188	39
C(8)	597	850	485	−165	−231	−86
C(9)	552	550	709	−23	−147	−226
C(10)	355	344	318	125	−61	51
C(11)	328	273	391	72	−33	−23
C(12)	358	576	576	195	131	55
C(13)	394	243	498	12	39	−119
C(14)	263	387	544	80	−96	46
C(15)	509	364	845	190	−36	38
C(16)	403	387	624	−30	−30	118
C(17)	384	532	974	144	142	188
C(18)	669	411	514	146	−280	−87
S(19)	693	439	786	142	−352	−137
N(20)	302	245	410	33	−64	−11
O(21)	343	364	452	103	16	121
O(22)	508	582	726	227	92	246
O(23)	359	432	390	77	−118	3
Br	575	602	407	60	−82	−144

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

The crystal structure is illustrated in Figure 2 and the shorter intermolecular distances are in Table 5. The O(3) $\cdots$ Br^- separation of 3·25 Å indicates a hydrogen bond. Other distances correspond to normal van der Waals interactions.

The geometry of the acetylcholine-like system of penthienate (1) is similar to that observed in the crystal structures of parpanit hydrochloride [3] (2) and adiphenine hydrochloride [4] (3). It differs, however, with respect to the arrangement about O(21)–C(12) from that observed in quinuclidin-3-yl benzilate hydrobromide [5]

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

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

[13] R. W. Brimblecombe, D. M. Green, T. D. Inch, and B. J. Thompson, *J. Pharm. Pharmacol.*, 1971, **23**, 745, and references therein.

TABLE 3

Molecular dimensions

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

C(1)–C(2)	1·550(13)	C(10)–O(23)	1·423(9)
C(2)–C(3)	1·526(14)	C(10)–C(11)	1·540(10)
C(3)–C(4)	1·510(18)	C(11)–O(22)	1·198(10)
C(4)–C(5)	1·532(15)	C(11)–O(21)	1·324(10)
C(5)–C(1)	1·523(12)	C(12)–O(21)	1·444(10)
C(6)–C(7)	1·369	C(12)–C(13)	1·480(13)
C(7)–C(8)	1·416	N(20)–C(13)	1·536(10)
C(8)–C(9)	1·346	N(20)–C(14)	1·525(10)
C(9)–S(19)	1·721	N(20)–C(16)	1·543(11)
S(19)–C(6)	1·708	N(20)–C(18)	1·519(10)
C(1)–C(10)	1·520(12)	C(14)–C(15)	1·514(13)
C(6)–C(10)	1·516(11)	C(16)–C(17)	1·486(14)

(*b*) Bond angles (°); mean standard deviation 0·6°

C(1)–C(2)–C(3)	102·2	C(6)–C(10)–O(23)	107·6
C(2)–C(3)–C(4)	107·8	C(1)–C(10)–C(6)	111·0
C(3)–C(4)–C(5)	107·6	O(23)–C(10)–C(11)	109·9
C(4)–C(5)–C(1)	104·1	C(10)–C(11)–O(21)	111·2
C(5)–C(1)–C(2)	105·4	C(10)–C(11)–O(22)	125·6
C(6)–C(7)–C(8)	114·7	O(21)–C(11)–O(22)	123·1
C(7)–C(8)–C(9)	111·3	C(11)–O(21)–C(12)	116·3
C(8)–C(9)–S(19)	112·0	O(21)–C(12)–C(13)	109·9
C(9)–S(19)–C(6)	92·5	C(12)–C(13)–N(20)	116·4
S(19)–C(6)–C(7)	109·5	C(13)–N(20)–C(14)	109·1
C(2)–C(1)–C(10)	115·2	C(13)–N(20)–C(16)	106·8
C(5)–C(1)–C(10)	114·6	C(13)–N(20)–C(18)	112·9
C(7)–C(6)–C(10)	130·1	N(20)–C(14)–C(15)	115·1
S(19)–C(6)–C(10)	120·4	N(20)–C(16)–C(17)	115·6
C(1)–C(10)–C(11)	111·4	C(14)–N(20)–C(16)	107·7
C(1)–C(10)–O(23)	111·3	C(14)–N(20)–C(18)	109·4
C(6)–C(10)–C(11)	105·5	C(16)–N(20)–C(18)	110·8

(*c*) Torsion angles (°);* mean standard deviation 0·9°

C(2)–C(1)–C(10)–C(11)	−64·3
C(5)–C(1)–C(10)–C(11)	173·2
C(2)–C(1)–C(10)–O(23)	58·7
C(5)–C(1)–C(10)–O(23)	−63·8
C(2)–C(1)–C(10)–C(6)	178·4
C(5)–C(1)–C(10)–C(6)	55·9
S(19)–C(6)–C(10)–C(11)	117·2
C(7)–C(6)–C(10)–C(11)	−60·2
S(19)–C(6)–C(10)–O(23)	−0·1
C(7)–C(6)–C(10)–O(23)	−177·6
S(19)–C(6)–C(10)–C(1)	−122·0
C(7)–C(6)–C(10)–C(1)	60·6
C(6)–C(10)–C(11)–O(21)	−73·5
C(1)–C(10)–C(11)–O(21)	165·9
O(23)–C(10)–C(11)–O(21)	42·2
O(23)–C(10)–C(11)–O(22)	−142·9
C(10)–C(11)–O(21)–C(12)	174·1
O(22)–C(11)–O(21)–C(12)	−0·9
C(11)–O(21)–C(12)–C(13)	−179·7
O(21)–C(12)–C(13)–N(20)	59·9
C(12)–C(13)–N(20)–C(14)	−88·3
C(12)–C(13)–N(20)–C(16)	155·6
C(12)–C(13)–N(20)–C(18)	33·6
C(13)–N(20)–C(14)–C(15)	173·6
C(13)–N(20)–C(16)–C(17	−70·9
C(15)–C(14)–N(20)–C(16)	−70·9
C(15)–C(14)–N(20)–C(18)	49·6
C(17)–C(16)–N(20)–C(18)	52·4
C(17)–C(16)–N(20)–C(14)	172·1

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

(4), quinuclidin-3-yl di-2-thienylglycolate [6] (5), glycopyrronium bromide [7] (6), and piperidolate hydrochloride [1] (7). Pertinent torsion angles and non-bonded interatomic distances for these related anticholinergic molecules are listed in Table 6.† Thus in

† Torsion angles refer to the enantiomers with a positive synclinal–positive anticlinal O–C–C–N conformation. The absolute configuration of the acyl group, at chiral centre C(10), however, influences anticholinergic activity to a much greater extent than does the absolute configuration of the choline system. In the case of glycopyrronium bromide (6) consideration of the absolute configuration at C(10) indicates that the listed torsion angles may refer to the less active enantiomer.[7]

TABLE 4

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)—(5)

$$4{\cdot}747x - 3{\cdot}119y + 13{\cdot}053z = 3{\cdot}810$$

C(1) −0·223, C(2) 0·198, C(3) −0·101, C(4) −0·030, C(5) 0·156

Plane (*b*): C(2)—(5)

$$5{\cdot}495x - 2{\cdot}367y + 11{\cdot}921z = 2{\cdot}788$$

C(2) 0·022, C(3) −0·036, C(4) 0·036, C(5) −0·022, C(1) −0·534

Plane (*c*): C(6)—(9), S(19)

$$-5{\cdot}242x - 0{\cdot}206y + 10{\cdot}135z = 3{\cdot}807$$

C(6) 0·001, C(7) −0·005, C(8) 0·008, C(9) −0·006, S(19) 0·003, C(10) 0·054, O(23) 0·094

Plane (*d*): C(10)—(12), O(21), O(22)

$$3{\cdot}625x + 4{\cdot}358y + 11{\cdot}671z = 2{\cdot}905$$

C(10) −0·033, C(11) 0·035, C(12) −0·035, O(21) 0·036, O(22) −0·003, C(1) 0·308, C(6) −1·458, N(20) −1·182, O(23) 0·826

(*b*) Dihedral angles (°)

(*a*)—(*c*) 89·6 (*a*)—(*d*) 126·4 (*c*)—(*d*) 88·3

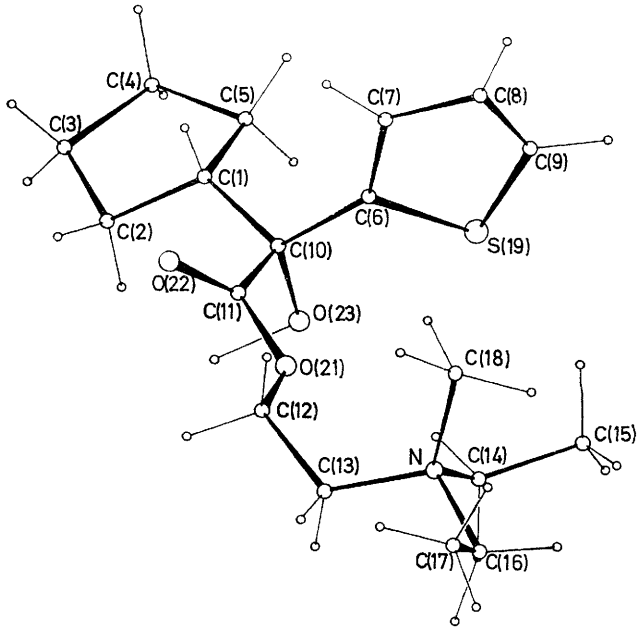


FIGURE 1 The penthienate cation as seen along the *a* axis (the positive direction of the *a* axis is towards the viewer), *b* and *c* axes as in Figure 2

TABLE 5

The shorter intermolecular contacts (Å) excluding hydrogen atoms

O(23) · · · Br	3·25	C(9) · · · O(22^{II})	3·67
C(18) · · · O(23^{I})	3·28	O(21) · · · Br	3·69
C(15) · · · O(22^{II})	3·53	S(19) · · · C(2^{II})	3·71
C(12) · · · O(23^{I})	3·57	C(8) · · · C(3^{III})	3·73
C(17) · · · C(14^{I})	3·58	C(9) · · · C(3^{III})	3·75
O(22) · · · C(4^{I})	3·63	C(15) · · · C(12^{II})	3·80
C(18) · · · S(19^{I})	3·66		

The superscripts refer to the following equivalent positions:

I $x-1, y, z$ II $x, y-1, z$ III $x-1, y-1, z$

(1)—(3) which are based on open-chain acetylcholine systems, C(11) is oriented antiplanar to C(13), corresponding to the normal conformation of primary esters and also the conformation adopted by acetylcholine in crystals of the chloride salt [14] and in solution.[15] In the

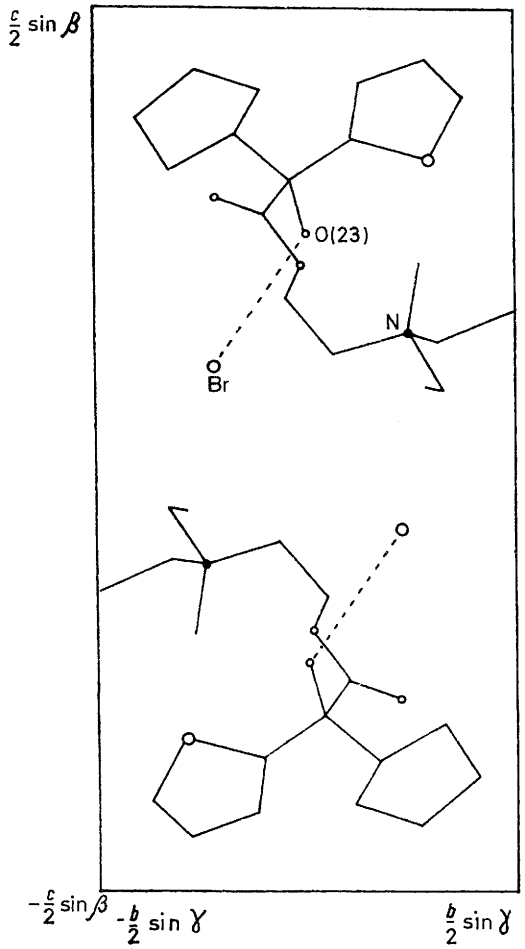


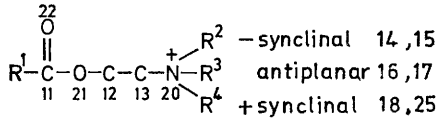
FIGURE 2 The crystal structure projected along the *a* axis

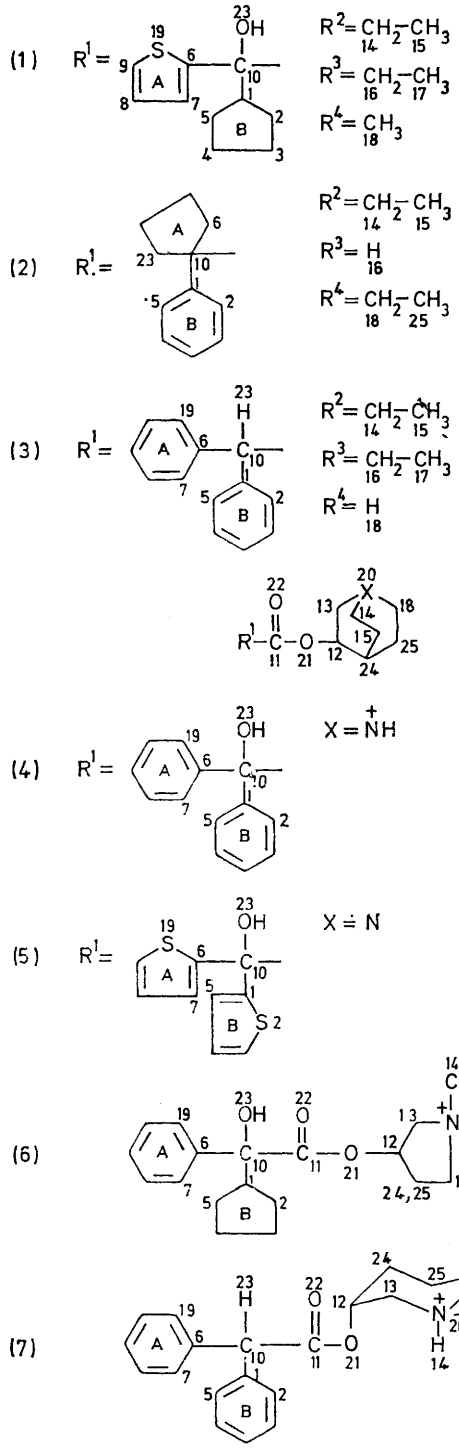
ring compounds (4)—(7), C(11) is antiplanar to C(24) and +synclinal to C(13), corresponding to the structure of acetylcholine bromide.[16] The structure [9] of the cyclohexyl analogue of glycopyrronium (hexapyrronium) in crystals of the bromide salt is so similar to glycopyrronium that references to glycopyrronium (6) apply, in general, also to hexapyrronium. Data for hexapyrronium are not presented separately in this paper.

The conformation of the cationic head in penthienate is similar to that in (3), but with a methyl group occupying the hydrogen site +synclinal to C(12). The arrangement about the C(13)–N bond deviates by *ca.* 26° from the perfectly staggered arrangement, presumably

[14] J. K. Herdklotz and R. L. Sass, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 583.
[15] P. Partington, J. Feeney, and A. S. V. Burgen, *Mol. Pharmacol.*, 1972, **8**, 269, and references therein.
[16] F. G. Canepa, P. J. Pauling, and H. Sorum, *Nature*, 1966, **210**, 907.
[17] G. N. J. Port and A. Pullman, *J. Amer. Chem. Soc.*, 1973, **95**, 4059.

to avoid an energetically unfavourable,[17] short C(14) · · · O(21) distance of 2·6 Å, as measured on a





model with a C(12)–C(13)–N–C(14) torsion angle of −60°. The actual C(14) · · · O(21) distance is 3·08 Å.

In (2) and (3) where the O–C–C–N torsion angles are larger, 94 and 83° compared to 60° in penthienate, the arrangement about C(13)–N approximates more closely to the ideal, and the C(14) · · · O(21) distances are 3·23 and 3·16 Å. The overall conformation of the cationic head in (2) differs, however, from that in (1) and (3) (*cf.* Table 6).

The ester group, atoms C(10)—(12), O(21), O(22), is planar to within 0·036 Å, and adopts the normal antiplanar conformation [torsion angle C(10)–C(11)–O(21)–C(12) 174°]. The cyclopentyl ring approximates to the envelope conformation with atoms C(2)—(5) coplanar to within 0·036 Å and C(1) displaced from this plane by 0·53 Å. The thienyl ring is essentially planar (Table 4).

The spatial arrangement of the ring substituents in the acyl group, relative to one another, and to the ester group and cationic head of the molecule, is governed by the conformations about bonds C(10)–C(1), C(10)–C(6), and C(10)–C(11). The conformation about C(10)–C(11) is such that C(6) of the thienyl ring is oriented —synclinal to the ester oxygen atom O(21), with C(1) of the cyclopentyl ring antiplanar and the hydroxy-oxygen atom, O(23), +synclinal to it. This differs from the conformation about the corresponding bond in (4)—(6), which also have a hydroxy-substituent in the acyl group, but where the hydroxy-group is antiplanar to the ester oxygen atom (*i.e.* synplanar to the carbonyl oxygen atom), with the ring substituents + and —synclinal to it. In (7) the conformation about C(10)–C(11) is similar to that of penthienate, but with a hydrogen atom in place of the hydroxy-group. The acyl group of parpanit (2) is not directly comparable but in this structure the orientation of the substituents on C(10) is also similar. The acyl group of adiphenine (3), however, does not conform to this pattern (Table 6). In the crystal structure of (—)-hyoscyaminehydrobromide [8] (8), the phenyl ring is oriented +synclinal to the ester oxygen atom.

Thus in all the structures (1)—(7), excepting (3), one ring substituent is oriented —synclinal to O(21) [torsion angle 6–10–11–O(21) in Table 6]. This ring is labelled A in the formulae. In (4)—(6), the second ring substituent is +synclinal to O(21), in (2) it is on the +synclinal to +anticlinal border, and in (1) and (7) it is antiplanar to O(21). A hydroxy-substituent is, in general, oriented antiplanar to O(21) as in structures (4)—(6), but not in penthienate.*

* *Note added in proof:* Since submission of this paper, Dr. A. Meyerhöffer kindly brought to our attention her paper ' The Molecular Structure of Some Anticholinergic Drugs,' FOA Reports, vol. 6, no. 13, 1972. This includes some structural parameters for the C(10)-hydroxy-analogue of adiphenine (3), benactyzine, as determined by crystal structure analysis of the hydrochloride salt (T. J. Petcher and P. Pauling, unpublished results). The conformation of the central portion of benactyzine is very similar to that of penthienate, but differs from those of the other C(10)-hydroxy-containing species (4)—(6), and hexapyrronium, with respect to the arrangements about bonds C(10)–C(11) and O(21)–C(12). It is noteworthy that penthienate and benactyzine are based on an open-chain acetylcholine system, whereas in the others, the nitrogen atom forms part of a ring system.

The orientations of the rings about bonds C(6)–C(10) and C(1)–C(10) are more varied and are probably affected to a greater extent by packing forces. In (1)—(5) and (7) torsion angles 7–6–10–11 are within the range —14 to —68°, and torsion angles 2–1–10–11, —36 to —98°. The acyl group of (6) bears a mirror image relationship to those of (1) and (8) (*cf.* footnote on p. 1128). In penthienate the orientation of the thienyl ring is such that the sulphur atom is synplanar to the hydroxy-oxygen atom [torsion angle S(19)–C(6)–C(10)–O(23) —0·1°] and atoms C(10) and

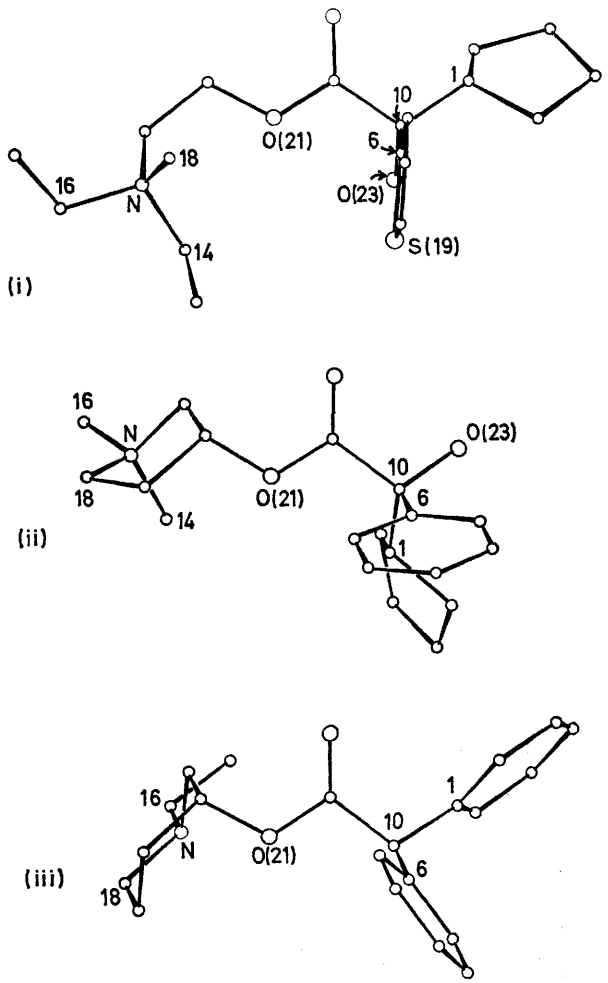


FIGURE 3 (i) Penthienate (1), (ii) glycopyrronium (6), and (iii) piperidolate (7) as viewed in a direction perpendicular to the mean plane of the ester group

O(23) lie within 0·09 Å of the ring plane. The distance S(19) · · · O(23) is 2·81 Å. In (5), the thienyl rings are oriented so that the hydroxy-oxygen atom is approximately equidistant (2·94 and 3·06 Å) from the two sulphur atoms.

Figure 3 shows views of molecules (1), (6), and (7) as seen in a direction perpendicular to the plane of the ester group. In each molecule the side of the ester group containing atoms C(10) and O(21) is partially blocked by the cationic head and one or both of the ring substituents in the acyl group. This is the case

also in (2), (4), (5), and (8), and to a lesser extent in (3). Molecules (1), (2), (7), and (8) possess only one ring substituent on this side of the ester group [oriented ±synclinal to O(21)], and in three of these [(1), (2), and (8)], the cationic head is on the same side of the ester plane as the ring substituent. In molecules (4)—(6) there are ring substituents both above and below the plane on this side of the ester group. Thus in all the molecules (1)—(8), excepting (3) and (7), there is a ring substituent on the same side of the ester plane as the cationic head * and both the ring and at least part of the cationic head are on the side of the ester group containing C(10) and O(21). Distances between the cationic head and the ring, expressed as the nitrogen–centre of ring separation, range from 5·20 to 6·12 Å in (1), (2), (4)—(6), and (8). This ring may be either aromatic [thienyl or phenyl in (1), (4), (5), and (8)] or saturated [cyclopentyl in (2) and (6)]. Molecules (3) and (7) which do not conform to this stereochemistry are relatively weak anticholinergics. If we accept tentative assignments of absolute configuration for the more active enantiomers of (1) and (6), then in both cases the cationic head is above the plane of the ester group, as viewed in Figure 2. The drawing of glycopyrronium (6) thus depicts the less active enantiomer (*cf.* footnote on p. 1128). However, the (−)-hyoscyamine structure (8), viewed in a similar manner would have the nitrogen atom and phenyl ring below the plane of the ester group.

TABLE 6

Comparison of molecular geometries of anticholinergic agents related to acetylcholine as determined in the solid state by *X*-ray crystallography. Some relevant data for (−)-hyoscyamine hydrobromide (8) and acetylcholine bromide (9) and chloride (10) are also included. Angles and distances involving a hydrogen atom are only approximate and are in parentheses. The letter *x* indicates that a particular angle or distance could not be obtained as hydrogen atom positions had not been determined. The atomic numbering is indicated in formulae (1)—(7), and Figure 1

	(1) [a]	(2) [b]	(3) [c]	(4) [d]	(5) [e]	(6) [f]	(7) [g]	(8) [h]	(9) [i]	(10) [j]
(i) Torsion angles (°)										
19–6–10–11	117		141	174	110	−141	163	−119		
7–6–10–11	−60		−43	−14	−68	45	−17	63		
2–1–10–11	−64	−91	−57	−79	−36	62	−98			
5–1–10–11	173	88	124	95	150	−179	81			
6–10–11–O(21)	−74	−32	−124	−67	−47	−79	−76	77	*x*	*x*
1–10–11–O(21)	166	93	110	54	73	42	159	*x*	*x*	*x*
23–10–11–O(21)	42	−143	(−7)	173	−165	160	(42)	−161	*x*	*x*
10–11–O(21)–12	174	−179	−175	176	180	175	−175	−170	−167	−175
11–O(21)–12–13	180	171	167	65	85	80	74		79	−167
11–O(21)–12–24				−175	−157	−164	−165			
O(21)–12–13–N	60	94	83	126	112	97	64		77	85
12–13–N–14	−88	−60	−75	−64	−56	−79	(−62)			−68
12–13–N–16	156	(180)	162	*x*		159	180		−176	171
12–13–N–18	34	68	(44)	59	63	39	54			54
13–N–14–15	174	−63	168	56	64					
13–N–16–17	−71		−73				60			
13–N–18–25		54		−69	−54	−42	−55			
(ii) Dihedral angles (°)										
Plane of ester group — plane of ring A [k]	88	86	44	106	92	114	97	90		
Plane of ester group — plane of ring B [k]	126	73	89	107	61	74	78			
Plane of ring A — plane of ring B [k]	90	21	82	78	83	75	86			
(iii) Non-bonded distances (Å)										
N · · · O(21)	2·99	3·28	3·21	3·55	3·45	3·23	2·96	3·74	3·29	3·26
N · · · C(11)	4·22	4·53	4·49	4·37	4·42	4·22	3·75	4·91	4·12	4·40
N · · O(22)	4·88	5·04	5·03	4·42	4·70	4·51	4·13	5·30	4·42	4·80
N · · · C(10)	5·04	5·57	5·46	5·66	5·60	5·41	4·66	5·93	5·07	5·38
N · · · 23	5·05	6·63	(5·02)	6·59	6·75	6·30	(4·26)		*x*	*x*
N · · Ring A centre [k]	5·20	5·85	7·58	7·64	6·84	7·44	7·01	6·12		
N · · · Ring B centre [k]	7·74	7·39	7·55	5·99	6·05	5·88	6·60			

[a] Present work. [b] Ref. 3. [c] Ref. 4. [d] Ref. 5. [e] Ref. 6. [f] Ref. 7. [g] Ref. 1. [h] Ref. 8. [i] From ref. 20. [j] Ref. 14. [k] Ring A is the ring substituent in the acyl group which is oriented −synclinal to the ester oxygen atom, as defined by torsion angle 6–10–11–O(21), except that in structure (3) it is oriented −anticlinal and in (8) + synclinal (see text). Ring B is the other ring substituent in the acyl group.

Angles between the mean planes of the ring substituents and the ester group are in Table 6. In general the rings are steeply inclined with respect to the ester plane, and to one another.

Chothia [18] has concluded from a study of the conformations of muscarinic and nicotinic agonists of acetylcholine, that the side of the molecule containing the methyl carbon atom and the ester oxygen atom [C(10) and O(21) in our numbering system] must be free of additional blocking groups for an acetylcholine analogue to show muscarinic activity. In molecules

* Because of the difference in conformation about the O(21)–C(12) bond, the open-chain acetylcholine derivatives (1) and (2) have the nitrogen atom on the same side of the ester plane as ring A, whereas in (4)—(6) it is on the same side as ring B.

[18] C. Chothia, *Nature*, 1970, **225**, 36.

(1)—(8), this side of the molecule is at least partially blocked by the large cationic head and at least one ring substituent. It is tempting to assume that the antagonist molecule approaches the muscarinic receptor with the acetylcholine-like system oriented in the same way as was suggested [18] for the interaction of acetylcholine with the receptor, *i.e.* that the ' methyl ' side of the acetylcholine molecule binds to the receptor. According to Beers and Reich,[19] muscarinic activity is caused by the interaction with the receptor of the cationic head, the ester oxygen atom, and the methyl group of the acetylcholine molecule. When the antagonist molecule approaches the receptor in this orientation, binding to the receptor is presumably achieved *via* the cationic head and the ring substituents in the acyl group. The ester oxygen atom, however, cannot approach the receptor closely enough for an interaction to occur. It is probable that the ring which is on the same side of the ester plane as the cationic head is of primary importance in the binding. The nitrogen–centre of ring distance (5·2—6·1 Å) is similar to the nitrogen–methyl carbon atom distance in acetylcholine chloride (5·4 Å), so it is possible that the antagonist makes use of the same binding sites as acetylcholine itself for the cationic head and the acyl group. However, the fact that inversion of absolute configuration at a chiral centre in the acyl group has a profound effect on anticholinergic activity, irrespective of the configuration at a chiral centre in the choline system may indicate that both rings, or possibly one ring and the hydroxy-group, are involved in interactions with the receptor. An alternative role for the hydroxy-group has been suggested [7] previously.

If we accept Beers and Reich's concept of muscarinic activity, then the antagonist properties of molecules (1)—(8) may be rationalised as being due to the prevention of the interaction between the ester oxygen atom and the receptor, required for muscarinic activity, by the large cationic head and acyl group. The antagonist molecule, accordingly, binds to the receptor in a non-functional manner, preventing the approach of acetylcholine molecules but without itself having the stimulatory effect of acetylcholine. The acetylcholine-like system, apart from the cationic head, does not seem to be directly involved in interactions with the receptor, and many anticholinergic molecules do not contain an ester group. Its function is thus merely to provide a suitable connector between the cationic head and the ring substituents.

Baker *et al.*,[20] in contrast to the views of Beers and Reich,[19] consider that the ester oxygen atom is not required for the muscarinic activity of acetylcholine, the essential pharmacodynamic groups being the trimethylammonium cationic head and the acetoxymethyl group. The distinction between antagonist and agonist is then attributed [21] merely to the stronger van der Waals interaction with the receptor of the larger acyl group of the antagonist, and for efficient antagonism, the presence of a hydroxy-group or other electrophilic group in a suitable spatial relationship to the charged nitrogen atom and the acyl binding group.

At the present time we should prefer to express our views in somewhat more general terms, that the stereochemistry of the interaction of the terminal groups of the antagonist with the receptor or with neighbouring accessory receptor areas is such that the acetylcholine-like system straddles the receptor, but that a critical part of it is prevented from coming into sufficiently close proximity for stimulatory interaction to occur, without, at this stage, attempting to specify what this critical part of acetylcholine may be.

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