Stereochemistry of Anticholinergic Agents. Part 10.[1] Crystal and Molecular Structure of the (*R*)-Enantiomer of *N*-[2-(2-Cyclohexylmandeloyloxy)ethyl]-*N*-methylpiperidinium Iodide

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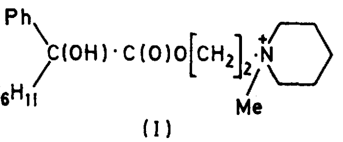
The title compound crystallises in the monoclinic space group $P2_1$ with a = 12.266(10), b = 9.190(10), c = 10.228(10) Å, β = 97.12 (5)°, and Z = 2. The structure was established by Fourier and Patterson methods from three-dimensional *X*-ray counter data and refined by least-squares to R 3.5% for 2 183 observed structure amplitudes. Estimated standard deviations for bond lengths, bond angles, and torsion angles average 0.011 Å, 0.6° and 0.9°. The cyclohexyl and piperidinium rings are in the chair conformation. The five-atom bridging chain is equatorial with respect to the cyclohexyl ring and axial with respect to the piperidinium ring. The overall shape of the cation is similar to that observed for other highly active anticholinergic agents in the solid state.

THE title compound (I) is an extremely potent anticholinergic agent with high affinity for the muscarinic receptor, the (*S*)-enantiomer being, however, *ca.* 100 times less active.[2] It belongs to a class of synthetic anticholinergics structurally related to acetylcholine, but differing from it in containing ring substituents and a hydroxy-group in the acyl moiety and a larger cationic head. Previous *X*-ray crystallographic work on this type of anticholinergic has been largely confined to two structural groups exemplified by penthienate bromide[3] and glycopyrronium bromide.[4] The former are esters of primary alcohols and are based on an open-chain acetylcholine system, while the latter are esters of secondary alcohols in which the nitrogen atom forms part of a ring system. In the solid state, both types of cation adopt a characteristic, overall similar, claw-like shape,[5] but differ in conformation about certain of the individual bonds.



(I)

The title compound (I), whose crystal structure is herein reported, cannot be categorised into either of these groups, since, although it is a primary ester, the onium nitrogen atom forms part of a ring.

EXPERIMENTAL

Crystallographic Measurements.—Crystals of (I) suitable for *X*-ray analysis were obtained from butan-2-one. Cell dimensions were determined initially from oscillation and Weissenberg photographs. 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, of dimensions 0.2 × 0.5 × 0.2 mm, was mounted about the direction of elongation (b). The ω-scan technique was employed with a stepping interval of 0.02° and a step time of 1 s. For layers $h0l$ and $h1l$ the scan range was 2.4°, and for reflections on the second and higher layers a variable-scan technique was used so as to increase the scan range at low values of the azimuth angle and high values of the equi-inclination angle. Backgrounds were measured for 30 s at each end of the scan. Of the 2 939 reflections scanned within the range $0.10 < \sin\theta/\lambda < 0.65$, 2 183, having $I > 2.5\sigma(I)$, were considered observed and were used in the structure analysis. Three reflections from the zero layer were re-measured after each layer of data collection to monitor the stability of the system. No significant variation of intensity was observed. Intensities were converted into structure amplitudes in the usual way, but absorption corrections were not applied.

Crystal Data.—$C_{22}H_{34}INO_3$, M = 487.5. Monoclinic, a = 12.266(10), b = 9.190(10), c = 10.228(10) Å, β = 97.12(5)°, U = 1 144.1 Å^3, Z = 2, D_c = 1.415 g cm^{-3}, $F(000)$ = 500. Systematic absences: $0k0$ with k odd; space group $P2_1$ ($P2_1/m$ excluded since the material is optically active). Mo-K_α radiation, λ = 0.710 69 Å; μ(Mo-K_α) = 13.1 cm^{-1}.

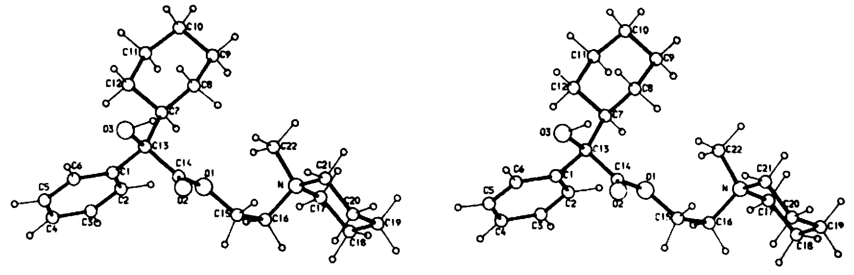


FIGURE 1 Stereoscopic view of the cation (I)

Structure Determination.—The co-ordinates of the iodide ion were obtained from a three-dimensional Patterson synthesis, the y co-ordinate being set at 0.5 to define the origin of the unit cell. The electron-density map phased on the iodide position exhibited the expected two-fold pseudosymmetry. A chemically reasonable fragment of 18 of the lighter atoms could, however, be identified and when

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[1] Part IX, T. A. Hamor, *Acta Cryst.*, 1976, **B32**, 1846.

[2] R. B. Barlow, F. M. Franks, J. D. M. Pearson, and A. A. Butt, *Brit. J. Pharmacol.*, 1972, **46**, 300.

[3] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1974, 1126.

[4] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 1875.

[5] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1975, 467.

these atoms were included in the phasing calculations, the resulting electron-density map no longer exhibited pseudo-symmetry and all the remaining atoms (apart from hydrogen atoms) could be located. Least-squares refinement of positional and isotropic temperature factors reduced *R* to 12.0%. The iodide ion was now allowed to vibrate anisotropically and least-squares refinement continued to *R* 5.6%. All atoms were then refined anisotropically and *R* reduced to 4.4%. The hydrogen atoms, except for the hydroxy-hydrogen atom, were now placed in their theoretical positions (assuming C–H 1.08 Å) and included in the

TABLE 1

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

	x	*y*	*z*
C(1)	6 398(6)	3 351(9)	3 027(8)
C(2)	6 440(5)	3 332(8)	1 678(6)
C(3)	5 684(6)	2 518(9)	850(8)
C(4)	4 892(6)	1 689(9)	1 377(10)
C(5)	4 847(6)	1 736(9)	2 727(10)
C(6)	5 590(5)	2 532(8)	3 536(8)
C(7)	7 205(6)	5 872(8)	3 433(7)
C(8)	7 989(6)	6 860(8)	4 313(7)
C(9)	8 042(6)	8 343(9)	3 684(7)
C(10)	6 900(7)	9 046(9)	3 475(8)
C(11)	6 075(7)	8 061(9)	2 679(8)
C(12)	6 066(7)	6 551(11)	3 276(9)
C(13)	7 205(6)	4 304(9)	3 944(7)
C(14)	8 345(5)	3 587(8)	4 023(7)
C(15)	9 916(5)	3 247(7)	2 881(7)
C(16)	10 388(6)	3 810(9)	1 674(7)
C(17)	11 304(5)	5 622(8)	440(6)
C(18)	12 301(6)	4 798(16)	243(7)
C(19)	13 218(4)	4 981(16)	1 380(7)
C(20)	12 807(5)	4 602(9)	2 680(7)
C(21)	11 817(6)	5 509(8)	2 844(6)
C(22)	9 996(7)	6 393(9)	1 903(10)
N	10 883(4)	5 312(5)	1 755(4)
O(1)	8 824(3)	3 870(5)	2 924(4)
O(2)	8 782(4)	2 919(7)	4 927(5)
O(3)	6 860(4)	4 234(6)	5 225(4)
H(2)	7 063	3 953	1 266
H(3)	5 713	2 528	−201
H(4)	4 323	1 023	747
H(5)	4 215	1 135	3 141
H(6)	5 552	2 528	4 585
H(7)	7 488	5 791	2 477
H(8A)	8 799	6 381	4 441
H(8B)	7 696	6 974	5 261
H(9A)	8 591	9 030	4 319
H(9B)	8 347	8 227	2 744
H(10A)	6 951	10 062	2 956
H(10B)	6 629	9 251	4 423
H(11A)	6 288	7 974	1 688
H(11B)	5 266	8 532	2 651
H(12A)	5 782	6 626	4 232
H(12B)	5 513	5 867	2 641
H(15A)	10 448	3 559	3 758
H(15B)	9 855	2 076	2 833
H(16A)	9 732	3 808	865
H(16B)	11 022	3 060	1 465
H(17A)	11 486	6 769	393
H(17B)	10 664	5 344	−343
H(18A)	12 092	3 657	148
H(18B)	12 593	5 173	−651
H(19A)	13 499	6 096	1 411
H(19B)	13 891	4 269	1 229
H(20A)	13 446	4 819	3 481
H(20B)	12 589	3 464	2 683
H(21A)	11 530	5 217	3 766
H(21B)	12 058	6 640	2 873
H(22A)	9 676	6 210	2 826
H(22B)	9 344	6 270	1 099
H(22C)	10 329	7 481	1 891
H[O(3)]	7 615	4 656	5 803
I	8 193(0)	5 000	8 491(0)

TABLE 2

Molecular dimensions

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

C(1)–C(2)	1.387(10)	C(13)–C(14)	1.539(10)
C(2)–C(3)	1.393(9)	C(14)–O(1)	1.356(8)
C(3)–C(4)	1.395(12)	C(14)–O(2)	1.181(8)
C(4)–C(5)	1.389(12)	C(15)–O(1)	1.462(7)
C(5)–C(6)	1.365(10)	C(15)–C(16)	1.518(9)
C(6)–C(1)	1.396(10)	C(16)–N	1.507(9)
C(1)–C(13)	1.548(11)	C(17)–N	1.526(7)
C(7)–C(13)	1.533(9)	C(17)–C(18)	1.474(11)
C(7)–C(8)	1.530(10)	C(18)–C(19)	1.524(10)
C(8)–C(9)	1.512(11)	C(19)–C(20)	1.520(9)
C(9)–C(10)	1.533(10)	C(20)–C(21)	1.499(10)
C(10)–C(11)	1.518(11)	C(21)–N	1.507(8)
C(11)–C(12)	1.518(14)	C(22)–N	1.495(8)
C(12)–C(7)	1.521(11)	O(3)–H[O(3)]	1.11
C(13)–O(3)	1.427(8)		

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

N ··· O(1)	3.21	N ··· C(13)	5.36
N ··· O(2)	4.91	N ··· A *	7.06
N ··· O(3)	6.50		
N ··· C(14)	4.40	N ··· B *	5.73

(*c*) Bond angles (°), with standard deviations in parentheses

C(2)–C(1)–C(6)	118.7(7)	C(7)–C(13)–O(3)	111.5(6)
C(2)–C(1)–C(13)	120.7(7)	C(14)–C(13)–O(3)	107.7(6)
C(6)–C(1)–C(13)	120.6(7)	C(13)–C(14)–O(1)	111.0(6)
C(1)–C(2)–C(3)	120.5(7)	C(13)–C(14)–O(2)	125.8(7)
C(2)–C(3)–C(4)	120.1(7)	O(1)–C(14)–O(2)	123.2(6)
C(3)–C(4)–C(5)	118.9(7)	C(14)–O(1)–C(15)	116.3(5)
C(4)–C(5)–C(6)	120.9(7)	O(1)–C(15)–C(16)	109.5(5)
C(5)–C(6)–C(1)	121.0(8)	C(15)–C(16)–N	117.3(6)
C(8)–C(7)–C(12)	108.7(7)	C(16)–N–C(17)	107.5(5)
C(8)–C(7)–C(13)	112.6(6)	C(16)–N–C(21)	114.5(5)
C(12)–C(7)–C(13)	112.5(8)	C(16)–N–C(22)	108.7(5)
C(7)–C(8)–C(9)	110.0(6)	C(17)–N–C(21)	108.7(4)
C(8)–C(9)–C(10)	110.7(7)	C(17)–N–C(22)	107.2(5)
C(9)–C(10)–C(11)	111.1(6)	C(21)–N–C(22)	110.0(5)
C(10)–C(11)–C(12)	111.5(7)	N–C(17)–C(18)	113.6(6)
C(11)–C(12)–C(7)	111.4(8)	C(17)–C(18)–C(19)	112.7(8)
C(1)–C(13)–C(7)	110.6(7)	C(18)–C(19)–C(20)	110.4(5)
C(1)–C(13)–C(14)	107.4(6)	C(19)–C(20)–C(21)	109.4(6)
C(1)–C(13)–O(3)	106.9(6)	C(20)–C(21)–N	113.7(5)
C(7)–C(13)–C(14)	112.5(7)	H[O(3)]–O(3)–C(13)	99

(*d*) Selected torsion angles (°) † mean standard deviation 0.9°

C(2)–C(1)–C(13)–C(14)	−72.2
C(2)–C(1)–C(13)–O(3)	172.5
C(6)–C(1)–C(13)–C(14)	109.9
C(6)–C(1)–C(13)–O(3)	−5.4
C(8)–C(7)–C(13)–C(14)	−60.2
C(8)–C(7)–C(13)–O(3)	60.9
C(12)–C(7)–C(13)–C(14)	176.6
C(12)–C(7)–C(13)–O(3)	−62.4
C(13)–C(7)–C(8)–C(9)	174.0
C(13)–C(7)–C(12)–C(11)	−175.9
C(12)–C(7)–C(8)–C(9)	−60.6
C(7)–C(8)–C(9)–C(10)	59.3
C(8)–C(9)–C(10)–C(11)	−55.3
C(9)–C(10)–C(11)–C(12)	53.0
C(10)–C(11)–C(12)–C(7)	−55.6
C(11)–C(12)–C(7)–C(8)	58.7
C(1)–C(13)–C(14)–O(1)	77.6
C(1)–C(13)–C(14)–O(2)	−104.9
C(7)–C(13)–C(14)–O(1)	−44.3
C(7)–C(13)–C(14)–O(2)	133.1
O(3)–C(13)–C(14)–O(1)	−167.6
O(3)–C(13)–C(14)–O(2)	9.9
C(13)–C(14)–O(1)–C(15)	179.9
C(14)–O(1)–C(15)–C(16)	−173.3
O(1)–C(15)–C(16)–N	79.8
C(15)–C(16)–N–C(17)	179.6
C(15)–C(16)–N–C(21)	58.7
C(15)–C(16)–N–C(22)	−64.7
C(16)–N–C(17)–C(18)	−72.5
C(16)–N–C(21)–C(20)	64.7

TABLE 2 (*Continued*)

C(22)–N–C(17)–C(18)	170.8
C(22)–N–C(21)–C(20)	−172.5
C(21)–N–C(17)–C(18)	52.0
N–C(17)–C(18)–C(19)	−53.0
C(17)–C(18)–C(19)–C(20)	54.1
C(18)–C(19)–C(20)–C(21)	−55.6
C(19)–C(20)–C(21)–N	58.7
C(20)–C(21)–N–C(17)	−55.5
H[O(3)]–O(3)–C(13)–C(14)	49

* A is centre of ring C(1)—(6). B is centre of ring C(7)—(12).

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

least-squares calculations, without, however, refining their parameters. A difference synthesis then enabled the hydroxy-hydrogen atom to be located with a reasonable degree of certainty. Least-squares refinement was terminated when all calculated shifts were $<0.1\sigma$ and R 3.5% for the 2 183 observed amplitudes.* The weighted R factor,[6] R' was 3.84%. To establish the absolute configuration, the enantiomer centrosymmetrically related to that depicted in Figure 1 was refined until all calculated shifts were $<0.1\sigma$. The values of R and R' were, however, higher (3.7 and 4.04%). The second absolute configuration can therefore be rejected with a very high degree of probability.[6]

The weighting scheme employed in the final cycles of least-squares calculations was: $w = 1/[\sigma^2(F) + 0.000\,3|F|^2]$, where $\sigma(F)$ is the standard deviation in the observed amplitude derived from counting statistics.

Computations were carried out on the Birmingham University 1906A computer using the SHELX[7] package of crystallographic programs together with local ancillary programs.

RESULTS AND DISCUSSION

Atomic positional parameters and molecular dimensions are listed in Tables 1—3. A stereoscopic view of the cation is shown in Figure 1, which also indicates the atomic numbering scheme used. The absolute configuration determined from consideration of anomalous dispersion effects confirms that established by Barlow and co-workers.[2] Intermolecular distances are in Table 4, and the packing arrangement is illustrated in Figure 2.

TABLE 3

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 (i): C(1)—(6)

$$-7.503x + 7.200y - 0.341z = -2.489$$

C(1) 0.002, C(2) 0.001, C(3) −0.008, C(4) 0.012, C(5) − 0.009, C(6) 0.003, C(13) −0.047

Plane (ii): C(7)—(12)

$$5.212x - 0.868y - 9.676z = -0.339$$

C(7) −0.262, C(8) 0.266, C(9) −0.241, C(10) 0.212, C(11) −0.214, C(12) 0.238

Plane (iii): C(13)—(15), O(1), O(2)

$$-4.441x - 7.679y - 3.735z = -7.976$$

C(13) 0.002, C(14) −0.012, C(15) −0.002, O(1) 0.007, O(2) 0.006, C(1) −1.430, C(7) 1.016, N 1.592

Plane (iv): C(17)—(21), N

$$-3.138x - 8.881y + 0.081z = -8.333$$

C(17) 0.204, C(18) −0.214, C(19) 0.228, C(20) −0.249, C(21) 0.245, N −0.214

(*b*) Dihedral angles (°)

(i)–(ii) 76.4, (i)–(iii) 67.2, (i)–(iv) 53.3, (ii)–(iii) 72.7, (ii)–(iv) 89.8, (iii)–(iv) 24.5

TABLE 4

Intermolecular contacts <3.8 Å for the heavier atoms [<4.0 Å for contacts involving the iodide ion]

C(21) ··· O(2^{I})	3.33	C(19) ··· C(4^{III})	3.66
C(10) ··· C(5^{II})	3.54	C(22) ··· O(2^{I})	3.68
C(10) ··· C(6^{II})	3.59	C(11) ··· C(5^{II})	3.70
O(3) ··· I	3.60	C(19) ··· C(5^{III})	3.76
C(20) ··· C(5^{III})	3.63	C(18) ··· C(3^{IV})	3.78
C(19) ··· C(3^{IV})	3.63	C(16) ··· I^{V}	3.92

Roman numeral superscripts refer to the following equivalent positions:

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

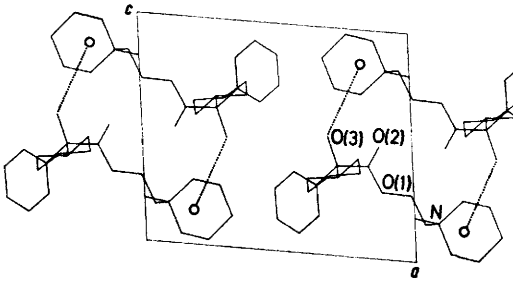

FIGURE 2 The contents of the unit cell projected along the crystallographic y axis. Hydrogen bonds are indicated by dotted lines. Circles denote iodide ions

The phenyl ring is planar to within 0.012 Å, and the bond lengths range from 1.365 to 1.396, mean 1.388 Å in good agreement with the accepted[8] aromatic bond length (1.394 Å). The cyclohexyl and piperidinium rings are in chair conformations with ring torsion angles 53.0—60.6, mean 57.1°, and 52.0—58.7, mean 54.8°, respectively. The five-atom bridging chain C(13)—(16) is equatorial with respect to the cyclohexyl ring and axial with respect to the piperidinium ring. The ester group [C(13), C(14), O(1), C(15), O(2)] is planar to within 0.012 Å and adopts the antiplanar conformation typical of esters [torsion angle C(13)–C(14)–O(1)–C(15) 179.9°]. Bond lengths and angles within the ester group are also in good agreement with previous results. The mean $C(sp^3)$–$C(sp^3)$ bond length is 1.515 Å and the mean $C(sp^3)$–N^+ length 1.509 Å. The angle C(15)–C(16)–N (117.3°) is larger than might be expected at an sp^3-hybridized carbon atom. Large C–C–N^+ angles, however, also occur in the crystal structures of penthienate bromide[3] and salts of acetylcholine.[9]

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* Observed and calculated structure amplitudes and thermal parameters are published in Supplementary Publication No. SUP 21890 (15 pp., 1 microfiche). See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1976, Index issue.

[6] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

[7] G. M. Sheldrick, SHELX 76, Program for Crystal Structure Determination, University of Cambridge, September 1975.

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

[9] 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; T. Svinning and H. Sorum, *Acta Cryst.*, 1975, **B31**, 1581; B. Jensen, *Acta Chem. Scand.*, 1975, **B29**, 531.

The conformation of the central six-atom chain [C(13),C(14),O(1),C(15),C(16),N] of (I) is very similar to the corresponding moiety in penthienate bromide,[3] but differs from the situation in glycopyrronium bromide[4] with respect to the O(1)–C(15) bond. The torsion angles C(14)–O(1)–C(15)–C(16) and O(1)–C(15)–C(16)–N are −173 and 80° in (I). Corresponding values are 180 and 60° in penthienate, but ∓80 and ∓97° in glycopyrronium.* The conformation about C(13)–C(14), however, closely resembles the situation in glycopyrronium, with the hydroxy-group synplanar to the carbonyl oxygen atom. In penthienate the substituents in the acyl group are rotated through *ca.* 150° about this bond, so that the cyclopentyl ring in penthienate occupies approximately the position of the hydroxy-group in the present structure.

The overall shape of the cation is, nevertheless, quite similar to that found for penthienate and glycopyrronium. The extremities of the 'claw'[5] are formed by the cationic head and the cyclohexyl ring with the nitrogen to centre-of-ring distance 5.73 Å. The cyclohexyl ring is inclined at 73° to the ester plane. In penthienate and glycopyrronium the extremities of the 'claw' are the cationic heads and a thienyl and cyclopentyl ring, respectively, with the nitrogen to centre-of-ring distances 5.20 and 5.88 Å, and the angles between the ester plane and the rings, 88 and 74°. In penthienate and the cation (I), the ring substituent which forms part of the 'claw' is oriented (−)-synclinal to O(1); in the case of glycopyrronium, because of the ambiguity in the absolute configuration, (−)-synclinal or (+)-synclinal.

The O(3) ··· O(2) distance is 2.69 Å, but as in the glycopyrronium structure, intramolecular hydrogen bonding does not occur. The hydroxy-hydrogen atom H[O-(3)], was located with a reasonable degree of certainty, and it appears to be situated favourably for hydrogen-bond formation to the iodide ion. The distances O(3) ··· I^- and H[O(3)] ··· I^- are 3.60 and 2.77 Å, and the angle H[O(3)]–O(3) ··· I^- is 35°, consistent[11] with O–H ··· I^- hydrogen bonding.

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* Anticholinergic activity is critically dependent on the absolute configuration of the acyl group.[10] The crystal structure analyses of penthienate and glycopyrronium were carried out on racemates. The absolute configuration of the more active enantiomer of penthienate was established[3] with some degree of certainty by extrapolation of results[10] on related anticholinergics. For glycopyrronium the extrapolation would be rather more tenuous so that the absolute configuration of the more active form cannot be safely predicted. Both possible signs are therefore quoted for the torsion angles.

[10] 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 P. B. J. Thompson, *ibid.*, 1971, **23**, 745.

[11] J. R. Clark, *Rev. Pure Appl. Chem.* (*Australia*), 1963, **13**, 50.