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The Crystal and Molecular Structure and Absolute Configuration of (+)-(1*S*,2*S*)-*trans*-Acetoxycyclopropyltrimethylammonium Iodide

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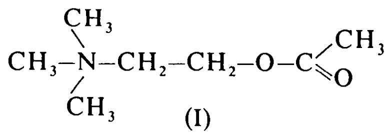
Crystals of (+)-*trans*-acetoxycyclopropyltrimethylammonium iodide, $C_8H_{16}NO_2I$, are orthorhombic, a = 23·628 (16), b = 7·898 (5), c = 6·242 (3) Å, space group $P2_12_12_1$ (D_2^4), Z = 4. The conformation of this cholinergic agonist can be considered in terms of two torsion angles: N C C O is observed at the fairly rigidly fixed value of +137° and C–C–O–C is observed at −147°, both in reasonable agreement with those observed in other muscarinic agonists. The absolute configuration of the (+) enantiomer was determined as (1*S*,2*S*).

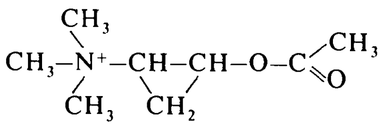
Introduction

In considering the relationships between the biological activities and the conformations of acetylcholine (I), one of the variable structural parameters is the torsion angle N^+–C–C–O.



(I)

Chiou, Long, Cannon & Armstrong (1969) fixed the possible value of this torsion angle by synthesizing the isomers of acetoxycyclopropyltrimethylammonium (ACTM) in which C(4) and C(5) form part of a cyclopropane ring (II).



(II)

They measured the muscarinic and nicotinic activities of the (∓)-*cis*, (+)-*trans* and (−)-*trans* isomers and also the rates at which these isomers are hydrolysed by acetylcholinesterase. In all cases, the (+)-*trans* isomer is the most active, and is also the most rapidly hydrolysed. To determine the stereochemistry and absolute configuration of (+)-*trans*-ACTM, we carried out an X-ray structural analysis of single crystals of the iodide.

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Experimental results

Dr J. G. Cannon provided us with (+)-*trans*-ACTM iodide in the form of a powder. Dr T. J. Petcher grew a number of crystals suitable for X-ray diffraction analysis by dissolving the powder in a 1:1:1 mixture of MeOH/acetone/ethyl acetate and allowing the solvent to evaporate slowly.

An optical examination of the crystals showed them to be square or rectangular thin plates with only a few well formed edges. Extinction occurred parallel to the edges or the diagonals of the plates. The interference figure was biaxial and indicated a large value of the optic angle (2V). Movement of the interference figure when viewed through a moving quartz wedge suggested the crystal was negative. This conclusion is only probable, because the large value of 2V does not make it certain that the acute bisectrix was being viewed. An X-ray examination showed the crystals to be orthorhombic and that the plate face is (110).

Crystal data

(+)-*trans*-Acetoxycyclopropyltrimethylammonium iodide, $C_8H_{16}NO_2I$, M_r = 285·21, a = 23·628 (16), b = 7·898 (5), c = 6·242 (3) Å, d_c = 1·626 g cm^{-3}, Z = 4. Laue symmetry *mmm*; systematic absences in the diffraction data: $h00$: $h = 2n + 1$; $0k0$: $k = 2n + 1$; $00l$: $l = 2n + 1$; space group $P2_12_12_1$ (D_2^4).

The diffraction data were collected from a crystal of approximate dimensions 0·30 × 0·30 × 0·05 mm. The a axis was parallel to the fibre on which it was mounted. The data were collected on a computer-controlled Stoe four-circle diffractometer.

Initially, the X-ray detector was centred on nine diffraction maxima and the values of the three angular coordinates thereby determined for each maximum were used to calculate the unit-cell parameters and the angular orientation of the crystal with respect to the diffractometer axes, by means of a least-squares refinement. Cu $K\alpha$ radiation, with the X-ray tube operated at 40 kV and 18 mA (with a Ni filter), was used to collect the diffraction data in two sets. The first had reflexions for which h, k and l were positive and the second set had those with h and k positive and l negative. The 2θ range for both sets was 1–45°. An instrument fault occurred during the collection of the second set and it was only used to determine the absolute configuration of the structure, the first set alone being used for the structure determination and refinement. A standard intensity was measured after every 25 measurements of other diffraction maxima.

The data were processed on an IBM 360/65 computer using a program, written by Miss Margaret Dellow and Dr T. J. Petcher, which corrected the data for the Lorentz–polarization factor. Of the 1968 measured diffraction maxima, 1451 had an intensity I greater than or equal to $3\sigma(I)$. Of these, 789 had hkl all positive or zero and were used for the structure analysis and refinement. The diffraction maxima measured twice had a stochastic R value, $\Sigma\sigma(I)/\Sigma I^2$, of 0·075.

Structure analysis

A three-dimensional Patterson synthesis calculated with $(F_{obs})^2$ as coefficients clearly showed peaks on the Harker sections due to vectors between symmetry-related iodine atoms, and gave the position of the iodine atom as $x = 0{\cdot}0700$, $y = 0{\cdot}0969$ and $z = 0{\cdot}1542$. A Fourier synthesis using phases calculated from the position of the iodine atom and the observed structure factors clearly showed all non-hydrogen atoms. The structure was refined by full-matrix least-squares analysis using a computer program written by Dr Shearing and his colleagues at Manchester University and adapted for use on the University of London Atlas Computer by Dr R. W. Baker. Each diffraction maximum $I(hkl)$ was given a weight $4I(hkl)/\sigma(I)$, where $\sigma(I)$ is the statistical standard deviation of the intensity calculated as the square root of the sum of the peak and background counts. The scattering factors used were those of Cromer & Waber (1965) and the anomalous-scattering factor of iodine for Cu $K\alpha$ radiation was that of Cromer (1965). The scattering factor for I^- was used for iodine.

The refinement of the structural parameters occurred in the following stages: (1) Overall temperature factor and scale factor. (2) x,y,z and B for all non-hydrogen atoms. (3) x,y,z and b_{ij} for iodine, and x,y,z and B for all other non-hydrogen atoms. (4) Calculation of the absolute configuration (see below). (5) Observed Fourier and difference Fourier syntheses. These functions allowed the determination of 13 H atoms (see below). (6) x,y,z,b_{ij} for iodine and x,y,z and B for the other non-hydrogen atoms with the correct absolute configuration and the positions of the H atoms fixed. After refinement, the conventional agreement index R is 0·067, and the weighted R is 0·080 (using the above weighting scheme).

The imaginary component of the anomalous-dispersion coefficient of iodine for Cu $K\alpha$ is 6·68 e. Using this value, calculations of structure factors (F_{calc}) for two octants of data (hkl and $hk\bar{l}$) gave in all eight Laue symmetric pairs of diffraction maxima which had differences of more than 2·0 e. The values of F_{calc} for the (1S) enantiomer are given in column 2 of Table 1. In column 3 are the observed structure factors F_{obs} for these diffraction maxima. The observed structure factors have been corrected for variation in experimental technique by comparison with several

Table 1. *Absolute configuration of (+)-trans-acetoxycyclopropyltrimethylammonium iodide*

$h\,k\,l$	F_{calc}*	F_{obs}	$F_{calc}(hkl) - F_{calc}(hk\bar{l})$	$F_{obs}(hkl) - F_{obs}(hk\bar{l})$
2 3 2	14·0	18·9	+3·1	+0·5
2 3 $\bar{2}$	10·9	18·4		
4 1 2	11·2	7·3	+3·0	−2·0
4 1 $\bar{2}$	8·2	9·3		
9 1 1	57·3	61·4	+2·8	+6·6
9 1 $\bar{1}$	54·5	54·8		
5 1 1	86·1	107·6	+2·7	+6·3
5 1 $\bar{1}$	83·4	101·3		
6 1 2	86·9	97·9	−2·6	−7·5
6 1 $\bar{2}$	89·5	105·4		
1 1 1	66·7	75·3	−2·5	−1·8
1 1 $\bar{1}$	69·2	77·1		
6 1 1	79·9	91·6	−2·2	−1·9
6 1 $\bar{1}$	82·1	93·5		
3 3 3	16·2	15·5	−2·0	+0·2
3 3 $\bar{3}$	18·2	15·3		

* Calculated for the (S,S) enantiomer.

Table 2. *Final positional* ($\times 10^4$) *and thermal parameters for the non-hydrogen atoms*

	x	y	z	B (Å^2)
I(1)	9293 (1)	9037 (3)	8527 (4)	*
N(1)	5899 (11)	6039 (44)	7717 (40)	4·5
C(1)	5814 (18)	7795 (46)	8932 (65)	6·1
C(2)	5402 (14)	5897 (54)	6175 (62)	6·1
C(3)	5849 (14)	4455 (41)	9181 (51)	3·9
C(4)	6486 (12)	5924 (46)	6846 (50)	3·4
C(8)	6628 (15)	4884 (46)	4917 (61)	3·8
C(5)	6601 (18)	6892 (50)	4852 (67)	4·6
O(1)	7133 (11)	7800 (33)	4867 (42)	5·1
C(6)	7461 (19)	8040 (33)	2955 (77)	7·5
O(2)	7215 (11)	7334 (32)	1440 (51)	6·3
C(7)	7993 (14)	8954 (47)	3305 (59)	5·0

* Anisotropic thermal parameters ($\times 10^4$) for the iodide ion:

b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
23	136	236	−1	0	−1

nearby (in reciprocal space) values of F_{calc} and F_{obs} which suffer little or no effects from anomalous dispersion. Comparison of F_{calc} and F_{obs}, columns 4 and 5, indicates that the absolute configuration of (+)-*trans*-acetoxycyclopropyltrimethylammonium iodide is (1*S*,2*S*).

From the difference Fourier synthesis calculated during the refinement of the structure analysis, ten H atoms were clearly seen above the noise of the map. Three more [H(32), H(33) and H(41)] were diffuse with lower peak heights. There was no indication of the H atoms of the acetoxy methyl group. The positions of the H atoms were not refined but the atoms were included in the refinement of the rest of the structure and were assigned isotropic thermal parameters with values similar to those of the C atoms to which they were bonded for the last stage of the refinement.

The final positional parameters and thermal parameters are given in Table 2 for the non-hydrogen atoms. Table 3 gives the positions of H atoms found in the final difference Fourier synthesis. The torsion angles are given in Table 4 and short intermolecular contacts in Table 5.*

Table 3. *H atom positional parameters* ($\times 10^3$) *as determined from the final difference Fourier synthesis*

Hydrogen atoms are numbered H(*nm*), where *n* indicates the number of the bonded carbon atom.

	x	*y*	*z*
H(11)	593	875	806
H(12)	553	737	1000
H(13)	610	750	978
H(31)	579	333	834
H(32)	557	583	967
H(33)	614	417	961
H(21)	503	637	667
H(22)	543	500	511
H(23)	543	687	500
H(41)	676	625	806
H(51)	633	750	406
H(81)	639	437	389
H(82)	704	446	483

Table 4. *Torsion angles* (°)

C(1)–N(1)–C(4)–C(5)	−78°	N(1)–C(4)–C(5)–O(1)	136°
C(1)–N(1)–C(4)–C(8)	−153	N(1)–C(4)–C(5)–C(8)	−115
C(3)–N(1)–C(4)–C(5)	160	N(1) C(4) C(8)–C(5)	106
C(3)–N(1)–C(4)–C(8)	85	C(4)–C(5)–O(1)–C(6)	−147
C(2)–N(1)–C(4)–C(5)	44	C(4)–C(8)–C(5)–O(1)	103
C(2)–N(1)–C(4)–C(8)	−31	C(8)–C(5)–O(1)–C(6)	81
		C(5)–O(1)–C(6)–C(7)	−179
		C(5)–O(1)–C(6)–O(2)	−1

Table 5. *Intermolecular contacts* (Å)

		Symmetry and translation of second atom			
C(1)–C(3)	3·77	$-x$,	$\frac{1}{2}+y$,	$\frac{1}{2}-z$;	$+a$, $+c$
C(1)–O(2)	3·67	x,	y,	z;	$+c$
C(4)–O(2)	3·52	x,	y,	z;	$+c$
C(2)–C(3)	4·08	$-x$,	$\frac{1}{2}+y$,	$\frac{1}{2}-z$;	$+a$, $-b$
C(2)–C(7)	3·88	$\frac{1}{2}-x$,	$-y$,	$\frac{1}{2}+z$;	$+a$, $+b$
C(4)–C(6)	4·06	$\frac{1}{2}-x$,	$-y$,	$\frac{1}{2}+z$;	$+a$, $+b$
C(8)–C(6)	3·68	$\frac{1}{2}-x$,	$-y$,	$\frac{1}{2}+z$;	$+a$, $+b$
C(8)–O(2)	3·38	$\frac{1}{2}-x$,	$-y$,	$\frac{1}{2}+z$;	$+a$, $+b$
C(8)–C(7)	3·80	$\frac{1}{2}-x$,	$-y$,	$\frac{1}{2}+z$;	$+a$, $+b$

Discussion

Molecular structure

Except for the bond angle C(4)–N(1)–C(2) all intramolecular bond lengths and angles (Fig. 1) are within one or two standard deviations of expected values. The expected C(sp^3)–N^+ bond length is 1·51 (1) Å (Singh & Ahmed, 1969). The values for C(1)–N(1), C(3)–N(1), C(2)–N(1) and C(4)–N(1) are 1·59 (5), 1·55 (5), 1·52 (4) and 1·49 (4) Å. The value for the bond angle C(4)–N(1)–C(2), 118·8 (2·7)°, is more than three standard deviations larger than the expected tetrahedral value of 109·5°. The methyl group C(2) eclipses the cyclopropane ring and is in very close contact with the atoms C(8) and C(5); C(2)–C(5) is 3·05 Å and C(2)–C(8) is 3·11 Å. The steric strain due to these close contacts probably causes the observed increase from the normal value of the C(4)–N(1)–C(2) bond angle. The distortions from the tetrahedral value (109·5°) of the observed values for C(1)–N(1)–C(3) (114·3°), C(1)–N(1)–C(2) (105·6°) and C(2)–N(1)–C(3) (104·8°) are quite consistent with the pattern expected to arise from an increase in the C(4)–N(1)–C(2) bond angle, though in themselves they are not significantly different from 109·5°.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32964 (4 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

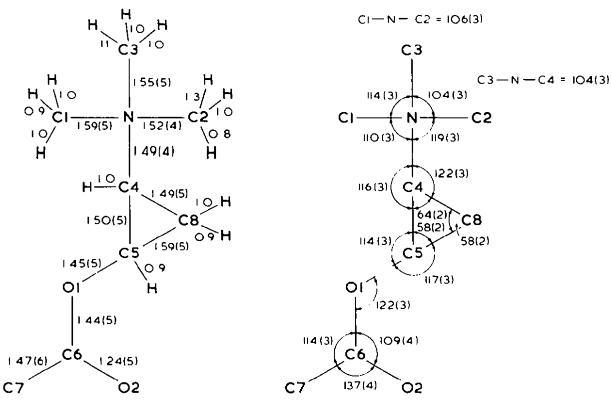

Fig. 1. (+)-*trans*-Acetoxycyclopropyltrimethylammonium cation: bond lengths (Å) and angles (°).

The bond lengths and angles of the cyclopropane ring [1·50 (5), 1·49 (5), 1·59 (5) Å, 64·4 (2·4), 57·5 (2·3) and 58·1° (2·4°)] are within two standard deviations of the 1·518 (3) Å and 60° found by Hartman & Hirshfeld (1966) in their accurate structure analysis of 1,2,3-tricyanocyclopropane. The bond angles between N, O and the ring [N(1)–C(4)–C(5) 116 (3)°, N(1)–C(4)–C(8) 122 (3)°, O(1)–C(5)–C(4) 114 (3)°, and O(1)–C(5)–C(8) 117 (3)°] are within two standard deviations of the corresponding values of C–C(ring)–C(ring), 118·56 (11) and 118·05 (10)°, found by Hartman & Hirshfeld (1966). These bond angles differ from the tetrahedral value of 109·5° because the sp^3 orbitals holding the ring together are 'bent in' so that the orbital–atom–orbital angle is 104° (Coulson, 1961). This allows more effective overlap of the orbitals between atoms in the ring, increases the value of the bond angles between the ring and its substituents to about 118° and gives the N^+–C–C–O torsion angle a value of +137°.

In ACTM there are two structural parameters which are not fixed by the covalent structure of the molecule: the torsion angles [C(3),C(2)]C(1)–N(1)–C(4)–C(5) and C(4)–C(5)–O(1)–C(6). The value of C(5)–O(1)–C(6)–C(7)[O(2)] is restricted to approximately 180° (0°) by the partial double-bond character of O(1)–C(6) (Baker, Chothia, Pauling & Petcher, 1971). As described above, the orientation of the quaternary group relative to the ring is fixed by van der Waals contacts between the methyl group C(2) and the atoms C(5) and C(8) in the cyclopropane ring. The observed value of [C(4)–C(5)–O(1)–C(6)] is −147°. Rotation about C(5)–O(1) is limited by the van der Waals contact between O(2) and the ring atoms C(8) and C(4). The observed distances are for O(2)–C(8) 3·22 (5) Å and for O(2)–C(4) 3·95 (4) Å. Thus the O(2)–C(8) contact would prevent C(4)–C(5)–O(1)–C(6) becoming much larger than the value found in the crystal, though it could become smaller. The precise observed value is presumably due to the packing forces of the crystal.

Packing of the molecules in the crystals

The packing of the molecules in the crystal can be described in terms of a bilayer structure whose plane is parallel to (100) (Fig. 2). In the 'interior' of the bilayers, at $x = \frac{1}{4}$ and $\frac{3}{4}$, van der Waals contacts occur between the acetoxy group and cyclopropyl rings in adjacent layers (Table 5). The bilayers themselves are held together by the ionic attraction between the iodide ions and quaternary ammonium groups in the planes $x = 0$ and $\frac{1}{2}$. The iodide ion is in van der Waals contact with or near one or more atoms of seven ACTM molecules (3·88–4·49 Å). Four of these molecules are in an approximately square arrangement in the xy plane; the other three molecules are related to these by a translation in the $+z$ direction. In the $+x$ direction, the ion is 4·48 and 4·28 Å from C(7) of a pair of molecules related to each other by a z translation; in the $-x$ direction it is 3·93 and 4·21 Å from C(2) of another pair of molecules also related by a z translation from C(3). In the $+y$ direction, the iodide ion is 3·88 Å from C(3) in one molecule and near two of the atoms in the molecule adjacent to this one in the z direction; these two distances are 4·29 Å to C(2) and 3·88 Å to C(8). In the $-y$ direction, C(2) in one molecule is 4·39 Å from I^-.

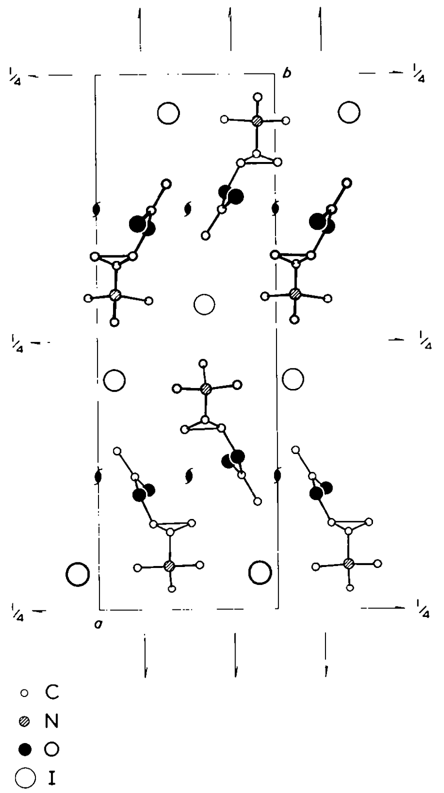

Fig. 2. (+)-*trans*-Acetoxycyclopropyltrimethylammonium iodide: view of the unit cell in the **c** direction.

The implications of the results of this structure analysis for the biological activity of cholinergic molecules are discussed by Chothia & Pauling (1970) and Baker, Chothia, Pauling & Petcher (1971).

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The Crystal and Molecular Structure of 2-Oxo-2-phenoxy-4*H*-1,3,2-benzodioxaphosphorin

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2-Oxo-2-phenoxy-4*H*-1,3,2-benzodioxaphosphorin, $C_{13}H_{11}O_4P$, crystallizes in the orthorhombic system, space group $P2_12_12_1$, $Z = 4$. The unit-cell dimensions are $a = 7{\cdot}563$ (2), $b = 27{\cdot}554$ (4), $c = 5{\cdot}835$ (1) Å. The structure was solved by direct methods and refined by full-matrix least-squares calculations with anisotropic thermal parameters (isotropic for H atoms) to a final R value of 0·045 for 1429 reflexions collected by means of a single-crystal diffractometer. The dioxaphosphorin ring is midway between a half-chair and sofa conformation with the phenoxy group in the axial position.

Introduction

The present study is a continuation of a series of investigations into the conformations of 1,3,2-dioxaphosphorinane systems (Gałdecki & Karolak-Wojciechowska, 1971; Gałdecki & Karolak-Wojciechowska, 1973; Cameron, Gałdecki & Karolak-Wojciechowska, 1976). Many structures of this type have been studied now, including 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (Geise, 1967). However, no molecule having a double bond in the 1,3,2-dioxaphosphorinane ring has been investigated. Such a ring should have a slightly different conformation.

Experimental

The crystals of 2-oxo-2-phenoxy-4*H*-1,3,2-benzodioxaphosphorin (abbreviated to PBDP) were crystallized from ligroin with benzene at room temperature in the form of plates. Weissenberg photographs showed the crystal system to be orthorhombic. Systematic absences indicated the non-centrosymmetric space group $P2_12_12_1$. 1429 independent reflexions were collected on a CAD-4 diffractometer from a crystal shaped into a sphere of diameter 0·3 mm (Cu radiation). The density of the crystals was determined by flotation in KI solution.

Crystal data

$C_{13}H_{11}O_4P$, $M_r = 262{\cdot}2$, $F(000) = 544$. Orthorhombic, space group $P2_12_12_1$ (D_2^4; No. 19) with $a = 7{\cdot}563$ (2), $b = 27{\cdot}554$ (4) and $c = 5{\cdot}835$ (1) Å; $V = 1216{\cdot}2$ Å^3; $Z = 4$. $D_m = 1{\cdot}44$, $D_x = 1{\cdot}432$ g cm^{-3}; μ(Cu $K\alpha$) = 20·41 cm^{-1}.

The phases of 200 reflexions were determined by means of *MULTAN* (Germain, Main & Woolfson, 1971). Table 1 shows the reflexions selected for the

Table 1. *Phase assignment for specifying the origin, and other reflexions contained in the starting set*

Set	*h k l*	E_{hkl}	Phase	
37	6 0 2	2·07	0	Determined from Σ_1 relationships
1	0,20,3	3·65	0	Specifying the origin
2	5,19,0	3·19	$\pi/2$	
3	4,21,0	2·77	0	
4	2 5 7	2·68		Other reflexions in starting set
15	4,14,1	2·29		
40	4 4 1	2·01		

Figures of merit	M_{abs}	ψ_0	R_{Karle}	COMBINED FOM
Maximum value	1·2474	617·2	49·07	2·072
Minimum value	0·8481	496·6	33·85	0·2821