$$\frac{\sigma_2}{2n}\left\{\delta_{\mathbf{k}}^{\mathbf{h}}+p\left(\frac{6p}{\pi p'}\right)^{\frac{1}{2}}\left[1-\frac{9}{8}\left(\frac{1}{3}-\frac{pp''}{5p'^2}\right)\right]\right\}(|\mathscr{E}_{\mathbf{h}}|^2-1).\quad(4\cdot11)$$

If $|\mathbf{h}|$ is small, then $p \simeq n$, $p' \simeq n^3$, $p'' \simeq n^5$ and both summands in the braces of (4·11) make approximately equal contributions. As $|\mathbf{h}|$ increases the first summand makes a constant contribution (equal to unity) while the contribution of the second summand decreases slowly. As $|\mathbf{h}|$ continues to increase, until finally $\mathbf{h}$ is no longer contained in the set $\{\mathbf{k}\}$, the contribution of the first summand drops suddenly to zero so that the second summand is the only contributor. These results are consistent with the observation that the cycling process yields values of $|\mathscr{E}_{\mathbf{h}}|^2-1$ proportional to the observed data, with slowly increasing scale factor $C(s)$, until at the boundary of the observed range a sharp increase in the scale factor (by a factor of order 4) occurs. This is followed again by a gradual increase in the scale factor.

We wish to express our appreciation to Dr J. Holden for his excellent cooperation in programming and carrying out the calculations and to Peter Gum and Stephen Brenner for carrying out certain auxiliary calculations.

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The Crystal Structure and Absolute Configuration of α-Bromoisotutin

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Crystals of α-bromoisotutin ($C_{15}H_{17}O_6Br$) are trigonal, space group $P3_12$, with lattice parameters $a=8\cdot449$, $c=36\cdot61$ Å and six molecules to the unit cell. The crystal structure has been determined by a three-dimensional X-ray analysis and the absolute configuration established by a study of the X-ray dispersion effect of the bromine atoms with Cu K radiation. The molecular structure of α-bromoisotutin has the unusual feature of a cyclopentane ring to which are attached two epoxy rings. One of these is a spiro ring while the other is fused to the cyclopentane ring in a position which is α, β with respect to the spiro ring. The molecular framework and its absolute configuration are the same as in the chemically and pharmacologically related members of the picrotoxinin series.

Introduction

Tutin ($C_{15}H_{18}O_6$) was first isolated by Easterfield & Aston (1901) and identified as the convulsive poison present in the leaves and seeds of the New Zealand species of *Coriaria*, a shrub known to the Maori as 'toi toi'. This poison is a considerable hazard to grazing animals.

Tutin is one of a series of chemically and pharmacologically similar compounds of which picrotoxinin ($C_{15}H_{16}O_6$) has been the most intensively studied. The structure (I) for picrotoxinin was proposed by Conroy (1951, 1957) and this was confirmed by the X-ray crystal structure analysis of α_1-bromopicrotoxinin (Craven, 1962). The absolute configuration of α_1-bromopicrotoxinin (II) was also determined from the X-ray dispersion effect. The structure (III) for tutin was proposed by Karyone & Okuda (1953) on the basis of chemical degradation studies and the picrotoxinin structure. Further chemical and spectral evidence led Johns & Markham (1961) to propose the structure (IV) for tutin.

A detailed account is now given of an X-ray crystal structure analysis of α-bromoisotutin (V) which has already been reported briefly (Craven, 1963) together with the crystal data of three other bromine derivatives of tutin.

In addition to the present work, the crystal structure of α-bromoisotutinone is being studied by Mrs MacKay (University of Melbourne, Australia) and Dr A. L. Mathieson (C.S.I.R.O., Melbourne, Australia). Their results (private communication) show that the molecule of this derivative possesses the same molecular framework as α-bromoisotutin.

Crystal data

The crystals of α-bromoisotutin, which were supplied through the courtesy of Dr Basil Johns (University

of Melbourne, Australia), were colourless trigonal rhombohedra showing only one form {10Ī1}.

α-Bromoisotutin ($C_{15}H_{17}O_6Br$), mol.wt. 373.
Trigonal,

$$a = 8\cdot449 \pm 0\cdot002, \quad c = 36\cdot607 \pm 0\cdot009 \text{ Å} .$$

$U = 2263$ Å^3, $D_m = 1\cdot64$ g.cm^{-3}, $D_x = 1\cdot65$ g.cm^{-3}.

$Z = 6$. Space group: $P3_12$.

Experimental

All the X-ray photographs were obtained from a crystal which was a section cut from the central portion of an elongated rhombohedron so as to produce two new surfaces almost parallel to (0001). The crystal dimensions were approximately 0·2 mm.

The intensity data for the layers $h = 0$ to 5 were recorded on multiple-film equi-inclination Weissenberg photographs with Cu K radiation, and the integrated intensities were estimated by eye against a standard scale. The six layers $h = 0$ to 5 were sufficient to obtain all the non-symmetry-related reflexions accessible with Cu K radiation. The diffraction symmetry ($\bar{3}m$) permitted a comprehensive correlation of the intensities measured in the various layers since a given recorded layer possessed at least one reciprocal lattice row in common with each of the other recorded layers. For example, all the points in the reciprocal lattice row $12\bar{3}l$ in the layer $h = 1$ appear as the symmetry-related points $21\bar{3}l$ in the layer $h = 2$ and again as the symmetry-related points $3\bar{1}\bar{2}l$ in the layer $h = 3$, thus providing a row of 89 lattice points common to these three layers. A sequence of FORTRAN programs was written for the IBM 7070 computer (Craven, unpublished) in order to reduce the observed intensities to structure amplitudes and to adjust the scaling factors for each recorded Weissenberg layer by a least-squares procedure similar to that described by Rollett & Sparks (1960).

A total of 1986 non-symmetry-related reflexions fell within the limiting sphere of reciprocal space for Cu K radiation. Of these, 289 were too weak to be observed and were assigned an intensity which was one half the minimum observable intensity. The observed intensities ranged on a relative scale from 1 to 5000. No absorption corrections were applied.

At an advanced stage of the structure analysis, a crystal was ground to a sphere of diameter 0·25 mm and examined by means of the G. E. XRD 5 diffractometer. This crystal was used for the dual purpose of

(I)
Picrotoxinin

(II)
α₁-Bromopicrotoxinin

(III)

(IV)

(V)
α - Bromo-iso-tutin

(VI)
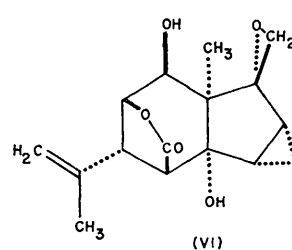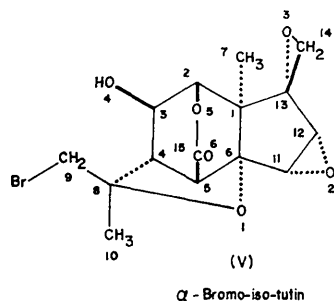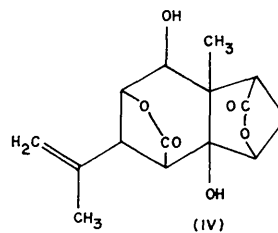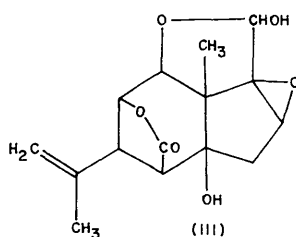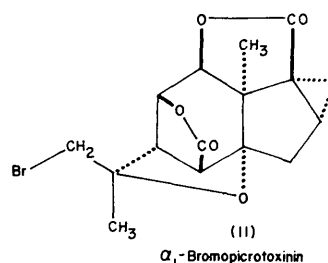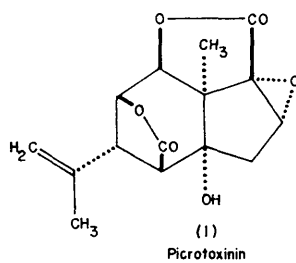
the accurate determination of the lattice parameters and for the determination of the absolute configuration of the structure.

The crystal density was measured by flotation in a mixture of bromoform and chloroform.

The structure determination

The observed diffraction symmetry ($\bar{3}m$) and the systematic spectral absences (000l when $l=3n$) limited the possible space groups to the enantiomorphous pair $P3_12$ and $P3_22$. Initially, the space group was arbitrarily assumed to be $P3_12$.

The approximate positions of the bromine atoms were established from a consideration of the Br–Br vectors which gave easily recognizable peaks in the three-dimensional Patterson map. The Patterson synthesis and subsequent Fourier syntheses were calculated by the program of McMullan & Chu (unpublished) for the IBM 7070 computer. For this program it was necessary to make a transformation to the monoclinic space group $C2$.

Structure factors were calculated for the bromine atoms alone with the program of Schapiro (unpublished) for the IBM 7070 computer, and these calculations were used to determine approximately the absolute scale factor for observed structure amplitudes. The bromine atom positional parameters derived from the Patterson synthesis were (0.56, 0.08, 0.1818) referred to the trigonal axes. The temperature factor was assumed to be isotropic with a value of 2.5 Å². The R index for all reflexions was found to be 0.41. It was observed that for all but about fifty non-symmetry-related reflexions, the amplitude of the bromine atom contribution was greater than 20% of the corresponding observed structure amplitude. These fifty reflexions were omitted from the first three-dimensional Fourier synthesis of electron density in which each observed structure amplitude was assigned the phase angle of the corresponding bromine atom contribution.

Although the number of electron density maxima in this map exceeded the number of atoms in the structure, the positions of all carbon and oxygen atoms were determined approximately, giving the molecular structure (V) which is also shown in Fig. 1. Although a distinction between carbon and oxygen atoms could not be made with certainty on the basis of peak height alone, the distinction could, in fact, be made on chemical grounds. Thus, in the spiro epoxy ring attached at C(13), the oxygen atom O(3) was distinguished from the carbon atom C(14) because of the close intermolecular approach of 2.7 Å compatible with an intermolecular hydrogen bond O(3) · · · HO(4).

Structure factors were calculated with the inclusion of all carbon and oxygen atoms and the bromine atom, assuming all atoms to have an isotropic temperature factor $B=2.5$ Å². This gave an R index for all reflexions of 0.28 after the observed structure amplitudes were placed on the same scale as the calculated values. A second three-dimensional Fourier synthesis of electron density with the revised phase angles confirmed the positions of all carbon and oxygen atoms and considerably reduced the false details which had appeared in the first map.

As a matter of convenience, it was decided to continue the refinement by full-matrix least-squares methods, using the program of Busing & Levy (1959) for the IBM 704 computer. In this refinement the structure amplitudes were weighted according to a Hughes scheme. The 89 parameters determined were
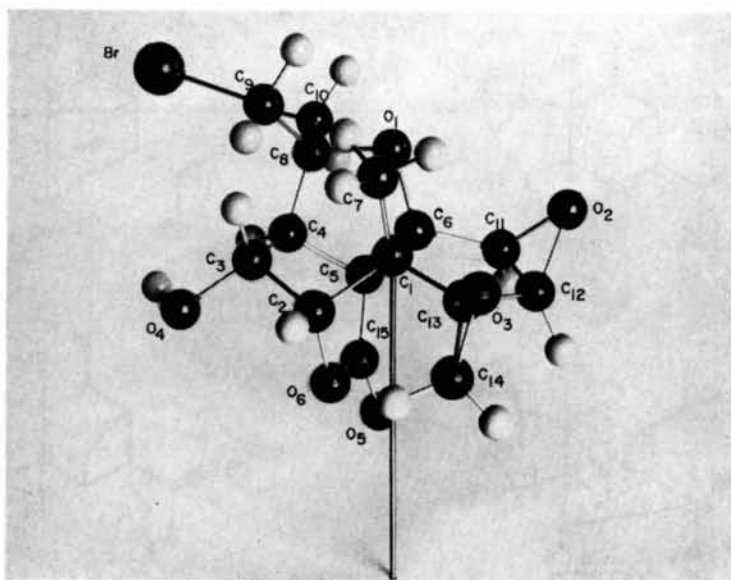

Fig. 1. The molecular structure of α-bromoisotutin.

the positional and isotropic thermal parameters for each atom and an overall scaling factor. Two cycles of least-squares reduced the R index to 0·18.

At this stage, the absolute configuration of the structure was determined by a study of the X-ray dispersion effect and in the continued refinement of the structure parameters, the real part of the dispersion correction ($\Delta f' = -0·9$, Dauben & Templeton, 1955) was applied to the bromine scattering factor (Thomas & Umeda, 1957).

Table 1. *The atomic parameters with their estimated standard deviations*

Atom	Fractional coordinates referred to trigonal axes			
	x $\sigma(x)$	y $\sigma(y)$	z $\sigma(z)$	B $\sigma(B)$
C(1)	0·0272 15	−0·4734 16	0·25255 26	2·49 Å^2 14
C(2)	0·2107 22	−0·4090 21	0·27229 35	3·91 22
C(3)	0·3586 20	−0·2296 20	0·25571 32	3·33 20
C(4)	0·2938 16	−0·0897 15	0·25366 27	2·91 17
C(5)	0·1127 17	−0·1737 18	0·27795 31	3·23 18
C(6)	−0·0158 16	−0·3269 17	0·25079 27	2·76 16
C(7)	0·0308 18	−0·5554 18	0·21491 29	3·28 18
C(8)	0·2104 25	−0·0796 24	0·21723 41	4·55 26
C(9)	0·2910 20	−0·0912 19	0·18233 33	3·75 20
C(10)	0·1937 26	0·1027 25	0·21723 43	4·79 26
C(11)	−0·2155 23	−0·4020 23	0·26002 39	4·00 24
C(12)	0·2842 22	−0·5882 22	0·27420 36	3·85 22
C(13)	−0·1331 22	0·6361 22	0·27571 35	3·75 22
C(14)	−0·1123 23	0·7313 24	0·30520 40	4·39 25
C(15)	0·1314 23	−0·2535 22	0·31498 36	4·39 24
O(1)	0·0266 12	0·2300 11	0·21673 19	2·72 13
O(2)	−0·3255 16	−0·5628 16	0·23678 24	4·31 17
O(3)	−0·1847 17	−0·8196 16	0·26990 28	4·34 18
O(4)	0·5193 15	−0·1682 15	0·27705 25	3·93 16
O(5)	0·0937 17	−0·2214 17	0·34220 29	4·54 19
O(6)	0·1924 13	−0·3719 13	0·31005 22	3·36 14
Br	0·5561 2	0·0841 2	0·18147 5	

The anisotropic thermal parameters for the bromine atom are:

(Å^2)	(Å^2)	(Å^2)	(Å^2)
$B_{11}=3·75$,	$\sigma(B_{11})=0·07$	$B_{12}=+0·73$,	$\sigma(B_{12})=0·06$
$B_{22}=3·35$,	$\sigma(B_{22})=0·07$	$B_{13}=+0·98$,	$\sigma(B_{13})=0·06$
$B_{33}=5·28$,	$\sigma(B_{33})=0·08$	$B_{23}=+0·06$,	$\sigma(B_{23})=0·06$

Table 2. *The bond angles*

Atoms	Angle	Atoms	Angle
C(6)–C(1)–C(2)	111°	C(9)–C(8)–C(10)	111°
C(1)–C(2)–C(3)	110	C(8)–C(10)–Br	111
C(2)–C(3)–C(4)	105	C(4)–C(3)–O(4)	113
C(3)–C(4)–C(5)	105	C(2)–C(3)–O(4)	108
C(4)–C(5)–C(6)	97	C(5)–C(15)–O(5)	125
C(5)–C(6)–C(1)	108	C(5)–C(15)–O(6)	111
C(2)–C(1)–C(13)	109	O(5)–C(15)–O(6)	124
C(5)–C(6)–C(11)	112	C(15)–C(6)–O(2)	114
C(1)–C(6)–C(11)	109	C(4)–C(5)–C(15)	113
C(6)–C(11)–C(12)	107	C(6)–C(5)–C(15)	112
C(11)–C(12)–C(13)	111	C(1)–C(2)–O(6)	109
C(12)–C(13)–C(1)	102	C(3)–C(2)–O(6)	107
C(13)–C(1)–C(6)	107	C(11)–O(2)–C(12)	60
C(2)–C(1)–C(7)	110	O(2)–C(11)–C(12)	59
C(6)–C(1)–C(8)	114	O(2)–C(12)–C(11)	60
C(13)–C(1)–C(8)	107	C(6)–C(11)–O(2)	108
C(5)–C(6)–O(1)	102	C(13)–C(12)–O(2)	112
C(1)–C(6)–O(1)	115	C(13)–O(3)–C(14)	59
C(11)–C(6)–O(1)	110	O(3)–C(13)–C(14)	63
C(6)–O(1)–C(8)	110	O(3)–C(14)–C(13)	58
O(1)–C(8)–C(4)	107	C(12)–C(13)–O(3)	110
C(8)–C(4)–C(5)	98	C(12)–C(13)–C(3)	123
C(8)–C(4)–C(3)	116	C(1)–C(13)–O(3)	122
C(4)–C(8)–C(9)	121	C(1)–C(13)–C(12)	127
C(4)–C(8)–C(10)	106	C(3)–O(4)···O(3')	122
O(1)–C(8)–C(9)	105	C(9)–Br···O(2')	113
O(1)–C(8)–C(10)	106		

Three cycles of least-squares were calculated in which the carbon and oxygen parameters were fixed and only the overall scale factor and the positional and anisotropic thermal parameters for the bromine atom were varied. This reduced R to 0·15. Finally, two cycles of least squares were calculated in which the bromine atom parameters were fixed and the light atom positional and isotropic thermal parameters were varied. This procedure was adopted because the least-squares program did not permit the simultaneous refinement of isotropic and anisotropic thermal parameters for different atoms. The final R index was 0·14.

Table 3

(a) Some intramolecular distances

C(7) ··· O(1)	2·77 Å	C(11) ··· C(5)	2·55 Å^2
C(7) ··· O(3)	2·88	C(11) ··· C(14)	3·70
C(7) ··· O(2)	3·09	C(11) ··· C(15)	3·25
C(7) ··· C(3)	3·14	C(12) ··· C(14)	2·57
C(7) ··· C(8)	3·52	C(12) ··· C(5)	3·43
C(14) ··· O(6)	2·84	C(12) ··· C(15)	3·55
C(14) ··· C(2)	2·98	C(10) ··· C(5)	3·00
C(14) ··· C(15)	3·51	C(9) ··· C(3)	3·09
C(13) ··· O(6)	2·83	O(1) ··· O(2)	2·99
C(13) ··· C(15)	3·21	O(2) ··· O(3)	3·19

(b) Some intermolecular distances

(i) Distances involving bromine atoms

Br ··· O(2)	(II)	3·32 Å	Br ··· O(2)	(V)	3·94 Å
Br ··· O(3)	(II)	3·76	Br ··· C(7)	(VIII)	3·94
Br ··· C(7)	(II)	3·83	Br ··· C(10)	(IX)	3·98
			Br ··· Br	(IX)	4·44

(ii) The oxygen to oxygen distances less than 3·5 Å

O(4)H ··· O(3) (II) 2·76 Å   O(5) ··· O(5) (IV) 3·30 Å

Table 3 (cont.)

(iii) The carbon to oxygen distances less than 3·8 Å

C(12)···O(6) (III)	3·23 Å	C(15)···O(5) (IV)	3·52 Å
C(9) ···O(1) (V)	3·35	C(4) ···O(5) (IV)	3·63
C(5) ···O(5) (IV)	3·36	C(10)···O(2) (II)	3·67
C(14)···O(4) (III)	3·42	C(11)···O(4) (VI)	3·71
C(9) ···O(2) (V)	3·44	C(3) ···O(3) (II)	3·71
C(12)···O(5) (III)	3·46	C(14)···O(6) (III)	3·76

(iv) The carbon to carbon distances less than 4·0 Å

C(7) ···C(7) (V)	3·56 Å	C(7) ···C(10) (VII)	3·77 Å
C(12)···C(15) (III)	3·73	C(15)···C(15) (IV)	3·95

Key to the numbering of molecules in Table 3(b).

The atom given on the left of each pair belongs to molecule (I) at x, y, z. This is the molecule corresponding to the parameters listed in Table 1. The molecules to which the atom on the right may belong are numbered as follows:

(II)	1+x, 1+y, z	(VI)	−1+x, −y, z
(III)	−1+x−y, −1−y, ⅔−z	(VII)	x, −1+y, z
(IV)	x−y, −y, ⅔−z	(VIII)	1−x, 1+y−x, ⅓−z
(V)	−x, y−x, ⅓−z	(IX)	1−x, y−x, ⅓−z

The observed and calculated structure factors have been deposited with the American Documentation Institute, Auxiliary Publications Project, Washington, D.C.* The atomic parameters with their estimated standard deviations are given in Table 1. The bond lengths are shown in Fig. 2 and the bond angles in Table 2. These were calculated with programs by Chu (unpublished) for the IBM 1620 computer. The mean

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* Document No. 7611, available from the Chief, Photo-duplication Service, Library of Congress, Washington, D.C., U.S.A. to whom checks or money orders should be made payable ($5·00 for photoprints or $2·25 for 35 mm microfilm).
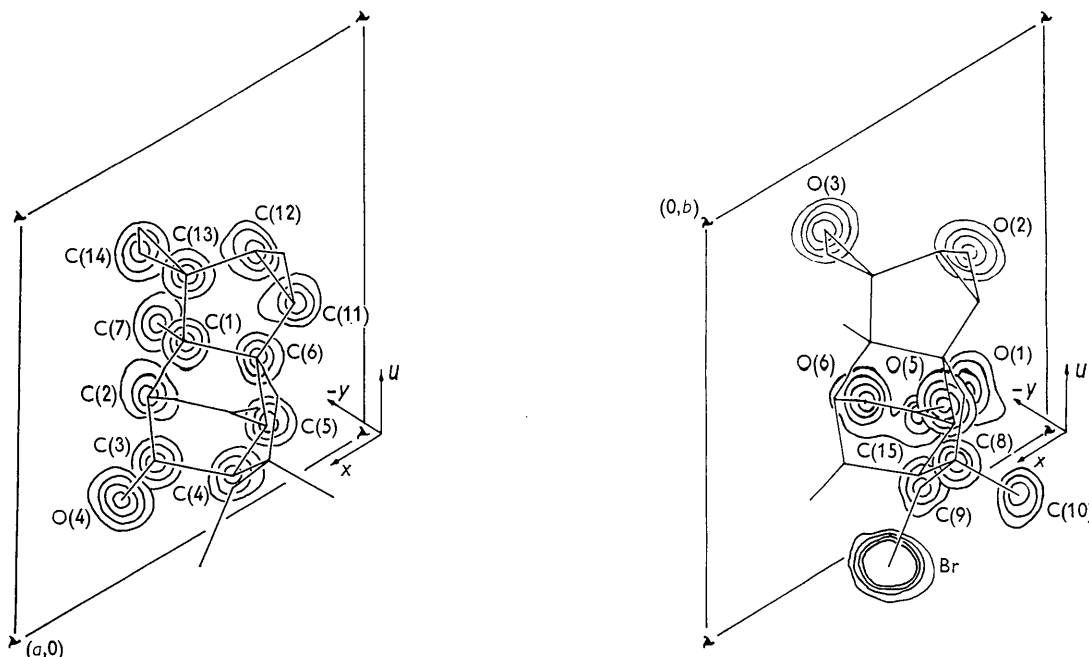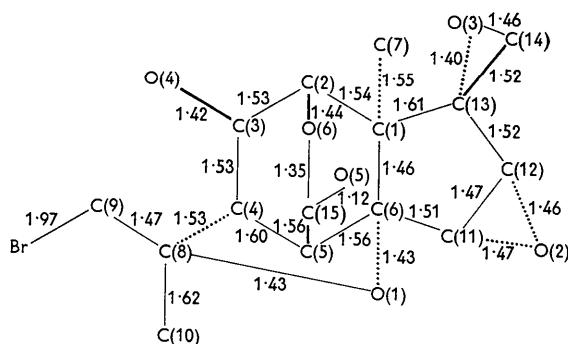

Fig. 2. The observed bond lengths in α-bromoisotutin.

e.s.d. in a bond length is 0·03 Å and in a bond angle is 1·8°, as derived from the least-squares inverse matrix. A mean value of 1·54 Å was obtained for the thirteen observed bond lengths for bonds between predominantly sp^3 hybridized carbon atoms and the estimated standard deviation from this mean was 0·047 Å. It is not certain the extent to which this higher e.s.d. represents real variations in the bond lengths or the effects of possible systematic errors in the observed structure amplitudes. Some intramolecular and intermolecular distances are given in Table 3.

An electron density map compiled from sections of a final three-dimensional Fourier synthesis is shown in Fig. 3.

The absolute configuration of the molecule

With Cu K radiation, the dispersion corrections for the bromine scattering factor have been given by Dauben & Templeton (1955) as $\Delta f' = −0·9$ and

Fig. 3. An electron-density map compiled from sections of the final three-dimensional Fourier synthesis.

$\Delta f'' = 1.5$. Although this dispersion effect is small, it was demonstrated by Peerdeman (1956) to be large enough to permit the determination of the absolute configuration of strychnine hydrobromide, a structure of comparable complexity to that of α-bromoisotutin. Assuming the structure of α-bromoisotutin to have the space group $P3_12$, the intensities of about 100 low order reflexions were calculated for the pairs $hkil$ and $\overline{hki}l$. The effect of assuming the structure to have all atoms inverted with respect to the crystallographic origin would be to interchange the calculated intensities $hkil$ and $\overline{hki}l$, thus changing the sign of the ratio $(I_{hkil}-I_{\overline{hki}l})/I_{hkil}$.

Certain of these ratios were then derived from intensity measurements made with a diffractometer and a spherically ground crystal. The crystal was mounted about c on a G.E. single-crystal orienter so that if a reflection $hkil$ were placed in the diffracting position, five other reflections could readily be brought into the diffracting position by rotating the crystal about c. Of these six reflections, three were symmetry-related to $hkil$ ($hkil$, $kihl$, $ihkl$) and three were related to $\overline{hki}l$ ($\overline{hik}l$, $\overline{khi}l$, $\overline{ikh}l$) and this enabled the intensities $hkil$ and $\overline{hki}l$ to be taken as the average intensity of a set of three reflections. Intensity measurements were made in two cases for which the calculated ratio $(I_{hkil}-I_{\overline{hki}l})/I_{hkil}$ was large and positive, two cases for which the ratio was large and negative and one case for which the ratio was small.

The comparison of observed and predicted ratios (Table 4) established the arbitrarily chosen configuration with space group $P3_12$ as the correct absolute configuration. The absolute configuration of the carbon atom framework is thus the same as in the related molecule of α_1-bromopicrotoxinin (Craven, 1962).

Table 4. *The determination of the absolute configuration of α-bromoisotutin*

			$100(I_{hkil}-I_{\overline{hki}l})/I_{hkil}$		Observed intensities	
h	k	i	l calc.	obs.	I_{hkil}	$I_{\overline{hki}l}$
1	2	$\bar{3}$	1	-14.1	-8.4	243	255
					239	269
					240	259
1	2	$\bar{3}$	2	$+1.3$	$+2.5$	5068	5133
					5401	5160
					5313	5092
1	2	$\bar{3}$	3	$+7.5$	$+10.5$	1802	1551
					1726	1600
					1737	1559
1	2	$\bar{3}$	9	-6.4	-8.3	2010	2057
					1886	2057
					1839	2095
2	1	$\bar{3}$	4	$+9.4$	$+6.1$	3315	3049
					3214	3172
					3256	2963

Discussion of the molecular structure

The molecule of α-bromoisotutin has a rigid cage-like structure made up of interlocking ring systems. The basic carbon atom framework, as in the picrotoxinin series, is a methylindane system in which a cyclohexane ring is *cis*-fused to a cyclopentane ring. The cyclohexane ring (C(1–6)) is in the boat form and is bridged bow to stern (C(5) to C(2)) by a γ-lactone group. On the opposite side from the lactone group, the cyclohexane ring also bears an ether bridge (C(6)O(1)C(8)C(4)) which, with C(5), makes up a five-membered ring. This ring is formed during the bromination of tutin(VI) as a result of reaction between the hydroxyl group at C(6) and the isopropylene group at C(4), these groups being *cis* and axial. The cyclohexane ring is also substituted by an axial methyl group at C(1) and by an equatorial hydroxyl group at C(3). This ring is not in a completely regular boat form since, although atoms C(2), C(3), C(5), C(6) are coplanar (*i.e.* these atoms are at distances from their best least-squares plane which are insignificant in terms of their e.s.d.'s), atom C(5) is further from this plane (0·96 Å) than C(2) (0·64 Å). This distortion is a consequence of the participation of C(5) in both the cyclohexane ring and the five-membered ether ring. In the ether ring, the atoms C(4), C(6), O(1), C(8) are coplanar and C(5) is distant 0·78 Å from this plane. There is a dihedral angle of 116° between the planes of the four coplanar atoms of the cyclohexane ring and the four coplanar atoms of the ether ring. The atoms in the lactone bridge (C(5)C(15)O(5)O(6)C(2)) show small displacements from coplanarity some of which may possibly be significant (O(5), −0·04 Å; O(6), +0·05 Å; C(2), −0·04 Å; with the positive sense of displacement directed away from C(14)). The best least-squares plane through the lactone group makes dihedral angles of 89° and 90° with the four coplanar atoms of the cyclohexane ring and the five-membered ether ring respectively.

The cyclopentane ring (C(1)C(6)C(11)C(12)C(13)) bears two epoxy rings which are both oriented with the oxygen atoms directed away from the lactone group. The cyclopentane ring is only approximately coplanar. The atoms C(1), C(6), C(11), C(12) are displaced from their best least-squares plane by −0·4, +0·06, −0·06, +0·04 Å respectively and C(13) is displaced from this plane by 0·25 Å. The positive sense of displacement is toward the lactone group.

In the spiro epoxy ring, atom O(4) is displaced further (−0·87 Å) from the plane of the atoms C(1), C(13), C(12) than C(14) (+0·58 Å). This configuration is believed to be a compromise resulting from the non-bonding intramolecular repulsions C(7)···O(3) (2·88 Å) and O(6)···C(14) (2·84 Å) which act in opposite senses. The epoxy ring C(11), C(12), O(2) is symmetrical with no unusual feature.

The conformation of the molecule of α-bromoisotutin is such that both epoxy rings are shielded from rearward nucleophilic attack by close approaches involving atoms of the lactone bridge. These intramolecular distances are listed in Table 3. Thus

although normally, epoxy groups are very reactive chemically, these particular groups are relatively inert so that their presence was not suspected in previous investigations.

It is believed (Browne, Johns & Markham, 1961) that the tutin series differs from the isotutin series only in that the lactone bridge in tutin is from C(5) to C(3) (as in picrotoxinin) rather than from C(5) to C(2). This would require that the cyclohexane ring be in the chair rather than in the boat form in order that the hydroxyl group at C(3) be directed axially for lactone bridging. When the lactone group bridges from C(5) to C(3) the cyclopentane ring tilts toward the lactone bridge so that both of the epoxy rings retain the rearward shielding characteristic of α-bromo-isotutin. Although the relationship between tutin and α-bromoisotutin is somewhat remote, it is likely that tutin has the structure (VI).

The molecular structures of α-bromoisotutin and α₁-bromopicrotoxinin are very similar but with some interesting differences in conformation arising from the differences in the functional groups in the two molecules. Thus although the lactone bridge in α₁-bromopicrotoxinin spans from C(5) to C(3), the cyclohexane ring is not in the chair form as was described for the postulated structure of tutin (VI) but in a half chair (or half boat) form with C(2) approximately coplanar with all other members of the ring except C(5). This is a result of the presence of the additional lactone bridge in the α₁-bromo-picrotoxinin molecule which spans from C(13) to C(2). The different arrangement of functional groups also gives rise to a different conformation of the cyclo-pentane ring in the two molecules. In α₁-bromopicro-toxinin, atoms C(11), C(12), C(13), C(1) are coplanar and C(6) is 0·96 Å out of this plane, whereas in α-bromoisotutin the ring is less buckled with C(13) displaced by only 0·25 Å from the best plane through the other atoms. The greater buckling of this ring in α₁-bromopicrotoxinin is believed to arise from distortions of the molecular framework necessary in order to form the second lactone bridge. The configuration of the five-membered ether ring and the bromoiso-propyl group $(BrC(9)C(8)C(10))$ is very similar in the two molecules and it is apparent that both molecules have been correctly assigned to the so-called α series. The β series presumably has the bromine atom attached at C(10) rather than C(9).

Since the molecular frameworks in derivatives of tutin and picrotoxinin have now been shown to have the same absolute configuration, it is reasonable to suppose that the parent compounds are similar in their biogenesis.

The molecular packing

In the model of the crystal structure of α-bromoiso-tutin shown in Fig. 4, the four vertical thick rods represent the threefold screw axes forming the edges of the unit cell parallel to c. The horizontal thin rods
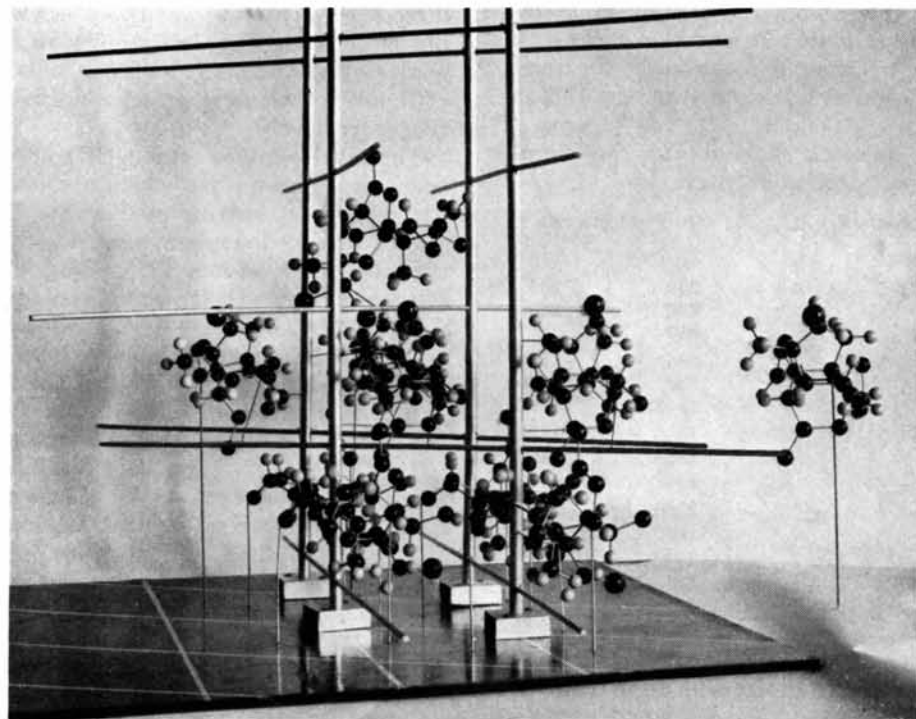

Fig. 4. The molecular packing in the crystal structure of α-bromoisotutin.

represent twofold rotation axes parallel to *a*, *b*, or [11$\bar{2}$0]. The twofold axes which intersect a given threefold screw axis are related successively by a translation of *c*/6 together with a rotation of 60°.

The model shows molecules belonging to three hexagonally packed layers which extend normal to *c*. There is only one molecule per cell in a given layer. Within a layer, the molecules are associated in parallel chains by the hydrogen bonding interaction O(4)H · · · O(3). The hydrogen bond length is 2·76 Å. The molecules in a chain may be associated by additional weak attractive interactions Br · · · O(2), since the separation of these atoms (3·32 Å) is slightly less than the sum of the van der Waals radii for bromine and oxygen atoms (3·35 Å; Pauling, 1960). The angle C(9)–Br · · · O is 113°. A very similar close approach was observed between the corresponding atoms Br · · · O(2) in the structure of α$_1$-bromopicrotoxinin (Craven, 1962).

In the bottom layer of molecules in Fig. 4, the two chains of associated molecules run almost towards the viewer and are parallel to the bottom pair of twofold axes. In the next higher layer, the chain axes are almost perpendicular to the viewer and individual molecules may be seen more easily. An isolated molecule in the same orientation as in this layer is shown at the right of Fig. 4.

The chains are held together in the structure by the usual van der Waals interactions, with no extraordinarily close intermolecular approaches (see Table 3).

The majority of compounds in the field of the organic natural products crystallize with the space groups $P2_12_12_1$ or $P2_1$. No simple explanation is apparent for the crystal structure of α-bromoisotutin having the space group $P3_12$, which is unusual for an asymmetrical molecule of this type, not only because of the rarely observed trigonal symmetry, but also because of the presence of twofold rotation axes. Although it is possible that asymmetric molecules related by either rotation or screw axes may be packed with the projections of one molecule fitting into the hollows of another, in general, the molecular packing about a rotation axis would be expected to be less favorable, since no atom in an asymmetric molecule can lie within one van der Waals radius of a rotation axis. Optimum packing might be expected about a rotation axis when the asymmetric molecules tend to a helical shape, because this permits molecular entwining with the possibility of a number of atoms lying close to the rotation axis, but this type of

packing is not observed in the case of α-bromoisotutin where each molecule makes only one close approach to two different twofold axes (O(5) · · · O(5), 3·30 Å; C(7) · · · C(7), 3·56 Å).* However, it cannot be said that the presence of twofold rotation axes causes this crystal structure to have a relatively loose form of molecular packing, since the observed crystal density (1·65 g.cm^{-3}) is very similar to that observed for the two α-bromotutins (1·62, 1·67 g.cm^{-3}) which crystallize in the commonly observed space group $P2_12_12_1$ (Craven, 1963). It is difficult to estimate the extent of close packing in a particular region of a crystal structure, but if there is any looseness in the packing of molecules of α-bromoisotutin about the twofold axes, there must be a compensating closeness in the packing elsewhere, perhaps between molecules which are hydrogen bonded.

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* Although hydrogen atom positions were not directly determined in this analysis, it is estimated that except possibly for the atoms of the methyl group (C(7)), no hydrogen atoms approach within 2·0 Å of a twofold rotation axis.