

from Fig. 1. Since the compound is derived from D-glucose the absolute configuration is established: the parameters of Table 2 referred to a right-hand set of axes give the true absolute configuration. Fig. 1 also depicts the correct absolute configuration.

The bond distances and valency angles in the molecule (Table 3) are all quite normal, and require no special comment.

All the intermolecular separations (Table 4) correspond to normal van der Waals interactions. The shortest distances are three C...O contacts of 3.1 Å, equal to the sum of the van der Waals radii of carbon and oxygen (Pauling, 1960). The shortest Br-O and Br-C contacts are 3.45 Å and 3.61 Å respectively (sum of van der Waals radii 3.35 Å and 3.65 Å respectively). The shortest O-O contact is 3.41 Å, and the shortest C-C separation is 3.55 Å.

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## The Crystal and Molecular Structure of 5-Iodo-2'-deoxyuridine

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Crystals of 5-iodo-2'-deoxyuridine and 5-bromo-2'-deoxyuridine are isomorphous; the compounds are triclinic with one molecule in the unit cell, space group *P1*, with dimensions  $a = 4.98$ ,  $b = 6.83$ ,  $c = 9.60$  Å,  $\alpha = 101^\circ 40'$ ,  $\beta = 109^\circ 18'$ ,  $\gamma = 98^\circ 20'$  for the iodo-compound, and  $a = 4.87$ ,  $b = 6.72$ ,  $c = 9.56$  Å,  $\alpha = 100^\circ 10'$ ,  $\beta = 107^\circ 24'$ ,  $\gamma = 98^\circ 31'$  for the bromo-derivative. The detailed structure of 5-iododeoxyuridine was determined from Mo  $K\alpha$  scintillation counter data. A three-dimensional Fourier synthesis with all phases zero (based on the I atom), although it contained a false centre of symmetry, revealed all the atoms in the molecule. The positional and isotropic thermal parameters were refined by least squares to an *R* value of 0.142; further refinement with anisotropic temperature factors indicated no further significant shifts in positional parameters, but reduced *R* to 0.054.

The atoms attached to the pyrimidine ring show small deviations from exact planarity. The deoxyribose ring is puckered with C(2') displaced 0.59 Å from the plane of the other four atoms. The angle between the planes of the two rings is  $81^\circ$ ; the conformation about the glycosidic C-N bond, as defined by the angle formed by the trace of the plane of the base with the projection of the C-O bond, is  $-67^\circ$ . The bond distances indicate that the pyrimidine base is in the keto form (both carbon-oxygen distances 1.22 Å); the C(4)-C(5) bond (1.34 Å) is a double bond, C(5)-C(6) is a single bond (1.49 Å), and the C-N distances in the pyrimidine ring all measure 1.37 Å. The glycosidic C-N bond length is 1.49 Å. The distances and angles in the deoxyribose ring are all normal.

The most significant intermolecular distance is an I...O (carbonyl) separation of 2.96 Å; this is very considerably shorter than the usual van der Waals contact (3.55 Å), and suggests charge transfer bonding involving donation of oxygen lone-pair electrons to vacant *5d* orbitals of the iodine atom. A strong intermolecular attraction of this type may be the explanation for the antiviral activity of 5-iodo-2'-deoxyuridine. The other short intermolecular separations correspond to O-H...O and O...H-N hydrogen bonds.

#### Introduction

5-Iodo-2'-deoxyuridine (IDU) (Fig. 2) has been used in the treatment and cure of *herpes simplex* keratitis

(Kaufman, Nesburn & Maloney, 1962; Kaufman, 1962), and this is the first clear-cut demonstration that true viral disease can be effectively treated without obvious harm to the host. It is postulated

that the blocking of the metabolic pathways of viral synthesis by IDU may be due either to competitive inhibition of the uptake of thymidine into deoxyribonucleic acid (DNA), or to incorporation of IDU itself into an aberrant DNA which presumably cannot be utilized to form infective virus particles. 5-Iodo-deoxyuridine and 5-bromodeoxyuridine certainly can be incorporated into DNA in place of thymidine (Szybalski, 1962), and the resultant DNA has a significantly higher melting temperature than normal DNA (Kit, 1962). The enhanced stability has been explained in terms of several effects, the most plausible of which is that replacement of CH<sub>3</sub> in thymidine by Br or I alters the electron density in the pyrimidine rings so as to strengthen the hydrogen bonding to the purine base in the complementary DNA chain.

We have investigated the crystal structures of 5-iodo-2'-deoxyuridine and 5-bromo-2'-deoxyuridine, in the hope that some direct information might be obtained of the possible role of these compounds in combating viral diseases.

### Experimental

Crystals of 5-iodo-2'-deoxyuridine and 5-bromo-2'-deoxyuridine are plates elongated along *a* with (001) developed. Most of the crystals were twinned, but some single ones were obtained from alcohol-water. The density of IDU was measured by flotation in a carbon tetrachloride-bromoform mixture, and the unit-cell dimensions of both compounds were determined from rotation, Weissenberg (Cu *K*α, λ = 1.5418 Å) and precession (Mo *K*α, λ = 0.7107 Å) films. The crystal data are given in Table 1.

The iodo-compound was chosen for detailed analysis, and the intensities of all reflexions with 2θ Mo *K*α ≤ 57.3° (corresponding to a minimum interplanar spacing *d* = 0.74 Å) were measured on a General Electric XRD 5 Spectrogoniometer, with Single Crystal Orienter, using a scintillation counter, approximately monochromatic Mo *K*α radiation (zirconium filter and

pulse height analyser), and the moving-crystal moving-counter technique (Furnas, 1957). All the intensities were corrected for background, Lorentz and polarization factors were applied, and the structure amplitudes were derived. The crystal used was mounted with *a*\* parallel to the φ axis of the goniostat, and had length 0.50 mm parallel to *a* and cross-section 0.16 × 0.07 mm perpendicular to *a*; with Mo *K*α radiation absorption is fairly low and no corrections were considered necessary. 1434 reflexions were observed, 99.2% of the total number (1445) in the range 0 < 2θ<sub>Mo *K*α</sub> ≤ 57.3°.

### Structure analysis

Since the compound is optically active the space group is *P*1, and with only one molecule in the unit cell the origin may be taken at the iodine atom. A three-dimensional Fourier series was summed with all phase angles taken as 0°. The resulting electron-density distribution necessarily contained a false centre of symmetry, but the sugar ring and all its substituent groups were very clearly resolved. The base was poorly resolved since it was situated close to a false centre of symmetry, but it was possible, by making use of the atoms which were resolved and by assuming conventional dimensions, to obtain coordinates for all the atoms (excluding hydrogen) in the molecule. Structure factors were calculated with the use of the scattering factors of *International Tables for X-ray Crystallography* (1962), with *B* = 4.5 Å<sup>2</sup> for all atoms; the iodine scattering factor was corrected for anomalous dispersion according to the relation:

$$f_{\text{corrected}} = \sqrt{\{f_o + \Delta f'\}^2 + (\Delta f'')^2},$$

and  $\Delta f'$ ,  $\Delta f''$  were taken from *International Tables* (1962). *R*, the usual discrepancy index, was 0.249. A second Fourier series was summed with phases based on all the atoms, and the resulting three-dimensional electron-density distribution showed very good resolution of all the atoms, with no spurious detail.

Refinement of the positional and isotropic thermal parameters and a scale factor was then carried out by (block-diagonal) least squares. The function minimized was  $\sum w(|F_o| - |F_c|)^2$ , with  $1/w = |F_o|/20$  when  $|F_o| < 20$  and  $1/w = 20/|F_o|$  when  $|F_o| \geq 20$ . Refinement was complete in four cycles, during which *R* was reduced from 0.249 to 0.142, and  $\sum w\Delta^2$  from  $12 \times 10^3$  to  $5.6 \times 10^3$ . At this stage facilities for computing anisotropic least squares became available, and two more cycles of refinement reduced *R* to 0.054 and  $\sum w\Delta^2$  to  $1.3 \times 10^3$ ; in the anisotropic refinement no significant changes in positional parameters were indicated, so that the improvement in structure factor agreement is entirely a result of introducing anisotropic thermal parameters.

The final calculated structure amplitudes are compared with the measured values in Table 2 (*R* = 0.054

Table 1. *Crystal data.*

	5-Iodo-2'- deoxyuridine	5-Bromo-2'- deoxyuridine
Formula	C <sub>9</sub> H <sub>11</sub> N <sub>2</sub> O <sub>5</sub> I	C <sub>9</sub> H <sub>11</sub> N <sub>2</sub> O <sub>5</sub> Br
M.W.	354.1	307.1
Crystal system	Triclinic	Triclinic
<i>a</i> (Å)	4.98 ± 0.01	4.87 ± 0.01
<i>b</i> (Å)	6.83 ± 0.01	6.72 ± 0.01
<i>c</i> (Å)	9.60 ± 0.02	9.56 ± 0.02
α	101° 40' ± 5'	100° 10' ± 5'
β	109° 18' ± 5'	107° 24' ± 5'
γ	98° 20' ± 5'	98° 31' ± 5'
<i>U</i> (Å <sup>3</sup> )	293	285
<i>D<sub>m</sub></i> (g.cm <sup>-3</sup> )	2.014	—
<i>Z</i>	1	1
<i>D<sub>x</sub></i> (g.cm <sup>-3</sup> )	2.008	1.789
<i>F</i> (000)	172	154
μ (for Cu <i>K</i> α) (cm <sup>-1</sup> )	222	—
μ (for Mo <i>K</i> α) (cm <sup>-1</sup> )	28	—
Space group	<i>P</i> 1	<i>P</i> 1





Table 2 (cont.)

Table with multiple columns containing numerical data and headers: M, K, L, F Obs, F CALC. It is divided into several vertical sections.

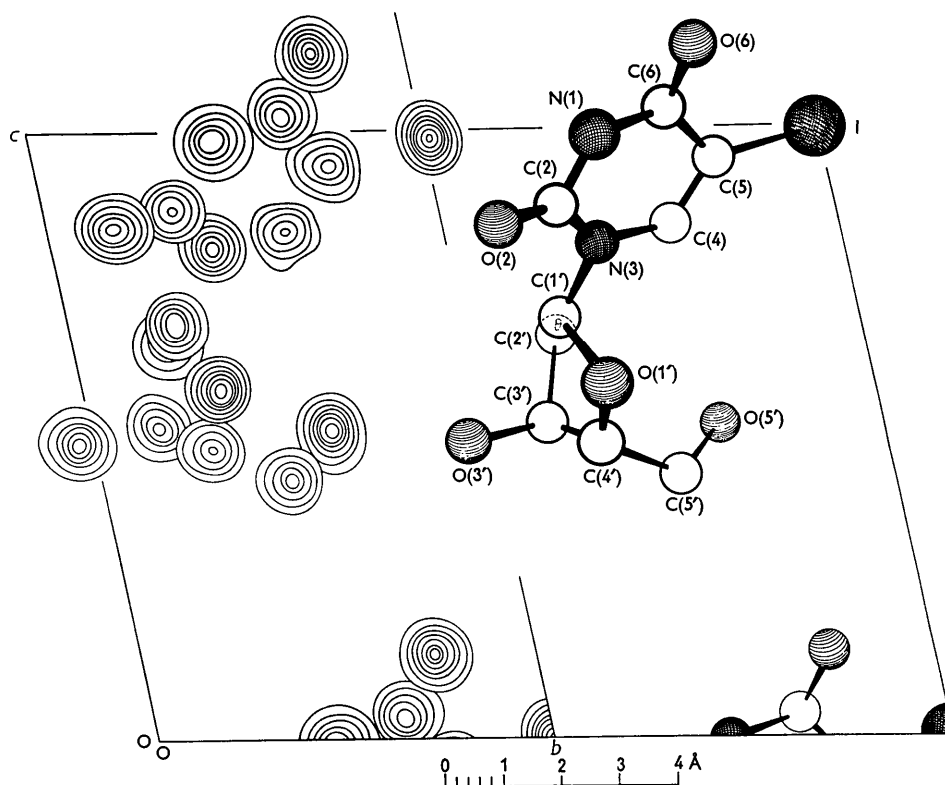


Fig. 1. Superimposed sections of the electron-density distribution, taken through the atomic centres parallel to (100). Contours start at zero and are at intervals of  $20 \text{ e.}\text{\AA}^{-3}$  about the iodine, and  $2 \text{ e.}\text{\AA}^{-3}$  about the light atoms. A perspective drawing of the molecule is also shown.

for all 1445 planes with  $d \geq 0.74 \text{ \AA}$ ). A final three-dimensional Fourier series was summed, and sections of the resulting electron-density distribution, taken through the atomic centres parallel to (100), are shown in Fig. 1.

#### Atomic parameters and molecular dimensions

The final positional and anisotropic thermal parameters are given in Table 3,  $x$ ,  $y$ , and  $z$  being fractional coordinates referred to the triclinic crystal axes. Since the compound is derived from D-ribose the absolute configuration is established; the coordinates in Table 3 referred to a right-hand set of axes give the correct absolute configuration, and all the diagrams also show the true configuration.  $B_{ij}$  in Table 3 are the coefficients in the expression:

$$\exp - \{B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{23}kl + B_{13}hl + B_{12}hk\}.$$

The standard deviations of the atomic coordinates (in  $\text{\AA}$ ) are included in Table 3; these were estimated from the inverses of the diagonal elements of the matrix of the least-squares normal equations.

The bond distances and valency angles in the molecule are shown in Fig. 2; the standard deviations of the bond lengths vary from  $0.015$ – $0.028 \text{ \AA}$ , and of the angles from  $1.4^\circ$ – $1.9^\circ$ .

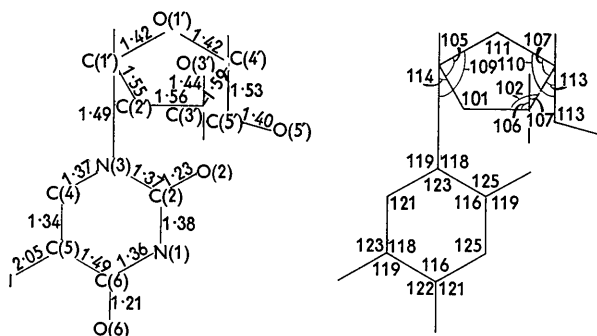


Fig. 2. Bond lengths and angles in 5-iodo-2'-deoxyuridine.

The best plane through the pyrimidine nucleus and the I, O(2), O(6), and C(1') atoms (all atoms, including I, given equal weight) has equation

$$0.82253X' + 0.56395Y' - 0.07341Z' + 0.80200 = 0 \quad (1)$$

where  $X'$ ,  $Y'$ , and  $Z'$  are coordinates in  $\text{\AA}$  referred to orthogonal axis  $a'$  ( $=a \cdot \sin \gamma$ ),  $b$ , and  $c^*$ . A least-squares plane was calculated through all five atoms of the deoxyribose ring, but the displacements indicated that the ring was significantly non-planar. Planes through all possible combinations of four atoms of the ring were calculated, and one of these was much

Table 3. *Final positional parameters (fractional), standard derivations (Å), and anisotropic thermal parameters ( $\times 10^5$ )*

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$	$B_{11}$	$B_{22}$	$B_{33}$	$B_{23}$	$B_{13}$	$B_{12}$
I	0.0000	1.0000	1.0000	0.0035	0.0034	0.0035	3422	1185	1099	687	1748	2322
N(1)	0.5809	0.6132	1.1563	0.0138	0.0137	0.0142	4215	1285	1238	508	2396	3338
C(2)	0.5719	0.4787	1.0257	0.0180	0.0179	0.0189	3479	927	1298	1516	1767	3720
O(2)	0.7339	0.3577	1.0370	0.0125	0.0125	0.0127	4978	2282	1366	1410	1994	5416
N(3)	0.3761	0.4918	0.8902	0.0143	0.0142	0.0145	3853	1340	709	395	1301	3387
C(4)	0.2192	0.6401	0.8804	0.0176	0.0173	0.0182	4162	976	579	-309	1507	958
C(5)	0.2357	0.7770	1.0065	0.0131	0.0128	0.0140	2070	1350	320	111	-246	2265
C(6)	0.4290	0.7627	1.1581	0.0147	0.0145	0.0153	2503	1060	887	736	1390	1493
O(6)	0.4554	0.8796	1.2769	0.0119	0.0119	0.0120	4824	1525	761	192	1324	1579
C(1')	0.3567	0.3480	0.7458	0.0164	0.0161	0.0169	2844	1215	900	474	1729	1643
O(1')	0.4699	0.4619	0.6613	0.0116	0.0116	0.0118	3101	1863	675	641	1162	1254
C(2')	0.0386	0.2374	0.6368	0.0166	0.0163	0.0170	3121	1352	1104	604	2038	1533
C(3')	0.0782	0.1796	0.4804	0.0169	0.0167	0.0174	3095	1101	793	614	1378	1748
O(3')	0.2026	0.0019	0.4789	0.0130	0.0130	0.0131	6380	893	1665	866	3541	3108
C(4')	0.3312	0.3672	0.5011	0.0159	0.0154	0.0161	3206	1070	926	414	2095	2316
C(5')	0.2177	0.5277	0.4163	0.0192	0.0190	0.0195	3088	1836	1230	1778	1418	2058
O(5')	-0.0101	0.5904	0.4526	0.0123	0.0124	0.0126	2891	1550	1517	1189	1562	2423

more satisfactory than the others, atoms C(1'), C(3'), C(4'), and O(1') being essentially coplanar, the plane having equation

$$0.68910X' - 0.72450Y' + 0.01496Z' + 0.98961 = 0 \quad (2)$$

with C(2') displaced 0.59 Å from this plane. The deviations of the atoms from the various planes are given in Table 4.

All the intermolecular separations  $\leq 4.5$  Å were calculated, and the more significant contacts are listed in Table 5.

Table 4. *Deviations from molecular planes*

Plane 1		Plane 2	
Atom	Deviation	Atom	Deviation
I	0.046 Å	C(1')	0.015 Å
N(1)	-0.046	C(3')	-0.013
C(2)	0.005	C(4')	0.032
O(2)	0.077	O(1')	-0.032
N(3)	-0.034		
C(4)	0.010	C(2')	-0.590
C(5)	0.017		
C(6)	-0.032		
O(6)	-0.033		
C(1')	0.007		

Table 5. *Shorter intermolecular contacts (Å)*

All distances  $\leq 4.5$  Å between a standard molecule (1) and neighbouring molecules were calculated. Only those  $< 3.9$  Å involving iodine, and  $< 3.5$  Å not involving iodine are listed

Atom (molecule 1)	to	atom in molecule	<i>d</i>
O(2)	.....	I	6 2.96 Å
O(5')	.....	H-N(1)	7 2.95
O(3')-H	.....	O(6)	4 2.70
O(3')	.....	H-O(5')	2 2.79
C(3')	.....	O(6)	8 3.19
C(5')	.....	O(6)	3 3.27
O(1')	.....	C(2')	5 3.46
O(3')	.....	C(5')	2 3.22
O(3')	.....	O(6)	8 3.46

Molecule 1	<i>x</i>	<i>y</i>	<i>z</i>
2	<i>x</i>	-1 + <i>y</i>	<i>z</i>
3	<i>x</i>	<i>y</i>	-1 + <i>z</i>
4	<i>x</i>	-1 + <i>y</i>	-1 + <i>z</i>
5	1 + <i>x</i>	<i>y</i>	<i>z</i>
6	1 + <i>x</i>	-1 + <i>y</i>	<i>z</i>
7	-1 + <i>x</i>	<i>y</i>	-1 + <i>z</i>
8	-1 + <i>x</i>	-1 + <i>y</i>	-1 + <i>z</i>

## Discussion

### *The pyrimidine base*

The base is in the diketo form, the two C=O bonds having an average length of 1.22 Å (1.21 and 1.23 Å). The four C-N bond distances are virtually identical (1.36, 1.37, 1.37, and 1.38 Å), averaging 1.37 Å. The value of 1.34 Å for the C(4)-C(5) distance confirms its true double-bond character, in better agreement with the results of 1.35 Å obtained for thymine monohydrate (Gerdil, 1961) and 1.31 Å for calcium thymidylate (Trueblood, Horn & Luzzati, 1961), than with the value of 1.41 Å obtained in a structural determination of uracil (Parry, 1954). The C(5)-C(6) bond is a single bond, measuring 1.49 Å, somewhat larger than the value of 1.45 Å found in thymine and calcium thymidylate, and very significantly longer than the 1.41 Å determined for uracil. The C(5)-I length of 2.05 Å is normal.

All of the bond angles are almost identical with those found in thymine, the difference exceeding 1° only in the *exo*-cyclic C-O angles. The values of 121 and 122° about C(6)-O(6) in IDU are more symmetrical than the corresponding 118 and 126° in thymine, but the distortions may be due to intermolecular packing in thymine; similarly the angles of 119 and 125° about C(2)-O(2) in IDU (122 and 123° in thymine) reflect the participation of O(2) in a short intermolecular contact.

The general agreement of the structure of the base in IDU with thymine (the structural determination of which was the most precise of the three cited above) demonstrates that the substitution of I for CH<sub>3</sub> does not significantly alter the structure of the base, and

suggests that perhaps the differences found between thymine and uracil are not real.

Least-squares planes calculated through all of the base and attached atoms, and through all but C(1'), showed that C(1') lies on the plane of the others. The maximum deviation from the plane (plane 1 of Table 4), is that of atom O(2) (0.077 Å) and probably is due to the short intermolecular I...O(2) distance. The significant displacements of the I and N(1) (0.046, -0.046 Å) from the plane are probably also caused by intermolecular contacts, the deviation of N(1) possibly to facilitate the hydrogen-bonding scheme.

#### The sugar

The deoxyribose ring is puckered with atom C(2') lying 0.59 Å out of the plane (plane 2 of Table 4) of the other four atoms (maximum deviation of the other four from the plane is 0.03 Å). This contrasts with calcium thymidylate, in which C(3') was the atom which was out of the plane of the others, and suggests that which of C(2') or C(3') deviates from planarity is a function of the packing in the individual crystal structures.

The bond distances in the ring are normal, the average C-C length being 1.56 Å, and C-O, 1.42 Å. The internal bond angles average 104° at C, and the angle is 111° at O(1'); the external angles average 112° at carbon. These values are similar to those (105°, 108°, 112°) predicted by Spencer (1959) from a survey of similar molecules.

The glycosidic N(3)-C(1') bond measures 1.49 Å, similar to that in adenosine-5'-phosphate (Kraut & Jensen, 1963) and close to the value of 1.47 Å in calcium thymidylate.

#### Conformation of the molecule

The plane of the sugar ring is at a dihedral angle of 81° to the base, a little larger than the values of 76° in adenosine-5'-phosphate and cytidine (Furberg, 1950), and 75° in calcium thymidylate.

In discussing the conformation about the glycosidic C-N bond, it is convenient to use the  $\varphi_{CN}$  torsion angle defined by Donohue & Trueblood (1960). This is defined as the angle formed by the trace of the plane of the base with the projection of the C(1')-O bond when the projection is taken along the glycosidic bond itself. As for all of the nucleosides and nucleotides

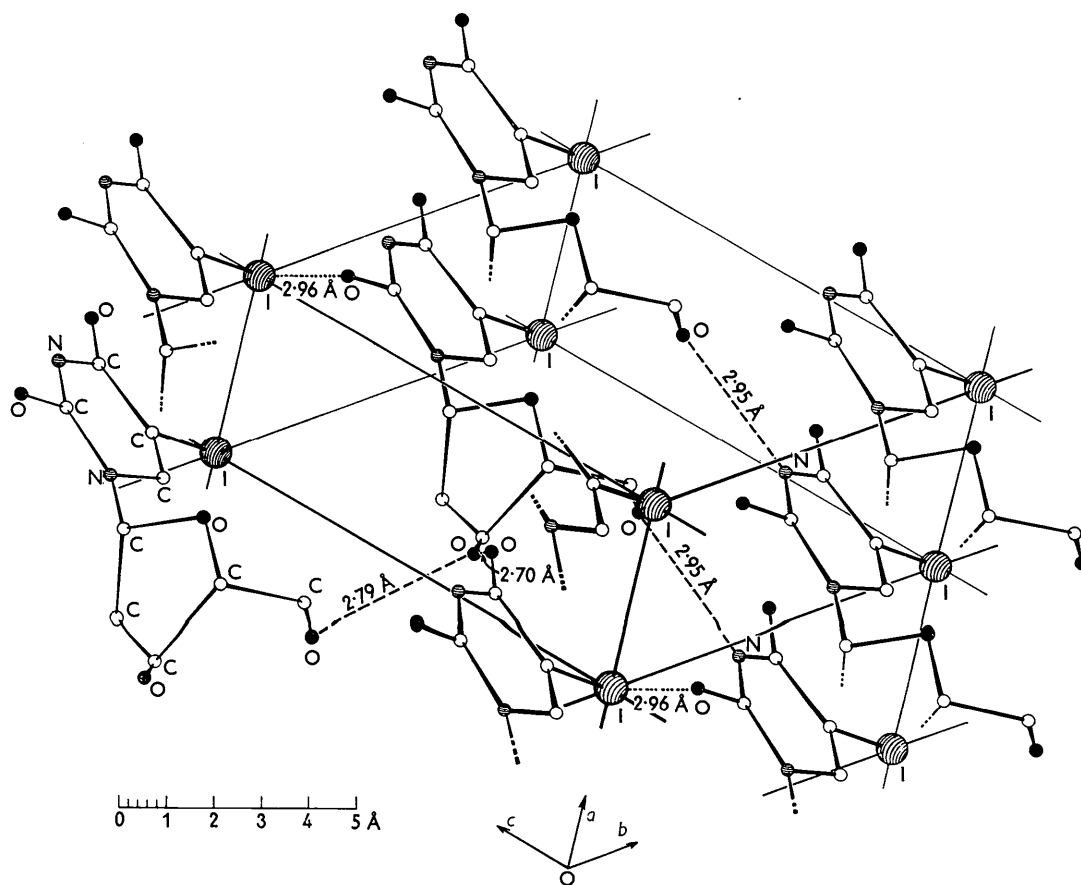


Fig. 3. Isometric projection showing the packing of the molecules. The short I...O(2) contact is shown by a dotted line, and the hydrogen bonds by dashed lines.



so far studied, IDU is in the *anti* conformation, with a value of  $\varphi_{CN}$  of  $-67^\circ$  (as contrasted with  $\varphi_{CN}$  of about  $150^\circ$  expected in the *syn* conformation).

#### Intermolecular distances

An isometric projection of the intermolecular packing is shown in Fig. 3. The most significant approach is an  $I \cdots O(2)$  distance of  $2.96 \text{ \AA}$ , which is considerably shorter than the normal iodine-oxygen van der Waals contact ( $3.55 \text{ \AA}$ ), and suggests a charge-transfer bond involving donation of oxygen lone-pair electrons to vacant  $5d$  orbitals on the iodine. The carbonyl group-iodine arrangement is not too far from linear, the  $C(2)-O(2)-I$  angle being  $166^\circ$ . Such charge-transfer bonds involving halogens as acceptors have been previously reported (Hassel & Rømming, 1962) with oxygen-, nitrogen-, and even sulfur- and selenium-containing compounds acting as donors. The stability of the bond increases with heavier halogens, and  $I \cdots O$  distances considerably shorter than even the one reported here have been found. The ability of the iodine to form such charge-transfer bonds may be the molecular basis for the anti-viral activity of 5-iododeoxyuridine. DNA which has had some thymidine substituted by IDU exhibits a higher melting temperature (temperature at which the two helices separate) than does normal DNA; this may reflect extra inter-coil attraction caused by the formation of a charge-transfer bond by the iodine with an oxygen or nitrogen on the complementary purine base (or possibly on the complementary helical skeleton itself), either in addition to the normal hydrogen-bonding scheme, or by replacing it with an alternative one. The result would be hindrance of strand separation, thus impairing the ability of the DNA to reproduce itself. In the case of *herpes simplex* keratitis treatment with IDU, this may kill the virus DNA, or merely retard its growth sufficiently to allow the body to overcome it (Camerman & Trotter, 1964).

The other short distances correspond to normal hydrogen bonds, and are shown by dashed lines in Fig. 3. Each hydroxyl group on the sugar ring ( $O(3')$  and  $O(5')$ ) is involved in two hydrogen bonds;  $O(3')$  uses its hydrogen atom in an H-bond to a

carbonyl  $O(6)$  and shares an  $O(5')$  hydrogen atom in a second attraction, while the second  $O(5')$  bond is through an  $N(1)$  hydrogen atom. The  $O \cdots H-N$  distance is  $2.95 \text{ \AA}$ , while the  $O \cdots H-O$  distances average  $2.75 \text{ \AA}$ . Together with the iodine- $O(2)$  contact, this system holds the crystal together in a three-dimensional network. Of the possible hydrogen-bonding atoms, only  $O(1')$  does not appear to take part in the intermolecular bonding scheme.

All other approaches correspond to normal van der Waals interactions.

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