

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

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(Received 1 December 1972; accepted 24 January 1973)

5-Chloro-2'-deoxyuridine ( $C_9H_{11}ClN_2O_5$ ) crystallizes in the space group  $P2_1$  with one molecule per asymmetric unit and with unit-cell dimensions  $a = 9.118$  (8),  $b = 5.090$  (5),  $c = 11.992$  (8) Å and  $\beta = 107^\circ 40'$  (3). The structure was solved by Patterson interpretation methods and the positional parameters were refined by the method of least squares, using anisotropic temperature factors for the non-hydrogen atoms. The final  $R$  index for the 1228 reflexions used in the refinement process is 0.038 and the standard deviations in the bond lengths and angles are about 0.005 Å and  $0.3^\circ$  respectively. The glycosidic torsion angle  $\chi_{CN}$  is  $41.1^\circ$  in the *anti* configuration and the atom C(2') of the sugar is displaced 0.62 Å *endo*. The conformation of the C(5')-O(5') bond is *gauche-trans* to C(4')-O(1') and C(4')-C(3') respectively.

### Introduction

The investigation of the structure of 5-chloro-2'-deoxyuridine was undertaken as part of a series of structure determinations of nucleic acid components in progress in this laboratory. The structural formula of 5-chloro-2'-deoxyuridine and the atomic numbering scheme adopted for this paper are shown in Fig. 1.

The crystal structure reported here is isomorphous with that of 5-bromo-2'-deoxyuridine determined by Iball, Morgan & Wilson (1966).

### Experimental

Crystals grown by slow evaporation from aqueous solution were colourless monoclinic prisms. Preliminary Weissenberg and precession X-ray photography showed the crystals to be monoclinic with systematic absences consistent with the space groups  $P2_1$  and  $P2_1/m$ . Since the molecule is optically active the space group was taken as  $P2_1$ . Preliminary unit-cell dimensions were calculated from these exploratory X-ray diffraction photographs and then more accurate values

obtained from measurements on a Hilger and Watts linear diffractometer using Mo  $K\alpha$  radiation ( $\lambda = 0.71069$  Å). The unit-cell dimensions thus obtained were,

$$\begin{aligned} a &= 9.118 \pm 0.008 \text{ \AA} \\ b &= 5.090 \pm 0.005 \\ c &= 11.992 \pm 0.008 \\ \beta &= 107^\circ 40' \pm 3' \end{aligned}$$

The calculated density with two molecules in the unit cell is  $1.494 \text{ g cm}^{-3}$ .

In all, 1232 significantly non-zero reflexions were measured on a Hilger and Watts linear diffractometer using Mo  $K\alpha$  radiation and balanced filters. The data collected were equivalent to 92% of those available within the Cu  $K\alpha$  limiting sphere. The diffraction intensities were measured from two different crystals about the  $a$  and  $b$  axes. The data on layer planes 0 to 3 about the  $a$  axis and on layer planes 0 to 6 about the  $b$  axis were collected. The crystals were small enough for absorption corrections to be ignored. The data so collected were scaled together to produce a value of the structure amplitude for each reflexion. The  $R$  value between the two independent sets of data for those reflexions in common was 0.06 where  $R = \sum |(F_b - F_a)| / \sum |F_b|$ .

### Structure determination

The chlorine atom, the pyrimidine residue and C(1') were expected to be planar. The  $I(\theta, \varphi)$  function of Tollin & Cochran (1964) was computed with the sharpened Patterson coefficients  $|F_s(h)|^2$ , calculated using the modification function proposed by Wunderlich (1965) with constants  $a = 2.0$  and  $p = 7.25$ . The results, obtained by integrating the Patterson function over a disc of radius 3.5 Å, were plotted on a Sanson-Flamsteed projection (Fig. 2). The largest peak in this map, representing the direction of the normal to the pyrimidine residue, has spherical polar angles  $\theta = 49.2^\circ$ ,  $\varphi = 114.6^\circ$  with respect to the axial set  $0(a^*, b, a^* \times b)$ .

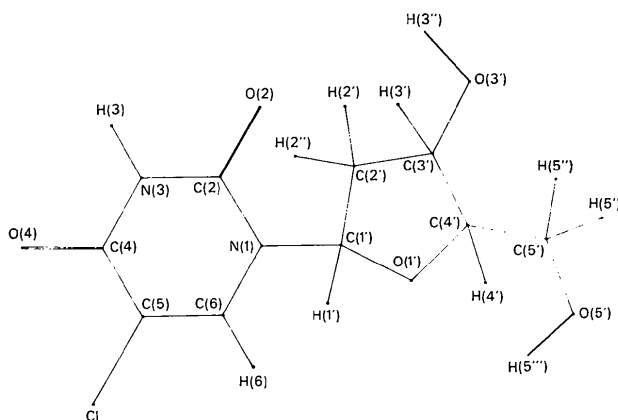


Fig. 1. 5-Chloro-2'-deoxyuridine and the atom numbering.

Comparison of the section through the origin of the sharpened Patterson function, computed in the orientation given by these  $\theta$  and  $\varphi$  values, and the theoretical vector set of the pyrimidine residue with its attachments gave the orientation of the molecular fragment in the plane.

The  $y$  coordinate of the chlorine atom was set to zero and the two others,  $x=0.471$  and  $z=0.098$ , were determined from the three-dimensional Patterson function. These coordinates were verified by calculating, for the molecular fragment, the  $Q(X_0, Z_0)$  function defined by Tollin (1966). A structure factor calculation using an overall isotropic temperature factor of  $3.0 \text{ \AA}^2$  had a reliability index,  $R$ , of 0.46, where

$$R = \frac{\sum_{\mathbf{h}} ||F_{\text{obs}}(\mathbf{h})| - |F_{\text{calc}}(\mathbf{h})||}{\sum_{\mathbf{h}} |F_{\text{obs}}(\mathbf{h})|}$$

An electron density map was computed using the phases obtained in this structure factor calculation and all the observed structure amplitudes. Most of the missing non-hydrogen atoms of the deoxyribose sugar could be identified. After two cycles of Fourier refinement, in which the overall temperature factor was kept at  $3.0 \text{ \AA}^2$ , all the non-hydrogen atoms had been located and the  $R$  value was 0.25.

### Refinement

The structure was refined by the method of least squares, using the block-diagonal approximation and a program written by Professor J. Trotter (Toronto University) modified by the staff of the Computing Laboratory (University of Dundee) for use on an Elliott 4130 computer.

The coordinates of the non-hydrogen atoms obtained from the electron density map and individual isotropic temperature factors were used, and all reflexions were assigned equal weight. After four cycles the  $R$  value was 0.12. At this stage all the hydrogen atom positions could be clearly seen as peaks in the difference Fourier synthesis. In two further cycles of isotropic least-squares refinement the hydrogen atoms were included with equal isotropic temperature factors of  $3.0 \text{ \AA}^2$  and their positional and thermal parameters kept fixed. The  $R$  value was reduced to 0.10.

The non-hydrogen atoms were then refined using individual anisotropic temperature factors of the form  $T = \exp \{ -(\beta_{11}h^2 + \beta_{12}hk + \beta_{13}hl + \beta_{22}k^2 + \beta_{23}kl + \beta_{33}l^2) \}$  and all the observed reflexions each with an individual weight  $w = 1/[1 + \{(|F_o| - a)/b\}^2]$ . The constants  $a$  and  $b$  were given values of 5.0 and 30.0 respectively in the latter stages of the refinement, during which it became clear that the calculated values of the structure factors for reflexions  $11\bar{1}$ ,  $11\bar{2}$ ,  $200$  and  $202$  were consistently too large. As the peak count rate for these reflexions at low X-ray output power was high enough to cause error arising from lost counts these four reflexions were excluded from the final stages of the refinement process. During these last stages the positional and isotropic

Table 1. Positional parameters and estimated standard deviations for the non-hydrogen atoms

	$x/a$	$y/b$	$z/c$
Cl	0.4766 (1)	0.0494 (3)	0.0983 (1)
O(2)	0.5660 (3)	-0.7052 (7)	0.4673 (2)
O(4)	0.7649 (3)	-0.0707 (7)	0.2941 (2)
O(1')	0.1767 (2)	-0.7372 (7)	0.2088 (2)
O(3')	0.0485 (3)	-0.8765 (6)	0.4260 (2)
O(5')	-0.0712 (3)	-0.7136 (8)	0.0086 (2)
N(1)	0.4032 (3)	-0.5087 (7)	0.3050 (2)
N(3)	0.6616 (3)	-0.3907 (7)	0.3764 (2)
C(2)	0.5449 (3)	-0.5472 (8)	0.3893 (3)
C(4)	0.6517 (4)	-0.2028 (9)	0.2936 (3)
C(5)	0.4994 (4)	-0.1761 (9)	0.2085 (3)
C(6)	0.3829 (4)	-0.3267 (8)	0.2175 (3)
C(1')	0.2728 (3)	-0.6598 (8)	0.3209 (3)
C(2')	0.1680 (4)	-0.5042 (8)	0.3727 (3)
C(3')	0.0260 (3)	-0.6784 (9)	0.3388 (3)
C(4')	0.0245 (4)	-0.7854 (8)	0.2183 (3)
C(5')	-0.0941 (4)	-0.6489 (10)	0.1183 (3)

thermal parameters of the hydrogen atoms were allowed to vary. The final root-mean-square positional parameter shift was about  $0.22 \sigma$  and the final average root-mean-square shift in the thermal parameters about  $0.25 \sigma'$ , where  $\sigma'$  is the average estimated standard

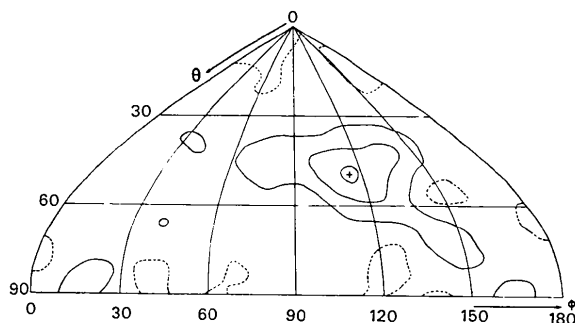


Fig. 2. The  $I(\theta, \varphi)$  map with  $R=3.5 \text{ \AA}$ .

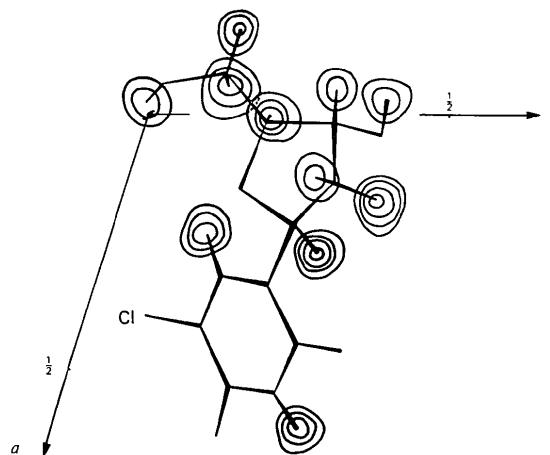


Fig. 3. Composite  $\Delta F$  synthesis showing the electron density in sections through the hydrogen atoms. Contours are at intervals of  $0.1 \text{ e \AA}^{-3}$  starting at  $0.2 \text{ e \AA}^{-3}$ .

Table 2. *Anisotropic thermal parameters ( $\times 10^5$ ) and estimated standard deviations for the non-hydrogen atoms*

	$\beta_{11}$	$\beta_{12}$	$\beta_{13}$	$\beta_{22}$	$\beta_{23}$	$\beta_{33}$
Cl	943 (10)	-447 (40)	352 (11)	3542 (37)	849 (28)	459 (5)
O(2)	559 (27)	64 (113)	117 (36)	3171 (115)	1030 (90)	590 (18)
O(4)	626 (27)	-1681 (118)	290 (37)	4889 (151)	607 (101)	642 (20)
O(1')	380 (23)	-611 (104)	291 (28)	4060 (128)	-742 (81)	366 (14)
O(3')	591 (26)	-1009 (103)	193 (32)	3703 (131)	328 (79)	375 (15)
O(5')	1025 (34)	-504 (143)	160 (38)	4574 (147)	-107 (97)	334 (16)
N(1)	398 (26)	-343 (102)	236 (33)	2372 (123)	125 (81)	364 (17)
N(3)	337 (26)	-237 (107)	175 (34)	2775 (134)	126 (86)	412 (17)
C(2)	423 (31)	-29 (122)	303 (39)	2194 (130)	-11 (95)	391 (20)
C(4)	530 (33)	-434 (144)	367 (42)	2695 (143)	-159 (108)	410 (21)
C(5)	597 (34)	-277 (135)	299 (41)	2467 (141)	233 (102)	365 (20)
C(6)	499 (33)	-162 (128)	145 (40)	2494 (138)	115 (98)	337 (19)
C(1')	392 (30)	-439 (125)	226 (38)	2358 (138)	-78 (96)	341 (19)
C(2')	508 (32)	-451 (123)	341 (39)	2336 (146)	-448 (95)	414 (20)
C(3')	406 (31)	-266 (129)	248 (39)	2586 (140)	-86 (100)	352 (19)
C(4')	390 (31)	-415 (128)	218 (38)	2650 (146)	-126 (99)	326 (19)
C(5')	602 (37)	114 (163)	134 (47)	4066 (197)	104 (125)	363 (22)

deviation in an anisotropic temperature factor parameter.

Eleven sets of structure-factor calculations were performed, in each of which one of the hydrogen atoms was omitted, and for each a difference Fourier synthesis was computed in the region of the omitted hydrogen atom. Fig. 3 is a composite of these difference electron density calculations.

The final values of the parameters of the heavy atoms with their estimated standard deviations are given in Tables 1 and 2, and the parameters of the hydrogen atoms are listed in Table 3. The observed and calculated structure factors are listed in Table 4. The

Table 3. *Positional and isotropic thermal parameters with estimated standard deviations for the hydrogen atoms*

	$x/a$	$y/b$	$z/c$	$B$
H(3)	0.753 (5)	-0.501 (12)	0.442 (4)	1.4 (2)
H(6)	0.275 (4)	-0.314 (9)	0.159 (3)	0.3 (2)
H(1')	0.320 (5)	-0.795 (10)	0.374 (4)	1.1 (2)
H(2')	0.208 (4)	-0.467 (10)	0.457 (3)	0.2 (2)
H(2'')	0.150 (5)	-0.320 (12)	0.335 (4)	1.9 (2)
H(3')	-0.068 (5)	-0.580 (11)	0.331 (4)	1.7 (2)
H(4')	0.008 (5)	-0.978 (11)	0.219 (4)	1.6 (2)
H(5')	-0.075 (5)	-0.451 (14)	0.129 (4)	2.0 (2)
H(5'')	-0.199 (5)	-0.727 (11)	0.111 (4)	0.9 (2)
H(3''')	-0.030 (6)	-1.008 (14)	0.407 (4)	3.2 (2)
H(5''')	-0.030 (6)	-0.568 (14)	-0.004 (6)	3.7 (2)

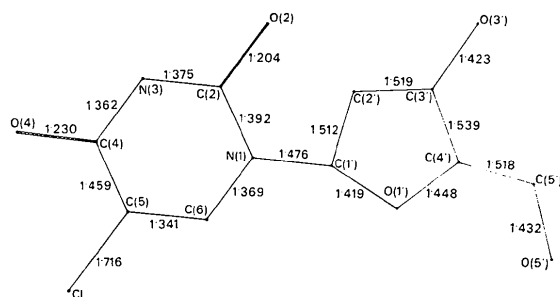


Fig. 4. Bond distances. The estimated standard deviations for bonds not involving hydrogen are 0.005 Å.

final value of the  $R$  index for all non-zero observed structure amplitudes, excluding the four reflexions with high peak count rate, was 0.038. The  $R$  index for all reflexions inside the copper  $K\alpha$  limiting sphere, including the unobservable reflexions, which were given an amplitude of 0.7 of the significant structure amplitude at the appropriate region in reciprocal space, was 0.049.

## Discussion

The intramolecular bond distances and bond angles are shown in Figs. 4 and 5 with estimated standard deviations for non-hydrogen interatomic bond lengths of about 0.005 Å and for bond angles of approximately 0.3°. The structure is essentially isomorphous with that of 5-bromo-2'-deoxyuridine, the published coordinates of which may be transformed by means of the relations

$$x_{\text{Cl}} = 0.5 - x_{\text{Br}}, \quad y_{\text{Cl}} \approx y_{\text{Br}} - 0.9, \quad z_{\text{Cl}} = 0.5 - z_{\text{Br}},$$

to enable direct comparison to be made with those of the present investigation.

### The pyrimidine base

The uracil base is virtually planar and the equation of the best plane calculated by least squares is

$$0.4291X - 0.6894Y - 0.5836Z = 0.8531,$$

where  $X, Y, Z$  are the coordinates of the atoms in Å, relative to the orthogonal axial set  $0(b \times c^*, b, c^*)$ . The deviations of the atoms from this plane are listed in Table 5. The deviation of atom C(1') from this plane of 0.11 Å is similar to those displacements observed in other nucleosides (Haschemeyer & Rich, 1967). Apparently, bending about the glycosidic bond is a way of reducing strains in these molecules due to steric interactions and crystal packing effects (Coulter, Hawkinson & Friedmann, 1969). In terms of the  $\theta, \varphi$  angles previously determined in the Patterson interpretation this plane corresponds to  $\theta = 49.6^\circ$  and  $\varphi = 115.2^\circ$ , in good agreement with the values found from the  $I(\theta, \varphi)$  function.





sidic bond (Donohue & Trueblood, 1960). This parameter, denoted the torsion angle and usually symbolized as  $\varphi_{\text{CN}}$  in the literature, is a descriptive one to use when C(1') is in the plane of the base. A more convenient parameter to use when C(1') is not in the plane of the base is  $\chi_{\text{CN}}$ , defined as the dihedral angle between the planes C(6)-N(1)-C(1') and N(1)-C(1')-O(1') (Sundaralingam, 1969). The value of  $\chi_{\text{CN}}$  found for 5-chloro-2'-deoxyuridine was  $41.1^\circ$ , which compares with the value of  $\chi_{\text{CN}}$  for 5-bromo-2'-deoxyuridine of  $47^\circ$ . This corresponds to the *anti* conformation, in the nomenclature of Sundaralingam (1969), and this conformation is illustrated in Fig. 6(b).

### Molecular packing and hydrogen bonding

The arrangement of 5-chloro-2'-deoxyuridine molecules in the unit cell is illustrated in Fig. 7, which is a projection down the *b* axis onto the *a,c* plane of the unit-cell contents. The hydrogen bond contacts are shown by dashed lines and are directly comparable with those of Iball *et al.* (1966). In the structure of 5-bromo-2'-deoxyuridine there was an ambiguity in the location of the hydrogen atom attached to O(5'). In the present structure determination this hydrogen atom is clearly visible in the three-dimensional difference map illustrated in Fig. 3, as are all the hydrogen atoms.

The atom N(3) of the pyrimidine base donates a hydrogen atom to O(3') of the molecule at  $1-x, \frac{1}{2}+y, 1-z$ , forming an N-H...O hydrogen bond of length 2.97 Å. This acceptor atom, O(3'), now donates a

hydrogen atom to O(4) of the molecule at  $2-x, -\frac{1}{2}+y, 1-z$ , forming a hydrogen bond of length 2.77 Å. This donor-acceptor circuit forms an infinite spiral arrangement of hydrogen bonds with the axis of the spiral parallel to **b**.

Atom O(5') donates a hydrogen atom to O(5') of the molecule at  $-x, \frac{1}{2}+y, -z$ , forming a hydrogen bond of length 2.89 Å. This forms once again a spiral arrangement of hydrogen bonds with axis parallel to **b**.

We wish to acknowledge the assistance given in this investigation by the staff of the Computing Laboratory of the University of Dundee.

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## Conformations Cristallines d'Adrénolytiques $\beta$ -Bloquants: Propranolol et Alprénolol

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(Reçu le 20 octobre 1972, accepté le 18 décembre 1972)

The non-isomorphous crystal structures of propranolol and alprenolol hydrochlorides ( $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{Cl}$  and  $\text{C}_{15}\text{H}_{24}\text{NO}_2\text{Cl}$ ), adrenergic  $\beta$ -blocking agents, have been solved by indirect methods (space group  $P2_1/c$ ). In both structures each  $\text{Cl}^-$  anion is related to a hydroxyl group and forms two hydrogen bonds with the  $-\text{NH}_3^+$  groups. Crystal conformations of levorotatory isomers are compared with those of (-)-noradrenaline ( $\text{Cl}^-$ ), (-)-isoproterenol ( $\text{SO}_4^{2-}$ ) and (-)-ephedrine ( $\text{Cl}^-$ ), which are respectively  $\alpha$ -,  $\beta$ - and  $\alpha,\beta$  adrenergic agents. Despite their flexibility, the different chains have a common feature: a torsion from  $50$  to  $75^\circ$  around the central bond of the  $-\text{CH}_2-\text{CHOH}-\text{CH}_2-\text{NH}_3^+\text{R}$  group brings the oxygen atom close to the nitrogen atom ( $d_{\text{O}\dots\text{N}}$  between 2.64 and 2.95 Å).

### Introduction

Le propranolol (I) et l'alprénolol (II) [dénominations chimiques respectives: isopropylamino-1 (naphtyl-1 oxy)-3 propanol-2 et isopropylamino-1 (allyl-2 phé-

noxy-1)-3 propanol-2], substances adrénolytiques  $\beta$ -bloquantes de synthèse, sont utilisés en thérapeutique depuis quelques années pour combattre l'angine de poitrine et certains troubles du rythme cardiaque.

La transmission de l'influx nerveux aux jonctions