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## Crystal and Molecular Structure of (–)-(5*S*)-5-Hydroxy-5,6-dihydrothymidine

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$C_{10}H_{16}N_2O_6$  is monoclinic, space group  $P2_1$ , with  $a = 5.534$  (2),  $b = 12.023$  (3),  $c = 9.242$  (3) Å,  $\beta = 97.91$  (3)°. The structure was refined to an  $R$  of 0.070 for 1138 significant reflexions. The pyrimidine ring displays a twisted half-chair conformation with C(5) and C(6) displaced by 0.286 and 0.362 Å on opposite sides of the plane. The conformation about the glycosyl linkage is *anti* with  $\chi = 68.7^\circ$ . The conformation of the hydroxymethyl exocyclic group about C(4')–C(5') is *gauche-gauche*. The deoxyribose ring has the O(1')-*endo* envelope conformation with O(1') situated 0.519 Å from the plane through C(1'), C(2'), C(3') and C(4').

### Introduction

Saturation of the heterocyclic ring of the pyrimidine bases represents a major type of radiation-induced damage in nucleic-acid *in vitro* models (Téoule, Bonicel, Bert, Cadet & Polverelli, 1974; Scholes, 1976), and in living cells (Hariharan & Cerutti, 1974). It was shown that ring-saturation pyrimidine radiation products could disrupt the ordered conformation of double-stranded deoxyribonucleic acids and interfere with their biological functions (Swinehart, Bobst & Cerutti, 1972). Important conformational changes take place in modified thymine derivatives, as demonstrated by the X-ray analyses of (–)-(5*S*)-5,6-dihydrothymidine (Konnert, Karle & Karle, 1970) and *cis*-5,6-dihydroxy-5,6-dihydrothymine (Flippen, 1973). We describe here the crystal structure and the sterically allowed conformations of a diastereoisomer of a pyrimidine ring-saturation nucleoside, (–)-(5*S*)-5-

hydroxy-5,6-dihydrothymidine, which was obtained by  $\gamma$  irradiation of oxygen-free aqueous solutions of thymidine (Cadet, Ducolomb, Grand & Téoule, 1976).

### Experimental

The compound was recrystallized from ethanol and mounted along  $c$ . The space group was determined from photographs with Cu  $K\alpha$  radiation. From the extinctions obtained ( $0k0$  absent for  $k$  odd), space groups  $P2_1$  or  $P2_1/m$  were indicated; however, as  $Z = 2$ , it was determined to be  $P2_1$ . Table 1 records the crystallographic data. Intensities were collected on a Siemens four-circle automatic diffractometer at the Laue-Langevin Institute (Grenoble) by the five-points method (Troughton, 1969) with Ni-filtered Cu  $K\alpha$  radiation. 1290 independent reflexions were recorded in the range  $3 < \theta < 70^\circ$ . A standard reflexion, checked periodically, showed no significant deviation. The data

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Table 1. *Crystallographic and physical data for (-)-(5S)-5-hydroxy-5,6-dihydrothymidine, C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>*

FW	260.22
F(000)	276
Crystal system	Monoclinic
Space group	<i>P</i> 2 <sub>1</sub> , <i>Z</i> = 2
<i>a</i>	5.534 (2) Å
<i>b</i>	12.023 (3)
<i>c</i>	9.242 (3)
$\beta$	97.91 (3)°
<i>V</i>	609.07 Å <sup>3</sup>
<i>D<sub>x</sub></i>	1.420 g cm <sup>-3</sup>

Table 2. *Fractional coordinates (×10<sup>4</sup>) of the non-hydrogen atoms with standard deviations in parentheses*

	<i>x</i>	<i>y</i>	<i>z</i>
N(1)	8812 (9)	9260 (0)	6379 (4)
C(2)	9553 (11)	9274 (7)	5053 (5)
N(3)	8278 (11)	9982 (7)	4055 (4)
C(4)	6861 (11)	10862 (7)	4278 (5)
C(5)	6538 (10)	11029 (7)	5957 (5)
C(6)	6695 (11)	9908 (7)	6689 (4)
O(2)	11231 (9)	8714 (6)	4685 (4)
O(4)	5982 (11)	11492 (7)	3358 (4)
O(5)	8604 (8)	11663 (6)	6566 (3)
C(7)	4178 (17)	11593 (10)	6103 (11)
C(1')	10159 (13)	8596 (7)	7536 (5)
C(2')	8605 (17)	7839 (9)	8368 (6)
C(3')	9892 (15)	7850 (7)	9948 (6)
C(4')	11997 (13)	8677 (7)	9912 (5)
O(1')	11387 (8)	9327 (6)	8599 (3)
C(5')	12325 (16)	9492 (8)	11178 (5)
O(5')	10088 (14)	10000 (6)	11375 (4)
O(3')	10730 (13)	6772 (6)	10372 (4)

Table 3. *Fractional coordinates of the hydrogen atoms (×10<sup>3</sup>)*

	<i>x</i>	<i>y</i>	<i>z</i>
H(N3)	854 (13)	998 (6)	321 (7)
H(6)1	509 (13)	954 (6)	629 (7)
H(6)2	694 (12)	998 (6)	779 (7)
H(O9)	862 (13)	1226 (7)	608 (7)
H(7)1	374 (15)	1183 (10)	719 (11)
H(7)2	302 (16)	1117 (8)	558 (11)
H(7)3	412 (15)	1225 (9)	567 (10)
H(1')	1137 (14)	805 (6)	734 (7)
H(2')1	641 (19)	810 (7)	884 (7)
H(2')2	817 (16)	704 (8)	820 (7)
H(3')	864 (16)	809 (7)	1046 (8)
H(4')	1353 (15)	830 (7)	998 (7)
H(5')1	1309 (15)	919 (9)	1201 (8)
H(5')2	1367 (16)	1004 (8)	1104 (7)
H(O5')	936 (19)	1049 (8)	1077 (9)
H(O3')	1095 (19)	687 (8)	1113 (10)

were corrected for Lorentz-polarization factors, but not for absorption.

### Structure determination and refinement

The structure was solved with *MULTAN* (Declercq, Germain, Main & Woolfson, 1973). The *E* map was calculated with 300 reflexions ( $E > 1.14$ ) and the solution with the best figure of merit revealed the positions of all 18 nonhydrogen atoms. The structure was refined by full-matrix least squares (*ORFLS*, Busing & Levy, 1959) with 1138 significant reflexions and anisotropic thermal factors until  $R_w = \{[\sum w(F_o - \text{Sq } F_c)^2 / \sum wF_o^2]^{1/2}\}$  and  $R = \{\sum |F_o - \text{Sq } F_c| / \sum |F_o|\}$  had reached 0.096 and 0.075 respectively.

A difference synthesis showed the positions of all the H atoms. On refinement of these positions, it was found that only the H atom belonging to O(18) had diverged.  $R_w$  and  $R$  reduced to 0.070 and 0.055 respectively.\*

The final atomic parameters are recorded in Tables 2 and 3, and bond distances and angles are in Table 4 and Figs. 1 and 2.

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33218 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond distances (Å) and angles (°) involving hydrogen atoms*

H(N3)–N(3)	0.819 (4)	H(7)3–C(7)–C(5)	110.1
C(6)–H(6)1	1.016 (9)	H(7)1–C(7)–H(7)2	113.9
C(6)–H(6)2	1.009 (4)	H(7)1–C(7)–H(7)3	100.3
O(5)–H(O5)	0.845 (1)	H(7)2–C(7)–H(7)3	106.4
C(7)–H(7)1	1.101 (6)	H(1')–C(1')–N(1)	122.2
C(7)–H(7)2	0.905 (9)	H(1')–C(1')–O(1')	105.5
C(7)–H(7)3	0.883 (1)	H(1')–C(1')–C(2')	98.1
C(1')–H(1')	0.871 (3)	H(4')–C(4')–O(1')	114.2
C(2')–H(2')1	1.267 (2)	H(4')–C(4')–C(3')	111.2
C(2')–H(2')2	0.995 (1)	H(4')–C(4')–C(5')	104.2
C(3')–H(3')	0.938 (9)	H(3')–C(3')–C(4')	115.0
C(4')–H(4')	0.953 (1)	H(3')–C(3')–C(2')	101.6
C(5')–H(5')1	0.902 (10)	H(3')–C(3')–O(4')	112.7
C(5')–H(5')2	1.011 (3)	H(2')–C(2')–C(1')	119.2
O(5')–H(O5')	0.871 (7)	H(2')2–C(2')–C(1')	129.6
O(3')–H(O3')	0.703 (3)	H(2')–C(2')–C(3')	105.7
H(N3)–N(3)–C(2)	119.9	H(2')2–C(2')–C(3')	103.0
H(N3)–N(3)–C(4)	109.4	H(2')1–C(2')–H(2')2	91.9
N(1)–C(6)–H(6)1	112.2	H(5')1–C(5')–C(4')	112.8
C(5)–C(6)–H(6)1	103.7	H(5')2–C(5')–C(4')	109.4
C(5)–C(6)–H(6)2	111.9	H(5')–C(5')–O(5')	112.5
N(1)–C(6)–H(6)2	103.8	H(5')2–C(5')–O(5')	114.1
H(6)1–C(6)–H(6)2	112.8	H(5')–C(5')–H(5')2	95.9
H(O5)–O(5)–C(5)	108.3	H(O5')–O(5')–C(5')	122.8
H(7)1–C(7)–C(5)	120.3	H(O3')–O(3')–C(3')	97.7
H(7)2–C(7)–C(5)	105.0		

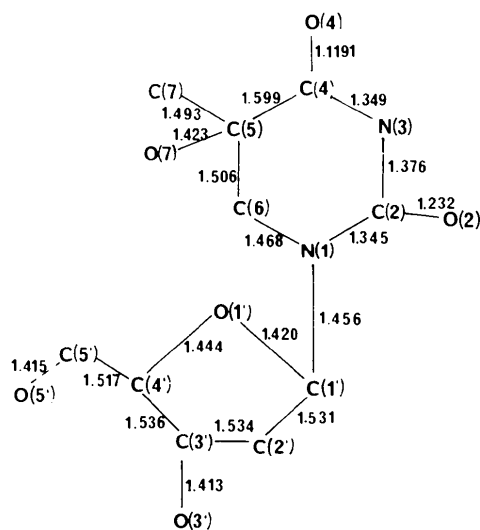


Fig. 1. Chemical structure and bond distances (Å) ( $0.007 < \sigma < 0.014$  Å). H atoms are omitted.

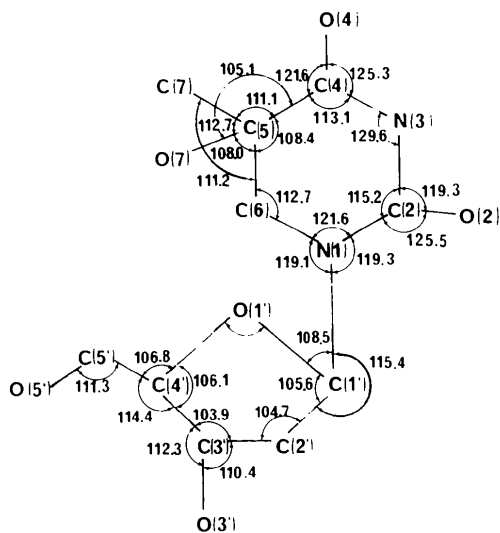


Fig. 2. Angles ( $^{\circ}$ ) ( $0.05 < \sigma < 0.08^{\circ}$ ) for (–)-(5*S*)-5-hydroxy-5,6-dihydrothymidine.

## Results and discussion

The configuration of the nucleoside is illustrated in Fig. 3.

### Pyrimidine moiety

In the 5-hydroxy-5,6-dihydrothymine moiety the bond lengths and angles are very similar to those reported for 5,6-dihydrothymine (Furberg & Jensen, 1968) and (–)-(5*S*)-5,6-dihydrothymidine (Konnert, Karle & Karle, 1970). The C(2)–O(2) and C(4)–O(4) distances indicate a double-bond character which

favors a diketo form, Shortening of N(1)–C(2) with respect to that in the 5,6 unsaturated pyrimidine was also observed for 5,6-dihydro-2,4-dithiouridine (Kojić-

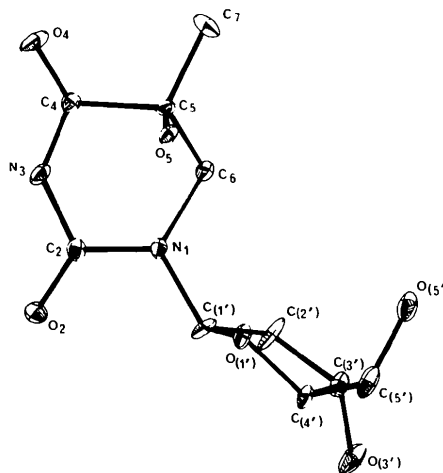


Fig. 3. Perspective drawing of (–)-(5*S*)-5-hydroxy-5,6-dihydrothymidine.

Table 5. Displacements (Å) from least-squares planes through the heterocyclic base and the deoxyribose moiety

The equations are of the form  $lX + mY + nZ + p = 0$ . Atoms used in fitting the plane are denoted by an asterisk.

### (a) Heterocycle

Plane 1:  $l = 4.068, m = 7.033, n = 2.801, p = 11.428$

Plane 2:  $l = 4.069, m = 7.428, n = 1.617, p = -11.520$

	Plane 1	Plane 2
N(1)	0.0671*	–0.0309*
C(2)	0.0884*	0.0682*
N(3)	–0.1458*	–0.0800*
C(4)	–0.0455*	0.0424*
C(5)	0.2899*	0.2856
C(6)	–0.2707*	–0.3620
O(2)	0.2972	0.2751
O(4)	–0.1753	–0.0099
O(5)	1.7241	1.7090
C(7)	–0.2407	–0.2311
C(1')	0.4119	0.2187

### (b) Deoxyribose moiety

Plane 1:  $l = -3.349, m = 9.325, n = 2.413, p = -6.431$

Plane 2:  $l = -3.749, m = 7.607, n = 4.297, p = -6.437$

	Plane 1	Plane 2
C(1')	–0.0180*	–0.4850
C(2')	0.0246*	–0.0966*
C(3')	–0.0260*	0.1022*
C(4')	0.0190*	–0.0899*
C(5')	0.9979	0.9747
O(1')	0.5195	0.0779*
O(3')	–1.1995	–0.8400
O(5')	2.2559	2.2662

Prodić, Kvić & Ružić-Toroš, 1976) and 5,6-dihydro-uridine (Sundaralingam, Rao & Abola, 1971; Suck, Saenger & Zechmeister, 1972).

The conformation of the base ring is described by the torsion angle about the ring bonds. The least-squares plane based on N(1), C(2), N(3) and C(4) shows considerable deviation from planarity (Table 5). The saturated pyrimidine ring exhibits a half-chair conformation with C(6) and C(5) respectively displaced by 0.362 and 0.286 Å on opposite sides of the mean base plane. O(2) and O(4) are also out of the plane by 0.275 and 0.010 Å respectively. O(5) assumes an axial conformation whereas the methyl group, which shows a smaller deviation from the best four-atom planes (Table 5), is attached at C(5) in a quasi-equatorial position. Similar conclusions were reached from an infrared analysis of 5-hydroxy-5,6-dihydrothymine in a KBr matrix (Nofre, Murat & Cier, 1965). The absolute configuration about the asymmetric C(5) is *S*. The methyl group and C(6) are located on the same side of the plane through N(1), C(2), N(3), C(4) as C(2'). An opposite trend was reported for (–)-(5*S*)-5,6-dihydrothymidine (Konnert, Karle & Karle, 1970).

#### Deoxyribofuranose ring

The conformation of the furanose ring of nucleosides may be depicted by three parameters: puckering of the sugar ring, conformation of the exocyclic hydroxymethyl group around C(4')–C(5'), and orientation of the heterocyclic base with respect to the sugar moiety. The best four-atom plane through the pentose ring is defined by C(1'), C(2'), C(3') and C(4'), none of which deviates by more than 0.03 Å from the mean plane. O(1') is displaced by 0.519 Å from this plane on the same side as C(5') (Table 5). The furanose ring exists in the envelope form. The saturation of the 5,6-pyrimidine bond induces the sugar ring to assume an O(1')-*endo* conformation whereas the parent molecule, thymidine, exhibits a C(3')-*endo* conformation (Young, Tollin & Wilson, 1969). A slight tendency to a (2')-*endo*, (3')-*exo* conformation is also assumed on the basis of the observed value of the C(1')–C(2')–C(3')–C(4') torsion angle (–3.6°) (Table 6) and the displacements of the C atoms from the common plane (Table 5). The puckering of the sugar ring can be described by means of the dihedral angles about the ring bonds (Sundaralingam, 1969). The values of these angles,  $\tau_0 = -37.1$ ,  $\tau_1 = 24.5$ ,  $\tau_2 = -3.6$ ,  $\tau_3 = -18.1$ ,  $\tau_4 = 34.9^\circ$ , are comparable with those calculated for (–)-5,6-dihydrothymidine (Altona & Sundaralingam, 1972) from the previously reported atomic coordinates (Konnert, Karle & Karle, 1970). The corresponding values for the phase angle of pseudorotation *P* and the amplitude of pucker  $\tau_m$  (Altona & Sundaralingam, 1972) are 95.5 and 37.4° respectively.

Table 6. Some dihedral angles (°) describing the conformation of (–)-(5*S*)-5-hydroxy-5,6-dihydrothymidine

These four-atom angles are considered positive when, looking along any bond, the rear bond rotates clockwise with respect to the front bond.

O(1')–C(1')–C(2')–C(3')	24.5 (0)
C(1')–C(2')–C(3')–C(4')	–3.6 (5)
C(2')–C(3')–N(4')–O(1')	–18.1 (4)
C(3')–C(4')–O(1')–C(1')	34.9 (6)
C(4')–O(1')–C(1')–C(2')	–37.1 (8)
C(2')–C(1')–N(1)–C(6)	–49.5 (9)
C(2')–C(1')–N(1)–C(2)	131.1 (7)
O(1')–C(1')–N(1)–C(6)	68.7 (2)
O(1')–C(1')–N(1)–C(2)	–110.6 (2)
O(5')–C(5')–C(4')–O(1')	–67.7 (7)
O(5')–C(5')–C(4')–C(3')	49.4 (9)
N(1)–C(2)–N(3)–C(4)	–17.8 (9)
C(2)–N(1)–C(6)–C(5)	38.3 (6)
N(3)–C(4)–C(5)–C(6)	30.5 (6)
C(4)–C(5)–C(6)–N(1)	–48.7 (3)
C(1')–N(1)–C(6)–H(6)1	102.6 (0)
C(1')–N(1)–C(6)–H(6)2	–20.0 (1)
H(1')–C(1')–C(2')–H(2')1	157.6 (9)
H(1')–N(1')–C(2')–H(2')2	36.9 (6)
H(2')1–C(2')–C(3')–H(3')	3.1 (6)
H(2')2–C(2')–C(3')–H(3')	99.0 (4)
H(3')–C(3')–C(4')–H(4')	–142.6 (1)
H(4')–C(4')–C(5')–H(5')1	20.7 (2)
H(4')–C(4')–C(5')–H(5')2	–62.2 (8)

The conformation about C(4')–C(5') is defined by the dihedral angles  $\varphi_{OO}$  [O(5')–C(5')–C(4')–O(1')] and  $\varphi_{OC}$  [O(5')–C(5')–C(4')–C(3')] (Shefter & Trueblood, 1965). In the present nucleoside  $\varphi_{OO} = -67.7^\circ$  and  $\varphi_{OC} = 49.4^\circ$ , so that C(5')–O(5') is *gauche* to both C(4')–O(1') and C(4')–C(3'), with O(5') located above the ribose. This result is different from the disordering of O(5') between the *gauche-trans* and the *gauche-gauche* conformations in (–)-(5*S*)-5,6-dihydrothymidine (Konnert, Karle & Karle, 1970) which displays a pyrimidine puckering in the opposite direction. Important differences in the orientation of the hydroxymethyl group about C(4')–C(5') were also reported for the two conformational diastereoisomers of 5,6-dihydrouridine (Sundaralingam, Rao & Abola, 1971; Suck, Saenger & Zechmeister, 1972).

The orientation of the base relative to the sugar ring is described in terms of rotation about the C(1')–N(1) glycosyl bond for the sequence of O(1')–C(1')–N(1)–C(2) (Sundaralingam, 1969) and C(2')–C(1')–N(1)–C(6) (Saenger & Scheit, 1970). The corresponding values  $\chi_{CN} = 68.7^\circ$  and  $\tau_{CN} = -49.5^\circ$  indicate that the nucleoside exists in the usual *anti* conformation with O(2) pointing away from the deoxyribose ring (Donohue & Trueblood, 1960).

*Hydrogen bonding*

Molecules are arranged into infinite chains parallel to  $c$  ( $x, y, 1 + z$ ) by an  $N(3)H \cdots O(5')$  bond, 2.80 Å. In addition to this hydrogen bond, a short intermolecular contact occurs between  $O(7)$  and  $C(7)$  parallel to  $a$  ( $1 + x, y, z$ ).

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