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Structure of 5-[(1*S*,2*S*)-2-Chlorocyclopropyl]-1-(2-deoxy-β-D-ribofuranosyl)-uracil

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Abstract. $C_{12}H_{15}ClN_2O_5$, $M_r = 302{\cdot}72$, monoclinic, $P2_1$, $a = 5{\cdot}0406$ (5), $b = 16{\cdot}363$ (3), $c = 7{\cdot}962$ (2) Å, $\beta = 90{\cdot}66$ (1)°, $V = 656{\cdot}6$ (2) Å^3, $Z = 2$, $D_x = 1{\cdot}531$ g cm^{-3}, λ(Cu $K\alpha_1$) = 1·54051 Å, $\mu = 73{\cdot}1$ cm^{-1}, $F(000) = 316$, $T = 293$ K, $R = 0{\cdot}028$ for 2046 unique reflections. The absolute configuration about C(7) and C(9) of the cyclopropane ring is *S*. The 5′-substituted pyrimidine is *anti* with respect to the deoxyribose, which is in the 2′-*endo* puckering mode. The torsion angle about C(4′)—C(5′) is *gauche–gauche*.

Introduction. Olefinic 5-substituted-2′-deoxyuridines are potent and selective antiviral agents against herpes simplex virus type 1 (HSV-1) (De Clerq, Descamp, De Somer, Barr, Jones & Walker, 1979; Goodchild, Porter, Raper, Sims, Upton, Vitney & Wadsworth, 1983). Here we report on the crystal and molecular structure of a 5-chlorocyclopropyl derivative of 2′-deoxyuridine as part of a program to evaluate the antiviral activity of such compounds.

Experimental. The title compound was recrystallized from methanol:chloroform [3:1(*v*/*v*)] as translucent rods. The space group was determined by systematic absences on a precession film and on diffractometer-collected intensity data. Least-squares refinement of 25 high-angle reflections [$43 \le 2\theta \le 119°$], constrained to a monoclinic cell, yielded unit-cell parameters. Intensity data were collected on an Enraf–Nonius CAD-4 diffractometer using Ni-filtered Cu $K\bar{\alpha}$ radiation. Background corrections were based on $\omega/2\theta$ scans. The crystal dimensions were 0·7 × 0·2 × 0·2 mm.

A hemisphere of data ($0 \le h \le 5$, $-18 \le k \le 18$, $-8 \le l \le 8$) corresponding to $1{\cdot}5 < \theta < 60°$ was collected. The resulting 2184 reflections yield an R_M of 0·023 ($R_M = \sum|I - \langle I\rangle|/\sum\langle I\rangle$, 1092 reflections) when Friedel equivalent reflections are averaged. To preserve anomalous-scattering information, only the 0*kl*'s of the 2184 reflections were averaged to give 1926 reflections, $R_M = 0{\cdot}025$. These measurements were considered observed and included in the subsequent refinement. Empirical absorption, Lorentz and polarization factors were applied. The maximum and minimum transmission factors were 1·000 and 0·917. Four check reflections ($0\bar{5}3$, 080, 212 and $22\bar{2}$) were collected every 4 h of exposure time and no significant variation in intensity was observed. Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974). All calculations were carried out using *XTAL*2.4 (Hall & Stewart, 1987), *ORTEP*II (Johnson, 1976) and *PLUTO* (Motherwell & Clegg, 1978).

The single chlorine position was determined from a Patterson map, and was used to generate a preliminary F_{obs} map ($R = 0{\cdot}572$). Since this resulted in the superimposition of each enantiomer, the non-H atoms of the cyclopropane ring were introduced with idealized coordinates prior to generating a second F_{obs} map ($R = 0{\cdot}592$). By breaking the symmetry of the previous map, the non-H atoms of the six-membered ring were located. At this point, an F_{obs} map ($R = 0{\cdot}529$) was generated using modified coor-

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dinates for the three-membered ring. This facilitated the location of all the remaining non-H atoms. Phasing and refining with all heavy atoms yielded an $R = 0.209$, and revealed the positions of the 15 H atoms. Isotropically treated H atoms were refined along with anisotropic heavy atoms in subsequent cycles of full-matrix least-squares refinement of $|F_{cal}|$. The 7*S*,9*S* enantiomer converged at $R = 0.028$, $wR = 0.029$ ($w = \sigma^{-2}$), GOF = 2·3 (241 parameters) while the 7*R*,9*R* enantiomer refined to $R = 0.049$, $wR = 0.053$ ($w = \sigma^{-2}$), GOF = 4·0 (241 parameters). Thus, the absolute configuration around C(7) and C(9) is *S*. This is confirmed by the correct stereochemistry of the 2′-deoxy-β-D-ribose. When converged, the maximum shift/e.s.d. was 0·01 and the average shift/e.s.d. was 0·003. The largest remaining peak was 0·154 e Å^{-3} while the largest remaining trough was −0·257 e Å^{-3}. This minimum in the ΔF map corresponds to the Cl-atom position, and is presumed to result from the inability to model accurately the relatively large absorption coefficient of Cl.

Discussion. The atomic coordinates and equivalent isotropic thermal parameters (U_{eq}'s) with e.s.d.'s are given in Table 1.* Bond lengths, bond angles, hydrogen-bonding information and the important torsion angles for deoxyribonucleosides are listed in Table 2. Fig. 1 is an *ORTEP*II (Johnson, 1976) plot using 50% probability thermal ellipsoids. Finally, Fig. 2 is a stereo *PLUTO* (Motherwell & Clegg, 1978) diagram representing the crystal packing and the intermolecular hydrogen-bonding network.

Bond lengths and bond angles are similar to those reported for deoxyuridine (Green, Rosenstein, Shiono, Abraham, Trus & Marsh, 1975) and other related compounds. When the 1-(2-deoxy-D-ribofuranosyl)-5-[(1*S*)-2,2-dibromocyclopropyl]uracil structure (Moore, Santarsiero, Lin, James, Tandon, Wiebe & Knauss, 1989) and the [(1*S*,2*S*)-2-chlorocyclopropyl]uracil derivative reported here are superimposed, the r.m.s. deviation for all C, N and O atoms is 0·370 Å. The r.m.s. deviation is primarily due to differences in both the χ[C(2′)–O(4′)–N(1)—C(2)] and C(4)—C(5)—C(7)—C(8) torsion angles. When the furanose rings are superimposed separately, the r.m.s. deviation is only 0·044 Å. Similarly, the pyrimidine rings alone yield an r.m.s. deviation of 0·062 Å, while the cyclopropyl-substituted pyrimidine rings have a 0·191 Å r.m.s. deviation.

* Lists of structure factors, anisotropic thermal parameters, least-squares-planes data, bond lengths including H atoms and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52940 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Non-hydrogen-atom coordinates and equivalent isotropic thermal parameters* (Å^2 × 10^3)

$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	U_{eq}
Cl	−0·1202 (1)	−0·2494	−1·2222 (1)	53·5 (5)
C(9)	0·2017 (6)	−0·2223 (2)	−1·1574 (3)	33 (1)
C(8)	0·2503 (8)	−0·1426 (2)	−1·0773 (4)	48 (2)
C(7)	0·2656 (7)	−0·2186 (2)	−0·9735 (3)	33 (2)
C(6)	−0·0648 (5)	−0·1746 (2)	−0·7626 (3)	27 (1)
C(5)	0·0568 (5)	−0·2353 (2)	−0·8471 (3)	27 (1)
C(4)	−0·0099 (6)	−0·3182 (2)	−0·8061 (3)	28 (1)
O(4)	0·0954 (4)	−0·3796 (1)	−0·8651 (2)	40 (1)
N(3)	−0·2128 (5)	−0·3267 (2)	−0·6928 (3)	29 (1)
C(2)	−0·3492 (5)	−0·2660 (2)	−0·6116 (3)	25 (1)
O(2)	−0·5342 (4)	−0·2804 (1)	−0·5197 (2)	35 (1)
N(1)	−0·2544 (5)	−0·1879 (1)	−0·6429 (3)	27 (1)
C(5′)	−0·4024 (7)	0·0542 (2)	−0·7963 (4)	45 (2)
O(5′)	−0·1400 (5)	0·0282 (2)	−0·8336 (3)	55 (1)
C(4′)	−0·4959 (6)	0·0138 (2)	−0·6398 (4)	32 (1)
O(4′)	−0·5281 (4)	−0·0729 (1)	−0·6687 (2)	32 (1)
C(3′)	−0·3109 (5)	0·0218 (2)	−0·4867 (3)	30 (1)
I(3′)	−0·4703 (5)	0·0303 (1)	−0·3395 (3)	39 (1)
C(2′)	−0·1642 (6)	−0·0590 (2)	−0·4834 (4)	33 (2)
C(1′)	−0·3699 (6)	−0·1181 (2)	−0·5533 (3)	27 (1)

Table 2. *Bond lengths* (Å), *angles* (°), *hydrogen-bond geometry* (Å, °) *and selected torsion angles* (°)

Cl—C(9)	1·754 (3)	C(2)—N(1)	1·387 (4)
C(9)—C(8)	1·471 (5)	N(1)—C(6)	1·375 (3)
C(9)—C(7)	1·496 (4)	N(1)—C(1′)	1·470 (3)
C(8)—C(7)	1·494 (4)	C(1′)—C(2′)	1·519 (4)
C(7)—C(5)	1·490 (4)	C(1′)—O(4′)	1·418 (3)
C(5)—C(4)	1·437 (4)	C(2′)—C(3′)	1·515 (4)
C(5)—C(6)	1·350 (4)	C(3′)—C(4′)	1·532 (4)
C(4)—O(4)	1·232 (4)	C(3′)—O(3′)	1·435 (3)
C(4)—N(3)	1·378 (4)	C(4′)—O(4′)	1·445 (3)
N(3)—C(2)	1·374 (4)	C(4′)—C(5′)	1·492 (4)
C(2)—O(2)	1·215 (3)	C(5′)—O(5′)	1·424 (4)

C(9)—C(8)—C(7)	60·6 (2)	O(2)—C(2)—N(3)	122·3 (3)
C(8)—C(9)—C(7)	60·4 (2)	O(2)—C(2)—N(1)	123·7 (2)
C(8)—C(9)—Cl	120·0 (2)	C(2)—N(3)—C(4)	127·9 (3)
C(8)—C(7)—C(9)	58·9 (2)	C(2)—N(1)—C(1′)	119·3 (2)
C(7)—C(9)—Cl	119·1 (2)	N(1)—C(1′)—C(2′)	113·6 (2)
C(6)—C(5)—C(7)	122·0 (3)	C(1′)—O(4′)—C(4′)	110·4 (2)
C(6)—C(5)—C(4)	118·2 (2)	C(2′)—C(3′)—C(4′)	103·4 (2)
C(6)—N(1)—C(2)	120·9 (2)	C(3′)—C(2′)—C(1′)	102·6 (2)
C(6)—N(1)—C(1′)	119·7 (2)	O(3′)—C(3′)—C(2′)	110·4 (2)
C(5)—C(7)—C(8)	119·6 (3)	O(3′)—C(3′)—C(4′)	108·5 (2)
C(5)—C(7)—C(9)	120·5 (2)	O(4′)—C(1′)—N(1)	108·3 (2)
C(5)—C(6)—N(1)	123·5 (3)	O(4′)—C(1′)—N(1)	108·3 (2)
O(4)—C(4)—N(3)	119·6 (3)	O(4′)—C(1′)—C(2′)	106·3 (2)
O(4)—C(4)—C(5)	125·5 (2)	O(4′)—C(4′)—C(3′)	106·1 (2)
C(4)—C(5)—C(7)	119·7 (2)	O(4′)—C(4′)—C(5′)	109·8 (2)
N(3)—C(4)—C(5)	114·9 (2)	C(5′)—C(4′)—C(3′)	115·5 (2)
N(3)—C(2)—N(1)	113·9 (2)	O(5′)—C(5′)—C(4′)	110·1 (3)

DH	*A*	*DH*···*A*	*D*—H···*A*
O(4)	O(5′)	2·84	134
O(3′)	N(3)	2·85	166
O(3′)	O(4)	2·89	150

C(2)—N(1)—C(1′)—O(4′)	−107·6 (2)	χ†
C(3′)—C(4′)—C(5′)—O(5′)	52·5 (4)	γ
C(5′)—C(4′)—C(3′)—O(3′)	143·4 (3)	δ
C(2′)—C(1′)—O(4′)—C(4′)	−18·0 (3)	μ_0
O(4′)—C(1′)—C(2′)—C(3′)	31·4 (3)	μ_1
C(4′)—C(3′)—C(2′)—C(1′)	−32·2 (3)	μ_2
O(4′)—C(4′)—C(3′)—C(2′)	22·5 (3)	μ_3
C(1′)—O(4′)—C(4′)—C(3′)	−3·00 (3)	μ_4

† Suggested notation (Saenger, 1984).

As commonly seen in pyrimidine deoxyribonucleosides, the pyrimidine ring is *anti* with respect to the furanose, $\chi = -107°$ (Saenger, 1984). The glycosidic C(1′)—N(1) bond length of 1·470 (3) Å is consistent with an *anti* conformer, as the C(1′)—N(1) bond length is linearly correlated to the C(1′)—N(1) torsion angle (Lin, Sundaralingam & Arora, 1971; Saenger, 1984). As the torsion angle varies from 180 to −140°, the glycosidic bond of the pyrimidine shortens from 1·51 to 1·48 Å. The furanose ring has a 2′-*endo* conformation as indicated by the pseudorotation phase angle. For $P = 166·4°$, the deoxyribose moiety has adopted the ${}^{2'}T_{3'}$ variant of C(2′)-*endo* puckering. This assignment indicates that the C(2′) and the C(3′) atoms will be displaced from a plane defined by the remaining three members of the furanose ring. This is the case, with the C(2′) being displaced by 0·42 Å from the plane [towards O(5′)] and C(3′) being 0·07 Å removed on the opposite side of the ring. Both the $\chi = -107°$ and the ring puckering amplitude, $\tau_m = 31·1°$, are typical for deoxyribonucleosides in the C(2′)-*endo* conformation.

Another important stereochemical feature of the deoxyribonucleosides is the γ or C(4′)—C(5′) torsion angle (Shefter & Trueblood, 1965). The preferred γ range in pyrimidine nucleotide crystal structures is *gauche–gauche* (Saenger, 1984) and, in agreement with this, $\gamma = 52·4°$.

Examination of the crystal packing diagram reveals three unique intermolecular hydrogen bonds. The bidentate hydrogen bonding of O(3′) and O(4) facilitates the network of pyrimidine to furanose, furanose to pyrimidine hydrogen bonding which occurs between symmetry-related molecules. Finally, it should be noted that an intramolecular close contact occurs between C(6)—H(6) and O(5′). This close contact has been observed in other structures and in this case it is 0·26 Å shorter than the sum of the van der Waals radii of these atoms (2·70 Å; Kitaigorodsky, 1973).

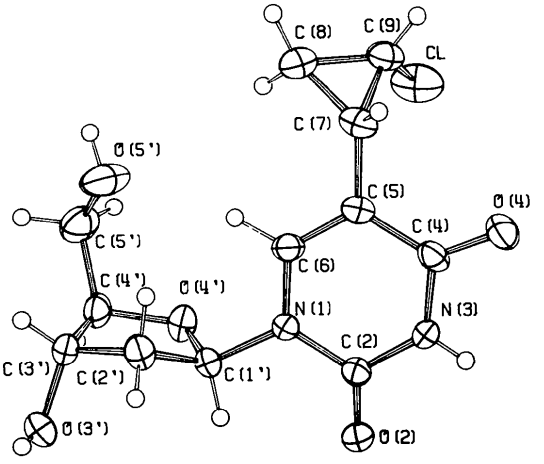

Fig. 1. *ORTEP*II plot of the molecule using 50% probability thermal ellipsoids.

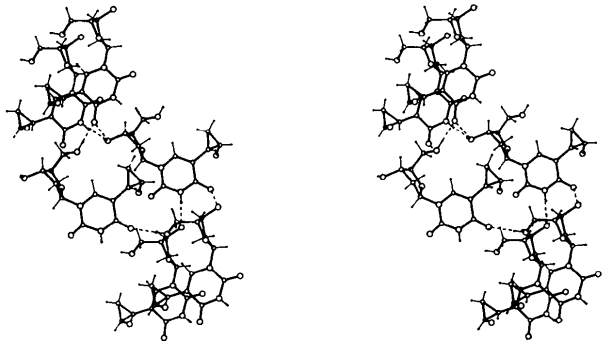

Fig. 2. Stereo *PLUTO* diagram representing the crystal packing and intermolecular hydrogen-bonding network.

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