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Structural Studies of Pyrimidine Cyclonucleoside Derivatives. IV.* Structure of 2,5′-Anhydro-1-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)-2-thiouracil

BY YURIKO YAMAGATA, SATOSHI FUJII, TAKAJI FUJIWARA AND KEN-ICHI TOMITA

Faculty of Pharmaceutical Sciences, Osaka University, Yamadakami, Suita, Osaka 565, *Japan*

AND TOHRU UEDA

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, *Nishi*-6, *Kita-ku, Sapporo* 060, *Japan*

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Abstract

The title compound, $C_{12}H_{14}N_2O_4S$, crystallizes in the orthorhombic system with space group $P2_12_12_1$, $Z = 4$ and unit-cell dimensions $a = 7{\cdot}694$ (1), $b = 9{\cdot}470$ (3) and $c = 17{\cdot}628$ (7) Å. The structure was solved by the heavy-atom method and refined to a final R value of 0·077 (weighted R = 0·088). The glycosyl torsion angle lies in the *syn* range ($\chi_{\rm CN}$ = 244·2°) and the ribose ring conformation is C(4′)-*endo*,O(1′)-*exo*.

Introduction

The fixed conformation of the cyclonucleosides is expected to be preserved both in the crystalline state and in solution, and this type of compound has been used to investigate the relationships between sign and magnitude of Cotton effects and glycosyl torsion angles (Rogers & Ulbricht, 1970; Ikehara, Kaneko, Nakahara, Yamada & Uesugi, 1971; Ueda & Shibuya, 1974) and to test the applicability of coupling constants to the Karplus relation (Manor, Saenger, Davies, Jankowski & Rabczenko, 1974). Structural considerations suggested that the title compound, 2,5′-anhydro-1-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)-2-thiouracil (2,5′-*S*-cyclo U), may adopt either of two conformations: the *exo* form ($\chi \simeq 180°$) with S positioned above O(1′), or the *endo* form ($\chi \simeq 240°$) with S over the center of the sugar ring. In order to clarify the situation, we have determined the molecular structure of 2,5′-*S*-cyclo U by X-ray diffraction. In this paper, the results of this study are described and compared with the molecular geometry of 2,5′-anhydro-1-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)uracil (2,5′-*O*-cyclo U).

Experimental

2,5′-*S*-cyclo U was synthesized from 2,5′-*O*-cyclo U (Ueda & Shibuya, 1974) and recrystallized as colorless needles from benzene containing a small amount of ethanol. X-ray photographs showed the crystals to be orthorhombic with space group $P2_12_12_1$. Unit-cell dimensions were determined from the 2θ values of 18 diffractometer-measured reflexions in the range $20° < 2\theta < 40°$ (Mo $K\alpha$) by a least-squares procedure. The density was measured by the flotation method in a benzene–carbon tetrachloride mixture. The crystallographic data are shown in Table 1.

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* Part III (Structural Studies of *O*-Cyclocytidine Derivatives): Yamagata, Suzuki, Fujii, Fujiwara & Tomita (1979).

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Table 1. *Crystal data*

$C_{12}H_{14}N_2O_4S$	$M_r = 282{\cdot}32$
Orthorhombic	Space group $P2_12_12_1$
$a = 7{\cdot}694\ (1)$ Å	$Z = 4$
$b = 9{\cdot}470\ (3)$	$F(000) = 592$
$c = 17{\cdot}628\ (7)$	$V = 1284{\cdot}3\ (7)$ Å^3
λ(Mo $K\alpha$) = 0·71069 Å	$D_m = 1{\cdot}448\ (1)$ Mg m^{-3}
$\mu = 0{\cdot}178$ mm^{-1}	$D_x = 1{\cdot}459$

The intensity data were collected within $\sin\theta/\lambda = 0{\cdot}65$ Å^{-1} on a Rigaku automatic four-circle diffractometer with Mo $K\alpha$ radiation and the ω–2θ scan technique. The total number of reflexions measured was 1608, of which 1175 had intensities above the $2\sigma(I)$ level. Intensities were corrected for Lorentz and polarization factors, but no absorption corrections were applied. All numerical calculations were carried out on an ACOS-800 computer of the Computer Center of Osaka University with *The Universal Crystallographic Computing System* (1973). Scattering factors used were those cited in *International Tables for X-ray Crystallography* (1974).

Structure determination and refinement

The structure was solved by the heavy-atom method. Successive Fourier syntheses revealed the locations of all the non-hydrogen atoms. The structure was refined by full-matrix least squares with isotropic temperature factors for all the non-hydrogen atoms and then by block-diagonal least squares with anisotropic temperature factors. All H atoms could be located from a difference Fourier synthesis. The final refinement including H atoms with isotropic temperature factors reduced the R value to 0·077 (weighted R_w = 0·088). Throughout the refinement each reflexion was given a weight based on counting statistics.

Table 2. *Final atomic coordinates for the non-hydrogen atoms* (×10^4) *with their estimated standard deviations in parentheses*

	x	y	z
S	508 (3)	−790 (2)	4893 (1)
N(1)	718 (9)	−2169 (6)	6260 (4)
C(2)	448 (12)	−2287 (8)	5492 (4)
N(3)	212 (9)	−3472 (7)	5137 (4)
C(4)	286 (12)	−4761 (9)	5530 (5)
C(5)	512 (14)	−4669 (8)	6342 (5)
C(6)	703 (12)	−3412 (9)	6671 (4)
O(4)	111 (8)	−5863 (6)	5178 (3)
C(1′)	1130 (11)	−859 (8)	6687 (4)
C(2′)	2711 (11)	−48 (9)	6402 (5)
C(3′)	1979 (10)	1365 (9)	6117 (5)
C(4′)	−8 (10)	1110 (7)	6106 (5)
O(1′)	−312 (7)	76 (6)	6691 (3)
C(5′)	−726 (13)	596 (8)	5355 (5)
O(2′)	3691 (8)	325 (6)	7054 (4)
O(3′)	2374 (8)	2337 (6)	6704 (4)
C(6′)	3880 (12)	1839 (9)	7080 (5)
C(7′)	3889 (13)	2323 (11)	7876 (6)
C(8′)	5535 (12)	2268 (12)	6638 (5)

Results and discussion

The atomic coordinates with their estimated standard deviations are given in Tables 2 and 3.* The bond lengths and angles are shown in Figs. 1 and 2.

Table 3. *Final atomic coordinates for the hydrogen atoms* (×10^3) *with their estimated standard deviations in parentheses*

The overall isotropic temperature factor is 3·26 Å^2.

	x	y	z
H(5)	65 (13)	−565 (10)	666 (5)
H(6)	69 (13)	−329 (10)	731 (5)
H(1′)	142 (14)	−115 (10)	728 (5)
H(2′)	359 (14)	−61 (10)	597 (5)
H(3′)	244 (14)	165 (11)	562 (5)
H(4′)	−65 (13)	204 (10)	618 (5)
H(5′)	−193 (13)	18 (10)	543 (5)
H(5″)	−66 (13)	146 (10)	503 (5)
H(Me1)	297 (13)	194 (11)	803 (6)
H(Me2)	391 (14)	332 (10)	782 (5)
H(Me3)	499 (13)	198 (10)	812 (5)
H(Me4)	537 (14)	319 (11)	679 (5)
H(Me5)	536 (14)	193 (10)	606 (5)
H(Me6)	685 (14)	196 (10)	678 (5)

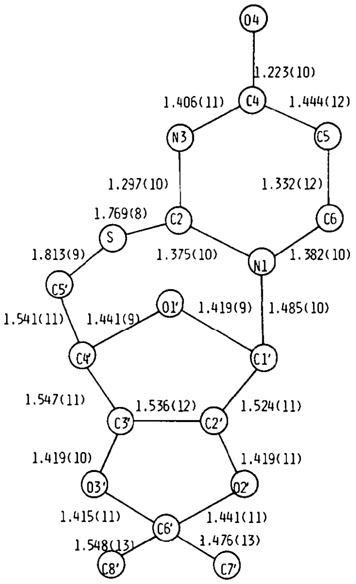

Fig. 1. Bond lengths (Å) with estimated standard deviations in parentheses.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34802 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

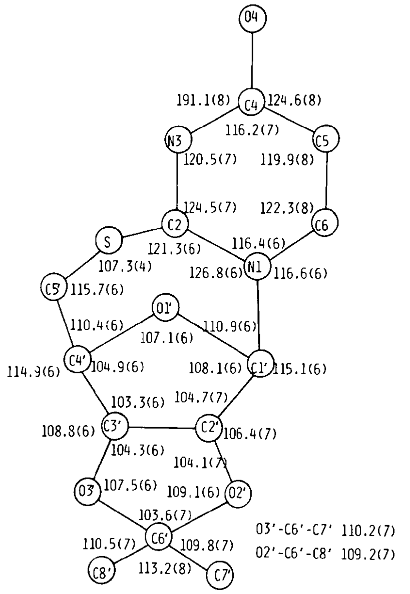

Fig. 2. Bond angles (°) with estimated standard deviations in parentheses.

(*a*) *Bond lengths and angles*

Owing to the S-alkylation, the bond lengths and angles of the base moiety differ considerably from those in 2-thiouridine and uridine but they are very similar to those in 2,5′-*O*-cyclo U (Table 4). On the other hand, in the two cyclonucleosides the bond lengths and angles involving S and O(2) differ significantly. Thus, C(2)–S bond lengths are longer than C(2)–O(2) and the C(2)–S–C(5′) angle, 107·3°, is smaller than C(2)–O(2)–C(5′), 118·2°, as usually observed for such systems (*Molecular Structures and Dimensions*, 1972). The angles N(1)–C(2)–*X* and C(4′)–C(5′)–*X* with *X* = S are larger than those with *X* = O, probably due to different steric requirements in the two seven-membered rings. Further, the angles around C(2′) and C(3′) in the cyclonucleosides differ from those in unsubstituted ribonucleosides, due to cyclization with the isopropylidene group.

Table 4. *Comparison of some bond lengths* (Å) *and angles* (°) *in* 2,5′-*S*-cyclo U *and related compounds*

	2,5′-*S*-cyclo U	2,5′-*O*-cyclo U[a]	2-Thiouridine[b]	Uridine[c]*
N(1)–C(2)	1·375	1·367	1·368	1·371
C(2)–N(3)	1·297	1·286	1·360	1·370
N(3)–C(4)	1·406	1·393	1·388	1·381
C(2)–S[O(2)]	1·769	1·351	1·677	1·222
C(6)–N(1)–C(6)	116·4	116·8	120·8	120·6
N(1)–C(2)–N(3)	124·5	125·7	116·0	115·4
C(2)–N(3)–C(4)	120·5	119·5	126·6	126·8
C(2)–N(1)–C(1′)	126·8	123·4	117·8	117·2
N(1)–C(2)–S[O(2)]	121·3	116·7	123·4	122·2
C(4′)–C(5′)–S[O(2)]	115·7	111·1	111·3	112·1
C(2)–S[O(2)]–C(5′)	107·3	118·2	—	—
C(1′)–O(1′)–C(4′)	107·1	106·5	109·8	109·6

References: (*a*) Delbaere & James (1974); Manor, Saenger, Davies, Jankowski & Rabczenko (1974); (*b*) Hawkinson (1977); (*c*) Green, Rosenstein, Shiono, Abraham, Trus & Marsh (1975).

* Averages of the two independent molecules in the asymmetric unit.

(*b*) *Molecular conformation*

The conformation of the molecule is shown in the stereographic representation in Fig. 3. The glycosyl torsion angle, χ_{CN} [O(1′)–C(1′)–N(1)–C(6), 244·2°], is in the *syn* region, in agreement with NMR results obtained for 2,5′-*S*-cyclo U in solution (Ueda & Shibuya, 1974). This orientation locates S over the

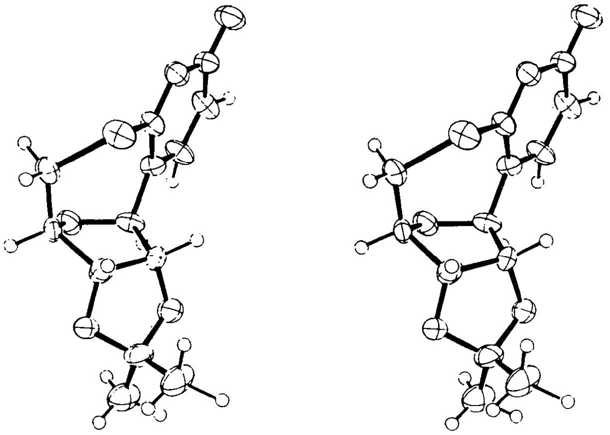

Fig. 3. Stereoview of the molecular conformation.

Table 5. *Deviations* (Å) *of atoms from least-squares planes through several parts of the molecule*

x, *y* and *z* refer to the orthogonal coordinate system (Å) with *x* along **a**, *y* along **b** and *z* along **c**. Asterisks denote atoms included in the calculations of the least-squares planes.

(*a*) Base and part of the sugar

$$0\cdot988x - 0\cdot065y - 0\cdot138z + 0\cdot856 = 0\cdot0$$

N(1)	0·016 (8)*	S	0·104 (11)
C(2)	0·005 (9)*	O(4)	0·043 (11)
N(3)	−0·017 (8)*	C(1′)	0·146 (12)
C(4)	0·023 (10)*	C(5′)	−1·031 (16)
C(5)	−0·008 (11)*		
C(6)	−0·018 (10)*		

(*b*) Sugar

$$-0\cdot126x - 0\cdot395y - 0\cdot910z + 10\cdot514 = 0\cdot0$$

C(1′)	0·000*	C(4′)	0·306 (21)
C(2′)	0·000*	O(1′)	−0·216 (19)
C(3′)	0·000*	C(5′)	1·772 (25)

(*c*) Isopropylidene ring

$$0\cdot814x + 0\cdot223y - 0\cdot537z + 4\cdot322 = 0\cdot0$$

C(2′)	−0·047 (11)*	C(6′)	0·442 (12)
C(3′)	0·062 (11)*	C(7′)	−0·204 (17)
O(2′)	0·028 (9)*	C(8′)	1·987 (13)
O(3′)	−0·041 (8)*	C(1′)	−1·478 (12)

Table 6. *Torsion angles* (°)

Notation	Designation	2,5′-*S*-cyclo U	2,5′-*O*-cyclo U[(a)]	8,5′-*S*-cyclo A[(b)]
χ	O(1′)–C(1′)–N(1)[N(9)]–C(6)[C(4)]	244·2 (7)	246·4	251
τ_0	C(4′)–O(1′)–C(1′)–C(2′)	28·4 (8)	35·0	29
τ_1	O(1′)–C(1′)–C(2′)–C(3′)	−9·2 (8)	−13·2	−16
τ_2	C(1′)–C(2′)–C(3′)–C(4′)	−11·7 (8)	−11·4	−4
τ_3	C(2′)–C(3′)–C(4′)–O(1′)	28·6 (7)	31·8	20
τ_4	C(3′)–C(4′)–O(1′)–C(1′)	−35·8 (7)	−42·3	−33
$\psi_{OS(O)}$	O(1′)–C(4′)–C(5′)–S[O(2)]	−73·8 (7)	−72·5	−82
$\psi_{CS(O)}$	C(3′)–C(4′)–C(5′)–S[O(2)]	44·6 (9)	41·8	39
λ_0	O(2′)–C(6′)–O(3′)–C(3′)	−34·9 (8)	−36·5	−6
λ_1	C(6′)–O(3′)–C(3′)–C(2′)	27·7 (8)	27·5	14
λ_2	O(3′)–C(3′)–C(2′)–O(2′)	−9·5 (8)	−8·2	−18
λ_3	C(3′)–C(2′)–O(2′)–C(6′)	−11·6 (8)	−13·9	15
λ_4	C(2′)–O(2′)–C(6′)–O(3′)	28·6 (8)	31·0	−10

References: (*a*) Delbaere & James (1974); Manor, Saenger, Davies, Jankowski & Rabczenko (1974); (*b*) Tomita, Nishida, Fujiwara & Ikehara (1970).

center of the sugar ring and gives the seven-membered ring a chair form. A similar conformation involving the sugar–uracil linkages was found for 2,5′-*O*-cyclo U where the χ_{CN} torsion angle is 246·4° (Delbaere & James, 1974; Manor, Saenger, Davies, Jankowski & Rabczenko, 1974). The pyrimidine ring in 2,5′-*S*-cyclo U is planar within ±0·02 Å (Table 5), and S is displaced from this plane by 0·10 Å, while S of 2-thiouridine is in the plane of the heterocycle. The sugar ring is puckered C(4′)-*endo*,O(1′)-*exo* (Table 5).

The isopropylidene ring is in an envelope conformation, with C(6′) displaced by 0·44 Å from the least-squares plane formed by the remaining four atoms [C(2′), C(3′), O(2′) and O(3′)] and in an *exo* position (*i.e.* pointing away from the ribose ring). The conformation of the sugar and isopropylidene ring system in 2,5′-*S*-cyclo U is similar to that found in 2,5′-*O*-cyclo U. Compared with the adenosine analog, 8,5′-anhydro-9-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)-8-thioadenine (8,5′-*S*-cyclo A), the ribose and S-heterocycle rings have a similar conformation (Table 6).

However, the torsion angles for the 2′,3′-*O*-isopropylidene ring differ significantly; this is because in the uridine derivatives this ring displays the *exo* form with C(6′) pointing away from the ribose while the ring has an *endo* puckering in the adenosine derivative with C(6′) bent towards the ribose. Other noncyclo-2′,3′-*O*-isopropylidene nucleosides and 2′,3′-cyclonucleotides whose crystal structures have been reported (Fujii, Fujiwara & Tomita, 1976; Sprang, Rohrer & Sundaralingam, 1978; Reddy & Saenger, 1978; Coulter, 1973) suggest that the 2′,3′-*O*-cyclized ring is not quite rigid but has at least two degrees of freedom – *endo* and *exo* envelope puckering with half-chair conformations as intermediates.

(*c*) *Molecular packing*

The molecular packing along the *a* axis is shown in Fig. 4. The base planes are nearly parallel to the (100) plane of the crystal lattice, but no base stacking is observed, while in the case of 2,5′-*O*-cyclo U (Delbaere & James, 1974; Manor, Saenger Davies, Jankowski & Rabczenko, 1974), overlaps between the electronegative O(4) and the pyrimidine ring and between O(1′) and pyrimidine are found. The stabilization of the present packing might result partly from van der Waals interactions.

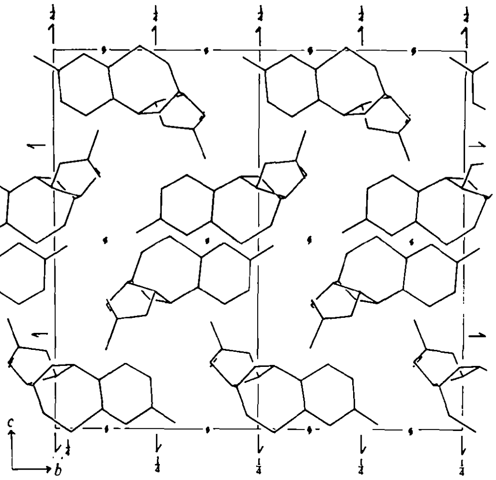

Fig. 4. Molecular packing along the *a* axis.

We thank Professor W. Saenger, Max-Planck-Institut für experimentelle Medizin, for his useful advice and his improvement of the manuscript during his stay in our laboratory, financed by a grant from the Yamada Science Foundation.

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Acta Cryst. (1980). B**36**, 343–346

Structural Studies of Pyrimidine Cyclonucleoside Derivatives.
V. Structure of 2,2′-Anhydro-1-β-D-arabinofuranosyl-2-thiouracil

BY YURIKO YAMAGATA, JUNKO YOSHIMURA, SATOSHI FUJII, TAKAJI FUJIWARA AND KEN-ICHI TOMITA

Faculty of Pharmaceutical Sciences, Osaka University, Yamadakami, Suita, Osaka 565, *Japan*

AND TOHRU UEDA

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, *Nishi*-6, *Kita-ku, Sapporo* 060, *Japan*

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Abstract

The title compound, $C_9H_{10}N_2O_4S$, crystallizes in space group $P2_1$ with $Z = 2$, and unit-cell dimensions a = 8·881 (1), b = 6·841 (2), c = 8·454 (1) Å, β = 105·84 (1)°. The structure was solved by the direct method and refined to a final R index of 0·036 (weighted R = 0·035). The glycosyl torsion angle χ_{CN} is 295·7° (*syn* conformation), the puckering of the ribose ring being C(4′)-*endo*. The orientation of the C(5′)—O(5′) bond is *gauche–trans*.

Introduction

As part of a series of studies on pyrimidine cyclonucleosides, we have reported the molecular structure of 2,5′-anhydro-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-2-thiouracil (2,5′-*S*-cyclo U) in a previous paper (part IV: Yamagata, Fujii, Fujiwara, Tomita & Ueda, 1980). The present paper describes the crystal and molecular structure of 2,2′-anhydro-1-β-D-arabinofuranosyl-2-thiouracil (2,2′-*S*-cyclo U) in which the cyclization occurred between C(2) and C(2′), in contrast to that between C(2) and C(5′) in 2,5′-*S*-cyclo U. The conformational comparison of this compound with other related ones is not only pertinent but also informative for CD and NMR studies in solution.

Experimental

2,2′-*S*-cyclo U was synthesized from 2,2′-anhydro-1-β-D-arabinofuranosyluracil (2,2′-*O*-cyclo U) (Ueda & Shibuya, 1974). The material crystallized from an aqueous ethanol solution as colorless prisms in the monoclinic space group $P2_1$. Unit-cell dimensions were determined by a least-squares procedure based on the 2θ values of 23 reflexions with $33° \leq 2\theta \leq 45°$. The density was measured by the flotation method in a carbon tetrachloride–ethylene dibromide mixture. The crystallographic data are shown in Table 1.

The intensities of 1185 independent reflexions within $\sin\theta/\lambda$ = 0·65 Å^{-1} were collected on a Rigaku automatic four-circle diffractometer with Mo $K\alpha$ radiation and corrected for Lorentz and polarization factors, but not for absorption. All numerical calculations were carried out on an ACOS-900 computer of the Computation Center of Osaka University with *The Universal Crystallographic Computing System* (1973). For structure factor calculation, the atomic scattering factors cited in *International Tables for X-ray Crystallography* (1974) were used.

Structure determination and refinement

The structure was solved by the direct method using the program *MULTAN* (Germain, Main & Woolfson,

Table 1. *Crystal data*

$C_9H_{10}N_2O_4S$
Monoclinic
a = 8·881 (1) Å
b = 6·841 (2)
c = 8·454 (1)
β = 105·84 (1)°
λ(Mo $K\alpha$) = 0·71069 Å
μ(Mo $K\alpha$) = 0·327 mm^{-1}

M_r = 242·25
Space group $P2_1$
Z = 2
F(000) = 252
V = 494·1 (2) Å^3
D_m = 1·627 (1) Mg m^{-3}
D_x = 1·628

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