

## Crystal Structures of Analogues of 3,1'-Anhydro Nucleosides. I. 3,1'-Anhydro-2-(4',6'-di-O-acetyl-2',3'-dideoxy- $\alpha$ -D-ribo-hexopyranose)-3-hydroxy-5-methyl-2H-1,2,6-thiadiazine-1,1-dioxide (TDR)

BY C. FOCES-FOCES, P. SMITH-VERDIER, F. FLORENCIO-SABATE AND S. GARCÍA-BLANCO

Departamento de Rayos X, Instituto 'Rocasolano', CSIC, Serrano 119, Madrid-6, Spain

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TDR was synthesized as a potential anticancer agent. 1450 independent reflexions were measured on an automatic single-crystal diffractometer. The crystal structure was solved by direct methods and successive Fourier syntheses. The structure was subsequently refined by full-matrix least-squares calculations to  $R=0.084$ . The thiadiazine ring is not planar and the glycosyl moiety forms a regular chair. The structure of this compound contains an unusual feature: the anomeric carbon atom C(1') is bonded to the oxygen atom.

### Introduction

$C_{14}H_{18}O_8N_2S$  is a nucleoside constituted by a bioisostere of the 6-methyluracil group and a glycosyl moiety. The base shows a light citostatic activity *in vitro* on *Hela* cellules but the increase of this activity in the nucleoside is noticeable, producing a total inhibition of the cellule growth when the test was done at a concentration of  $100 \mu\text{g ml}^{-1}$ . Several possible formulae are given for this substance (Fig. 1) and it appears particularly important to establish the correct one. This work was undertaken to study the relations between the molecular structure and its biological activity.

The correct structure was found to be that shown in Fig. 1(d) and Fig. 4.

### Experimental

Crystals of TDR were prepared and kindly supplied by Dr Garcia-Muñoz (Instituto Química Orgánica General, CSIC). The lattice constants were measured from 12 separate reflexions at  $\theta=25^\circ$  (Cu  $K\alpha$ ) and are shown in Table 1. A single crystal of  $0.58 \times 0.33 \times 0.17$  mm was selected for the X-ray investigation. The crystals belong to the orthorhombic system. The experimental density was measured by flotation in an aqueous potassium iodide solution. The crystal data are listed in Table 1. The intensities were measured on an automatic Hilger-Watts four-circle diffractometer. 1520 independent reflexions were collected in the range  $0 < \theta < 63^\circ$  for this radiation. Of this total, 1376 were directly observed, 79 had  $C_b$  (background counts) larger than  $C_p$  (peak count) and 75 were considered as unobserved according to the criterion  $I < 2\sigma(I)$ , where  $I = C_p - C_b$  and  $\sigma^2(I) = C_p + C_b + 0.03^2(C_p^2 + C_b^2)$ ,  $I$  being the integrated intensity and  $\sigma(I)$  its estimated standard deviation.

The structure amplitudes were obtained after the

Table 1. Crystal data for TDR

Standard deviations, given in parentheses, refer to the least significant digits.

$C_{14}H_{18}N_2O_8S$ , M.W. 374.06	$V = 1687.0 \text{ \AA}^3$
Space group: $P2_12_12_1$	$D_{\text{obs}}(\text{flotation}) = 1.40 \text{ g cm}^{-3}$
$a = 19.80$ (2) $\text{ \AA}$	$D_x = 1.47$
$b = 10.66$ (1)	$F(000) = 784$
$c = 7.938$ (9)	$\mu = 19.918 \text{ cm}^{-1}$
$Z = 4$	

usual Lorentz and polarization reduction. No correction for absorption was made.

### Solution and refinement of the structure

The  $|F_h|$  values were normalized in the usual (Karle) way to give  $|E_h| = d(K|F_h| \cdot M(s))/\varepsilon(\mathbf{h}) \cdot \sum f_j(s)$ , where

$$M(s) = \exp \left[ -\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* \cos \gamma^* + 2B_{13}hla^*c^* \cos \beta^* + 2B_{23}klb^*c^* \cos \alpha^*) \right];$$

$\varepsilon(h00) = \varepsilon(0k0) = \varepsilon(00l) = 2$  and  $\varepsilon = 1$  otherwise;  $d$  is an internal scale factor to ensure that  $\langle |E|^2 \rangle = 1$ . The  $B_{11} = 0.0013$ ,  $B_{12} = -0.00025$ ,  $B_{13} = -0.00196$ ,  $B_{22} = -0.00068$ ,  $B_{23} = 0.00147$ ,  $B_{33} = 0.00114$  and  $K = 0.3054$  were obtained by using the X-RAY system (Stewart, Kundell & Baldwin, 1970).

The structure was solved by direct methods with the *MULTAN* program (Main, Woolfson & Germain, 1971) adapted for the UNIVAC 1108 of the Ministerio de Educación y Ciencia (Madrid).

The first attempts to determine phases were unsuccessful. We found later that this resulted from the choice of the starting set for tangent refinement. In the unsuccessful attempt, a reflexion with one of the highest  $|E|$  values (10,2,1) was used in the starting set. This reflexion occurred in several false  $\sum_2$  relationships. Therefore, a considerable number of reflexions had incorrect phases at the beginning of the refinement. The phase determination was successful when the

10,2,1 reflexion was eliminated from the starting set. The  $E$  map calculated with 210 reflexions and  $|E| \geq 1.40$  revealed the positions of 21 atoms. A Fourier map, phased by the known positions of those atoms, showed the locations of the remaining atoms N(6), C(7), C(5') and C(8'). A subsequent structure-factor calculation yielded an  $R$  index of 0.186. Three cycles of full-matrix least-squares refinement of atomic positions, isotropic temperature factors and scale factor reduced the  $R$  index to 0.145. The introduction of anisotropic thermal parameters lowered the  $R$  value to 0.106.

The positions of the 18 hydrogen atoms were determined from a difference Fourier synthesis, calculated with  $(\sin \theta)/\lambda = 0.45$ . A structure-factor calculation including the hydrogen atoms with isotropic temperature factors equal to those of the bonded carbon atoms reduced  $R$  to 0.086.

During the later stages of refinement the weighting scheme was  $w = 1/\sigma^2(F)$ .

At the beginning of the refinement we found 13 low-order reflexions suffering seriously from secondary extinction effects, which were corrected by a least-squares fit of  $|F_c| = |F_o| \cdot (\exp 2gI_e)$  giving a  $g$  value of  $0.15525 \times 10^{-4}$ . These reflexions, excluded from refinement, were corrected with this value and then included in the calculation to give  $R = 0.084$  for the observed reflexions. The structure factors showed changes of up to 99%.

As a final check of the correctness of the structure a difference synthesis with the structure factors from the last cycle of refinement was calculated. The resulting electron density map showed no peak exceeding  $\pm 0.46 \text{ e } \text{Å}^{-3}$ .

The positional and thermal parameters with standard deviations (e.s.d.'s) are given in Tables 2 and 3.\*

Table 3. Fractional coordinates for hydrogen atoms

	$x$	$y$	$z$
H(4)	0.6250	-0.9100	-0.2000
H(7a)	0.6594	-0.9600	0.1211
H(7b)	0.6000	-0.9600	0.2300
H(7c)	0.6000	-0.0300	0.0700
H(1')	0.5962	-0.6015	-0.6200
H(2'a)	0.5500	-0.4500	-0.5000
H(2'b)	0.5050	-0.5700	-0.4568
H(3')	0.5200	-0.4600	-0.2000
H(4')	0.6150	-0.3350	-0.3000
H(5')	0.7000	-0.5600	-0.2200
H(7'a)	0.6850	-0.2900	0.1900
H(7'b)	0.6200	-0.2100	0.1900
H(7'c)	0.6100	-0.3300	0.3100
H(8'a)	0.7900	-0.4600	-0.3800
H(8'b)	0.7670	-0.3758	-0.2200
H(10'a)	0.7500	-0.0600	-0.5700
H(10'b)	0.6750	-0.0100	-0.4300
H(10'c)	0.6650	-0.1100	-0.5200

The scattering factors for carbon, nitrogen, oxygen and sulphur were those given by Hanson, Herman, Lea & Skillman (1964). Those for hydrogen were interpolated from the values given by Stewart, Davidson & Simpson (1965).

\* A list of observed and calculated structure factors is available from the authors on request. This table has also been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30609 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. Final atomic parameters for non-hydrogen atoms

Thermal parameters ( $\times 10^4$ ) as defined in the expression  $\exp(-2\pi^2 \sum U_{ij} a_i^* a_j^* h_i h_j)$ . The least-squares e.s.d.'s are given in parentheses.

	$x$	$y$	$z$	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$
S(1)	0.5241 (1)	-0.6429 (2)	0.0199 (3)	328 (11)	333 (11)	357 (13)	52 (9)	132 (10)	-9 (11)
O(1a)	0.4585 (3)	-0.6870 (7)	-0.0354 (9)	272 (32)	794 (50)	413 (39)	91 (32)	28 (29)	99 (41)
O(1b)	0.5267 (4)	-0.5259 (7)	0.1070 (10)	761 (52)	428 (39)	610 (50)	120 (50)	356 (48)	136 (39)
N(2)	0.5691 (3)	-0.6212 (7)	-0.1619 (10)	288 (37)	226 (38)	458 (45)	-28 (31)	128 (35)	-64 (35)
C(3)	0.5977 (4)	-0.7239 (8)	-0.2320 (12)	279 (43)	290 (47)	411 (53)	34 (39)	58 (41)	34 (44)
C(4)	0.6072 (5)	-0.8361 (8)	-0.1406 (13)	468 (56)	227 (49)	597 (66)	29 (43)	65 (51)	-11 (47)
C(5)	0.5939 (4)	-0.8378 (9)	0.0317 (14)	323 (44)	355 (52)	543 (63)	61 (40)	-102 (45)	-111 (53)
N(6)	0.5654 (4)	-0.7483 (8)	0.1197 (10)	393 (44)	559 (54)	350 (45)	21 (44)	-35 (40)	-117 (44)
C(7)	0.6160 (5)	-0.9489 (11)	0.1305 (18)	496 (60)	579 (67)	876 (94)	-1 (57)	-169 (67)	-373 (70)
O	0.6222 (3)	-0.7186 (6)	-0.3882 (8)	543 (41)	285 (34)	452 (40)	10 (31)	197 (34)	24 (32)
C(1')	0.6138 (4)	-0.6085 (8)	-0.4951 (11)	408 (46)	358 (46)	287 (48)	55 (38)	47 (42)	60 (43)
O(1')	0.6716 (3)	-0.5323 (6)	-0.4877 (8)	346 (31)	444 (35)	260 (35)	62 (28)	48 (28)	60 (32)
C(2')	0.5504 (4)	-0.5357 (9)	-0.4408 (13)	328 (48)	432 (54)	462 (64)	121 (44)	-12 (43)	29 (49)
C(3')	0.5609 (4)	-0.5021 (8)	-0.2547 (12)	272 (43)	272 (46)	370 (53)	44 (37)	78 (42)	8 (40)
C(4')	0.6248 (4)	-0.4200 (7)	-0.2423 (11)	229 (39)	265 (43)	261 (44)	5 (34)	-6 (35)	15 (39)
O(4')	0.6440 (3)	-0.4029 (5)	-0.0689 (7)	288 (28)	245 (30)	318 (34)	-62 (25)	-21 (26)	28 (27)
C(5')	0.6869 (4)	-0.4825 (8)	-0.3197 (11)	216 (41)	328 (47)	289 (48)	52 (37)	46 (36)	-25 (41)
C(6')	0.6112 (4)	-0.3094 (8)	0.0167 (12)	400 (49)	373 (48)	355 (51)	-86 (43)	66 (46)	46 (47)
O(6')	0.5672 (4)	-0.2484 (7)	-0.0464 (10)	717 (49)	515 (44)	605 (51)	-376 (43)	-59 (42)	47 (42)
C(7')	0.6381 (7)	-0.2978 (12)	0.1907 (15)	804 (82)	584 (71)	557 (75)	-95 (64)	57 (65)	97 (63)
C(8')	0.7459 (4)	-0.3928 (9)	-0.3418 (13)	196 (41)	423 (52)	468 (57)	-17 (37)	-9 (39)	-82 (48)
O(8')	0.7280 (3)	-0.2847 (6)	-0.4433 (8)	335 (33)	423 (36)	444 (41)	97 (29)	-36 (30)	-60 (33)
C(9')	0.7178 (5)	-0.1745 (10)	-0.3625 (16)	402 (57)	443 (63)	663 (80)	141 (50)	-3 (54)	54 (59)
O(9')	0.7216 (5)	-0.1621 (7)	-0.2136 (11)	1102 (72)	492 (50)	590 (55)	262 (51)	45 (50)	109 (44)
C(10')	0.7018 (6)	-0.0714 (10)	-0.4817 (18)	593 (64)	485 (62)	784 (85)	74 (53)	-131 (70)	-1 (70)



The thiadiazine ring is not planar. The five atoms (excluding the sulphur atom) almost lie on a plane, the maximum deviation being 0.03 Å for C(4) in the same direction as that of the S(1) atom, with a value of 0.569 Å (Fig. 3). This ring therefore shows an envelope configuration. The short S(1)–O(1*b*) bond apparently allows the oxygen atom to approach closer to the S(1)–N(2) bond. The repulsion between the two oxygen

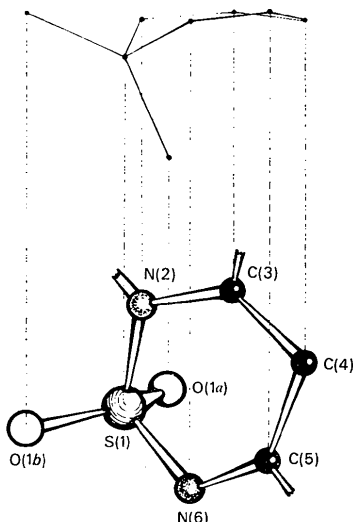


Fig. 3. The six-membered ring projected onto the mean plane through N(2), C(3), C(4), C(5) and N(6) and the atomic deviations from the plane.

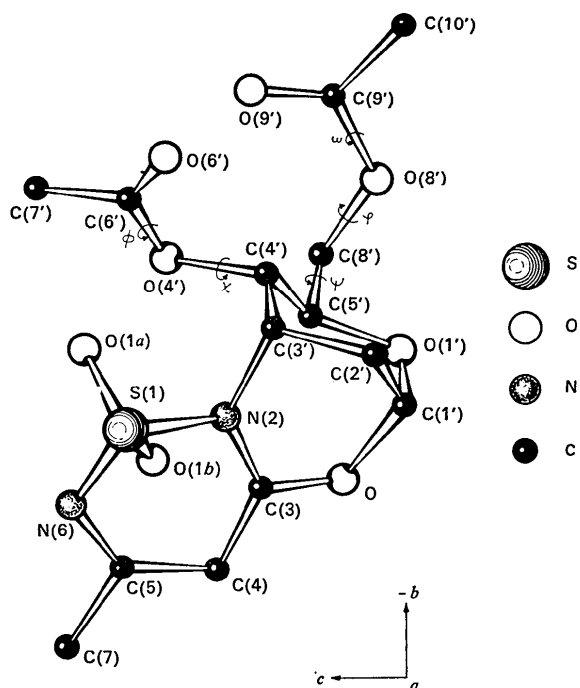


Fig. 4. A view of the TDR molecule conformation showing the torsional angles  $\chi = -96.83^\circ$ ,  $\phi = -177.22^\circ$ ,  $\psi = -128.75^\circ$ ,  $\varphi = 104.24^\circ$  and  $\omega = -178.82^\circ$ .

Table 5. Bond distances

Numbers in parentheses are standard deviations.

S(1)—O(1 <i>a</i> )	1.451 (7) Å	C(3')—C(4')	1.541 (11) Å
S(1)—O(1 <i>b</i> )	1.426 (8)	C(4')—C(5')	1.528 (11)
S(1)—N(2)	1.712 (8)	C(5')—O(1')	1.467 (11)
S(1)—N(6)	1.598 (9)	O(1')—C(1')	1.405 (10)
N(2)—C(3)	1.353 (11)	C(4')—O(4')	1.440 (10)
C(3)—C(4)	1.412 (13)	O(4')—C(6')	1.370 (11)
C(4)—C(5)	1.394 (11)	C(6')—O(6')	1.197 (12)
C(5)—C(7)	1.487 (13)	C(6')—C(7')	1.486 (15)
C(5)—N(6)	1.310 (8)	C(5')—C(8')	1.520 (12)
N(2)—C(3')	1.476 (11)	C(8')—O(8')	1.451 (12)
C(3)—O	1.332 (12)	O(8')—C(9')	1.354 (13)
O—C(1')	1.458 (11)	C(9')—O(9')	1.192 (16)
C(1')—C(2')	1.537 (13)	C(9')—C(10')	1.484 (17)
C(2')—C(3')	1.535 (14)		

Table 6. Bond distances and angles involving hydrogen atoms

C(4)—H(4)	0.961 Å	C(5)—C(4)—H(4)	112.1°
C(7)—H(7 <i>a</i> )	0.853	C(3)—C(4)—H(4)	119.3
C(7)—H(7 <i>b</i> )	0.873	C(5)—C(7)—H(7 <i>a</i> )	110.1
C(7)—H(7 <i>c</i> )	1.019	C(5)—C(7)—H(7 <i>b</i> )	117.0
		C(5)—C(7)—H(7 <i>c</i> )	109.0
		H(7 <i>a</i> )—C(7)—H(7 <i>b</i> )	115.6
		H(7 <i>a</i> )—C(7)—H(7 <i>c</i> )	101.3
		H(7 <i>b</i> )—C(7)—H(7 <i>c</i> )	102.2
C(1')—H(1')	1.042	O—C(1')—H(1')	129.8
		O(1')—C(1')—H(1')	106.0
		C(2')—C(1')—H(1')	111.6
C(2')—H(2' <i>a</i> )	1.007	C(1')—C(2')—H(2' <i>a</i> )	109.2
C(2')—H(2' <i>b</i> )	0.974	C(3')—C(2')—H(2' <i>a</i> )	121.1
		C(1')—C(2')—H(2' <i>b</i> )	121.1
		C(3')—C(2')—H(2' <i>b</i> )	131.0
		H(2' <i>a</i> )—C(2')—H(2' <i>b</i> )	107.4
C(3')—H(3')	1.016	C(2')—C(3')—H(3')	121.3
C(4')—H(4')	1.014	C(4')—C(3')—H(3')	111.7
		C(5')—C(4')—H(4')	111.7
		O(4')—C(4')—H(4')	111.6
		C(3')—C(4')—H(4')	108.9
C(5')—H(5')	1.165	C(4')—C(5')—H(5')	113.6
		O(1')—C(5')—H(5')	114.7
		C(8')—C(5')—H(5')	110.4
		C(6')—C(7')—H(7' <i>a</i> )	110.0
		C(6')—C(7')—H(7' <i>b</i> )	86.4
		C(6')—C(7')—H(7' <i>c</i> )	123.4
		H(7' <i>a</i> )—C(7')—H(7' <i>b</i> )	108.0
		H(7' <i>a</i> )—C(7')—H(7' <i>c</i> )	121.7
		H(7' <i>b</i> )—C(7')—H(7' <i>c</i> )	97.3
C(8')—H(8' <i>a</i> )	1.153	O(8')—C(8')—H(8' <i>a</i> )	110.4
C(8')—H(8' <i>b</i> )	1.066	C(5')—C(8')—H(8' <i>a</i> )	102.5
		O(8')—C(8')—H(8' <i>b</i> )	117.3
		C(5')—C(8')—H(8' <i>b</i> )	107.5
		H(8' <i>a</i> )—C(8')—H(8' <i>b</i> )	93.8
		C(9')—C(10')—H(10' <i>a</i> )	112.4
		C(9')—C(10')—H(10' <i>b</i> )	107.9
		C(9')—C(10')—H(10' <i>c</i> )	91.2
		H(10' <i>b</i> )—C(10')—H(10' <i>a</i> )	130.4
		H(10' <i>b</i> )—C(10')—H(10' <i>c</i> )	91.4
		H(10' <i>a</i> )—C(10')—H(10' <i>c</i> )	115.0

atoms, greater than the repulsion between an oxygen atom and a sulphur atom, is shown by the larger magnitude of the O(1*a*)–S(1)–O(1*b*) angle ( $117.6^\circ$ ) versus the O(1*b*)–S(1)–N(2) angle ( $105.8^\circ$ ). We think this could be due to the greater electronegativity of oxygen (3.5) in comparison with that of sulphur (2.5) and nitrogen (3.0) (Pauling, 1960).

Table 7. Deviations of the atoms (Å) from some least-squares planes in the molecule, with their dihedral angles (\* denotes the atoms used in the plane calculations.)

Plane 1		Plane 2		Plane 3	
N(6)	-0.012*	N(2)	-0.004*	O(1')	0.053*
N(2)	-0.007*	C(3)	-0.019*	C(1')	0.694
C(3)	0.024*	O	0.032*	C(2')	-0.050*
C(4)	-0.035*	C(3')	0.012*	C(3')	0.048*
C(5)	0.030*	C(2')	-0.762	C(4')	-0.661
S(1)	-0.569	C(1')	-0.022*	C(5')	-0.050*
O(1a)	-2.016				
O(1b)	0.049				
Plane 4		Plane 5			
O(4')	0.000*	C(8')	0.011*		
C(6')	0.000*	O(8')	-0.013*		
O(6')	0.000*	C(9')	-0.005*		
C(7')	0.000*	O(9')	-0.001*		
		C(10')	0.009*		
Plane					
1	0.9156X - 0.3310Y + 0.2284Z +	7.8482 = 0.0			
2	0.8932X - 0.3137Y + 0.3221Z +	7.5874 = 0.0			
3	0.0903X + 0.9568Y + 0.2766Z +	5.5114 = 0.0			
4	-0.6780X + 0.6614Y + 0.3207Z -	5.9889 = 0.0			
5	0.9718X - 0.2201Y - 0.0848Z +	13.6647 = 0.0			
	∠ (plane 1) (plane 2)	174.39°			
	∠ (plane 2) (plane 3)	97.49°			

All distances in the six-membered ring are much shorter than the corresponding single-bond distance. In the pyrimidine ring there are C-N distances similar to those found by us, but in the ring systems containing a sulphur group all C-N distances are longer than 1.310 Å but shorter than the corresponding C=N double bond. The bond length S(1)-N(6) is shorter than the lengths found for 7-chloro-1,2-benzisothiazolin-3-one (Cavalca, Fava Gasparri, Mangia & Pelizzi, 1969) and 1,2-benzisothiazol-3-yl methyl ketoxime (Braibanti, Pellinghelli, Tiripicchio & Tiripicchio Camellini, 1973) and similar to that in *S*,*S*-diphenyl-*N*-toluene-*p*-sulphonyl sulphilimine (Kálmán, Duffin & Kucsman, 1971).

All angles excluding the N(2)-S(1)-N(6) angle are similar to those found in a planar ring like benzene. The average is 120.4° while N(2)-S(1)-N(6) is 104.3°, similar to the corresponding tetrahedral bond. Thus a certain amount of aromatic character can be assigned to the six-membered ring.

The pyranosyl moiety has a chair conformation and all distances and angles are within the usual limits (Fries, Rao & Sundaralingam, 1971).

The structure of this compound contains an unusual feature. In many structures the usual bond between the base ring and the glycosyl moiety is between the anomeric carbon atom C(1') and the nitrogen atom N(2). In the title compound we have found one exception: the anomeric carbon atom C(1') is bonded to the oxygen atom.

Acetoxymethyl and acetyl groups are planar, and their bond lengths indicate the presence of some resonance character.

The most interesting twist angles are shown in Table 8 and corroborate the molecular conformation found.

A three-dimensional model of the TDR molecule showing the torsional angles  $\chi$ ,  $\phi$ ,  $\psi$ ,  $\varphi$ , and  $\omega$  is illustrated in Fig. 4.

Table 8. Twist angles

The sign convention is that of Klyne & Prelog (1960).

Thiadiazine ring		
S(1)-N(6)-C(5)-C(4)		-17.45°
C(4)-C(3)-N(2)-S(1)		17.33
N(6)-C(5)-C(4)-C(3)		-8.55
C(5)-C(4)-C(3)-N(2)		7.84
C(3)-N(2)-S(1)-N(6)		-36.67
N(2)-S(1)-N(6)-C(5)		36.23
Pyranosyl moiety		
O(1')-C(1')-C(2')-C(3')		-64.60°
C(1')-C(2')-C(3')-C(4')		61.39
C(2')-C(3')-C(4')-C(5')		-56.89
C(3')-C(4')-C(5')-O(1')		49.77
C(4')-C(5')-O(1')-C(1')		-60.25
C(5')-O(1')-C(1')-C(2')		60.40
Acetyl group		
$\chi$ : C(3')-C(4')-O(4')-C(6')		-96.83°
$\phi$ : C(4')-O(4')-C(6')-C(7')		-177.22
Acetoxymethyl group		
$\psi$ : C(4')-C(5')-C(8')-O(8')		-128.75°
$\varphi$ : C(5')-C(8')-O(8')-C(9')		104.24
$\omega$ : C(8')-O(8')-C(9')-C(10')		-178.82

The packing of the molecules is entirely due to van der Waals forces.

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