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A CRYSTALLOGRAPHIC DETERMINATION OF A CHEMICAL STRUCTURE: 6-AMINO-10-(β-D-RIBOFURANOSYLAMINO)PYRIMIDO-[5,4-*d*]PYRIMIDINE, AN EXAMPLE OF AN UNUSUAL D-RIBOSE CONFORMATION

POOJAPPAN NARAYANAN AND HELEN M. BERMAN*

The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111 (U. S. A.)

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ABSTRACT

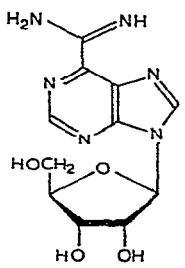
The crystal and molecular structure of 6-amino-10-(β-D-ribofuranosylamino)-pyrimido[5,4-*d*]pyrimidine has been determined by single crystal X-ray diffraction methods. The crystals are triclinic, of noncentric space group P1, with cell dimensions a = 5.434 (5), b = 12.269 (19), c = 4.574 (4) Å, α = 92.3 (1), β = 94.0 (1), γ = 95.3° (1) and Z = 1. The structure has been refined to an R value of 0.049 (Rw = 0.063), by use of counter measured intensity data for 1063 observed reflections. The pyrimido-pyrimidine ring is planar. The sugar moiety is in the envelope conformation with O-1′-*endo* (^{O}E), and there is an intramolecular hydrogen bond (2.58 Å) (O-3′–H-O3′ ... O-2′). All oxygen atoms except O-1′ ring oxygen-atom are involved in hydrogen bonding. The pyrimidopyrimidine rings lie in planes 3.4 Å apart.

INTRODUCTION

The compound under investigation was reported by Ishido *et al.*[1,2]. Its structure was originally thought to be **1**. The p.m.r. spectra indicated, however, that the proton at C=NH of the amidine group was splitting the resonances of the anomeric proton. Since coupling through this distance had never been observed, a single crystal X-ray structure analysis was undertaken to determine the correct structure. The results showed[3] that the structure is **2**, indicating that, in the course of the synthesis of the compound, the C-8–N-7 bond was broken and subsequently rearranged. We give here final details of the structure analysis of which a preliminary report[3] has been made†. In that report[3], we noted that the D-ribose ring was in the very unusual O-1′-*endo* conformation. A more complete description of the results of that structure analysis is presented herein.

*To whom communications should be addressed.

†For the purpose of making the numbering consistent with that of other pyrimidines and purines, the atoms are renumbered in the Discussion section of this paper.



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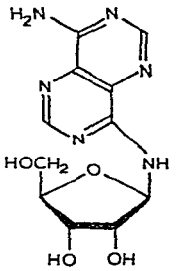

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EXPERIMENTAL

6-Amino-10-(β-D-ribopyranosylamino)pyrimido[5,4-*d*]pyrimidine (**2**) was crystallized from water as thin, fan-shaped plates. The crystals were triclinic with the crystallographic data: $C_{11}H_{14}N_6O_4$; F.W. = 294.3; a = 5.434(5), b = 12.269 (19), c = 4.574 (4) Å; $\alpha = 92.3$ (1), $\beta = 94.0$ (1), $\gamma = 95.3°$ (1); V = 302.6 (6)* Å^3; $D_{cal} = 1.61$ g.cm^{-3}; μ(CuKα) = 10.8 cm^{-1}; space group = P1; and Z = 1.

A rectangular plate, 0.4 × 0.5 × 0.05 mm, was cut from a crystal and was used to collect three dimensional intensity data on a Syntex automated diffractometer by the θ–2θ scan technique. Intensities for 1123 reflections ($\theta \leq 70°$) were measured employing CuKα radiation. Sixty of the reflections had intensities with $I_{obs} < 2\sigma(I)$; these were treated as unobserved during the refinement. Values for $\sigma(I)$ were derived from counting statistics and measured instrumental uncertainties. When $I \geq \sigma(I)$, the measured value of I was used in computing F, and when $I < \sigma(I)$, F was set equal to 0.77 (I). The intensity data were converted to structure amplitudes with the usual Lorentz and polarization factor corrections. Absorption and extinction corrections were not applied.

Structure determination and refinement. — Structure determination was effected by direct methods and refinement by the full-matrix-least squares method. Positional parameters of one atom were held constant during the refinements; hydrogen atoms were located in difference electron-density maps. These were included in further refinement; the heavier atoms were refined anisotropically; the hydrogen atoms were refined isotropically. The function minimized was $\Sigma\omega[(|F_o| - |F_c|)]^2$, where $\omega = 1/\sigma(F_o)^2$. Unit weights were applied during early stages of refinement; in later stages, a weighting scheme was used where $\sigma = 0.4$ for $F < 7.0$ and $\sigma = 0.4 + 0.76\,(F - 7)$ for $F > 7.0$; zero weight was given to unobserved reflections. Refinement was terminated at an R value 0.049 (Rw = 0.063).

The atomic scattering factors for C, N, and O atoms were taken from International Tables for X-ray Crystallography[4] and from Stewart *et al.*[5] for the hydrogen atoms. The computer programs used were the X-RAY 70 system[6], and the program

*E.s.d.'s refer to the last digit here and elsewhere in the text.

TABLE I

POSITIONAL AND THERMAL PARAMETERS OF ATOMS IN COMPOUND 2[a]

	X	*Y*	*Z*	*B11*	*B22*	*B33*	*B12*	*B13*	*B23*
C-2	712 (–)	–25 (–)	–1204 (–)[b]	1.93 (11)	1.78 (10)	2.26 (11)	0.07 (9)	0.63 (10)	–0.34 (9)
C-4	–955 (7)	1098 (3)	1931 (8)	1.66 (11)	1.26 (13)	1.84 (12)	–0.09 (9)	–0.01 (10)	–0.08 (10)
C-5	–2726 (7)	260 (3)	2568 (7)	1.81 (11)	1.23 (8)	1.88 (10)	0.08 (9)	0.17 (9)	–0.39 (8)
C-6	–2639 (7)	–796 (3)	1031 (8)	1.90 (12)	1.21 (11)	1.85 (14)	–0.04 (9)	–0.09 (11)	–0.05 (11)
C-8	–4404 (8)	1375 (3)	5715 (9)	2.33 (13)	1.32 (12)	2.68 (14)	–0.15 (10)	0.71 (12)	–0.55 (12)
C-10	–1030 (7)	2137 (3)	3480 (8)	1.85 (13)	1.07 (11)	2.10 (11)	0.03 (10)	–0.02 (10)	–0.26 (10)
C-1′	1184 (7)	3931 (3)	5000 (9)	1.83 (12)	1.24 (10)	2.13 (12)	–0.28 (10)	0.20 (10)	–0.62 (10)
C-2′	3941 (7)	4374 (3)	5483 (9)	1.75 (12)	1.59 (12)	2.10 (12)	0.02 (11)	0.24 (10)	–0.36 (10)
C-3′	3877 (8)	5635 (3)	5938 (9)	2.27 (14)	1.36 (13)	2.34 (15)	–0.39 (11)	0.03 (12)	–0.37 (11)
C-4′	1083 (7)	5765 (3)	5598 (9)	1.79 (13)	1.26 (14)	2.70 (14)	–0.26 (11)	0.26 (11)	–0.66 (12)
C-5′	501 (11)	6798 (4)	4041 (11)	2.72 (18)	1.48 (17)	3.58 (22)	0.18 (15)	–0.03 (16)	–0.63 (16)
N-1	–889 (7)	–921 (3)	–794 (8)	2.37 (12)	1.13 (11)	2.36 (11)	–0.04 (10)	0.40 (11)	–0.48 (10)
N-3	788 (8)	968 (3)	–15 (8)	1.88 (11)	1.58 (13)	2.58 (11)	0.04 (10)	0.48 (10)	–0.24 (10)
N-6	–4331 (8)	–1633 (3)	1477 (9)	2.16 (14)	1.36 (14)	3.09 (16)	–0.50 (11)	0.79 (12)	–0.76 (11)
N-7	–4474 (8)	380 (3)	4479 (9)	1.88 (13)	1.55 (13)	2.61 (13)	–0.11 (10)	0.36 (12)	0.09 (11)
N-9	–2761 (8)	2270 (3)	5313 (10)	2.05 (13)	1.28 (11)	2.39 (14)	0.05 (10)	0.47 (11)	–0.40 (11)
N-10	738 (8)	2972 (4)	3080 (10)	2.36 (14)	1.27 (14)	2.47 (13)	–0.36 (12)	0.56 (12)	–0.62 (11)
O-1′	–11 (8)	4829 (3)	3793 (10)	1.94 (11)	1.30 (13)	3.10 (12)	–0.09 (10)	–0.10 (10)	–0.68 (10)
O-2′	5083 (8)	3940 (4)	8016 (10)	2.97 (14)	1.85 (16)	2.81 (13)	0.91 (13)	–0.20 (11)	–0.45 (12)
O-3′	5047 (10)	6035 (4)	8722 (13)	3.58 (18)	1.92 (15)	3.19 (16)	0.27 (13)	–0.99 (14)	–1.14 (13)
O-5′	1710 (13)	7743 (5)	5566 (16)	3.02 (17)	1.42 (13)	4.42 (18)	–0.12 (12)	0.67 (15)	–0.93 (13)

Table continued p. 172.

TABLE 1 (*continued*)

	X	*Y*	*Z*	*B*
H-2	195 (12)	−12 (5)	−244 (13)	2.8 (11)
H-8	−584 (25)	147 (12)	729 (30)	7.3 (31)
H-11	38 (14)	378 (6)	708 (16)	4.9 (12)
H-21	477 (17)	425 (7)	386 (21)	1.6 (17)
H-31	458 (14)	596 (7)	429 (17)	3.4 (14)
H-41	53 (14)	570 (7)	748 (17)	3.2 (14)
H-51	120 (18)	677 (7)	192 (20)	4.8 (19)
H-52	−167 (18)	690 (8)	359 (19)	7.2 (18)
H-10	183 (16)	290 (7)	199 (18)	2.8 (15)
H-61	−542 (14)	−160 (6)	287 (15)	2.1 (12)
H-62	−456 (18)	−219 (9)	52 (22)	3.9 (17)
HO-2′	508 (18)	330 (8)	811 (21)	10.0 (19)
HO-3′	530 (20)	536 (10)	903 (24)	3.4 (21)
HO-5′	79 (45)	826 (21)	627 (61)	23.8 (70)

[a]The positional parameters are fractions of cell edges multiplied by 10^4 for non-hydrogen and by 10^3 for hydrogen atoms. Anisotropic temperature factor T is of the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k_2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$ and isotropic temperature factor is of the form $T = \exp(-B \sin^2\theta/\lambda^2)$. [b]Fixed atom in refinement.

library at Brookhaven National Laboratory. The final positional and thermal parameters of the atoms are tabulated in Table I, and the list of structure factors has been deposited with NAPS-ASIS*.

DISCUSSION

Description of the structure — Fig. 1 shows the numbering system used for (**2**). The numbering corresponds to the convention for pyrimidines and purines The numbers in brackets correspond to the original ribosylamidine numbering (see Introduction). Fig. 2 shows the distances and angles in the molecule.

The pyrimidopyrimidine moiety. — There is an approximate two-fold axis through the C-4–C-5 bond in the pyrimidopyrimidine system; the bond distances, angles, and the atom types related by this two-fold axis are nearly identical. Each pyrimidine ring is planar and the two rings are coplanar (dihedral angle = 179.4°) (Table III and Fig. 3). The dihedral angle between pyrimidopyrimidine plane and the D-ribose ring (C-1′–C-2′–C-3′–C-4′) is 50.0°.

The D-ribose moiety. — The bond distances and angles of the D-ribose moiety are compared to those found in other D-ribose derivatives in Table II. The least squares planes are listed in Table IV, and certain torsion angles are listed in Table V. The glycosidic bond C-1′–N-10 is shorter than what has been observed in nucleosides.

The D-ribose ring is in the very unusual O-1′-*endo* (^0E) conformation (Fig. 4). Altona and Sundaralingam[7] have pointed out that this sugar ring conformation is intermediate between C-3′-*endo* and C-2′-*endo* conformations, and that there is a large strain-energy involved in forcing the molecule into this conformation. The pseudorotation value (P 89°) indicates that this ring is a nearly symmetrical envelope.

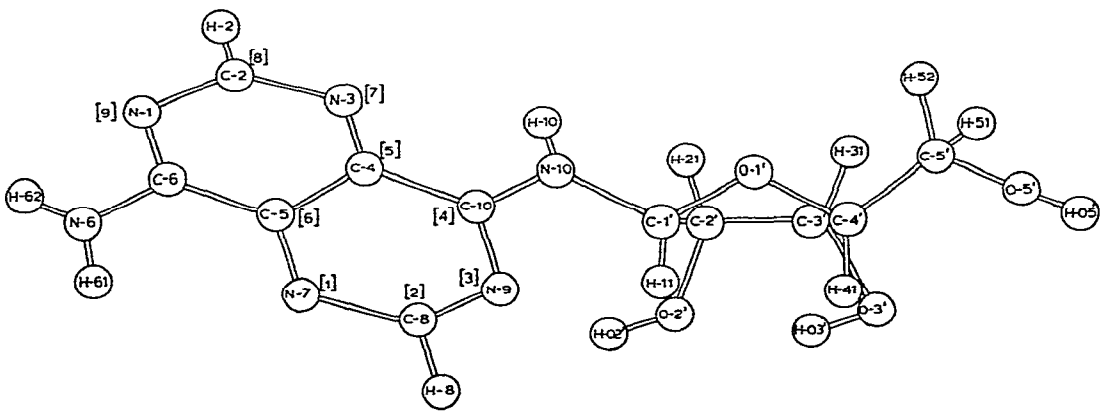

Fig. 1. Numbering of the atoms in compound **2**. The numbers in square brackets refer to the original ribosylamidine numbering scheme.

*Microfilm copies of this table can be obtained from the NAPS-ASIS Agency, New York, U. S. A.

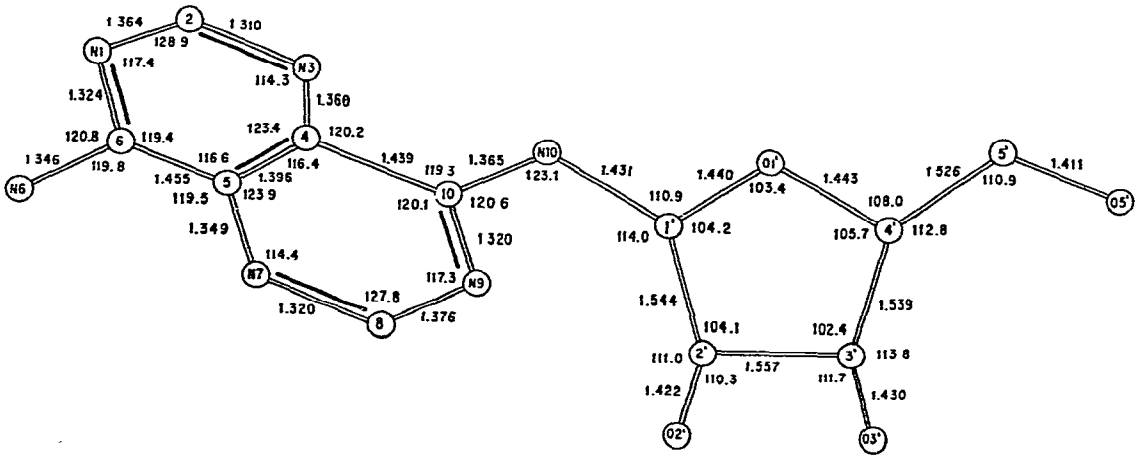

Fig. 2. Bond distances and angles. Only the carbon, nitrogen, and oxygen atoms are shown. The average e.s.d. for bond lengths is 0.004 Å; the average e.s.d. for angles is 0.4°.

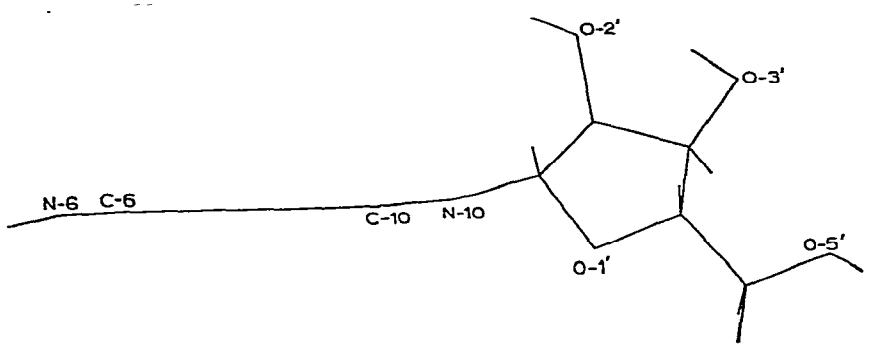

Fig. 3. View of compound 2 showing planarity of pyrimidine rings and relationship to sugar moiety.

The torsion angle τ_2 is the smallest one in the ring, and the others are symmetric about it. Atoms C-1′, C-2′, C-3′, C-4′ are coplanar; C-2′, C-3′, O-3′, and O-2′ are also coplanar so that O-2′ and O-3′ are eclipsed; O-1′ deviates by 0.6 Å from the C-1′, C-2′, C-3′, C-4′ plane. The dihedral angle between the plane O-2′–C-2′–C-3′–O-3′ and plane C-1′–C-2′–C-3′–C-4′ is 120.5°. The dihedral angle between the plane H-21–C-2′–C-3′–H-31 and plane C-1′–C-2′–C-3′–C-4′ is 115° (see Fig. 4). In addition, this conformation of the D-ribose ring has the following effects on the detailed geometry of the sugar: (a) The C-4′–O-1′ and C-1′–O-1′ bond lenghts are nearly equal rather than differing by 0.04 Å as is common in C-2′-*endo* or C-3′-*endo* D-ribose rings[8]. (b) The C-2′–C-3′ bond length is 1.56 Å, which is significantly longer than C–C bonds in most sugars (1.52 Å). (c) The bonds C-2′–O-2′ and C-3′–O-3′ do not differ signifi-

TABLE II

COMPARISON OF BOND LENGTHS AND ANGLES OF THE SUGAR MOIETY WITH THE AVERAGE VALUES FOUND IN OTHER D-RIBOSE DERIVATIVES

Bond	*Distance* (Å)	
	Compound **2**	*C-3′- and C-2′*-endo *sugars*[a]
C-1′–O-1′	1.440 (4)	1.410
C-4′–O-1′	1.443	1.449
C-1′–N-10	1.431	1.469
C-1′–C-2′	1.544	1.519
C-2′–C-3′	1.557	1.520
C-2′–O-2′	1.422	1.415
		1.408
		1.411
C-3′–O-3′	1.430	1.435
C-3′–C-4′	1.539	1.524
C-4′–C-5′	1.526	1.509
C-5′–O-5′	1.411	1.444
Angle	*Angle* (°)	
	Compound **2**	*C-3′- and C-2′*-endo *sugars*[a]
C-1′–O-1′–C-4′	103.4 (4)	110.0
		109.2
		109.6
O-1′–C-1′–C-2′	104.2	107.3
		105.6
		106.5
O-1′–C-1′–N-10	110.9	108.3
C-2′–C-1′–N-10	114.0	112.9
		114.2
		113.6
C-1′–C-2′–C-3′	104.1	101.3
C-1′–C-2′–O-2′	111.0	107.3
		112.7
		110.0
C-3′–C-2′–O-2′	110.3	111.2
		114.7
		113.0
C-2′–C-3′–C-4′	102.4	102.4
C-2′–C-3′–O-3′	111.7	113.7
		110.0
		111.9
C-4′–C-3′–O-3′	113.8	112.6
		109.5
		111.1
C-3′–C-4′–O-1′	105.7	104.4
		106.1
		105.3
C-3′–C-4′–C-5′	112.8	116.5
		114.9
		115.7
O-1′–C-4′–C-5′	108.0	109.0
C-4′–C-5′–O-5′	110.9	111.1

[a]The first value is for C-3′-*endo*, the second for C-2′-*endo*, and the third is the average value.

TABLE III

DEVIATION OF THE ATOMS FROM THE LEAST SQUARES PLANES[a]

Plane I		*Plane II*		*Plane III*	
Atom	*Δ* (Å)	*Atom*	*Δ* (Å)	*Atom*	*Δ* (Å)
N-1	0.015	C-1′	0.005	C-2′	0.010
C-2	0.005	C-2′	−0.007	C-3′	−0.10
N-3	−0.020	C-3′	0.007	O-2′	−0.006
C-4	−0.005	C-4′	−0.005	O-3′	−0.006
C-5	−0.001				
C-6	−0.010				
N-7	0.005	O-1′[b]	−0.615	H-O3′[b]	0.008
C-8	−0.007	C-5′[b]	−0.841		
N-9	−0.001	O-5′[b]	−0.366		
C-10	0.019	N-10[b]	−0.693		
		C-10[b]	−0.276		
N-6[b]	−0.043				
N-10[b]	0.092				
C-1′[b]	0.442				
r.m.s. dev. of atoms from the plane	0.011		0.006		0.008

[a]The equations of the planes where x, y, and z are the coordinates relative to the orthogonal axes are: I = 0.595x − 0.305y + 0.744z + 0.157 = 0; II = 0.108x + 0.138y − 0.985z + 1.586 = 0; III = 0.905x + +0.154y − 0.397z − 1.134 = 0. [b]These atoms are not included in the calculation of the plane.

TABLE IV

TORSION ANGLES IN COMPOUND 2

Angle	*Value* (°)	*Atoms involved*			
		A	*B*	*C*	*D*
ϕC-1′–C-10	−75.8	O-1′–C-1′–C-10–N-9			
ϕC-1′–N-10	−99.2	O-1′–C-1′–N-10–C-10			
ϕC-4′–C-5′	−58.3	C-3′–C-4′–C-5′–O-5′			
ϕC-4′–C-5′	−174.7	O-1′–C-4′–C-5′–O-5′			
ϕC-4′–C-3′	+96.1	C-5′–C-4′–C-3′–O-3′			
ϕC-1′–C-2′	−93.2	N-10–C-1′–C-2′–O-2′			
ϕC-2′–C-3′	−1.9	O-3′–C-2′–C-3′–O-2′			
τ_0	−44.0	C-4′–O-1′–C-1′–C-2′			
τ_1	+27.1	O-1′–C-1′–C-2′–C-3′			
τ_2	+1.1	C-1′–C-2′–C-3′–O-4′			
τ_3	−25.4	C-2′–C-3′–C-4′–O-1′			
τ_4	+43.9	C-3′–C-4′–O-1′–C-1′			

TABLE V

PSEUDO ROTATION PHASE ANGLES (P) AND MAXIMUM AMPLITUDES OF TWIST (τ_m) FOR SUGAR MOIETIES IN THE PRESENT STRUCTURE AND IN SOME OTHER RELATED STRUCTURES[a]

Compound	*P* (°)	τ_m (°)	*Sugar conformation*	*Deviation* endo/exo (Å)	C-5′–O-5′ *conformation*	*Intra H...bonding*	*Ref.*
Pyrimidopyrimidine	88.6	45.0	O-1′-*endo* (^0E)	(0.62)	*trans–gauche*	yes	
Dihydrothymidine	84.4	31.6	O-1′-*endo* (^0E)	(0.42)	*gauche–gauche*	no	15
1-β-D-Arabinofuranosyl-5-bromouracil	74.0	36.2	O-1′-*endo* C-1′-*exo* ($^0T_1$)	(0.50/0.52)	*gauche–gauche*	no	16
1-β-D-Arabinofuranosylthymidine	75.2	41.1	O-1′-*endo* C-1′-*exo* ($^0T_1$)	0.32/0.28	*gauche–gauche*	no	17
Disodium deoxyguanosine 5′-phosphate tetrahydrate	83.5	40.6	O-1′-*endo* C-4′-*exo* ($^0T_4$)	0.24/0.20	*gauche–trans*	no	18
2′,3′-Dideoxy-2′,3′-didehydroadenosine	52.7	9.2	C-4′-*endo* (^4E)	(0.11)	*gauche–trans*	no	19

[a]Nomenclature is as defined by Altona and Sundaralingam[7].

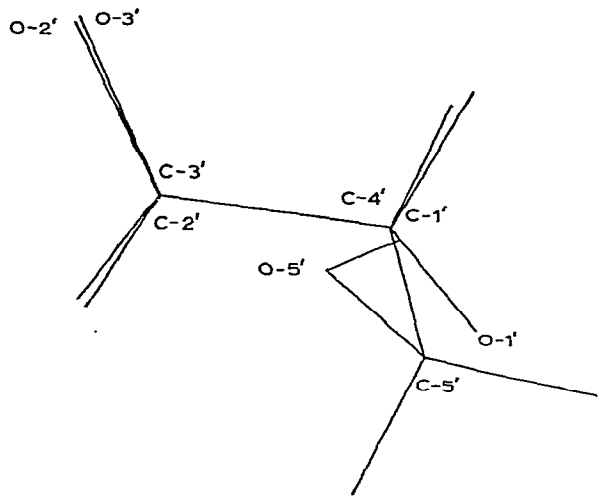

Fig. 4. Conformation of the D-ribose ring as viewed along C-2'–C-3', showing the O-1'-*endo* conformation, the planarity of other four atoms of the ring, and the eclipsing of atoms O-2' and O-3'.

cantly from one another. In C-2'- or C-3'-*endo* sugars the C-2'–O-2' bond is usually somewhat shorter than the C-3'–O-3' bond. (d) The C-4'–O-1'–C-1'angle is significantly smaller than the 110° angle found in C-2'-*endo* and C-3'-*endo* D-ribose sugars. (e) There is an intramolecular hydrogen bond between the O-3' and O-2' hydroxyl oxygen atoms (see Fig. 5 and Table VI). Table V compares the conformations of the five reported O-1' and C-4' *endo*-sugars with that found in **2**. Compound **2** is the only one of these in which two oxygen atoms *and* two hydrogen atoms can be eclipsed; the O-3'–O-2' hydrogen bond is thus obviously necessary to reduce the very high strain-energy.

No other D-ribose structures having O-3'–O-2' hydrogen bonds have been reported. In fact, intramolecular hydrogen bonds are not commonly found in nucleoside structures. There have been some reported between O-5' of the sugar moiety and N-3 of the purine moiety[9]. In these cases, the base is *syn* to the sugar and the C-4'–C-5' bond is in the *gauche–gauche* conformation[10]. In the other structures having intramolecular hydrogen bonds within the sugar portion of the nucleosides [1-β-D-arabinofuranosylcytosine (Ara-C)[11], β-D-arabinofuranosyluracil[12,13], and 1-β-D-arabinofuranosylcytosine[14]], the hydrogen bond is between O-2' and O-5'.

Hydrogen bonding and packing. — The hydrogen-bonding scheme is given in Table VI and in Fig. 5. All the potential donor atoms except N-10 donate hydrogen bonds. The potential acceptor nitrogen atoms N-3 and N-7 do not take part in hydrogen bonding. However, both the atoms N-3 and N-7 are involved in close intramolecular contacts (2.79 Å) with N-10 and N-6, respectively; the H ... N distances (2.49) and the N–H ... N angles (101° average) preclude hydrogen bonding. The pyrimidopyrimidine rings are stacked 3.4 Å apart.

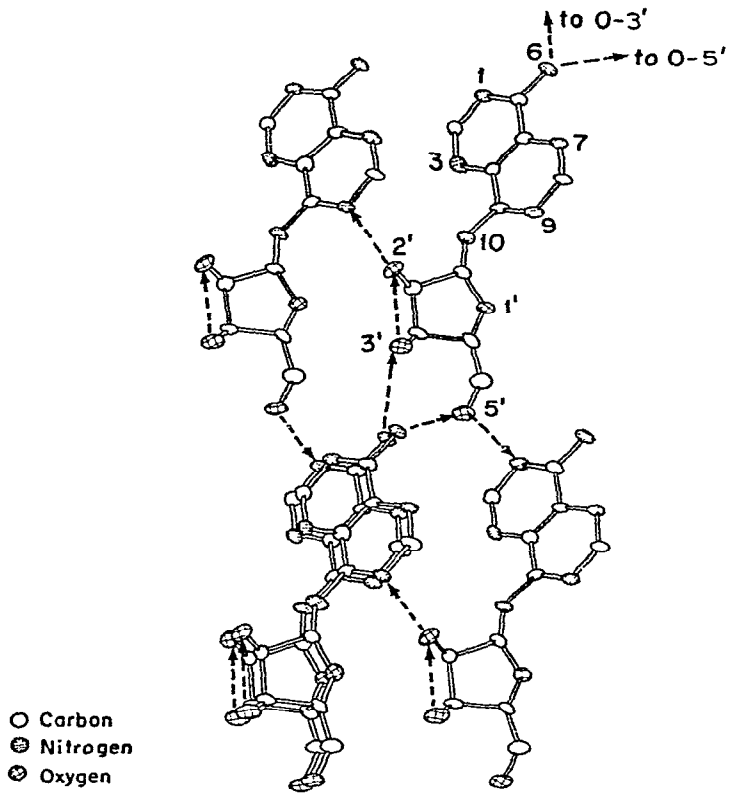

Fig. 5. Hydrogen bonding. The nitrogen and oxygen atoms are labelled. The arrows point from the donor to the acceptor atoms.

TABLE VI

HYDROGEN BOND ENVIRONMENT[a]

D–H...A	*Distances* (Å)			*Angles* (°)		
	D–H	H...A	D...A	D–H...A	D...A...H	A...D–H
N-6–H-61...O-5′^{i}	0.90	2.17	3.014	155	7	18
N-6–H-62...O-3′^{ii}	0.80	2.29	3.060	167	3	10
O-2′–H-O2′...N-9^{iii}	0.79	2.23	2.746	124	14	42
O-3′–H-O3′...O-2′	0.87	1.78	2.580	154	9	18
O-5′–H-O5′...N-1^{iv}	0.90	1.97	2.827	157	7	16

[a]D, donor atom; A, acceptor atom; and H, hydrogen atom. Symmetry tag (Superscript/symmetry): none/x, y, z; i/−1+x, −1+y, z; ii/−1+x, −1+y, −1+z; iii/1+x, y, z; and iv/x, 1+y, 1+z.

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