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THE CRYSTAL STRUCTURE OF THE *C*-NUCLEOSIDE, 1,3-DIMETHYL-8-β-D-RIBOFURANOSYLXANTHINE MONOHYDRATE*

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ABSTRACT

1,3-Dimethyl-8-β-D-ribofuranosylxanthine monohydrate, $C_{12}H_{16}N_4O_6 \cdot H_2O$, is monoclinic, $P2_1$, with two molecules in a unit cell having $a = 8.186(1)$, $b = 19.222(3)$, $c = 4.7655(8)$ Å, $\beta = 103.79(1)°$, $V = 728.2$ Å, and $D_x = 1.506$ g·cm^{-3}. The structure was solved by the direct methods, using Mo$K\alpha$ radiation and refined with anisotropic temperature-factors. The final agreement factors were $R = 0.061$, $R_w = 0.042$ for 2254 structure amplitudes having $|F_o| > 2\sigma(F_o)$. The ribose ring has the C-2′-*exo*–C-3′-*endo* ($_2T^3$) conformation with pseudorotation parameters $P = -3.2$, $\tau_m = 39.9°$, and a *gauche–gauche* conformation around the ribose C-4′–C-5′ bond. The β-link conformation is *anti*, with O-4′–C-1′–C-8–N-9 = −162.6°. The pyrimidine and imidazole rings are planar, making an interplanar angle of 1.0(1)°. The molecular conformation is stabilized by an unsymmetrical, three-center hydrogen bond from N-7-H to O-5′–H as the major component and to O-4′–H as the minor component. The hydrogen bonding includes a cooperative cycle involving the HN–C–C=O moiety, two hydroxyl groups, and a water molecule.

INTRODUCTION

C-Nucleosides are of interest because of their potential anti-viral and anti-tumor properties. Crystal-structural analyses have been reported for formycin A monohydrate[1], formycin A hydrobromide monohydrate[2], formycin B and oxoformycin B[3], and 8-(2-deoxy-β-D-*erythro*-pentofuranosyl)hypoxanthine[4].

The present compound, **1** was synthesized by Professor H. S. El Khadem[5], who provided the crystals. The crystal-structure analysis was performed to verify the β-nucleoside configuration, because of some uncertainty in the interpretation of the Cotton effect for *C*-nucleosides. Related *N*-nucleosides, for which crystal-structure analyses are available, are xanthosine[6] and xanthosine dihydrate[7].

*Dedicated to Dr. R. Stuart Tipson.

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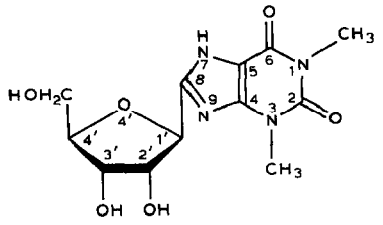

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EXPERIMENTAL

The crystal data, structure determination, and structure refinement data are given in Table I. The atomic parameters are given in Table II. All hydrogen atoms were located by Fourier-difference syntheses and refined with isotropic temperature-factors. The atomic notation and thermal ellipsoids are shown in Fig. 1.

TABLE I

SUMMARY OF EXPERIMENTAL DATA FOR 1,3-DIMETHYL-8-β-D-RIBOFUIRANOSYLXANTHINE MONOHYDRATE

Crystal data

Formula, molecular weight: $C_{12}H_{16}N_4O_6 \cdot H_2O$, 330.3
Space group $P2_1$, $Z = 2$
Cell dimensions, based on 25 reflections having $17° \leq \theta \leq 20°$, $a = 8.186(1)$, $b = 19.222(3)$, $c = 4.7655(8)$ Å, $\beta = 103.79(1)°$
Unit-cell volume = 728.24 Å^3
D_c (calculated density) = 1.506 g/cm^3

Experimental and refinement data[a]

Crystal dimensions, 0.5 × 0.5 × 0.1 mm
Diffractometer and method, CAD-4, $\omega/2\theta$ scan
Wavelength (MoKα radiation, Nb filter) = 0.7107 Å;
$\mu_{MoK\alpha} = 1.34$ cm^{-1}
Total number of reflections measured, 3602
Number of reflections observed 2254, $I > 1\ \sigma(I)$
Range of $h,k,l = -11 \leq h \leq 11, -27 \leq k \leq 0, 0 \leq l \leq 6$
$\theta_{max} = 35°$
Structure determined by MITHRIL (ref. 10)
Function minimized: $R = \Sigma[w(k|F_o| - |F_c|)^2]$, using program UPALS (Ref. 11), $w = 1/\sigma^2(F)$ based on counting statistics
Number of parameters refined, 279
Range of final electron density (e/Å^3) on difference Fourier map, −0.26 to 0.33
Final agreement factors: $R(F) = 0.061$, $R_w(F) = 0.042$, S (goodness of fit) = 1.27

[a]In response to a referee's criticism, the final refinement was repeated with weighting scheme $w = [\sigma(F_o)^2 + (PF_o)^2]^{-1}$, $P = 0.1$, 0.2, and 0.3. There were no significant differences in the atomic parameters. For the bond lengths, the changes were $<0.8\sigma$, for the angles $<0.3\sigma$. With $P = 0.03$, the values of R, R_w and S were 6.10, 5.81, 1.02, respectively.

TABLE II

POSITIONAL AND THERMAL PARAMETERS FOR 1,3-DIMETHYL-8-β-D-RIBOFURANOSYLXANTHINE MONOHYDRATE[a]

Atom	x	y	z	B_{eq}
C-1	1341(5)	4583(3)	1295(11)	3.38(11)
N-1	2922(3)	4752(2)	3409(6)	2.42(6)
C-2	4318(4)	4340(2)	3330(7)	2.48(8)
C-3	7348(4)	4103(2)	5213(10)	2.76(9)
N-3	5799(3)	4489(2)	5257(6)	2.14(6)
C-4	5846(3)	5017(2)	7229(6)	1.81(7)
C-5	4449(4)	5406(2)	7257(6)	2.05(7)
C-6	2886(4)	5306(2)	5284(7)	2.32(8)
N-7	4969(3)	5869(2)	9505(6)	2.22(6)
C-8	6613(3)	5736(2)	10637(6)	2.02(7)
N-9	7199(3)	5209(2)	9316(5)	2.15(6)
O-2	4209(3)	3863(2)	1566(5)	3.43(7)
O-6	1597(3)	5644(2)	5147(6)	3.67(7)
C-1′	7670(4)	6158(2)	13042(6)	2.05(7)
C-2′	8701(4)	6711(2)	11959(6)	1.99(7)
C-3′	7448(4)	7303(2)	11335(6)	1.87(7)
C-4′	6579(4)	7260(2)	13803(6)	2.11(7)
C-5′	4809(4)	7521(2)	13200(8)	2.85(9)
O-2′	10096(3)	6925(2)	14159(5)	2.99(6)
O-3′	8232(3)	7953(2)	11176(5)	2.77(6)
O-4′	6600(3)	6525(0)	14531(4)	2.46(6)
O-5′	3785(3)	7140(2)	10853(6)	3.80(7)
O-W	1035(3)	7912(2)	8588(7)	3.45(7)
H-1	66(6)	503(3)	140(11)	7.6(1.4)
H-2	92(7)	413(3)	198(12)	8.5(1.5)
H-3	146(7)	448(3)	−36(12)	6.3(1.5)
H-4	788(8)	395(3)	709(14)	9.6(1.8)
H-5	828(7)	443(3)	509(11)	7.0(1.9)
H-6	718(6)	389(3)	378(10)	5.0(1.2)
H-7	456(4)	622(2)	993(8)	3.0(8)
H-1′	844(3)	585(1)	1434(6)	1.2(5)
H-2′	900(4)	652(2)	1027(8)	2.9(7)
H-3′	666(3)	722(1)	969(6)	1.1(5)
H-4′	719(4)	748(2)	1540(7)	1.9(6)
H-5′	482(4)	801(2)	1258(7)	3.3(8)
H-5″	442(5)	746(2)	1491(8)	4.1(9)
H–O-2′	1071(4)	654(2)	1453(7)	2.8(7)
H–O-3′	757(5)	821(2)	1052(9)	3.5(1.0)
H–O-5′	284(6)	738(3)	1021(9)	5.2(1.1)
H–W-1	34(7)	786(3)	938(11)	5.8(1.4)
H–W-2	64(6)	789(2)	709(10)	5.4(1.2)

[a]Fractional coordinates $\times 10^4$ for non-hydrogen atoms; $\times 10^3$ for hydrogen atoms. B_{eq} (in Å^2) for non-hydrogen atoms is defined by $B = {}^4/_3\Sigma_i\Sigma_j\beta_{ij}(\mathbf{a}_i \cdot \mathbf{a}_j)$. Estimated standard deviations, given in parentheses, refer to the least significant digit.

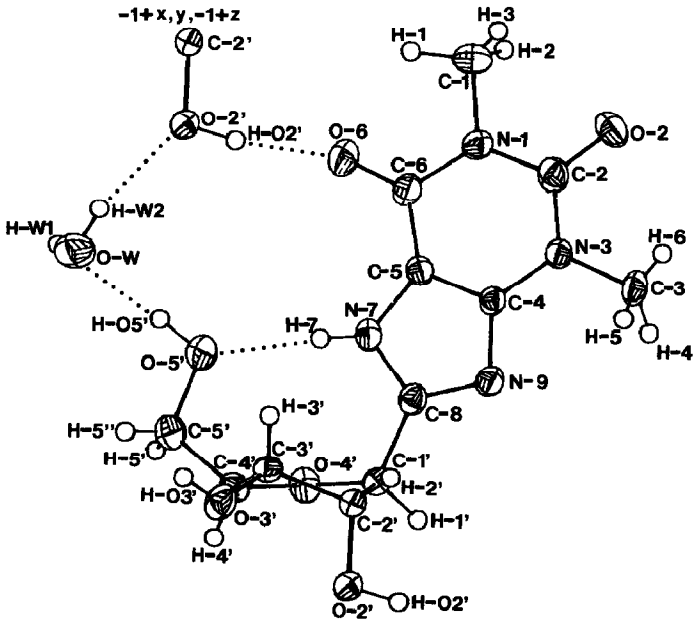


Fig. 1. 1,3-Dimethyl-8-β-D-ribofuranosylxanthine monohydrate (thermal ellipsoids at 50% probability).

DISCUSSION

The molecular structure. — The ribofuranosyl ring has an unsymmetrical C-2′-*exo*–C-3′-*endo* conformation ($_2T^3$) with the Altona and Sundaralingam[8] parameters: $P = -3.2°$ and $\tau_m = 39.9°$. The corresponding Cremer and Pople[9] parameters are $q_2 = 0.385(3)$ Å, $\phi_2 = 267.1(5)°$. The distance from the plane through C-1′, O-4′, C-4′ to the atoms C-3′ and C-2′ is −0.261 and 0.373 Å, respectively. The torsion angles around the C-4′–C-5′ bond (ϕ_{OO} and ϕ_{OC}) of −59.6(4) and 58.9(4)°, respectively, indicate the *gauche–gauche* conformation. The conformation about the glycosyl link is *anti*, with O-4′–C-1′–C-8–N-9 = −162.6(3). Both the pyrimidine and imidazole rings are planar, within 3 and 1 σ, respectively. They are inclined at 1.0(1)° to each other. The bond lengths and some important torsion angles are given in Table III and are compared with those in some related structures. The table of valence angles has been deposited*.

The more-significant differences in bond lengths between the different molecules in Table III correspond to the difference in the formal character of the ring bonds. In the pyrimidine ring, the C-2–N-3 formal single-bonds in **1**, **3**, and **4**

*Lists of structure factors, anisotropic thermal parameters, and valence angles have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/379/*Carbohydr. Res.*, 169 (1987) 35–42.

TABLE III

BOND DISTANCES AND SELECTED TORSION-ANGLES FOR 1,3-DIMETHYL-8-β-D-RIBOFURANOSYLXANTHINE MONOHYDRATE AND RELATED STRUCTURES[a]

	This work (1)	*8-(2-Deoxy-β-D-erythro-pento-furanosyl)-hypoxanthine*[4] (2)	*Xanthosine*[6] (3)	*Xanthosine · 2 H_2O*[7] (4)	
Pyrimidine group					
N-1–C-2	1.398(5)	1.361(9)	1.384(3)	1.380(5)	
C-2–N-3	1.366(4)	1.308(11)	1.377(3)	1.380(5)	
N-3–C-4	1.379(4)	1.384(7)	1.371(3)	1.364(5)	
C-4–C-5	1.368(4)	1.380(10)	1.370(3)	1.367(6)	
C-5–C-6	1.409(5)	1.411(11)	1.427(4)	1.429(6)	
C-6–N-1	1.396(4)	1.390(8)	1.399(3)	1.394(6)	
N-1–C-1	1.474(6)				
N-3–C-3	1.473(5)				
C-2–O-2	1.232(4)		1.227(3)	1.229(6)	
C-6–O-6	1.227(4)	1.239(10)	1.215(3)	1.223(6)	
Imidazole group					
C-5–N-7	1.380(4)	1.369(8)	1.393(3)	1.386(6)	
N-7–C-8	1.349(4)	1.357(10)	1.314(3)	1.304(6)	
C-8–N-9	1.340(4)	1.332(8)	1.388(3)	1.389(5)	
N-9–C-4	1.352(4)	1.366(10)	1.363(3)	1.376(5)	
Glycosylic bond					
C-1′–C-8	1.500(4)	1.489(9)			
C-1′–N-9			1.459(3)	1.405(5)	
Ribofuranosyl group					
O-4′–C-1′	1.437(4)	1.451(7)	1.409(3)	1.410(5)	
C-1′–C-2′	1.522(4)	1.529(11)	1.531(5)	1.535(5)	
C-2′–C-3′	1.514(4)	1.540(9)	1.532(5)	1.525(6)	
C-3′–C-4′	1.515(5)	1.536(9)	1.523(5)	1.533(6)	
C-4′–O-4′	1.453(4)	1.445(10)	1.464(4)	1.455(5)	
C-2′–O-2′	1.414(4)		1.402(4)	1.409(5)	
C-3′–O-3′	1.414(4)	1.403(10)	1.414(4)	1.436(5)	
C-4′–C-5′	1.496(5)	1.472(8)	1.495(4)	1.520(6)	
C-5′–O-5′	1.429(5)	1.404(8)	1.438(4)	1.438(5)	
O-2′–H-O-2′	0.88(4)				
O-3′–H-O-3′	0.75(4)				
O-5′–H-O-5′	0.89(5)				
Selected torsion angles					*Symb.*[b]
N-9–C-8–C-1′–O-4′	−162.6(3)	−91.2			χ
N-7–C-8–C-1′–O-4	20.1(3)	81.3			
C-4–N-9–C-1′–O-4′			48.9(3)	53.4	
C-4′–O-4′–C-1′–C-2′	14.8(3)	−7.8	−26.7(3)	−27.4	τ_0
O-4′–C-1′–C-2′–C-3′	−33.3(3)	−18.6	38.0(3)	39.8	τ_1
C-1′–C-2′–C-3′–C-4′	38.8(3)	36.2	−34.3(3)	−36.0	τ_2
C-2′–C-3′–C-4′–O-4′	−31.2(3)	−41.3	20.2(3)	21.3	τ_3
C-3′–C-4′–O-4′–C-1′	10.3(3)	31.0	38.3(3)	3.8	τ_4
O-4′–C-4′–C-5′–O-5′	−59.6(4)	60.0	−65.6(3)	−66.6	ϕ_{OO}
C-3′–C-4′–C-5′–O-5′	58.9(4)	54.4	54.5(3)	52.7	ϕ_{CO}

[a]Bond lengths in Å, torsion angles in degrees. Estimated standard deviations, given in parentheses, refer to the least significant digit. [b]Symbols according to ref. 8.

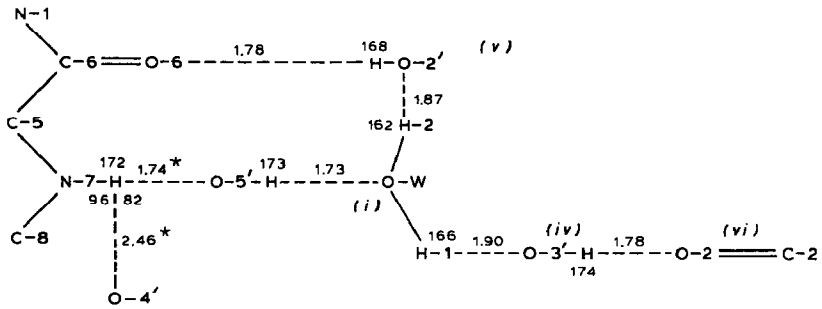
are longer than the formal double-bond in **2**. Similarly in the imidazole ring, the single N-7–C-8 bonds in **1** and **2** are longer than the double bonds in **3** and **4**, whereas the reverse is observed for the C-8–N-9 bonds. The substitution of the glycosylic link at C-8 in **1** and **2** rather than N-9 in **3** and **4** results in a greater equivalence of the N-7–C-8 and C-8–N-9 bond lengths and a small shortening of N-7–C-5.

TABLE IV

HYDROGEN-BOND GEOMETRY IN 1,3-DIMETHYL-8-β-D-RIBOFURANOSYLXANTHINE MONOHYDRATE[a]

Bond	*A–H*	*H---B*	*A–H---B*	*Symmetry operation*[b]
N-7–H-7---O-5′–H	0.81	1.96*	173	(i)
N-7–H-7---O-4′–H	0.81	2.49*	101	(i)
O-2′–H-O-2′---O-6=C	0.88	1.87	168	(ii)
O-3′–H-O-3′---O-2=C	0.75	2.00	175	(iii)
O-5′–H-O-5′---O-W	0.89	1.81	174	(i)
O-W–H-W-1---O-3′–H	0.76	2.11	167	(iv)
O-W–H-W-2---O-2′–H	0.83	2.00	163	(v)

Normalized bond lengths and angles: N–H = 1.03 Å, O–H = 0.97 Å.



[a]Bond lengths in Å, angles in degrees. * indicates an intramolecular bond. [b]Symmetry operation: (*i*) *x,y,z*; (*ii*) 1 + *x,y*,1 + *z*; (*iii*) 1 − *x*, ½ + *y*,1 − *z*; (*iv*) −1 + *x,y,z*; (*v*) −1 + *x,y*, −1 + *z*; (*vi*) −*x*,½ + *y*,1 − *z*.

The hydrogen bonding. — The hydrogen-bond geometry (Table IV) shows some interesting features. The molecular conformation is stabilized by a three-center unsymmetrical intramolecular hydrogen-bond from N-7–H to the primary alcohol hydroxyl group (O-5′–H) and the ring oxygen atom (O-4′). There is no intramolecular hydrogen bond between O-2′–H and O-3′–H such as had been observed in the crystal structure of anhydrous xanthosine[6].

As shown in Fig. 1, the hydrogen bonding forms a cooperative cycle consisting of the formamide group, two hydroxyl groups, and the water molecule. The other hydrogen of the water molecule bonds to a C=O group. All of the functional

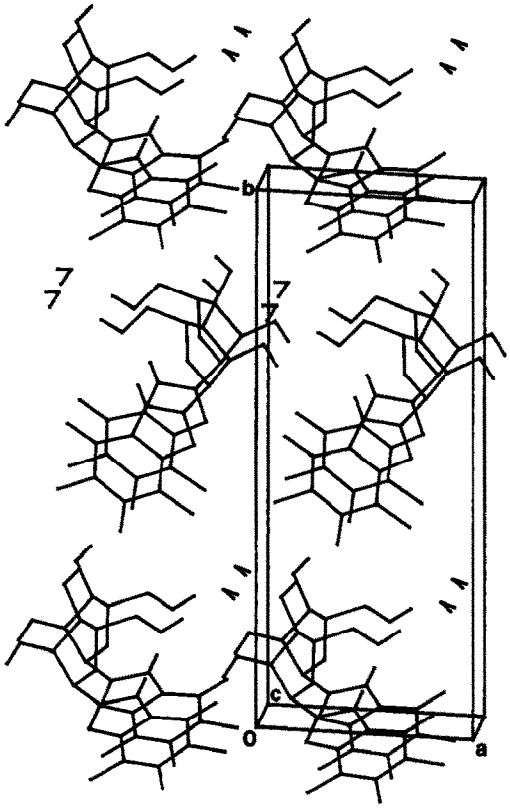


Fig. 2. The crystal structure of 1,3-dimethyl-8-β-ribofuranosylxanthine monohydrate viewed down the *c* axis.

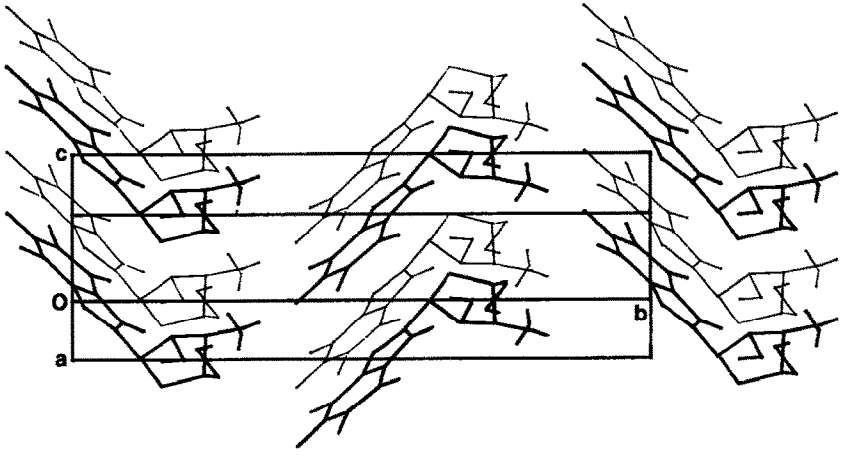


Fig. 3. The crystal structure of 1,3-dimethyl-8-β-ribofuranosylxanthine monohydrate viewed down the [101] axis.

hydrogen-bonding groups are involved. The water molecule is three-coordinated (pyramidal) and each carbonyl oxygen accepts only one hydrogen bond.

The molecular packing. — The molecular packing is shown in Fig. 2. The molecules form stacks with parallel xanthine rings separated by 3.40 Å. The planes of the rings are inclined by 80° to each other in adjacent stacks. Viewed in the [101] direction, as shown in Fig. 3, there are alternate rows of hydrogen-bonded ribose moieties and stacked xanthine rings.

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