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Precursors in the Biosynthesis of Purine Nucleotides. The Crystal Structures of 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR) and its 5′-(Dihydrogen Phosphate)

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Abstract

The structures of the title compounds, $C_9H_{14}N_4O_5$ and $C_9H_{15}N_4O_8P.H_2O$, have been determined. The nucleoside is monoclinic with $a = 10{\cdot}783\ (3)$, $b = 10{\cdot}206\ (3)$, $c = 5{\cdot}037\ (2)$ Å, $\beta = 94{\cdot}1\ (2)°$, $Z = 2$, space group $P2_1$. The nucleotide is orthorhombic, space group $P2_12_12_1$, with $a = 4{\cdot}777\ (2)$, $b = 17{\cdot}259\ (3)$, $c = 17{\cdot}077\ (3)$ Å, $Z = 4$. Both structures were solved by direct methods and refined to $R = 0{\cdot}039$ and $0{\cdot}058$ for the nucleoside and nucleotide respectively. Ribose puckerings are C(2′)-*endo*,C(3′)-*exo* in the nucleoside and C(2′)-*exo*,C(3′)-*endo* in the nucleotide. The conformation about C(4′)–C(5′) is *gauche–gauche* and both molecules exist in the preferred *anti* form. The nucleotide exists as a zwitterion with N(3) protonated. In both molecules, the 4-carboxamide residue is oriented such that a strong intramolecular hydrogen bond is formed to the amino group at position 5 of the heterocycles. In the crystal structures, all the donor and acceptor groups of the heterocycles are further involved in intermolecular hydrogen bonds.

Introduction

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-(dihydrogen phosphate) (AICAR-5′-P) plays a role as central intermediate in the biosynthesis of purine nucleotides (Lehninger, 1976; Litchfield & Shaw, 1971). Its unique structure shows possibilities of intra- and intermolecular interactions which are important from chemical and biochemical points of view. X-ray analyses of this compound and of the corresponding nucleoside (AICAR) were carried out in order to find a key for suitable chemical substitution to transform this metabolite into an antimetabolite. The atomic nomenclature is depicted in Fig. 1.

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Experimental

AICAR and AICAR-5′-P were kindly supplied by Boehringer–Mannheim, Tutzing, and recrystallized from water to yield prismatic crystals. Intensities for both compounds were recorded with an automatic Stoe four-circle diffractometer operated in the $\theta/2\theta$ scan mode (Ni-filtered Cu $K\alpha$ radiation) and corrected for Lorentz and polarization factors but not for absorption. Crystal and intensity-measurement data are given in Table 1. By the use of Wilson's (1942) method, overall temperature and scale factors were evaluated for both data sets and used to compute normalized structure factors (Karle & Hauptman, 1956). The structures were solved with *MULTAN* (Germain, Main & Woolfson, 1970) from all E's $> 1{\cdot}3$ for the nucleoside and $>1{\cdot}5$ for the nucleotide. In each case, E maps calculated with the most consistent of 64 phase sets revealed the complete structures except the H atoms. Full-matrix least-squares cycles (Busing, Martin & Levy, 1962) were carried out refining non-hydrogen atoms anisotropically. The weighting scheme applied was based on counter statistics with a 2% allowance for machine instability (Stout & Jensen, 1968).

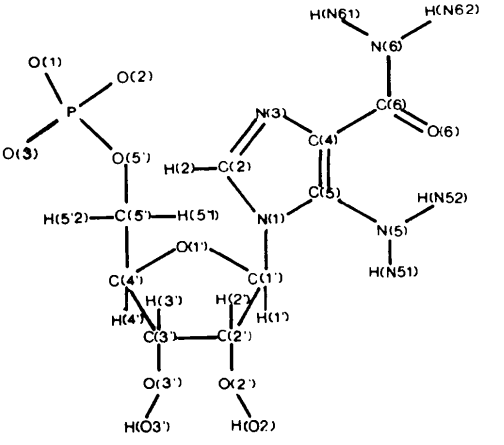

Fig. 1. Numbering scheme for the nucleoside and nucleotide.

Positions of H atoms were calculated geometrically and compared with difference maps. Their coordinates were refined and the final $R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.039$ for the nucleoside and 0·058 for the nucleotide. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974).

Table 1. *Crystal and intensity-measurement data*

	Nucleoside	Nucleotide
Formula	$C_9H_{14}N_4O_5$	$C_9H_{15}N_4O_8P.H_2O$
System	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
Unit-cell parameters:		
a	10·783 (3) Å	4·777 (2) Å
b	10·206 (3)	17·259 (3)
c	5·037 (2)	17·077 (3)
β	94·1 (2)°	
Z	2	4
Calculated density	1·55 Mg m^{-3}	1·68 Mg m^{-3}
Crystal dimensions	0·20 × 0·18 × 0·50 mm	0·45 × 0·23 × 0·20 mm
2θ scan rate	1° min^{-1}	
Time for reflexion	40 s	
Time for each background	10 s	
Number of independent reflexions	1026	1245

Table 2. *Fractional coordinates for the nucleoside*

E.s.d.'s for the last decimal place are given in parentheses.

	x	y	z
O(1′)	0·6496 (2)	0·7466 (0)	0·4282 (5)
C(1′)	0·7592 (3)	0·7462 (5)	0·5965 (7)
C(2′)	0·7502 (3)	0·6334 (5)	0·7911 (7)
O(2′)	0·8679 (2)	0·5774 (4)	0·8684 (6)
C(3′)	0·6685 (3)	0·5358 (5)	0·6271 (7)
O(3′)	0·7399 (3)	0·4611 (4)	0·4564 (7)
C(4′)	0·5830 (3)	0·6242 (5)	0·4553 (7)
C(5′)	0·4571 (3)	0·6516 (6)	0·5575 (8)
O(5′)	0·4690 (2)	0·6953 (4)	0·8275 (5)
N(1)	0·7716 (3)	0·8744 (4)	0·7284 (6)
C(2)	0·6874 (3)	0·9222 (5)	0·8991 (8)
N(3)	0·7133 (3)	1·0420 (4)	0·9708 (7)
C(4)	0·8210 (3)	1·0758 (5)	0·8463 (7)
C(5)	0·8554 (3)	0·9723 (5)	0·6912 (7)
N(5)	0·9529 (3)	0·9595 (4)	0·5374 (7)
C(6)	0·8812 (3)	1·2011 (4)	0·8773 (7)
N(6)	0·8277 (3)	1·2907 (4)	1·0240 (8)
O(6)	0·9810 (2)	1·2242 (4)	0·7724 (6)
H(1′)	0·8336 (34)	0·7275 (43)	0·4791 (82)
H(2′)	0·6997 (34)	0·6676 (44)	0·9443 (81)
H(O2′)	0·8987 (36)	0·6404 (47)	1·0017 (82)
H(3′)	0·6160 (27)	0·4704 (40)	0·7541 (80)
H(O3′)	0·8029 (53)	0·4266 (61)	0·5333 (71)
H(4′)	0·5713 (33)	0·5840 (43)	0·2729 (82)
H(5′1)	0·4034 (34)	0·5697 (40)	0·5451 (79)
H(5′2)	0·4098 (34)	0·7200 (48)	0·4401 (89)
H(O5′)	0·4121 (37)	0·6452 (49)	0·9082 (89)
H(2)	0·6125 (41)	0·8753 (49)	0·9372 (94)
H(N51)	0·9595 (32)	0·9040 (40)	0·4308 (74)
H(N52)	0·9841 (35)	1·0299 (45)	0·4973 (92)
H(N61)	0·7571 (35)	1·2769 (46)	1·1061 (84)
H(N62)	0·8600 (39)	1·3607 (48)	1·0363 (87)

Atomic parameters for the nucleoside and nucleotide are listed in Tables 2 and 3 respectively.*

Description of the structures and discussion

The two molecules exist in differently ionized states; the nucleoside is neutral while the nucleotide occurs as a zwitterion with the phosphate group negatively charged and N(3) protonated.

Bond distances and angles are given in Tables 4 and 5, torsion angles in Table 6. Geometrical data for the imidazole moieties correspond to those described for the neutral and protonated parts in guanine (Voet & Rich, 1970). Slight differences are evident in the

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34101 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Fractional coordinates for the nucleotide*

E.s.d.'s for the last decimal place are given in parentheses.

	x	y	z
P	1·0057 (4)	0·8439 (0)	0·3769 (1)
O(1)	0·7602 (9)	0·8524 (2)	0·4306 (2)
O(2)	1·2394 (11)	0·7964 (3)	0·4197 (3)
O(3)	1·1251 (11)	0·9161 (2)	0·3429 (2)
O(5′)	0·8990 (9)	0·7881 (2)	0·3086 (2)
O(1′)	1·0816 (9)	0·6356 (2)	0·2700 (2)
C(1′)	0·8919 (14)	0·5743 (3)	0·2568 (3)
C(2′)	0·7337 (14)	0·5914 (3)	0·1807 (3)
O(2′)	0·8947 (10)	0·5644 (2)	0·1160 (2)
C(3′)	0·7431 (15)	0·6803 (3)	0·1814 (3)
O(3′)	0·6750 (11)	0·7172 (2)	0·1115 (3)
C(4′)	1·0390 (14)	0·6948 (3)	0·2104 (3)
C(5′)	1·0908 (15)	0·7738 (3)	0·2455 (3)
N(1)	0·6957 (11)	0·5695 (3)	0·3239 (3)
C(2)	0·6526 (14)	0·6226 (3)	0·3807 (3)
N(3)	0·4541 (11)	0·5987 (3)	0·4276 (3)
C(4)	0·3608 (15)	0·5260 (3)	0·4011 (3)
C(5)	0·5133 (15)	0·5083 (3)	0·3352 (3)
N(5)	0·4932 (14)	0·4471 (3)	0·2870 (3)
C(6)	0·1409 (15)	0·4777 (4)	0·4343 (4)
N(6)	0·0252 (14)	0·4989 (3)	0·5027 (3)
O(6)	0·0669 (11)	0·4194 (3)	0·3974 (3)
O(*W*)	0·3451 (12)	−0·1719 (3)	0·0316 (3)
H(1′)	0·9837	0·5262	0·2577
H(2′)	0·5354	0·5592	0·1789
H(O2′)	0·9123	0·5196	0·1138
H(3′)	0·6155	0·6861	0·2213
H(O3′)	0·7100	0·6882	0·0679
H(4′)	1·1778	0·6945	0·1616
H(5′1)	1·1009	0·8157	0·2045
H(5′2)	1·3095	0·7584	0·2785
H(2)	0·7018	0·6657	0·3761
H(N51)	0·6032	0·4363	0·2608
H(N52)	0·3875	0·4222	0·3061
H(N61)	−0·0612	0·4713	0·5249
H(N62)	0·0665	0·5383	0·5115
H(N3)	0·9167	0·8777	0·5216

elongated N(3)–C(4) and C(4)–C(5) bonds as a result of the amide group substituent. The imidazole rings are planar within ±0·01 Å, the amide and amino substituents deviating slightly (Table 7). The latter form a nearly planar six-membered ring, with hydrogen-bond formation between amino group and amide O atom. Partial double-bond character is observed for the unusually short C(4)–C(6) bond (Table 8) due to conjugation of the amide group with the imidazole ring. In the comparable salicylamide acid, C_α–C (1·479 Å) is longer than observed here but the C–N and C–O distances are similar (Hsu & Craven, 1974).

Bond lengths and angles in the ribose rings are generally in good agreement with averaged values for the ribose moieties of C(2′)-*endo* and C(3′)-*endo* nucleosides (Saenger & Eckstein, 1970). Slight deviations may be due to hydrogen-bonding and packing effects. Ribose puckering in the nucleoside is C(2′)-*endo*, C(3′)-*exo* with displacements C(2′) 0·347, C(3′) −0·203, C(5′) 1·256 Å, from the C(1′)–O(1′)–C(4′) plane. For the nucleotide, C(3′)-*endo* puckering is observed with displacements C(2′) −0·122, C(3′) 0·547, C(5′) 0·800 Å. The conformation about C(4′)–C(5′) is *gauche*, *gauche* (Table 6), and both molecules exist in the preferred *anti* form.

The phosphate group is negatively charged, the charge being equally distributed between O(1) and O(3); the respective P–O lengths are 1·497 and 1·488 Å. The P–O(5′) ester bond, 1·595 Å, is significantly longer as is P–O(2), 1·566 Å. O(2) probably carries a

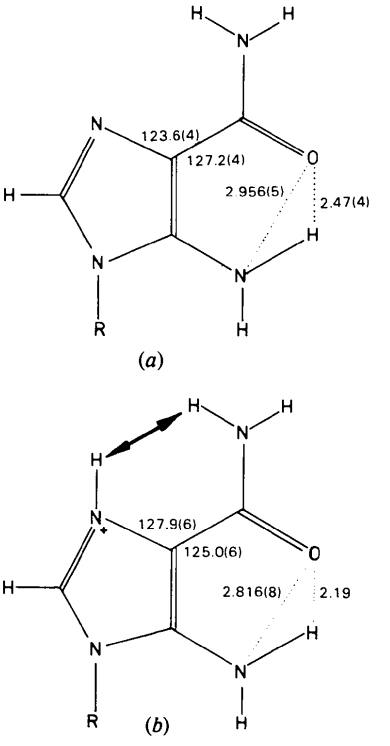

Fig. 2. Short intramolecular contacts (Å) (*a*) in the nucleoside, (*b*) in the nucleotide. Note changes in the geometry around C(4) when N(3) becomes protonated in the nucleotide zwitterion. In that case, the protons attached to N(3) and N(6) are too close and the molecule widens the angle at C(4) to relieve steric strain.

Table 4. *Bond distances* (Å) *with e.s.d.'s in parentheses*

	Nucleoside	Nucleotide		Nucleoside	Nucleotide		Nucleoside	Nucleotide
O(1′)–C(1′)	1·405 (4)	1·411 (7)	C(4′)–C(5′)	1·512 (5)	1·509 (8)	C(5)–N(5)	1·355 (5)	1·342 (7)
O(1′)–C(4′)	1·453 (5)	1·457 (7)	C(5′)–O(5′)	1·428 (5)	1·437 (8)	C(6)–N(6)	1·333 (6)	1·343 (8)
C(1′)–C(2′)	1·520 (6)	1·532 (8)	N(1)–C(2)	1·384 (5)	1·350 (7)	C(6)–O(6)	1·255 (5)	1·239 (8)
C(1′)–N(1)	1·469 (6)	1·484 (8)	N(1)–C(5)	1·369 (5)	1·383 (8)	P–O(1)		1·497 (5)
C(2′)–O(2′)	1·421 (5)	1·426 (7)	C(2)–N(3)	1·299 (6)	1·308 (8)	P–O(2)		1·566 (5)
C(2′)–C(3′)	1·533 (6)	1·534 (8)	N(3)–C(4)	1·402 (5)	1·406 (8)	P–O(3)		1·488 (4)
C(3′)–O(3′)	1·417 (5)	1·391 (7)	C(4)–C(6)	1·437 (6)	1·455 (9)	P–O(5′)		1·595 (4)
C(3′)–C(4′)	1·516 (6)	1·519 (9)	C(4)–C(5)	1·381 (6)	1·376 (8)			

Table 5. *Bond angles* (°) *with e.s.d.'s in parentheses*

	Nucleoside	Nucleotide		Nucleoside	Nucleotide		Nucleoside	Nucleotide
C(1′)–O(1′)–C(4′)	109·9 (3)	108·9 (4)	C(4′)–C(5′)–O(5′)	111·1 (4)	110·5 (5)	C(4)–C(5)–N(5)	130·4 (4)	129·7 (6)
O(1′)–C(1′)–C(2′)	107·5 (3)	107·9 (5)	C(1′)–N(1)–C(2)	123·5 (3)	127·8 (5)	C(4)–C(6)–N(6)	117·4 (4)	118·6 (6)
C(1′)–C(2′)–O(2′)	112·6 (3)	109·1 (5)	C(1′)–N(1)–C(5)	128·8 (3)	123·7 (5)	C(4)–C(6)–O(6)	121·1 (4)	118·3 (6)
C(1′)–C(2′)–C(3′)	101·9 (3)	99·9 (5)	C(2)–N(1)–C(5)	107·3 (3)	108·9 (5)	N(6)–C(6)–O(6)	121·5 (4)	123·1 (6)
O(2′)–C(2′)–C(3′)	110·7 (3)	108·5 (5)	N(1)–C(2)–N(3)	111·5 (4)	109·6 (5)	P–O(5′)–C(5′)		116·7 (4)
C(2′)–C(3′)–O(3′)	111·1 (3)	116·5 (5)	C(2)–N(3)–C(4)	106·0 (3)	108·4 (5)	O(1)–P–O(2)		108·9 (2)
C(2′)–C(3′)–C(4′)	102·9 (3)	101·3 (5)	N(3)–C(4)–C(6)	123·6 (4)	127·9 (6)	O(1)–P–O(3)		117·2 (2)
O(3′)–C(3′)–C(4′)	108·0 (3)	114·9 (5)	N(3)–C(4)–C(5)	109·2 (3)	107·0 (5)	O(1)–P–O(5′)		104·9 (2)
O(1′)–C(4′)–C(3′)	106·4 (3)	104·0 (5)	C(6)–C(4)–C(5)	127·2 (4)	125·0 (6)	O(2)–P–O(3)		110·3 (3)
O(1′)–C(4′)–C(5′)	109·5 (3)	109·4 (5)	N(1)–C(5)–C(4)	105·9 (3)	106·1 (5)	O(2)–P–O(5′)		104·7 (2)
C(3′)–C(4′)–C(5′)	116·1 (3)	115·6 (5)	N(1)–C(5)–N(5)	123·7 (4)	124·1 (5)	O(3)–P–O(5′)		110·0 (2)

Table 6. *Torsion angles (°) with e.s.d.'s in parentheses*

The torsion angles $A-B-C-D$ are defined as zero when, looking down the central $B-C$ bond, $A-B$ and $C-D$ are *cis*-planar to each other, and regarded as positive when $C-D$ is twisted clockwise relative to $A-B$.

	Nucleoside	Nucleotide
O(1′)–C(1′)–C(2′)–O(2′)	148·1 (3)	85·0 (6)
O(1′)–C(1′)–C(2′)–C(3′)	29·5 (4)	−28·7 (6)
O(1′)–C(1′)–N(1)–C(2)	62·7 (4)	14·0 (8)
O(1′)–C(1′)–N(1)–C(5)	−110·0 (4)	−169·3 (5)
O(1′)–C(4′)–C(3′)–C(2′)	26·0 (4)	−39·0 (6)
O(1′)–C(4′)–C(3′)–O(3′)	−91·6 (4)	−165·4 (5)
O(1′)–C(4′)–C(5′)–O(5′)	−69·3 (4)	−60·8 (6)
C(1′)–O(1′)–C(4′)–C(3′)	−8·0 (4)	21·7 (6)
C(1′)–O(1′)–C(4′)–C(5′)	118·2 (3)	145·8 (5)
C(1′)–C(2′)–C(3′)–O(3′)	82·4 (4)	165·6 (5)
C(1′)–C(2′)–C(3′)–C(4′)	−32·9 (4)	40·2 (6)
C(1′)–N(1)–C(2)–N(3)	−174·4 (4)	177·2 (5)
C(1′)–N(1)–C(5)–C(4)	175·1 (4)	−177·8 (5)
C(1′)–N(1)–C(5)–N(5)	−7·3 (6)	−0·1 (9)
C(2′)–C(1′)–O(1′)–C(4′)	−13·9 (4)	4·8 (6)
C(2′)–C(1′)–N(1)–C(2)	−56·4 (5)	−104·5 (7)
C(2′)–C(1′)–N(1)–C(5)	130·9 (4)	72·1 (7)
C(2′)–C(3′)–C(4′)–C(5′)	−96·1 (4)	−159·0 (5)
O(2′)–C(2′)–C(1′)–N(1)	−92·3 (4)	−155·8 (5)
O(2′)–C(2′)–C(3′)–O(3′)	−37·6 (4)	51·4 (7)
O(2′)–C(2′)–C(3′)–C(4′)	−152·9 (3)	−74·0 (6)
C(3′)–C(2′)–C(1′)–N(1)	149·1 (3)	90·5 (5)
C(3′)–C(4′)–C(5′)–O(5′)	51·1 (5)	56·1 (7)
O(3′)–C(3′)–C(4′)–C(5′)	146·3 (4)	74·6 (7)
C(4′)–O(1′)–C(1′)–N(1)	−136·4 (3)	−115·6 (5)
N(1)–C(2)–N(3)–C(4)	−0·9 (5)	0·3 (7)
N(1)–C(5)–C(4)–N(3)	−2·0 (4)	0·7 (7)
N(1)–C(5)–C(4)–C(6)	179·2 (4)	179·4 (6)
C(2)–N(1)–C(5)–C(4)	1·4 (4)	−0·6 (7)
C(2)–N(1)–C(5)–N(5)	179·1 (4)	177·1 (6)
C(2)–N(3)–C(4)–C(6)	−179·3 (4)	−179·2 (6)
C(2)–N(3)–C(4)–C(5)	1·9 (5)	−0·6 (7)
N(3)–C(2)–N(1)–C(5)	−0·3 (5)	0·2 (7)
N(3)–C(4)–C(5)–N(5)	−179·5 (4)	−176·7 (6)
C(6)–C(4)–C(5)–N(5)	1·8 (7)	1·9 (9)
N(3)–C(4)–C(6)–N(6)	−2·9 (6)	−7·2 (9)
N(3)–C(4)–C(6)–O(6)	176·3 (4)	171·9 (6)
N(6)–C(6)–C(4)–C(5)	175·7 (4)	174·4 (6)
O(6)–C(6)–C(4)–C(5)	−5·1 (7)	−6·5 (9)
P–O(5′)–C(5′)–C(4′)		150·8 (4)
O(1)–P–O(5′)–C(5′)		176·4 (4)
O(2)–P–O(5′)–C(5′)		−69·1 (4)
O(3)–P–O(5′)–C(5′)		49·4 (5)
O(5′)–P–C(4′)–O(1′)		−60·8 (6)
O(5′)–C(5′)–C(4′)–C(3′)		56·1 (7)

Table 7. *Least-squares planes*

The equations are of the form $lx + my + nz + p = 0$ where x,y,z are along a,b,c^* (nucleoside) and along a,b,c (nucleotide). Atoms which define the planes are marked with an asterisk. Average e.s.d.'s are (±) 0·003 for the nucleoside and (±) 0·005 Å for the nucleotide.

Equations of the imidazole ring (*A*):

Nucleoside: $-0{\cdot}5199X + 0{\cdot}3461Y - 0{\cdot}7810Z + 3{\cdot}9535 = 0$
Nucleotide: $-0{\cdot}6830X + 0{\cdot}4534Y - 0{\cdot}5727Z + 0{\cdot}9798 = 0$

Deviations (Å) from the planes

	Nucleoside	Nucleotide		Nucleoside	Nucleotide
N(1)*	−0·005	−0·002	N(5)	−0·007	0·062
C(2)*	−0·002	−0·001	C(6)	−0·022	0·010
C(3)*	0·008	0·004	N(6)	0·047	−0·115
C(4)*	−0·011	−0·005	O(6)	−0·108	0·156
C(5)*	0·010	0·004			

Equations of the ring *B*:

Nucleoside: $-0{\cdot}4915X + 0{\cdot}3732Y - 0{\cdot}7868Z + 3{\cdot}4354 = 0$
Nucleotide: $-0{\cdot}6545X + 0{\cdot}5141Y - 0{\cdot}5544Z + 0{\cdot}2761 = 0$

Deviations (Å) from the planes

	Nucleoside	Nucleotide		Nucleoside	Nucleotide
C(4)*	−0·014	0·018	C(6)*	0·027	−0·037
C(5)*	−0·005	0·008	O(6)*	−0·018	0·026
N(5)*	0·010	−0·016	N(6)	0·098	−0·135

Table 8. *Comparison of bond lengths* (Å) *in the amide groups*

	C···N	C···O	C_α–C
Nucleoside	1·333 (6)	1·255 (5)	1·437 (6)
Nucleotide	1·343 (8)	1·239 (8)	1·455 (9)
Salicylamide acid	1·323 (2)	1·253 (2)	1·479 (3)

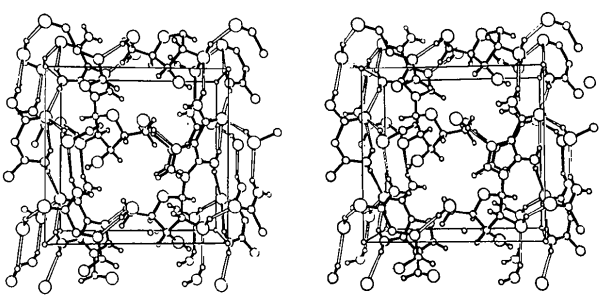

Fig. 3. A stereoscopic view of the crystal structure of the nucleoside viewed along *c*.

H atom which, however, could not be located from difference maps.

In the crystal structure of the nucleoside, all potential hydrogen-bond donors and acceptors are involved in hydrogen-bond formation except O(2′) and H(N61) (Figs. 2 and 3 and Table 9). In the nucleotide structure, the hydrogen-bonding scheme utilizes all donor and acceptor sites except one donor site at N(6), the scheme being even more complicated due to the presence of a water molecule of hydration. The H atom attached to O(2) is evidenced by the O(2)–H···O(1) interaction, 2·676 Å (Table 10 and Fig. 4).

A recent systematic study (Kálmán, Párkányi, Schawartz & Simon, 1978) on substituted 5-amino-imidazole- and -1,2,3-triazole-4-carboxamides revealed that in all cases the same intramolecular hydrogen bond is formed between the vicinal 5-amino and 4-carbox-

Table 9. *Distances* (Å) *and angles* (°) *for possible intermolecular hydrogen-bonded contacts in the nucleoside*

	A–*B*	H···*B*	∠*A*–H···*B*
O(5′)–H(O5′)···N(3^{i})	2·762 (5)	1·851 (35)	172·8 (9)
N(5)–H(N51)···O(7^{ii})	2·978 (6)	2·218 (42)	162·4 (10)
O(2′)–H(O2′)···O(7^{iii})	2·784 (6)	1·870 (45)	155·7 (9)
N(6)–H(N62)···O(2′^{iv})	3·068 (5)	2·372 (38)	146·8 (8)

Symmetry code

None	x,y,z	(iii)	$2-x,-\frac{1}{2}+y,2-z$
(i)	$1-x,-\frac{1}{2}+y,2-z$	(iv)	$x,1+y,z$
(ii)	$2-x,-\frac{1}{2}+y,1-z$		

Table 10. *The shorter intermolecular contacts* (Å) *in the nucleotide*

O(*W*)···O(2′)	3·155 (8)	O(1)···N(3^{iv})	2·727 (8)
O(*W*)···O(3′)	2·838 (8)	O(1)···N(6^{iv})	3·024 (8)
O(*W*)···O(3′^{i})	2·673 (7)	O(3)···N(5^{ii})	2·921 (7)
O(*W*)···O(6^{ii})	2·798 (8)	N(6)···O(2′^{iii})	2·994 (7)
O(1)···O(2^{iii})	2·676 (7)		

Symmetry code

None	x,y,z	(iii)	$-1+x,y,z$
(i)	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$	(iv)	$\frac{1}{2}+x,\frac{3}{2}-y,1-z$
(ii)	$\frac{3}{2}-x,1-y,-\frac{1}{2}+z$		

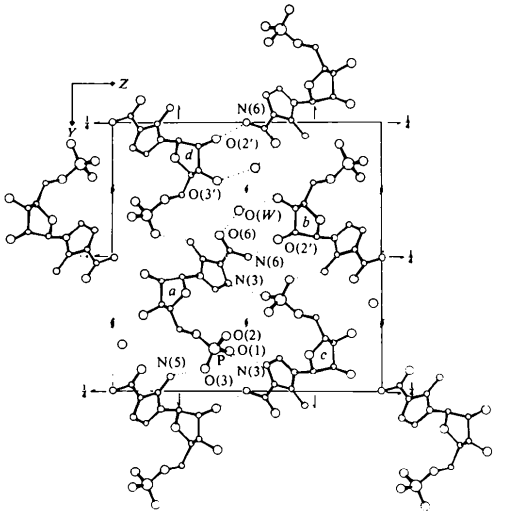

Fig. 4. The molecular-packing diagram of the nucleotide excluding H atoms, viewed down *a*.

amide groups. This particular structural feature requires that, in the purine biosynthesis, ring closure to produce the pyrimidine moiety of the resulting hypoxanthine heterocycle is only possible if the 4-carboxamide group rotates by 180° out of its preferred orientation.

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