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7-Amino-1-(2-deoxy-β-*erythro*-pentofuranosyl)-1*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine: an 8-azaadenine nucleoside with the nucleobase in a *syn* conformation

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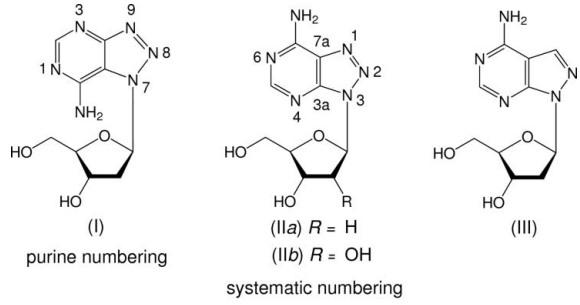
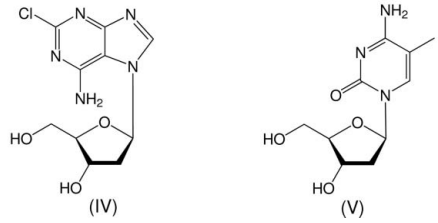
The title compound, $C_9H_{12}N_6O_3$, shows a *syn*-glycosylic bond orientation [χ = 64.17 (16)°]. The 2′-deoxyfuranosyl moiety exhibits an unusual C1′-*exo*–O4′-*endo* ($_1T^0$; *S*-type) sugar pucker, with P = 111.5 (1)° and τ_m = 40.3 (1)°. The conformation at the exocyclic C4′—C5′ bond is +*sc* (*gauche*), with γ = 64.4 (1)°. The two-dimensional hydrogen-bonded network is built from intermolecular N—H···O and O—H···N hydrogen bonds. An intramolecular bifurcated hydrogen bond, with an amino N—H group as hydrogen-bond donor and the ring and hydroxymethyl O atoms of the sugar moiety as acceptors, constrains the overall conformation of the nucleoside.

Comment

The formation of regioisomeric glycosylation products is a common problem in nucleoside synthesis and has been investigated in detail for purine nucleosides (Garner & Ramakanth, 1988; Robins *et al.*, 1996; Golankiewicz *et al.*, 2002). It was reported that the outcome of the glycosylation reaction depends on the catalyst, solvent, temperature and time, and is also influenced by the structure of the base and the activated sugar. Under kinetically controlled conditions, the formation of the N7-isomer is favoured, whereas the N9-isomers predominate under thermodynamic control (Garner & Ramakanth, 1988). The incorporation of unusual N7-glycosylated nucleosides into DNA can lead to new base-pairing modes and eventually to new DNA structures. N7-Glycosylated adenine and guanine form stable base pairs in double-stranded DNA (Seela & Winter, 1993, 1994; Seela & Leonard, 1996, 1997) and triplex DNA (Hunziker *et al.*, 1995; Brunar & Dervan, 1996).





Glycosylation of 8-azapurines is further complicated, due to the additional N atom enlarging the number of regioisomers. The synthesis of 8-aza-2′-deoxyadenosine, (II*a*), was first described by Tong *et al.* (1965), followed by other reports employing various protocols (Montgomery & Thomas, 1972; Kazimierczuk *et al.*, 1989; Rose *et al.*, 2002). Our laboratory used nucleobase–anion glycosylation conditions (NaH, MeCN) for the synthesis and isolated 8-aza-2′-deoxyadenosine, (II*a*), and its N7-isomer, the title compound, (I) (Kazimierczuk *et al.*, 1989).

We report here the conformation and hydrogen bonding of (I) in the crystalline state and compare the structure with those of the related molecules of 8-azaadenosine, (II*b*) (Singh & Hodgson, 1974, 1977), 8-aza-7-deaza-2′-deoxyadenosine, (III) (Seela *et al.*, 1999), and the N-7 regioisomer of 2-chloro-2′-deoxyadenosine, (IV) (Worthington *et al.*, 1995). The three-dimensional structure of (I) is shown in Fig. 1 and selected geometric parameters are listed in Table 1.

For the common N9-glycosylated purine nucleosides, the orientation of the nucleobase relative to the sugar moiety (*syn*/*anti*) is defined by the torsion angle χ(O4′—C1′—N9—C4) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983). The corresponding torsion angle in (I), χ(O4′—C1′—N7—C5) = 64.17 (16)°, reflects a *syn* conformation. This is in contrast with the usually preferred *anti* conformation at the N-glycosylic bond of the common purine nucleosides (Saenger, 1984). However, inspection of the hydrogen-bonding pattern of (I) reveals a bifurcated intramolecular hydrogen bond between the amino group of the nucleobase and atoms O5′ and O4′ of the sugar moiety, imposing the *syn* conformation of nucleoside (I). A very similar situation was observed for the closely related N-7 regioisomer of 2-chloro-2′-deoxyadenosine, (IV). In this case,

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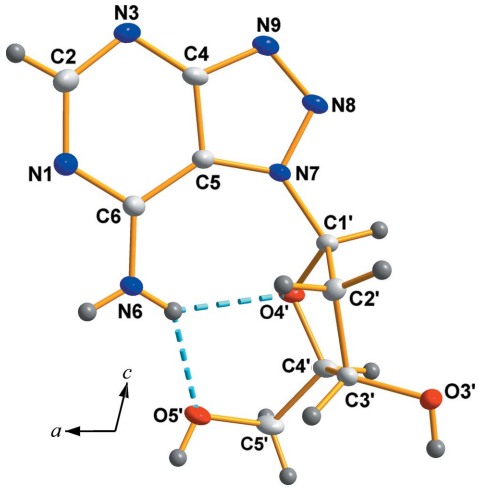

Figure 1
A perspective view of the molecule of (I), showing the intramolecular bifurcated hydrogen bond (dashed lines) and the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

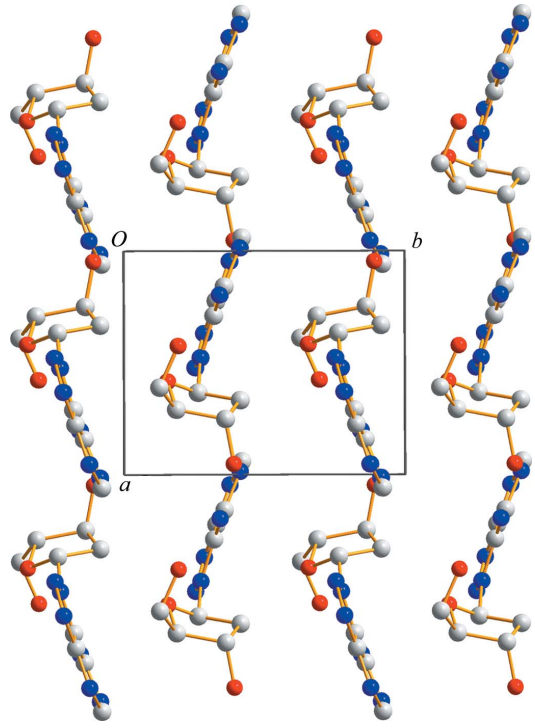

Figure 2
The crystal packing of (I), showing the 'staircase'-like arrangement of nucleosides. For the sake of clarity, H atoms have been omitted.

the *syn* conformation (χ = 67.0°) is also stabilized by a bifurcated intramolecular hydrogen bond, with atom H6 of the amino group as donor and atoms O5′ and O4′ of the glycon as acceptors (Worthington *et al.*, 1995).

The regular 8-azaadenine ribonucleoside, (II*b*), with atom N9 as the glycosylation site, shows a conformation within the high-*anti* range, with χ = −78.0° (Singh & Hodgson, 1974, 1977). The corresponding 8-aza-7-deaza-2′-deoxyadenosine, (III), however, adopts an *anti* conformation of the glycosyl bond [χ = −106.3 (2)°; Seela *et al.*, 1999]. The length of the N7—C1′ glycosylic bond is 1.459 (1) Å for (I), which is longer than the N9—C1′ glycosylic bonds of 8-azaadenosine, (II*b*) [1.447 (3) Å; Singh & Hodgson, 1974, 1977], and 8-aza-7-deaza-2′-deoxyadenosine, (III) [1.442 (2) Å; Seela *et al.*, 1999].

C2′-*endo* (south, *S*) and C3′-*endo* (north, *N*) are the most frequently observed sugar-ring conformations of nucleosides (Saenger, 1984). In the crystalline state of (I), the sugar moiety shows a less common conformation with a major C1′-*exo* sugar pucker (C1′-*exo*–O4′-*endo*, ${}_1T^0$), corresponding to an *S*-type. The pseudorotation phase angle *P* is 111.5 (1)° and the maximum amplitude τ_m is 40.3 (1)°. Again, the situation is very close to that of the N-7 regioisomer of 2-chloro-2′-deoxyadenosine, (IV) (*S*-type, C1′-*exo*–O4′-*endo*, ${}_1T^0$, *P* = 110° and τ_m = 38.6°; Worthington *et al.*, 1995). The N9 nucleosides (II*b*) and (III) also adopt an *S* sugar-ring conformation, but with the common C2′-*endo* sugar pucker [in (II*b*), C2′-*endo*–C1′-*exo*, ${}^2T_1$; Singh & Hodgson, 1974, 1977; in (III), C2′-*endo*–C3′-*exo*, ${}^2T_3$ with *P* = 182.2 (2)° and τ_m = 41.2 (1)°; Seela *et al.*, 1999].

The conformation about the exocyclic C4′—C5′ bond is defined by the torsion angle γ(O5′—C5′—C4′—C3′), which is 64.36 (14)° for (I), corresponding to a +*sc* (*gauche*) conformation. This conformation was also observed for the hydroxy group of (IV) (γ = 57.8°; Worthington *et al.*, 1995). By contrast, for 8-azaadenosine, (II*b*) (γ = 179.1; Singh & Hodgson, 1974, 1977), and 8-aza-7-deaza-2′-deoxyadenosine, (III) [γ = −178.7 (2)°; Seela *et al.*, 1999], conformations about the C4′—C5′ bond were reported which are situated in the *ap* (*gauche*, *trans*) range. The 8-azapurine ring system of (I) is nearly planar. The deviations of the ring atoms from the least-squares plane of atoms N1/C2/N3/C4–C6/N7–N9 range from −0.054 (1) (atom C6) to 0.046 (1) Å (atom C2), with an r.m.s. deviation of 0.0337 Å. The C1′ substituent lies 0.261 (2) Å above this plane and atom N6 0.161 (2) Å below.

A nonsymmetric bifurcated intramolecular hydrogen bond (Table 2) is formed between N6—H6*B* of the amino group as donor and atoms O5′ and O4′ of the sugar residue as acceptors. According to Steiner (2002), for bifurcated hydrogen bonds with distinctly different hydrogen–acceptor separations, the shorter interaction is defined as the major component and the longer one as the minor. In the case of nucleoside (I), the major component of the bifurcated hydrogen bond is N6—H6*B*···O5′, with N6···O5′ = 2.8194 (15) Å and N6—H6*B*···O5′ = 138°. The minor component utilizes atom O4′ as acceptor, with N6···O4′ = 3.1676 (15) Å and N6—H6*B*···O4′ = 143°. A similar intramolecular bifurcated hydrogen-bonding pattern was also observed in the crystal structures of 2-chloro-2′-deoxyadenosine, (IV) (Worthington *et al.*, 1995), and 2′-deoxy-5-methylisocytidine, (V) (Seela *et al.*, 2000).

These findings indicate that the additional N atom of the 8-azapurine nucleoside, (I), compared with the corresponding purine nucleoside (IV) – both having the same glycosylation sites – has a negligible effect, and the intramolecular hydrogen bonding is mainly controlled by the spatial arrangement of the amino group in both nucleosides.

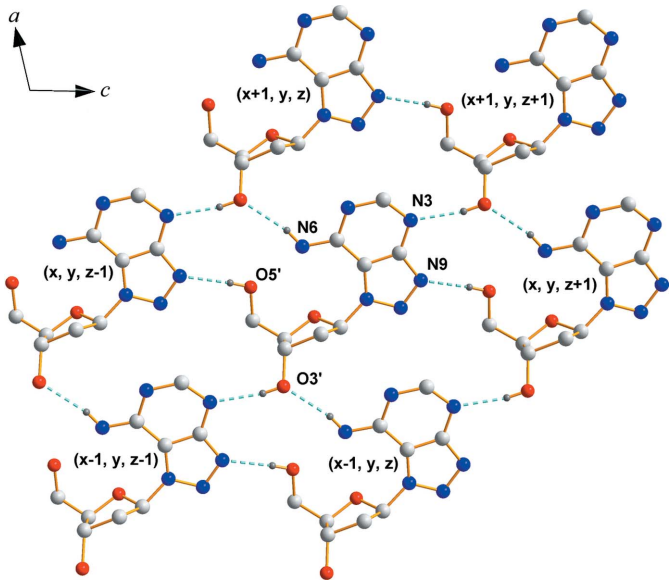

Figure 3
A detailed view of the two-dimensional hydrogen-bonded (dashed lines) network of (I). The projection is parallel to the *ac* plane. For the sake of clarity, H atoms not involved in the intermolecular hydrogen-bonding motifs shown have been omitted.

The crystal structure of (I) contains a two-dimensional hydrogen-bond network generated by translation. Within the crystal structure, the nucleosides form reverse-ordered strands with respect to each other. The sugar moieties are perpendicular to the nucleobases, leading to a 'staircase'-like arrangement of nucleosides within each strand (Fig. 2). Every second strand shows the same orientation, and the nucleobases are parallel to each other.

This highly ordered array is connected by several intermolecular hydrogen bonds (Fig. 3 and Table 2). The hydroxy groups of the sugar residues function as H-atom donors and atoms N3 and N9 of the heterocycle as H-atom acceptors (O3′—H3′O···N3^{ii} and O5′—H5′O···N9^{iii}; see Table 2 for symmetry codes and geometry), and another hydrogen-bond is found between the N6—H6*A* amino group and atom O3′ of the ribofuranosyl moiety (N6—H6*A*···O3′^{i}), leading to the formation of a hydrogen-bonded sheet parallel to (010) (Fig. 3).

Experimental

Compound (I) was synthesized as reported previously by Kazimierczuk *et al.* (1989). Slow crystallization from EtOH afforded (I) as colourless needles (decomposition >473 K). For the diffraction experiment, a single crystal was mounted on a MiTeGen MicroMesh fibre in a thin smear of oil.

Crystal data

$C_9H_{12}N_6O_3$
M_r = 252.25
Monoclinic, $P2_1$
a = 7.1469 (3) Å
b = 8.7025 (4) Å
c = 9.1100 (4) Å
β = 104.056 (2)°
V = 549.64 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.12 mm^{-1}
T = 130 K
0.25 × 0.25 × 0.20 mm

Table 1
Selected geometric parameters (Å, °).

N6—C6	1.3323 (14)	N7—C1′	1.4586 (14)
N7—N8	1.3464 (13)	N8—N9	1.3113 (15)
N6—C6—C5	124.36 (11)	C5—N7—C1′	131.66 (10)
N8—N7—C1′	117.76 (10)	N9—N8—N7	109.02 (10)
C2—N1—C6—N6	−175.31 (14)	O4′—C4′—C5′—O5′	−54.35 (13)
N8—N7—C1′—O4′	−127.06 (11)	C3′—C4′—C5′—O5′	64.36 (14)
C5—N7—C1′—O4′	64.17 (16)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N6—H6*B*···O5′	0.86	2.12	2.8194 (15)	138
N6—H6*B*···O4′	0.86	2.44	3.1676 (15)	143
N6—H6*A*···O3′^{i}	0.86	2.08	2.9211 (14)	164
O3′—H3O···N3^{ii}	0.82	2.01	2.8184 (14)	170
O5′—H5O···N9^{iii}	0.82	1.98	2.8027 (14)	176

Symmetry codes: (i) $x+1, y, z$; (ii) $x-1, y, z-1$; (iii) $x, y, z-1$.

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2008)
T_{min} = 0.971, T_{max} = 0.977
21532 measured reflections
1693 independent reflections
1673 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.028
$wR(F^2)$ = 0.076
S = 1.07
1693 reflections
165 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to an inconclusive value [0.4 (6)]. Therefore, 1693 Friedel equivalents were merged before the final refinement and the known configuration of the parent molecule was used to define the enantiomer of the final model. All H atoms were found in a difference Fourier synthesis. The OH groups were refined as rigid groups allowed to rotate but not to tilt, with O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O). The remaining H atoms were placed in geometrically idealized positions, with C—H = 0.93–0.98 Å and N—H = 0.86 Å, and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C,N).

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Release 5.1; Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *DIAMOND* (Brandenburg, 1999); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3369). Services for accessing these data are described at the back of the journal.

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