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2′-Deoxy-7-propynyl-7-deaza-adenosine: a DNA duplex-stabilizing nucleoside

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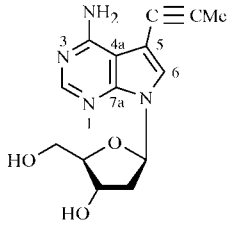
In the title compound, 2′-deoxy-7-propynyl-7-deazaadenosine, $C_{14}H_{16}N_4O_3$, the torsion angle of the N-glycosylic bond is *anti* [χ = −130.7 (2)°]. The sugar pucker of the 2′-deoxyribofuranosyl moiety is C2′-*endo*–C3′-*exo*, $^2T_3$ (*S*-type), with P = 185.9 (2)° and τ_m = 39.1 (1)°, and the orientation of the exocyclic C4′—C5′ bond is −*ap* (*trans*). The 7-substituted propynyl group is nearly coplanar with the heterocyclic base moiety. Molecules of the nucleoside form a layered network in which the heterocyclic bases are stacked head-to-tail with a closest distance of 3.197 (1) Å. The crystal structure of the nucleoside is stabilized by three intermolecular hydrogen bonds of types N—H···O, O—H···N and O—H···O.

Comment

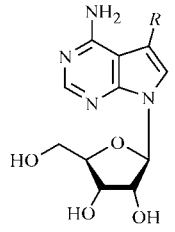
7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides occur naturally and have been isolated as monomers and as constituents of nucleic acids (Suhadolnik, 1970, 1979). Among them are ribonucleosides such as tubercidin, (II*a*), isolated from *Streptomyces tubercidicus* (Nakamura, 1961), as well as its 7-substituted derivatives toyocamycin, (II*b*), and sangivamycin, (II*c*), which are produced by *Streptomyces toyocaensis* or other *Streptomyces* strains (Nishimura *et al.*, 1956; Ohkuma, 1961) (see scheme; unless otherwise stated, purine numbering is used throughout this discussion). The natural occurrence and extraordinary biological and pharmacological properties of 7-deazapurine nucleosides have been the reasons for active study of their synthesis, their biochemical and physical properties, and their incorporation into nucleic acids. 7-Deazapurine 2′-deoxyribonucleosides are used as biochemical probes (Mizusawa *et al.*, 1986; Prober *et al.*, 1987; Seela *et al.*, 1993; Murchie & Lilley, 1994), in nucleic acid diagnostics (Bailly & Waring, 1998) and in antisense technology (Lamm *et al.*, 1991; Uhlmann *et al.*, 2000).

Among the various modifications carried out on purine and pyrimidine nucleosides to stabilize duplex and triplex DNA, the propynyl group has attracted particular attention. This group has been introduced into the 5-position of pyrimidine nucleosides (Froehler *et al.*, 1992; Sági *et al.*, 1993; Barnes & Turner, 2001*a*,*b*; Gutierrez *et al.*, 1997; Ahmadian *et al.*, 1998; Graham *et al.*, 1998) and the 7-position of 7-deazapurine or 8-aza-7-deazapurine nucleosides (Buhr *et al.*, 1996; He & Seela, 2002*a*,*b*; Seela & Shaikh, 2005). Our laboratory has shown that a propynyl group introduced into the 7-position of 8-aza-7-deazapurine exerts a stronger stabilizing effect on DNA duplexes (He & Seela, 2002*a*,*b*) than do the pyrimidine bases.

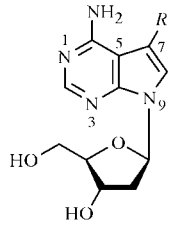
The introduction of the propynyl group at the 7-position of 7-deazaadenosine, (III*a*) (Seela & Thomas, 1995), lowers the pK_a value. The title compound, (I), shows a pK_a of 4.5, while the non-fuctionalized nucleoside (III*a*) has a pK_a of 4.9. The incorporation of (I) into oligonucleotides significantly increases the stability of the Watson–Crick base pair dA–dT and the tandem base pair dA–dG in DNA (Seela, Budow *et al.*, 2005). The 7-propynyl residue of (I) also stabilizes DNA–RNA duplexes (Buhr *et al.*, 1996). Against this background, we became interested in undertaking a single-crystal X-ray analysis of compound (I) and present the results here.



(I)
systematic numbering



(II*a*) R = H
(II*b*) R = CN
(II*c*) R = $CONH_2$



(III*a*) R = H
(III*b*) R = I
purine numbering

Compound (I) was synthesized from (III*b*) (Buhr *et al.*, 1996). The three-dimensional structure of (I) {7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine} is shown in Fig. 1 and selected geometric parameters are listed in Table 1. The orientation of the nucleobase relative to the sugar moiety (*syn*/*anti*) is defined, in analogy with the purine nucleosides, by the torsion angle χ (O4′—C1′—N9—C4) (purine numbering; IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983); the preferred conformation around the N-glycosylic bond for natural purine 2′-deoxyribonucleosides is usually in the *anti* range. In the crystalline state of (I), the glycosylic bond torsion angle is *anti* [χ = −130.7 (2)°], which is similar to those of 2′-deoxy-7-iodotubercidin, (III*b*) [χ = −147.1 (8)°; Seela *et al.*, 1996] and 7-deaza-2′-deoxy-7-propynylguanosine [χ = −117.1 (5)°; Seela *et al.*, 2004], while for 2′-deoxytubercidin, (III*a*), and 2′-deoxy-7-fluorotubercidin, the glycosylic bond torsion angles are χ = −104.4 (2) and −101.1 (3)°, respectively, which are in the range of the high-*anti* conformation (Zabel *et al.*, 1987; Seela, Xu & Eickmeier, 2005).

The sugar moiety of (I) exhibits a pseudorotational phase angle P = 185.9 (2)° with an amplitude τ_m = 39.1 (1)°, indi-

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cating an *S*-type sugar pucker (2′-*endo*–3′-*exo*, $^2T_3$) (Rao *et al.*, 1981). This type of sugar conformation is also found for 2′-deoxytubercidin (Zabel *et al.*, 1987), while 2′-deoxy-7-iodotubercidin shows an envelope sugar ring conformation ($_3E$) (Seela *et al.*, 1996). The torsion angle γ [O5′—C5′—C4′—C3′ = −172.7 (3)°] describing the orientation of the 5′-hydroxy group relative to the sugar ring shows that the C4′—C5′ bond is in a −*ap* (*trans*) orientation (Saenger, 1984). The *S*-type sugar puckering of compound (I) in the solid state is similar to the preferred conformation found in solution (71% *S*). The

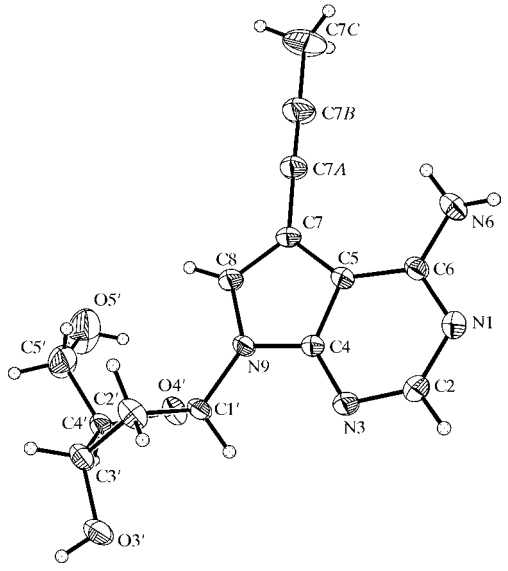

Figure 1
A perspective view of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary size.

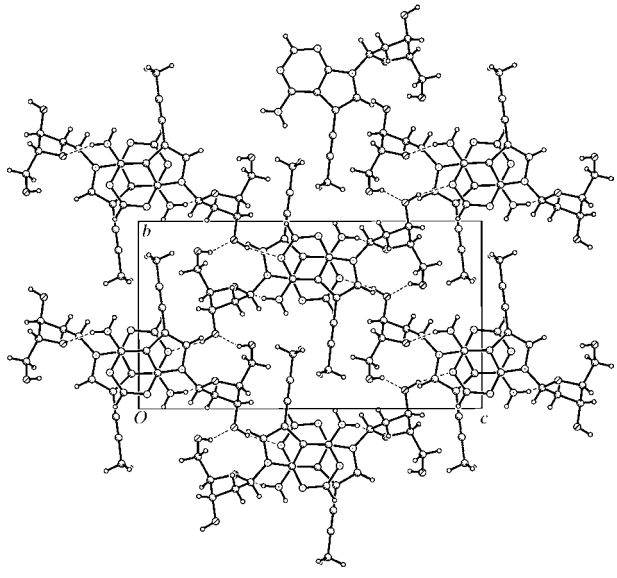

Figure 2
Details of the layered network, showing the hydrogen bonds (dashed lines) within the layers and the stacking of the nucleobases.

conformational analysis was carried out on the basis of ^{1}H NMR vicinal [^{1}H, ^{1}H] coupling constants using the program *PSEUROT6.3* (Van Wijk *et al.*, 1999).

The base moiety of (I) is almost planar, the r.m.s. deviation of ring atoms from their calculated least-squares planes being 0.0095 Å. The propynyl group of (I) is slightly inclined by 1.6° with respect to the aromatic ring of the molecule. This is smaller than the angles observed for 7-deaza-7-propynyl-2′-deoxyguanosine (4.6°; Seela *et al.*, 2004) and 8-aza-7-deaza-7-propynyladenosine (4.0°; Lin *et al.*, 2005). The group is almost linear, with bond angles C7—C7*A*—C7*B* = 178.5 (3)° and C7*A*—C7*B*—C7*C* = 178.2 (4)°. The triple-bond length of (I) is 1.185 (3) Å, which is within the range of non-conjugated triple bonds (Cygler *et al.*, 1984).

The structure of nucleoside (I) is stabilized by three intermolecular hydrogen bonds (N6—H6···O4′, O3′—H3′···N1 and O5′—H5′···O3′), leading to the formation of a layered network (Fig. 2 and Table 2) with head-to-tail stacking of the nucleobases, which is different from the head-to-head stacking of 7-deaza-2′-deoxy-7-propynylguanosine (Seela *et al.*, 2004). The shortest distance between the stacked bases for nucleoside (I) is 3.197 (1) Å, which is less than the average base-pair stacking distance in B-DNA (3.5 Å). It is also smaller than that observed for the related 7-deaza-2′-deoxy-7-propynylguanosine [3.728 (1) Å; Seela *et al.*, 2004].

Experimental

Compound (I) was synthesized from (III*b*) as described previously by Buhr *et al.* (1996) and was crystallized slowly from double-distilled water as colourless crystals (m.p. 479–480 K). For the diffraction experiment, a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{14}H_{16}N_4O_3$
M_r = 288.31
Orthorhombic, $P2_12_12_1$
a = 6.5812 (11) Å
b = 10.5084 (13) Å
c = 19.216 (2) Å
V = 1328.9 (3) Å^3
Z = 4
D_x = 1.441 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 63 reflections
θ = 4.9–14.0°
μ = 0.10 mm^{-1}
T = 293 (2) K
Block, colourless
0.5 × 0.3 × 0.3 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2918 measured reflections
2214 independent reflections
1852 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 30.0°
$h = -9 \rightarrow 1$
$k = -14 \rightarrow 1$
$l = -27 \rightarrow 1$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.146
S = 1.03
2214 reflections
197 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0951P)^2 + 0.1584P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Absolute structure: established by known chemical absolute configuration

Table 1
Selected geometric parameters (Å, °).

C7—C7*A*	1.427 (3)	C7*B*—C7*C*	1.470 (4)
C7*A*—C7*B*	1.185 (3)	N9—C1′	1.457 (3)
N1—C6—N6	118.14 (19)	C4—N9—C1′	123.67 (18)
N6—C6—C5	122.6 (2)	C8—N9—C1′	127.51 (18)
C8—C7—C7*A*	126.2 (2)	O4′—C1′—N9	108.19 (18)
C7*A*—C7—C5	127.6 (2)	N9—C1′—C2′	116.1 (2)
C7*B*—C7*A*—C7	178.5 (3)	O5′—C5′—C4′	114.5 (3)
C7*A*—C7*B*—C7*C*	178.2 (4)		
C2—N1—C6—N6	−179.9 (3)	C4—N9—C1′—C2′	109.6 (3)
C4—C5—C6—N6	178.6 (2)	C8—N9—C1′—C2′	−78.3 (3)
C7—C5—C6—N6	−0.3 (5)	O4′—C4′—C5′—O5′	56.0 (3)
C4—N9—C1′—O4′	−130.7 (2)	C3′—C4′—C5′—O5′	172.7 (3)
C8—N9—C1′—O4′	41.5 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···O4′^{i}	0.86	2.53	3.173 (3)	132
O3′—H3′*B*···N1^{ii}	0.86 (4)	2.02 (4)	2.851 (3)	165 (4)
O5′—H5′*C*···O3′^{iii}	0.90 (5)	2.05 (5)	2.884 (4)	155 (5)

Symmetry codes: (i) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (ii) $-x+\frac{3}{2}, -y, z+\frac{1}{2}$; (iii) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$.

In the absence of suitable anomalous scattering, the Flack (1983) parameter could not be used to determine the absolute structure. Therefore, 508 Friedel equivalents were merged before the final refinement. The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. All H atoms were initially found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, the 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). The coordinates of the hydroxy groups were refined freely starting from difference-map positions, with U_{iso}(H) = 1.5U_{eq}(O). Standard DFIX restraints were used for the quivalent O—H bond lengths.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997); program(s) used to solve structure: *SHELXTL*; program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1183). Services for accessing these data are described at the back of the journal.

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