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5-Methyl-6-aza-2′-deoxyisocytidine

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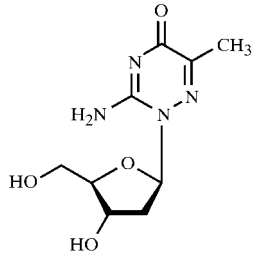
In the title compound, 3-amino-2-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-1,2,4-triazin-5(2*H*)-one, $C_9H_{14}N_4O_4$, the conformation of the N-glycosidic bond is high-*anti* and the 2-deoxyribofuranosyl moiety adopts a North sugar pucker ($^2T_3$). The orientation of the exocyclic C—C bond between the –CH_2OH group and the five-membered ring is *ap* (*gauche*, *trans*). The crystal packing is such that the nucleobases lie parallel to the *ac* plane; the planes are connected *via* hydrogen bonds involving the five-membered ring.

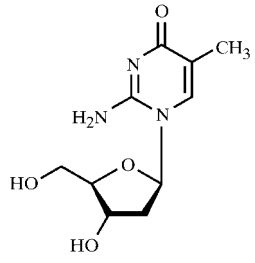
Comment

Transposition of the amino and oxo groups of 2′-deoxycytidine results in 2′-deoxyisocytidine. This reversal of the substituent pattern of the nucleobase results in a change of the hydrogen-bond donor–acceptor motif. As a result, parallel-stranded (ps) DNA will be formed *via* reverse Watson–Crick base pairs between 2′-deoxyisocytidine and 2′-deoxyguanosine (Seela & He, 2000). Such ps DNAs have also been found for oligonucleotide duplexes incorporating either 5-methyl-2′-deoxyisocytidine by base pairing with 2′-deoxyguanosine or 2′-deoxyisoguanosine by base pairing with 2′-deoxycytidine (Sugiyama *et al.*, 1996; Seela *et al.*, 1999). However, because of the low acid stability of 2′-deoxyisocytidine and its 5-methyl derivative, oligonucleotides containing these two compounds show substantial degradation at the N-glycosidic bond. This degradation occurs in solution as well as during matrix-assisted laser desorption/ionisation-time of flight spectrometric analysis (positive mode; matrix: 3-hydroxypicolinic acid). To overcome this problem, 5-methyl-6-aza-2′-deoxyisocytidine, (I), which is a much more acid stable, was used as a replacement. Oligonucleotides containing (I) can form parallel DNA duplexes with slightly lower thermal stability than those containing 5-methyl-2′-deoxyisocytidine, (II) (Seela & He, 2003); acidic degradation was not observed under the conditions described above. As it is expected that the additional N atom of (I) will cause stereochemical changes in the sugar moiety, the X-ray structure of (I) was determined and compared with that of (II).

The maximum deviation from the least-squares plane of the nucleobase of (I) is ±0.016 Å [N1 = 0.021, C2 = −0.024, N3 = 0.007, C4 = 0.012, C5 = −0.015 and N6 = 0.000 (1) Å; the atom-numbering scheme is given in Fig. 1]. The maximum deviation of the pyrimidine ring of (II) is 0.043 Å. Selected bond lengths of the base residue are summarized in Table 1. The C5═N6 bond of the base of (I) is 0.059 Å shorter than the C5═C6 bond of (II). This shortening is similar to that observed between 6-azacytidine and cytidine (0.056 Å; Singh & Hodgson, 1974*a*). The glycosidic bond length of (I) (N1—C1′) is approximately the same as that of (II) [1.478 (5) Å; Seela, He *et al.*, 2000].



(I)



(II)

Compounds (I) and (II) adopt different conformations around the glycosidic bond. While (II) displays a *syn* conformation (χ_{CN} = 58.2°), the conformation of (I) is high *anti* with χ_{CN} (O4′—C1′—N1—C2) equal to −103.4°. This value is in accordance with the observation that the favored conformation of *ortho* azanucleosides with an N atom next to the glycosidic bond would have a χ_{CN} value close to −90°, because of the Coulomb repulsion between the non-bonding electron pairs of O4′ and the N atom next to the glycosidic bond (N8 for azapurine nucleosides and N6 for azapyrimidine nucleosides). For 6-azapyrimidine ribonucleosides, the values of χ_{CN} for 6-azacytidine and 6-azauridine were reported to be −80 and −93°, respectively (Singh & Hodgson, 1974*b*; Schwalbe & Saenger, 1973). The glycosidic torsion angle of the corresponding 2′-deoxyribonucleosides is also in the high-*anti* range (χ_{CN} for 6-aza-2′-deoxythymidine is −86.6°; Banerjee & Saenger, 1978). For 8-azapurine nucleosides, the χ_{CN} value for 8-azaadenosine is −77° (Singh & Hodgson, 1974*c*) and that for 8-aza-1,3-dideaza-2′-deoxyadenosine is −77.1° (Seela *et al.*, 2001). For 8-aza-7-deaza-2′-deoxyadenosine, χ_{CN} moves towards the *anti* range (−106.3°; Seela, Zulauf *et al.*, 1999). 8-Aza-7-deaza-7-iodo-2′-deoxyadenosine shows a smaller value (χ_{CN} = −73.2°), similar to that of the corresponding 7-bromo compound (χ_{CN} = −74.1°), which also displays a high-*anti* conformation (Seela, Zulauf *et al.*, 2000).

The other major conformational parameter of interest is the pucker of the deoxyribofuanosyl moiety. The maximum amplitude of puckering (Ψ_m) of (I) is 26.3 (3)°, which is significantly smaller than the average value of 38.6 (3)° (Saenger, 1984). The phase angle of pseudorotation (*P*) of (I) is 344.6°, which corresponds to a $^2T_3$ sugar pucker. Therefore, the additional N atom of the nucleobase of (I) causes the sugar moiety to adopt an *N*-type instead of the *S*-type sugar pucker preferred by most 2′-deoxy-β-D-ribofuranosyl nucleosides.

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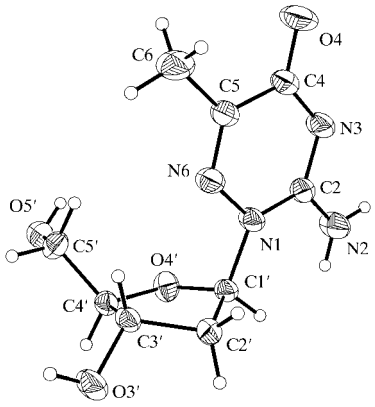

Figure 1
A perspective view of (I). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as spheres of arbitrary size.

The *N*(3′-*endo*) ⇌ *S*(2′-*endo*) equilibrium of the sugar moiety is controlled by various *gauche* effects. It is known that the *N*-type conformer population increases linearly with the electronegativity of the 2′-substituent (Guschlbauer & Jankowski, 1980). It was also reported from a measurement performed in solution that the higher the electron-withdrawing effect of the 7-substituents of 7-deaza-2′-deoxyadenosines, the more the $N \rightleftharpoons S$ equilibrium of the sugar moieties is biased towards the *N* conformation (Rosemeyer *et al.*, 1997). In the crystalline state, 8-aza-7-deaza-2′-deoxyadenosine adopts an *S*-type sugar pucker ($P = 182.2^\circ$, $^2T_3$; Seela, Zulauf *et al.*, 1999), while 8-aza-7-deaza-7-iodo-2′-deoxyadenosine ($P = 309.4^\circ$, ^1E) and 8-aza-7-deaza-7-bromo-2′-deoxyadenosine ($P = 310.9^\circ$, ^1E) adopt a sugar pucker that is close to *N*-type (Seela, Zulauf *et al.*, 2000). For comparison, 7-halogenated 8-aza-7-deaza-2′-deoxyguanosines also exhibit an *N*-type sugar pucker (Seela, Becher *et al.*, 1999).

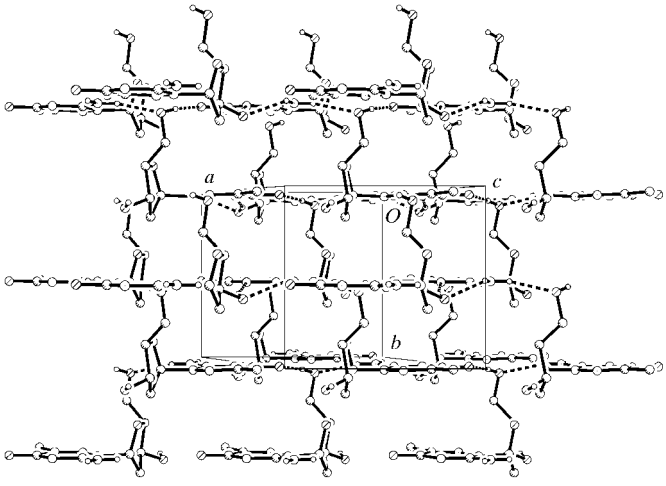

Figure 2
The intermolecular hydrogen-bond network and crystal packing, viewed perpendicular to the *ab* plane. Hydrogen bonds are indicated by dashed lines and H atoms not involved in hydrogen bonding have been omitted.

The conformation about the C5′—C4′ bond of (I) is *ap* (*gauche*, *trans*), with an O5′—C5′—C4′—C3′ torsion angle of 179.50 (11)°. Thus, atom O5′ is located away from the sugar ring. The *ap* conformation means that the nucleobase and the $-CH_2OH$ group undergo a disrotatory motion, so that the Coulomb repulsion between N6 (pyrimidine numbering) and O5′, as well as O4′, is minimized.

Intermolecular hydrogen bonds generate a three-dimensional network and provide additional crystal stabilization (Table 2). The crystal packing shows the formation of distinct layers (Fig. 2). All nucleobases show a parallel orientation to the *ac* plane. Two types of hydrogen bonds are observed within the planes: type (i) (see Table 2) connects an H atom of the amino group of one molecule to the O atom of the 3′-hydroxyl group of another molecule, and type (iii) connects atom N3 with the H atom of the 3′-hydroxyl group. The sugar rings are approximately perpendicular to the nucleobase plane. Neighboring planes are connected *via* a type (ii) hydrogen bond from the second H atom of the amino group to the O atom of the 5′-hydroxyl group and a type (iv) hydrogen bond from the H atom of the 5′-hydroxyl group to an N atom of the amino group.

Experimental

Compound (I) was synthesized as described by Seela & He (2003) and crystallized from acetone and MeOH (8:2).

Crystal data

$C_9H_{14}N_4O_4$
$M_r = 242.24$
Monoclinic, $P2_1$
$a = 8.682$ (2) Å
$b = 7.8835$ (16) Å
$c = 8.998$ (3) Å
$\beta = 118.088$ (18)°
$V = 543.3$ (2) Å^3
$Z = 2$
$D_x = 1.481$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 39 reflections
$\theta = 5.3$–$20.6°$
$\mu = 0.12$ mm^{-1}
$T = 293$ (2) K
Transparent needle, colorless
0.6 × 0.3 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2000 measured reflections
1848 independent reflections
1801 reflections with $I > 2\sigma(I)$
$R_{int} = 0.013$
$\theta_{max} = 31.1°$
$h = -12 \rightarrow 1$
$k = -1 \rightarrow 11$
$l = -11 \rightarrow 13$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.105$
$S = 1.07$
1848 reflections
169 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0769P)^2 + 0.0237P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.068 (12)

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 inconclusive values (Flack & Bernadinelli, 2000) for this parameter [−0.3 (0)]. Therefore, Friedel equivalents (20) were merged before the final refinement. The

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.3531 (15)	N3—C4	1.352 (2)
N1—N6	1.3656 (15)	C4—O4	1.2395 (17)
N1—C1′	1.4789 (15)	C4—C5	1.472 (2)
C2—N2	1.3310 (17)	C5—N6	1.2863 (17)
C2—N3	1.3373 (16)		
N6—N1—C2—N3	5.0 (3)	O4′—C1′—C2′—C3′	−25.28 (12)
N1—C2—N3—C4	−3.6 (3)	C1′—C2′—C3′—C4′	25.17 (12)
C2—N3—C4—C5	0.1 (3)	C2′—C3′—C4′—O4′	−17.09 (12)
N3—C4—C5—N6	2.3 (3)	O3′—C3′—C4′—C5′	102.46 (13)
C4—C5—N6—N1	−1.1 (3)	C2′—C1′—O4′—C4′	14.91 (13)
C2—N1—N6—C5	−2.5 (3)	C3′—C4′—O4′—C1′	1.56 (13)
C2—N1—C1′—O4′	−103.38 (16)	C3′—C4′—C5′—O5′	179.50 (11)

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

Type	D—H···A	D—H	H···A	D···A	D—H···A
(i)	N2—H2A···O3′^{i}	0.87 (3)	2.21 (3)	2.982 (2)	147 (2)
(ii)	N2—H2B···O5′^{ii}	0.81 (3)	2.16 (3)	2.9243 (18)	159 (3)
(iii)	O3′—H3′···N3^{iii}	0.87 (3)	2.06 (3)	2.8117 (19)	145 (2)
(iv)	O5′—H5′···O4^{iv}	0.75 (3)	1.98 (3)	2.707 (2)	166 (3)

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

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, H atoms bonded to C atoms were placed in idealized positions (C—H = 0.93–0.98 Å) and constrained to ride on their parent atoms. The coordinates of the other H atoms were refined freely, starting from difference-map positions. An overall isotropic displacement parameter was refined for all H atoms.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Sheldrick, 1997*b*); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*a*); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1548). Services for accessing these data are described at the back of the journal.

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