

6-Aza-2'-deoxyuridine and N^3 -anisoyl-6-aza-2'-deoxyuridineFrank Seela,^{a*} Padmaja Chittepu,^a Yang He,^a Henning Eickmeier^b and Hans Reuter^b^aLaboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, 49069 Osnabrück, Germany, and^bAnorganische Chemie II, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, 49069 Osnabrück, Germany

Correspondence e-mail: frank.seela@uni-osnabrueck.de

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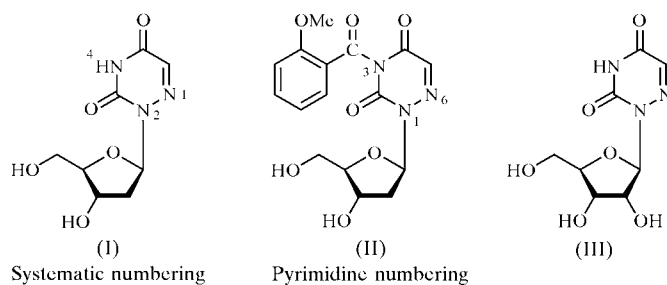
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In 2-(2-deoxy- β -D-erythro-pentofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (6-aza-2'-deoxyuridine), $C_8H_{11}N_3O_5$, (I), the conformation of the glycosylic bond is between *anti* and high-*anti* [$\chi = -94.0$ (3) $^\circ$], whereas the derivative 2-(2-deoxy- β -D-erythro-pentofuranosyl)- N^4 -(2-methoxybenzoyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (N^3 -anisoyl-6-aza-2'-deoxyuridine), $C_{16}H_{17}N_3O_7$, (II), displays a high-*anti* conformation [$\chi = -86.4$ (3) $^\circ$]. The furanosyl moiety in (I) adopts the *S*-type sugar pucker (2T_3), with $P = 188.1$ (2) $^\circ$ and $\tau_m = 40.3$ (2) $^\circ$, while the sugar pucker in (II) is *N* (3T_4), with $P = 36.1$ (3) $^\circ$ and $\tau_m = 33.5$ (2) $^\circ$. The crystal structures of (I) and (II) are stabilized by intermolecular N—H...O and O—H...O interactions.

Comment

6-Azapyrimidine nucleosides show significant antiviral activity (Mitchell *et al.*, 1986), while the N^3 -substituted derivatives possess hypnotic and sedative properties and exhibit central depressant effects in mice (Koshigami *et al.*, 1991). 6-Aza-uridine 5'-monophosphate is a strong inhibitor of the enzyme orotidine 5'-monophosphate decarboxylase (Miller *et al.*, 2000), which, when linked to agarose, leads to an affinity resin used for the purification of this enzyme (Rosemeyer & Seela, 1979). The first synthesis of an anomeric mixture of 6-aza-2'-deoxyuridine was reported in 1963 (Pliml *et al.*, 1963), employing Hg derivatives of 6-azauracil and 2-deoxy-3,5-di-*O*-(4-methylbenzoyl)- α -D-erythro-pentofuranosyl chloride. Introducing an N atom at the 6-position of the pyrimidine group has a profound effect on the physical and biological properties of the nucleobase, which plays a significant role in the catalytic activity of ribozymes (Oyelere & Strobel, 2001) and promotes *M*-DNA formation under neutral conditions (Seela, Peng *et al.*, 2005). The pK_a value of (I) is 6.8 and that of 2'-deoxyuridine is 9.5. Compared with these pK_a values, the 6-azapyrimidine nucleoside is acidic and therefore it is already deprotonated under neutral conditions. We have shown that

this influences the duplex stability when (I) is a constituent of a nucleic acid. Oligonucleotides containing 6-aza-2'-deoxyuridine show a pH dependence on base-pair formation. The lower pK_a value of (I) causes problems during phosphoramidite synthesis. To circumvent this problem, various protecting groups were introduced at the N^3 -position. The *o*-anisoyl residue was found to be an efficient protecting group, allowing multiple incorporations into the oligonucleotide chain using phosphoramidite chemistry, with coupling yields identical to those of standard phosphoramidites. These properties prompted single-crystal analyses of (I) and its N^3 -protected derivative, (II) (see scheme).



6-Aza-2'-deoxyuridine, (I), has an O4'—C1'—N1—C2 torsion angle χ of -94.0 (3) $^\circ$ (IUPAC—IUB Joint Commission on Biochemical Nomenclature, 1983) (Fig. 1 and Table 1), which falls into the range of *anti*/high-*anti* conformations and which is almost identical to that of the corresponding ribonucleoside, (III), with $\chi = -93.3$ $^\circ$ (Schwalbe *et al.*, 1971; Schwalbe & Saenger, 1973). The protected nucleoside, (II), exhibits a high-*anti* conformation, with a torsion angle χ of -86.4 (3) $^\circ$ (Fig. 2 and Table 3), and these values are similar to those of other *ortho*-aza-nucleosides with an N atom next to the glycosylation position, with χ values close to -90 $^\circ$. This results from the Coulombic repulsion between the non-bonding electron pairs of atom O4' and the atom at position N-6 in pyrimidine nucleosides or N-8 in 8-azapurine nucleosides (8-aza-7-deaza-7-iodo-2'-deoxyadenosine, with $\chi = -106.3$ $^\circ$; Seela *et al.*, 1999). The glycosylic torsion angles of related nucleosides, such as 6-aza-2'-deoxythymidine ($\chi = -86.6$ $^\circ$; Banerjee & Saenger, 1978) and 6-aza-2'-deoxy-5-methylisocytidine ($\chi = -103.4$ $^\circ$; Seela *et al.*, 2003), also lie in the *anti*/high-*anti* range.

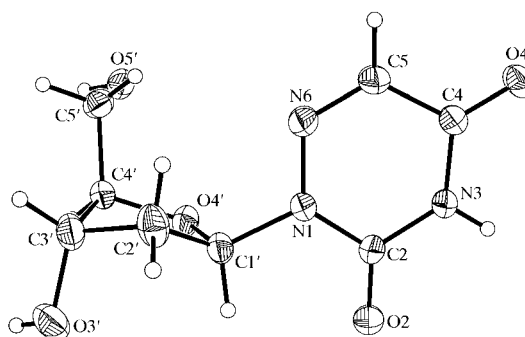


Figure 1
A perspective view of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

The sugar moiety of (I) shows a pseudorotational phase angle P of $188.1(2)^\circ$ with an amplitude τ_m of $40.3(2)^\circ$, indicating an *S*-type sugar pucker ($C2'$ -endo- $C3'$ -exo, 2T_3 ; Rao *et al.*, 1981), whereas its anisoyl-protected derivative, (II), adopts an *N* sugar conformation ($C4'$ -exo, 3T_4), with $P = 36.1(3)^\circ$ and $\tau_m = 33.5(2)^\circ$. This is similar to that of ribonucleoside (III) ($C3'$ -endo, 3E ; Schwalbe & Saenger, 1973), which has $P = 27.6^\circ$ and $\tau_m = 37.6^\circ$. The *N* conformation is uncommon for 2'-deoxyribonucleosides. The conformation around the $C4'-C5'$ bond defined by the torsion angle χ ($O5'-C5'-C4'-C3'$) is similar for these two nucleosides [$-175.3(2)^\circ$ for (I) and $-176.2(2)^\circ$ for (II)], representing an *ap* (*trans*) orientation.

The base moiety of (I) is nearly planar, with an r.m.s. deviation of the ring atoms (N1/C2/N3/C4/C5/N6) from the plane of $0.0173(2)$ Å and a maximum deviation of $0.025(7)$ Å for atom C2. The maximum deviation of the pyrimidine ring (N1/N2/C3/C4/N5/C6) of (II) is $0.023(2)$ Å [$0.034(5)$ Å for atom N5 and $0.020(3)$ Å for atom N1]. The presence of the N^3 -anisoyl protecting group does not show much influence on the bond lengths of the nucleobase.

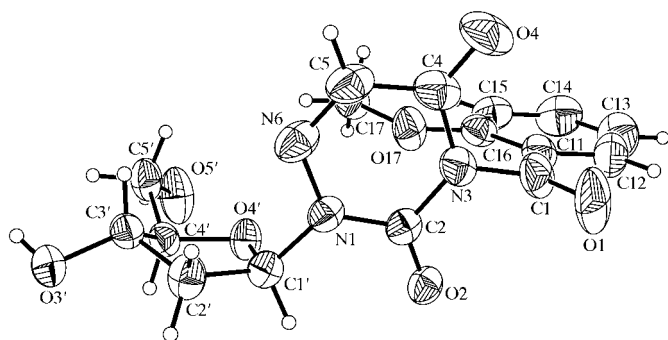


Figure 2

A perspective view of (II), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

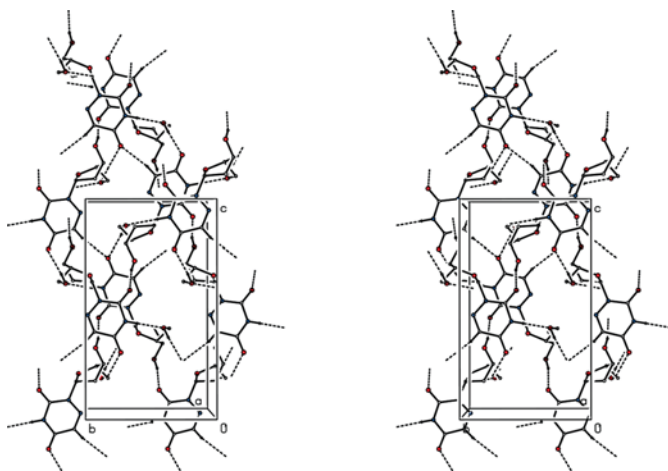


Figure 3

A stereoview of the packing in (I), viewed in the bc plane, with hydrogen bonds shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

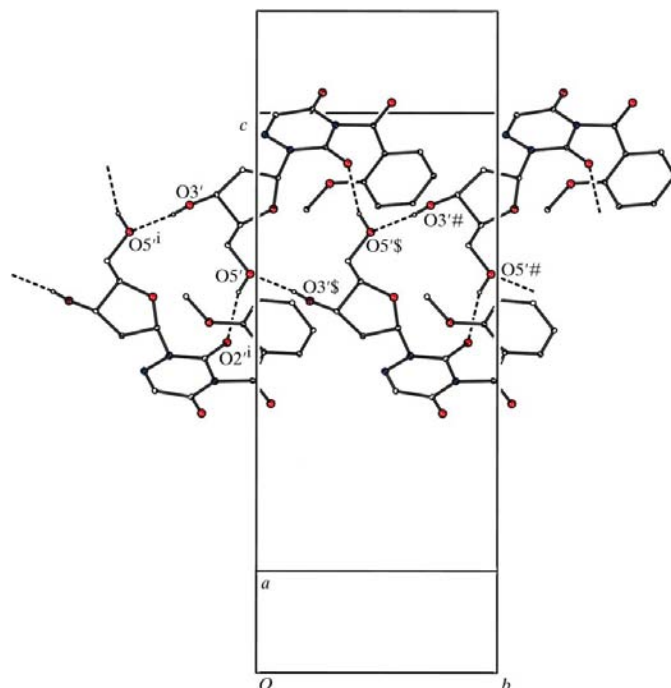


Figure 4

The principal interactions in (II), shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $-x, y - \frac{1}{2}, \frac{3}{2} - z$; (#) $x, 1 + y, z$; (\$) $-x, y + \frac{1}{2}, \frac{3}{2} - z$.]

Compound (I) is stabilized by three intermolecular hydrogen bonds ($N3-H3 \cdots O5^{iii}$, $O3'-H3' \cdots O2^{ii}$ and $O5'-H5' \cdots O4^i$; symmetry codes are given in Table 2) and two intramolecular hydrogen bonds ($C1'-H1' \cdots O2$ and $C2'-H2' \cdots N6$), leading to the formation of layered sheets (Fig. 3 and Table 2) where the nucleobases stack. Compound (II) forms a three-dimensional network which is stabilized by both intermolecular hydrogen bonds ($O3'-H3' \cdots O5^{iv}$ and $O5'-H5' \cdots O2^{iv}$; symmetry code given in Table 4) and intramolecular hydrogen bonds formed between the sugar and the nucleobase ($C1'-H1' \cdots O2$ and $C2'-H2' \cdots N6$). In the close-packed network of (II), the protecting group shows a perpendicular orientation with respect to the nucleobase in the ac plane. The aromatic H atoms (on atoms C15 and C17) form weak intermolecular hydrogen bonds with atoms O2 (3.310 Å) and O4 (3.211 Å) of the adjacent nucleobase, and there is also an intramolecular $C12-H12 \cdots O1$ hydrogen bond (Fig. 4 and Table 4).

Experimental

Compound (I) was prepared according to the method described by Freskos (1989). The anomeric configuration assignment has been reported previously (Seela *et al.*, 2003). Suitable crystals were grown from $CH_2Cl_2-CH_3OH$ (9:1 *v/v*). Compound (II) was prepared from (I) by protection of the lactam group with *o*-anisoyl chloride using transient protection (Seela, Chittepu *et al.*, 2005). Crystallization from methanol furnished colourless crystals (m.p. 414 K).

Compound (I)

Crystal data

$C_8H_{11}N_3O_5$	$D_x = 1.527 \text{ Mg m}^{-3}$
$M_r = 229.20$	Mo $K\alpha$ radiation
Orthorhombic, $P2_12_12_1$	$\mu = 0.13 \text{ mm}^{-1}$
$a = 7.8817 (17) \text{ \AA}$	$T = 293 (2) \text{ K}$
$b = 8.6832 (11) \text{ \AA}$	Block, colourless
$c = 14.5715 (15) \text{ \AA}$	$0.4 \times 0.3 \times 0.2 \text{ mm}$
$V = 997.2 (3) \text{ \AA}^3$	
$Z = 4$	

Data collection

Bruker $P4$ diffractometer	$\theta_{\max} = 30.0^\circ$
$\omega/2\theta$ scans	3 standard reflections
2127 measured reflections	every 97 reflections
1580 independent reflections	intensity decay: none
1313 reflections with $I > 2\sigma(I)$	
$R_{\text{int}} = 0.020$	

Refinement

Refinement on F^2	$(\Delta/\sigma)_{\max} = 0.001$
$R[F^2 > 2\sigma(F^2)] = 0.045$	$\Delta\rho_{\max} = 0.37 \text{ e \AA}^{-3}$
$wR(F^2) = 0.121$	$\Delta\rho_{\min} = -0.23 \text{ e \AA}^{-3}$
$S = 1.07$	Extinction correction: <i>SHELXTL</i>
1580 reflections	(Sheldrick, 1997)
148 parameters	Extinction coefficient: 0.026 (4)
H-atom parameters constrained	
$w = 1/[\sigma^2(F_o^2) + (0.055P)^2 + 0.2159P]$	
where $P = (F_o^2 + 2F_c^2)/3$	

Table 1

Selected geometric parameters (\AA , $^\circ$) for (I).

N1—N6	1.362 (3)	C4—O4	1.219 (3)
N1—C2	1.380 (3)	C4—C5	1.462 (4)
N1—C1'	1.462 (3)	C5—N6	1.277 (3)
C2—N3	1.372 (3)	C1'—O4'	1.425 (4)
N3—C4	1.365 (3)	C4'—O4'	1.440 (3)
C2—N1—C1'	118.9 (2)	O4'—C1'—C2'	106.4 (2)
O4—C4—N3	122.5 (2)	C1'—C2'—C3'	101.2 (2)
N6—N1—C2—O2	-174.4 (3)	C1'—C2'—C3'—C4'	-39.1 (3)
N1—C2—N3—C4	-3.9 (4)	C2'—C3'—C4'—O4'	35.9 (3)
N3—C4—C5—N6	1.0 (5)	O3'—C3'—C4'—C5'	161.3 (2)
C4—C5—N6—N1	0.9 (5)	N1—C1'—O4'—C4'	-130.9 (2)
C2—N1—N6—C5	-4.6 (4)	C2'—C1'—O4'—C4'	-7.3 (3)
C2—N1—C1'—O4'	-94.0 (3)	C3'—C4'—O4'—C1'	-18.2 (3)
O4'—C1'—C2'—C3'	29.4 (3)	O4'—C4'—C5'—O5'	66.8 (3)
N1—C1'—C2'—C3'	149.2 (2)	C3'—C4'—C5'—O5'	-175.2 (2)

Table 2

Hydrogen-bond geometry (\AA , $^\circ$) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O5'-H5'\cdots O4^i$	0.82	2.02	2.816 (3)	163
$O3'-H3'\cdots O2^{ii}$	0.82	2.15	2.948 (4)	164
$N3-H3\cdots O5^{iii}$	0.86	1.97	2.825 (3)	176
$C1'-H1'\cdots O2$	0.98	2.39	2.764 (3)	102
$C2'-H2'1\cdots N6$	0.97	2.45	2.862 (4)	105

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

Compound (II)

Crystal data

$C_{16}H_{17}N_3O_7$	$D_x = 1.433 \text{ Mg m}^{-3}$
$M_r = 363.33$	Mo $K\alpha$ radiation
Orthorhombic, $P2_12_12_1$	$\mu = 0.11 \text{ mm}^{-1}$
$a = 7.452 (3) \text{ \AA}$	$T = 293 (2) \text{ K}$
$b = 9.1170 (10) \text{ \AA}$	Block, colourless
$c = 24.780 (3) \text{ \AA}$	$0.4 \times 0.2 \times 0.1 \text{ mm}$
$V = 1683.6 (7) \text{ \AA}^3$	

Data collection

Bruker $P4$ diffractometer	$R_{\text{int}} = 0.036$
$\omega/2\theta$ scans	$\theta_{\max} = 25.0^\circ$
7561 measured reflections	3 standard reflections
1732 independent reflections	every 97 reflections
1367 reflections with $I > 2\sigma(I)$	intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0574P)^2 + 0.0428P]$
$R[F^2 > 2\sigma(F^2)] = 0.035$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.094$	$(\Delta/\sigma)_{\max} < 0.001$
$S = 1.02$	$\Delta\rho_{\max} = 0.11 \text{ e \AA}^{-3}$
1732 reflections	$\Delta\rho_{\min} = -0.14 \text{ e \AA}^{-3}$
239 parameters	Extinction correction: <i>SHELXTL</i>
H-atom parameters constrained	(Sheldrick, 1997)
	Extinction coefficient: 0.0083 (16)

Table 3

Selected geometric parameters (\AA , $^\circ$) for (II).

C11—C1	1.459 (5)	C2—N3	1.376 (3)
C16—O17	1.357 (4)	N3—C4	1.373 (4)
C1—O1	1.197 (4)	C4—O4	1.215 (4)
C1—N3	1.480 (4)	C4—C5	1.450 (5)
N1—C2	1.363 (3)	C5—N6	1.282 (4)
N1—N6	1.367 (3)	C1'—O4'	1.416 (3)
N1—C1'	1.474 (3)	C4'—O4'	1.431 (3)
C16—C11—C12	117.8 (3)	C11—C1—N3	116.7 (3)
C16—C11—C1	126.5 (3)	O4—C4—N3	121.7 (3)
C12—C11—C1	115.7 (3)	O4'—C1'—C2'	107.5 (2)
C16—O17—C17	119.8 (2)	N1—C1'—C2'	114.1 (2)
O1—C1—N3	116.8 (3)	C1'—C2'—C3'	104.7 (2)
C11—C12—C13—C14	-0.5 (6)	O4'—C1'—C2'—C3'	-11.0 (3)
C11—C16—O17—C17	174.0 (2)	N1—C1'—C2'—C3'	107.2 (3)
C16—C11—C1—O1	176.3 (3)	C1'—C2'—C3'—C4'	26.5 (3)
C16—C11—C1—N3	-5.1 (5)	C2'—C3'—C4'—O4'	-33.0 (3)
N6—N1—C2—O2	-173.8 (3)	O3'—C3'—C4'—C5'	87.9 (3)
N1—C2—N3—C4	-8.6 (4)	O4'—C4'—C5'—O5'	65.7 (3)
N3—C4—C5—N6	-4.3 (5)	C3'—C4'—C5'—O5'	-176.2 (2)
C4—C5—N6—N1	3.2 (6)	N1—C1'—O4'—C4'	-133.2 (2)
C2—N1—N6—C5	-4.8 (5)	C2'—C1'—O4'—C4'	-10.4 (3)
C2—N1—C1'—O4'	-86.4 (3)	C3'—C4'—O4'—C1'	27.7 (3)

Table 4

Hydrogen-bond geometry (\AA , $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O3'-H3'\cdots O5^{iv}$	0.82	1.98	2.789 (3)	171
$O5'-H5'\cdots O2^{iv}$	0.82	1.96	2.743 (3)	161
$C1'-H1'\cdots O2$	0.98	2.41	2.750 (3)	100
$C2'-H2'1\cdots N6$	0.97	2.51	2.839 (5)	100
$C12-H12\cdots O1$	0.93	2.49	2.802 (6)	100

Symmetry code: (iv) $-x, y - \frac{1}{2}, -z + \frac{3}{2}$.

In the absence of suitable anomalous scattering, refinement of the Flack (1983) parameter led to inconclusive values. Therefore, Friedel equivalents were merged before the final refinements. The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. All H atoms were found in a difference Fourier synthesis. In order to maximize the data-parameter ratio, 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 $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C,N})$.

For both compounds, 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: GG3052). Services for accessing these data are described at the back of the journal.

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