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9-(2-Deoxy-α-D-ribofuranosyl)-7-iodo-7-deazaadenine

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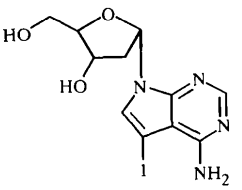
Abstract

The structure of 4-amino-7-(2-deoxy-α-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine, $C_{11}H_{13}IN_4O_3$, has been determined. The N-glycosidic bond torsion angle χ is in the *anti* range [128.7 (12)°]. Both, the bulky iodo substituent and the N atom of the 6-amino group lie out of the 7-deazapurine plane, with deviations of −0.013 (10) and −0.0632 (12) Å, respectively.

Comment

Oligonucleotides containing the β-D-configurated 7-iodo-2′-deoxytubercidin (purine skeleton numbering is used throughout the discussion) show an enhanced duplex stability with antiparallel (aps) chain orientation (Seela & Zulauf, 1998). As duplexes with parallel (ps) chains can be formed when one oligonucleotide strand contains the sugar in α-D-configuration (Imbach *et al.*, 1989) and these oligonucleotides show nuclease resistance, it was of interest to study the conformational properties of the α-D-anomer (I) of 7-iodo-2′-deoxytubercidin.



(I)

The most frequently observed sugar conformation of 2′-deoxy-α-D-ribonucleosides is C2′-*endo* with either a half-chair or envelope sugar-ring conformation (Hamor *et al.*, 1977; Revankar *et al.*, 1990; Leumann *et al.*, 1995; Marfurt *et al.*, 1996; Melenewski, 1998).

In contrast to these observations, the sugar part of (I) shows the C3′-*endo* ($^{3'}E$) conformation with a puckering amplitude (Rao *et al.*, 1981) of τ_m = 37.7 (3)° and a pseudorotation phase angle (Rao *et al.*, 1981) of P = 21.7 (5)°. This can also be seen from the torsion angle ν_0 (C2′—C1′—O4′—C4′) of −2.5 (5)°, implying the almost planar arrangement of these four atoms with a deviation of 0.573 (8) Å of C3′ from their least-squares plane. A C3′-*endo* envelope conformation is also found for the β-D-anomer of 2′-deoxyadenosine, but not for the β-D-anomers of 2′-deoxytubercidin ($^{2'}T_{3'}$) and 7-iodo-2′-deoxytubercidin ($_{3'}E$) (Seela *et al.*, 1996).

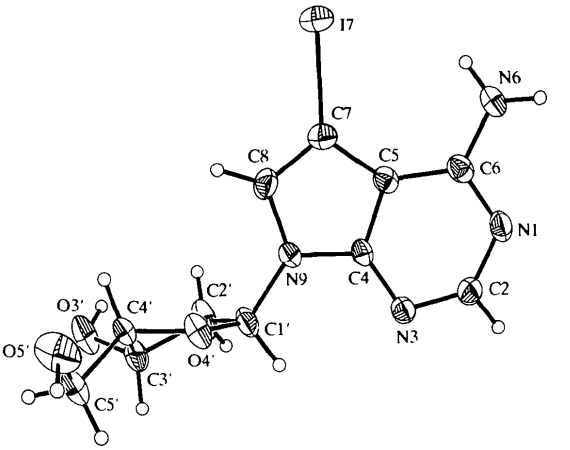


Fig. 1. Perspective view of (I) showing the atomic numbering scheme. Displacement ellipsoids of non-H atoms are drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

The 7-deazapurine base of (I) is planar. The deviations of its C and N atoms from the least-squares plane are in the range of +0.026 to −0.029 Å [N1 = 0.009 (6), C2 = 0.026 (8), N3 = −0.029 (8), C4 = 0.009 (16), C5 = 0.001 (9), C6 = −0.021 (7), C7 = 0.001 (7), C8 = 0.012 (7), N9 = −0.006 (8) Å]. Both the bulky iodo substituent and the nitrogen of the 6-amino group lie out of the 7-deazapurine plane, with a deviation of −0.013 (10) (I7) and −0.0632 (12) Å (N6), respectively.

Bond lengths and angles within the base are similar to those in the β-D-anomer of 7-iodo-2′-deoxytubercidin (Seela *et al.*, 1996). The iodo-substituent of (I) leads only to a small lengthening of the N-glycosidic bond (0.017 Å) and also of the C6—N6 (0.013 Å) distance compared to 2′-deoxytubercidin (Seela *et al.*, 1996, 1997, 1999).

The exocyclic angles about the N-glycosidic bond are sensitive to the N-glycosidic conformation. The C4—N9—C1′ angle of (I) is 2.2° smaller than the C8—N9—C1′ angle as it was observed for nucleosides adopting the classical *anti* N-glycosidic conformation (Sundaralingam *et al.*, 1978; Seela *et al.*, 1996). The conformation about the C4′—C5′ bond of (I) is in the *trans* (−*ap*) (Klyne & Prelog, 1960) range [γ = −173.9 (4)°].

The orientation of the base relative to the sugar (*syn*/*anti*) is defined by the torsion angle χ (O4′—C1′—N9—C4) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983); the preferred conformation

around the N-glycosidic bond of a natural 2′-deoxynucleoside is usually in the *anti* range. Compound (I) adopts an *anti* orientation [χ = 128.7 (12)°] similar to that of the 7-iodo-2′-deoxytubercidin (β-D-anomer) [χ = −147.1 (8)°] (Seela *et al.*, 1996). Stacking interactions and hydrogen bonds between molecules, including a bifurcated hydrogen bond (N6—H61···O3′, N6—H61···O5′), provide additional crystal stabilization (see Table 2).

Experimental

Compound (I) was prepared by treatment of 4-chloro-7-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl]-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (Thomas, 1995) (100 mg, 0.16 mmol) with 25% aqueous NH_3/1,4-dioxane (100 cm^3, 3:1, *v*/*v*) for 28 h at 383 K in an autoclave. The solvent was evaporated and the residue purified by flash chromatography on silica gel (column 10 × 2 cm, methanol–dichloromethane 1:9). Crystallization from ^{i}PrOH/H_2O furnished pale yellow needles (52 mg, 39%). Spectroscopic data for (I): m.p. 469–470 K; R_f (methanol–dichloromethane 1:9) 0.35; UV: λ_{max}(MeOH)/nm 282 (ε/dm^3 mol^{-1} cm^{-1} 9000); ^{1}H NMR (250 MHz, DMSO-d_6), p.p.m.: 2.14 (*m*, 1H, C2′-H$_\alpha$), 2.74 (*m*, 1H, C2′-H$_\beta$), 3.44 (*m*, 2H, C5′-H$_{\alpha,\beta}$), 4.06 (*m*, 1H, C4′-H), 4.30 (*m*, 1H, C3′-H), 4.79 (*t*, 1H, C5′-OH, *J* = 5.6 Hz), 5.54 (*d*, 1H, C3′-OH, *J* = 4.0 Hz), 6.51 (*dd*, C1′-H, *J* = 3.1 Hz), 6.63 (*br s*, 2H, NH_2), 8.11 (*s*, 1H, C2-H), 8.80 (*s*, 1H, C6-H); ^{13}C NMR (125 MHz; DMSO-d_6), p.p.m.: 51.3 (C7), 61.7 (C5′), 70.7 (C3′), 83.9 (C1′), 88.0 (C4′), 102.9 (C5), 127.6 (C8), 149.6 (C4), 151.8 (C2), 157.1 (C6), C2′ is superimposed by DMSO; analytical data for $C_{11}H_{13}IN_4O_3$ = 376.15: calculated C 35.13, H 3.48, N 14.90%; found C 35.33, H 3.69, N 15.01%. For the diffraction experiment a single crystal was fixed at the top of a Lindemann capillary with epoxy resin.

Crystal data

$C_{11}H_{13}IN_4O_3$
M_r = 376.15
Monoclinic
$P2_1$
a = 8.5158 (8) Å
b = 7.0115 (6) Å
c = 10.9335 (13) Å
β = 97.375 (12)°
V = 647.42 (11) Å^3
Z = 2
D_x = 1.930 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 23 reflections
θ = 4.72–12.51°
μ = 2.484 mm^{-1}
T = 293 (2) K
Prism
0.45 × 0.23 × 0.17 mm
Pale yellow

Data collection

Siemens *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: empirical (*SHELXTL*; Sheldrick, 1997*a*)
T_{min} = 0.557, T_{max} = 0.656
2004 measured reflections
1246 independent reflections (plus 758 Friedel-related reflections)
1965 reflections with $I > 2\sigma(I)$
θ_{max} = 25°
$h = -10 \rightarrow 10$
$k = -7 \rightarrow 8$
$l = 0 \rightarrow 12$
3 standard reflections every 97 reflections
intensity decay: 6.02%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.023
$wR(F^2)$ = 0.057
S = 1.051
2004 reflections
178 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0281P)^2 + 0.5354P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.706 e Å^{-3}
$\Delta\rho_{min}$ = −0.493 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997*b*)
Extinction coefficient: 0.0221 (11)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.03 (3)

Table 1. *Selected geometric parameters (Å, °)*

C6—N6	1.351 (5)	C4′—O4′	1.436 (5)
C1′—O4′	1.419 (5)		
C4—N9—C1′	124.6 (3)	C8—N9—C1′	126.8 (3)
C4—N9—C1′—O4′	128.7 (12)	C3′—C4′—C5′—O5′	−173.9 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H61···O3′^{i}	0.88	2.78	3.188 (6)	109
N6—H62···O4′^{ii}	0.88	2.42	3.066 (7)	131
N6—H61···O5′^{ii}	0.88	2.58	3.163 (5)	125
O3′—H3′O···O5′^{iii}	0.82	2.13	2.911 (6)	159
O5′—H5′O···O3′^{iv}	0.82	2.10	2.911 (6)	168

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

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *SHELXTL* (Sheldrick, 1997*a*). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*c*). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*b*). 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: KA1326). Services for accessing these data are described at the back of the journal.

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Azole. 42.† Über Nitropiperidinoimidazolderivate

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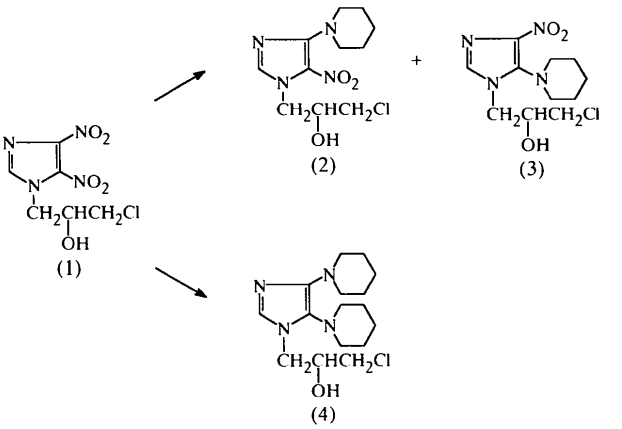
Abstract

3-Chloro-1-(4-nitro-5-piperidinylimidazol-1-yl)propan-2-ol, $C_{11}H_{17}ClN_4O_3$, (3), is formed together with its unstable isomer 3-chloro-1-(5-nitro-4-piperidinylimidazol-1-yl)propan-2-ol, (2), by treatment of 3-chloro-1-(4,5-dinitroimidazol-1-yl)propan-2-ol, $C_6H_7ClN_4O_5$, (1), with piperidine in a 1:2 ratio. In order to explain the position of the piperidine residue in the two isomeric products, (2) and (3), the X-ray investigation of the stable isomer, (3), was undertaken. It has two enantiomers, and in the centrosymmetric crystal lattice both enantiomers of (3) are present. In the asymmetric unit, four molecules of (3) are linked into two dimers, *A*/*B* [(*S*)-enantiomers] and *C*/*D* [(*R*)-enantiomers], by two three-centre hydrogen bonds. The piperidine least-squares plane is nearly perpendicular to the planar imidazole system and the nitro group lies approximately in the plane of the imidazole ring. In (1), both nitro groups are rotated significantly from the imidazole plane and can be replaced by piperidine rings. The asymmetric unit contains only one molecule of (1). In the crystal lattice of (1), molecules are linked in chains by hydrogen bonds.

† Teil 41: Bernard (1997).

Kommentar

Die Umsetzung von 3-Chlor-1-(4,5-dinitroimidazol-1-yl)propan-2-ol, (1), mit Piperidin im Molverhältnis von 1:2 führt in wasserfreiem Tetrahydrofuran und bei Raumtemperatur zu den stellungsisomeren Mononitropiperidinoimidazolderivaten (2) und (3). Bei einem molaren Verhältnis 1:6 zwischen Substrat (1) und Piperidin erfolgt die Substitution beider Nitrogruppen und man erhält das 3-chlor-1-(4,5-dipiperidinylimidazol-1-yl)propan-2-ol, (4). Eine Substitution des Chloratoms in der Seitenkette findet weder bei Raumtemperatur noch unter Sieden statt.



Die Verbindungen (1)–(4) mit dem asymmetrischen C7-Kohlenstoffatom in der Seitenkette liegen als Racemate vor. Die Lage des Piperidinrestes in den Stellungsisomeren (2) und (3) ließ sich auf Grund spektroskopischer Untersuchungen nicht eindeutig klären. In dieser Mitteilung berichten wir über die rentgenographische Ermittlung der Lage des Aminorestes in (3) und somit auch in (2). Von der zuletzt genannten Verbindung ließen sich wegen ihrer Labilität keine Einkristalle herstellen.

Die Einkristalle von (3) wurden aus Methanol erhalten. Im zentrosymmetrischen Gitter sind beide Enantiomere des Racemats vorhanden. Die asymmetrische Einheit enthält vier Moleküle, die zwei Enantiomeren-Paare *A*/*B* (*S*) und *C*/*D* (*R*) bilden (Abb. 1). Die Paare sind jeweils durch zwei dreizentrische Wasserstoffbrückenbindungen zu Dimeren verbunden, an deren Bildung sich die Hydroxylgruppen der Seitenketten, die N3-Stickstoffatome der Imidazolringe und die O12-Sauerstoffatome der C4-Nitrogruppen beteiligen (Tabelle 2). Außerdem liegen im Kristallnetz von (3) weitere intermolekulare nicht-konventionelle Wasserstoffbrückenbindungen vor (Tabelle 2).