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Two isomeric dideoxynucleosides

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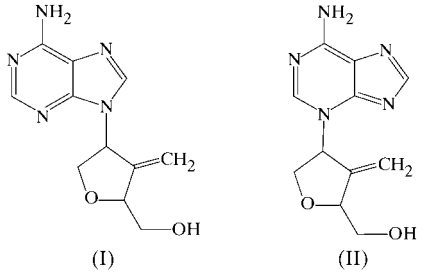
We have synthesized two isomeric dideoxynucleosides. 4(*S*)-(6-Amino-9*H*-purin-9-yl)-3-methylene-2,3,4,5-tetrahydrofuran-2(*S*)-ylmethanol, $C_{11}H_{13}N_5O_2$, is an analogue of the anti-HIV compound (*S,S*)-isodideoxyadenosine (isoDDA) with an exocyclic methylene group and is found to be anti-HIV inactive. The solid-state comformation is very similar to that of isoDDA. 4(*S*)-(6-Amino-3*H*-purin-3-yl)-3-methylene-2,3,4,5-tetrahydrofuran-2(*S*)-ylmethanol, $C_{11}H_{13}N_5O_2$, has an isomeric arrangement of the carbohydrate and base moieties, as confirmed by the crystal structure analysis. The asymmetric unit contains two independent molecules that differ in conformations at the sugar moiety.

Comment

4(*S*)-6-Amino-9*H*-purin-9-yl)2,3,4,5-tetrahydrofuran-2(*S*)-ylmethanol [(*S,S*)-isodideoxyadenosine or isoDDA; Bolon *et al.*, 1994] has potent anti-HIV activity against HIV-1 and HIV-2 (Nair *et al.*, 1995). Our interest in this compound led to the design and synthesis (using the Mitsunobu reaction as the key step) of compound (I), which was characterized by NMR, UV and HRMS data. Surprisingly compound (I) was found to



(I) (II)

be anti-HIV inactive from *in vitro* studies with infected CEM-SS cells. We determined the crystal structure in a search for possible explanations of the inactivity.

The solid-state conformation of compound (I) shows the sugar ring to have an O1′-envelope conformation *anti* to the adenine. This conformation is very similar to the solid-state comformation of isoDDA, the only difference being the O1′,C5′-half-chair conformation of the sugar ring of isoDDA. In both compounds, an intramolecular hydrogen-bond-like interaction is present between H8 of adenine and O6′ of the sugar moiety [C8—O6′ = 3.261 (2) Å for isoDDA and 3.444 (2) Å for compound (I)]. The methylene substituent of compound (I) may impart sufficient conformational rigidity to the sugar ring to preserve this conformation in solution, thus preventing cellular phosphorylation which is a requirement for anti-HIV activity.

Intermolecular hydrogen bonding occurs between the N6 amine and O6′ hydroxyl H atoms and the ring N atoms of the adenine moiety of adjacent molecules forming interlocked chains two molecules wide along the *c* axis.

The novel isomer, compound (II), has the sugar ring attachment at N3 of the base and has methylene substitution at C3′. The key step in the synthesis was a Mitsunobu coupling reaction. The title compound was characterized by NMR, UV and HRMS data. The crystal structure confirms the structure of the isomer.

The asymmetric unit contains two independent molecules (*A* and *B*) that have different carbohydrate-ring conformations. The conformations differ in three respects: (i) the ring of molecule *A* has an O5′*A*-envelope conformation, while the ring of molecule *B* has an O1′*B*,C5′*B*-half-chair conformation; (ii) in molecule *A*, the O6′*A* atom is *anti* to C3′*A* [C3′*A*—C2′*A*—C6′*A*—O6′*A* = −167.2 (4)°] and in molecule *B*, the O6′*B* atom is *anti* to H2′*B* [H2′*B*—C2′*B*—C6′*B*—O6′*B* = 173°]; (iii) the molecules differ in the relative orientation of the carbohydrate ring to the base; molecule *A*, C2*A*—N3*A*—C4′*A*—C5′*A* = 39.3 (6)°, and molecule *B*, C2*B*—N3*B*—C4′*B*—C5′*B* = 24.0 (6)°.

The hydrogen bonds between the amine H atoms and the ring N atoms of adjacent molecules form doubly linked ribbons of molecules parallel to the *a* axis. The O6′ hydroxyl H atoms form hydrogen bonds that link the ribbons.

Experimental

Preparation of compound (I): to a suspension of 2-(*S*)-(*tert*-butyl diphenylsilyloxymethyl)-3-methylenetetrahydrofuran-4-(*R*)-ol (1.66 mmol), Ph_3P (0.65 g) and adenine in dioxane (80 ml) at room temperature, DEAD (0.4 ml) was added dropwise and the resulting solution was stirred at room temperature for 22 h. The solvent was evaporated and the residue was purified on a silica-gel column. The major product (N-9 isomer; 0.34 g, 42% yield) was deprotected with NH_4F (0.4 g) in MeOH (30 ml) to give, after chromatographic separation on silica gel, compound (I) in 85% yield. Compound (I) crystallized from MeOH as white prisms: m.p. 463 K; ^{1}H NMR (DMSO-d_6) δ 8.15 (2 × *s*, 2H, H-2 and H-8), 7.25 (*bs*, 2H, NH_2), 5.56 (*t*, 1H, H-4′), 5.30 (*bs*, 1H, vinyl), 5.06 (*t, J* = 5.6 Hz, 1H, OH), 4.44 (*bs*, 1H, H-2′), 3.73 (*m*, 2H, H-5′), 3.31 (*t, J* = 6.7 Hz, 2H, CH_2); UV (MeOH) λ_{max} 260.6 nm (ε 14 000). HRMS (FAB): $(M + Na)^+$ calculated for $C_{11}H_{13}N_5NaO_2$ 270.0966, found 270.0959. Preparation of the compound (II): to a suspension of 2-(*S*)-(*tert*-butyldiphenylsilyloxymethyl)-3-methylenetetrahydrofuran-4-(*R*)-ol (1.66 mmol), Ph_3P (0.65 g), and adenine in dioxane (80 ml) at room temperature, DEAD (0.4 ml) was added dropwise and the reaction mixture was stirred at room temperature for 22 h. The solvent was then evaporated and the residue was separated on a silica-gel column. The minor product (N-3 isomer; 0.15 g, 19% yield) was deprotected with

NH_4F to give, after chromatographic purification on silica gel, the compound (II) in 86% yield. The title compound crystallized from methanol as white prisms: m.p. 529 K; ^{1}H NMR (CD_3OD) δ 8.62 (*s*, 1H, H-8), 7.90 (*s*, 1H, H-2), 5.85 (*m*, *i*H, H-4′), 5.49 (*m*, 2H, vinyl), 4.52 (*bs*, 1H, H-2′), 4.29 (*dd*, *J* = 2.7, 10.6 Hz, 1H, H-5′a), 4.22 (*dd*, *J* = 5.9,10.6 Hz, 1H, H-5′b), 4.00 (*dd*, *J* = 2.9, 12.5Hz, 1 H, one of CH_2), 3.90 (*dd*, *J* = 3.3, 12.4 Hz, 1H, one H of CH_2); UV (MeOH) λ_{max} 274.5 nm (ε 13 300); HMRS (FAB): $(M + Na)^+$ calculated for $C_{11}H_{13}N_5NaO_2$ 270.0966, found 270.0954.

Compound (I)

Crystal data

$C_{11}H_{13}N_5O_2$
M_r = 247.26
Orthorhombic, $P2_12_12_1$
a = 9.727 (2) Å
b = 16.632 (4) Å
c = 7.104 (2) Å
V = 1149.3 (5) Å^3
Z = 4
D_x = 1.429 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 24 reflections
θ = 12.1–17.5°
μ = 0.104 mm^{-1}
T = 210 (2) K
Prism, colourless
0.36 × 0.24 × 0.21 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
θ–2θ scans
4469 measured reflections
1193 independent reflections
1133 reflections with $I > 2\sigma(I)$
R_{int} = 0.0242
θ_{max} = 25.0°
$h = -11 \rightarrow 11$
$k = -1 \rightarrow 19$
$l = -8 \rightarrow 8$
4 standard reflections
frequency: 120 min
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.023
$wR(F^2)$ = 0.064
S = 1.107
1193 reflections
166 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0349P)^2 + 0.1889P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.008
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.10 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.031 (3)

Table 1
Selected geometric parameters (Å, °) for (I).

N1—C2	1.340 (2)	C8—N9	1.370 (2)
N1—C6	1.354 (2)	N9—C4′	1.473 (2)
C2—N3	1.336 (2)	O1′—C5′	1.430 (2)
N3—C4	1.349 (2)	O1′—C2′	1.435 (2)
C4—N9	1.375 (2)	C2′—C3′	1.515 (2)
C4—C5	1.383 (2)	C2′—C6′	1.521 (2)
C5—N7	1.387 (2)	C3′—C7′	1.316 (2)
C5—C6	1.410 (2)	C3′—C4′	1.521 (2)
C6—N6	1.336 (2)	C4′—C5′	1.532 (2)
N7—C8	1.314 (2)	C6′—O6′	1.420 (2)
C2—N1—C6	118.34 (14)	C8—N9—C4′	126.52 (14)
N3—C2—N1	129.29 (16)	C4—N9—C4′	127.26 (14)
C2—N3—C4	110.58 (14)	C5′—O1′—C2′	106.28 (13)
N3—C4—N9	127.52 (15)	O1′—C2′—C3′	104.11 (13)
N3—C4—C5	126.90 (15)	O1′—C2′—C6′	109.48 (14)
N9—C4—C5	105.54 (14)	C3′—C2′—C6′	115.18 (15)
C4—C5—N7	110.88 (14)	C7′—C3′—C2′	126.86 (17)
C4—C5—C6	116.73 (15)	C7′—C3′—C4′	126.04 (17)
N7—C5—C6	132.31 (15)	C2′—C3′—C4′	106.99 (13)
N6—C6—N1	118.50 (15)	N9—C4′—C3′	110.65 (13)
N6—C6—C5	123.47 (16)	N9—C4′—C5′	112.93 (14)
N1—C6—C5	118.02 (15)	C3′—C4′—C5′	102.22 (13)
C8—N7—C5	103.83 (14)	O1′—C5′—C4′	105.15 (13)
N7—C8—N9	113.59 (15)	O6′—C6′—C2′	113.27 (14)
C8—N9—C4	106.16 (14)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6*A*···N1^{i}	0.86	2.17	2.979 (2)	156
N6—H6*B*···N7^{ii}	0.86	2.13	2.975 (2)	168
O6′—H6′···N3^{iii}	0.82	2.18	2.957 (2)	158
C8—H8···O6′	0.93	2.61	3.444 (2)	150

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

Compound (II)

Crystal data

$C_{11}H_{13}N_5O_2$
M_r = 247.26
Monoclinic, $P2_1$
a = 8.496 (4) Å
b = 18.530 (6) Å
c = 7.226 (2) Å
β = 90.81 (4)°
V = 1137.5 (7) Å^3
Z = 4
D_x = 1.444 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 22 reflections
θ = 10.0–13.6°
μ = 0.105 mm^{-1}
T = 200 (2) K
Prism, colourless
0.31 × 0.25 × 0.24 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
θ–2θ scans
5428 measured reflections
2031 independent reflections
1665 reflections with $I > 2\sigma(I)$
R_{int} = 0.0691
θ_{max} = 25.0°
$h = -10 \rightarrow 10$
$k = -21 \rightarrow 21$
$l = -6 \rightarrow 8$
4 standard reflections
frequency: 120 min
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.133
S = 0.973
2031 reflections
327 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0794P)^2 + 0.9198P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.015
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

N1*A*—C2*A*	1.318 (7)	N1*B*—C2*B*	1.314 (7)
N1*A*—C6*A*	1.377 (7)	N1*B*—C6*B*	1.380 (6)
C2*A*—N3*A*	1.333 (7)	C2*B*—N3*B*	1.351 (7)
N3*A*—C4*A*	1.379 (6)	N3*B*—C4*B*	1.379 (6)
N3*A*—C4′*A*	1.489 (6)	N3*B*—C4′*B*	1.476 (7)
C4*A*—N9*A*	1.345 (7)	C4*B*—N9*B*	1.341 (7)
C4*A*—C5*A*	1.377 (7)	C4*B*—C5*B*	1.392 (8)
C5*A*—N7*A*	1.391 (7)	C5*B*—N7*B*	1.383 (7)
C5*A*—C6*A*	1.421 (7)	C5*B*—C6*B*	1.408 (7)
C6*A*—N6*A*	1.310 (7)	N6*B*—C6*B*	1.308 (7)
N7*A*—C8*A*	1.343 (7)	N7*B*—C8*B*	1.339 (7)
C8*A*—N9*A*	1.369 (7)	C8*B*—N9*B*	1.355 (7)
O1′*A*—C5′*A*	1.425 (7)	O1′*B*—C5′*B*	1.440 (7)
O1′*A*—C2′*A*	1.448 (6)	O1′*B*—C2′*B*	1.447 (7)
C2′*A*—C6′*A*	1.482 (8)	C2′*B*—C6′*B*	1.497 (8)
C2′*A*—C3′*A*	1.507 (7)	C2′*B*—C3′*B*	1.512 (8)
C3′*A*—C7′*A*	1.321 (8)	C3′*B*—C7′*B*	1.328 (8)
C3′*A*—C4′*A*	1.516 (7)	C3′*B*—C4′*B*	1.522 (8)
C4′*A*—C5′*A*	1.535 (8)	C4′*B*—C5′*B*	1.526 (7)
C6′*A*—O6′*A*	1.417 (7)	O6′*B*—C6′*B*	1.402 (7)
C2A—N1A—C6A	119.0 (4)	C2*A*—N3*A*—C4′*A*	124.4 (4)
N1*A*—C2*A*—N3*A*	127.3 (5)	C4*A*—N3*A*—C4′*A*	119.8 (4)
C2*A*—N3*A*—C4*A*	115.8 (4)	N9*A*—C4*A*—N3*A*	127.8 (4)

N9*A*—C4*A*—C5*A*	111.5 (4)	C2*B*—N3*B*—C4′*B*	125.1 (4)
N3*A*—C4*A*—C5*A*	120.6 (4)	C4*B*—N3*B*—C4′*B*	119.0 (4)
C4*A*—C5*A*—N7*A*	108.2 (4)	N9*B*—C4*B*—N3*B*	127.6 (5)
C4*A*—C5*A*—C6*A*	120.4 (5)	N9*B*—C4*B*—C5*B*	111.6 (4)
N7*A*—C5*A*—C6*A*	131.4 (5)	N3*B*—C4*B*—C5*B*	120.6 (4)
N6*A*—C6*A*—N1*A*	118.3 (5)	N7*B*—C5*B*—C4*B*	108.0 (4)
N6*A*—C6*A*—C5*A*	124.8 (5)	N7*B*—C5*B*—C6*B*	131.9 (5)
N1*A*—C6*A*—C5*A*	116.8 (5)	C4*B*—C5*B*—C6*B*	120.0 (5)
C8*A*—N7*A*—C5*A*	102.1 (4)	N6*B*—C6*B*—N1*B*	117.8 (4)
N7*A*—C8*A*—N9*A*	116.6 (5)	N6*B*—C6*B*—C5*B*	124.8 (5)
C4*A*—N9*A*—C8*A*	101.6 (4)	N1*B*—C6*B*—C5*B*	117.3 (5)
C5′*A*—O1′*A*—C2′*A*	105.5 (4)	C8*B*—N7*B*—C5*B*	101.2 (4)
O1′*A*—C2′*A*—C6′*A*	108.8 (4)	N7*B*—C8*B*—N9*B*	118.6 (5)
O1′*A*—C2′*A*—C3′*A*	103.4 (4)	C4*B*—N9*B*—C8*B*	100.5 (4)
C6′*A*—C2′*A*—C3′*A*	117.6 (5)	C5′*B*—O1′*B*—C2′*B*	105.4 (4)
C7′*A*—C3′*A*—C2′*A*	127.0 (5)	O1′*B*—C2′*B*—C6′*B*	108.3 (5)
C7′*A*—C3′*A*—C4′*A*	125.3 (5)	O1′*B*—C2′*B*—C3′*B*	104.4 (4)
C2′*A*—C3′*A*—C4′*A*	107.8 (4)	C6′*B*—C2′*B*—C3′*B*	115.0 (5)
N3*A*—C4′*A*—C3′*A*	111.7 (4)	C7′*B*—C3′*B*—C2′*B*	126.9 (5)
N3*A*—C4′*A*—C5′*A*	112.9 (4)	C7′*B*—C3′*B*—C4′*B*	125.6 (5)
C3′*A*—C4′*A*—C5′*A*	101.5 (4)	C2′*B*—C3′*B*—C4′*B*	107.4 (4)
O1′*A*—C5′*A*—C4′*A*	105.3 (4)	N3*B*—C4′*B*—C3′*B*	111.2 (4)
O6′*A*—C6′*A*—C2′*A*	113.4 (5)	N3*B*—C4′*B*—C5′*B*	114.8 (4)
C2*B*—N1*B*—C6*B*	119.6 (4)	C3′*B*—C4′*B*—C5′*B*	101.4 (4)
N1*B*—C2*B*—N3*B*	126.5 (5)	O1′*B*—C5′*B*—C4′*B*	104.8 (4)
C2*B*—N3*B*—C4*B*	115.9 (4)	O6′*B*—C6′*B*—C2′*B*	111.4 (4)

Due to the lack of heavy atoms, the Friedel pair reflections were averaged together for each structure. For compound (I), 825 Friedel pairs were averaged and for compound (II), 1786 Friedel pairs were averaged. The absolute configurations of molecules *A* and *B* were inferred from the configuration of the starting materials.

For both compounds, data collection: *CAD*-4 *Operations Manual* (Enraf–Nonius, 1977); cell refinement: *CAD*-4 *Operations Manual*; data reduction: *MolEN* (Fair, 1990); program(s) used to solve structure: *SHELXTL* (Sheldrick, 1995); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL*.

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Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6*A*—H6*A*1···N7*B*^{i}	0.86	2.08	2.937 (6)	174
N6*A*—H6*A*2···N1*B*^{ii}	0.86	2.28	3.127 (6)	168
O6′*A*—H6′*A*···O6′*B*^{iii}	0.82	1.94	2.745 (6)	167
N6*B*—H6*B*1···N7*A*^{iv}	0.86	2.07	2.924 (6)	172
N6*B*—H8*B*2···N1*A*^{v}	0.86	2.29	3.130 (6)	167
O6′*B*—H6′*B*···N9*A*^{vi}	0.82	1.91	2.731 (5)	175

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

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