Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

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Electronic paper
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A dideoxydidehydronucleoside derivative

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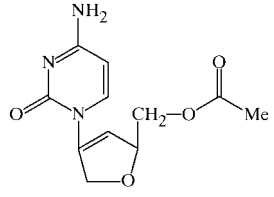
Received 20 September 2000
Accepted 9 November 2000

Data validation number: IUC0000325

We have synthesized a dideoxydidehydronucleoside derivative, 2(*S*)-acetoxymethyl-4-[4-amino-2-oxopyrimidin-1(2*H*)-yl]-2,5-dihydrofuran, $C_{11}H_{13}N_3O_4$, which is an analogue of the potently anti-HIV active compound, dideoxy-didehydrocytidine (d4C). The target compound crystallizes with two molecules in the asymmetric unit that differ primarily in the orientation of the C6′-acetyl group. One molecule has an extended conformation and the orientation of the acetyl group in the second molecule gives an unusual hooked-shaped conformation. The two conformers form *A*–*B* dimers *via* N—H···N hydrogen bonds. The dimers link *via* N—H···O hydrogen bonds to form chains parallel to the *b* cell axis.

Comment

Dideoxydidehydrocytidine (d4C) has potent anti-HIV activity (Balzarini *et al.*, 1986). Our interest in the design of novel isomeric nucleosides of potential anti-HIV activity (Nair *et al.*, 1995) led to the synthesis of compound (II) and its lipophilic derivative (I) which are structural analogues of d4C. Because of the complex synthetic pathway to (II), it was necessary to



(I)

confirm its structure through its more crystalline pro-drug derivative (I). Compound (I) was synthesized *via* a rearrangement reaction of 4(*R*)-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-2(*R*)-(benzoyloxymethyl)tetrahydrofuran-3(*S*)-*O*-methanesulfonate followed by conversion of the uracil base to cytosine (Bera *et al.*, 1999, Nair & Nuesca, 1992; Kakefuda *et al.*, 1994). Compound (I) was characterized by NMR and HRMS data.

Compound (I) crystallizes with two confomers, *A* and *B*, in the asymmetric unit (atoms of a conformer are identified by *A* or *B* in the labels). For both conformers, the pyrimidine rings are planar (0.025 and 0.006 Å r.m.s. deviation from planarity for *A* and *B*, respectively) as are the acetyl substituents (0.004 and 0.001 Å r.m.s. deviation for *A* and *B*, respectively). Although the dihydrofuran (DHF) ring of *A* is planar (0.014 Å r.m.s. deviation) the DHF ring of *B* has an O1′*B*-envelope conformation [O1′*B* is 0.231 (6) Å from the C2′*B*, C3′*B*, C4′*B*, C5′*B* plane, 0.004 Å r.m.s. deviation]. Rotation about the N1—C4′ bond relieves steric repulsion between the pyrimidine and DHF rings; however, the sense of rotation is reversed between *A* and *B* (see Table 1) and *B* is rotated to a greater degree. The greatest difference in conformation between *A* and *B* is the orientation of the C6′ acetyl substituent. When considering rotation about the C2′—C6′ bond, in *A*, O6′*A* is *anti* to C3′*A* which positions the acetyl moiety *anti* to the DHF ring resulting in an extended conformation. In *B*, O6′*B* is *gauche* to C3′*B* which positions the acetyl group *syn* to the DHF ring giving a hook-shaped molecule.

The two conformers form dimers *via* two N4—H4···N3 hydrogen bonds (see Table 2) to a symmetry-related molecule generated *via* the $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}\ z$ symmetry operation. The dimers are linked *via* N4—H4···O2 hydrogen bonds to form chains of dimers parallel to the *b* unit-cell direction.

Experimental

To a solution of 2(*S*)-(hydroxymethyl)-4-[(3,4-dihydro-2-oxo-4-amino-1(2*H*)-pyrimidinyl]-2,5-dihydrofuran (0.08 g, 0.38 mmol) in pyridine (10 ml), Ac_2O was added and the reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ solution (30 ml) was then added and the solution was extracted with $CHCl_3$ (3 × 20 ml). The combined $CHCl_3$ part was evaporated to dryness and the residual pyridine was co-evaporated with toluene. The gummy residue was purified on a silica gel column to give the acetyl derivative (0.09 g, 94%). Triethylamine (0.1 ml, 0.72 mmol) was added to a solution of the acetyl derivative (0.09 g, 0.35 mmol) in CH_3CN (10 ml) containing TPSCl (0.22 g, 0.72 mmol) and DMAP (0.90 g, 0.72 mmol) at 273 K. The reaction mixture was stirred at room temperature for 3.5 h. Concentrated NH_4OH solution (28% solution, 6 ml) was added and the solution was further stirred at room temperature for 2 h. The solvent was evaporated to dryness, the residue was purified on a silica-gel column and crystallized from methanol to give (II) (0.048 g, 54% for two steps): m.p. 384 K; ^{1}H NMR (DMSO-d_6): δ 7.56 (*d, J* = 7.5 Hz, 1H, H-6), 7.40 (*bd*, 2H, NH_2), 6.05 (*m*, 1H, H-3′), 5.78 (*d, J* = 7.5 Hz, 1H, H-5), 4.98 (*m*, 1H, H-2′), 4.87 (*m*, 2H, H-5′), 4.06 (*m*, 2H, CH_2), 2.01 (*s*, 3H, acetyl CH_3); ^{13}C NMR (DMSO-d_6): δ 172.7 (ester CO), 167.6 (C-2), 157.0 (C-4), 145.1 (C-6), 141.4 (C-4′), 115.9 (C-3′), 97.1 (C-5), 84.3 (C-2′) 74.1 (C-5′) 67.1 (CH_2), 20.7 (CH_3); HRMS (FAB): $(M + H)^+$ calculated for $C_{11}H_{14}$-tpbgc=^st_head3_bgcolour]>N_3O_4 252.0984, found 252.0979.

Crystal data

$C_{11}H_{13}N_3O_4$
M_r = 251.24
Monoclinic, *I*2
a = 15.995 (2) Å
b = 6.865 (1) Å
c = 21.934 (5) Å
β = 94.16 (2)°
V = 2402.1 (7) Å^3
Z = 8
D_x = 1.389 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 22 reflections
θ = 10.0–13.6°
μ = 0.108 mm^{-1}
T = 213 (2) K
Prism, colourless
0.33 × 0.22 × 0.18 mm

Data collection

Enraf–Nonius CAD-4 diffractometer	$\theta_{max} = 25.0°$
θ–2θ scans	$h = -18 \rightarrow 18$
8222 measured reflections	$k = -8 \rightarrow 8$
2283 independent reflections	$l = -25 \rightarrow 25$
1774 reflections with $I > 2\sigma(I)$	4 standard reflections
$R_{int} = 0.052$	frequency: 120 min
	intensity decay: <2%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0514P)^2 + 0.4716P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.035$	$(\Delta/\sigma)_{max} = 0.003$
$wR(F^2) = 0.098$	$\Delta\rho_{max} = 0.19$ e Å^{-3}
$S = 1.095$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
2283 reflections	
327 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

N1*A*—C6*A*	1.379 (4)	N1*B*—C6*B*	1.376 (4)
N1*A*—C2*A*	1.407 (4)	N1*B*—C2*B*	1.401 (4)
N1*A*—C4′*A*	1.425 (4)	N1*B*—C4′*B*	1.432 (4)
C2*A*—O2*A*	1.239 (4)	C2*B*—O2*B*	1.235 (4)
C2*A*—N3*A*	1.359 (4)	C2*B*—N3*B*	1.350 (4)
N3*A*—C4*A*	1.331 (4)	N3*B*—C4*B*	1.346 (4)
C4*A*—N4*A*	1.331 (4)	C4*B*—N4*B*	1.323 (4)
O1′*A*—C5′*A*	1.421 (4)	O1′*B*—C5′*B*	1.429 (4)
O1′*A*—C2′*A*	1.428 (4)	O1′*B*—C2′*B*	1.442 (5)
C6′*A*—O6′*A*	1.452 (5)	C6′*B*—O6′*B*	1.440 (5)
O6′*A*—C7′*A*	1.315 (6)	O6′*B*—C7′*B*	1.340 (6)
C7′*A*—O7′*A*	1.210 (8)	C7′*B*—O7′*B*	1.181 (5)
C6*A*—N1*A*—C2*A*	119.7 (3)	C6*B*—N1*B*—C2*B*	120.7 (3)
C6*A*—N1*A*—C4′*A*	119.1 (3)	C6*B*—N1*B*—C4′*B*	120.1 (3)
C2*A*—N1*A*—C4′*A*	121.1 (3)	C2*B*—N1*B*—C4′*B*	119.1 (3)
O2*A*—C2*A*—N3*A*	121.9 (3)	O2*B*—C2*B*—N3*B*	121.9 (3)
O2*A*—C2*A*—N1*A*	119.2 (3)	O2*B*—C2*B*—N1*B*	119.0 (3)
N3*A*—C2*A*—N1*A*	118.9 (3)	N3*B*—C2*B*—N1*B*	119.0 (3)
C4*A*—N3*A*—C2*A*	120.2 (3)	C4*B*—N3*B*—C2*B*	120.0 (3)
N4*A*—C4*A*—N3*A*	118.2 (3)	N4*B*—C4*B*—N3*B*	117.5 (3)
N4*A*—C4*A*—C5*A*	119.9 (3)	N4*B*—C4*B*—C5*B*	120.3 (3)
N3*A*—C4*A*—C5*A*	121.8 (3)	N3*B*—C4*B*—C5*B*	122.2 (3)
C5*A*—C6*A*—N1*A*	121.7 (3)	C5*B*—C6*B*—N1*B*	120.9 (3)
C5′*A*—O1′*A*—C2′*A*	110.3 (3)	C5′*B*—O1′*B*—C2′*B*	109.1 (3)
O1′*A*—C2′*A*—C6′*A*	109.9 (4)	O1′*B*—C2′*B*—C3′*B*	104.3 (3)
O1′*A*—C2′*A*—C3′*A*	104.6 (3)	O1′*B*—C2′*B*—C6′*B*	111.3 (3)
C3′*A*—C4′*A*—N1*A*	126.0 (3)	C3′*B*—C4′*B*—N1*B*	126.1 (3)
N1*A*—C4′*A*—C5′*A*	123.0 (3)	N1*B*—C4′*B*—C5′*B*	122.8 (3)
O1′*A*—C5′*A*—C4′*A*	104.7 (3)	O1′*B*—C5′*B*—C4′*B*	103.8 (3)
O6′*A*—C6′*A*—C2′*A*	111.8 (3)	O6′*B*—C6′*B*—C2′*B*	109.4 (3)
C7′*A*—O6′*A*—C6′*A*	116.2 (4)	C7′*B*—O6′*B*—C6′*B*	119.7 (3)
O7′*A*—C7′*A*—O6′*A*	124.0 (6)	O7′*B*—C7′*B*—O6′*B*	122.9 (5)
O7′*A*—C7′*A*—C8′*A*	125.6 (6)	O7′*B*—C7′*B*—C8′*B*	125.9 (5)
O6′*A*—C7′*A*—C8′*A*	110.4 (6)	O6′*B*—C7′*B*—C8′*B*	111.1 (4)

C6*A*—N1*A*—C4′*A*—C3′*A*	−38.5 (5)	C6*B*—N1*B*—C4′*B*—C3′*B*	54.7 (5)
C3′*A*—C2′*A*—C6′*A*—O6′*A*	−169.8 (3)	C2′*B*—O1′*B*—C5′*B*—C4′*B*	−15.3 (4)
C2′*A*—C6′*A*—O6′*A*—C7′*A*	−88.5 (5)	C3′*B*—C4′*B*—C5′*B*—O1′*B*	8.9 (4)
C5′*B*—O1′*B*—C2′*B*—C3′*B*	15.9 (4)	C3′*B*—C2′*B*—C6′*B*—O6′*B*	−61.6 (4)
O1′*B*—C2′*B*—C3′*B*—C4′*B*	−10.2 (4)	C2′*B*—C6′*B*—O6′*B*—C7′*B*	108.8 (4)
C2′*B*—C3′*B*—C4′*B*—C5′*B*	0.8 (4)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4*A*—H4*A*1···N3*B*^{i}	0.86	2.19	3.031 (4)	164
N4*A*—H4*A*2···O2*A*^{ii}	0.86	2.27	3.002 (4)	144
N4*B*—H4*B*1···N3*A*^{iii}	0.86	2.15	3.004 (4)	170
N4*B*—H4*B*2···O2*B*^{iv}	0.86	2.12	2.901 (4)	150

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

H atoms were refined as riding (N—H = 0.86 Å and C—H = 0.93–0.98 Å). 950 Friedel pair reflections were merged for the last four cycles of refinement.

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* (Sheldrick, 1995).

We thank the NIH (NIAID) for support of these studies.

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