$C_{13}H_{17}NO$

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A (±)-Cyclocytidine Analogue with a Low-*anti* Conformation around the Glycosyl Bond

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Abstract

The crystal structure of the cytidine analogue (±)-6,6'-anhydro-2'-deoxy-6,6'β-dihydroxycarbacytidine hydrate (alternative name: 3-amino-7-hydroxy-6-hydroxymethyl-6,7,8,8a-tetrahydro-1*H*,5a*H*-cyclopenta[1',2':1,2]oxazolo[3,2-c]pyrimidin-1-one hydrate), $C_{10}H_{13}N_3O_4 \cdot H_2O$, in which the glycosyl torsion angle was fixed by cyclization between the C6' atom of the cyclopentane ring and the C6 atom of the cytosine base with one O

atom, was determined by X-ray analysis. The crystal belongs to the monoclinic space group $P2_1/c$ and the unit cell contains four cytidine analogue and four water molecules. The terminal O5' atom of the cytidine analogue molecule is hydrogen bonded to a water molecule. The glycosyl torsion angle is low-*anti* (χ = 176.3°) and the puckering of the cyclopentane ring is C3'-envelope.

Comment

Progress in a recent gene analysis has resulted in the discovery of many important genes which cause genetic diseases. In order to inhibit the expression of the target gene, diagnostic and therapeutic antisense application has been developed, which is based on the double-helix formation between a particular mRNA fragment of the target gene and its complementary oligodeoxyribonucleotide analogue. Urata *et al.* (1993) solved by NMR studies the molecular structure of the heterochiral dodecadeoxynucleotide d(CGCGAATTCGCG), which has a single 'chiral defect' at the G4 residue and whose sugar moiety has an unnatural L chirality, and demonstrated that the unnatural G4 residue formed stable Watson–Crick-type base pairing with the natural C9 residue, with S-type sugar geometry (C2'-*endo*) and a low-*anti* (χ *ca* 180°) glycosyl conformation in a right-handed B-form duplex. These studies may give a new insight into the chemistry of the antisense application of oligodeoxyribonucleotides having a low-*anti* glycosyl conformation.

As part of the synthesis of oligodeoxyribonucleotide analogues, cyclocarbacytidine, (I), was synthesized by cyclization between the C6 atom of the base and the C6' atom (adjacent to C1') of the cyclopentane ring for fixation of the glycosyl torsion angle in the low-*anti* region. This paper deals with the crystal structure analysis of (±)-cyclocarbacytidine.

(I)
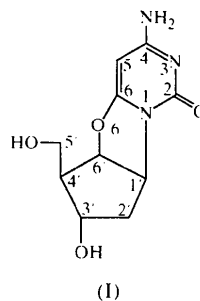
An *ORTEP*III (Burnett & Johnson, 1996) drawing of cyclocarbacytidine is shown in Fig. 1, and for comparison, the molecular structure of cytidine determined by Furburg (1951) is shown in Fig. 2. The conformational details are given in Table 1. Normally the glycosyl torsion angle of a nucleoside with an *anti* conformation is in the range *ca* 90 to *ca* 270° [(±)-anticlinal and

(±)-antiperiplanar] (Saenger, 1988), and that of cyclo-carbacytidine is fixed at the low-*anti* conformation (χ = 176.3°) by cyclization with the O6 atom between the C6 atom of the cytosine base and the C6' atom (adjacent to C1') of the cyclopentane ring instead of the O4' atom of the deoxyribose ring in the case of the natural nucleoside. The puckering of the cyclopentane ring in this compound is of the C3'-envelope form (C3'-*endo*). On the other hand, the crystal structure of cytidine indicated that the glycosyl torsion angle was *anti* (χ = 162.6°) and the sugar puckering was of the C3'-*endo* form (Furburg, 1951). Furthermore, in this crystal, there are three hydrogen bonds which connect neighbouring cyclocarbacytidine molecules and form three-dimensional networks, as shown in Table 2.
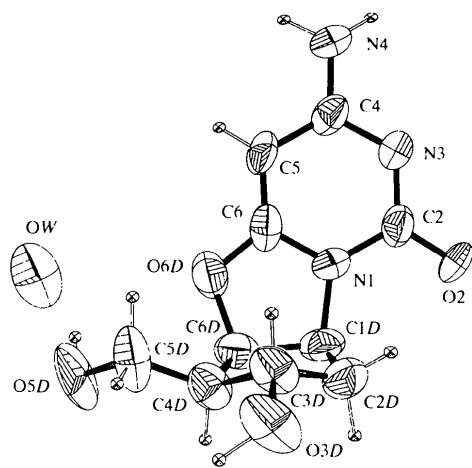

Fig. 1. An *ORTEP*III (Burnett & Johnson, 1996) drawing of the crystal structure of cyclocarbacytidine. Displacement ellipsoids are plotted at the 80% probability level.
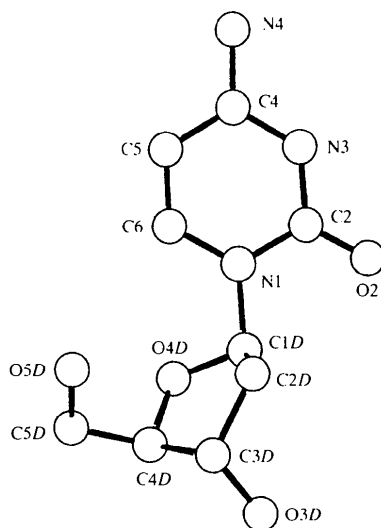

Fig. 2. An *ORTEP*II (Johnson, 1976) drawing of the crystal structure of cytidine (Furburg, 1951).

Experimental

The title compound was synthesized from uracil according to a method reported previously (Urata *et al.*, 1998) and was recrystallized from EtOH/H$_2$O.

Crystal data

C$_{10}$H$_{13}$N$_3$O$_4$.H$_2$O	Cu $K\alpha$ radiation
M_r = 257.25	λ = 1.5418 Å
Monoclinic	Cell parameters from 20
$P2_1/c$	reflections
a = 6.870 (2) Å	θ = 15–30°
b = 20.711 (2) Å	μ = 0.989 mm^{-1}
c = 8.526 (1) Å	T = 293 (2) K
β = 100.69 (1)°	Prism
V = 1192.1 (4) Å^3	0.50 × 0.10 × 0.05 mm
Z = 4	Colourless
D_x = 1.433 Mg m^{-3}	
D_m not measured	

Data collection

Rigaku AFC-5R diffractometer	1458 reflections with $I > 2\sigma(I)$
$2\theta-\omega$ scans	R_{int} = 0.014
Absorption correction:	θ_{max} = 61.86°
ψ scan (North *et al.*, 1968)	h = 0 → 7
	k = 0 → 23
T_{min} = 0.79, T_{max} = 0.95	l = –9 → 9
2018 measured reflections	3 standard reflections
1852 independent reflections	every 100 reflections
	intensity decay: 0.02%

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max}$ = 0.026
$R(F)$ = 0.052	$\Delta\rho_{max}$ = 0.695 e Å^{-3}
$wR(F^2)$ = 0.134	$\Delta\rho_{min}$ = –0.267 e Å^{-3}
S = 2.259	Extinction correction: none
1851 reflections	Scattering factors from
211 parameters	*International Tables for*
All H atoms refined	*Crystallography* (Vol. C)
$w = 1/[\sigma^2(F_o^2) + (0.037P)^2 + 0.31P]$	
where $P = (F_o^2 + 2F_c^2)/3$	

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

N1—C6	1.359 (3)	C1D—C2D	1.539 (4)
N1—C2	1.392 (3)	C1D—C6D	1.548 (4)
N1—C1D	1.469 (3)	C2D—C3D	1.534 (4)
C2—O2	1.233 (3)	C3D—O3D	1.436 (3)
C2—N3	1.354 (3)	C3D—C4D	1.538 (4)
N3—C4	1.353 (3)	C4D—C5D	1.513 (4)
C4—N4	1.334 (4)	C4D—C6D	1.535 (4)
C4—C5	1.414 (4)	C5D—O5D	1.433 (4)
C5—C6	1.345 (4)	C6D—O6D	1.469 (3)
C6—O6D	1.330 (3)		
C6—N1—C2	121.4 (2)	N1—C1D—C6D	101.1 (2)
C6—N1—C1D	112.1 (2)	C2D—C1D—C6D	105.4 (2)
C2—N1—C1D	126.5 (2)	C3D—C2D—C1D	104.7 (2)
O2—C2—N3	123.4 (2)	O3D—C3D—C2D	114.0 (2)
O2—C2—N1	118.3 (2)	O3D—C3D—C4D	110.2 (2)
N3—C2—N1	118.3 (2)	C2D—C3D—C4D	103.2 (2)
C4—N3—C2	119.4 (2)	C5D—C4D—C6D	114.9 (3)
N4—C4—N3	117.1 (2)	C5D—C4D—C3D	113.0 (2)
N4—C4—C5	119.7 (2)	C6D—C4D—C3D	104.2 (2)

$C_{10}H_{13}N_3O_4.H_2O$

N3—C4—C5	123.3 (2)	O5D—C5D—C4D	111.4 (3)
C6—C5—C4	115.8 (2)	O6D—C6D—C4D	109.8 (2)
O6D—C6—C5	126.7 (2)	O6D—C6D—C1D	105.5 (2)
O6D—C6—N1	111.6 (2)	C4D—C6D—C1D	107.1 (2)
C5—C6—N1	121.7 (2)	C6—O6D—C6D	109.8 (2)
N1—C1D—C2D	113.0 (2)		

C2—N1—C1D—C2D	−71.5 (3)
C1D—C2D—C3D—C4D	−38.4 (3)
C2—N1—C1D—C6D	176.3 (3)
C2D—C3D—C4D—C5D	162.6 (3)
C6—N1—C1D—C2D	111.9 (3)
C2D—C3D—C4D—C6D	37.2 (3)
C6—N1—C1D—C6D	−0.2 (3)
O3D—C3D—C4D—C5D	−75.4 (3)
N1—C6—O6D—C6D	−1.4 (3)
O3D—C3D—C4D—C6D	159.3 (2)
C5—C6—O6D—C6D	178.6 (3)
C3D—C4D—C5D—O5D	178.7 (3)
N1—C1D—C2D—C3D	−84.9 (3)
C6D—C4D—C5D—O5D	−62.0 (4)
C6D—C1D—C2D—C3D	24.6 (3)
C3D—C4D—C6D—C1D	−22.1 (3)
N1—C1D—C6D—C4D	116.4 (2)
C3D—C4D—C6D—O6D	92.0 (3)
N1—C1D—C6D—O6D	−0.5 (3)
C5D—C4D—C6D—C1D	−146.2 (3)
C2D—C1D—C6D—C4D	−1.5 (3)
C5D—C4D—C6D—O6D	−32.1 (3)
C2D—C1D—C6D—O6D	−118.4 (2)
C1D—C6D—O6D—C6	1.2 (3)
C1D—C2D—C3D—O3D	−158.0 (2)
C4D—C6D—O6D—C6	−113.9 (3)

Table 2. Contact distances (Å)

OW···O5D	2.793 (4)	N3···O3D'''	2.871 (3)
O2···N4^i	2.893 (4)	OW···N3^{iv}	3.168 (4)
N4···O5D''	2.821 (4)	OW···O3D^v	2.821 (4)

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

Intensities were measured with a scan rate of 4° min^{-1} in 2θ and a scan width of $d(2\theta) = (1.2 + 0.15\tan\theta)°$. Background intensities were measured for 4 s at each side of a scan. The initial E map gave a partial structure around the pyrimidine skeleton. The positions of the remaining non-H atoms were located stepwise from the subsequent Fourier syntheses. The structure was refined by the block-diagonal least-squares procedure and the full-matrix least-squares refinement was carried out with SHELXL93 (Sheldrick, 1993).

Data collection: Rigaku/AFC Diffractometer Control Software (Rigaku Co. Ltd, 1997). Cell refinement: Rigaku/AFC Diffractometer Control Software. Data reduction: UNICS (Universal Crystallographic Computation Program System Osaka, 1979). Program(s) used to solve structure: MULTAN87 (Debaerdemaeker et al., 1987). Molecular graphics: ORTEPII (Johnson, 1976) and ORTEPIII (Burnett & Johnson, 1996).

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Methyl Ester of the Bioactive Metabolite of Thromboxane A2 Receptor Antagonist ON-579

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Abstract

The title compound, methyl (RS)-{4-[2-(4-chlorophenylsulfonylamino)ethylsulfinyl]-2,6-difluorophenoxy}acetate, $C_{17}H_{16}ClF_2NO_6S_2$, crystallizes in space group $P2_1/c$. In the crystal, the enantiomeric molecules, related by a center of symmetry, form pairs joined by N—H···O hydrogen bonds.

Comment

In the course of our investigation of the pharmacodynamics of 4-[2-(4-chlorophenylsulfonylamino)ethylthio]-2,6-difluorophenoxyacetic acid (ON-579), which is a novel thromboxane A2 antagonist (Sato et al., 1995), the corresponding sulfoxide, namely ON-579M2, was detected as a major and bioactive metabolite in animal urines. This paper reports the crystal structure of the synthetic racemate, (I), of the title compound.

(I)