Data collection

Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems variable temperature device (Cosier & Glazer, 1986)	1238 reflections with $I > 2\sigma(I)$
ω–θ scans	$R_{int} = 0.026$
Absorption correction: none	$\theta_{max} = 60.05°$
3393 measured reflections	$h = -18 \rightarrow 16$
1535 independent reflections	$k = -6 \rightarrow 6$
	$l = -24 \rightarrow 15$
	3 standard reflections
	frequency: 120 min
	intensity decay: 5%

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} < 0.001$
$R[F^2 > 2\sigma(F^2)] = 0.035$	$\Delta\rho_{max} = 0.135$ e Å^{-3}
$wR(F^2) = 0.094$	$\Delta\rho_{min} = -0.132$ e Å^{-3}
$S = 1.048$	Extinction correction: *SHELXTL*
1533 reflections	Extinction coefficient: 0.0012 (2)
146 parameters	Scattering factors from *International Tables for Crystallography* (Vol. C)
H atoms not refined	
$w = 1/[\sigma^2(F_o^2) + (0.0549P)^2 + 0.058P]$ where $P = (F_o^2 + 2F_c^2)/3$	

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

C1—O1	1.238 (2)	C3a—C7a	1.384 (2)
C1—N2	1.346 (2)	C3a—C4	1.385 (2)
C1—C7a	1.479 (2)	C4—C5	1.385 (2)
N2—C3	1.456 (2)	C5—C6	1.386 (3)
C3—C3a	1.513 (2)	C6—C7	1.380 (2)
C3—C31	1.516 (2)	C7—C7a	1.388 (2)
O1—C1—N2	125.8 (2)	C4—C3a—C3	129.8 (2)
O1—C1—C7a	127.56 (15)	C3a—C4—C5	117.7 (2)
N2—C1—C7a	106.60 (14)	C4—C5—C6	121.5 (2)
C1—N2—C3	114.19 (13)	C7—C6—C5	120.9 (2)
N2—C3—C3a	101.40 (12)	C6—C7—C7a	117.6 (2)
N2—C3—C31	113.16 (13)	C3a—C7a—C7	121.6 (2)
C3a—C3—C31	113.71 (13)	C3a—C7a—C1	108.30 (14)
C7a—C3a—C4	120.7 (2)	C7—C7a—C1	130.1 (2)
C7a—C3a—C3	109.50 (14)		

The presence of the low-temperature device limited $2\theta_{max}$ to 120°.

Data collection: *DIF*4 (Stoe & Cie, 1990*a*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1990*b*). Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). 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: MU1321). Services for accessing these data are described at the back of the journal.

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3,4-Etheno-5-methoxymethyl-2′-deoxycytidine†

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Abstract

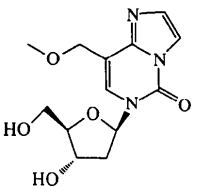
In the title compound, $C_{13}H_{17}N_3O_5$, the deoxyribose sugar ring adopts a C2′-*exo*–C3′-*endo* symmetrical half-chair conformation (^3_2T), with pseudorotational parameters of $P = 2.54(1)°$ and $\tau_m = 27.82(7)°$. The deoxyribose sugar ring is in the anticlinal (–*ac*) conformation with respect to the base [$\chi = -93.2(4)°$]. The exocyclic side chain at C5′ is in the *gg* conformation [$\gamma = 57.2(3)°$]. The methoxymethyl side chain at C5 is oriented towards the exocyclic side chain at C5′.

Comment

The title compound (3,4-etheno-MMdCyd), (I), is a structural analogue of 5-methoxymethyl-2′-deoxy-

† Alternative name: 6-(4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-8-(methoxymethyl)imidazo[1,2-*c*][1,3]diazin-5(6*H*)-one.

cytidine (MMdCyd), which is a nanomolar inhibitor of the Herpes Simplex I virus (HSV-I) (Aduma, Gupta, Stuart & Tourigny, 1990, 1991; Aduma, Gupta, Allaudeen, Stuart & Tourigny, 1991; Gupta *et al.*, 1992). However, 3,4-etheno-MMdCyd shows no antiviral activity (unpublished data). In this report, the molecular structure of 3,4-etheno-MMdCyd is presented, and structure/antiviral activity of this class of compounds is discussed.



(I)

The bond distances and angles of 3,4-etheno-MMdCyd (Fig. 1) are similar to those in both 2′-deoxycytidine (dCyd) and MMdCyd (Young & Wilson, 1975; Jia, Tourigny, Delbaere, Stuart & Gupta, 1990). The exocyclic 5′-CH_2OH side chain of 3,4-etheno-MMdCyd is in the *gg* conformation [γ = 57.2 (3)°], and is similar to that of both MMdCyd and dCyd (Young & Wilson, 1975; Jia *et al.*, 1990). The glycosidic bond is in the anticlinal (*–ac*) conformation, with the torsion angle C2—N1—C1′—O4′ being χ = −93.2 (4)°. The glycosidic bond in MMdCyd is also in the *anti* conformation, yet the χ angle differs from that of 3,4-etheno-MMdCyd by 40–50° in the two crystallographically independent molecules of MMdCyd (Jia *et al.*, 1990).

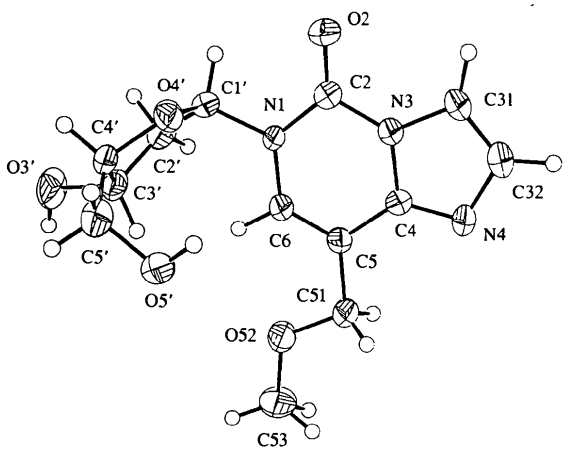


Fig. 1. An *ORTEP* (Johnston, 1976) plot of 3,4-etheno-MMdCyd. Non-H-atom displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as spheres of small arbitrary size.

Another difference between 3,4-etheno-MMdCyd and MMdCyd is in the conformation of the deoxyribose sugar ring. 3,4-Etheno-MMdCyd adopts a symmetrical C2′-*exo*-C3′-*endo* half-chair conformation (^3_2T). The pseudorotational parameters (Altona & Sundaralingam, 1972) of the furanose ring are the pseudorotational phase angle, P = 2.54 (1)°, and puckering amplitude, τ_m = 27.82 (7)°. This differs from MMdCyd, which has the deoxyribose sugar ring of one molecule in the C3′-*exo* ($_3E$) envelope and the other molecule in the C2′-*endo* (^2E) envelope conformations (Jia *et al.*, 1990).

A third difference between 3,4-etheno-MMdCyd and MMdCyd is in the orientation of the 5-methoxymethyl substituent on the base. In 3,4-etheno-MMdCyd, the C6—C5—C51—O52 torsion angle is −5.1 (3)°, and is on the opposite side of the pyrimidine ring plane to O4′. In the crystal structure of MMdCyd, the 5-methoxymethyl substituent adopts two conformations, one molecule where it is situated on the same side of the pyrimidine ring plane as O4′, and one molecule where it is on the opposite side. The C6—C5—C51—O52 torsion angles for MMdCyd are 129.5 (4) and −115.8 (4)°, respectively (Jia *et al.*, 1990). This difference in orientation of the 5-methoxymethyl group may be attributed to the presence of the 3,4-etheno group on the pyrimidine ring. The presence of this bulky group would make it unfavorable for the methoxymethyl group to orient towards N4 of the pyrimidine base, as seen in the structure of MMdCyd (Jia *et al.*, 1990).

The final difference between 3,4-etheno-MMdCyd and MMdCyd is the presence of the 3,4-etheno group in 3,4-etheno-MMdCyd. Not only does the addition of the 3,4-etheno group add a bulky planar group to the pyrimidine ring, but it also alters the hydrogen-bonding nature of N4. In MMdCyd, N4 is a hydrogen-bond donor. The addition of the 3,4-etheno group to the molecule removes the hydrogen-bonding donor capacity of N4, as well as the possibility of the formation of intramolecular hydrogen bonds, such as that between N4 and O52.

Intermolecular hydrogen bonds occur between symmetry-related molecules in the crystal. The geometry of these hydrogen bonds is shown in Table 2.

These differences between 3,4-etheno-MMdCyd and MMdCyd provide a possible explanation for the inactivity of 3,4-etheno-MMdCyd as an antiviral agent. With the addition of the bulky 3,4-etheno group to the pyrimidine ring, the compound is likely to be unable to fit into the binding pocket of the pyrimidine kinase which would otherwise phosphorylate it, or it is unable to fit into a binding pocket in the DNA polymerase, and hence unable to be incorporated into the viral DNA and disrupt Watson–Crick base pairing. Also, the alteration of N4 from being a hydrogen-bond donor to being a hydrogen-bond acceptor may play a role in 3,4-etheno-MMdCyd's inactivity as an antiviral agent. If N4 is required to be a hydrogen-bond donor in the binding pocket of either the pyrimidine kinase or DNA polymerase, altering it to a hydrogen-bond acceptor removes its capacity to play an active role in the compound's antiviral activity. Thus, 3,4-etheno-MMdCyd would be ineffective as an antiviral compound.

Experimental

The title compound was supplied by Mr W. M. Zoghaib (Zoghaib, 1996), Department of Chemistry, University of Saskatchewan, Canada. Single crystals were obtained using the vapor diffusion method at 284 K with methanol as the solvent and 2-propanol as the precipitant.

Crystal data

$C_{13}H_{17}N_3O_5$	Mo $K\alpha$ radiation
M_r = 295.29	λ = 0.71069Å
Orthorhombic	Cell parameters from 25 reflections
$P2_12_12$	θ = 8.3–12.7°
a = 7.122 (2) Å	μ = 0.11 mm^{-1}
b = 18.113 (4) Å	T = 293 K
c = 10.389 (4) Å	Rod
V = 1340.2 (7) Å^3	0.40 × 0.25 × 0.17 mm
Z = 4	Colourless
D_x = 1.464 Mg m^{-3}	
D_m not measured	

Data collection

Nonius CAD-4 diffractometer	R_{int} = 0.017
ω scan	θ_{max} = 24.93°
Absorption correction: none	$h = -8 \rightarrow 0$
2609 measured reflections	$k = -21 \rightarrow 0$
2342 independent reflections	$l = -12 \rightarrow 12$
2342 reflections with $I_{net} > 0$	3 standard reflections frequency: 100 min intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F) + 0.001F^2]$
R = 0.094 (all data)	$(\Delta/\sigma)_{max} < 0.001$
wR = 0.076	$\Delta\rho_{max}$ = 0.34 e Å^{-3}
S = 1.43	$\Delta\rho_{min}$ = −0.46 e Å^{-3}
2333 reflections	Extinction correction: none
190 parameters	Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
H-atom coordinates and U_{iso} not refined	

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

O52—C51	1.397 (3)	N4—C32	1.377 (3)
O52—C53	1.410 (3)	C5—C51	1.499 (3)
N3—C31	1.389 (3)	C31—C32	1.328 (4)
C51—O52—C53	115.69 (18)	C6—C5—C51	123.21 (19)
C2—N3—C31	127.52 (18)	N3—C31—C32	105.8 (2)
C4—N3—C31	106.06 (19)	N4—C32—C31	111.9 (2)
C4—N4—C32	105.00 (19)	O52—C51—C5	107.04 (18)
C4—C5—C51	119.99 (19)		
C2—N1—C1′—O4′	−93.2 (4)	C1′—C2′—C3′—C4′	27.8 (3)
C6—C5—C51—O52	−5.1 (3)	C2′—C3′—C4′—O4′	−23.5 (2)
O4′—C1′—C2′—C3′	−22.3 (2)	C3′—C4′—C5′—O5′	57.2 (3)
C2′—C1′—O4′—C4′	7.6 (2)	C3′—C4′—O4′—C1′	10.2 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3′—H3″···O5′^{i}	0.90	1.89	2.775 (2)	165
O5′—H5″···N4^{ii}	0.90	1.95	2.839 (2)	167

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

All non-H atoms were refined anisotropically using the *NRCVAX LSTSQ* program (Gabe, Le Page, Charland, Lee & White, 1989). Bijvoet pairs were included during refinement (963 Bijvoet pairs). To obtain the absolute configuration of the compound, the chiral parameter was investigated (Flack, 1983). Also, refinements were performed on both possible conformations, using x, y, z and $x, y, -z$ coordinates. Although the x, y, z conformation gave slightly better R and wR factors, 0.92 and 0.075, respectively, *versus* 0.094 and 0.076 for the x, y, z configuration, comparison of the chiral parameter between the two configurations indicated that the x, y, z configuration was correct. When both x, y, z and $x, y, -z$ configurations had the chiral parameter set to 1.0, Bijvoet analysis indicated that the x, y, z configuration was correct, with a probability of incorrectness of 0.1790. This confirmed the configuration of the sugar ring used in the synthesis, which was D-2-deoxyribose (Zoghaib, 1996). Hydroxyl H atoms were located from a difference map, and all other H atoms were placed in calculated positions (C—H = 1.00 Å). H atoms were not refined. U_{iso} of each H atom was assigned as equal to U_{eq} of the attached non-H atom plus 0.01.

Data collection and cell refinement were performed using the *CAD-4 Manual* (Enraf–Nonius, 1988). Structure solution was performed *via* direct methods using the *Xtal*3.2 software package (Hall, Flack & Stewart, 1992). Data reduction was performed using *NRCVAX DATRD2*, preserving the sense of Friedel mates. The structure was refined using *NRCVAX LSTSQ*. Molecular graphics were prepared using *NRCVAX ORTEP*. Software used to prepare material for publication was *NRCVAX TABLES* (version of January 1994).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1253). Services for accessing these data are described at the back of the journal.

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