C6—O4	1.352 (2)	O4—H4O	1.04 (3)
C7—O1	1.255 (2)	N1′—H1N	0.97 (3)
C6—C1—C2	118.1 (2)	O1—C7—C1	119.20 (14)
C6—C1—C7	121.94 (15)	O2—C7—C1	118.3 (2)
C2—C1—C7	119.9 (2)	C2′—N1′—C6′	121.3 (2)
O3—C2—C3	119.2 (2)	N1′—C2′—C3′	120.2 (2)
O3—C2—C1	120.4 (2)	C4′—C3′—C2′	118.6 (2)
C3—C2—C1	120.5 (2)	C5′—C4′—C3′	120.5 (2)
C4—C3—C2	119.6 (2)	C6′—C5′—C4′	119.2 (2)
C3—C4—C5	121.7 (2)	N1′—C6′—C5′	120.2 (2)
C4—C5—C6	119.4 (2)	C2—O3—H3O	100.5 (14)
O4—C6—C5	118.0 (2)	C6—O4—H4O	103.4 (16)
O4—C6—C1	121.2 (2)	C2′—N1′—H1N	120.2 (15)
C5—C6—C1	120.8 (2)	C6′—N1′—H1N	118.4 (15)
O1—C7—O2	122.5 (2)		

Symmetry code: (i) $x, \frac{3}{2} - y, z$.

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(I)				
O3—H3O···O1	0.93 (4)	1.74 (4)	2.596 (3)	152
O2—H2O···O4	0.89 (4)	1.68 (4)	2.522 (3)	156
O4—H4O···O1^{i}	0.76 (3)	1.95 (3)	2.683 (3)	161
(II)				
O1—H1O···O3	1.14 (14)	1.57 (13)	2.540 (3)	139 (10)
O3—H3O*B*···O1	1.06 (10)	1.61 (11)	2.540 (3)	143 (8)
O3—H3O*A*···O1*W*	0.71 (7)	2.03 (7)	2.705 (4)	159 (6)
O1*W*—H1*W*···O3	0.85 (10)	1.92 (11)	2.705 (4)	152 (10)
O1*W*—H2*W*···O1^{ii}	0.88 (10)	2.33 (9)	3.069 (6)	143 (5)
(III)				
O3—H3O···O1	1.08 (3)	1.46 (3)	2.497 (2)	158 (2)
O4—H4O···O2	1.04 (3)	1.59 (3)	2.556 (2)	152 (3)
N1′—H1N···O2	0.97 (3)	1.73 (3)	2.692 (2)	175 (2)
C2′—H2′···O1	0.93 (2)	2.50 (2)	3.211 (3)	133 (2)

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

The γ-resorcylic acid molecule in (II) lies on a mirror plane through C7, C1 and C4, therefore the carboxyl and phenolic OH groups are disordered. The molecule adopts two overlapping orientations related by the mirror plane. The positions of all H atoms except for H1*W* were determined from a ΔF map. H1O and H3O*B* were identified as a broad peak between O1 and O3, which was probably the superposition of the electron densities of these two closely situated H atoms, and were both given a site occupancy of 0.5 and refined. The position of H1*W* was calculated assuming hydrogen-bond formation with O(3) and refined.

Data collection, cell refinement, and data reduction: Kuma KM-4 software (Kuma, 1991). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1994). Molecular graphics: *Stereochemical Workstation* (Siemens, 1989). Software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1067). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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3′-Azido-2′,3′-dideoxy-5-hydroxymethyluridine

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Abstract

In the title compound, $C_{10}H_{13}N_5O_5$, the furanose ring adopts a C(2′)-*endo* envelope conformation (^2E), with the glycosyl linkage *anti* [$\chi = 219.0$ (2)°]. The

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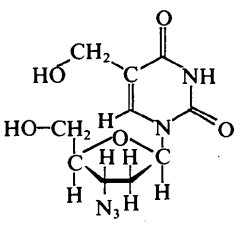
pseudorotational parameters are $P = 159.2\ (3)°$ and $\tau_m = 34.3\ (2)°$. In the deoxyribose ring, the side chain on C(5′) is partially disordered and exhibits two distinct conformations, g^+ [$\gamma = 58.6\ (5)°$] and g^- [$\gamma = -58.2\ (9)°$]. The hydroxymethyl side chain at C(5) is on the same side of the pyrimidine plane as O(4′) of the furanose ring.

Comment

5-Hydroxymethyl-2′-deoxyuridine (HMdUrd) is a novel antimetabolite which replaces thymidine in certain lytic bacteriophages (Kallen, Simon & Mamur, 1962). This naturally occurring nucleoside is a moderate inhibitor of HIV replication in *T*-cell cultures which prolonged the life of mice implanted with Friend Leukemia Virus Complex (Gupta, Stuart, Kumar, De Clercq, Qualtiere, Cozens, Lazdins & Qualtiere, 1992). HMdUrd has low systemic toxicity and, most interestingly, was devoid of bone-marrow toxicity in mice (Meldrum, Gupta, Lowes & Paterson, 1985). 3′-Azido-2′,3′-dideoxy-5-hydroxymethyluridine (AZHMddUrd) (I) was synthesized to improve potency against HIV. Its crystal structure was determined to establish the relationship between molecular conformation and substrate antiviral activity.



(I)

The glycosidic bond has an *anti* conformation and the 5′-CH_2OH exocyclic side chain is partially disordered, having both g^+ and g^- conformations. The furanose ring adopts a C2′-*endo* envelope conformation (^2E) and the 5-hydroxymethyl group is on the same side of the pyrimidine plane as O(4′) of the furanose ring. The glycosidic torsion angle C(2)—N(1)—C(1′)—O(4′), χ, is $219.0\ (2)°$, within the normal range for pyrimidine-2′-deoxyribonucleosides with an *anti* conformation. This value is similar to that in molecule *A* of AZT [$\chi = 234.1\ (4)°$] and higher than in molecule *B* of AZT [$\chi = 188.1\ (2)°$] (Dyer, Low, Tollin, Wilson & Howie, 1988). A pseudorotational analysis of the furanose ring torsion angles with two degrees of freedom for ring puckering (Altona & Sundaralingam, 1972) gives a phase angle $P = 159.2\ (3)°$ and a puckering amplitude $\tau_m = 34.3\ (2)°$; the displacement of C(2′) from the mean plane through the other four ring atoms is 0.53 (7) Å. As the 5′-CH_2OH side chain of the deoxyribose ring in (I) adopts two distinct positions, the subsequent refinement included occupancies for these two sites; these converged at 0.74 and 0.26 for the major and minor sites, respectively. Occupancies were fixed at these values for the final cycle. This disorder, which can be expressed in terms of the torsion angles C(3′)—C(4′)—C(5′)—O(5′) and C(3′)—C(4′)—C(5′)—O(5″) [$\gamma = 58.6\ (5)$ and $-58.2\ (9)°$, respectively], results in either a g^+ or a g^- conformation. A similar disordered conformation for the hydroxy group at the C(5′) position of the deoxyribose ring has been reported for 1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (Everaert, Peeters, Blaton & De Ranter, 1992). The pyrimidine ring is slightly non-planar; the largest deviation from the mean plane is 0.05 (5) Å. The bond angles C(2)—N(1)—C(1′), C(6)—N(1)—C(1′) and N(1)—C(1′)—O(4′) are 118.8 (2), 120.7 (2) and 107.4 (3)°, respectively.

There are two intermolecular hydrogen bonds [O(5,2)—H(5,2)···O(4)($\frac{3}{2} - x$, $y - \frac{1}{2}$, $1 - z$); O(4)···H(5,2) 1.79 (5), O(5,2)···O(4) 2.79 (4) Å and N(3)—H(3)···O(5,2)($\frac{1}{2} + x$, $\frac{1}{2} + y$, z); O(5,2)···H(3) 1.95 (4), O(5,2)···N(3) 2.80 (3) Å]. Preliminary studies indicate that AZHMddUrd has moderate anti-HIV activity.

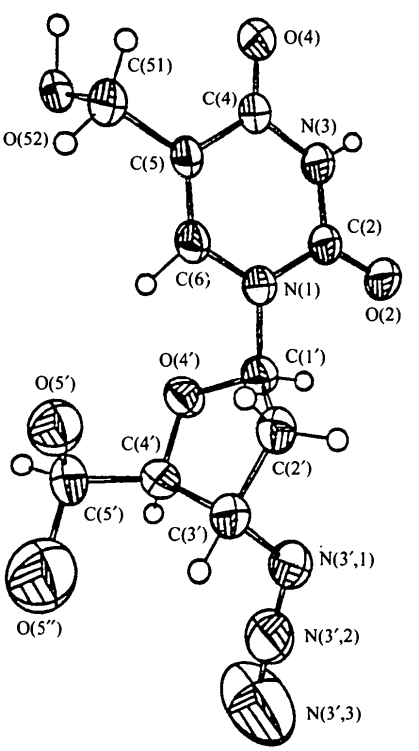


Fig. 1. A perspective view of AZHMddUrd (Johnson, 1976). Displacement ellipsoids are drawn at the 50% probability level.

Experimental

AZHMddUrd was synthesized by the method of Kumar, Shi, Stuart, Qualtiere & Gupta (1993). Crystals for X-ray analysis were obtained from a methanol/ethanol/butanol/water solution (25% *v/v*) at 287 K over several weeks.

Crystal data

$C_{10}H_{13}N_5O_5$	Cu $K\alpha$ radiation
M_r = 283.2	λ = 1.5418 Å
Monoclinic	Cell parameters from 25 reflections
$C2$	θ = 13.53–24.98°
a = 12.470 (1) Å	μ = 1.008 mm^{-1}
b = 5.6590 (6) Å	T = 287 (1) K
c = 17.700 (2) Å	Prism
β = 91.43 (9)°	0.50 × 0.30 × 0.075 mm
V = 1248.7 (2) Å^3	Colourless
Z = 4	
D_x = 1.507 Mg m^{-3}	
D_m = 1.523 Mg m^{-3}	

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.0072
$\omega/2\theta$ scans	θ_{max} = 75°
Absorption correction: none	$h = 0 \rightarrow 15$
1544 measured reflections	$k = 0 \rightarrow 7$
1403 independent reflections	$l = -22 \rightarrow 22$
1403 observed reflections	3 standard reflections frequency: 83.33 min intensity variation: insignificant

Refinement

Refinement on F	Extinction correction: $(1 + gI_c)^{-1}$ applied to I_c (Larson, 1970)
R = 0.044	Extinction coefficient: $g = 7.01\ (3) \times 10^{-6}$
wR = 0.060	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
S = 4.285	
1403 reflections	
224 parameters	
$w = 1/\sigma^2(F)$	
$(\Delta/\sigma)_{max}$ = 0.0083	
$\Delta\rho_{max}$ = 0.387 e Å^{-3}	
$\Delta\rho_{min}$ = −0.163 e Å^{-3}	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	Occupancy	x	y	z	U_{eq}
N(1)	1	0.7557 (2)	0.70218	0.7214 (1)	0.0410 (7)
C(2)	1	0.8590 (2)	0.7095 (8)	0.6953 (2)	0.0413 (8)
O(2)	1	0.9312 (2)	0.8235 (7)	0.7273 (1)	0.0555 (7)
N(3)	1	0.8756 (2)	0.5802 (8)	0.6315 (1)	0.0457 (8)
C(4)	1	0.7997 (2)	0.4592 (8)	0.5875 (1)	0.0408 (8)
O(4)	1	0.8256 (2)	0.3526 (7)	0.5307 (1)	0.0526 (7)
C(5)	1	0.6915 (2)	0.4755 (7)	0.6154 (1)	0.0404 (8)
C(5,1)	1	0.6025 (2)	0.3637 (9)	0.5692 (2)	0.0500 (1)
O(5,2)	1	0.5893 (2)	0.1162 (7)	0.5867 (1)	0.0518 (7)
C(6)	1	0.6749 (2)	0.5949 (8)	0.6790 (1)	0.0424 (8)
C(1′)	1	0.7323 (2)	0.8210 (8)	0.7929 (1)	0.0416 (8)
C(2′)	1	0.6784 (2)	1.0601 (8)	0.7841 (2)	0.0459 (9)
C(3′)	1	0.6167 (2)	1.0783 (8)	0.8566 (2)	0.0471 (9)
N(3′,1)	1	0.6918 (2)	1.1742 (9)	0.9166 (2)	0.0610 (1)
N(3′,2)	1	0.6516 (3)	1.233 (1)	0.9739 (2)	0.0740 (1)
N(3′,3)	1	0.6232 (4)	1.293 (2)	1.0296 (3)	0.178 (5)
C(4′)	1	0.5869 (2)	0.8192 (9)	0.8735 (2)	0.0473 (9)
O(4′)	1	0.6597 (2)	0.6755 (7)	0.8321 (1)	0.0496 (7)
C(5′)	1	0.4721 (3)	0.754 (1)	0.8523 (2)	0.0660 (1)
O(5′)	0.74	0.4459 (3)	0.7877 (9)	0.7774 (2)	0.0618 (8)
O(5″)	0.26	0.404 (1)	0.909 (4)	0.8929 (9)	0.106 (5)

Table 2. *Bond distances* (Å) *and bond angles* (°)

N(1)—C(2)	1.380 (3)	C(1′)—C(2′)	1.517 (6)
N(1)—C(6)	1.381 (4)	C(1′)—O(4′)	1.418 (4)
N(1)—C(1′)	1.469 (4)	C(2′)—C(3′)	1.517 (4)
C(2)—O(2)	1.234 (4)	C(3′)—N(3′,1)	1.499 (4)
C(2)—N(3)	1.365 (4)	C(3′)—C(4′)	1.544 (6)
N(3)—C(4)	1.391 (4)	N(3′,1)—N(3′,2)	1.190 (5)
C(4)—O(4)	1.222 (4)	N(3′,2)—N(3′,3)	1.110 (7)
C(4)—C(5)	1.451 (4)	C(4′)—O(4′)	1.434 (5)
C(5)—C(5,1)	1.501 (4)	C(4′)—C(5′)	1.517 (5)
C(5)—C(6)	1.334 (4)	C(5′)—O(5′)	1.369 (5)
C(5,1)—O(5,2)	1.445 (6)	C(5′)—O(5″)	1.43 (2)
C(2)—N(1)—C(6)	120.4 (2)	N(1)—C(1′)—O(4′)	107.4 (3)
C(2)—N(1)—C(1′)	118.8 (2)	C(2′)—C(1′)—O(4′)	106.4 (3)
C(6)—N1)—C(1′)	120.7 (2)	C(1′)—C(2′)—C(3′)	101.9 (3)
N(1)—C(2)—O(2)	122.6 (3)	C(2′)—C(3′)—N(3′,1)	107.6 (2)
N(1)—C(2)—N(3)	115.0 (2)	C(2′)—C(3′)—C(4′)	103.2 (3)
O(2)—C(2)—N(3)	122.4 (2)	N(3′,1)—C(3′)—C(4′)	110.8 (3)
C(2)—N(3)—C(4)	127.7 (2)	C(3′)—N(3′,1)—N(3′,2)	115.8 (3)
N(3)—C(4)—O(4)	120.8 (2)	N(3′,1)—N(3′,2)—N(3′,3)	173.6 (5)
N(3)—C(4)—C(5)	113.8 (3)	C(3′)—C(4′)—O(4′)	106.3 (3)
O(4)—C(4)—C(5)	125.4 (3)	C(3′)—C(4′)—C(5′)	114.3 (3)
C(4)—C(5)—C(5,1)	118.0 (3)	O(4′)—C(4′)—C(5′)	110.0 (3)
C(4)—C(5)—C(6)	119.0 (3)	C(1′)—O(4′)—C(4′)	109.9 (3)
C(5,1)—C(5)—C(6)	123.0 (2)	C(4′)—C(5′)—O(5′)	114.0 (3)
C(5)—C(5,1)—O(5,2)	112.3 (3)	C(4′)—C(5′)—O(5″)	107.3 (8)
N(1)—C(6)—C(5)	123.7 (2)	O(5′)—C(5′)—O(5″)	105.8 (7)
N(1)—C(1′)—C(2′)	114.7 (2)		

A Bayesian treatment was applied to the data using *Xtal*3.0 (Hall & Stewart, 1990). The structure was solved by direct methods with *Xtal*3.0. All non-H atoms [except O(5′) and O(5″)] were found on an E map and refined anisotropically. The positions of most H atoms were located by using difference Fourier maps and refined isotropically, a further two were placed at calculated positions and the final two H atoms were not found. All calculations were performed on a VAX 3100 Model 90 computer at the University of Saskatchewan.

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Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: ST1088). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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DCMCIT, an Analogue of the Antitumour Drugs Mitozolomide and Temozolomide

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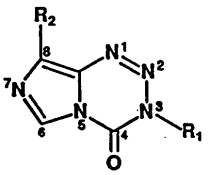
Abstract

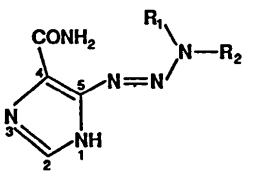
The crystal structure of 3-(2-chloroethyl)-*N*,*N*-dimethyl-4-oxo-3,4-dihydroimidazo[5,1-*d*]-1,2,3,5-tetrazine-8-carboxamide, (1), $C_9H_{11}ClN_6O_2$, an analogue of the novel bicyclic antitumour agents mitozolomide (2) and temozolomide (3), has been determined at 290 K. Although, as in structures (2) and (3), the imidazotetrazinone ring system is essentially planar, the substitution of the —$CONH_2$ group at C8 by a —$CON(CH_3)_2$ group in (1) negates the possibility of forming an intramolecular hydrogen bond at either N7 or N1 and thus allows rotation of this group about the C8—C81 bond by *ca* 45°.

Comment

Structure–activity studies on 8-substituted imidazotetrazinones show very good antitumour activity for both unsubstituted and a range of N-monosubstituted carboxamides (Lunt *et al.*, 1987). The proposed mode of action is that of a prodrug for two cytotoxic alkylating species: MCTIC (4) for analogues of mitozolomide and MTIC (5) for analogues of temozolomide. The model proposes that this is effected by ring opening at the weak C4—N5 bond following nucleophilic attack at the C4 atom by water molecules in the major groove of DNA (Clark, Stevens, Sansom & Schwalbe, 1990). It is further postulated that the carboxamide substitutent may play an important role in DNA sequence recognition (Lowe, Sansom, Schwalbe, Stevens & Clark, 1992).



(1) R_1 = $(CH_2)_2Cl$, R_2 = $CON(CH_3)_2$ DCMCIT
(2) R_1 = $(CH_2)_2Cl$, R_2 = $CONH_2$ Mitozolomide
(3) R_1 = CH_3, R_2 = $CONH_2$ Temozolomide



(4) R_1 = H, R_2 = $(CH_2)_2Cl$ MCTIC
(5) R_1 = H, R_2 = CH_3 MTIC

The fact that the title compound differs from (2) only in that it is N-disubstituted, and yet has very impaired activity, points to the importance of the nature of the carboxamide substituent; it is proposed that DCMCIT has to undergo metabolic demethylation to become active (Lowe, Sansom, Schwalbe, Stevens & Clark, 1992).

Although, in general, the bond lengths in the planar bicyclic ring system are similar in compounds (1), (2) and (3), a difference does occur in the N1—N2, N1—C8*A* and C8—C8*A* bond lengths which are shorter, longer and shorter, respectively, by greater than 3σ in structure (1) than in structures (2) and (3), suggesting considerably less conjugation (Lowe, Schwalbe & Stevens, 1985; Lowe, Sansom, Schwalbe, Stevens & Clark, 1992). While it is tempting to attribute this largely to the coplanar nature of the carboxamide group and ring system in structures (2) and (3) compared with the observed twist in structure (1) [C8*A*—C8—C81—O82 46.1 (4)°] which reduces the conjugative effect between them, it is not substantiated by the C8—C81 bond length which shows little variation among the three compounds.

The C81—N82 bond length of 1.334 (3) Å suggests considerable double-bond character, which is consistent with sp^2 hybridization of the amide N atom shown by the closeness to 360° of the sum of the bond angles around the N82 atom [359.8 (4)°]. As such, conjugation appears to be restricted to the ring system and the carboxamide group separated by the rotation about the C8—C81 bond.

Since the title compound (1) is N-disubstituted, no strong hydrogen bonds exist, as demonstrated by the relatively low melting point of 389 K. However, there is a somewhat weaker interaction, namely

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