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Antiviral Nucleic Acid Derivatives.
III.* Crystal Structure of 5-Ethynyl-2′-deoxyuridine

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The crystal structure of the antiviral nucleoside 5-ethynyl-2′-deoxyuridine, $C_{11}H_{12}N_2O_5$, has been determined from three-dimensional X-ray counter data. The crystals are monoclinic, space group $P2_1$, with a = 5·72 (1), b = 11·79 (1), c = 8·79 (1) Å, β = 106·60 (5)°, Z = 2. Least-squares refinement converged to R = 3·85% for 1162 observed amplitudes. The pyrimidine ring is planar and the glycosidic torsion angle O(1′)—C(1′)—N(1)—C(6) is 18·6° (*anti* conformation). The sugar ring has the C(2′)-*endo* conformation. The arrangement about the C(4′)—C(5′) bond is *gauche–trans* with the torsion angle C(3′)—C(4′)—C(5′)—O(5′) −174°. All H atoms linked to N and O atoms take part in intermolecular hydrogen bonding. An unusual feature is that O(1′) acts as an acceptor atom in a hydrogen bond.

Introduction

Nucleoside analogues are finding an increasingly widespread use as antimetabolites of nucleic acid metabolism (Bloch, 1975; Langen, 1975). One such group of analogues, the 5-substituted 2′-deoxyuridines, are receiving particular attention due to their capacity for viral and tumour inhibition (Heidelberger, 1965; Torrence, Spencer, Bobst, Descamps & De Clercq, 1978). This paper describes the structure of one member of this group, 5-ethynyl-2′-deoxyuridine, a nucleoside which exerts strong activity against herpes simplex-1 strain LYONS and KOS, and vaccinia virus in culture (De Clercq, 1977) and also leukaemia L1210 cells in culture (Sharma, Perman, Bloch & Bobek, 1976).

X-ray studies on crystals of the related 5-vinyl-2′-deoxyuridine (Hamor, O'Leary & Walker, 1978) have revealed an isomorphism with thymidine which may correlate with its mode of action upon carcinoma cells, which is believed to be by incorporation into DNA (Langen & Bärwolff, 1975). Thus if 5-vinyl- or 5-ethynyl-2′-deoxyuridine can be incorporated into DNA, then it is possible that these bases might provide a site for making the DNA radiation-sensitive. It was therefore of interest to determine the structure of this analogue and compare it with those of thymidine and 5-vinyl-2′-deoxyuridine.

Experimental

Suitable crystals were obtained by recrystallization from methanol–water. Cell dimensions and intensities were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation and a scintillation counter. The ω-scan technique was employed with a scan speed of 0·6° $\min^{-1}$ and 30 s background counts at the beginning and end of each scan. For layers $0kl$ and $1kl$ $\Delta\omega$ was 1·4° and for the highest layers it was calculated from $(A + B\sin\mu/\tan\theta')°$, where μ is the equi-inclination angle, $2\theta'$ is the azimuth angle and A and B were assigned the values 1·0 and 0·5. 1162 reflexions for which $I > 2{\cdot}5\sigma(I)$ were considered to be observed and were used in the analysis.

Crystal data

$C_{11}H_{12}N_2O_5$, M_r = 252·2, monoclinic, a = 5·72 (1), b = 11·79 (1), c = 8·79 (1) Å, β = 106·60 (5)°, U = 568·1 Å^3, D_c = 1·474 g cm^{-3}, Z = 2; systematic absences: $0k0$ when k is odd, space group $P2_1$; Mo $K\alpha$ radiation, λ = 0·71069 Å.

Structure determination

The structure was solved by direct methods with *SHELX* (Sheldrick, 1975). Refinement of atomic parameters was carried out by least squares, initially employing isotropic temperature factors and finally anisotropic parameters. H atoms were located from a difference synthesis and in subsequent calculations their coordinates and isotropic temperature factors were refined. Refinement was terminated when all calculated shifts were $<0{\cdot}15\sigma$ and R was 3·85% for the 1162 observed reflexions. The weighting scheme was $w = 1/[\sigma^2(F)]$, where $\sigma(F)$ is the standard deviation in the

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* Part II: Hamor, O'Leary & Walker (1978).

observed amplitudes based on counting statistics. Final atomic coordinates are in Table 1.*

Results and discussion

The structure of the molecule and the numbering of the atoms are illustrated in Fig. 1. Molecular dimensions are in Table 2 and the results of mean-plane calculations in Table 3.

Table 1. *Fractional atomic coordinates* (×10⁴)

	x	*y*	*z*
N(1)	3466 (4)	2438 (0)	−1345 (3)
C(2)	4314 (5)	1375 (3)	−764 (3)
O(2)	5781 (4)	843 (3)	−1250 (3)
N(3)	3370 (5)	968 (3)	400 (3)
C(4)	1660 (5)	1470 (3)	1007 (4)
O(4)	928 (5)	971 (3)	2005 (3)
C(5)	902 (5)	2590 (3)	367 (3)
C(7)	−789 (5)	3197 (3)	986 (3)
C(8)	−2164 (6)	3654 (4)	1572 (4)
C(6)	1829 (5)	3022 (3)	−771 (3)
C(1′)	4577 (5)	2914 (3)	−2532 (4)
C(2′)	3379 (5)	2554 (3)	−4218 (4)
C(3′)	4284 (5)	3484 (3)	−5120 (3)
O(3′)	6763 (4)	3319 (3)	−5076 (3)
C(4′)	4210 (6)	4536 (3)	−4113 (3)
C(5′)	1995 (6)	5280 (3)	−4707 (4)
O(5′)	2261 (5)	6283 (3)	−3763 (3)
O(1′)	4297 (4)	4114 (3)	−2534 (2)
H[C(6)]	1396 (64)	3771 (33)	−1293 (39)
H[C(8)]	−3142 (75)	4072 (41)	2073 (47)
H[C(1′)]	6256 (49)	2713 (23)	−2154 (28)
H1[C(2′)]	1603 (63)	2588 (32)	−4417 (40)
H2[C(2′)]	3888 (60)	1806 (31)	−4443 (37)
H[C(3′)]	3215 (59)	3582 (33)	−6233 (37)
H[C(4′)]	5625 (47)	4966 (26)	−3950 (29)
H1[C(5′)]	1842 (69)	5485 (35)	−5869 (46)
H2[C(5′)]	519 (61)	4904 (31)	−4708 (36)
H[N(3)]	3795 (60)	331 (33)	743 (39)
H[O(5′)]	1479 (78)	6185 (38)	−3178 (49)
H[O(3′)]	6713 (77)	2676 (44)	−5547 (51)

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

N(1)–C(2)	1·387 (4)	N(1)–C(1′)	1·478 (3)
C(2)–O(2)	1·218 (3)	C(1′)–C(2′)	1·505 (4)
C(2)–N(3)	1·372 (4)	C(2′)–C(3′)	1·527 (4)
N(3)–C(4)	1·374 (4)	C(3′)–O(3′)	1·420 (4)
C(4)–O(4)	1·224 (3)	C(3′)–C(4′)	1·532 (4)
C(4)–C(5)	1·452 (4)	C(4′)–C(5′)	1·506 (5)
C(5)–C(7)	1·430 (4)	C(5′)–O(5′)	1·426 (4)
C(7)–C(8)	1·184 (4)	C(4′)–O(1′)	1·462 (3)
C(5)–C(6)	1·357 (4)	O(1′)–C(1′)	1·422 (3)
C(6)–N(1)	1·369 (4)		
N(3)–H[N(3)]	0·820 (37)	C(3′)–H[C(3′)]	1·001 (31)
C(6)–H[C(6)]	0·993 (37)	O(3′)–H[O(3′)]	0·860 (49)
C(8)–H[C(8)]	0·943 (45)	C(4′)–H[C(4′)]	0·930 (28)
C(1′)–H[C(1′)]	0·953 (26)	C(5′)–H1[C(5′)]	1·029 (39)
C(2′)–H1[C(2′)]	0·981 (35)	C(5′)–H2[C(5′)]	0·953 (35)
C(2′)–H2[C(2′)]	0·966 (36)	O(5′)–H[O(5′)]	0·780 (43)

(*b*) Bond angles (°) (mean estimated standard deviation 0·25°)

C(6)–N(1)–C(2)	121·5	C(5)–C(6)–N(1)	122·3
C(6)–N(1)–C(1′)	123·1	N(1)–C(1′)–O(1′)	107·9
C(2)–N(1)–C(1′)	115·3	N(1)–C(1′)–C(2′)	114·9
N(1)–C(2)–N(3)	114·8	O(1′)–C(1′)–C(2′)	105·1
N(1)–C(2)–O(2)	122·7	C(1′)–C(2′)–C(3′)	100·5
N(3)–C(2)–O(2)	122·5	C(2′)–C(3′)–C(4′)	102·2
C(2)–N(3)–C(4)	127·9	C(2′)–C(3′)–O(3′)	111·8
N(3)–C(4)–C(5)	114·0	O(3′)–C(3′)–C(4′)	106·6
N(3)–C(4)–O(4)	119·9	C(3′)–C(4′)–C(5′)	115·5
O(4)–C(4)–C(5)	126·1	C(3′)–C(4′)–O(1′)	105·9
C(4)–C(5)–C(6)	119·4	O(1′)–C(4′)–C(5′)	109·0
C(4)–C(5)–C(7)	117·9	C(4′)–C(5′)–O(5′)	109·9
C(6)–C(5)–C(7)	122·7	C(4′)–O(1′)–C(1′)	108·2
C(5)–C(7)–C(8)	176·0		

(*c*) Selected torsion angles (°) (mean standard deviation 0·4°)

C(1′)–C(2′)–C(3′)–C(4′)	−38·1
C(2′)–C(3′)–C(4′)–O(1′)	22·1
C(3′)–C(4′)–O(1′)–C(1′)	3·8
C(4′)–O(1′)–C(1′)–C(2′)	−29·0
O(1′)–C(1′)–C(2′)–C(3′)	42·0
O(1′)–C(4′)–C(5′)–O(5′)	66·8
C(3′)–C(4′)–C(5′)–O(5′)	−174·2
O(3′)–C(3′)–C(4′)–C(5′)	144·0
O(3′)–C(3′)–C(4′)–O(1′)	−95·3
O(1′)–C(1′)–N(1)–C(6)	18·6
C(5)–C(7)–C(8)–H[C(8)]	105·0
C(4)–C(5)–C(7)–C(8)	13·1
C(6)–C(5)–C(7)–C(8)	−166·3
N(1)–C(1′)–O(1′)–C(4′)	−152·0

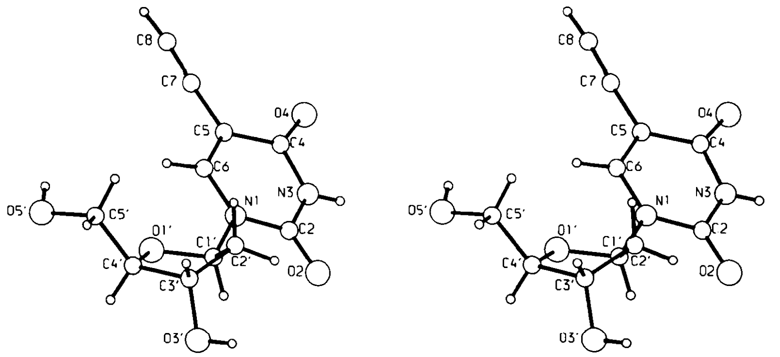

Fig. 1. Stereoscopic view of the nucleoside along the *c* axis.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33576 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Mean-plane calculations*

Deviations (Å) of atoms from least-squares planes. Distances marked with an asterisk refer to atoms defining the plane.

	(I)	(II)	(III)	(IV)
N(1)	−0·011*			
C(2)	−0·001*			
N(3)	0·015*			
C(4)	−0·017*			
C(5)	0·005*			
C(6)	0·008*			
O(2)	−0·009			
O(4)	−0·052			
C(7)	0·038			
C(8)	0·083			
C(1′)	0·051	0·224*	0·014*	0·090
C(2′)		−0·259*	−0·631	−0·562
C(3′)		0·195*	−0·013*	0*
C(4′)		−0·068*	0·020*	0*
O(1′)		−0·092*	−0·022*	0*
C(5′)		−1·353	−1·109	−1·170
O(5′)		−1·415	−0·892	−0·984

Equations of planes (x, y, and z are in Å)

(I) $-0{\cdot}5688x - 0{\cdot}4225y - 0{\cdot}7057z = -1{\cdot}7434$
(II) $-0{\cdot}9746x + 0{\cdot}1130y - 0{\cdot}1934z = -2{\cdot}1442$
(III) $-0{\cdot}9644x - 0{\cdot}0841y - 0{\cdot}2509z = -2{\cdot}8751$
(IV) $-0{\cdot}9625x - 0{\cdot}0456y - 0{\cdot}2675z = -2{\cdot}6253$

Interplanar angle

(I)–(II) 50·0°

Stereochemistry and conformation of the molecule

(*a*) *The pyrimidine base.* The pyrimidine ring is planar to within ±0·02 Å. The substituents O(2), O(4), C(7) and C(1′) all lie within 0·05 Å of the ring plane and C(8) of the ethynyl group is displaced by 0·08 Å. Bond lengths and angles agree, within the limits of experimental error, with averaged values for uridines (Voet & Rich, 1970). There is some indication of a slight degree of conjugation between the C(5)—C(6) double bond and the ethynyl group, C(5)—C(6) being slightly longer than the averaged value for this bond. A similar effect may also occur in 5-vinyl-2′-deoxyuridine (Hamor, O'Leary & Walker, 1978).

(*b*) *The deoxyribose residue.* The sugar ring can be described as having the envelope conformation. C(1′), C(3′), C(4′) and O(1′) are coplanar to within ±0·022 Å, and C(2′) is displaced by 0·63 Å from the four-atom plane on the same side as C(5′). The sugar therefore has the C(2′)-*endo* conformation: ^2E in the nomenclature of Sundaralingam (1975). The alternative description of the sugar ring in terms of a half-chair is $^2T_1$ (plane IV in Table 3). This conformation is similar to that found in the crystal structures of 5-chloro-, 5-bromo- and 5-iodo-2′-deoxyuridine (Young & Morris, 1973; Iball, Morgan & Wilson, 1966; Camerman & Trotter, 1965). The arrangement about C(4′)—C(5′) is *gauche–trans*: *t* in the nomenclature of Sundaralingam (1975) (Table 2). Similar conformations occur in 5-chloro-, 5-bromo- and 5-vinyl-2′-deoxyuridine and in thymidine (Young, Tollin & Wilson, 1969).

Bond lengths and angles are generally in very good agreement with those determined for 5-chloro-2′-deoxyuridine (where the sugar residue has a similar conformation).

(*c*) *The glycosidic link.* The torsion angle O(1′)—C(1′)—N(1)—C(6) is 18·6° so that the conformation is *anti* (Sundaralingam, 1975). This conformation is very common in nucleoside structures and is adopted by all the 5-substituted 2′-deoxyuridines whose crystal structures are known. The glycosidic torsion angle of 18·6° in the present structure is, however, smaller than in the other 5-substituted 2′-deoxyuridines where values of 39–63° are found. In unsubstituted deoxyuridine this angle is *ca* 27° (Rahman & Wilson, 1972).

(*d*) *Overall conformation of the molecule.* In standard nomenclature the conformational parameters which define the overall shape of the molecule are C(2′)-*endo* (^2E or $^2T_1$), *gauche–trans* (*t*), *anti*. These describe the sugar-ring pucker and the arrangements about C(4′)—C(5′) and the glycosidic bond, respectively (see above).

In Table 4 we have listed in order of increasing glycosidic torsion angle the corresponding conformational parameters for 2′-deoxyuridine and all 5-substituted 2′-deoxyuridines whose crystal structures have, to our knowledge, been determined. Of these, the 5-chloro and 5-bromo compounds have a similar conformation to the title compound. Sundaralingam (1975) has noted that there is a strong tendency for the sugar pucker to be 2′-*endo* and, related to this, a tendency for the conformation about C(4′)—C(5′) to be *gauche–trans* (*t*) or *trans–gauche* (g^-). The conformation of the title compound is consistent with this. However, the small value for the glycosidic torsion angle to some extent sets the present structure apart from the other 5-substituted 2′-deoxyuridines.

Packing and hydrogen bonding

The arrangement of the molecules in the unit cell is shown in Fig. 2, and the shorter intermolecular contact distances are listed in Table 5. All the H atoms linked to N and O take part in hydrogen bonding. O(5′) of the reference molecule donates a H atom forming a hydrogen bond with O(4) of the screw-related molecule, and O(1′) acts as acceptor in a hydrogen bond with N(3) of the molecule related to the latter molecule by a unit-cell translation along *x*. Nucleosides linked in this way form layers in the *ab* plane. These layers are linked by O(3′)—H···O(5′) hydrogen bonds. The participation of O(1′) in the hydrogen bonding is unique amongst the 5-substituted 2′-deoxyuridines whose crystal structures have so far been determined, and appears to occur only rarely in other nucleoside crystal structures (Sprang & Sundaralingam, 1973).

Table 4. *Overall conformations of* 5-*substituted* 2'-*deoxyuridines*

Parameters not quoted in the original publication have been taken from Sundaralingam (1975).

5-Substituent	Sugar conformation	Glycosidic torsion angle (°)*	C(4')–C(5') conformation	References
Ethynyl	$^2T_1$	18·6 (*anti*)	*gauche–trans* (*t*)	Present study
H (molecule *A*)	$^2T_3$	26·3 (*anti*)	*trans–gauche* (g^-)	Rahman & Wilson (1972)
(molecule *B*)	$^2T_3$	28·4 (*anti*)	*trans–gauche* (g^-)	
Vinyl	$_3T^2$	38·7 (*anti*)	*gauche–trans* (*t*)	Hamor *et al.* (1978)
Methyl	$_3T^2$	39·1 (*anti*)	*gauche–trans* (*t*)	Young *et al.* (1969)
Chloro	$^2T_1$	41·8 (*anti*)	*gauche–trans* (*t*)	Young & Morris (1973)
Bromo	$^2T_1$	47·2 (*anti*)	*gauche–trans* (*t*)	Iball *et al.* (1966)
Fluoro	$^2T_3$	59·0 (*anti*)	*trans–gauche* (g^-)	Harris & MacIntyre (1964)
Iodo	$^2T_1$	63·3 (*anti*)	*gauche–gauche* (g^+)	Camerman & Trotter (1965)

* Torsion angle O(1')—C(1')—N(1)—C(6).

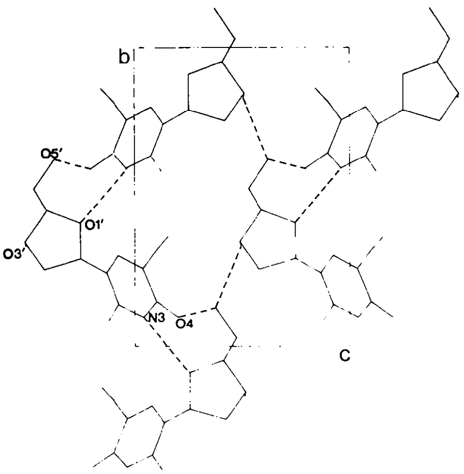

Fig. 2. The crystal structure projected onto the *bc* plane. Hydrogen bonds are shown as dashed lines. (The hydrogen bonds do not form closed circuits as they appear to do in this projection but form an infinite three-dimensional network throughout the crystal.)

Table 5. *The shorter intermolecular contact distances* (Å)

For contacts between the heavier atoms distances up to 3·4 Å are listed, for those involving H atoms distances up to 2·3 Å are shown.

O(3')···O(5'$^{\text{i}}$)	2·73	C(8)···O(2$^{\text{ii}}$)	3·27
O(5')···O(4$^{\text{ii}}$)	2·73	N(3)···O(5'$^{\text{iii}}$)	3·30
O(1')···N(3$^{\text{iii}}$)	2·94	C(4')···O(4$^{\text{iii}}$)	3·33
C(8)···N(3$^{\text{ii}}$)	3·20	C(5')···O(4$^{\text{ii}}$)	3·37
H[O(3')]···O(5'$^{\text{i}}$)	1·90	O(1')···H[N(3$^{\text{iii}}$)]	2·18
H[O(5')]···O(4$^{\text{ii}}$)	1·96		

Symmetry code (atoms without a superscript belong to the reference molecule at *x,y,z*)

(i)	$1-x,$	$-\frac{1}{2}+y,$	$-1-z$
(ii)	$-x,$	$\frac{1}{2}+y,$	$-z$
(iii)	$1-x,$	$\frac{1}{2}+y,$	$-z$

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