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2',3'-Dideoxy-3'-C,2'-N-[(3R,5R)-5-ethoxy-carbonyl-2-methyl-1,2-isoxazolidine]-ribothymidine†

BRIAN M. BURKHART

Department of Chemistry, The Ohio State University, 055 Rightmire Hall, Columbus, Ohio 43210, USA

ALEXANDER PAPCHIKHIN AND JYOTI CHATTOPADHYAYA

Department of Bioorganic Chemistry, Uppsala University, Box 581, S-751 23 Uppsala, Sweden

MUTTAIYA SUNDARALINGAM

Departments of Chemistry and Biochemistry, The Ohio State University, 012 Rightmire Hall, Columbus, Ohio 43210, USA

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Abstract

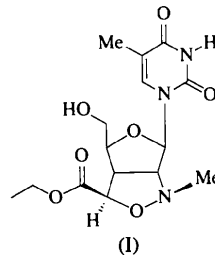
The title compound, C₁₅H₂₁N₃O₇, is a thymidine derivative with a tetrahydroisoxazole (THI) ring fused to the sugar ring at the 2'- and 3'-C atoms. The thymine base is in an *anti* conformation [$\chi = -122.5(3)^\circ$] while the ribose moiety has a C2'-*exo*,C3'-*endo* (³T₂) conformation with a highly flattened sugar ring [$P = -5.8$, $\tau_m = 13.1^\circ$]. The molecule contains a pseudo-twofold axis on the C2'—C3' bond with the ethyl ester group acting

† Alternative name: ethyl 4-(2-hydroxymethyl)-1-methyl-6-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-1,3,3a,6a-tetrahydro-4H-,6H-furano[3,4-c][1,2]isoxazole-3-carboxylate.

as the base and the *N*-methyl group acting as the 5'-hydroxyl group in a nucleoside. The THI ring fused to the furanose has a C3'-*endo*,C4'-*exo* (³T₄) conformation [$P = 41.8$, $\tau_m = 19.3^\circ$]. The ethyl ester moiety is disordered with respect to two conformations, the population of the major form being 87.4 (8)% and that of the minor form 12.6 (8)%.

Comment

Nucleoside analogues combat viruses by blocking replication and/or transcription. They function as chain terminators because they lack the O3' hydroxyl groups required for chain elongation. Two notable examples of these compounds, zidovudine (AZT) and didanosine (ddI), are in current use as anti-HIV drugs. In our search for new nucleoside analogues for therapeutic use against HIV, the title compound (I) was synthesized and its structure determined. The 2',3'- α -fused isoxazolidine nucleoside was prepared by a ring-closure dipolar cycloaddition reaction in which the stereochemistries of four prochiral centers were fixed in one step (Papchikhin & Chattopadhyaya, 1994) in a yield of >90%. The one-dimensional NOE difference (¹H at 500 MHz) studies (Papchikhin & Chattopadhyaya, 1994) of this isoxazolidine nucleoside have already shown C2'(R), C3'(S), C3''(R) and N2''(R) configurations which are consistent with the results of the present X-ray study.



The title compound is a thymidine derivative which is bonded to the five-membered disubstituted tetrahydroisoxazole (THI) ring at the sugar 2'- and 3'-positions. The molecule contains an approximate local dyad (r.m.s. deviation for the two five-membered rings and the immediate substituent atoms is 0.252 Å) normal to the C2'—C3' bond in the best plane of the fused rings. In this orientation, the *N*-methyl group of the THI ring acts as the ribose 5'-hydroxyl group and the ethyl ester group of THI acts as the nucleosidic base. An ORTEPII (Johnson, 1976) drawing with the atom-labeling scheme is shown in Fig. 1. Conformational parameters are given in Table 2.

The crystal structure confirms the structure predicted by the synthesis. The bond lengths and angles for the molecule are normal within e.s.d. limits. The sugar pucker of the disubstituted ribose has a C2'-*exo*,C3'-*endo* conformation [$P = -5.8^\circ$] (Altona & Sundar-

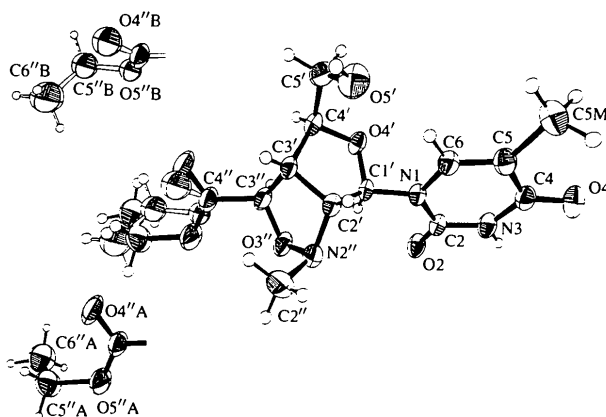


Fig. 1. ORTEP (Johnson, 1976) drawing at the 50% probability level of the title compound illustrating the atom numbering. The upper and lower insets show the conformation of the minor form (hollow bonds) and major form (solid bonds), respectively. H atoms are drawn as small circles of arbitrary radii.

alingam, 1972). The base lies in an *anti* conformation [$\chi = -122.5(3)^\circ$] (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983) and the conformation around the C4'—C5' bond places the 5'-hydroxyl group in the *+gauche*, *+gauche* region. The THI ring puckers into a C3'-*endo*, C4'-*exo* conformation [$P = 41.8^\circ$]. The angle between the best planes of the two five-membered rings is $107.2(1)^\circ$. The ethyl ester substituent is in an *R* configuration. The *N*-methyl group extends above the best plane of the five-membered THI ring by $1.648(5) \text{ \AA}$ and is in a pseudo-*R* configuration. There is a twofold disorder in the ethyl ester substituent consisting of a rotation of -42.9° around the C—C bond connecting the ester to the tetrahydroisoxazole ring.

The crystal packing is held together primarily through van der Waals interactions, with discrete layers normal to the crystallographic *a* axis. Table 3 lists the three

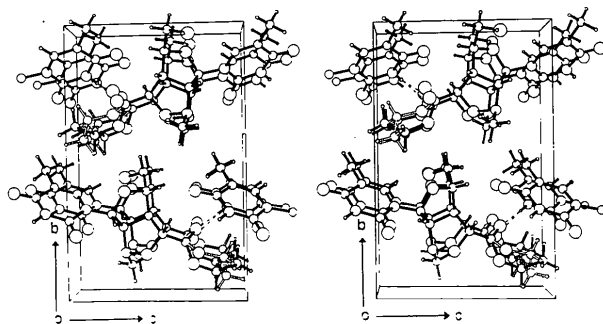


Fig. 2. A view down the crystallographic *a* axis of the crystal. Two layers are shown illustrating the intermolecular hydrogen bonds between atom N3 of the thymine base and atom O4'' in both the disordered conformations. These hydrogen bonds stabilize the crystal along the crystallographic *b* and *c* directions. Partially obscured is a hydrogen bond between O5' and O4' of the next layer which holds successive layers together.

intermolecular hydrogen bonds. Two layers of the molecular packing, viewed down the *a* axis, are shown in Fig. 2, illustrating the hydrogen-bonding interactions in the lattice. Surprisingly, both disordered ethyl ester carbonyl O atoms, O4'', participate in an intermolecular hydrogen bond with the same donor, N3, of the thymine, with lengths of $2.846(4)$ and $3.07(2) \text{ \AA}$ for the major and minor forms, respectively. Partially obscured in Fig. 2 is a hydrogen bond from atom O5', which donates an H atom, to atom O4' of a symmetry-related molecule in the layer above.

Experimental

Crystal data

$C_{15}H_{21}N_3O_7$
 $M_r = 355.35$
 Monoclinic
 $P2_1$
 $a = 5.5020(10) \text{ \AA}$
 $b = 15.3840(10) \text{ \AA}$
 $c = 9.918(2) \text{ \AA}$
 $\beta = 93.43(2)^\circ$
 $V = 838.0(2) \text{ \AA}^3$
 $Z = 2$
 $D_x = 1.408 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation
 $\lambda = 0.71070 \text{ \AA}$
 Cell parameters from 25 reflections
 $\theta = 11\text{--}15^\circ$
 $\mu = 0.113 \text{ mm}^{-1}$
 $T = 295(2) \text{ K}$
 Trapezoid
 $0.50 \times 0.38 \times 0.27 \text{ mm}$
 Colorless

Data collection

Rigaku AFC-5S four-circle diffractometer
 $\omega/2\theta$ scans
 Absorption correction: none
 2010 measured reflections
 2010 independent reflections
 1447 observed reflections
 $[I > 2\sigma(I)]$

$\theta_{\max} = 27.56^\circ$
 $h = 0 \rightarrow 7$
 $k = 0 \rightarrow 20$
 $l = -12 \rightarrow 12$
 6 standard reflections monitored every 50 reflections
 intensity decay: 4.5%

Refinement

Refinement on F^2
 $R(F) = 0.0369$
 $wR(F^2) = 0.1311$
 $S = 1.050$
 2003 reflections
 291 parameters
 $w = 1/[\sigma^2(F_o^2) + (0.0279P)^2 + 0.1537P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.165 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.144 \text{ e \AA}^{-3}$

Extinction correction: SHELXL93 (Sheldrick, 1993)
 Extinction coefficient: 0.0037 (25)
 Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
 Absolute configuration: Flack (1983)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)

$$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
C1'	0.0701 (5)	0.8156 (2)	0.7464 (3)	0.0303 (7)
C2'	-0.1569 (6)	0.7657 (2)	0.6944 (3)	0.0321 (7)
C3'	-0.2028 (6)	0.8039 (2)	0.5513 (3)	0.0314 (7)

C4'	-0.1088 (6)	0.8963 (2)	0.5606 (3)	0.0355 (7)
O4'	0.0693 (4)	0.8969 (2)	0.6760 (2)	0.0375 (6)
C5'	-0.2996 (7)	0.9640 (3)	0.5808 (4)	0.0454 (9)
O5'	-0.4374 (5)	0.9435 (2)	0.6936 (3)	0.0538 (7)
C2''	-0.3274 (9)	0.6231 (3)	0.6558 (5)	0.0605 (12)
N2''	-0.1052 (5)	0.6741 (2)	0.6798 (3)	0.0402 (7)
O3''	0.0313 (5)	0.6722 (2)	0.5580 (2)	0.0485 (7)
C3''	-0.0533 (7)	0.7417 (2)	0.4698 (3)	0.0405 (9)
C4''	-0.1931 (7)	0.7091 (3)	0.3424 (3)	0.0504 (10)
O4''A	-0.3438 (10)	0.7521 (4)	0.2842 (4)	0.084 (2)
O5''A	-0.1229 (8)	0.6321 (3)	0.3015 (3)	0.0661 (14)
C5''A	-0.2284 (12)	0.5992 (4)	0.1729 (4)	0.064 (2)
C6''A	-0.0975 (11)	0.6323 (4)	0.0591 (5)	0.068 (2)
O4''B	-0.4014 (19)	0.7157 (20)	0.308 (3)	0.055 (8)
O5''B	-0.0235 (24)	0.6755 (16)	0.2685 (16)	0.046 (6)
C5''B	-0.0908 (52)	0.6546 (20)	0.1277 (16)	0.060 (11)
C6''B	-0.2665 (79)	0.583 (3)	0.116 (4)	0.078 (16)
N1	0.0879 (5)	0.8341 (2)	0.8906 (2)	0.0319 (6)
C2	0.2818 (6)	0.7984 (2)	0.9681 (3)	0.0340 (7)
O2	0.4308 (4)	0.7500 (2)	0.9237 (2)	0.0479 (7)
N3	0.2926 (5)	0.8240 (2)	1.1009 (3)	0.0410 (7)
C4	0.1402 (6)	0.8806 (2)	1.1633 (3)	0.0368 (8)
O4	0.1812 (5)	0.8982 (2)	1.2825 (2)	0.0550 (7)
C5	-0.0610 (6)	0.9142 (2)	1.0766 (3)	0.0375 (8)
C5M	-0.2368 (7)	0.9754 (3)	1.1377 (4)	0.0514 (10)
C6	-0.0762 (6)	0.8892 (2)	0.9475 (3)	0.0337 (7)

Table 2. Selected geometric parameters (Å, °)

C1'—O4'	1.432 (4)	C4''—O5''A	1.319 (5)
C1'—N1	1.457 (3)	C4''—O5''B	1.326 (10)
C1'—C2'	1.528 (4)	O5''A—C5''A	1.459 (5)
C2'—N2''	1.446 (5)	C5''A—C6''A	1.466 (7)
C2'—C3'	1.542 (4)	O5''B—C5''B	1.459 (11)
C3'—C4'	1.514 (5)	C5''B—C6''B	1.462 (12)
C3'—C3''	1.525 (4)	N1—C6	1.383 (4)
C4'—O4'	1.462 (4)	N1—C2	1.390 (4)
C4'—C5'	1.501 (5)	C2—O2	1.209 (4)
C5'—O5'	1.424 (4)	C2—N3	1.373 (4)
C2''—N2''	1.461 (5)	N3—C4	1.381 (4)
N2''—O3''	1.460 (4)	C4—O4	1.220 (4)
O3''—C3''	1.442 (4)	C4—C5	1.456 (5)
C3''—C4''	1.524 (5)	C5—C6	1.335 (4)
C4''—O4''B	1.180 (10)	C5—C5M	1.503 (5)
C4''—O4''A	1.182 (5)		
O4'—C1'—N1	107.8 (2)	O4''B—C4''—C3''	130.1 (13)
O4'—C1'—C2'	107.2 (2)	O4''A—C4''—C3''	121.7 (4)
N1—C1'—C2'	115.8 (2)	O5''A—C4''—C3''	114.1 (3)
N2''—C2'—C1'	111.1 (3)	O5''B—C4''—C3''	104.4 (7)
N2''—C2'—C3'	107.5 (3)	C4''—O5''A—C5''A	118.1 (4)
C1'—C2'—C3'	101.9 (3)	O5''A—C5''A—C6''A	111.4 (5)
C4'—C3'—C3''	115.3 (3)	C4''—O5''B—C5''B	117.9 (11)
C4'—C3'—C2'	105.3 (2)	O5''B—C5''B—C6''B	111.7 (11)
C3''—C3'—C2'	100.7 (2)	C6—N1—C2	121.0 (2)
O4'—C4'—C5'	109.5 (3)	C6—N1—C1'	120.9 (3)
O4'—C4'—C3'	105.3 (2)	C2—N1—C1'	118.0 (3)
C5'—C4'—C3'	114.9 (3)	O2—C2—N3	122.3 (3)
C1'—O4'—C4'	111.0 (2)	O2—C2—N1	123.9 (3)
O5'—C5'—C4'	111.1 (3)	N3—C2—N1	113.8 (3)
C2'—N2''—O3''	102.5 (3)	C2—N3—C4	128.2 (3)
C2'—N2''—C2''	111.9 (3)	O4—C4—N3	119.5 (3)
O3''—N2''—C2''	108.7 (3)	O4—C4—C5	125.7 (3)
C3''—O3''—N2''	108.8 (2)	N3—C4—C5	114.8 (3)
O3''—C3''—C4''	112.8 (3)	C6—C5—C4	117.8 (3)
O3''—C3''—C3'	108.0 (2)	C6—C5—C5M	124.2 (3)
C4''—C3''—C3'	112.6 (3)	C4—C5—C5M	118.0 (3)
O4''A—C4''—O5''A	124.2 (4)	C5—C6—N1	124.3 (3)
O4''B—C4''—O5''B	125.3 (12)		
C1'—C2'—C3'—C4'	-30.3 (3)		
C3'—C4'—O4'—C1'	-6.7 (3)		
O4'—C1'—C2'—C3'	26.6 (3)		
C2'—C1'—N1—C2	117.6 (3)		
C2'—N2''—O3''—C3''	-31.2 (3)		
O3''—C3''—C3'—C2'	7.3 (3)		
C3'—C3''—C4''—O5''A	-152.5 (4)		
C3''—C4''—O5''A—C5''A	-173.8 (4)		

C4''—O5''A—C5''A—C6''A	84.4 (6)
C2'—C3'—C4'—O4'	23.4 (3)
C4'—O4'—C1'—C2'	-13.0 (3)
O4'—C1'—N1—C6	54.3 (3)
C3'—C2'—N2''—O3''	35.9 (3)
N2''—O3''—C3''—C3'	14.4 (3)
C3''—C3'—C2'—N2''	-27.0 (3)
C3'—C3''—C4''—O5''B	165 (1)
C3''—C4''—O5''B—C5''B	-168 (2)
C4''—O5''B—C5''B—C6''B	-67 (3)

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

D—H...A	D—H	H...A	D...A	D—H...A
O5'—H5'...O4' ⁱ	0.79 (5)	2.1 (3)	2.803 (4)	157 (4)
N3—H3...O4'' ⁱⁱ	0.88 (4)	1.97 (4)	2.846 (4)	174 (2)
N3—H3...O4' ⁱⁱ	0.88 (4)	2.24 (4)	3.07 (2)	159 (6)

Symmetry codes: (i) $x - 1, y, z$; (ii) $1 + x, y, 1 + z$.

The structure was solved by direct methods using *SHELXS86* (Sheldrick, 1990). Refinement was by full-matrix least squares minimizing the function $\sum w = (|F_o|^2 - |F_c|^2)^2$ using the program *SHELXL93* (Sheldrick, 1993). All non-H atoms were refined with anisotropic temperature factors, except for the four atoms of the minor form which were refined isotropically. The bond lengths and angles of the minor form were restrained to those of the major form. The H atoms were refined with isotropic temperature factors.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *MSC/AFC Diffractometer Control Software*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry, including H-atom geometry, and torsion angles have been deposited with the IUCr (Reference: CR1159). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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