Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

2,2′-Anhydro-2′-*C*-methyl-1-(β-D-arabino-furanosyl)uracil (2,2′-anhydro-2′-*C*-methyl-uridine)

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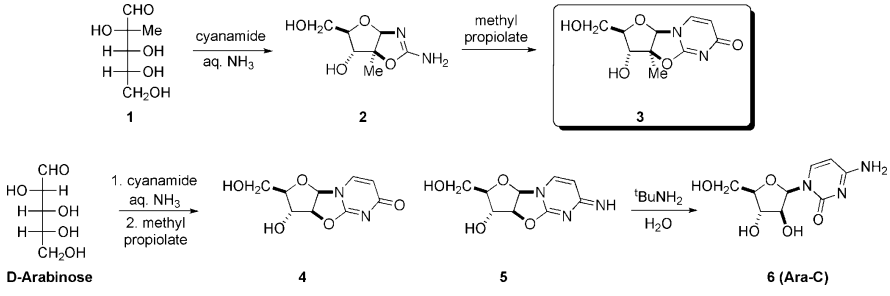
Received 8 March 2007
Accepted 26 March 2007

The structure of anhydro-2′-*C*-methyluridine, $C_{10}H_{12}N_2O_5$, is firmly established by X-ray crystallography, with the sugar adopting a furanose ring. The absolute stereochemistry is inferred from the use of 2-*C*-methyl-D-arabinose as the starting material. The molecules are linked by two conventional O—H···O hydrogen bonds, and one C—H···π hydrogen bond.

Comment

Nucleosides with methyl branches on the sugar group have been known for a long time (Walton *et al.*, 1966), and a number of 2′-*C*-methyl nucleoside analogues have shown promise as agents for the treatment of hepatitis C (Eldrup *et al.*, 2004; Pierra *et al.*, 2006; Toniutto *et al.*, 2007). Anhydronucleosides are key intermediates in the synthesis of nucleosides (Tolman & Robins, 1971; Holý, 1973*b*; Holý & Cech, 1974). There are, however, no other examples of 2′-*C*-methyl branched anhydronucleosides.



The Holý reaction of cyanamide with sugars has been widely used to generate oxazoline intermediates (Holý, 1972; Sanchez & Orgel, 1970; Anastasi *et al.*, 2007) which, when reacted with methyl propiolate, have been seen to generate anhydrouridine analogues (Holý, 1974; Shannahof & Sanchez, 1973). In this fashion, anhydrouridine, (4), was synthesized from D-arabinose (Holý, 1973*a*). The corresponding anhydrocytosine, (5), when opened with *tert*-butylamine in water gave Ara-C, (6) (Karimian, 1991), which is used in the treatment of leukaemia (Rosowsky *et al.*, 1982).

Anhydro-2′-*C*-methyluridine, (3), was synthesized in two steps from 2-*C*-methyl-D-arabinose, (1), *via* a Holý condensation reaction with cyanamide and aqueous ammonia to give the oxazoline intermediate, (2), followed by reaction with methyl propiolate (Jenkinson *et al.*, 2007). X-ray crystallography firmly established that the sugar is in a furanose ring (Fig. 1), rather than a pyranose ring, with the anhydrobase on the β face. The absolute configuration was determined by the use of 2-*C*-methyl-D-arabinose as the starting material.

Key indicators

Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.003 Å
R factor = 0.031
wR factor = 0.065
Data-to-parameter ratio = 8.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

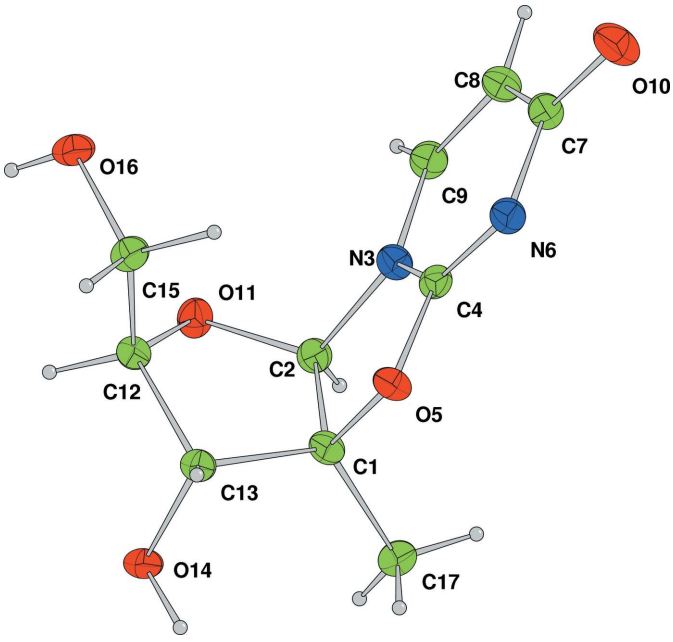


Figure 1
The molecular structure of the title compound, (3), with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitary radii.

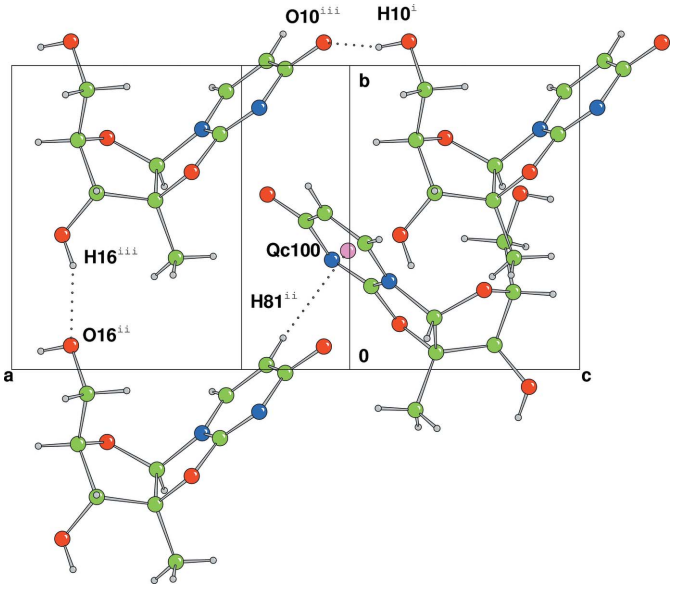


Figure 2
The structure of (3) consists of hydrogen-bonded sheets lying parallel to the *ab* face of the unit cell. The pseudo-atom Qc100 lies at the centre of the aromatic ring. [Symmetry codes: (i) $-x, y+\frac{1}{2}, 1-z$; (ii) $1-x, y-\frac{1}{2}, 1-z$; (iii) $1-x, y+\frac{1}{2}, 1-z$.]

The crystal structure of (3) consists of sheets of molecules linked together by two independent conventional (O—H···O) hydrogen bonds lying parallel to the *ab* face of the unit cell (Fig. 2). There is a potential C—H···phenyl hydrogen bond to the N3/C4/N6/C7–C9 ring, whose centroid is represented by the pseudo-atom Qc100 in Fig. 2 (H81···Qc100 = 2.69 Å and C8—H81···Qc100 = 152°) There are no particularly close contacts between the sheets.

Experimental

The title compound was crystallized from methanol (m.p. 513–516 K). $[\alpha]_D^{20}$ −52.0 (*c* 0.23 in MeOH).

Crystal data

$C_{10}H_{12}N_2O_5$
M_r = 240.22
Monoclinic, $P2_1$
a = 8.6134 (3) Å
b = 7.4803 (3) Å
c = 8.8106 (3) Å
β = 115.0716 (18)°
V = 514.19 (3) Å^3
Z = 2
Mo *Kα* radiation
μ = 0.13 mm^{-1}
T = 150 K
0.50 × 0.30 × 0.20 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*DENZO* and *SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.919, T_{max} = 1.0
3462 measured reflections
1242 independent reflections
1242 reflections with $I > -3\sigma(I)$
R_{int} = 0.022

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.065
S = 0.98
1242 reflections
154 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O16—H10···O10^{i}	0.85	1.92	2.724 (2)	158
O14—H16···O16^{ii}	0.85	1.99	2.732 (2)	145

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

In the absence of significant anomalous scattering, 744 Friedel pairs were merged. The absolute configuration was inferred from the use of 2-*C*-methyl-D-arabinose as the starting material.

The H atoms were all located in a difference map, but those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

Funding from Novartis and Idenix for SFJ and NAJ is gratefully acknowledged.

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