

Ethyl 3-(2'-deoxyuridin-5-yl)-3-hydroxy-2-iodopropanoate, a nucleoside analogue

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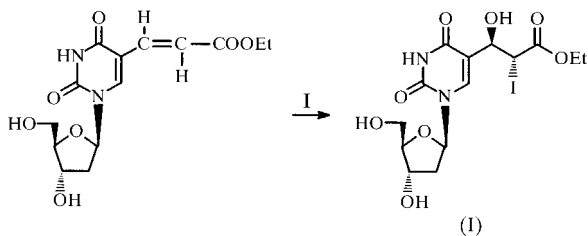
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In the title compound, C₁₄H₁₉IN₂O₈, an almost planar heterocyclic base is oriented *anti* with respect to the puckered sugar moiety. The sugar pucker is *C2'-endo/C3'-exo*, the *N*-glycosidic torsion angle is 166.4 (4)° and the conformation of O5' is *+sc*. The molecules are linked by hydrogen bonds of the types N—H···O and O—H···O.

Comment

The title compound, (I), is an example of the 5-vinyl-2'-deoxyuridine derivatives which have been found to inhibit replication of the *Herpes simplex* virus type I (De Clercq *et al.*, 1979). Studies of the structure–activity relationships of these 5-substituted derivatives indicated that the activity is associated with analogues in which the 5-substituent is conjugated with the pyrimidine ring (Griengl *et al.*, 1985). The structural analysis of (I) is a continuation of our earlier work involving systematic conformational studies on modified nucleosides with the aim of understanding structure–function relationships.



The absolute configuration of the structure has been determined, as indicated by the Flack parameter of $-0.04(3)$ (Flack, 1983) (Friedel number = 181). The 5-substituent is an aliphatic chain with a terminal carboxyl ethoxy group and it is twisted away from the N1–C6 ring

[C4–C5–C7–C8 torsion angle = $-61.6(7)^\circ$], allowing the bulky I atom to lie out of the plane of the ring. The chain skeleton has an extended conformation. The terminal ethoxy group has a *gauche* conformation with respect to the skeleton [C9–O10–C10–C11 = $76.7(9)^\circ$]. The C–I bond distance of 2.137 (6) Å compares closely with the value of 2.139 Å found for CH₃I (Bowen *et al.*, 1958).

The heterocyclic base moiety is almost planar, the r.m.s. deviation of the atoms from their least-squares mean plane being 0.027 (5) Å and the maximum deviation being 0.044 (5) Å for C2. The bond lengths and angles for the nucleoside analogue are normal (Allen *et al.*, 1987) with no significant deviation, indicating that the substitution at C5 has no effect on the molecular geometry. The C4=O4 [1.245 (6) Å] bond is 0.042 (6) Å longer than the C2=O2 [1.203 (7) Å] and C9=O9 [1.204 (7) Å] bonds; this elongation is attributed to the formation of a hydrogen bond between O4 and O3'; O2 and O9 do not form any hydrogen bonds in the structure of (I). Similar effects have been reported for the 1:1 complex of thiourea and parabanic acid (TUPA; Weber & Craven, 1987).

The glycosyl torsion angle χ (C2–N1–C1'–O4'), showing the relative orientation of the base with respect to the sugar ring, has a value of $-193.6(4)^\circ$, which lies at the extreme end of the range -160 to -175° for torsion angles χ observed in active anti-HIV nucleosides (Van Roey *et al.*, 1989). This glycosyl angle χ places the C1'–O4' bond close to the plane of the conjugated system of the base, bringing O4' into close contact with hydrogen H6 on C6 of the base [H6···O4' = 2.352 (7) Å], resulting in steric hindrance between the base and sugar ring. The structural effects include lengthening of the C1'–N1 bond, which has a value 1.482 (7) Å in (I). Saenger (1984) has correlated the C1'–N1 bond length with the angle χ , and for χ near -167° , the expected N1–C1' bond length is 1.48 Å.

The C1'–O4' bond [1.411 (6) Å] is shorter than C4'–O4' [1.440 (7) Å], due to the anomeric effect (Kirby, 1983), which is a common feature of nucleosides. The pseudo rotation phase angle P [168.3 (6)°] and the maximum torsion angle ν_{\max} [38.2 (7)°] are calculated from intraring torsion angles and describe the puckering of the five-membered ring of the sugar moiety; these values indicate an unsymmetrical twist of the sugar ring with *C2'-endo/C3'-exo* (²T₃; Saenger, 1984) and are similar to those of active anti-HIV compounds, which have P values in the range 165 – 220° with *C2'-endo/C3'-exo* (Van Roey *et al.*, 1989). The active conformer of 3'-azido-3'-deoxythymidine (known as AZT) has $P = 175^\circ$ with *C2'-endo/C3'-exo* (Dyer *et al.*, 1988). The *C3'-exo* conformation places C5' in an axial position. The torsion angle γ [C3'–C4'–C5'–O5' = $74.9(7)^\circ$] describing the orientation of the 5'-hydroxyl group relative to the sugar ring shows that C5'–O5' is in a *gauche-gauche* orientation (*+sc*) (Van Roey *et al.*, 1989).

Each molecule of (I) has four H atoms available for hydrogen-bond formation. These are bonded to three hydroxyl O atoms, O3', O5' and O7, and to the pyrimidine N atom N3. The hydroxyl groups act as both hydrogen-bond donors and acceptors. The hydroxyl groups and the ring-N

atom N3 form O—H...O and N—H...O hydrogen bonds with molecules related by translational symmetry along the *a* and *b* axes (Table 2), resulting in a two-dimensional network in the *ab* plane.

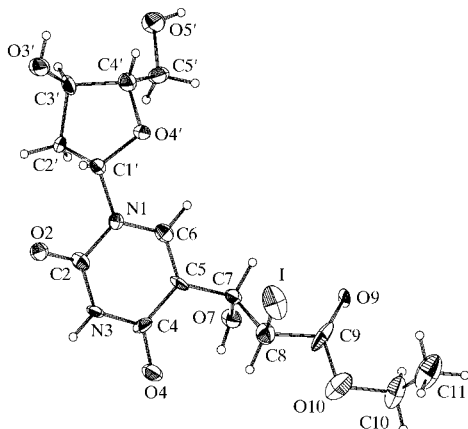


Figure 1
An ORTEPII (Johnson, 1976) plot of the molecule of (I) drawn at the 30% probability level. H atoms are drawn as small spheres of arbitrary radii.

Experimental

Compound (I) was synthesized by the reaction of ethyl 3-(2'-deoxyuridine-5-yl)propanoate with iodine and potassium iodate, as illustrated in the Scheme, according to the method of Kumar *et al.* (1989). Crystals of (I) were obtained from methanol by slow evaporation at room temperature.

Crystal data

$C_{14}H_{19}IN_2O_8$
 $M_r = 470.21$
Monoclinic, $P2_1$
 $a = 6.748$ (3) Å
 $b = 10.466$ (4) Å
 $c = 12.555$ (4) Å
 $\beta = 92.36$ (3)°
 $V = 885.9$ (6) Å³
 $Z = 2$

$D_x = 1.763$ Mg m⁻³
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
 $\theta = 10.3$ – 14.4 °
 $\mu = 1.852$ mm⁻¹
 $T = 293$ (2) K
Block, colourless
 $0.35 \times 0.25 \times 0.20$ mm

Data collection

Enraf–Nonius CAD-4 diffractometer
 ω – 2θ scans
Absorption correction: empirical via ψ scan (North *et al.*, 1968)
 $T_{\min} = 0.607$, $T_{\max} = 0.690$
3290 measured reflections
1649 independent reflections
1545 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.046$
 $\theta_{\text{max}} = 25$ °
 $h = -8 \rightarrow 8$
 $k = 0 \rightarrow 12$
 $l = 0 \rightarrow 14$
3 standard reflections every 100 reflections
intensity decay: negligible

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.036$
 $wR(F^2) = 0.137$
 $S = 0.928$
1585 reflections
231 parameters
H-atoms: see below

$w = 1/[\sigma^2(F_o^2) + (0.0399P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.002$
 $\Delta\rho_{\text{max}} = 0.34$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.31$ e Å⁻³
Absolute structure: Flack (1983)
Flack parameter = -0.04 (3)

Table 1

Selected torsion angles (°).

C5—C7—C8—C9	−172.8 (5)	C8—C9—O10—C10	−175.3 (7)
C7—C8—C9—O10	−139.7 (6)	C9—O10—C10—C11	76.7 (9)

Table 2

Hydrogen-bonding geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O5'—H5'...O3' ⁱ	0.82	2.01	2.732 (6)	147
O7—H7...O5' ⁱⁱ	0.82	2.29	2.912 (7)	133
O3'—H3'...O4' ⁱⁱⁱ	0.82	1.98	2.650 (7)	138
N3—H3...O7' ^{iv}	0.86	2.07	2.860 (6)	152

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

The number of Friedel-related reflections was 181. All H atoms attached to C or N were located geometrically and refined as part of a riding model, with $U_{\text{iso}}(\text{H}) = 0.078$ (6) Å². All H atoms attached to hydroxyl-O atoms were located in circular difference Fourier syntheses and thereafter refined freely with a common $U_{\text{iso}}(\text{H})$ of 0.078 (6) Å². The atom-numbering scheme used in Fig. 1 is consistent with the rules of the IUPAC–IUB Joint Commission on Biochemical Nomenclature (IUPAC–IUB, 1983).

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *CAD-4 Software*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL93*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1390). Services for accessing these data are described at the back of the journal.

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