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5-Phenyluridine trihydrate

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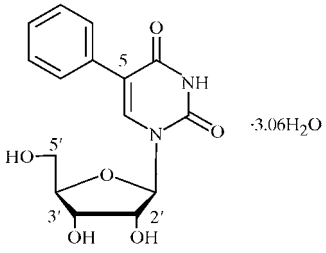
In the title compound, $C_{15}H_{16}N_2O_6\cdot\sim3H_2O$, the substituted uracil ring is oriented in the *anti* position relative to the ribose ring, and the phenyl and uracil rings are oriented in a noncoplanar fashion. The furanose ring adopts a conformation close to 3′-*endo*, in contrast to the furanose conformation seen in the crystal structure of the synthetic precursor 5-bromouridine, which is close to 2′-*endo*. The molecule is involved in an extensive hydrogen-bonding network with several water molecules, some of which are disordered.

Comment

The shape of nucleosides depends mainly on three conformational parameters: (i) the glycosyl torsion angle, which determines the *syn* or *anti* orientation of the base relative to the ribose; (ii) the orientation of the primary hydroxy group; and (iii) the conformation of the furanose ring (Blackburn & Gait, 1996). Analogues of naturally occurring nucleosides are sought after as biological tools and enzyme inhibitors, *e.g.* for antiviral therapy, and insights into structural modifications that allow manipulation of the conformation of nucleosides are therefore highly valuable.



(I)

5-Phenyluridine was prepared from 5-bromouridine and phenylboronic acid *via* Suzuki–Miyaura cross-coupling. Clear colourless prisms of the 3.06-hydrate, (I), were obtained after recrystallization from dry ethanol at room temperature. The structure determined for (I) provides, for the first time, insights into the conformational preferences of a 5-arylated uridine derivative. In (I) (Fig. 1), the substituted uracil ring is oriented in the *anti* position relative to the ribose ring, *i.e.* the O4—C1—N11—C12 torsion angle is −170.0 (4)°; viewed down the N11—C1 bond, the C22—H22 bond is above, and pointing towards, atom O5 of the CH_2OH group of the sugar moiety, and the N13—H13 bond points away from O5. The furanose ring adopts a conformation close to 3′-*endo*, an envelope shape with atom C3 displaced 0.601 (8) Å from the mean plane of the other four ring atoms. This conformation is similar to the conformation seen in the crystal structure of the parent nucleoside uridine (Green *et al.*, 1975). In contrast, most previously reported uridine derivatives with additional substituents at position 5, including 5-bromouridine (Cervi *et al.*, 1991), preferentially adopt a furanose conformation close to 2′-*endo*. For the present study, 5-bromouridine was prepared as a synthetic precursor for the title compound and its structure solved (data not shown). Our crystallographic data for 5-bromouridine indeed confirmed the preference of this uridine derivative for the 2′-*endo* conformation, as previously described (Cervi *et al.*, 1991). The furanose conformational differences between 5-phenyluridine and other 5-substituted uridine derivatives suggest that the conformation of furanose in uridine nucleosides can be modulated by the nature of the substituent in position 5. This finding may have important implications for the design of bioactive nucleoside analogues. The biological activity of nucleoside antivirals, for example, hinges on their recognition by several virus-encoded enzymes (*e.g.* thymidine kinase, DNA polymerase). The substrate specificity of these enzymes is at least partly controlled by the conformation of furanose (Choi *et al.*, 2003), and the role of substituents in position 5 for the furanose conformation therefore warrants further investigation.

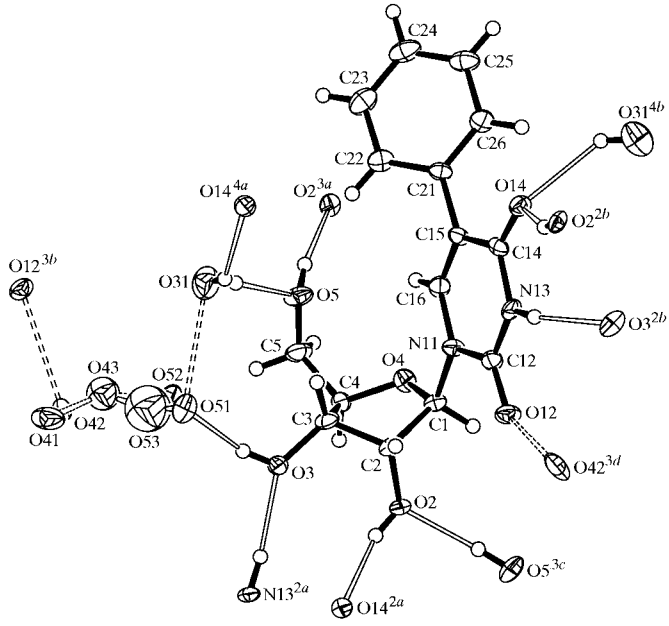


Figure 1
A view of the molecule of 5-phenyluridine and its hydrogen-bonded neighbours, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. [Symmetry codes: (2*a*) $\frac{3}{2}-x, -y, z-\frac{1}{2}$; (2*b*) $\frac{3}{2}-x, -y, \frac{1}{2}+z$; (3*a*) $2-x, \frac{1}{2}+y, \frac{1}{2}-z$; (3*b*) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (3*c*) $2-x, y-\frac{1}{2}, \frac{1}{2}-z$; (3*d*) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (4*a*) $x-\frac{1}{2}, \frac{1}{2}-y, 1-z$; (4*b*) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$.] The site occupancies of the disordered O atoms are as follows: O41 0.49, O42 0.41, O43 0.12, O51 0.46, O52 0.46 and O53 0.12.

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To date, no structural information has been available for uridine derivatives with an aryl or heteroaryl substituent in position 5. However, the structures of four 2′-deoxyuridine derivatives with a heterocyclic substituent (thienyl, thiazolyl, oxazolyl or thiazolyl) in position 5 have been reported (Creuven *et al.*, 1996; Srivatsan & Tor, 2007; Greco & Tor, 2007). All of these known 5-heteroaryl-2′-deoxyuridines show a coplanar, or near coplanar, orientation of the heterocyclic substituent and the uracil base (Creuven *et al.*, 1996; Srivatsan & Tor, 2007; Greco & Tor, 2007). In stark contrast, the phenyl and uracil rings in 5-phenyluridine are oriented in a noncoplanar fashion. The torsion angles about the C15—C21 bond show a rotation of *ca* 37.5° between the planes of the uracil and phenyl rings. These conformational differences have implications for stacking and packing. In our crystal structure, molecules of 5-phenyluridine are stacked along a twofold screw symmetry axis which passes close to the mid-point of the C15—C21 bond; the aromatic rings are arranged so that the phenyl and uracil rings lie overlapping, alternately, on each side of the axis and essentially parallel, about 3.42 Å apart, in infinite stacks (Fig. 2). Additionally, the molecules in a stack are connected in a spiral arrangement through hydrogen bonds through the fully occupied water molecules (O5···H31*A*—O31—H31*B*···O14^{4a}; symmetry code as in Fig. 1). Each stack is linked to its four neighbours through further hydrogen bonds, either directly or through the O31 water molecules. The disordered water molecules lie in zigzag chains, parallel to the *a* axis and between the stacks, and it is estimated that they are linked to each other and to the uridine molecules through further hydrogen bonds, some of which are not well defined since the H atoms were not located or well refined. A listing of the recognized hydrogen bonds is given in Table 1.

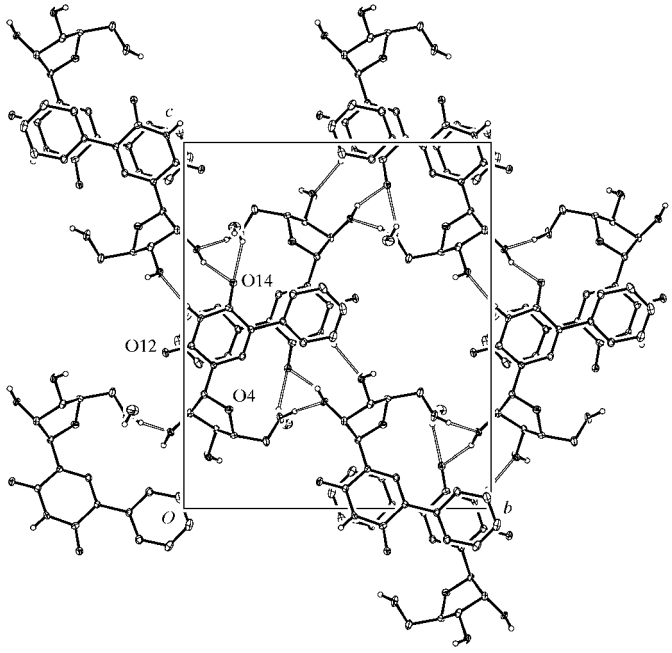

Figure 2
A view of the packing down the *a* axis. A 2_1 symmetry axis (parallel to the *a* axis) passes close to the mid-point of the C15—C21 bond, and the stacking of phenyl/uracil rings in infinite columns about this axis can be seen.

Of the previously reported 5-heteroaryl-2′-deoxyuridines, only the structure of 5-(thien-2-yl)-2′-deoxyuridine shows an alternating stacking arrangement of the uracil base and the 5-substituent similar to that observed in 5-phenyluridine (Creuven *et al.*, 1996). However, in the 5-(thien-2-yl)-2′-deoxyuridine crystal structure, the molecules are stacked with offset overlap of the planar systems; in a pair of the two independent molecules, the inter-ring bonds overlap the thiophene ring of the opposite molecule. These pairs, repeated by translation along the *c* axis, then overlap with the inter-ring bonds above the edge of the uracil rings, and the overall stacking is a continuation of these stepwise offset pairings. In summary, the different substituents in position 5 of 5-(thien-2-yl)-2′-deoxyuridine and 5-phenyluridine induce substantially different stacking patterns. These differences may be exploited for the generation of specific supramolecular architectures, and further studies into the differential effects different substituents in position 5 have on packing and stacking of 5-(hetero)aryluridines are currently underway.

Experimental

For the preparation of 5-phenyluridine, 5-bromouridine (50 mg, 0.155 mmol), phenylboronic acid (34 mg, 0.280 mmol) and K_2CO_3 (43 mg, 0.311 mmol) were suspended in degassed water (5 ml). The mixture was stirred under nitrogen for 10 min at room temperature. Tris(3-sulfonatophenyl)phosphine trisodium salt (6 mg, 0.011 mmol) and Na_2Cl_4Pd (1 mg, 0.005 mmol) were added and the reaction was stirred under nitrogen for 4 h at 313 K. Once all the starting material had been consumed, the reaction was cooled to room temperature. Triethylammonium bicarbonate (0.05 *M* aqueous, 50 ml) was added and the pH was adjusted to pH 7 with 1% aqueous HCl. The aqueous solution was filtered through Celite and the filtrate evaporated. The crude product was purified by column chromatography (silica, 5–10% methanol in $CHCl_3$) to give the title compound as a white amorphous powder (yield 22.4 mg, 45%). This material was recrystallized from dry ethanol at room temperature to give crystals suitable for diffraction experiments.

Crystal data

$C_{15}H_{16}N_2O_6{\cdot}3.06H_2O$
M_r = 371.02
Orthorhombic, $P2_12_12_1$
a = 7.2144 (3) Å
b = 14.0623 (6) Å
c = 16.7536 (8) Å
V = 1699.67 (13) Å^3
Z = 4
Mo- *Kα* radiation
μ = 0.12 mm^{-1}
T = 140 (1) K
0.52 × 0.09 × 0.07 mm

Data collection

Oxford Diffraction Xcalibur-3 CCD diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2005)
T_{min} = 0.544, T_{max} = 0.997
17587 measured reflections
1731 independent reflections
1363 reflections with $I > 2\sigma(I)$
R_{int} = 0.092

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.111
S = 1.12
1731 reflections
281 parameters
5 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N13—H13···O3^{i}	0.86	2.00	2.822 (5)	158
O2—H2O···O14^{ii}	0.82 (6)	1.95 (4)	2.727 (5)	158 (7)
O3—H3O···O51	0.81 (5)	1.85 (4)	2.594 (10)	152 (7)
O3—H3O···O52	0.81 (5)	1.90 (3)	2.690 (11)	164 (7)
O3—H3O···O53	0.81 (5)	2.27 (9)	3.08 (8)	176 (7)
O5—H5O···O2^{iii}	0.83 (5)	1.90 (3)	2.716 (5)	166 (6)
O31—H31A···O5	0.83 (2)	1.92 (3)	2.741 (6)	170 (9)
O31—H31B···O14^{iv}	0.82 (2)	2.20 (7)	2.878 (6)	140 (9)

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

The analysis shows that, in addition to the 5-phenyluridine molecule, there is a well defined water molecule, and two other water molecules each split over two (or perhaps more) sites. The H atoms of the hydroxy groups of the 5-phenyluridine molecule and of the ordered water molecule were located in difference maps and were refined with distance constraints. Other H atoms in the uridine molecule were included in idealized positions and their U_{iso} values were set to ride on the U_{eq} values of the parent C and N atoms.

The partially occupied O atoms were refined isotropically, initially varying the site-occupancy-factor and U_{iso} values in alternate cycles. A few H-atom sites were identified from difference maps, but these did not refine satisfactorily and were not included in the model.

The Flack (1983) parameter was not a reliable indicator of the absolute configuration, and the Friedel equivalent reflections were then merged. Since the crystals were prepared from uridine, the results shown were set to conform to the known configuration of that molecule.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2005); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2005); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3149). Services for accessing these data are described at the back of the journal.

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