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Hydrogen-bonding and C—H···π interactions in 7-hydroxy-3-methoxy-4-methyl-5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidin-1(9*H*)-one

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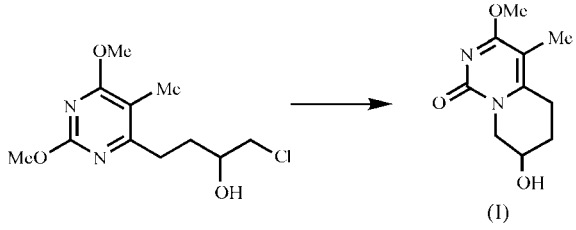
In the title compound, $C_{10}H_{14}N_2O_3$, a pyrimidine ring is fused with a piperidine ring. The pyrimidine ring is planar, whereas the piperidine ring adopts a half-chair conformation. The molecules of the title compound are connected *via* O—H···O intermolecular hydrogen bonds into infinite zigzag chains. The pyrimidine ring is involved in three C—H···π interactions, which link the hydrogen-bonded chains into a three-dimensional framework.

Comment

Pyrimidine derivatives substituted at the C5 or C6 position, and their nucleosides, have great biological significance because they exhibit a wide range of antiviral and anticancer activities (Kim *et al.*, 1997; Pontikis *et al.*, 1997; Botta *et al.*, 1999). This prompted us to synthesize a series of novel 5-methyl 6-acyclic side-chain-substituted pyrimidine derivatives in order to evaluate their cytostatic and antiviral activities (Prekupec *et al.*, 2005). We report here the structure of the title bicyclic product, (I), formed by intramolecular cyclization of the acyclic side chain with atom N1 of the pyrimidine ring.



(I)

The title 5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidin-1-one derivative, (I), crystallizes in the non-centrosymmetric space group $P2_12_12_1$ from a racemic mixture (Prekupec *et al.*, 2005) by spontaneous resolution. A view of (I) (*S* configuration) is shown in Fig. 1 and selected geometric parameters are given in Table 1.

The molecule of (I) consists of two six-membered rings fused *via* the common atoms N9 and C10. A survey of the Cambridge Structural Database (July 2004 update, Version 5.25; Allen, 2002) revealed that this is the first structure comprising these two fused heterocyclic rings with a carbonyl O atom at the 1-position and a methoxy group at the 3-position. The bond lengths and angles in (I) are well within the ranges reported for 4-methoxy-5-methylpyrimidin-2-ones (Brennan *et al.*, 1986; Paquette *et al.*, 2001) and piperidin-3-ols (Herdeis *et al.*, 1996; Kirfel *et al.*, 1996). As expected, the exception is the N9—C10 bond, which in (I) is significantly shorter (*ca* 0.09 Å) than the corresponding bond in the piperidin-3-ols, due to the delocalization effect of the pyrimidine ring.

The pyrimidine ring in (I) is planar. The largest observed deviation of the ring atoms from their mean plane is 0.008 (2) Å for atom C10. Atom C11 of the methoxy group is in a synperiplanar position relative to atom N2 of the ring; the C11—O2—C3—N2 torsion angle is 2.1 (3)°. The piperidine ring adopts a half-chair conformation, in which atoms C6 and C7 are −0.369 (3) and 0.381 (2) Å, respectively, from the mean plane of the other ring atoms (C8/N9/C10/C5). The plane of atoms C8/N9/C10/C5 [torsion angle = −0.1 (3)°] is almost coplanar with the pyrimidine ring, which is substantiated by the dihedral angle between their mean planes amounting to 1.1 (1)°. Furthermore, hydroxyl atom O3 is in an axial position with respect to the piperidine ring, as illustrated by the O3—C7—C6—C5 and O3—C7—C8—N9 torsion angles (Table 1).

Molecules of (I) are linked into infinite zigzag chains by O—H···O intermolecular hydrogen bonds (Fig. 2 and Table 2). Atom O3 in the molecule at (*x*, *y*, *z*) acts as a donor to atom O1 in the molecule at $(\frac{1}{2}+x, \frac{1}{2}-y, 1-z)$, so producing a spiral *C*(7) chain (Bernstein *et al.*, 1995) running parallel to the [100] direction and generated by the 2_1 screw axis along $(x, \frac{1}{4}, \frac{1}{2})$. There are a number of C—H···π interactions that link these hydrogen-bonded chains (Fig. 3). The position of methyl atom H12*B* with respect to the pyrimidine ring in an adjacent molecule enables a geometric type-II C—H···π interaction ($\alpha \simeq 153°$ and $\theta \simeq 76°$), according to the classification of Malone *et al.* (1997). The H12*B*···N9^{ii} distance

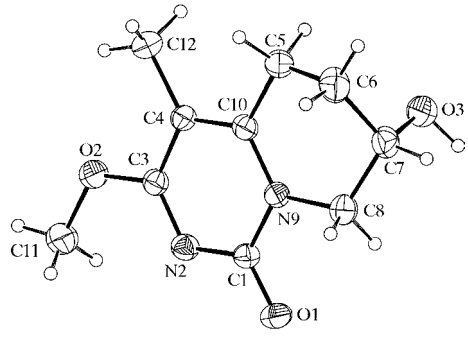


Figure 1
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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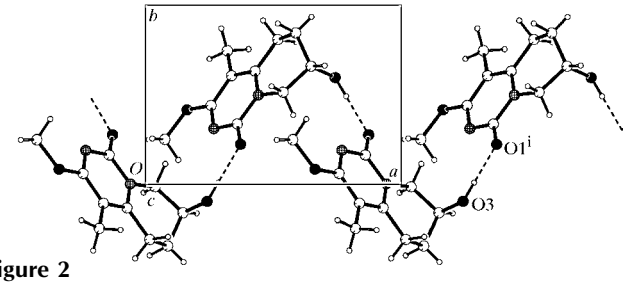

Figure 2
A crystal packing diagram of (I), viewed along [001], showing the formation of infinite zigzag chains parallel to [100]. Hydrogen bonds are indicated by dashed lines. [Symmetry code: (i) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$.]

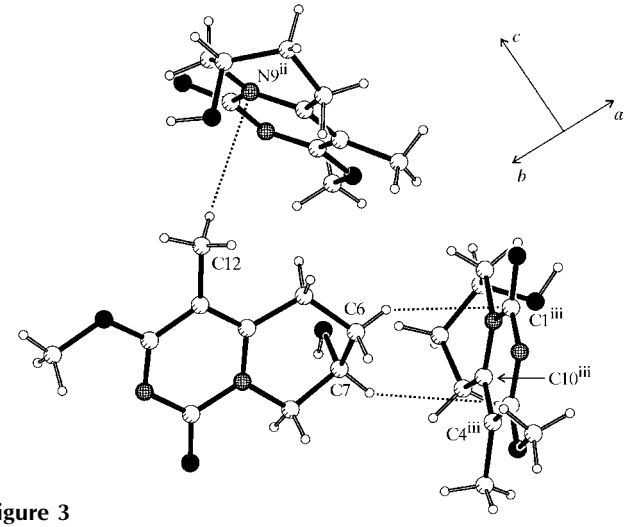

Figure 3
Part of the crystal structure of (I), showing the C—H···π interactions linking the hydrogen-bonded chains into a three-dimensional framework. The C12—H12*B*, C6—H61 and C7—H7 bonds point towards atom N9^{ii}, atom C1^{iii} and the C4—C10^{iii} bond, respectively. C—H···π interactions are indicated by dotted lines and the unit-cell box has been omitted for clarity. [Symmetry codes: (ii) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iii) $\frac{1}{2}+x, -\frac{1}{2}-y, 1-z$.]

is shorter than the distance between the H atom and the pyrimidine-ring centroid [symmetry code: (ii) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$; Table 2]. The second shortest H···C contact is to atom C1 and the C12—H12*B* bond points more to ring atom N9 than to the ring centroid (*Cg*). The C6—H61···*Cg*^{iii} interaction exhibits a similar geometry [symmetry code: (iii) $\frac{1}{2}+x, -\frac{1}{2}-y, 1-z$]. The shortest H···C contact is to atom C1, but this could be classified as a geometric type-III interaction ($\alpha \simeq 120^\circ$ and $\theta \simeq 69^\circ$). In the same class of interaction is C7—H7···*Cg*^{iii} ($\alpha \simeq 123^\circ$ and $\theta \simeq 65^\circ$), with the H7···C10^{iii} and H7···C4^{iii} distances being approximately equal and all other H···C contacts being longer than 3.37 Å. According to this observation, the C7—H7 bond points more to the C4—C10 bond of the pyrimidine ring. Thus, these three C—H···π interactions link the hydrogen-bonded chains into a three-dimensional framework.

Experimental

The synthesis of the racemic compound, (I), has been described by Prekupec *et al.* (2005). A mixture of 6-(4-chloro-3-hydroxybutyl)-2,4-dimethoxy-5-methylpyrimidine (250 mg, 0.95 mmol) in methanol (5 ml) was saturated with gaseous NH_3. The flask was firmly stoppered and the reaction was stirred overnight at 333 K. The solvent was then evaporated under reduced pressure and the product was purified on a silica-gel column using petroleum ether–ethyl acetate (1:1) as eluent. Crystals of (I) were isolated (144 mg, 72%; m.p. 482–484 K). Crystals suitable for X-ray diffraction were grown at room temperature from a very dilute ethanol solution (96%).

Crystal data

$C_{10}H_{14}N_2O_3$
$M_r = 210.23$
Orthorhombic, $P2_12_12_1$
$a = 9.955$ (4) Å
$b = 6.9722$ (12) Å
$c = 14.673$ (4) Å
$V = 1018.4$ (5) Å^3
$Z = 4$
$D_x = 1.371$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 3.8$–11.4°
$\mu = 0.10$ mm^{-1}
$T = 293$ (2) K
Prismatic, colourless
0.55 × 0.28 × 0.21 mm

Data collection

Philips PW1100 diffractometer, updated by Stoe
ω scans
5738 measured reflections
1574 independent reflections
1084 reflections with $I > 2\sigma(I)$
$R_{int} = 0.047$
$\theta_{max} = 29.0^\circ$
$h = -13 \rightarrow 13$
$k = -9 \rightarrow 9$
$l = -20 \rightarrow 20$
4 standard reflections
frequency: 120 min
intensity decay: 2.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.108$
$S = 1.06$
1574 reflections
168 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0621P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.13$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N2—C3	1.308 (2)	N9—C1	1.398 (3)
N2—C1	1.358 (3)	C3—C4	1.417 (3)
N9—C10	1.369 (3)	C4—C10	1.369 (3)
C3—N2—C1	118.84 (17)	N2—C3—C4	125.47 (18)
C10—N9—C1	121.55 (16)	C10—C4—C3	115.34 (17)
C10—N9—C8	123.57 (18)	C4—C10—N9	120.01 (18)
C1—N9—C8	114.86 (17)	C4—C10—C5	120.91 (19)
N2—C1—N9	118.75 (16)	N9—C10—C5	119.08 (18)
C11—O2—C3—N2	2.1 (3)	O3—C7—C8—N9	−72.6 (3)
C5—C6—C7—O3	60.6 (3)	C8—N9—C10—C5	−0.1 (3)

Table 2
Hydrogen-bond geometry (Å, °).

Cg is the centroid of the pyrimidine ring (C1/N2/C3/C4/C10/N9).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O1^{i}	0.94 (4)	1.78 (4)	2.709 (3)	168 (3)
C12—H12*B*···*Cg*^{ii}	0.96	3.08	3.956 (3)	153
C12—H12*B*···N9^{ii}	0.96	3.04	3.856 (4)	144
C12—H12*B*···C1^{ii}	0.96	3.17	4.116 (4)	168
C6—H61···*Cg*^{iii}	0.87 (3)	3.21 (3)	3.718 (3)	120 (2)
C6—H61···C1^{iii}	0.87 (3)	3.00 (3)	3.745 (4)	144 (2)
C6—H61···N2^{iii}	0.87 (3)	3.22 (3)	3.788 (4)	125 (2)
C7—H7···*Cg*^{iii}	0.99 (2)	3.11 (2)	3.736 (3)	123 (1)
C7—H7···C10^{iii}	0.99 (2)	2.86 (2)	3.655 (3)	138 (2)
C7—H7···C4^{iii}	0.99 (2)	2.91 (2)	3.783 (4)	148 (2)

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

The H atoms attached to atoms C11 and C12 were included in calculated positions as riding atoms, with C—H distances of 0.96 Å and with $U_{iso}(H) = 1.5U_{eq}(C)$. All other H atoms were found in difference Fourier maps and their coordinates and isotropic displacement parameters were refined freely. In the absence of significant anomalous scattering, the Flack (1983) parameter [−0.3 (14)] was inconclusive (Flack & Bernardinelli, 2000) and the Friedel equivalents were therefore merged prior to the final refinement. The enantiomer shown in Fig. 1 was chosen arbitrarily.

Data collection: *STADI4* (Stoe & Cie, 1995); cell refinement: *STADI4*; data reduction: *X-RED* (Stoe & Cie, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1186). Services for accessing these data are described at the back of the journal.

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