1-Methoxymethyl-5-ethyl-6-(1-naphthyl-methyl)uracil

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Key indicators

Single-crystal X-ray study
$T = 293$ K
Mean σ(C–C) = 0.004 Å
R factor = 0.060
wR factor = 0.138
Data-to-parameter ratio = 12.1

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

The title compound, $C_{19}H_{20}N_2O_3$ is composed of two moieties, the pyrimidinyl plane and the naphthyl aromatic plane; the dihedral angle betwen them is 90.9 (3)°. A centrosymmetric dimer is formed in the crystal through pairs of N—H···O hydrogen bonds.

Comment

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), an RNA-dependent retrovirus (Barre-Sinoussi *et al.*, 1983; Gallo *et al.*, 1983). Reverse transcriptase (RT) is crucial for the whole life cycle of HIV, and is a special target for designing selective HIV-1 reverse transcriptase inhibitors (RTI's; Spence *et al.*, 1995; Cox & Sinclair, 2000). The synthesis of HIV-RT inhibitors, which may have a better interaction with the active binding pocket, is a major challenge facing modern medicinal chemistry (Hopkins *et al.*, 1999). The title compound, (I), was synthesized for the first time as a potential HIV-RT inhibitor (De Clercq *et al.*, 1991; Pedersen & Pedersen, 2000).


(I)
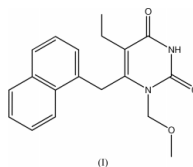
The structure of (I) consists of two aromatic planes; one is the pyrimidinyl and the other the naphthyl moiety (Fig. 1). This kind of butterfly configuration of HEPT {HEPT = 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine]} analogs has been proposed by Arnold *et al.* (1996) and was verified by our work. Centrosymmetric dimers are formed by pairs of N3—H3···O2^i [symmetry code: (i) $1 - x, -y, -z$] hydrogen bonds. The dimers are further linked by C—H···O interactions (Table 1 and Fig. 2). The distance between the two naphthyl planes related by an inversion center is about 3.5 Å, from which it can be deduced that a π–π stacking effect might exist between the naphthyl planes in the whole crystal structure. On the other hand, there is no π–π stacking between the pyrimidinyl planes.

The X-ray results may be compared with those obtained from *MM*2 calculations (Leach, 1996; Pople *et al.*, 1967). While agreement between most of the calculated and measured parameters is good, the observed C7—O3 bond length is a little less than the value calculated by the *MM*2 method; this implies that C—O has some double-bond character, which could be accounted for by conjugation between the lone pair of electrons on the O atom and the pyrimidinyl ring.
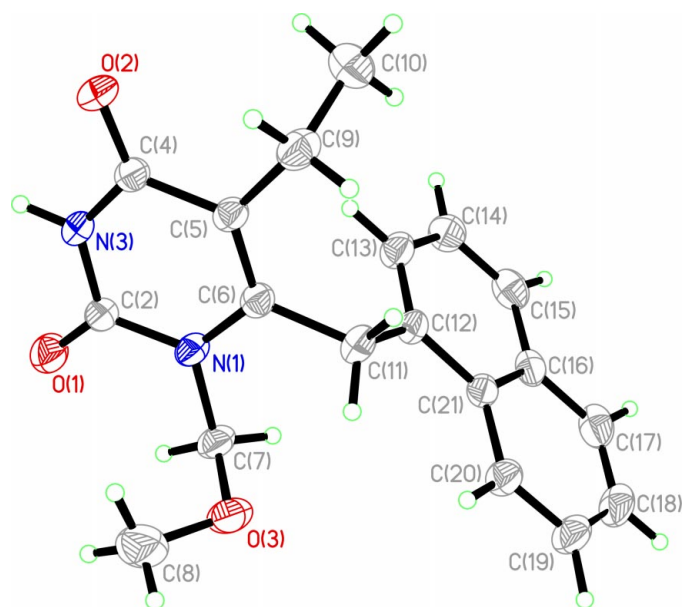
Figure 1
The molecular structure of (I), showing 30% probability displacement ellipsoids.

Figure 2
Packing diagram for (I), viewed down the *c* axis.

Experimental

To 5-ethyl-6-(1-naphthylmethyl)uracil (7 g, 25 mmol) suspended in CH_2Cl_2 (30 ml) was added *N,O*-bis(trimethylsilyl)acetamide (13.6 ml, 55 mmol) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 3 h. When the silylation was completed, tetrabutylammonium iodide (93 mg, 0.25 mmol) and chloromethyl methyl ether (2.8 ml, 30.0 mmol) were added to the above solution. The mixture was then heated to reflux for 3 h and allowed to cool to room temperature. When the reaction was finished (TLC analysis), the reaction mixture was poured into cold saturated $NaHCO_3$ solution (10 ml) and EtOH (5 ml), and stirred for an additional 2 h. The organic phase was washed with brine (15 ml), dried over anhydrous $MgSO_4$ and evaporated to dryness. Column chromatography gave a white foam, which was recrystallized from ethyl acetate to give the title compound as colorless block crystals suitable for X-ray diffraction (3.02 g, 9.3 mmol, 37.2%). The product was characterized by IR, mass spectrometry (EI–HR), ^1H NMR, ^{13}C NMR and ^1H–^1H NOESY.
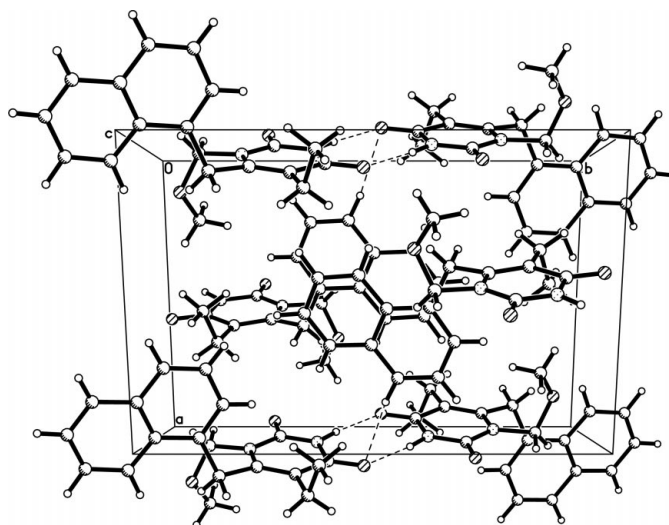
Crystal data

$C_{19}H_{20}N_2O_3$	$D_x = 1.333$ Mg m^{-3}
$M_r = 324.14$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 783
$a = 10.325$ (4) Å	reflections
$b = 14.813$ (5) Å	$\theta = 2.4$–$26.6°$
$c = 11.295$ (4) Å	$\mu = 0.09$ mm^{-1}
$\beta = 110.709$ (5)°	$T = 293$ (2) K
$V = 1616.0$ (10) Å^3	Block, colorless
$Z = 4$	$0.25 \times 0.20 \times 0.15$ mm

Data collection

Bruker SMART CCD area-detector diffractometer	3583 independent reflections
ω scans	2193 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	$R_{int} = 0.040$
	$\theta_{max} = 27.2°$
$T_{min} = 0.978$, $T_{max} = 0.987$	$h = -12 \rightarrow 13$
7908 measured reflections	$k = -19 \rightarrow 14$
	$l = -14 \rightarrow 13$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o{}^2) + (0.0557P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.060$	$+ 0.2622P]$
$wR(F^2) = 0.138$	where $P = (F_o{}^2 + 2F_c{}^2)/3$
$S = 1.01$	$(\Delta/\sigma)_{max} < 0.001$
3583 reflections	$\Delta\rho_{max} = 0.20$ e Å^{-3}
297 parameters	$\Delta\rho_{min} = -0.13$ e Å^{-3}
All H-atom parameters refined	

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N3—H3$\cdots$O2^i	0.91 (2)	1.94 (3)	2.843 (3)	170 (2)
C15—H15$\cdots$O2^{ii}	1.00 (3)	2.48 (3)	3.476 (3)	171.7 (19)

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

All H atoms were refined isotropically. The C—H and N—H bond lengths are 0.89 (4)–1.03 (6) Å and 0.91 (2) Å, respectively.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*97 (Sheldrick, 1995); programs used to prepare material for publication: *SHELXL*97.

References

Arnold, E., Das, K., Ding, J. P., Yadav, P. N. S., Hsiou, Y., Boyer, P. L. & Hughes, S. H. (1996). *Drug Des. Discovery*, **13**, 29–47.
Barre-Sinoussi, F., Chermann, J. C., Rey, F., Nugeyre, M. T., Chamaret, S., Gruest, J., Dauguet, C. & Axler-Blin, C. (1983). *Science*, **220**, 868–871.
Bruker. (1997). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Cox, T. M. & Sinclair, J. (2000). *Molecular Biology in Medicine*, pp. 271–281 Beijing: Science Press.
De Clercq, E., Baba, M., Walker, R. T. & Ubasawa, E. M. (1991). Eur. Pat. 0420763 (Sep. 28, 1990). *Chem. Abstr.* **115**, 158838g.
Gallo, R. C., Sarin, P. S., Gelmann, E. P., Robert-Guroff, M. & Richardson, E. (1983). *Science*, **220**, 865–867.

Hopkins, A. L., Ren, J., Tanaka, H., Baba, M., Okamato, M., Stuart, D. I. & Stammers, D. K. (1999). *J. Med. Chem.* **42**, 4500–4505.

Leach, A. R. (1996). *Molecular Modeling: Principles and Applications*, pp. 90–105. London: Addison Wesley Longman.

Pedersen, O. S. & Pedersen, E. B. (2000). *Synthesis*, **4**, 479–495.

Pople, J. A., Beveridge, D. L. & Dobosh, P. A. (1967). *J. Chem. Phys.* **47**, 2026–2033.

Sheldrick, G. M. (1995). *SHELXTL*. University of Göttingen, Germany.

Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.

Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.

Spence, R. A., Kati, W. M., Anderson, K. S. & Johnson, K. A. (1995). *Science*, **267**, 988–993.