Crystal structure of 2-(5-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine)glycin, $C_8H_8FN_3O_5$

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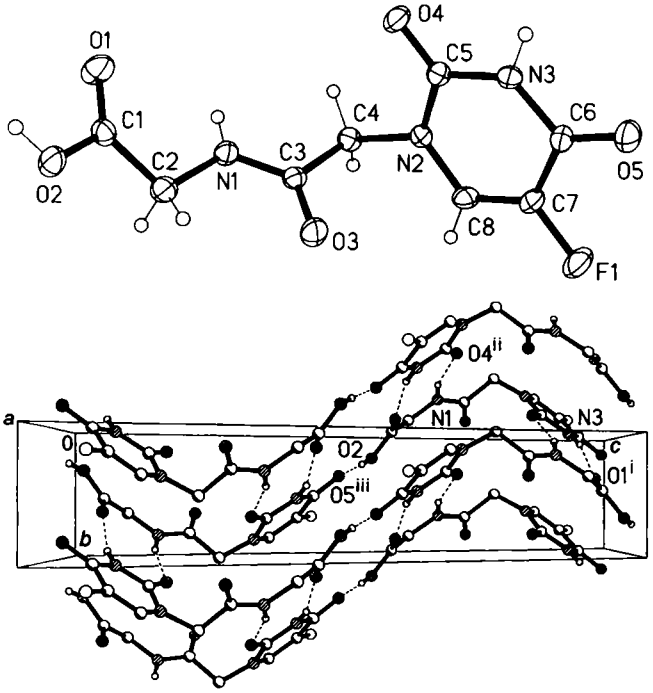

Abstract

$C_8H_8FN_3O_5$, monoclinic, $P12_1/c1$ (no. 14), a = 10.207(1) Å, b = 4.5723(6) Å, c = 22.760(3) Å, β = 112.007(5)°, V = 984.8 Å^3, Z = 4, $R_{gt}(F)$ = 0.068, $wR_{ref}(F^2)$ = 0.140, T = 298 K.

Source of material

The starting material of 5-fluorouracil-1-acetic acid was prepared from 5-fluorouracil and bromoacetic acid following the method of the literature [1]. The key intermediate methyl 2-(5-fluorouracil-1-aceto)amino acetate was synthesized from 5-fluorouracil-1-acetic acid, dicyclohexyl carbodiimide (dcc), and 1-hydroxybenzotriazole (btOH). An *N,N*-dimethylformamide (dmf) solution (25 ml) of dcc (0.024 mol, 4.94 g) was dropped in a dmf solution (75 ml) of 5-fluorouracil-1-acetic acid (0.02 mol, 3.76 g) and btOH (0.02 mol, 2.70 g) at 273 K. After 5 h reaction at room temperature, methyl glycinate (0.02 mol, 2.51 g) and triethylamine (0.02 mol, 2.02 g) were added to the above mixture. After 4 h reaction, a white solid methyl 2-(5-fluorouracil-1-aceto) amino acetate was obtained after filtration, reduced pressure distillation of dmf, and column chromatography separation. The title compound was obtained by hydrolysis with 1 M sodium hydroxide solution. The purified product was dissolved in 95 % ethanol and single crystals were separated after 10 days. Mass, IR, ^{1}H NMR and ^{13}C NMR data are available in the CIF.

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Discussion

5-Fluorouracil (5FU) is one of the antitumor agents most frequently used for treating solid tumors, such as breast, colorectal, and gastric cancers, in either monotherapy or combination therapy with various cytotoxic drugs [2,3]. However, because of its poorly tumor selective and high incidences of toxicity in the bone marrow, gastrointestinal tract, central nervous system and skin, many derivatives of 5FU have been developed to improve its topical delivery and reduce the side effects [4-6]. In an extension of this research, we synthesized the title compound, a dipeptide derivative of 5FU, 2-(5-fluorouracil-1-aceto) amino acetic acid, and determined its crystal structure.

The atoms (C5, C6, C7, C8, N2 and N3) in the heterocyclic ring are essentially planar with r.m.s. deviations of 0.0142 Å. The N1—C3 bond distance (1.323(3) Å) is shorter than a typical C—N bond length (ca. 1.443(4) Å), but longer than a typical double C=N bond (ca. 1.269 Å), indicating the electron delocalization at the O3, C3 and N1 atoms. Three distinct hydrogen bonds occur in the crystal structure: each pair molecules are linked by intermolecular O2–H2···O5^{iii} (iii: x,–y+½,z–½) hydrogen bond to form a ribbon-like structure, and adjacent ribbons are linked by two different intermolecular N1–H1···O4^{ii} (ii: –x+1,y–½,–z+3/2) and N3–H3···O1^{i} (i: –x+1,y+½,–z+3/2) hydrogen bonds forming corrugated layers (figure, bottom).

Table 1. Data collection and handling.

Crystal:	colorless sheet, size 0.08 x 0.13 x 0.24 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	1.50 cm^{-1}
Diffractometer, scan mode:	Bruker APEX SMART CCD, φ/ω
$2\theta_{max}$:	50.4°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	4871, 1773
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 1497
$N(param)_{refined}$:	154
Programs:	SHELXS-97 [7], SHELXL-97 [8], SHELXTL [9]

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(2)	4e	0.2315	1.2437	0.5086	0.058
H(1)	4e	0.2914	0.5635	0.6506	0.044
H(3)	4e	0.5033	1.0731	0.9125	0.042
H(2A)	4e	0.1039	1.0160	0.6094	0.056
H(2B)	4e	0.0723	0.7349	0.5669	0.056
H(4A)	4e	0.2292	0.3104	0.7553	0.039
H(4B)	4e	0.3701	0.4462	0.7547	0.039
H(8)	4e	0.1158	0.5362	0.8217	0.043

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(1)	4*e*	0.1062(2)	0.8185(5)	0.91472(9)	0.050(1)	0.087(2)	0.064(1)	−0.022(1)	0.040(1)	−0.024(1)
O(1)	4*e*	0.3501(2)	0.8671(6)	0.5691(1)	0.049(2)	0.061(2)	0.069(2)	0.029(1)	0.035(1)	0.029(1)
O(2)	4*e*	0.1802(2)	1.1905(5)	0.5269(1)	0.047(1)	0.055(2)	0.049(1)	0.019(1)	0.027(1)	0.023(1)
O(3)	4*e*	0.1032(2)	0.8470(6)	0.7081(1)	0.050(1)	0.066(2)	0.042(1)	0.027(1)	0.022(1)	0.007(1)
O(4)	4*e*	0.5116(2)	0.8277(5)	0.8201(1)	0.042(1)	0.064(2)	0.047(1)	−0.018(1)	0.029(1)	−0.015(1)
O(5)	4*e*	0.3460(2)	1.1529(5)	0.9672(1)	0.051(1)	0.057(2)	0.043(1)	−0.009(1)	0.024(1)	−0.018(1)
N(1)	4*e*	0.2251(3)	0.6774(6)	0.6515(1)	0.035(1)	0.043(2)	0.036(1)	0.014(1)	0.017(1)	0.008(1)
N(2)	4*e*	0.3033(2)	0.6378(5)	0.8178(1)	0.029(1)	0.032(1)	0.028(1)	−0.002(1)	0.010(1)	−0.002(1)
N(3)	4*e*	0.4277(2)	0.9718(6)	0.8948(1)	0.029(1)	0.043(2)	0.035(1)	−0.013(1)	0.013(1)	−0.008(1)
C(1)	4*e*	0.2384(3)	0.9664(7)	0.5637(1)	0.036(2)	0.037(2)	0.030(2)	0.008(2)	0.011(1)	0.003(1)
C(2)	4*e*	0.1473(3)	0.8526(8)	0.5964(2)	0.038(2)	0.060(2)	0.045(2)	0.014(2)	0.018(2)	0.021(2)
C(3)	4*e*	0.1951(3)	0.6910(6)	0.7031(1)	0.028(2)	0.030(2)	0.032(2)	−0.002(1)	0.011(1)	−0.005(1)
C(4)	4*e*	0.2800(3)	0.4920(7)	0.7576(1)	0.034(2)	0.029(2)	0.033(2)	0.000(1)	0.012(1)	−0.005(1)
C(5)	4*e*	0.4210(3)	0.8117(7)	0.8427(1)	0.031(2)	0.035(2)	0.030(2)	−0.001(1)	0.012(1)	0.002(1)
C(6)	4*e*	0.3290(3)	0.9904(7)	0.9222(1)	0.037(2)	0.035(2)	0.028(2)	−0.001(1)	0.015(1)	−0.002(1)
C(7)	4*e*	0.2091(3)	0.8101(7)	0.8911(1)	0.033(2)	0.045(2)	0.038(2)	−0.004(2)	0.022(1)	−0.001(2)
C(8)	4*e*	0.1971(3)	0.6465(7)	0.8412(1)	0.027(2)	0.041(2)	0.041(2)	−0.008(1)	0.014(1)	0.001(2)

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