Communications to the Editor

[Chem. Pharm. Bull. 30(7)2629—2632(1982)]

THE CRYSTAL STRUCTURE OF FTORAFUR

Yoshinobu Nakai,*[,a] Keiji Yamamoto,[a] Katsuhide Terada,[a] Takeshi Uchida,[a] Nobuyuki Shimizu,[b] and Sadao Nishigaki[b]

Faculty of Pharmaceutical Sciences, Chiba University,[a] Yayoicho, Chiba 260, and Pharmaceutical Institute, School of Medicine, Keio University,[b] Shinjuku-ku, Tokyo 160, Japan

The crystal structure of ftorafur, $C_8H_9FN_2O_3$, has been determined by single-crystal X-ray diffraction techniques. The crystal is triclinic, space group $P\bar{1}$; its unit-cell dimensions are a=8.994(8), b=16.612(9), c=5.981(5) Å, α=86.40(6), β=94.06(15), γ=80.29(8)°, Z=4. The structure was solved by the direct method and the final R value was 0.056.

KEYWORDS——————crystal structure; ftorafur; X-ray diffraction; antitumor agent; polymorphism

Ftorafur, 5-fluoro-1-(tetrahydro-2-furyl)-uracil, is a potent antitumor agent widely used in the treatment of various cancers. Nakajima and co-workers reported the existence of two crystalline forms which melted at 165-166°C and 172-173°C respectively.[1] We are determining the crystal structures of both polymorphic forms and one of them is presented in this report.

We have undertaken an X-ray crystallographic study of ftorafur. Single crystals of ftorafur (racemic) were grown by the slow evaporation of an acetone solution. Weissenberg photographs showed no systematic absences. A crystal with dimensions of about 0.60x0.37x0.25 mm was used for data collection on a Rigaku four-circle diffractometer with graphite-monochromated Cu Kα radiation. The crystal data are summarized in Table I. The 2θ-ω scan technique was used for the intensity measurement at a rate of 4°/min. Three reference reflections showed no significant intensity deterioration throughout data collection. The intensities obtained were corrected for Lorentz and polarization factors but not for absorption effect. Of 3364 unique reflections in the range $3<2\theta<145°$, 3125 reflections with $F_o \geq 3.0\sigma(F_o)$, were used for structure determination. The structure was solved by the direct method with the MULTAN 78 program,[2] and refined by the full-matrix least-squares method.[3]

Table I. Crystal Data of Ftorafur

Triclinic	$C_8H_9FN_2O_3$
Space group $P\bar{1}$	M_w=200.16
a=8.994(8) Å	F(000)=416
b=16.612(9)	Z=4
c=5.981(5)	μ(Cu Kα)=1.152 mm^{-1}
α=86.40(6)°	λ(Cu Kα)=1.5418 Å
β=94.06(15)	D_c=1.51 g cm^{-3}
γ=80.29(8)	D_m=1.51
V=876.0(12) $Å^3$	(pycnometer)

Figure 1 shows the ORTEP plot[4] of ftorafur molecules with the atom

Table II. Positional Parameters ($\times 10^4$ for non-hydrogen atoms, $\times 10^3$ for H atoms) and Equivalent Isotropic (non-hydrogen atoms) and Isotropic (H atoms) Thermal Parameters ($\AA^2$) with e.s.d.'s in Parentheses

(A)	x	y	z	$*B_{eq}$ or B_{iso}	(B)	x	y	z	$*B_{eq}$ or B_{iso}
N(1)	633(3)	1428(1)	8699(4)	3.50	N(1)	6348(2)	6393(1)	6622(4)	3.07
C(1)	412(4)	884(2)	7149(5)	3.87	C(1)	5821(3)	5838(2)	8034(5)	3.40
O(1)	-499(3)	1045(1)	5504(4)	5.59	O(1)	5096(3)	6053(1)	9616(4)	4.87
N(2)	1306(3)	120(1)	7541(4)	4.30	N(2)	6182(3)	5036(1)	7562(4)	3.55
C(2)	2384(4)	-143(2)	9301(6)	4.62	C(2)	6990(3)	4725(2)	5841(5)	3.56
O(2)	3142(3)	-830(1)	9441(5)	6.91	O(2)	7204(3)	4000(1)	5547(4)	5.07
C(3)	2481(4)	468(2)	10867(5)	4.39	C(3)	7509(4)	5361(2)	4494(5)	4.06
F	3469(3)	255(1)	12681(4)	7.31	F	8330(3)	5113(1)	2789(4)	6.93
C(4)	1643(4)	1211(2)	10558(5)	3.97	C(4)	7195(3)	6143(2)	4887(5)	3.60
C(5)	-248(3)	2274(2)	8373(5)	3.83	C(5)	5895(4)	7281(2)	7031(5)	3.74
C(6)	-1326(4)	2487(2)	10205(7)	4.99	C(6)	4301(4)	7614(2)	6107(7)	4.99
C(7)	-635(4)	3073(2)	11574(7)	5.70	C(7)	4490(4)	7872(2)	3685(7)	5.75
C(8)	254(3)	3454(2)	9903(6)	4.53	C(8)	5969(4)	8194(2)	3940(6)	4.54
O(3)	811(2)	2813(1)	8536(4)	4.27	O(3)	6834(2)	7728(1)	5853(4)	3.78
H(N2)	110(3)	-25(2)	639(6)	3.12	H(N2)	601(4)	470(2)	849(6)	3.96
H(C4)	175(3)	162(2)	1161(5)	1.29	H(C4)	741(4)	656(2)	391(6)	3.54
H(C5)	-81(3)	231(2)	680(5)	1.82	H(C5)	619(3)	732(2)	867(5)	2.14
H(C61)	-228(5)	280(3)	931(8)	7.19	H(C61)	370(4)	724(2)	604(6)	4.05
H(C62)	-146(4)	206(2)	1097(6)	4.16	H(C62)	397(4)	815(2)	705(7)	5.22
H(C71)	-147(6)	350(3)	1193(9)	5.65	H(C71)	461(4)	732(2)	268(6)	4.66
H(C72)	17(5)	271(3)	1288(8)	7.23	H(C72)	402(4)	847(2)	430(7)	6.36
H(C81)	112(4)	365(2)	1064(6)	3.70	H(C81)	647(4)	810(2)	265(7)	5.47
H(C82)	-48(4)	393(2)	883(6)	3.29	H(C82)	578(4)	879(2)	453(6)	3.79

$*B_{eq}$ defined according to Hamilton(1959). 5)

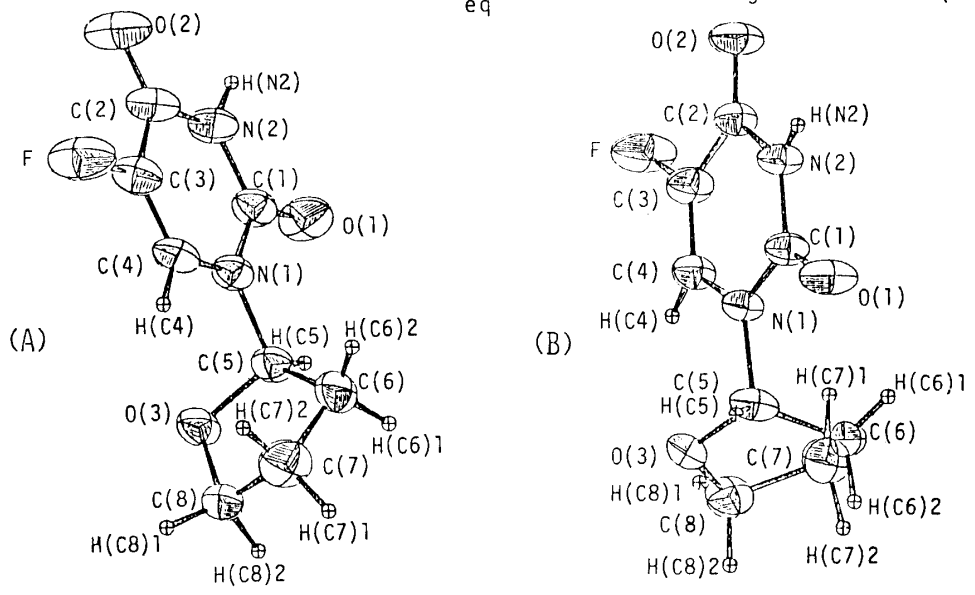

Fig. 1. An ORTEP Drawing of the Molecule A and Molecule B

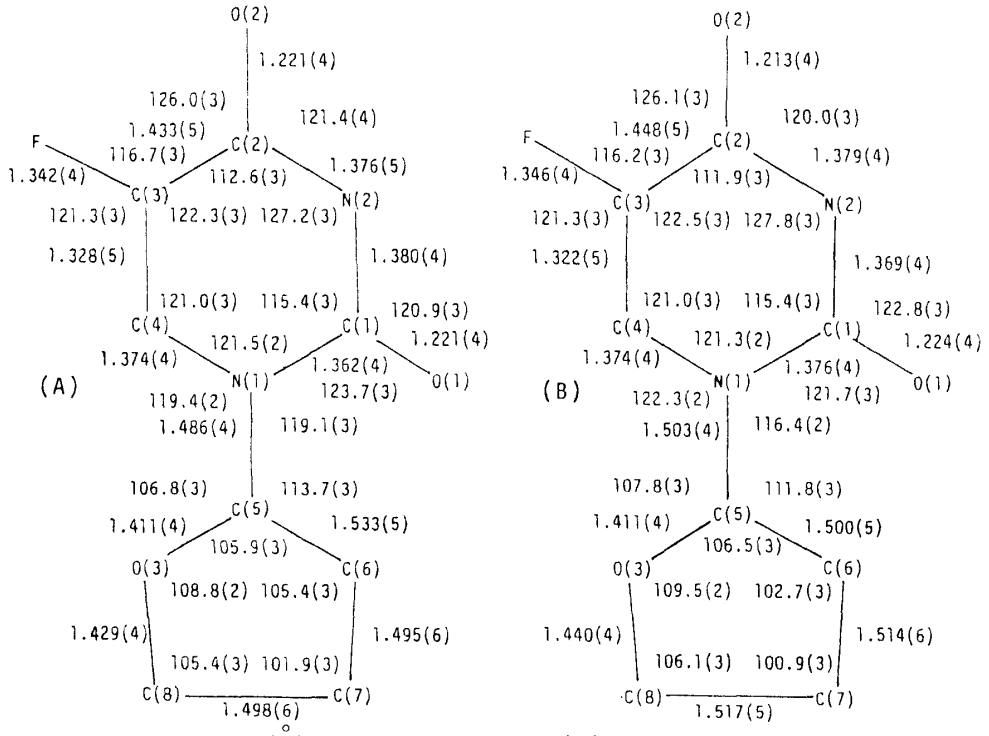

Fig. 2. Bond Lengths (Å) and Bond Angles (°) for Molecule A and Molecule B

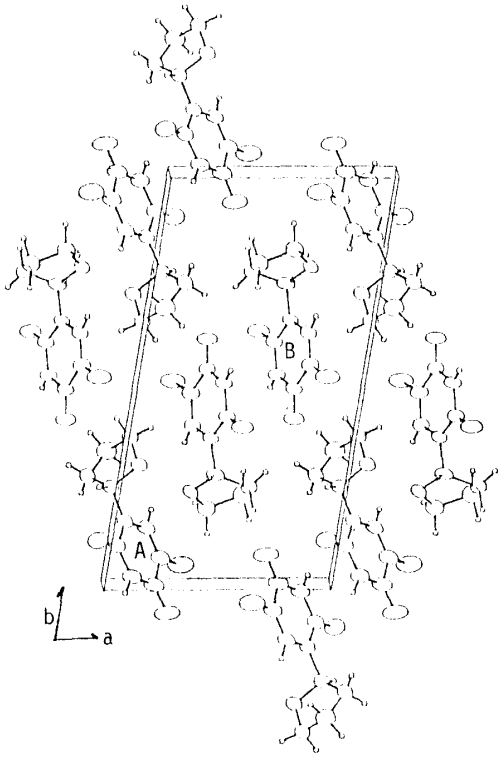

Fig. 3. The Molecular Packing in the Crystal Structure of Ftorafur

numbering. The structure consists of two types of ftorafur, molecule A and molecule B. Positional parameters and thermal parameters are listed in Table II. All the H atoms of the molecules were determined from a difference synthesis.

The non-hydrogen atoms and H atoms were refined with anisotropic and isotropic temperature factors, respectively. The bond lengths and bond angles involving the non-hydrogen atoms of both molecules are given in Fig. 2. The C–H and N–H bond lengths range from 0.80(4) to 1.12(4) Å. With regard to bond lengths and bond angles, there is little difference in these values between molecule A and molecule B. However, the torsion angles C(4)–N(1)–C(5)–O(3), 52.6(6)° (in molecule A) and -17.3(7)° (in molecule B), are significantly different from each other. The packing of the molecules is shown in Fig. 3. There are intermolecular hydrogen bonds between N(2) and O(1) with N(2)---O(1) distances of 2.884(4) and 2.835(4) Å, as shown in Table III.

Table III. Hydrogen Bond Parameters

	Distances (Å)		Angle (°)
	N(2)---O(1)	H(N2)---O(1)	N(2)–H(N2)---O(1)
N(2)–H(N2)---O(1)[a)]	2.884(4)	1.91(4)	170(3)
N(2)–H(N2)---O(1)[b)]	2.835(4)	2.06(4)	162(3)

a) Hydrogen bond between molecule A and its enantiomer.
b) Hydrogen bond between molecule B and its enantiomer.

REFERENCES

1) S. Nakajima, S. Sato, and K. Machijima, The 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August (1979).
2) P. Main, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M.M. Woolfson, "MULTAN 78 A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data," Univs. of York,England, and Louvain, Belgium (1978).
3) "UNICS The Universal Crystallographic Computation Program System," edited by T. Sakurai, The Crystallographic Society of Japan (1967).
4) C.K. Johnson, "ORTEP Report ORNL-3794," Oak Ridge National Laboratory, Tennessee (1965).
5) W.C.Hamilton, Acta Cryst., 12, 609 (1959).

(Received April 20,1982)