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Studies on Fluorinated Pyrimidines. IV.[1] Stereochemistry of 6-Alkoxy-5-fluoro-5,6-dihydrouracils and 5-Alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils

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Both *cis* (**6**)and *trans* (**7**) isomers of 6-alkoxy-5-fluoro-5,6-dihydrouracils were prepared by catalytic hydrogenolysis of *t*-6-alkoxy-*r*-5-halogeno-5-fluoro-5,6-dihydrouracils (**4** and **5**). The structures were estimated by comparing coupling constants (J_{H6F}) in the proton magnetic resonance (PMR) spectra and confirmed by a single-crystal X-ray analysis of *cis*-6-ethoxy-5-fluoro-5,6-dihydrouracil (**6a**). The stereochemistry of 6-alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (**11**—**13**) was clarified similarly on the basis of the PMR data. The chemical behavior of these compounds in acidic and basic media was examined.

Keywords——*t*-6-alkoxy-*r*-5-chloro-5-fluoro-5,6-dihydrouracils; *cis*- and *trans*-6-alkoxy-5-fluoro-5,6-dihydrouracils; stereoisomers of 6-alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils; catalytic hydrogenolysis; TAC-278; 5-fluorouracil; single-crystal X-ray analysis

Introduction

In the course of our studies on fluorinated pyrimidines,[1] we found that some 5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils possess good antitumor activity against P388 leukemia in mice. These fluorinated dihydropyrimidine esters were considered to be a new class of masked 5-fluorouracil (**1**) compounds based on their chemical property of ready hydrolysis under acidic or basic conditions to afford **1** in excellent yields.

However, the stereochemistry of these compounds had remained to be determined, although the 6-substituent and the 5-alkoxycarbonyl group were assumed to be located *trans* to each other judging from the J_{HF} values in their proton magnetic resonance (PMR) spectra.

On the other hand, the synthesis and stereochemistry of several 5-fluoro-6-substituted-5,6-dihydrouracils have been reported by several groups of researchers.[2-5] In every case, only one of the possible stereoisomers was isolated and the stereochemistry of these dihydrouracils had remained uncertain until Robins *et al.*[3] and James *et al.*[4] carried out X-ray analysis of (±)-5-fluoro-6-methoxy-1-methyl-5,6-dihydrouracil (prepared from 1-methyluracil by direct fluorination with CF_3OF in methanol); which established its *cis* stereochemistry (J_{HF}=2.5 Hz)[3] (Fig. 1).

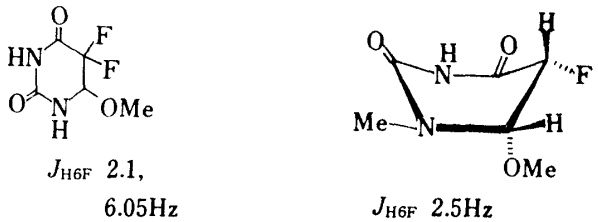

Fig. 1

In the present paper, we wish to report the isolation of previously unknown *cis* (**13**) isomers of some 6-alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (**11**) and the synthesis of both *cis* (**6**) and *trans* (**7**) isomers of some 6-alkoxy-5-fluoro-5,6-dihydrouracils. The stereochemistry of these compounds, including **11** and **12**, is discussed on the basis of J_{HF} values. The conclusions were confirmed by an X-ray analysis of **6a**.

I. Synthesis and Isolation of *cis* (6) and *trans* (7) Isomers of 6-Alkoxy-5-fluoro-5,6-dihydrouracils

A suspension of **1** in water was treated with chlorine, giving the 5-chloro-6-hydroxy derivative (**2**) in 88% yield. Also, fluorination of 5-chlorouracil (**8**) in acetic acid[6] followed by hydrolysis of the resulting 6-acetoxy-5-chloro-5-fluoro derivative (**3**) gave the same **2**. The hydroxyl group at C-6 in **2** is readily replaceable by a nucleophile such as an alcohol in the presence of an acid catalyst, giving 6-alkoxy-5-chloro-5-fluoro derivatives (**5**) in high yields; these products were identical to those obtained by treatment of **1** with chlorine in an alcohol. The PMR spectra of **2** and **5** were composed of a set of sharp peaks, which suggested the presence of only one geometrical isomer in each case (Chart 1, Table I).

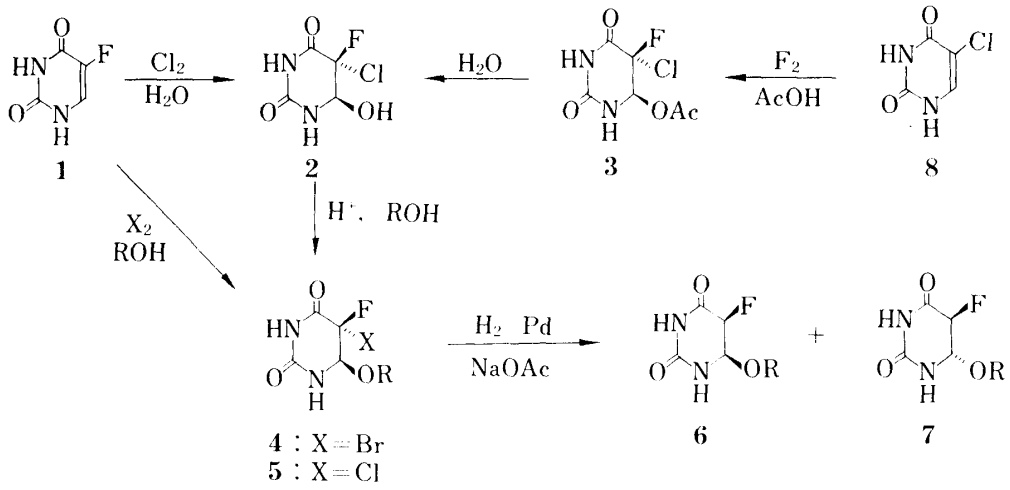

Chart 1

TABLE I. Yields and J_{HF} Values of 6-Alkoxy-5-mono- and 5,5-dihalogeno-5,6-dihydrouracils (**2**, **4**, **5**, **6**, and **7**)

i) *t*-6-Alkoxy-5-fluoro-*r*-5-halogeno Derivatives (**2**, **4**, and **5**)

No.	R	X	Yield	J_{HF}	No.	R	X	Yield	J_{HF}
2	H	Cl	88(%)	2 (Hz)	**5d**	C_6H_{13}	Cl	—[a]	1 (Hz)
4	Bu	Br	65	1	**5e**	Cyclohexyl	Cl	—[a]	1
5a	Et	Cl	91	1	**5f**	C_7H_{15}	Cl	—[a]	1
5b	iso-Pr	Cl	74	1	**5g**	C_8H_{17}	Cl	67(%)	1
5c	Bu	Cl	62	1	**5h**	$C_{12}H_{25}$	Cl	—[a]	1

ii) 6-Alkoxy-5-fluoro-5,6-dihydrouracils (**6** and **7**)

R	*cis* Derivatives (**6**)			*trans* Derivatives (**7**)		
	No.	Yield	J_{HF}	No.	Yield	J_{HF}
Et	**6a**	44(%)	1 (Hz)	**7a**	—[b]	
iso-Pr	**6b**	34	0	**7b**	—[b]	
Bu	**6c**	47[c]	2	**7c**	4[c](%)	6 (Hz)
C_6H_{13}	**6d**	68	2	**7d**	—[d]	7
Cyclohexyl	**6e**	55	0	**7e**	—[b]	
C_7H_{15}	**6f**	64	2	**7f**	2	7
C_8H_{17}	**6g**	74	2	**7g**	8	6.5
$C_{12}H_{25}$	**6h**	72	2	**7h**	7	7

a) Isolated as a crude solid and hydrogenated without purification.
b) Not detected.
c) Yield from **1**.
d) Isolated as a mixture with **6d**.

A *trans* relation between H-6 and F-5 in **2**, **5**, and the 5-bromo-6-butoxy-5-fluoro compound (**4**) was presumed based on the small coupling values (J_{H6F}=1—2 Hz) observed in their PMR spectra. Thus, both electrophilic halogenation of **1** at C-5 and removal of the 6-hydroxy group in **2** under acidic conditions give a cation, which then undergoes addition of a nucleophile at C-6 to produce the energetically favorable *cis* F-5 and RO-6[7] isomers **4** and **5**, selectively. The preferred *cis* orientation of the alkoxy and the fluoro groups may be further promoted by 1) a favored *trans* electronic orientation of chloro (or bromo) and alkoxy groups, and 2) a larger steric repulsion between the alkoxy and chloro (or bromo) groups (Chart 2). The same determinants would be operating during the stepwise synthesis of **5** *via* **3**.

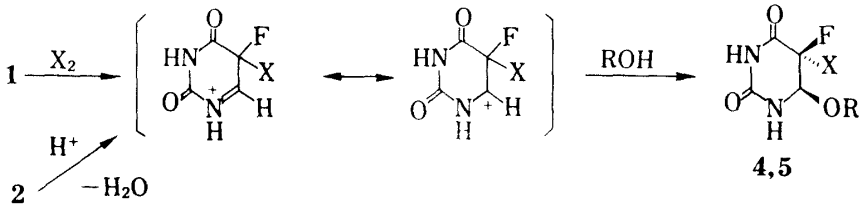

Chart 2

Removal of the chloro or bromo group in **4** or **5** by catalytic hydrogenolysis in the presence of sodium acetate,[2,3] gave a mixture of three products including **1**. Of the other two products, the major one showed a relatively small coupling value in the PMR spectrum between H-6 and F-5 (J_{H6F}=0—2 Hz) compared to that of the minor one (J_{H6F}=6—7 Hz), and was assigned as the *cis* isomer (**6**), the latter being assigned as the *trans* one (**7**). For example, *cis*-6-butoxy-5-fluoro-5,6-dihydrouracil (**6c**) shows signals at δ 4.74 (J_{H6F}=2 Hz, H-6) and at δ 5.38 (J_{H5F}=46 Hz, H-5), while the *trans*-6-butoxy-5-fluoro derivative (**7c**) shows signals at δ 4.73 (J_{H6F}=6 Hz, H-6) and at δ 4.77 (J_{H5F}=47 Hz, H-5).[5] Finally, *cis* configuration of the 6-ethoxy-5-fluoro derivative (**6a**) was confirmed by an X-ray analysis (Fig. 2). From these results, it is clear that the compounds which have J_{H6F} values of around 2 Hz are assignable as *cis* isomers or compounds having a *cis* relation between F-5 and RO-6 (**2**, **4**—**6**), and those which have values of around 6 Hz are assignable as *trans* isomers (**7**) irrespective of the presence or absence of the N-1 substituent.

In the reduction of the 6-ethoxy- (**5a**), the 6-isopropyloxy- (**5b**), and the 6-cyclohexyloxy-5-chloro-5-fluoro (**5e**) derivatives, only the *cis* isomers **6a**, **b**, and **e** were isolated, and the corresponding *trans* isomers did not exist in the mother liquor in any detectable amount (Table I).

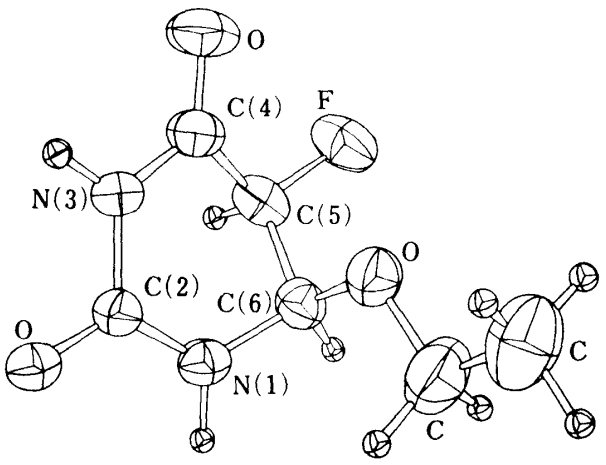

Fig. 2. Perspective View of *cis*-6-Ethoxy-5-fluoro-5,6-dihydrouracil (**6a**)

II. Synthesis and Isolation of *trans* (11 and 12) and *cis* (13) Isomers of 6-Alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils

The isolation of *trans* isomers (**7**) as the minor components prompted us to search for the stereoisomers of the 5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracils (**11** and **12**).[1] Direct fluorination of 5-alkoxycarbonyluracils (**9**) with fluorine in water or acetic acid yield 5-alkoxycarbonyl-5-fluoro-6-hydroxy- or -6-acetoxy-5,6-dihydrouracils (**10**). They were converted into **11**—**16** as reported in the previous paper (Chart 3).[1] The compounds **10**—**12**

have coupling values (J_{HF}) ranging between 2—4 Hz (Table II), which are consistent with a *trans* relation between H-6 and F-5 as discussed in the preceding section.

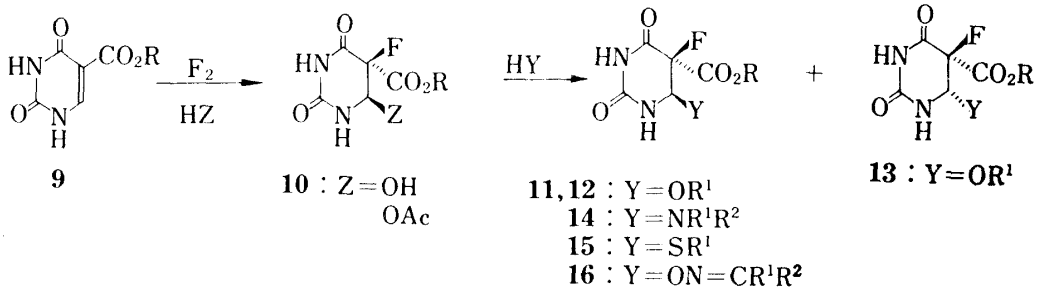

Chart 3

TABLE II. J_{HF} Values of (±)-*r*-5-Alkoxycarbonyl-*t*-6-hydroxy- and -*t*-6-acetoxy-5-fluoro-5,6-dihydrouracils (**10**)

No.	R	Z	J_{HF} (Hz)	No.	R	Z	J_{HF} (Hz)
10a	Me	OH	4	**10e**	iso-Pr	OH	3
10b	Me	OAc	2	**10f**	Bu	OH	3
10c	Et	OH	3	**10g**	*sec*-Bu	OH	—[a]
10d	Et	OAc	2	**10h**	C_8H_{17}	OAc	2

a) Not determined.

The reactions of **10c** with a series of straight-chain alcohols were investigated. When **10c** was heated with octyl alcohol in benzene in the presence of methanesulfonic acid, the reaction gave the desired *cis* isomer (**13g**) (PMR: δ 5.13, J_{HF}=11 Hz; H-6) in 5% yield together with the *trans* isomer (**11g**) (PMR: δ 5.12, J_{HF}=2 Hz, H-6) as the main product (48% from **10c**) (Table III).

Similarly, *cis* isomers (**13**) were obtained as minor components in the reactions of **10c** with several long-chain alcohols (Table III). The ratio of *trans* (**11**) to *cis* (**13**) isomers formed was in the range of 5—10. There was no definite relationship between the ratio and the length of the carbon chain. In the reaction of **10c** with other alcohols consisting of less than four carbons, no detectable amount of the *cis* isomer (**13**) was obtained (Table IV).

After several unfruitful attempts to isolate the *c*-6-butoxy-*r*-5-ethoxycarbonyl derivative (**13c**) from laboratory-scale preparations of the *t*-6-butoxy-*r*-5-ethoxycarbonyl derivative (**11c**), we isolated **13c** (PMR: δ 4.98, J_{HF}=12 Hz, H-6) in 0.8% yield from the mother liquor of the first recrystallization of **11c** in a kilogram-scale preparation[8] of **11c**.

TABLE III. Yields and J_{HF} Values of (±)-*t*- and (±)-*c*-6-Alkoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracils (**11** and **13**)

R	R^1	*trans* Isomers (**11**)			*cis* Isomers (**13**)			Ratio of yield 11/13
		No.	J_{HF}	Yield	No.	J_{HF}	Yield	
Et	Bu	**11c**	2 (Hz)	79(%)	**13c**	12 (Hz)	0.8(%)	98.8
Et	C_5H_{11}	**11d**	2[a]	56	**13d**	11[a]	7	8.0
Et	C_6H_{13}	**11e**	2	62	**13e**	11[a]	10	6.2
Et	C_7H_{15}	**11f**	2[a]	54	**13f**	11[a]	9	6.0
Et	C_8H_{17}	**11g**	2[a]	48	**13g**	11[a]	5	9.6
Et	$C_{12}H_{25}$	**11h**	2[a]	54	**13h**	11[a]	10	5.4

a) $CDCl_3$ was used as the solvent.

Table IV. J_{HF} Values of (±)-*t*-6-Alkoxy-*r*-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (**11** and **12**)

No.	R	R^1	J_{HF} (Hz)	No.	R	R^1	J_{HF} (Hz)
11a	Et	Me	2	**12a**	Me	Me	2
11b	Et	Et	2	**12b**	Me	Et	2
11i	Et	$CH_2CH=CH_2$	2	**12c**	Me	Bu	2
11j	Et	$CH_2C\equiv CH$	2	**12d**	Me	Cyclohexyl	2
11k	Et	iso-Pr	2	**12e**	Me	CH_2Ph	2
11l	Et	iso-Bu	2	**12f**	Me	C_8H_{17}	2
11m	Et	Ph	2	**12g**	iso-Pr	iso-Pr	2
11n	Et	CH_2Ph	2	**12h**	Bu	Bu	2
11o	Et	CH_2CF_3	2	**12i**	C_8H_{17}	Et	2

III. Stereochemical Aspects of 6-(Substituted)amino (14), 6-(Substituted)mercapto (15), and 6-Alkylideneaminooxy (16) Derivatives.

Several 5-alkoxycarbonyl-6-(substituted)amino (**14**) and -6-(substituted)mercapto-5-fluoro-5,6-dihydrouracils (**15**) have been prepared from **10**.[1] The J_{HF} values of **14** and **15** varied in the ranges of 4—16 and 3—12 Hz, respectively (Tables V and VI). The compounds which shows a J_{HF} value larger than 6 Hz may have *cis* configuration of the substituent at C-6 with reference to the alkoxycarbonyl group at C-5. However, *trans* configurations of **14** and **15** were supposed on the basis of the fact that they are effectively converted into **1** on alkaline hydrolysis, as described later (Table VIII).

Table V. J_{HF} Values of (±)-6-(Substituted)amino Derivatives (**14**)

No.	R	Y	J_{HF} (Hz)	No.	R	Y	J_{HF} (Hz)
14a	Et	NH_2	12	**14g**	Me	Piperidino	4
14b	Et	NH-allyl	8	**14h**	Et	Piperidino	4
14c	Et	NHBu	9	**14i**	Et	NHAc	6
14d	Et	NHPh	10	**14j**	Et	$NHCOC_5H_{11}$	7
14e	Et	$NHCH_2Ph$	10	**14k**	Et	$NHCOC_7H_{15}$	7
14f	Et	NEt_2	16	**14l**	Et	NHCOPh	4

Table VI. J_{HF} Values of (±)-6-(Substituted)mercapto Derivatives (**15**)

No.	R	$Y=SR^1$	J_{HF} (Hz)	No.	R	$Y=SR^1$	J_{HF} (Hz)
15a	Me	Bu	7.5	**15e**	Et	*tert*-Bu	12
15b	Me	Ph	3	**15f**	Et	Cyclohexyl	8
15c	Et	Et	6	**15g**	Et	Ph	3
15d	Et	Allyl	—[a]	**15h**	Et	CH_2Ph	7

a) Not determined.

The magnitude of the coupling value is influenced[9] by 1) the dihedral angle between the two resonating nuclei and 2) the electronegativity of the substituent. In the present case, the nature of the substituents at C-5 and C-6 seems to play an important role in determining the J_{HF} value. In the case of 6-alkylideneaminooxy derivatives (**16**), the J_{HF} values are smaller than 2 Hz (Table VII). Based on these observations, **16** was assumed to have the *trans* configuration.

TABLE VII. J_{HF} Values of (±)-6-Alkylideneaminooxy Derivatives (16)

No.	R	R^1	R^2	J_{HF} (Hz)	No.	R	R^1	R^2	J_{HF} (Hz)
16a	Me	$-(CH_2)_5-$		1	**16g**	Et	Me	2-Furyl	1
16b	Et	Me	H	—[a]	**16h**	Et	Me	2-Thienyl	0
16c	Et	Me	Me	1	**16i**	Et	H	C_5H_{11}	1
16d	Et	$-(CH_2)_3-$		1	**16j**	Et	Me	4-Pyridyl	0.5
16e	Et	$-(CH_2)_4-$		1	**16k**	Et	H	Ph	1
16f	Et	$-(CH_2)_5-$		1	**16l**	Et	Me	$PhCH_2$	0.5

a) Not determined.

IV. Chemical Behavior of 11c (TAC-278), 13c, 6c, and 7c

Being very interested in examining whether differences in chemical properties exist between the pairs of stereoisomers **11c**—**13c** and **6c**, **7c**, especially in relation to their possible nature as pro-drugs of **1**, we studied the hydrolysis of these compounds under acidic or basic conditions. Table VIII shows the results of these experiments. Under acidic conditions, **11c** and **13c**, having an ethoxycarbonyl group at C-5, were converted into **1** more readily than **6c** and **7c**, which lack the ethoxycarbonyl group.

TABLE VIII. Yield[a] of 5-Fluorouracil (1) from the Hydrolysis of Stereoisomers

No.	Under acidic conditions[b]	Under basic conditions[c]
11c	95 (%)	80 (%)
13c	62	—[d]
6c	48	102
7c	42	—[e]
14c	—[f]	76
15e	—[f]	90

a) Determined by the UV method.
b) Each compound was heated under reflux for 1 h in 1 N HCl.
c) Each compound was treated with EtOH/1 N NaOH=1/1(v/v) at room temperature for 1 h.
d) No **1** was found. The product has absorption maxima as follows: λ_{max} nm: 263 (pH 1.0), 254 (pH 7.0 and 13.0).
e) A mixture of **1** and unknown products was obtained.
f) Not determined.

With the compound **11c** and **13c**, decarboxylation, which comes after the hydrolysis of the ethoxycarbonyl group, is expected to promote the extrusion of the butoxy group from C-6 to give **1**. The data in Table VIII show that *trans* orientation of the ethoxycarbonyl group at C-5 to the butoxy group at C-6 as in **11c** is more favorable for this elimination than the *cis* orientation of these substituents as in **13c**, and that in the absence of this pushing effect of the carboxyl group, the substrates (**6c** and **7c**) were converted into **1** less effectively. More severe conditions were needed to attain a better conversion. The difference in the yields of **1** between **11c** and **13c** is much larger than that between **6c** and **7c**. This may show that a concerted decarboxylation-dealkoxylation is at work in the case of **11c**.

In contrast, under alkaline conditions, **6c** gave the highest (almost quantitative) yield of **1** among these four compounds, and **11c** the next highest yield. Very surprisingly, **13c** gave little **1** and gave mainly unidentified product(s) under these conditions. A mixture of **1** and some unidentified products were obtained from **7c**. The unknown product(s) obtained from **13c** differed from those derived from **7c** in their ultraviolet (UV) spectra. In contrast to the fact that alkaline hydrolysis of *cis* isomer **13c** gave no **1**, that of **14c** or **15e** gave **1** in high yield.

Compounds **14c** and **15e** are supposed to have *trans* stereochemistry on the basis of these results even though they have relatively large J_{HF} values (**14c**: 9 Hz, **15e**: 12 Hz).

Based on these results, we concluded that **11c** is superior to **13c**, **6c**, or **7c** as a pro-drug of **1**.

Experimental

Melting points are uncorrected. PMR spectra were recorded on Varian T-60 and XL-100A spectrometers. Tetramethylsilane was used as an internal standard for all spectra, and deuterated dimethylsulfoxide was used as the solvent unless otherwise specified. Chemical shifts are expressed in δ (ppm) values. In some cases, only the data for H-5 and/or H-6 are cited. UV spectra were recorded on a Hitachi EPS-3T spectrometer. Thin-layer chromatography (TLC) was performed using pre-coated Kieselgel 60 F 254 sheets. Column chromatography was carried out using Kieselgel 60. All evaporations were carried out *in vacuo*. The solvents used for recrystallization are abbreviated as follows; A=acetone, C=chloroform, E=ethanol, EA=ethyl acetate, H=hexane, and W=water.

(±)-*r*-5-Chloro-5-fluoro-*t*-6-hydroxy-5,6-dihydrouracil (2)——a) Cl_2 was bubbled into a suspension of **1** (130.7 g, 1.0 mol) in 1.0 l of H_2O at room temperature until a clear solution was obtained. The solvent was evaporated off until colorless needles began to separate. They were collected by filtration after the mixture had been cooled in an ice bath, then dried over P_2O_5 *in vacuo* giving 161.4 g (88%) of **2**.

b) F_2 ($F_2/N_2=20\%$) was bubbled into a suspension of **8** (2.35 g, 16 mmol) in 250 ml of AcOH until a clear solution was obtained. The reaction mixture was concentrated to give a colorless syrup, which was treated with 30 ml of H_2O for 1 h at room temperature. The solution was evaporated to dryness. The resulting colorless syrup was dissolved in 30 ml of acetone and the solution was passed through an alumina column (Woelm neutral, acetone as the solvent). The effluent was evaporated to dryness giving a pale yellow oil, which was treated with $CHCl_3$, giving 1.67 g (57%) of a white powder. The product was identified as **2** by comparison of the PMR spectra.

(±)-*r*-5-Chloro-*t*-6-ethoxy-5-fluoro-5,6-dihydrouracil (5a)——a) A solution of **2** (9.2 g, 50 mmol) and 1.0 g of $MeSO_3H$ in 160 ml of EtOH was heated under reflux for 20 h with continuous removal of H_2O as an azeotropic mixture with EtOH using a Soxlet apparatus filled with pellets of molecular sieves (3A, 10.0 g). The reaction mixture was neutralized by the addition of NaOAc (1.5 g), then applied to a column of silica gel ($CHCl_3$–MeOH), giving 6.8 g (91%) of **5a** and 2.7 g of **2**.

b) Cl_2 was bubbled into a suspension of **1** (13.0 g 0.1 mol) in 200 ml of EtOH at room temperature until a clear solution was obtained. The resulting solution was evaporated to dryness, giving a white solid. It was recrystallized from EtOH–hexane affording 15.6 g (74%) of **5a** as colorless needles.

(±)-*t*-6-Butoxy-*r*-5-chloro-5-fluoro-5,6-dihydrouracil (5c)——A mixture of **2** (84.3 g, 0.46 mol), 60 ml of BuOH, 4.5 ml of $MeSO_3H$, and 850 ml of toluene was heated under reflux for 2 h with continuous removal of H_2O as an azeotropic mixture with toluene. The resulting solution was diluted with 500 ml of EtOAc, washed with aq. $NaHCO_3$ solution and H_2O, then dried (Na_2SO_4). The solvent was removed to leave a white solid, which was recrystallized from EtOH–hexane, giving 47.6 g of **5c** as colorless needles. The mother liquor was concentrated, and the resulting solid was recrystallized similarly to obtain another crop of **5c** (26.0 g). The total yield of **5c** was 73.6 g (62%).

(±)-*t*-6-Alkoxy-*r*-5-chloro derivatives prepared in a similar manner are listed below. (**2**): mp 190—191°C (A—C). *Anal.* Calcd for $C_4H_4ClFN_2O_3$: C, 26.32; H, 2.21; N, 15.35. Found: C, 26.03; H, 2.06; N, 15.45. PMR: 5.03 (1H, ddd, $J_{HF}=2$ Hz, $J=5$ and 5 Hz). (**5a**): mp 200—202°C (E—H). *Anal.* Calcd for $C_6H_8ClFN_2O_3$: C, 34.22; H, 3.83; N, 13.30. Found: C, 34.18; H, 3.84; N, 13.20. PMR: 5.07 (1H, dd, $J_{HF}=1$ Hz, $J=5$ Hz). (**5c**): mp 148—149°C (E—H). *Anal.* Calcd for $C_8H_{12}ClFN_2O_3$: C, 40.26; H, 5.07; N, 11.74. Found: C, 40.25; H, 5.11; N, 11.85. PMR: 4.98 (1H, dd, $J_{HF}=1$ Hz, $J=5$ Hz). (**5g**): mp 113—114°C (E–H). *Anal.* Calcd for $C_{12}H_{20}ClFN_2O_3$: C, 48.89; H, 6.84; N, 9.51. Found: C, 49.09; H, 7.06; N, 9.51. PMR: 5.00 (1H, dd, $J_{HF}=1$ Hz, $J=5$ Hz).

(±)-*r*-5-Bromo-*t*-6-butoxy-5-fluoro-5,6-dihydrouracil (4)——A solution of Br_2 (1.7 ml, 33 mmol) in 30 ml of BuOH was added to a suspension of **1** (3.90 g, 30 mmol) in 100 ml of BuOH. The mixture was stirred at room temperature for 5.5 h, and then Br_2 (1.0 ml, 19 mmol) was added to it. The reaction mixture was allowed to stand at room temperature overnight. The orange solution thus obtained was concentrated to about one-half of its original volume, then diluted with 100 ml each of $CHCl_3$ and hexane. Colorless needles that separated were collected by filtration and washed with $CHCl_3$/hexane=1/1 (v/v), then dried, giving 5.53 g (65%) of **4**. PMR: 5.00 (1H, dd, $J_{HF}=1$ Hz, $J=5$ Hz).

(±)-*cis*- (6c) and (±)-*trans*-6-Butoxy-5-fluoro-5,6-dihydrouracil (7c)——a) A solution of **5c** (66.7 g, 0.28 mol) and NaOAc (39.0 g, 0.48 mol) in 700 ml of MeOH and 200 ml of H_2O was hydrogenated over 10.0 g of 5% palladium on carbon at atmospheric pressure until the uptake of H_2 ceased. The catalyst was removed by filtration, and filtrate was concentrated, giving crystals. They were collected by filtration, and the filtrate was extracted with 500 ml of EtOAc. The extract was washed with aq. $NaHCO_3$ solution and H_2O, and then

dried ($MgSO_4$). Removal of the solvent gave a white solid. Another run of hydrogenolysis of **5c** (163.3 g) was carried out similarly and after similar work-up, it gave another crop of the crystals and a white solid that were combined and recrystallized from acetone–EtOAc–$CHCl_3$, giving 96.0 g of pure **6c**. The mother liquor was chromatographed on silica gel ($CHCl_3$ and 2% MeOH in $CHCl_3$) to recover 13.9 g of **7c** and 25.6 g of **6c**. Recrystallization of the combined **6c** from EtOH–H_2O gave 94.9 g (47% from **1**) of pure **6c** as colorless needles. Recrystallization of **7c** from EtOH–hexane gave 7.4 g (4% from **1**) of pure **7c** as colorless needles. Each isomer showed a single spot on a TLC plate at *Rf* values of 0.44 for **7c** and 0.24 for **6c** ($CHCl_3$/EtOAc/MeOH=10/2/1).

b) A solution of **4** (5.53 g, 19.5 mmol) and NaOAc (2.50 g, 30.5 mmol) in 200 ml of EtOH was hydrogenated over 10% palladium on carbon (750 mg) at atmospheric pressure until the uptake of H_2 stopped. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. H_2O (50 ml) was added to the residue to crystallize crude **6c**, which was collected by filtration and recrystallized from H_2O, giving 1.30 g (33%) of **6c** as colorless flakes. The PMR spectrum was superimposable on that of **6c** prepared by method a).

The other (±)-*cis*- and (±)-*trans*-6-alkoxy-5-fluoro-5,6-dihydrouracils (**6** and **7**) prepared in a similar manner are listed below.

cis Derivatives (**6**). (**6a**): mp 207—209°C (W). *Anal.* Calcd for $C_6H_9FN_2O_3$: C, 40.91; H, 5.15; N, 15.91. Found: C, 40.89; H, 5.29; N, 15.74. PMR: 4.87 (1H, m, $J_{H6F}=1$ Hz, $J=4$ Hz), 5.45 (1H, dd, $J_{H5F}=46$ Hz, $J=4$ Hz). (**6b**): mp 196—198°C (W). *Anal.* Calcd for $C_7H_{11}FN_2O_3$: C, 44.21; H, 5.83; N, 14.73. Found: C, 44.04; H, 5.79; N, 14.71. PMR: 4.97 (1H, dd, $J_{H6F}=0$, $J=4$ Hz), 5.37 (1H, dd, $J_{H5F}=48$ Hz, $J=4$ Hz). (**6c**): mp 185°C (E–W). *Anal.* Calcd for $C_8H_{13}FN_2O_3$: C, 47.05; H, 6.42; N, 13.72. Found: C, 47.26; H, 6.38; N, 13.78. PMR: 4.74 (1H, m, $J_{H6F}=2$ Hz, $J=4$ Hz), 5.38 (1H, dd, $J=4$ Hz, $J_{H5F}=46$ Hz). (**6d**): mp 166—168°C (E–H). *Anal.* Calcd for $C_{10}H_{17}FN_2O_3$: C, 51.71; H, 7.38; N, 12.06. Found: C, 51.78; H, 7.50; N, 11.97. PMR: 4.85 (1H, m, $J_{H6F}=2$ Hz, $J=4$ Hz), 5.43 (1H, dd, $J_{H5F}=46$ Hz, $J=4$ Hz). (**6e**): mp 213—215°C (A–E–H). *Anal.* Calcd for $C_{10}H_{15}FN_2O_3$: C, 52.16; H, 6.57; N, 12.17. Found: C, 52.02; H, 6.53; N, 12.17. PMR: 5.00 (1H, m, $J_{H6F}=0$, $J=4$ Hz), 5.40 (1H, dd, $J_{H5F}=47$ Hz, $J=4$ Hz). (**6f**): mp 171—173°C (E–H). *Anal.* Calcd for $C_{11}H_{19}FN_2O_3$: C, 53.64; H, 7.78; N, 11.38. Found: C, 53.58; H, 7.85; N, 11.11. PMR: 4.87 (1H, m, $J_{H6F}=2$ Hz, $J=4$ Hz), 5.47 (1H, dd, $J_{H5F}=47$ Hz, $J=4$ Hz). (**6g**): mp 172—174°C (E–H). *Anal.* Calcd for $C_{12}H_{21}FN_2O_3$: C, 55.36; H, 8.13; N, 10.76. Found: C, 55.11; H, 8.21; N, 10.74. PMR: 4.79 (1H, m, $J_{H6F}=2$ Hz, $J=4$ Hz), 5.39 (1H, dd, $J_{H5F}=46$ Hz, $J=4$ Hz). (**6h**): mp 158—160°C (E). *Anal.* Calcd for $C_{16}H_{29}FN_2O_3$: C, 60.73; H, 9.24; N, 8.86. Found: C, 60.90; H, 9.35; N, 8.76. PMR: 4.83 (1H, m, $J_{H6F}=2$ Hz, $J=4$ Hz), 5.24 (1H, dd, $J_{H5F}=46$ Hz, $J=4$ Hz).

trans Derivatives (**7**). (**7c**): mp 143—145°C (E–H). *Anal.* Calcd for $C_8H_{13}FN_2O_3$: C, 47.05; H, 6.42; N, 13.72. Found: C, 47.24; H, 6.56; N, 13.70. PMR: 4.73 (1H, m, $J_{H6F}=6$ Hz, $J=3$ Hz), 4.77 (1H, dd, $J=3$ Hz, $J_{H5F}=47$ Hz). (**7d**): 4.77 (1H, dd, $J_{H5F}=47$ Hz, $J=3$ Hz), 4.83 (1H, m, $J=3$ Hz, $J_{H6F}=7$ Hz). (**7f**): PMR: 4.80 (1H, m, $J_{H6F}=7$ Hz, $J=3$ Hz), 4.80 (1H, dd, $J=3$ Hz, $J_{H5F}=48$ Hz). (**7g**): mp 135—137°C (E). *Anal.* Calcd for $C_{12}H_{21}FN_2O_3$: C, 55.36; H, 8.13; N, 10.76. Found: C, 55.35; H, 8.35; N, 10.72. PMR: 4.76 (1H, m, $J_{H6F}=6.5$ Hz, $J=3$ Hz), 4.77 (1H, dd, $J_{H5F}=46$ Hz, $J=3$ Hz). (**7h**): PMR: 4.82 (1H, dd, $J_{H5F}=48$ Hz, $J=3$ Hz), 4.82 (1H, m, $J=3$ Hz, $J_{H6F}=7$ Hz).

(±)-*r*-5-Ethoxycarbonyl-5-fluoro-*t*-6-octyloxy-5,6-dihydrouracil (11g) and Its Stereoisomer (13g)——A mixture of **10c** (72.8 g, 0.36 mol), octyl alcohol (52.0 g, 0.4 mol), and $MeSO_3H$ (7.0 g, 0.07 mol) in toluene (500 ml) was heated under reflux for 1 h with continuous removal of H_2O as an azeotropic mixture with toluene. The resulting solution was directly chromatographed on silica gel ($CHCl_3$ and 1% MeOH in $CHCl_3$). After removal of the solvent from the fractions rich in **11g**, 96.8 g of a crude mixture of **11g**, **13g**, and octyl alcohol was obtained. From other fraotions, 10.2 g of **1** and 4.3 g (5%) of **11b** were obtained. The crude mixture obtained as above was recrystallized from acetone–hexane first, then from EtOH–hexane, giving 40.2 g (37%) of **11g** as colorless needles. The combined mother liquor from these recrystallizations was chromatographed again on silica gel ($CHCl_3$/benzene=4/1 and 7/1, then 5% MeOH in $CHCl_3$), giving 10.7 g of **11g**, 4.3 g of a mixture of **11g** and **13g**, and 3.0 g of **13g**. The total yield of **11g** was 53.1 g (48%), and that of **13g** was 5.1 g (5%).

(±)-*t*-6-Butoxy-*r*-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (11c, TAC-278) and Its Stereoisomer (13c)——a) A solution of **10c** (11.2 g, 51 mmol), BuOH (4.2 g, 57 mmol), and $MeSO_3H$ (2.7 g, 28 mmol) in 100 ml of dioxane was heated at 60—70°C for 5.5 h. The reaction mixture was diluted with 400 ml of $CHCl_3$, washed with aq. $NaHCO_3$ solution then with H_2O, and dried (Na_2SO_4). Removal of the solvent gave 10.1 g (73%) of **11c** as a white solid.

b) A solution of **10c** (9.90 g, 45 mmol) in 50 ml of acetone was treated with pyridine (9.0 ml, 0.11 mol) and Ac_2O (5.2 g, 51 mmol) at room temperature for a day. After addition of BuOH (10 ml), the solvent was removed by distillation at atmospheric pressure. The crude product was chromatographed on silica gel ($CHCl_3$/benzene=6/1), giving 4.9 g (39%) of **11c** as colorless needles after crystallization from acetone–$CHCl_3$–hexane.

c) A suspension of **10d** (5.58 kg, 21.3 mol) in 27 l of BuOH was heated at 95—100°C for 4 h, giving a yellow solution. Next, 6.0 l of H_2O was added to the reaction mixture, and the resulting mixture was heated at 50—60°C for 2 h. Excess BuOH was removed by distillation as an azeotropic mixture with H_2O until

a white solid began to separate. The solid was collected by filtration and purified by recrystallization once from EtOH–H_2O then twice from EtOH–hexane, giving 4.65 kg (79%) of **11c** as colorless needles. The filtrate obtained from the first recrystallization was extracted with 30 l of EtOAc, and the extract was dried (Na_2SO_4). The solvent was removed to give 230 g of a pale yellow solid. It was purified carefully on silica gel (10.5 g each of the solid on 300 g of silica gel) using 1% MeOH in $CHCl_3$ as the solvent, giving 44.7 g (0.8%) of **13c** after recrystallization from EtOH–hexane. Each isomer showed a single spot on a TLC plate at *Rf* values of 0.64 for **11c** and 0.57 for **13c** [$CHCl_3$/EtOAc/dioxane=5/1/1 (v/v)].

The following compounds were prepared similarly by the use of method a) and/or b).

trans Derivatives (**11**). (**11c**): mp 141—142°C (E–H). *Anal.* Calcd for $C_{11}H_{17}FN_2O_5$: C, 47.82; H, 6.20; N, 10.14. Found: C, 47.88; H, 6.06; N, 10.06. PMR: 4.74 (1H, dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**11d**): mp 114—115°C (EA–H). *Anal.* Calcd for $C_{12}H_{19}FN_2O_5$: C, 49.65; H, 6.60; N, 9.65. Found: C, 49.40; H, 6.53; N, 9.41. PMR ($CDCl_3$): 5.10 (1H, dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**11e**): mp 108—109°C (EA–H). *Anal.* Calcd for $C_{13}H_{21}FN_2O_5$: C, 51.31; H, 6.96; N, 9.21. Found: C, 51.18; H, 6.84; N, 9.06. PMR: 4.83 (1H, dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**11f**): mp 118—119°C (C–H). *Anal.* Calcd for $C_{14}H_{23}FN_2O_5$: C, 52.82; H, 7.28; N, 8.80. Found: C, 52.86; H, 7.35; N, 8.96. PMR ($CDCl_3$): 5.06 (1H, dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**11g**): mp 126—127°C (E–H). *Anal.* Calcd for $C_{15}H_{25}FN_2O_5$: C, 54.20; H, 7.58; N, 8.43. Found: C, 54.40; H, 7.79; N, 8.32. PMR ($CDCl_3$): 5.12 (1H, dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**11h**): mp 113—114°C (EA–H). *Anal.* Calcd for $C_{19}H_{33}FN_2O_5$: C, 58.74; H, 8.56; N, 7.21. Found: C, 58.77; H, 8.64; N, 7.05. PMR ($CDCl_3$): 5.07 (1H, dd, $J_{HF}=2$ Hz, $J=4$ Hz).

cis Derivatives (**13**). (**13c**): mp 134—135°C (E–H). *Anal.* Calcd for $C_{11}H_{17}FN_2O_5$: C, 47.82; H, 6.20; N, 10.14. Found: C, 47.60; H, 6.13; N, 10.26. PMR: 4.98 (1H, dd, $J_{HF}=12$ Hz, $J=2$ Hz). (**13d**): mp 109—111°C (EA–H). *Anal.* Calcd for $C_{12}H_{19}FN_2O_5$: C, 49.65; H, 6.60; N, 9.65. Found: C, 49.43; H, 6.59; N, 9.67. PMR ($CDCl_3$): 5.12 (1H, dd, $J_{HF}=11$ Hz, $J=2$ Hz). (**13e**): mp 68—69°C (C–H). *Anal.* Calcd for $C_{13}H_{21}FN_2O_5$: C, 51.31; H, 6.96; N, 9.21. Found: C, 51.50; H, 7.04; N, 9.45. PMR ($CDCl_3$): 5.15 (1H, br d, $J_{HF}=11$ Hz). (**13f**): *Anal.* Calcd for $C_{14}H_{23}FN_2O_5$: C, 52.82; H, 7.28; N, 8.80. Found: C, 52.84; H, 7.39; N, 8.83. PMR ($CDCl_3$): 5.10 (1H, dd, $J_{HF}=11$ Hz, $J=2$ Hz). (**13g**): mp 148—149°C (E–H). *Anal.* Calcd for $C_{15}H_{25}FN_2O_5$: C, 54.20; H, 7.58; N, 8.43. Found: C, 54.43; H, 8.19; N, 8.45. PMR ($CDCl_3$): 5.13 (1H, br d, $J_{HF}=11$ Hz). (**13h**): mp 101—102°C (E–H). *Anal.* Calcd for $C_{19}H_{33}FN_2O_5$: C, 58.74; H, 8.56; N, 7.21. Found: C, 58.96; H, 8.67; N, 7.16. PMR ($CDCl_3$): 5.12 (1H, dd, $J_{HF}=11$ Hz, $J=2$ Hz).

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References and Notes

1) Part II: O. Miyashita, K. Matsumura, T. Kasahara, H. Shimadzu, and N. Hashimoto, *Chem. Pharm. Bull.*, **30**, 887 (1982); Part III: O. Miyashita, K. Matsumura, H. Shimadzu, and N. Hashimoto, *ibid*, **30**, 1860 (1982).
2) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J.H. Buchenal, and J.J. Fox, *J. Med. Chem.*, **10**, 47 (1967); H.A. Lozeron, M.P. Gordon, T.Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry*, **3**, 1844 (1964).
3) M.J. Robins, M. MacCoss, S.R. Naik, and G. Ramani, *J. Am. Chem. Soc.*, **98**, 7381 (1976); M. Fikus, K.L. Wierzchowski, and D. Shugar, *Biochem. Biophys. Res. Commun.*, **16**, 478 (1964); *idem*, *Photochem. Photobiol.*, **4**, 521 (1965).
4) M.N.G. James and M. Matsushima, *Acta Crystallogr., Sec. B*, **32**, 957 (1976).
5) Y. Kobayashi, I. Kumadaki, and A. Nakazato, *Tetrahedron Lett.*, **21**, 4605 (1980); these authors are preparing another report on the stereochemistry of 6-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (private communications).
6) D. Cech, L. Hein, R. Wuttke, M. von J.-Lipinski, A. Otto, and P. Langen, *Nucleic Acid Res.*, **2**, 2177 (1975).
7) L. Phillips and V. Wray, *J. Chem. Soc., Chem. Commun.*, **1973**, 90.
8) We are indebted to Dr. Y. Sawa and coworkers of the Chemical Development Laboratories of this Division for their generous gift of the mother liquor from a kilogram-scale preparation of **11c** and for information on the details of the preparation, which are described in the experimental section.
9) L.M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Pergamon Press, London, 1969.