[Chem. Pharm. Bull. 30(3) 887—898 (1982)]

Studies on Fluorinated Pyrimidines. II.[1] Synthesis and Antitumor Activity of 5-Fluoro-6-substituted-5,6-dihydrouracil-5-carboxylic Acid Derivatives

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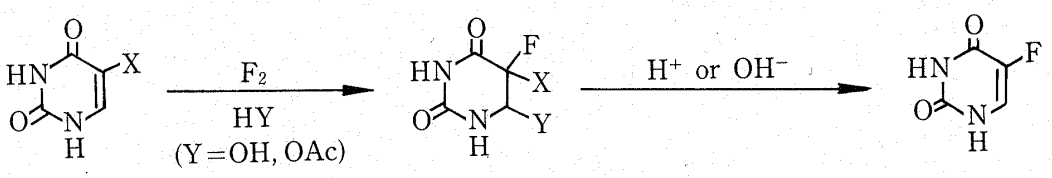
(Received August 6, 1981)

Various derivatives of 5-fluoro-5,6-dihydrouracil with an alkoxycarbonyl, substituted carbamoyl, or cyano group at C-5, and one of a variety of substituents, *i.e.*, alkoxy, substituted mercapto, substituted amino, acyl amino, and alkylidene- and arylideneaminooxy at C-6, have been synthesized as a class of potential pro-drugs of autitumor agents, 5-fluorouracil (5-FU) and 1-(2-tetrahydrofuryl)-5-fluorouracil (Ftorafur). Antitumor activity of these compounds against leukemia P388 or L1210 in mice and antifungal activity against *Botrytis cinerea* are described.

Keywords——5-fluoro-6-hydroxy-5,6-dihydrouracil-5-carboxylic acid derivatives; 6-acetoxy-5-fluoro-5,6-dihydrouracil-5-carboxylic acid derivatives; 5-alkoxycarbonyl-5-fluoro-6-substituted-5,6-dihydrouracil; 5-fluorouracil; P388; L1210; *Botrytis cinerea*; TAC-278; fluorination

In a previous paper,[1] the synthesis of some 5-fluoro-6-hydroxy- and 5-fluoro-6-methoxy-5,6-dihydrouracil-5-carboxylic acid derivatives by fluorination of the corresponding uracil-5-carboxylic acid derivatives (**1**—**3**) with trifluoromethyl hypofluorite or fluorine and the preparation of 5-fluorouracil (5-FU) and 1-(2-tetrahydrofuryl)-5-fluorouracil (Ftorafur) in excellent yields by subjecting them to hydrolysis under mild conditions were described (Chart 1).



	X	X	Y
1	CO_2R	**4**	CO_2R OH
2	$CONR^1R^2$	**5**	CO_2R OR^1
3	CN	**6**	CO_2R OAc
		7	$CONR^1R^2$ OH, OAc
		8	CN OH, OAc

Chart 1

This time, we examined the antitumor activity of 5-fluoro-6-methoxy-5-methoxycarbonyl-5,6-dihydrouracil (**5a**, abbreviated as MeO–HFU–COOMe)[2] and 5-alkoxycarbonyl-5-fluoro-6-hydroxy-5,6-dihydrouracils (HO–HFU–COOR: **4a**; R=Me and **4b**; R=Et) against leukemia P388 in mice and found that the first had a good antitumor activity, whereas the other two were rather toxic. The toxicity was different from that of 5-FU. These results suggest that **5a** is converted *in vivo* into 5-FU, but **4a** and **4b**, which have a hydroxyl group on C-6, are metabolized through another path that yields some toxic substances containing fluorine other than 5-FU.

Thus, a series of compounds with a variety of substituents at C-5 and C-6 were prepared

in order to obtained a compound with more favorable pharmacokinetic properties than those of 5-FU, *e.g.*, the ability to release 5-FU over a long period, or a different tissue distribution.

First, fluorination of 5-(higher alkoxy)carbonyl- (**1c**—**k**), 5-(*N*-substituted carbamoyl)- (**2a**—**c**), 5-cyano- (**3**) -uracils with fluorine was studied (Chart 1). The lower alkyl esters (**1a**—**g**) underwent fluorination readily in water, presumably because of their moderate solubility in it. Fluorination of the higher alkyl esters did not take place in water. However, fluorination of octyl ester (**1j**) in acetic acid proceeded satisfactorily and gave AcO–HFU–$COOC_8H_{17}$ (**6c**) as an unstable oil that was used immediately for the next step without further purification. Fluorination of the lower alkyl esters (**1a** and **1b**) in acetic acid also proceeded smoothly, giving the corresponding 6-acetoxy derivatives (**6a** and **6b**) in high yields and purity (Table I). Attempted purification of AcO–HFU–COOMe (**6a**) by column chromatography on silica gel resulted in hydrolysis of the 6-acetoxy group, giving **4a**. Hexyl (**1h**), heptyl (**1i**), and stearyl (**1k**) esters, which were insoluble in both water and acetic acid, resisted fluorination and were recovered unchanged.

Preparation of R^1O–HFU–COOR (5)

1) Acid-catalyzed Substitution of the 6-Hydroxyl Group of HO–HFU–COOR (4) with an Alcohol as a Nucleophile, HZ——Method I: Treatment of the methanolic solution of HO–

Table I. Fluorination Products (**4**—**8**) of Uracil-5-carboxylic Acid Derivatives (**1**—**3**)

No.	X Y	Solv.[a] F_2/N_2 (%)	Yield (%) mp (°C)	Recryst. solv.[b] Formula	Analysis (%) Calcd (Found)		
					C	H	N
4a	COOMe	W	79	A-C	34.96	3.42	13.59
	OH	25(2.0 eq)	171—172	$C_6H_7FN_2O_5$	(35.07	3.41	13.58)
4b	COOEt	W	51	M-C-H	38.19	4.12	12.73
	OH	25(2.6)	163—165	$C_7H_9FN_2O_5$	(37.90	3.94	12.87)
4c	COOPr-iso	W	58	A-H	41.03	4.74	11.96
	OH	25(3.0)	179—181	$C_8H_{11}FN_2O_5$	(41.08	4.52	11.60
4d	COOBu	W	50	A-C	43.55	5.28	11.29
	OH	25(4.0)	162—163	$C_9H_{13}FN_2O_5$	(43.26	5.16	11.46)
4e	COOBu-*sec*	W	29	A-C	43.55	5.28	11.29
	OH	23(1.8)	183—184	$C_9H_{13}FN_2O_5$	(43.40	5.26	11.19)
6a	COOMe	AA	81	EE	38.72	3.65	11.29
	OAc	10(2.0)	157—159	$C_8H_9FN_2O_6$	(38.45	3.86	11.25)
6b	COOEt	AA	72	—[c]		—[d]	
	OAc	15(1.8)	—[d]	$C_9H_{11}FN_2O_6$			
6c	$COOC_8H_{17}$	AA	—[d]	—[c]		—[d]	
	OAc	10(2.1)	—[d]	$C_{15}H_{23}FN_2O_6$			
6d	$COOC_{18}H_{37}$	AA	—[d,e]	—[c]		—[d]	
	OAc	15(5.0)	—[d]	$C_{25}H_{43}FN_2O_6$			
7a	$CONH_2$	W	39	A-C	31.42	3.16	21.99
	OH	25(5.0)	188—189(dec.)	$C_5H_6FN_3O_4$	(31.25	3.21	22.09)
7b	CONHMe	W	36	A-C	35.13	3.93	20.48
	OH	25(3.5)	193—194(dec.)	$C_6H_8FN_3O_4$	(34.92	3.98	20.51)
7c	$CONEt_2$	W	14	EA	43.72	5.71	17.00
	OH	25(5.0)	190—192(dec.)	$C_9H_{14}FN_3O_4$	(43.61	5.57	16.98)
7d	$CONH_2$	AA	—[d]	—[c]		—[c]	
	OAc	15(1.5)	—[d]	$C_7H_8FN_3O_5$			
8a	CN	W	72	A-C-H	34.69	2.33	24.27
	OH	25(4.5)	158—160	$C_5H_4FN_3O_3$	(34.39	2.27	24.16)
8b	CN	AA	—[d]	—[c]		—[d]	
	OAc	15(1.5)	—[d]	$C_7H_6FN_3O_4$			

a) AA=acetic acid, W=water.
b) A=acetone, C=chloroform, EA=ethyl acetate, EE=ethyl ether, H=hexane, M=methanol.
c) Reacted with nucleophile without further purification.
d) Not determined.
e) Recovered 89% of the starting material.

HFU-COOMe (**4a**) with an excess of hydrogen chloride in the cold gave MeO-HFU-COOMe (**5a**) in high yield. Similarly, treatment of HO-HFU-COOEt (**4b**) with ethanolic hydrogen chloride gave EtO-HFU-COOEt (**5h**) in excellent yield. When **4b** was treated with methanolic hydrogen chloride, a mixture of MeO-HFU-COOMe (**5a**) and MeO-HFU-COOEt (**5g**) was obtained, and increase of the reaction time resulted in complete transesterification of **5g** into **5a**. The 6-lower alkoxy derivatives (**5**) such as 6-methoxy, -ethoxy, or -propoxy derivatives were prepared from **4** and the corresponding alcohol, which also served as the solvent, in the presence of an acid catalyst (Chart 2, Table II).

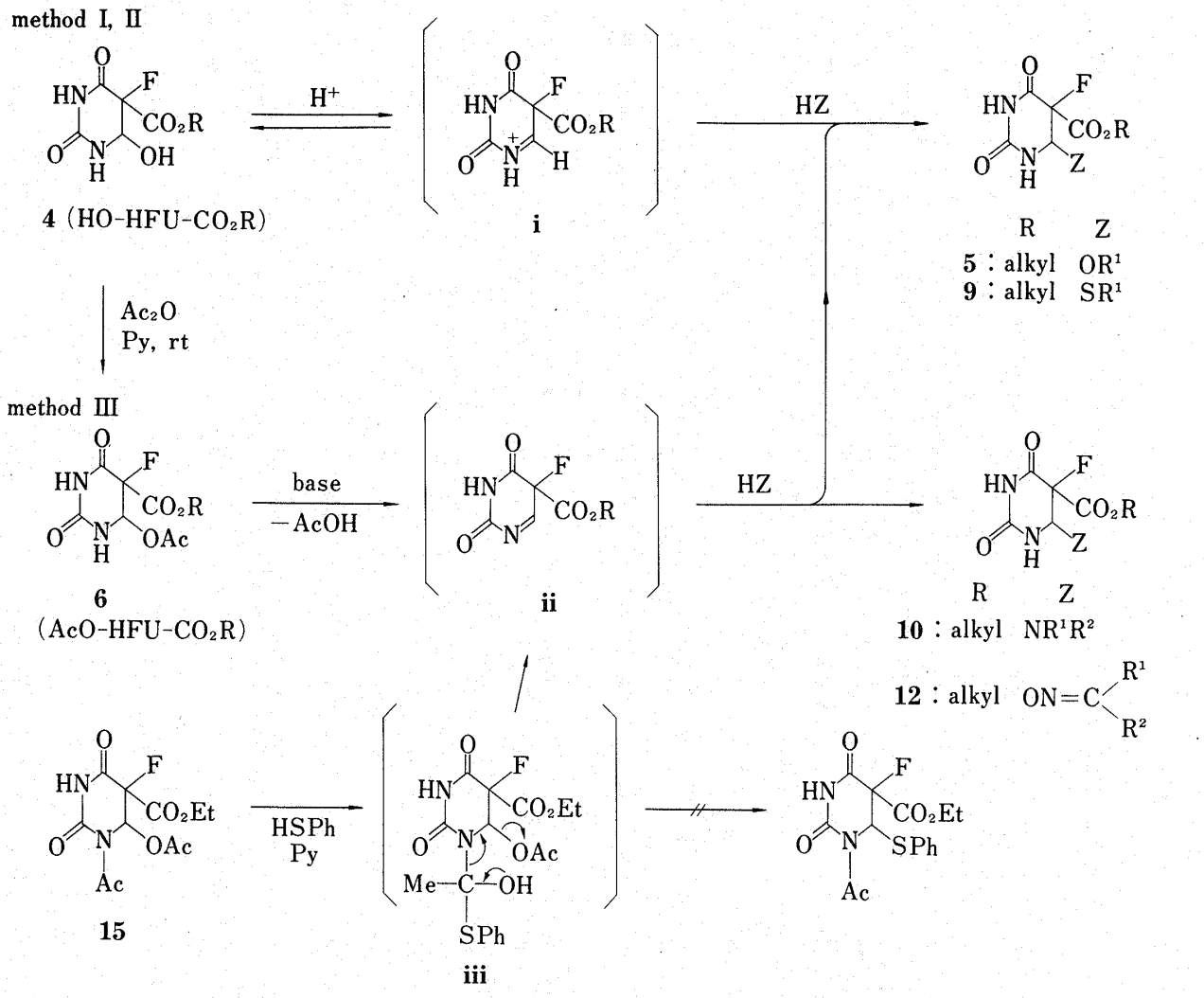


Chart 2

Method II: When an alcohol of a higher boiling point was used as the nucleophile, a small excess of it and **4** were heated in the presence of an acid catalyst in dioxane or 1,2-dimethoxyethane. In these cases, replacement of the 6-hydroxyl group occurred almost exclusively, giving **5**, and the transesterification was minimized. The water formed in the course of the reaction was removed as an azeotropic mixture using benzene or toluene as the solvent. This represents an improved method. With a weak nucleophile such as 2,2,2-trifluoroethanol, the yield of CF_3CH_2O-HFU-COOEt (**5i**) was as low as 13%.

2) **Base-catalyzed Substitution of the 6-Acetoxy Group of AcO-HFU-COOR (6) with an Alcohol**——Method III: Treatment of **4** with acetic anhydride and pyridine, or fluorination of **1** in acetic acid gave AcO-HFU-COOR (**6**). As the 6-acetoxy group is labile to the attack

Table II. 6-Alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (R^1O–HFU–COOR, **5**)

No.	R R^1	Start. mat. Method, cat.[a]	Yield (%) mp (°C)	Recryst. solv.[b] Formula	Analysis (%) Calcd (Found) C	H	N
5a	Me Me	**4a** I, HCl (**4b**, I, HCl; 91%) (**6a**, III, py; 93%)	89 165—166	A-H $C_7H_9FN_2O_5$	38.19 (38.49	4.12 4.06	12.73 12.50)
5b	Me Et	**4a** I, HCl	91 185—187	A-H $C_8H_{11}FN_2O_5$	41.03 (40.75	4.73 4.55	11.96 11.68)
5c	Me Bu	**4a** I, M	62 140—141	C-H $C_{10}H_{15}FN_2O_5$	45.80 (45.83	5.77 5.59	10.68 10.57)
5d	Me cyclohexyl	**4a** II, HCl	49 196—197	C-H $C_{12}H_{17}FN_2O_5$	50.00 (49.94	5.94 5.83	9.72 9.78)
5e	Me CH_2Ph	**4a** II, M	56 173—174	C-H $C_{13}H_{13}FN_2O_5$	52.71 (52.50	4.42 4.28	9.46 9.35)
5f	Me C_8H_{17}	**4a** II, T	81 147—148	C-H $C_{14}H_{23}FN_2O_5$	52.82 (52.84	7.28 7.27	8.80 8.71)
5g	Et Me	**4b** I, M	83 135—137	A-C-H $C_8H_{11}FN_2O_5$	41.03 (41.06	4.73 4.58	11.96 11.95)
5h	Et Et	**4b** I, HCl	94 179—181	A-C-H $C_9H_{13}FN_2O_5$	43.55 (43.37	5.28 5.21	11.29 11.13)
5i	Et CH_2CF_3	**4b** I, M	13 166—173	—[c] $C_9H_{10}F_4N_2O_5$		—	
5j	Et iso-Pr	**6b** III, py	71 216—218	A-C-H $C_{10}H_{15}FN_2O_5$	45.80 (45.79	5.77 5.74	10.68 10.72)
5k	Et $CH_2CH{=}CH_2$	**4b** I, M	62 153—154	A-C-H $C_{10}H_{13}FN_2O_5$	46.16 (49.91	5.04 4.99	10.76 10.61)
5l	Et $CH_2C{\equiv}CH$	**4b** I, M	50 151—152	A-C-H $C_{10}H_{11}FN_2O_5 \cdot 1/4H_2O$	45.96 (45.97	4.43 4.24	10.84 10.80)
5m	Et Bu	**4b** II, M (**6b**, III, py; 69%)	73 141—142	E-H $C_{11}H_{17}FN_2O_5$	47.82 (47.52	6.20 6.22	10.14 10.11)
5n	Et iso-Bu	**4b** II, M	58 187—188	A-C-H $C_{11}H_{17}FN_2O_5$	47.82 (47.53	6.20 6.20	10.14 10.04)
5o	Et Ph	**6b** III, py	34 164—167	A-C-H $C_{13}H_{13}FN_2O_5$	52.71 (52.14	4.42 4.30	9.46 9.87)
5p	Et CH_2Ph	**4b** II, M	52 132—133	A-C-H $C_{14}H_{15}FN_2O_5$	54.19 (54.19	4.87 4.84	9.03 9.08)
5q	Et C_8H_{17}	**4b** II, T	42 123—124	EA-H $C_{15}H_{25}FN_2O_5$	54.21 (54.32	7.58 7.73	8.42 8.39)
5r	iso-Pr iso-Pr	**4c** I, T	53 231—232	A-C-H $C_{11}H_{17}FN_2O_5$	47.82 (47.75	6.20 6.16	10.14 9.95)
5s	Bu Bu	**4d** I, HCl	82 138—139	E-H $C_{13}H_{21}FN_2O_5$	51.31 (51.39	6.96 6.94	9.21 9.36)
5t	C_8H_{17} Et	**6c** III, py	95 127—128	C-H $C_{15}H_{25}FN_2O_5$	54.21 (54.10	7.58 7.59	8.43 8.38)
5u	$C_{18}H_{37}$ Et	**6d** III, py	20 104—106	C-H $C_{25}H_{45}FN_2O_5 \cdot 1/2H_2O$	62.34 (62.52	9.62 9.45	5.82 5.85)

a) M=methanesulfonic acid, T=*p*-toluenesulfonic acid.
b) A=acetone, C=chloroform, E=ethanol, EA=ethyl acetate, H=hexane.
c) Obtained as a crude solid.
d) Not determined.

of a nucleophile,[3] heating of AcO–HFU–COOEt (**6b**) with butanol in the presence of pyridine, for example, gave BuO–HFU–COOEt (**5m**, TAC-278) in high yield (Table II, Chart 2).

Preparation of the other Z–HFU–COOR Compounds (9—12)

Reaction of a mercaptan as a nucleophile, HZ, with **4** was facilitated in the presence of an acid catalyst and gave the 6-(substituted mercapto) derivative [R^1S–HFU–COOR (**9**)] in good yield [Method II]. Replacement of the 6-acetoxy group of **6b** with phenylmercaptan

also took place smoothly, giving PhS–HFU–COOEt (**9g**) [Method III] (Chart 2, Table III).

The 6-acetoxy group of **6** was replaced with an amine as a nucleophile, HZ, giving the 6-(substituted amino) derivative R^1R^2N–HFU–COOR (**10**) in good yield (Chart 2, Table IV). These compounds seem to be rather unstable and colored with decomposition after standing for several months at room temperature. The lability may be attributed to the presence of the basic amino group on C-6. 6-Acylamino derivatives (**11**) may be more stable, and to obtain them, acylation of the 6-amino derivative (**10b**) was investigated. The 6-benzylamino compound (**10g**) was hydrogenated over palladium on carbon, giving **10b** in high yield. Treatment of **6b** with concentrated ammonium hydroxide solution gave the same product **10b** in similar yield. Acylation of **10b** by ordinary methods gave the 6-acylamino derivative [R^3CONH–HFU–COOEt (**11**)] in high yield (Chart 3, Table IV). These 6-acylamino compounds remained unchanged for several months on standing at room temperature.

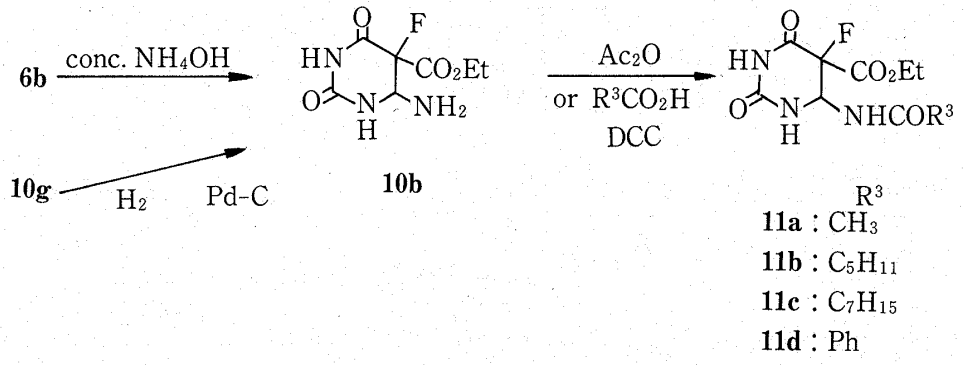


Chart 3

Various oximes as nucleophiles, HZ, reacted with **6** smoothly to give 6-alkylidene- or 6-arylideneaminooxy derivatives [$R^1R^2C{=}NO$–HFU–COOR (**12**)] in excellent yields (Chart 2, Table V), although replacement of the 6-hydroxyl group of **4** with an oxime in the presence of an acid catalyst was unsuccessful and the starting material was recovered.

Table III. 5-Alkoxycarbonyl-6-(substituted mercapto) Derivatives (R^1S–HFU–COOR, **9**)

No.	R R_1	Start. mat. Method, cat.[a]	Yield (%) mp (°C)	Recryst. solv.[b] Formula	Analysis (%) Calcd (Found) C	H	N
9a	Me	**4a**	75 (%)	A-C-H	43.16	5.43	10.07
	Bu	II, M	123—125	$C_{10}H_{15}FN_2O_4S$	(43.21	5.24	10.02)
9b	Me	**4a**	86	A-C-H	48.32	3.72	9.39
	Ph	II, M	173—176	$C_{12}H_{11}FN_2O_4S$	(48.16	3.60	9.53)
9c	Et	**4b**	29	A-C-H	40.90	4.96	10.60
	Et	II, M	178—180	$C_9H_{13}FN_2O_4S$	(40.75	4.85	10.57)
9d	Et	**4b**	31	A-C-H	43.47	4.74	10.14
	allyl	II, M	122—123	$C_{10}H_{13}FN_2O_4S$	(43.52	4.44	10.12)
9e	Et	**4b**	49	C-H	45.20	5.86	9.58
	tert-Bu	II, M	211—212	$C_{11}H_{17}FN_2O_4S$	(45.04	5.77	9.60)
9f	Et	**4b**	49	A-C-H	49.04	6.02	8.80
	cyclohexyl	II, M	168—170	$C_{13}H_{19}FN_2O_4S$	(48.68	6.00	8.43)
9g	Et	**6b**	39	A-C-H	49.99	4.20	8.97
	Ph	III, py	164—166	$C_{13}H_{13}FN_2O_4S$	(49.55	3.98	9.09)
		(from **15**, III, py; 78%)					
9h	Et	**4b**	46	A-C-H	51.53	3.63	8.58
	CH_2Ph	II, M	149—150	$C_{14}H_{15}FN_2O_4S$	(51.51	4.47	8.73)

a) M=methanesulfonic acid.
b) A=acetone, C=chloroform, H=hexane.

TABLE IV. 5-Alkoxycarbonyl-6-(substituted amino) (**10**)[a] and -6-Acylamino (**11**) Derivatives

No.	R Z	Yield (%) mp (°C)	Recryst. solv.[b] Formula	Analysis (%) Calcd (Found) C	H	N
10a	Me piperidino	17 142—144	C-H $C_{11}H_{16}FN_3O_4$	48.35 (48.29	5.90 5.67	15.38 15.64)
10b	Et NH_2	70 (66)[c] 151—154	M $C_7H_{10}FN_3O_4$	38.36 (38.43	4.60 4.58	19.17 19.04)
10c	Et piperidino	52 149—150	C-H $C_{12}H_{18}FN_3O_4$	50.17 (50.11	6.31 6.38	14.63 14.60)
10d	Et NH-allyl	43[d] —[e]	—		—[e]	
10e	Et NHBu	54 112—113	C-H $C_{11}H_{18}FN_3O_4$	47.99 (47.59	6.59 6.63	15.27 15.18)
10f	Et NHPh	82 143—144	A-B-H $C_{13}H_{14}FN_3O_4 \cdot 1/4H_2O$	52.08 (52.13	4.89 4.73	14.01 13.69)
10g	Et $NHCH_2Ph$	66 157—158	EA $C_{14}H_{16}FN_3O_4$	54.36 (54.22	5.22 5.17	13.59 13.65)
10h	Et NEt_2	75[d] —[e]	—		—[e]	
11a	Et NHAc	61 99—102	E-H $C_9H_{12}FN_3O_5 \cdot CH_3CH$	40.96 (40.76	5.50 5.46	14.33 14.36)
11b	Et $NHCOC_5H_{11}$	46 128—130	E-H $C_{13}H_{20}FN_3O_5$	49.21 (49.02	6.35 6.14	13.24 13.36)
11c	Et $NHCOC_7H_{15}$	62 101—103	E-H $C_{15}H_{24}FN_3O_5$	52.16 (51.94	7.00 6.95	12.17 12.17)
11d	Et NHCOPh	47 103—104	EA $C_{14}H_{14}FN_3O_5$	52.02 (51.57	4.36 4.48	13.00 12.65)

a) Prepared from AcO–HFU–COOR (**6**).
b) A=acetone, B=benzene, C=chloroform, E=ethanol, EA=ethyl acetate, H=hexane, M=methanol.
c) Prepared from **10g** by catalytic hydrogenolysis.
d) Isolated as a crude solid.
e) Not determined.

Synthesis of compounds with a carbamoyl or cyano group at C-5 was carried out similarly, *i.e.*, treatment of AcO–HFU–$CONH_2$ (**7d**) and AcO–HFU–CN (**8b**) with ethanol gave EtO–HFU–$CONH_2$ (**13**) and EtO–HFU–CN (**14**) in good yields.

An Alternative Method for Synthesizing 5m (TAC-278)

As described in the following section, **5m** was chosen as a candidate antitumor agent for man. For pharmacokinetic and metabolic studies of **5m** in animals preceding clinical studies, an economicol synthetic procedure for **5m** with ^{14}C at C-2 was investigated. Ballard *et al.*[4] reported that the condensation of an equimolar mixture of thiourea and ethyl ethoxymethylenemalonate in the presence of sodium ethoxide gave ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**16**) in 85% yield. Fluorination of **16** gave **4b** directly and the procedure for the synthesis of 2-^{14}C-TAC-278 starting from ^{14}C-thiourea *via* **16** and **4b** was established (Chart 4).

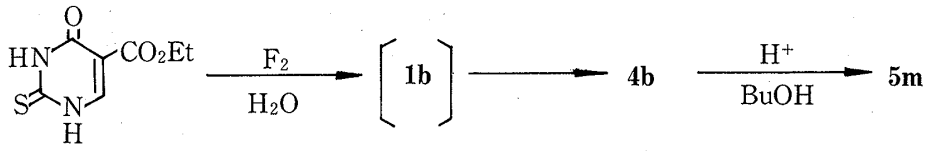


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Chart 4

Discussion on the Reaction Mechanisms

Chart 2 shows the supposed reaction mechanism for the exchange reaction decsribed

Table V. 5-Alkoxycarbonyl-6-alkylideneaminoxy Derivatives (R^1R^2C=NO–HFU–COOR, **12**)[a]

No.	R: R^1	R: R^2	Yield (%) mp (°C)	Recryst. solv.[b] Formula	Analysis (%) Calcd (Found) C	H	N
12a	Me	-$(CH_2)_5$-	67 171—175(dec.)	A-C-H $C_{12}H_{16}FN_3O_5$	47.84 (47.82	5.35 5.37	13.95 13.87)
12b	Et	H	35 128—129(dec.)	A-C-H $C_9H_{12}FN_3O_5$	41.38 (41.38	4.63 4.57	16.09 16.08)
12c	Et	Me	67 173—178(dec.)	A-C-H $C_{10}H_{14}FN_3O_5$	43.64 (43.63	5.13 5.09	15.27 15.21)
12d	Et	-$(CH_2)_3$-	44 188—190	A-C-H $C_{11}H_{14}FN_3O_5$	46.00 (45.85	4.91 4.80	14.63 14.85)
12e	Et	-$(CH_2)_4$-	68 170—171	A-C-H $C_{12}H_{16}FN_3O_5$	47.84 (47.72	5.35 5.18	13.95 14.06)
12f	Et	-$(CH_2)_5$-	83 185—187	A-C-H $C_{13}H_{18}FN_3O_5$	49.52 (49.56	5.75 5.86	13.33 13.34)
12g	Et	Me 2-furyl	58 196—197	A-C-H $C_{13}H_{14}FN_3O_6$	47.71 (47.54	4.31 4.15	12.84 12.91)
12h	Et	Me 2-thienyl	49 201—204(dec.)	A-C-H $C_{13}H_{14}FN_3O_5S$	45.48 (45.33	4.11 4.04	12.24 12.22)
12i	Et	H C_5H_{11}	54 128—129	C-H $C_{13}H_{20}FN_3O_5$	49.21 (49.17	6.35 6.37	13.24 13.23)
12j	Et	Me 4-pyridyl	86[c] —[d]	—		—[d]	
12k	Et	H Ph	19 198—199(dec.)	A-C-H $C_{14}H_{14}FN_3O_5$	52.02 (52.18	4.37 4.21	13.00 13.12)
12l	Et	Me CH_2Ph	67 135—139	A-C-H $C_{16}H_{18}FN_3O_5$	54.70 (54.54	5.16 4.95	11.96 11.86)

a) Prepared from AcO–HFU–COOR (**6**).
b) A=acetone, C=chloroform, H=hexane.
c) Isolated as a crude solid.
d) Not determined.

above. The cation **i** and **4** were equilibrated in the presence of an acid catalyst and the nucleophile, HZ, attacks **i** at C-6 to give **5** and **9**. Removal of the water produced in the course of reaction or use of an excess of the nucleophile shifts the equilibrium towards the products. In the reaction of the 6-acetoxy derivatives (**6**—**8**), an intermediate **ii** is obtained in the presence of a base such as pyridine, that then reacts with the nucleophile to afford the adducts **5**, **9**, **10**, and **12**—**14**. In the case of the 1-acetyl-6-acetoxy derivative (**15**), the reaction did not proceed under the usual conditions. Using more severe conditions, **15** reacted with phenylmercaptan to give **9g** probably *via* intermediate (**iii**), accompanied by the elimination of AcSPh. These mechanisms show that the formation of cation **i** or imine **ii** may be essential for the replacement of the substituent on C-6 to take place. It is presumed on this basis that the formation of thermodynamically stable products (*trans* orientation between the alkoxycarbonyl group on C-5 and the substituent Z on C-6) will be favored under these reaction conditions. The stereochemistry of the 5-fluoro-6-substituted-5,6-dihydrouracil-5-carboxylic acid derivatives will be discussed in a subsequent report.

Biological Activities

Antifungal activity of several Z–HFU–COOR (**5**, **9**, and **10**) was tested, and the results are listed in Table VI. These compounds showed strong growth inhibitory activity against *Botrytis cinerea*, although they had weak or no activity against most of the fungi tested. Since 5-FU had the strongest activity among the tested compounds, it seems that there is a close relationship between the antifungal activity and the ease of conversion of Z–HFU–COOR into 5-FU *in vivo* or under near-physiological conditions. As for the alkoxycarbonyl group,

it seems that the longer the carbon chain of the alkyl group, the less active the compound, because the hydrolysis of the ester group leading to the release of 5-FU will be suppressed due to steric hindrance. Also, it seems that the activity decreases in compounds which have N, S, and O atoms adjacent to C-6, in that order, and in the order of methyl, allyl, benzyl, ethyl, and octyl linked to the hetero atoms. Generally speaking, a compound with a good leaving group on C-6 shows higher activity against the fungus. However, the 6-(substituted amino) compounds (**10**) were found to be unstable at room temperature, and decomposed gradually on standing (toxicity caused by the liberated amines *in vivo* should also be considered). As for the 6-mercapto compounds (**9**), the offensive odor of the mercaptans released *in vivo* prevented further investigations on their biological activity.

Finally, the antitumor activity of the 6-alkoxy (**5**) and 6-alkylideneaminooxy (**12**) compounds was tested against P388 or L1210 in BDF_1 mice; the results are summarized in Table VII. Among them, **5a** was considered to be converted into 5-FU most effectively. The highest T/C value was obtained with **5a** against leukemia P388, in accord with expectation.

Table VI. Antifungal Activity of Z–HFU–COOR against *Botrytis cinerea*[a]

No.	MIC[b] (μg/ml)	ID_{50}[c] (μg/ml)	No.	MIC (μg/ml)	ID_{50} (μg/ml)
5a	12.5	2.4	**9c**	25	4.2
5e	12.5	3.7	**9d**	50	3.7
5f	25	21	**9h**	25	4.5
5h	25	8.0	**10a**	6.25	1.1
5k	25	3.9	**10e**	12.5	3.3
5s	25	18.5	**10g**	25	4.3
5-FU	0.78	0.15			

a) The fungus was incubated on nutrient agar plates at 28°C for 4 d.
b) MIC: miniumum inhibitory concentration.
c) ID_{50}: inhibitory dose of 50% growth.

Table VII. Antitumor Activity of **5a**, **5h**, **5m**, and **12f** against Murine Leukemia P388 or L1210[a]

No.	R	Z	Tumor[b]	Doses mg/kg/day	T/C[c] (%)
5a	Me	OMe	P388	200	243
				100	217
				50	160
5h	Et	OEt	P388	200	160
				100	143
				50	130
5m	Et (TAC-278	OBu	L1210	1000	165
				800	160
				600	158
12f	Et	O-N=⟨⟩	L1210	200	157
Ftorafur			L1210	300	160
				200	150
				100	113
5-FU			L1210	40	125
				20	121

a) The drugs were administered intraperitoneally (for P388) or orally (for L1210) once daily for 9 days for 9 days starting from 24 h after transplantation of tumor cells.
b) Tumor cells (1×10^6 cells of P388 or 1×10^5 cells of L1210) were implanted intraperitoneally.
c) The T/C % values were calculated on the basis of the median survival time for P388 or mean survival time for L1210 of the treated animals relative to the control animals.

However, it was rather toxic (LD_{50} in mice; 2500—5000 mg/kg). The compound **5h** was also active. The other compounds were tested using the L1210 system with Tegafur as the reference, because these compounds (including Tegafur) showed activity only in that system. The compound **12f** showed antitumor activity at relatively low doses, but it might be toxic. BuO–HFU–COOEt (**5m**, TAC-278) showed potent antitumor activity against L1210 over a relatively wide range of dosages and at relatively higher doses without producing any significant symptoms of toxicity (LD_{50} in mice; over 6000 mg/kg). Clinical studies are now in progress.

Experimental

Melting points were determined on a Yanagimoto hot plate apparatus and are uncorrected. PMR spectra were recorded on a Varian T-60 spectrometer. 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-6 are cited. UV spectra were recorded on a Hitachi EPS-3T spectrometer. Thin-layer chromatography (TLC) was performed using precoated Kieselgel 60 F 254 (Merck) sheets. Column chromatography was carried out using Kieselgel 60 (Merck). All evaporations were carried out *in vacuo*.

5-Alkoxycarbonyluracils (**1**)——$SOCl_2$ (238 g, 2.0 mol) was added dropwise with stirring to a suspension of 5-carboxyuracil[1] (156 g, 1.0 mol) in 750 ml of DMF at a temperature below 50°C. The reaction mixture was kept between 45—50°C for 1 h, and between 50—60°C for 1 h, then allowed to stand at room temperature overnight. Precipitates were collected by filtration, washed with dry DMF and benzene successively, and dried at 80°C *in vacuo* giving 210 g of uracil-5-carbonylchloride–DMF–hemihydrochloride as a white powder. mp 180°C (dec.). PMR: 2.72 (3H, s), 2.87 (3H, s), 7.88 (1H, s), 8.18 (1H, br), 11.8—12.2 (2H, br), 13.4 (1H, br). *Anal.* Calcd for $C_5H_3ClN_2O_3 \cdot C_3H_7NO \cdot 1/2HCl$: C, 36.14; H, 3.98; N, 15.80. Found: C, 36.04; H, 3.73; N, 15.82.

Reaction of the carbonyl chloride (13.3 g, 50 mmol) thus obtained with various alcohols (1.1 equivalents) in 50—100 ml of toluene under reflux for 20 min gave the corresponding esters (**1c—k**) (Table VIII).

5-Carbamoyluracil (**2a**)——A suspension of 5-methoxycarbonyluracil (**1a**) (20.0 g, 0.12 mol) in 200 ml of conc. NH_4OH was warmed at 60°C overnight. White precipitates that separated were collected by filtration and washed with H_2O and EtOH, then dried to give 7.1 g of **2a** as a white powder. The mother liquor and washings were combined and concentrated, giving another crop of **2a** (8.9 g). The total yield of **2a** was 16.0 g (88%). mp>300°C. *Anal.* Calcd for $C_5H_5N_3O_3$: C, 38.71; H, 3.25; N, 27.09. Found: C, 38.54; H, 3.19; N, 26.77.

Table VIII. 5-Alkoxycarbonyluracils (**1c—k**)

No.	R	Yield (%)	Recryst. solv.[a]	Formula mp (°C)	Analysis (%) Calcd (Found) C	H	N
1c	Pr	58	W	$C_8H_{10}N_2O_4$ 231—232	48.48 (48.55	5.09 4.98	14.14 14.31)
1d	iso-Pr	78	W	$C_8H_{10}N_2O_4$ 243—244(dec.)		—[b]	
1e	Bu	77	W	$C_9H_{12}N_2O_4$		—[b]	
1f	*sec*-Bu	71	W	$C_9H_{12}N_2O_4$ 225—226	50.94 (50.79	5.70 5.65	13.20 13.13)
1g	C_5H_{11}	52	W	$C_{10}H_{14}N_2O_4$ 228—229	53.09 (53.39	6.24 6.28	12.38 12.30)
1h	C_6H_{13}	45	W	$C_{11}H_{16}N_2O_4$ 196—199	54.99 (55.21	6.71 6.57	11.66 11.24)
1i	C_7H_{15}	63	D	$C_{12}H_{18}N_2O_4 \cdot 1/2H_2O$ 210—216	54.74 (54.65	7.27 7.36	10.64 11.02)
1j	C_8H_{17}	57	D	$C_{13}H_{20}N_2O_4$ 224—226	58.19 (58.03	7.51 7.42	10.44 10.44)
1k	$C_{18}H_{37}$	78	D	$C_{23}H_{40}N_2O_4$ 206—207	67.61 (67.51	9.87 10.06	6.86 6.88)

a) D=dioxane, W=water.
b) Not determined.

Uracil-5-(*N*-methyl)carboxamide (**2b**) and uracil-5-(*N*,*N*-diethyl)carboxamide (**2c**, mp: 248—249°C) were prepared in a similar manner from **1a** and aqueous methylamine or diethylamine solution, respectively.

Fluorination of Uracil-5-carboxylic Acid Derivatives (1—3)——a) In Water: A suspension of **1a** (monohydrate, 15.04 g, 80 mmol) in 400 ml of H_2O was treated with 1.95 equivalents of F_2 ($F_2/N_2=25\%$). $CaCO_3$ (15.6 g) and $NaHSO_3$ (5.2 g) were added to the chilled reaction mixture. Removal of the solvent gave a white solid (23.7 g) which was chromatographed on silica gel (acetone/$CHCl_3$=1/3 v/v) to give 13.00 g (79%) of **4a** as colorless needles.

PMR data for 5-fluoro-6-hydroxy derivatives obtained in a similar manner are listed below. (**4a**): 4.90 (m, $J_{HF}=4$ Hz, $J=5$ Hz). (**4b**): 4.93 (m, $J_{HF}=3$ Hz). (**4c**): 4.92 (m, $J_{HF}=3$ Hz). (**4d**): 4.90 (m, $J_{HF}=3$ Hz, $J=5$ Hz). (**4e**): 4.7—5.1 (m). (**7a**): 4.86 (m). (**7b**): 4.86 (m, $J_{HF}=2$ Hz). (**8a**): 5.35 (m, $J_{HF}=3$ Hz).

b) In Acetic Acid: A suspension of 5-ethoxycarbonyluracil (**1b**) (57 g, 0.3 mol) in 1.0 l of AcOH was treated with 1.8 equivalents of F_2 ($F_2/N_2=15\%$). The reaction mixture was evaporated to dryness, giving a white solid. The solid was collected by filtration and washed with toluene to give 58.4 g (72%) of crude **6b**. It was used for the next step without further purification.

PMR data for 5-fluoro-6-acetoxy derivatives obtained in a similar manner are listed below. (**6a**): 6.23 (dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**6b**): 6.15 (dd, $J_{HF}=2$ Hz, $J=5$ Hz). (**6c**): 6.19 (dd, $J_{HF}=2$ Hz).

Acetylation of 6-hydroxy derivatives. A solution of **4a** (2.06 g, 10 mmol) in 5 ml of acetone was treated with pyridine 1.03 g, 13 mmol) and Ac_2O (1.12 g, 11 mmol) overnight in a refrigerator. Removal of the solvent gave 2.62 g of a colorless syrup. Although it contained a small amount of pyridine, its PMR spectrum was superimposable on that of **6a** obtained by fluorination of **1a** in AcOH.

5-Fluoro-6-methoxy-5-methoxycarbonyl-5,6-dihydrouracil (**5a**)——Method I: a) HCl (14 g) was dissolved in an ice-cooled solution of **4a** (8.0 g, 39 mmol) in 200 ml of MeOH. The mixture was allowed to stand in a refrigerator overnight. The solvent was removed, leaving a white solid that was chromatographed on silica gel (acetone/$CHCl_3$=1/4 v/v). Removal of the solvent gave 7.6 g (89%) of **5a** as colorless needles.

b) HCl (10 g) was dissolved in an ice-cooled solution of **4b** (2.2 g, 10 mmol) in 100 ml of MeOH, and the mixture was allowed to stand in a refrigerator for 2 d. Removal of the solvent gave a white solid, found to be a mixture of **5a** and **5g** by analysis of its PMR spectrum. The white solid was treated with HCl and MeOH again at room temperature overnight. Removal of the solvent by evaporation gave a white solid that was purified by chromatography on silica gel, giving 2.0 g (91%) of **5a** as colorless needles.

6-Ethoxy-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**5h**)——Method I: HCl was dissolved in an ice-cooled solution of **4b** (5.0 g, 23 mmol) in 200 ml of absolute EtOH, and the mixture was allowed to stand at room temperature overnight. After removal of the solvent, the residue was chromatographed on silica gel, giving 5.3 g (94%) of **5h** as colorless needles.

6-Butoxy-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**5m, TAC-278**)——Method II: A solution of **4b** (11.2 g, 51 mmol), BuOH (4.2 g, 57 mmol), and $MeSO_3H$ (2.7 g) in 100 ml of dioxane was heated at 60—70°C for 5.5 h with addition of 5.0 g of molecular sieves (3A). Insoluble substances were filtered off and the filtrate was evaporated to dryness, giving a yellow oil. The oil was dissolved in $CHCl_3$ and washed with aqueous $NaHCO_3$ solution and H_2O. Removal of the solvent gave 10.1 g (73%) of **5m** as a white solid.

Method III: A suspension of **6b** (658 g, 2.5 mol) in BuOH (500 ml, 5.4 mol) and pyridine (400 ml, 5.1 mol) was stirred at 65—75°C for 3 h, giving a dark violet solution. The mixture was poured into 7.5 l of H_2O with stirring. White precipitates that separated were collected by filtration and washed with H_2O. The wet solid was dissolved in 1.0 l of hot EtOH, and the insoluble substance was filtered off. The filtrate was diluted with 1.1 l of H_2O, and the solution was allowed to stand in the cold overnight. The colorless needles that separated were collected by filtration, washed with H_2O (250 ml×3), then dried *in vacuo* to give 585 g of **5m** as crude crystals. They were recrystallized from 930 ml of EtOH and 600 ml of hexane, giving 475 g (69%) of **5m** as colorless needles.

PMR data (the H-6) for 6-alkoxy-5-alkoxycarbonyl-5-fluoro-5,6-dihydrouracils (R^1O-HFU-COOR, **5**) prepared in a similar manner are listed below. (**5a**): 4.77 (dd, $J_{HF}=2$ Hz). (**5b**): 4.82 (dd, $J_{HF}=2$ Hz). (**5c**): 4.82 (dd, $J_{HF}=2$ Hz). (**5d**): 4.97 (dd, $J_{HF}=2$ Hz). (**5e**): 4.98 (dd, $J_{HF}=2$ Hz). (**5f**): 4.82 (dd, $J_{HF}=2$ Hz). (**5g**): 4.70 (dd, $J_{HF}=2$ Hz). (**5h**): 4.80 (dd, $J_{HF}=2$ Hz). (**5i**): 5.15 (dd, $J_{HF}=2$ Hz). (**5j**): 4.83 (dd, $J_{HF}=2$ Hz). (**5k**): 4.82 (dd, $J_{HF}=2$ Hz). (**5l**): 5.00 (dd, $J_{HF}=2$ Hz). (**5m**): 4.78 (dd, $J_{HF}=2$ Hz). (**5n**): 4.77 (dd, $J_{HF}=2$ Hz). (**5o**): 4.74 (dd, $J_{HF}=2$ Hz). (**5p**): 4.97 (dd, $J_{HF}=2$ Hz). (**5q**) ($CDCl_3$): 5.11 (dd, $J_{HF}=2$ Hz). (**5s**): 4.74 (dd, $J_{HF}=2$ Hz). (**5t**): 4.81 (dd, $J_{HF}=2$ Hz). (**5u**): 4.82 (m, $J_{HF}=2$ Hz).

5-Ethoxycarbonyl-6-ethylmercapto-5-fluoro-5,6-dihydrouracil (**9c**)——Method II: A mixture of **4b** (4.40 g, 20 mmol), EtSH (1.50 g, 24 mmol), and a catalytic amount of $MeSO_3H$ in 20 ml of 1,2-dimethoxyethane (DME) was heated at 80—90°C for 1 h in a stainless steel pressure-resistant tube. The reaction mixture was concentrated, giving a yellow oil that was chromatographed on silica gel (acetone/$CHCl_3$—1/4 v/v) to yield 1.52 g (29%) of **9c** as colorless needles.

5-Ethoxycarbonyl-5-fluoro-6-phenylmercapto-5,6-dihydrouracil (**9g**)——A mixture of **4b** (4.40 g, 20 mmol), Ac_2O (2.35 g, 23 mmol), and pyridine (2.05 g, 26 mmol) in 10 ml of acetone was allowed to stand at room temperature overnight. PhSH (3.30 g, 30 mmol) and pyridine (5.0 g, 63 mmol) were added to the above mixture, and the reaction mixture was warmed at 60°C for 1.5 h. The solvent was removed, giving a brown oil that was chromatographed on silica gel (acetone/$CHCl_3$=1/4 v/v) to yield 4.82 g (39%) of **9g**

as pale yellow needles.

Method III: A mixture of **4b** (25.6 g, 0.11 mol), pyridine (57 g, 0.72 mol), and Ac_2O (49 g, 0.48 mol) in 50 ml of acetone was allowed to stand at room temperature overnight, then warmed at 50°C for 15 min. The solvent was removed, giving a yellow oil that was chromatographed on alumina (Merck, neutral; acetone/benzene=1/9 v/v) to yield 29.1 g (82%) of the 1-acetyl-6-acetoxy derivative (**15**) as a yellow-orange oil. PMR: 1.17 (3H, t, J=7.5 Hz), 2.07 (3H, s), 2.43 (3H, s), 4.28 (2H, q, J=7.5 Hz), 7.38 (1H, d, J_{HF}=3 Hz), 12.2 (1H, br).

A mixture of **15** (7.2 g, 24 mmol), PhSH (3.64 g, 33 mmol), and pyridine (5 ml, 63 mmol) in 30 ml of DME was heated under reflux for 8 h. The solvent was removed, giving a yellow solid that was chromatographed on silica gel (acetone/$CHCl_3$=1/4 v/v) to yield 5.8 g (78%) of **9g** as pale yellow needles.

PMR data (H-6) for 5-alkoxycarbonyl-6-(substituted mercapto)-5-fluoro-5,6-dihydrouracils (R^1S-HFU-COOR, **9**) prepared in a similar manner are listed below. (**9a**): 5.08 (dd, J_{HF}=7.5 Hz). (**9b**): 5.38 (dd, J_{HF}=3 Hz, J=3 Hz). (**9c**): 5.12 (dd, J_{HF}=6 Hz). (**9d**): 4.8—6.2 (m). (**9e**): 5.04 (dd, J_{HF}=12 Hz). (**9f**): 5.12 (dd, J_{HF}=8 Hz). (**9g**): 5.37 (dd, J_{HF}=3 Hz). (**9h**): 5.02 (dd, J_{HF}=7 Hz).

5-Ethoxycarbonyl-5-fluoro-6-piperidino-5,6-dihydrouracil (**10c**)——A solution of **6b**, prepared from **4b** (4.40 g, 20 mmol), Ac_2O (2.5 g, 25 mmol), and 2 ml of pyridine in 20 ml of acetone, was treated with 5 ml of piperidine at room temperature. The reaction mixture was kept at that temperature for 5.5 h. Removal of the solvent gave a yellow oil that was chromatographed on silica gel ($CHCl_3$), giving a white solid. Recrystallization of the crude solid from $CHCl_3$–hexane gave 2.99 g (52%) of **10c** as colorless needles.

6-Benzylamino-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**10g**)——Benzylamine (5.0 g, 46 mmol) was added to a solution of **6b**, prepared from **4b** (4.40 g, 20 mmol), Ac_2O (2.5 g, 25 mmol), and pyridine in 20 ml of acetone. The reaction mixture was kept at room temperature for 3 h. The colorless flakes that separated were collected by filtration, and recrystallized from EtOAc, giving 4.1 g (66%) of **10g** as colorless flakes.

6-Amino-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**10b**)——a) A solution of **10g** (7.5 g, 24 mmol) in 150 ml of dioxane was hydrogenated over 2.0 g of 5% palladium on carbon at atmospheric pressure. The catalyst was removed by filtration, and the filtrate was concentrated, giving a solid that was crystallized from MeOH to yield 2.38 g of **10b** as colorless needles. Another crop of **10b** was obtained from the mother liquor. The total yield of **10b** was 3.51 g (66%).

b) A solution of **6b** (40.24 g, 0.15 mol) in 500 ml of THF was treated with 30 ml of conc. NH_4OH at room temperature for 30 min. The pink precipitate that separated was filtered off and washed with THF. The combined filtrate and washings were concentrated to a volume of about 50 ml, giving a semi-solid that was triturated with 100 ml of EtOH. The colorless prisms that separated were collected by filtration and washed with EtOH giving 23.52 g (70%) of **10b** as colorless prisms. The PMR spectrum of the product coincided with that of **10b** obtained in procedure a).

6-Acetamido-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (**11a**)——A solution of **10b** (12.0 g, 55 mmol), Ac_2O (15 ml), and pyridine (10 ml) in 100 ml of dioxane was allowed to stand at room temperature for 3 h. The mixture was concentrated, giving a yellow syrup that was dissolved in a mixture of 20 ml of MeOH and 20 ml of EtOAc to decompose excess Ac_2O. Removal of the solvent gave a yellow syrup that was chromatographed on silica gel ($CHCl_3$/MeOH=15/1 v/v), giving 9.87 g (61%) of **11a** as colorless needles.

5-Ethoxycarbonyl-5-fluoro-6-hexanoylamino-5,6-dihydrouracil (**11b**)——A solution of **10b** (10.47 g, 48 mmol) in 140 ml of dioxane was added to a mixture of DCC (15.12 g, 73 mmol) and hexanoic acid (8.51 g, 73 mmol) in 100 ml of dioxane. The reaction mixture was allowed to stand at room temperature for 4 h. Dicyclohexylurea was filtered off and the filtrate was concentrated. The resulting syrup was chromatographed on silica gel ($CHCl_3$ and 5% MeOH in $CHCl_3$), giving a white solid. It was recrystallized from ether–hexane giving 8.44 g (46%) of **11b** as colorless needles.

PMR data for 6-(substituted amino) (R^1R^2N-HFU-COOR, **10**) and 6-acylamino (R^3CONH-HFU-COOEt, **11**) derivatives prepared in a similar manner are listed below. (**10a**): 4.53 (dd, J_{HF}=4 Hz). (**10b**): 4.3—4.8 (br d, J_{HF}=12 Hz). (**10c**): 4.52 (dd, J_{HF}=4 Hz). (**10d**): 4.47 (m, J_{HF}=8 Hz). (**10e**): 4.50 (m, J_{HF}=9 Hz). (**10f**): 5.33 (m, J_{HF}=10 Hz). (**10g**): 4.52 (m, J_{HF}=10 Hz). (**10h**): 4.77 (dd, J_{HF}=16 Hz, J=2 Hz). (**11a**): 5.63 (ddd, J_{HF}=6 Hz, J=5 and 9 Hz). (**11b**): 5.7 (m, J_{HF}=6 Hz). (**11c**): 5.7 (m, J_{HF}=6 Hz). (**11d**): 5.87 (m, J_{HF}=4 Hz, J=9 Hz).

5-Carbamoyl-6-ethoxy-5-fluoro-5,6-dihydrouracil (**13**)——A suspension of **2a** (2.10 g, 13 mmol) in 400 ml of AcOH was treated with 1.5 equivalents of F_2 (F_2/N_2=15%) at room temperature with vigorous stirring. The mixture was concentrated, giving **7a** as a colorless oil that was dissolved in 100 ml of EtOH. The solution was heated under reflux for 2 h. Removal of the solvent gave a white solid that was recrystallized from EtOH, giving 1.70 g (56%) of **13** as colorless prisms. mp 224—226°C. PMR: 0.9—1.3 (4.5H, m), 3.3—3.9 (3H, m), 4.78 (1H, m), 7.84 (1H, br), 8.06 (1H, br), 8.75 (1H, br), 10.55 (1H, br). *Anal.* Calcd for $C_7H_{10}FN_3O_4 \cdot 1/2EtOH$: C, 39.67; H, 5.41; N, 17.35. Found: C, 39.44; H, 5.37; N, 17.37.

5-Cyano-6-ethoxy-5-fluoro-5,6-dihydrouracil (**14**)——A suspension of **3** (2.05 g, 15 mmol) in 400 ml of AcOH was treated with 1.5 equivalents of F_2 (F_2/N_2=15%) at room temperature. After removal of the solvent, the resulting colorless syrup was dissolved in 70 ml of EtOH, and the solution was heated under reflux for 2 h. Removal of the solvent gave a pale yellow solid that was chromatographed on silica gel

(acetone/benzene=1/4 v/v), giving a white solid. Recrystallization of the product from EtOAc–benzene gave 1.54 g (51%) of **14** as colorless needles. mp 195—196°C. PMR: 1.22 (3H, t, J=7 Hz), 3.68 (2H, q, J=7 Hz), 5.48 (1H, dd, J_{HF}=2 Hz), 9.4 (1H, br), 11.6 (1H, br). *Anal.* Calcd for $C_7H_8FN_3O_3$: C, 41.44; H, 3.95; N, 20.70. Found: C, 41.11; H, 3.91; N, 20.50.

6-Cyclohexylideneaminooxy-5-ethoxycarbonyl-5-fluoro-5,6-dihydrouracil (12f)——A mixture of **4b** (8.80 g, 40 mmol) and 20 ml of pyridine in 10 ml of acetone was treated with Ac_2O (5.10 g, 50 mmol) at room temperature overnight. Cyclohexanone oxime (9.04 g, 80 mmol) and 10 ml of pyridine were added to the above mixture. The whole mixture was allowed to stand at room temperature for 2 d, then the solvent was removed to leave a yellow solid. The crude product was chromatographed on silica gel (acetone/$CHCl_3$=15%), giving 10.50 g (83%) of **12f** as colorless needles.

PMR data (the H-6) for 5-alkoxycarbonyl-6-alkylideneaminooxy derivatives (R^1R^2C=NO-HFU-COOR, **12**) prepared in a similar manner are listed below. (**12a**): 5.38 (dd, J_{HF}=1 Hz). (**12b**): 5.41 (m). (**12c**): 5.42 (dd, J_{HF}=1 Hz, J=5 Hz). (**12d**): 5.32 (dd, J_{HF}=1 Hz, J=5 Hz). (**12e**): 5.36 (dd, J_{HF}=1 Hz, J=5 Hz). (**12f**): 5.43 (dd, J_{HF}=1 Hz, J=5 Hz). (**12g**): 5.60 (dd, J_{HF}=1 Hz, J=5 Hz). (**12h**): 5.62 (d, J=5 Hz). (**12i**): 5.34 (dd, J_{HF}=1 Hz, J=5 Hz). (**12j**): 5.75 (dd, J_{HF}=0.5 Hz, J=5 Hz). (**12k**): 5.64 (dd, J_{HF}=1 Hz, J=4 Hz). (**12l**): 5.50 (dd, J_{HF}=0.5 Hz, J=5 Hz).

Ethyl 4-Oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16)——Compound **16** was prepared in 91% yield according to the method developed by Ballard and Johnson.[4]

5-Ethoxycarbonyl-5-fluoro-6-hydroxy-5,6-dihydrouracil (4b) from 16——A suspension of finely powdered **16** (20.0 g, 0.1 mol) in 1 l of H_2O was treated with F_2 (F_2/N_2=1/1) at 18—20°C with vigorous stirring. The completion of the reaction was confirmed by the completelioss of UV absorption at 270 nm due to **1b** produced from **16** as a result of oxidative desulfurization. After addition of $CaCO_3$ (117 g) and $NaHSO_3$ (5 g), white precipitates were filtered off through a mat of celite and washed with H_2O. The combined filtrate and washings were evaporated to dryness, giving a white solid. The crude product was dissolved in 50 ml of acetone and the insoluble substances were filtered off. The filtrate was passed through a column of alumina (Woelm, neutral; 50 g), giving a yellow solid. Washing of the solid with EtOAc gave 7.49 g of **4b** as a white solid. The combined washings were evaporated to dryness and the residue was chromatographed on silica gel ($CHCl_3$/EtOAc=2/1 and 1/1), giving 4.10 g of **4b** as a white solid. The total yield of **4b** was 11.59 g (52%). The physicochemical data were identical with those of the authentic sample.

Acknowledgement We are grateful to Dr. K. Morita of this Division for his encouragement throughout this work. We thank Drs. Y. Kozai and K. Konishi for testing the biological activities of our compounds. Thanks are also due to the members of this Division for elemental analyses.

References and Notes

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