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5-Fluorouracil Derivatives. X.[1] Synthesis and Antitumor Activities of α-Alkoxyalkyl-5-fluorouracils

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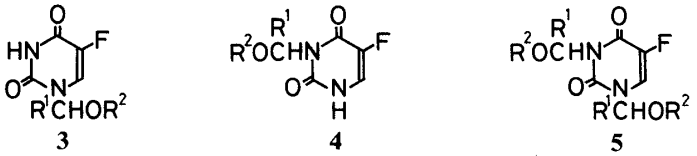
With the aim of diminishing the toxicity of 5-fluorouracil (**1**) and obtaining biologically active derivatives of **1** suitable for oral administration, α-alkoxyalkyl groups were introduced at the 1-, 3- and 1,3-positions of **1**. Alkoxyalkylation can be effected by four methods: (i) reaction of 1-alkoxyalkyl chloride (**2**) with **1**, (ii) reaction of acetal with 2,4-bis(trimethylsiloxy)-5-fluoropyrimidine, (iii) addition reaction of α-unsaturated ether with **1**, (iv) aminolysis of 1-alkylthiocarbonyl-3-(1-alkoxyalkyl)-5-fluorouracil. The toxicity of the products was less than that of **1**, and some of these compounds showed moderate antitumor activity against L-1210 leukemia.

Keywords——5-fluorouracil; α-alkoxyalkyl-5-fluorouracil; antitumor agent; 1-alkylthiocarbonyl-3-(1-alkoxyalkyl)-5-fluorouracil; 2,4-bis(trimethylsiloxy)-5-fluoropyrimidine

5-Fluorouracil (**1**) is well known to have strong antitumor activity, but its toxicity limits the use of **1** as a practical antitumor agent for human beings. With the aim of diminishing the toxicity of **1** and obtaining biologically active derivatives of **1** suitable for oral administration, we have prepared various modified 5-fluorouracil derivatives, such as 1-carbamoyl-,[2] 1-acyloxyalkyl-,[3] 1-alkylthiocarbamoyl-,[1] 5-fluorouracils and so on. We also prepared *N*-alkyl-substituted 5-fluorouracils, but found that these materials have no antitumor activity, presumably because the bond between the 1-nitrogen of **1** and the α-carbon of the alkyl group in such compounds is too strong to be split *in vivo*. If oxygen is introduced at the α-position to the alkyl group, the bond between nitrogen and carbon may become labile under hydrolytic conditions. Therefore 1-acyloxyalkyl, 1-alkoxyalkyl, and tetrahydro-2-furyl groups were chosen for study.

α-Alkoxyalkyl-5-fluorouracils, such as 1-methoxymethyl,[4] 1-ethoxymethyl,[5] 1-(tetrahydro-2-furyl),[6] and 1-(tetrahydro-2-pyranyl)[6]-5-fluorouracils have been synthesized by several groups. We also have reported the synthesis of alkoxyalkyl derivatives briefly in a patent.[7] In this paper, we wish to present details of newer synthetic methods for 1-(1-alkoxyalkyl)-5-fluorouracils (**3**), 3-(1-alkoxyalkyl)-5-fluorouracils (**4**) and 1,3-bis(1-alkoxyalkyl)-5-fluorouracils (**5**) and of the antitumor activities of the products. A convenient method to determine the position of substituents is also described.

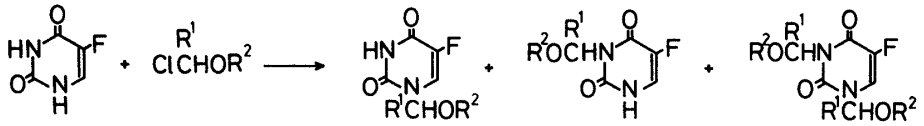


3 **4** **5**

Chart 1

The 1-alkoxyalkyl-substituted 5-fluorouracils and their cyclic ether derivatives were obtained by one of the following four methods.

Method 1. Reaction of **1** with 1-Alkoxylalkyl Chloride (**2**) to Afford **3**, **4** and **5**: This type

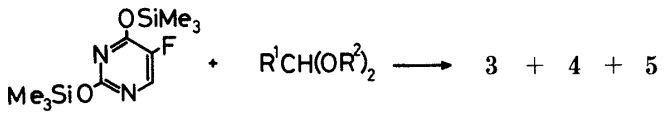


1 **2** **3** **4** **5**

Chart 2

of reaction was carried out in the presence of a base such as triethylamine, sodium carbonate or sodium hydride, in a polar solvent such as *N*,*N*-dimethylacetamide or pyridine. When equimolar amounts of **1** and **2** were reacted, the reaction mixture consisted mostly of **3** along with small amounts of **4** and **5**. As the molar ratio of **2** to **1** was increased, the yields of **4** and **5** increased.

Method 2. Reaction of 2,4-Bis(trimethylsiloxy)-5-fluoropyrimidine (**6**) with Acetal (**7**) to Afford **3**, **4** and **5**: This reaction was carried out in the presence of a Friedel–Crafts type

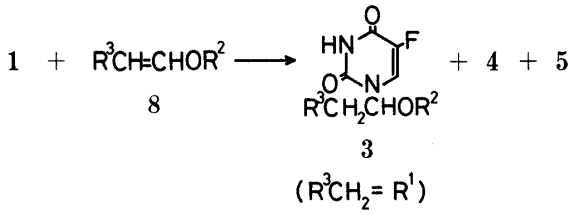


6 **7**

Chart 3

catalyst such as tin (IV) chloride, titanium (IV) chloride, or aluminium chloride. Compound **3** was the main product in most cases, but in the case of diethoxymethane, **3**, **4** and **5** were obtained in almost equal amounts.

Method 3. Reaction of **1** with α-Unsaturated Ether (**8**) to Afford **3**, **4** and **5**: The addition



8 **3** ($R^3CH_2 = R^1$)

Chart 4

reaction of an α-unsaturated ether such as 2,3-dihydrofuran with 6-chloropurine is known to proceed easily in the presence of acidic catalysts.[8] This method was applied to the synthesis of alkoxyalkyl-substituted 5-fluorouracils. However, the reaction of **1** with α-unsaturated ether afforded the desired adducts **3**, **4** and **5** in very low yields, presumably because **1** has no basic character, in contrast to a purine base, and cationic polymerization of α-unsaturated ether predominates over the addition reaction in a neutral solvent. A basic solvent might prevent this cationic polymerization. Indeed, when pyridine was used as a solvent the addition reaction of **1** with α-unsaturated ether became predominant over polymerization of the ether even in the presence of a cationic catalyst.

Method 4. Aminolysis of 1-Alkylthiocarbonyl-3-(1-alkoxyalkyl)-5-fluorouracil (**10**) to Afford **4**: The reaction of 1-alkylthiocarbonyl-5-fluorouracil (**9**)[9] and **2** afforded **10**, and **10** was partially decomposed with isopropylamine at room temperature in a short period of time

TABLE I. 1-, 3-, and 1,3-Bis-(1-alkoxyalkyl)-5-fluorouracils

Run No.	Compound No.	Substituents	Synthetic method	Yield (%)	mp (°C)	NMR δ	Formula	Analysis (%) Calcd (Found)		
								C	H	N
1	**3a**	CH_2OCH_3	1	11.4	132	3.42 (3H, s, OCH_2), 5.12 (3H, s, CH_2), 7.42 (1H, d, C_6-H), 9.88 (1H, br, NH)	$C_6H_7FN_2O_3$	41.38 (40.99	4.02 4.02	16.09 15.84)
1	**4a**	CH_2OCH_3	1	9.2	Oil	3.23 (3H, s, CH_3), 5.16 (2H, s, CH_2), 7.88 (1H, t, C_6-H), 12.1 (1H, br, NH)	$C_6H_7FN_2O_3$	41.38 (40.98	4.02 4.29	16.09 15.69)
1	**5a**	CH_2OCH_3	1	19.4	Oil	3.38 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 5.11 (2H, s, CH_2), 7.37 (1H, d, C_6-H)	$C_8H_{11}FN_2O_4$	44.04 (43.68	5.05 4.82	12.84 14.89)
2	**3b**	$CH_2OC_2H_5$	2	14.7	116[5]	1.26 (3H, t, CH_3), 3.64 (2H, q, CH_2), 5.16 (2H, s, OCH_2N), 7.43 (1H, d, C_6-H), 9.89 (1H, br, NH)	$C_7H_9FN_2O_3$	44.68 (44.98	4.82 4.99	14.89 14.89)
2	**4b**	$CH_2OC_2H_5$	2	9.2	120	1.22 (3H, t, CH_3), 3.67 (2H, t, CH_3), 5.42 (2H, s, OCH_2N), 7.37 (1H, t, C_6-H), 10.02 (1H, br, NH)				
2	**5b**	$CH_2OC_2H_5$	2	14.2	Oil	1.14 (3H, t, CH_3), 1.18 (3H, t, CH_3), 3.58 (2H, q, CH_2), 3.62 (2H, q, CH_2), 5.21 (2H, s, N_1OCH_2), 5.37 (2H, s, N_3OCH_2), 7.78 (1H, d, CH)	$C_{10}H_{15}FN_2O_4$	48.78 (49.97	6.14 6.27	11.38 11.22)
3	**3c**	CH_3 $CHOCH_3$	2	61.8	174	1.37 (3H, d, CH_3), 3.22 (3H, s, OCH_3), 5.67 (1H, q, CH), 8.02 (1H, d, C_6-H), 11.90 (1H, br, NH)	$C_7H_9FN_2O_3$	44.68 (44.38	4.82 4.79	14.89 14.59)
4	**3d**	CH_3 $CHOC_2H_5$	3	58.8	124	1.23 (3H, t, CH_2CH_3), 1.45 (3H, d, CH_3), 3.58 (2H, q, CH_2), 5.93 (1H, dq, CH), 7.55 (1H, d, C_6-H), 10.25 (1H, br, NH)	$C_8H_{11}FN_2O_3$	47.52 (47.22	5.48 5.67	13.86 14.14)
4	**4d**	CH_3 $CHOC_4H_9$	3	10.8	154—155	1.10 (3H, t, CH_2CH_3), 1.66 (3H, d, CH_3), 3.45 (2H, q, CH_2), 6.09 (1H, q, CH), 7.85 (1H, t, C_6-H), 11.02 (1H, d, NH)	$C_8H_{11}FN_2O_3$	47.52 (47.22	5.48 5.72	13.86 13.92)

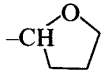
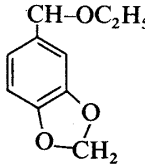
5	**3e**	CH_3 $CHOC_4H_9$	3	49.3	61	0.94 (3H, t, CH_3), 1.46 (7H, m, CH_2, $CHCH_3$), 3.48 (2H, t, CH_2), 5.92 (1H, m, CH), 7.52 (1H, d, C_6-H)	$C_{10}H_{15}FN_2O_3$	52.12 (51.87	6.57 6.36	12.17 12.11)
5	**4e**	CH_3 $CHOC_4H_9$	3	5.0	Oil	1.10 (3H, t, CH_3), 1.65 (7H, m, CH_2, $CHCH_3$), 3.45 (2H, t, OCH_2), 6.08 (1H, q, $CHCH_3$), 7.90 (1H, t, C_6-H), 11.0 (1H, d, N_1-H)	$C_{10}H_{15}FN_2O_3$	52.12 (51.93	6.57 6.29	12.17 11.95)
5	**5e**	CH_3 $CHOC_4H_9$	3	17.0	Oil	0.93 (6H, m, CH_3), 1.2—1.9 (14H, m, CH_2CHCH_3), 3.50 (4H, m, OCH_2), 5.7—6.5 (2H, m, CH), 7.48 (1H, d, C_6-H)	$C_{16}H_{27}FN_2O_4$	58.16 (58.49	8.28 8.50	8.48 8.19)
6	**3f**		1	75	167[6]	1.03—2.96 (4H, br), 3.32—4.36 (2H, m), 5.47—6.16 (1H, br, OCH), 7.37 (1H, d, J=7 Hz, C_6-H), 10.60 (1H, br, N_3-H)				
7	**4f**		4	100	128[12,13]	1.68—2.86 (4H, m), 4.25—3.90 (2H, m), 7.13 (1H, m, C_6-H), 9.49—10.14 (1H, br, N_1-H)				
6	**5f**		1	80	111[14]					
7	**3g**		3	65	172	1.70 (6H, m, CH_2), 3.5—4.4 (2H, m, OCH_2), 5.65 (1H, m, OCH), 7.56 (1H, d, C_6-H), 9.25 (1H, br, NH)	$C_9H_{11}FN_2O_3$	50.47 (50.16	5.18 5.36	13.03 12.77)
8	**3h**	$CHOC_2H_5$ C_6H_5	2	60	124	1.37 (3H, t, CH_3), 3.78 (2H, q, CH_2), 6.90 (1H, s, CH), 7.75 (1H, d, C_6-H), 6.80 (1H, d, C_6-H), 7.41 (5H, s, C_6H_5)	$C_{13}H_{13}FN_2O_3$	59.07 (59.32	4.96 5.07	10.60 10.89)
9	**3i**	CH_3 $CHOCH_2CHOH$ C_6H_5	2	11	157—158	1.30 (3H, br, CH_3), 3.75 (1H, br, CH), 4.30 (2H, br, CH_2), 6.80 (1H, br, CH), 7.20 (1H, br, C_6-H), 7.30 (5H, s, C_6H_5)	$C_{14}H_{15}FN_2O_4$	57.14 (57.44	5.14 4.87	9.52 9.82)
10	**3j**	$CH–OC_2H_5$ C_6H_4-*p*-OEt	2	12	163	1.50 (6H, s, CH_3, CH_3), 3.9—4.1 (5H, m, CH_2, CH_2, CH), 7.0 (2H, aromatic), 7.80 (3H, aromatic+C_6-H)	$C_{16}H_{19}FN_2O_5$	56.80 (56.95	5.66 5.36	8.28 7.92)
11	**3k**		2	44	138	1.30 (3H, t, CH_3), 3.68 (2H, q, CH_2), 5.95 (2H, s, CH_2), 5.68—6.85 (3H, C_6H_3), 7.12 (1H, d, C_6-H), 11.50 (1H, br, N_3-H)	$C_{15}H_{15}FN_2O_5$	55.90 (55.55	4.69 4.32	8.69 8.73)
12	**3l**	$CH–OCH_2CH_2OCOCH_3$ C_6H_5	2	22	136	2.05 (3H, s, CH_3), 4.10—3.80 (2H, m, CH_2O), 4.45—4.25 (2H, m, CH_2C), 6.92 (1H, s, CH), 7.30 (1H, d, C_6-H), 7.43 (5H, s, C_6H_5)	$C_{15}H_{15}FN_2O_5$	55.90 (55.87	4.69 4.72	8.69 8.78)

TABLE II. Antitumor Activity of 5-FU Derivatives in the L-1210 Leukemia System

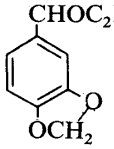
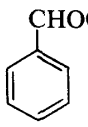
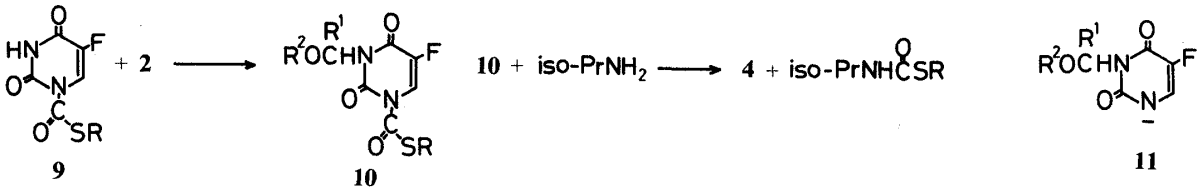
Compound No.	R	Dose (mg/kg/d)		ILS (%)
3a	CH_2OCH_3	*i.p.*	30	6
		i.p.	100	8
		p.o.	100	2
4a	CH_2OCH_3	*i.p.*	30	13
		i.p.	100	18
		p.o.	100	13
3b	$CH_2OC_2H_5$	*i.p.*	100	24
		p.o.	100	25
4b	$CH_2OC_2H_5$	*i.p.*	100	14
		p.o.	100	16
5b	$CH_2OC_2H_5$	*i.p.*	100	0
		p.o.	100	0
3c	CH_3 $CHOCH_3$	*i.p.*	30	5
		i.p.	100	17
		p.o.	100	8
3d	CH_3 $CHOC_2H_5$	*i.p.*	30	15
		i.p.	100	20
		p.o.	100	21
3e	CH_3 $CHOC_4H_9$	*i.p.*	100	0
		p.o.	100	0
3f		*i.p.*	30	0
		i.p.	70	9
		i.p.	100	34
		i.p.	150	15
		i.p.	200	−2
		p.o.	30	0
		p.o.	70	15
		p.o.	100	31
		p.o.	150	12
		p.o.	200	16
4f		*i.p.*	30	5
		i.p.	100	36
		i.p.	300	22
		p.o.	30	8
		p.o.	100	36
		p.o.	300	38
5f		*i.p.*	30	9
		i.p.	100	30
		i.p.	300	46
		p.o.	100	8
		p.o.	300	40
3g		*i.p.*	100	9
3h	C_6H_5 $CHOC_2H_5$	*p.o.*	30	2
		p.o.	100	4
3i	C_6H_5 CH_3 $CHOCH_2CHOH$	*p.o.*	30	0
3j	$C_6H_4OEt(p)$ $CHOCH_2CHOH$ CH_3	*p.o.*	100	−4
3k	$CHOC_2H_5$ 	*p.o.*	100	18

TABLE II. Continued

Compound No.	R	Dose (mg/kg/d)		ILS (%)
3l		*p.o.*	30	−4
5-FU	H	*i.p.*	1	38
		i.p.	10	73
		i.p.	30	60
		p.o.	10	9
		p.o.	30	33
		p.o.	70	15



9 **10** **11**

Chart 5 Chart 6

to afford **4**.

This is the most suitable method among the present four procedures to obtain **4**, which is rather difficult to obtain in good yield by the other three methods. α-Alkoxyalkyl-5-fluorouracils obtained by these four methods are shown in Table I.

The structure of the alkoxyalkylation products **3**, **4** and **5** were confirmed by elemental analysis, and infrared (IR), nuclear magnetic resonance (NMR) and ultraviolet (UV) spectral analyses.

Thus, the UV spectra of uracils having a substituent at position 1, **3** and **5**, showed no shifts between acidic and alkaline media, whereas uracils having no substituent at position 1 showed a bathochromic shift in NaOH solution, because of the extended conjugation in structure **11**.

The NMR spectra also gave a clear-cut distinction between **3** and **5**, in which N-1 is substituted, and **4** in which N-1 is not substituted. The ^{1}H-NMR spectra of 1-methoxymethyl-5-fluorouracil (**3a**) and 1,3-dimethoxymethyl-5-fluorouracil (**5a**) showed the presence of a sharp doublet ($J=6$ Hz) at $\delta=7.4$ due to C_6-H coupled with F. The ^{1}H-NMR spectrum of 3-methoxymethyl-5-fluorouracil (**4a**) showed the presence of a triplet-like doublet of doublets ($J=6$ Hz) at $\delta=7.9$ assignable to C_6-H double-coupled with F and N_1-H. In general, C_6-H in 3-substituted 5-fluorouracils dissolved in $CDCl_3$ shows a broad triplet- or broad singlet-like signal. Such a signal is changed to a sharp doublet on adding D_2O or decoupling N_1-H. These observations provide a general rule for deciding the position of the substituent on 5-fluorouracil as follows. a) A sharp doublet due to C_6-H at around $\delta=7$—8 indicates that 5-fluorouracil has a substituent at the N-1 position, that is, the compound is a 1-monosubstituted or 1,3-disubstituted 5-fluorouracil. b) A broad triplet due to C_6-H at around $\delta=7$—8 indicates that 5-fluorouracil has no substituent at the N-1 position, that is, the compound is 3-substituted.

The antitumor activity of these 17 compounds was tested against L-1210 leukemia in mice,[10] and the results (increase in life span) are shown in Table II. Many of the compounds tested (except **3a**, **3d**, **3e**, **3h**, **3i** and **3l**) showed moderate antitumor activity, though the

activity is not so strong as that of 1-carbamoyl-5-fluorouracils.[11] In an oral administration test, the most active compound was **4f**. This compound seems to be better than **3f**, which is the widely used antitumor agent "Tegafur." As regards the position of the substituent, 3-substituted compounds are generally better than 1-substituted compounds, whereas, when the ethoxymethyl or 1-ethoxyethyl group was used as an N-substituent group, 1-substituted compounds are better than 3-substituted compounds.

Experimental

The melting points were recorded on a Büchi melting-point apparatus. The ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 (E. Merck) on JEOL 60HL and JEOL JNM-FX100S apparatus. The IR spectra were obtained on a JASCO IR-A-1 apparatus.

Typical Procedure for Method 1. 1-Methoxymethyl-5-fluorouracil (3a), 3-Methoxymethyl-5-fluorouracil (4a) and 1,3-Bis(methoxymethyl)-5-fluorouracil (5a)——Potassium carbonate (2.8 g, 0.02 mol) was added to a solution of **1** (2.6 g, 0.02 mol) in *N*,*N*-dimethylacetamide (20 ml) to afford a white milky suspension. A solution of chloromethyl methyl ether (5.9 g, 0.07 mol) in *N*,*N*-dimethylacetamide (10 ml) was added and the reaction mixture was stirred for 5 h at 30 °C, then the solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using benzene–ethyl acetate (3 : 1) as a solvent to afford three compounds. The first fraction gave **5a** (0.80 g, 19.4%): oil. *Rf*: 0.59 (silica gel–ethyl acetate). IR (neat), 1742, 1700 cm^{-1} (C=O); NMR and elemental analysis data are shown in Table I. UV, λ_{max} 269 (in 0.1 N HCl and in pure water), 266 (in 0.1 N NaOH). The second fraction gave **3a** (0.40 g, 11.4%): mp, 132 °C. *Rf*: 0.437 (silica gel–ethyl acetate); IR (KBr), 1720 cm^{-1} (C=O); UV, λ_{max} 267 (in 0.1 N HCl, pure water, 0.1 N NaOH). The third fraction gave **4a** (0.32 g, 9.2%): viscous oil. *Rf*: 0.406 (silica gel–ethyl acetate); IR (neat), 1740, 1670 cm^{-1}; UV, λ_{max} 268 (in 0.1 N HCl and in pure water), 300 (in 0.1 N NaOH).

Typical Procedure for Method 2. 1-(1-Methoxyethyl)-5-fluorouracil (3c)——A solution of tin (IV) chloride (1.30 g, 0.005 mol) in chloroform (5 ml) was added to a mixture of 2,4-bis(trimethylsiloxy)-5-fluoropyrimidine (2.06 g, 0.0075 mol), acetaldehyde dimethyl acetal (0.81 g, 0.009 mol) and chloroform (15 ml) over a period of 1 h at room temperature. Ten minutes after the end of the addition, the chloroform was evaporated off, and the residue was extracted with water (25 ml) four times. Aqueous extracts were treated with active carbon, and then extracted with chloroform (50 ml) three times. The organic layer was dried and evaporated to afford **14** (0.87 g, 61.8%): mp. 174 °C; IR, 3400, 1715 (s), 1690, 1668, 1472, 1338, 1257 (s), 1105, 1050, 875 cm^{-1}.

The Reaction of 2,4-Bis(trimethylsiloxy)-5-fluoropyrimidine with Diethoxymethane——Tin (VI) chloride (10.0 g, 0.038 mol) was added to a mixture of 2,4-bis(trimethylsiloxy)-5-fluoropyrimidine (23.88 g, 0.087 mol), diethoxymethane (9.06 g, 0.087 mol) and chloroform (100 ml) at room temperature over a period of 20 min. The reaction mixture was concentrated under reduced pressure. Chloroform (100 ml) and water (100 ml) were added to the residue and the chloroform layer was separated. The water layer was washed with chloroform (100 ml) three times, and the combined chloroform layer was dried and evaporated. The residue was purified by column chromatography on silica gel using benzene–ethyl acetate (9 : 1) as a solvent to afford three compounds.

The first fraction gave **3b** (3.04 g, 14.2%): oil. *Rf*: 0.71 (silica gel–ethyl acetate); IR (neat), 3600, 3090, 3000, 2955, 2910, 1748, 1710, 1690, 1680, 1482, 1373 cm^{-1}.

The second fraction gave **4b** (2.41 g, 14.7%): mp 116 °C. *Rf*: 0.51 (silica gel–ethyl acetate). IR (KBr), 3400, 3160, 3060, 1720, 1704, 1695, 1660, 1464, 1340, 1327, 1258, 1227, 1205, 1140, 1118, 1083 cm^{-1}.

The third fraction gave **5b** (1.51 g, 9.2%): mp 120 °C. *Rf*: 0.39 (silica gel–ethyl acetate). IR (KBr), 3600, 3095, 3000, 2955, 2910, 1748, 1711, 1690, 1680, 1482, 1375, 1362, 1280, 1261, 1176, 1118, 1068, 1050 cm^{-1}.

Typical Procedure for Method 3. 1-(α-Ethoxyethyl)-5-fluorouracil (3d) and 3-(1-Ethoxyethyl)-5-fluorouracil (4d)——A mixture of **1** (6.5 g, 0.05 mol), ethyl vinyl ether (5.41 g, 0.075 mol) and pyridine (40 ml) was heated at 60 °C and then titanium (IV) chloride (0.5 g) was added. The reaction mixture was heated for 2 h at reflux. The products were extracted into chloroform after the removal of the solvent *in vacuo*. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a viscous oil, which was chromatographed on a silica gel column with benzene–ethyl acetate (3 : 1) as a solvent.

3d (5.85 g, 58.8%) was obtained from the first eluate.

This compound was identical with that obtained from 2,4-bis(trimethylsiloxy)-5-fluoropyrimidine and acetaldehyde diethyl acetal.

4d (1.06 g, 10.6%) was obtained from the second eluate: mp 154—155 °C. *Rf*: 0.37 (silica gel–ethyl acetate); IR (KBr), 3400, 3240, 3160, 3110, 2970, 1715, 1655 (s), 1375, 1250 (s), 1180, 1122, 895 cm^{-1}.

1-(1-Butoxyethyl)-5-fluorouracil (3e), 3-(1-Butoxyethyl)-5-fluorouracil (4e) and 1,3-Bis(1-butoxyethyl)-5-fluorouracil (5e)——Aluminium chloride (0.5 g) was added to a mixture of **1** (6.5 g, 0.05 mol) and butyl vinyl ether (7.5 g, 0.075 mol) at 80 °C, and the whole was heated at 110 °C for 1 h. Pyridine was distilled off and chloroform

(200 ml) and water (100 ml) were added. The aqueous layer was washed with chloroform (50 ml) three times. The combined chloroform extracts were washed with water (30 ml) and then evaporated. The residue was purified to afford three compounds by column chromatography on silica gel using benzene–ethyl acetate (1 : 1) as a solvent. The first fraction gave **5e** (2.80 g, 17.0%), viscous oil, IR (neat), 2960, 2870, 1720, 1685, 1660 (s), 1460, 1375, 1270 (s), 1105, 760 cm^{-1}.

The second fraction gave **3e** (5.68 g, 49.3%): mp 60—61 °C. IR (KBr), 3170, 3040, 2920, 1719 (s), 1685, 1663, 1465, 1378, 1242 (s), 1120, 870 cm^{-1}.

Synthesis of 1-(Octylthio)carbonyl-3-(tetrahydrofuryl)-5-fluorouracil (10)[9]——Tetrahydrofuran (THF, 12 ml) and sulfuryl chloride (0.54 g, 4 mmol) were stirred together for 15 min at room temp. This solution and a solution of triethylamine (0.81 g, 8 mmol) in THF (2 ml) were added to a solution of 1-octylthiocarbonyl-5-fluorouracil (**9**) (0.605 g, 2 mmol) in THF (2 ml) and the whole was stirred for 1 h at room temperature. CH_2Cl_2 (30 ml) was added to the reaction mixture and the solution was washed twice with H_2O (20 ml), then dried over Na_2SO_4, and the CH_2Cl_2 was evaporated off. Purification of the residue by column chromatography (SiO_2, C_6H_{14}–EtOAc, 5 : 1) afforded **10** (687 mg, 92%): mp 64—65 °C. IR (Nujol), 1730 (C=O), 1700, 1680, 1640 cm^{-1}. NMR ($CDCl_3$): 0.58—2.65 (19H, br, CH_3+CH), 2.94 (2H, t, J=6 Hz, SCH_2), 3.67—4.47 (2H, m, OCH_2), 6.56 (1H, t, J=6 Hz, OCH), 8.17 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{17}H_{25}FN_2O_4S$: C, 54.82; H, 6.49; N, 7.52. Found: C, 54.67; H, 6.66; N, 7.27.

Typical Procedure for Method 4. 3-(2-Tetrahydrofuryl)-5-fluorouracil (4f)——A mixture of **10** (298 mg, 0.8 mmol) and isopropylamine (47 mg, 0.8 mmol) in ether (8 ml) was stirred for 10 min at room temperature. After evaporation of the ether, the residue was purified by PTLC (SiO_2; EtOAc–CH_2Cl_2, 1 : 1) to afford **4f** (161 mg, quant): mp, (C_6H_6–C_6H_{14} 1 : 1) 128 °C (lit.[12] 129 °C). IR, 1720 (C=O), 1700, 1640, 1630, 1620, 1595 cm^{-1}.

Animals and Tumor System——Male BDF_1 mice weighing 20±2 g were used. Six mice in each group, either test or control, were implanted intraperitoneally with 1×10^5 cells of L1210 leukemia. The compound to be tested was injected intraperitoneally or administered orally once daily for 5 d, starting 24 h after tumor implantation.

Evaluation of Antitumor Activity——The increase in life span was calculated by using the following formula:

$$\text{ILS (increase of life span) } (\%) = (T - C)/C \times 100$$

where T is the average number of days before death in the test group and C is the average number of days before death in the control group.[10]

References and Notes

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