[Chem. Pharm. Bull.]
35(10)4137—4143(1987)

A Facile Method for Synthesis of *N*-Acyloxymethyl-5-fluorouracils, as a Class of Antitumor Agents¹⁾

SUHAIL AHMAD,^{a,2)} SHOICHIRO OZAKI,^{*,a} TOSHIO NAGASE,^a
MASAAKI IIGO,^b REIKO TOKUZEN,^b and AKIO HOSHI^b

Faculty of Engineering, Ehime University,^a Bunkyo-cho, Matsuyama 790,
Japan and National Cancer Center Research Institute,^b
Tsukiji, Chuo-ku, Tokyo 104, Japan

(Received March 18, 1987)

Antitumor-active derivatives of 5-fluorouracil were prepared *via* a new method by introducing an acyloxymethyl group at the 1-, 3-, or 1,3-position(s). These derivatives were obtained by condensing 1,3-bis(hydroxymethyl)-5-fluorouracil with various short-/long-chain carboxylic acids or their derivatives, in the presence of dicyclohexylcarbodiimide and a catalytic amount of *N,N*-dimethylaminopyridine. Some of the derivatives showed strong antitumor activity against the leukemia L1210 system when administered orally.

Keywords—5-fluorouracil; 1,3-bis(hydroxymethyl)-5-fluorouracil; acyloxymethyl-5-fluorouracil; dicyclohexylcarbodiimide; antitumor agent; 1-undecenoyloxymethyl-5-fluorouracil

Various types of 5-fluorouracil derivatives have been used as antitumor agents in recent years. For example, 1,3-bis(hydroxyalkyl)-5-fluorouracils (Fig. 1) have been described as anticancer compounds³⁾ and long-chain alkenoyl-5-fluorouracils as blood platelet aggregation and neoplasm inhibitors.⁴⁾ Buur *et al.*⁵⁾ have also studied various *N*-acyloxymethyl-5-fluorouracils to assess their potential as prodrugs with the aim of enhancing the delivery characteristics of the parent drug, 5-fluorouracil. In the course of our synthetic studies on 5-fluorouracil derivatives, aimed at obtaining more biologically active and less toxic compounds than 5-fluorouracil itself, we have synthesized and tested a series of compounds such as 1-carbamoyl-,⁶⁾ 1-acyloxyalkyl-,⁷⁾ 1-alkylthiocarbonyl-,⁸⁾ and α -alkoxyalkyl-5-fluorouracils⁹⁾ (Fig. 2). Among our synthesized compounds, 1-hexylcarbamoyl-5-fluorouracil (HCFU, Mifuro) is in clinical use in Japan. HCFU is remarkably effective on colorectal, lung, breast, and gastric cancers,^{10–12)} but its side effects, such as hot sensation and pollakiuria syndrome, mean that it is still desirable to develop a better drug.

During our previous studies it was found that *N*-acyloxyalkyl-5-fluorouracil derivatives showed very strong antitumor activity. Among them the compounds having an acyloxymethyl group at the N-1 position were markedly active. These results prompted us to develop a new and convenient method for the preparation of 1-acyloxymethyl-5-fluorouracils.

These acyloxymethyl derivatives are known⁵⁾ to be easily hydrolyzed under slightly basic conditions to afford 5-fluorouracil (1) in quantitative yield *via* an unstable *N*-hydroxymethyl-

Fig. 1

Fig. 2

5-fluorouracil intermediate. Consequently these compounds are thought to be suitable for use as antitumor drugs because the generation of **1** is necessary for antitumor activity after administration of the drug. It has also been reported⁵⁾ that the hydrolytic rate of acyloxymethyl-5-fluorouracil derivatives increases in the presence of human plasma or rat liver homogenate, which further suggests the utility of these derivatives as prodrugs. These derivatives have high lipophilicity, which is the predominant factor controlling the permeability of the drug through the biomembrane. It may also be possible to obtain prodrugs with various physicochemical properties such as lipophilicity just by varying the acyl part of these derivatives.

Keeping these points in mind, we have been studying the syntheses of *N*-acyloxymethyl-5-fluorouracil derivatives, especially those with an acyloxymethyl group at the N-1 position. Now we wish to describe a new synthesis of *N*-acyloxymethyl-5-fluorouracil derivatives and the antitumor activity of these compounds against the leukemia L1210 system.

Results and Discussion

This method of acyloxymethylation involves a two-step process (Chart 1). The first step was the preparation of 1,3-bis(hydroxymethyl)-5-fluorouracil (**2**). Compound **1** was heated with formalin for about 45 min below 70 °C to give **2** in quantitative yield. In the second step the various carboxylic acids (**3a—m**) were coupled with **2** in the presence of dicyclohexylcar-

Chart 1

bodiimide (DCC) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP). The choice of solvent depended upon the solubility of the carboxylic acids (**3**). In most cases, CH₃CN was used. In a few cases, mixed solvents were used. The reaction was usually completed in 4–6 h with stirring at room temperature, but in some cases, the reaction was slow at room temperature. In these cases, raising the temperature (40 °C) and increasing the reaction time improved the yield.

The advantage of the present method over the previous one⁷⁾ is that long-chain carboxylic acids could be condensed easily with **2** even in the presence of many functional groups such as hydroxyl and keto groups, oxathiolane and dithiolane, and a carbon–carbon double bond in the carbon chain. Since the reaction conditions were very mild, these functionalities remained intact. The previous method for the preparation and the purification of α -chloroalkyl carboxylates of medium- and long-chain acids was troublesome, especially in

TABLE I. Synthesis of *N*-Acyloxymethyl-5-fluorouracil Derivatives

	Carboxylic acid	Conditions	Product	Yield (%)	mp (°C)
3a	CH ₂ =CHCH ₂ COOH 3-Butenoic acid	CH ₃ CN 0—r.t., 4 h	4a	59	87—88
3b	CH ₃ CH ₂ CH=CHCH ₂ COOH 3-Hexenoic acid	CH ₃ CN r.t., 4 h	4b	75	88
3c	CH ₃ (CH ₂) ₄ CH=CHCH ₂ COOH 3-Nonenoic acid	CH ₃ CN r.t., 4 h	4c	65	92—93
3d	CH ₂ =CH(CH ₂) ₈ COOH 10-Undecenoic acid	CH ₃ CN r.t., 4 h	4d 5d	79 Trace	100 67—68
			6d	11	Liquid
3e	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ COOH Oleic acid	CH ₃ CN r.t., 4 h	4e 6e	61 11	91 Liquid
3f	CH ₃ (CH ₂) ₃ (CH ₂ CH=CH) ₂ (CH ₂) ₇ COOH Linoleic acid	CH ₃ CN r.t., 4 h	4f	65	Semisolid
3g	CH ₃ (CH ₂) ₁₆ COOH Stearic acid	DMF+CH ₂ Cl ₂ r.t.—40 °C, 24 h	4g	54	114
3h	C ₆ H ₅ CH ₂ CONHCH ₂ COOH <i>N</i> -Carbobenzyloxycysteine	CH ₃ CN r.t., 4 h	4h	65	128—129
3i	HOOC(CH ₂) ₈ COOH Sebacic acid	CH ₃ CN r.t., 6 h	4i	51	177—178
3j	CH ₃ (CH ₂) ₅ CH(OH)(CH ₂) ₁₀ COOH 12-Hydroxystearic acid	DMF+CH ₃ CN r.t.—40 °C, 24 h	4j	49	98
3k	CH ₃ CO(CH ₂) ₂ COOH Levulinic acid	CH ₃ CN r.t., 4 h	4k 6k	66 10	119 Liquid
3l	CH ₃ -C-(CH ₂) ₂ COOH	CH ₃ CN r.t., 2 h	4l	75	114
	4,4-(Ethyleneoxothio)- pentanoic acid				
3m	CH ₃ -C-(CH ₂) ₂ COOH	CH ₃ CN r.t., 2 h	4m	79	142
	4,4-(Ethylenedithio)- pentanoic acid				

r.t., room temperature.

the case of carboxylic acids having different types of functional groups in the chain.

A further advantage of our method is that 1-substituted derivatives (**4**) were obtained as a major product and in some cases as the sole product. The yield of **4** varied in the range of 49—79% and was maximum when 1.1—1.2 eq of **3** was used. A very small amount of bis product was formed, because there is a large difference in reactivity between the two *N*-hydroxymethyl groups of **2**. Since the hydroxymethyl group was very unstable and hydrolyzed easily to leave the free N-H group, we obtained 1-acyloxymethyl-5-fluorouracil as a major product after work-up of the reaction mixture.

The *N*-acyloxymethylated products (**4**, **5**, and **6**) were obtained in a pure state and gave elemental analysis, infrared (IR), and nuclear magnetic resonance (NMR) data (detailed in Table II) in agreement with their proposed structures. The 3-substituted products were characterized by the NMR and IR data as described earlier.⁹⁾

The antitumor activity of thirteen compounds against the leukemia L1210 system was examined, and the results are summarized in Table III. We found that 5-fluorouracil derivatives having a 10-undecenoyloxymethyl group at the N-1 and N-3 positions (**4d** and **5d**, respectively) were the best antitumor agents among the tested derivatives. These two

TABLE II. Elemental Analysis and Spectral Data of *N*-Acyloxymethyl-5-fluorouracils

Compd.	Molecular formula	Analysis (%)			IR (Nujol) cm ⁻¹	¹ H-NMR <i>J</i> (Hz)	NMR solvent ^{a)}
		Calcd	(Found)				
		C	H	N			
4a	C ₉ H ₉ FN ₂ O ₄	47.38 (46.06)	3.98 (4.16)	12.28 (11.98)	3200, 1735, 1700, 1645	3.16 (2H, d, <i>J</i> =6, CH ₂ CH=CH ₂), 5.2 (2H, m, CH=CH ₂), 5.62 (2H, s, N-CH ₂), 5.8—6.0 (1H, m, CH=CH ₂), 7.62 (1H, d, <i>J</i> =5.6, C ₆ -H), 9.85 (1H, br, NH)	C
4b	C ₁₁ H ₁₃ FN ₂ O ₄	51.56 (51.42)	5.11 (5.07)	10.93 (11.08)	3120, 1705, 1650, 1370	0.99 (3H, t like, CH ₃), 2.19 (2H, m, CH ₂ -CH ₃), 3.12 (2H, d, <i>J</i> =6, OCOCH ₂), 5.5 (2H, m, CH=CH ₂), 5.6 (2H, s, N-CH ₂), 7.73 (1H, d, <i>J</i> =5.5, C ₆ -H), 10.06 (1H, br, NH)	C
4c	C ₁₄ H ₁₉ FN ₂ O ₄	56.37 (56.48)	6.42 (6.46)	9.39 (9.47)	3200, 1720, 1700, 1650	0.88 (3H, t like, CH ₃), 1.28 (6H, brs, chain CH ₂), 2.05 (2H, m, CH ₂ CH=CH), 3.1 (2H, d, <i>J</i> =5.6, OCOCH ₂), 5.5 (2H, m, CH=CH ₂), 5.6 (2H, s, N-CH ₂), 7.6 (1H, d, <i>J</i> =5.5, C ₆ -H), 9.8 (1H, br, NH)	C
4d	C ₁₆ H ₂₃ FN ₂ O ₄	58.89 (58.77)	7.10 (7.17)	8.58 (8.51)	3150, 1750, 1730, 1700, 1650	1.28 (12H, s, chain CH ₂), 2.05 (2H, m, CH ₂ CH=CH ₂), 2.4 (2H, t, <i>J</i> =7, OCOCH ₂), 4.9—5.1 (2H, m, CH=CH ₂), 5.62 (2H, s, N-CH ₂), 5.65—6.0 (1H, m, CH=CH ₂), 7.6 (1H, d, <i>J</i> =5.6, C ₆ -H), 9.4 (1H, br, NH)	C
5d	C ₁₆ H ₂₃ FN ₂ O ₄	58.89 (58.70)	7.10 (6.95)	8.58 (8.35)	3200, 1760, 1740, 1720, 1680, 1640	1.25 (12H, s, chain CH ₂), 2.02 (2H, m, CH ₂ CH=CH ₂), 2.3 (2H, t, <i>J</i> =7, OCOCH ₂), 4.69—5.12 (2H, m, CH=CH ₂), 5.6 (2H, s, N-CH ₂), 5.7—6.11 (1H, m, CH=CH ₂), 7.43 (1H, d, <i>J</i> =4.5, C ₆ -H), 9.98 (1H, brs, NH)	C
6d	C ₂₈ H ₄₃ FN ₂ O ₆	64.35 (64.10)	8.29 (8.30)	5.36 (5.52)	1740, 1700, 1650	0.98—2.58 (32H, m, chain CH ₂), 4.68—5.15 (4H, m, 2 × (CH=CH ₂)), 5.52—6.08 (6H, m, 2 × (N-CH ₂ , CH=CH ₂)), 7.63 (1H, d, <i>J</i> =5.5, C ₆ -H)	C
4e	C ₂₃ H ₃₇ FN ₂ O ₄	65.07 (64.95)	8.78 (8.81)	6.59 (6.49)	3250, 1740, 1700, 1660	0.92 (3H, t like, CH ₃), 1.3 (22H, brs, chain CH ₂), 1.9—2.3 (6H, m, OCOCH ₂ , CH ₂ CH=CHCH ₂), 5.25 (2H, m, CH=CH ₂), 5.6 (2H, s, N-CH ₂), 7.6 (1H, d, <i>J</i> =6, C ₆ -H), 9.75 (1H, br, NH)	C
6e	C ₄₂ H ₇₁ FN ₂ O ₆	70.16 (70.27)	9.95 (9.78)	3.89 (3.89)	1740, 1695, 1640	0.95 (6H, t like, CH ₃), 1.3 (44H, brs, chain CH ₂), 1.85—2.4 (12H, m, 2 × (OCOCH ₂ , CH ₂ CH=CHCH ₂)), 5.3 (4H, m, 2 × (CH=CH ₂)), 5.7 (2H, s, N-CH ₂), 5.9 (2H, s, N-CH ₂), 7.7 (1H, d, <i>J</i> =7, C ₆ -H)	C
4f	C ₂₃ H ₃₅ FN ₂ O ₄	65.38 (64.98)	8.35 (8.35)	6.63 (6.59)	2920, 1735, 1700, 1640, 1140	0.9 (3H, t like, CH ₃), 1.24 (16H, brs, chain CH ₂), 2.04 (4H, m, α to double bonds), 2.4 (2H, t like, OCOCH ₂), 2.75 (2H, m, =CH-CH ₂ CH=), 5.3 (4H, m, 2 × CH=CH ₂), 5.6 (2H, s, N-CH ₂), 7.6 (1H, d, <i>J</i> =6, C ₆ -H), 9.6 (1H, br, NH)	C
4g	C ₂₃ H ₃₉ FN ₂ O ₄	64.76 (65.01)	9.22 (9.30)	6.57 (6.43)	3150, 1730, 1690, 1650	0.9 (3H, t like, CH ₃), 1.25 (30H, brs, chain CH ₂), 2.35 (2H, m, OCOCH ₂), 5.6 (2H, s, N-CH ₂), 7.8 (1H, d, <i>J</i> =6, C ₆ -H), 9.7 (1H, br, NH)	C + D
4h	C ₁₅ H ₁₄ FN ₃ O ₆	51.29 (51.15)	4.02 (4.08)	11.96 (12.01)	3400, 3150, 1745, 1705, 1680, 1650, 1490, 860	3.98 (2H, d, <i>J</i> =6, COCH ₂ NH), 5.1 (2H, s, C ₆ H ₅ CH ₂), 5.62 (2H, s, OCOCH ₂ -N), 6.5 (1H, brs, CH ₂ NHCO), 7.3 (5H, s, aromatic), 7.6 (1H, d, <i>J</i> =5.6, C ₆ -H), 11.6 (1H, br, NH)	C + D

TABLE II. (continued)

Compd.	Molecular formula	Analysis (%)			IR (Nujol) cm ⁻¹	¹ H-NMR <i>J</i> (Hz)	NMR solvent ^{a)}
		Calcd	(Found)				
		C	H	N			
4i	C ₂₀ H ₂₄ F ₂ N ₄ O ₈	49.38 (49.64)	4.97 5.07	11.52 11.24	3300, 3200, 1740, 1720, 1700, 1670, 1640	1.3 (12H, s, chain CH ₂), 2.28 (4H, t, <i>J</i> = 7, 2 × OCOCH ₂), 5.6 (4H, s, 2 × (N-CH ₂)), 7.85 (2H, d, <i>J</i> = 6, 2 × C ₆ -H), 11.92 (2H, br, 2 × NH)	C + D
4j	C ₂₃ H ₃₉ FN ₂ O ₅	62.42 (62.60)	8.88 9.06	6.33 6.31	3400, 3200, 1730, 1695, 1650	0.9 (3H, like, CH ₃), 1.25 (28H, br s, chain CH ₂), 2.4 (2H, t, <i>J</i> = 7, OCOCH ₂), 3.58 (1H, br s, CH-OH), 5.6 (2H, s, N-CH ₂), 7.6 (1H, d, <i>J</i> = 6, C ₆ -H), 9.7 (1H, br, NH)	C
4k	C ₁₀ H ₁₁ FN ₂ O ₅	46.52 (46.62)	4.29 4.31	10.85 10.53	3150, 1740, 1720, 1700, 1655	2.18 (3H, s, CH ₃), 2.5—2.9 (4H, m, (CH ₂) ₂), 5.6 (2H, s, N-CH ₂), 7.66 (1H, d, <i>J</i> = 5.6, C ₆ -H), 11.66 (1H, br, NH)	C + D
6k	C ₁₆ H ₁₉ FN ₂ O ₈	49.74 (49.78)	4.96 4.85	7.25 7.30	1740, 1705, 1690, 1665	2.2 (6H, s, 2 × CH ₃), 2.45—2.9 (8H, m, 2 × (CH ₂) ₂), 5.68 (2H, s, N-CH ₂), 5.96 (2H, s, N-CH ₂), 7.68 (1H, d, <i>J</i> = 6, C ₆ -H)	C
4l	C ₁₂ H ₁₅ FN ₂ O ₅ S	45.28 (45.47)	4.75 4.84	8.80 8.73	3200, 1710, 1680, 1650, 1435, 1250, 1060	1.58 (3H, s, CH ₃), 2.18 (2H, t, <i>J</i> = 7, CH ₂ α to ring), 2.58 (2H, t, <i>J</i> = 7, OCOCH ₂), 3.05 (2H, t like, CH ₂ -S of ring), 4.1 (2H, m, CH ₂ -O of ring), 5.65 (2H, s, N-CH ₂), 7.65 (1H, d, <i>J</i> = 6, C ₆ -H), 9.9 (1H, br, NH)	C
4m	C ₁₂ H ₁₅ FN ₂ O ₄ S ₂	43.12 (43.44)	4.52 4.53	8.38 8.34	3250, 1720, 1700, 1695, 1650, 1445, 1260	1.76 (3H, s, CH ₃), 2.18 (2H, t, <i>J</i> = 7, CH ₂ α to ring), 2.64 (2H, t, <i>J</i> = 7, OCOCH ₂), 3.3 (4H, s, CH ₂ of ring), 5.6 (2H, s, N-CH ₂), 7.84 (1H, d, <i>J</i> = 6, C ₆ -H), 12.24 (1H, br, NH)	C + D

a) C and D represent CDCl₃ and DMSO-*d*₆, respectively.

compounds showed the highest ILS (increase in life span) percentage, when administered orally. When we compared these derivatives with Tegafur, we found that in the case of Tegafur the ILS decreased from 31 to 13 when its dose was increased from 100 to 300 mg/kg/d. This indicated that it had some toxicity at higher dose. However, in the case of **5d** the ILS increased from 20 to 28 at the same doses.

In conclusion, we can say that the *N*-acyloxymethylation of 5-fluorouracil by this new method is a potentially useful approach to obtain effective antitumor agents. The advantages of the present method are the very mild reaction conditions, the easy isolation, and the high yield of the 1-substituted product. 1-Undecenoyloxymethyl and 3-undecenoyloxymethyl-5-fluorouracils, which showed very good results, may serve as better antitumor agents than Tegafur and HCFU. Further testing of some of the *N*-acyloxymethyl-5-fluorouracils is in progress.

Experimental

All melting points were determined on a Buchi melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded in CDCl₃ and dimethyl sulfoxide-*d*₆ (DMSO-*d*₆) (E. Merck) on Hitachi R-24 (60 MHz) and JEOL FX-100 (100 MHz) spectrometers with tetramethylsilane as an internal standard. IR spectra were obtained on a Hitachi EPI G-3 spectrometer.

General Procedure for the Preparation of *N*-Acyloxymethyl-5-fluorouracils: 1-(4-Oxopentanoxyloxymethyl)-5-fluorouracil (4k**) and 1,3-Bis(4-oxopentanoxyloxymethyl)-5-fluorouracil (**6k**)**—5-Fluorouracil (**1**) (1.3 g, 10 mmol) and formalin (1.78 g, 22 mmol) were stirred in a 100 ml round-bottomed flask on an oil bath (about 60 °C; above this temperature the 1,3-bis(hydroxymethyl)-5-fluorouracil decomposed to 5-fluorouracil or polymerized) for about

Compd.	R	Dose ^{a)}		ILS ^{b)} %
		mg/kg/d		
4a	CH ₂ =CH-CH ₂ -	<i>p.o.</i>	100	9
4b	CH ₃ CH ₂ CH=CH-CH ₂ -	<i>p.o.</i>	30	7
4c	CH ₃ (CH ₂) ₄ CH=CH-CH ₂ -	<i>p.o.</i>	100	18
4d	CH ₂ =CH(CH ₂) ₈ -	<i>p.o.</i>	30	16
		<i>p.o.</i>	100	28
		<i>p.o.</i>	300	18
5d	CH ₂ =CH(CH ₂) ₈ -	<i>p.o.</i>	30	3
		<i>p.o.</i>	100	20
		<i>p.o.</i>	300	28
4e	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ -	<i>p.o.</i>	100	11
		<i>i.p.</i>	100	44
4g	CH ₃ (CH ₂) ₁₆ -	<i>p.o.</i>	100	0
		<i>p.o.</i>	300	0
		<i>i.p.</i>	100	53
4h	C ₆ H ₅ CH ₂ OCONHCH ₂ -	<i>p.o.</i>	30	0
		<i>p.o.</i>	100	26
		<i>p.o.</i>	300	-2
4i	5-FU-CH ₂ OCO(CH ₂) ₈ -	<i>p.o.</i>	100	0
		<i>p.o.</i>	300	6
		<i>i.p.</i>	100	63
4j	CH ₃ (CH ₂) ₅ CH(OH)(CH ₂) ₁₀ -	<i>p.o.</i>	100	4
		<i>p.o.</i>	300	29
		<i>i.p.</i>	100	42
4k	CH ₃ CO(CH ₂) ₂ -	<i>p.o.</i>	100	23
		<i>i.p.</i>	100	19
4l		<i>p.o.</i>	100	4
		<i>p.o.</i>	300	41
		<i>i.p.</i>	100	31
4m		<i>p.o.</i>	100	0
		<i>p.o.</i>	300	48
		<i>i.p.</i>	100	25
		<i>p.o.</i>	30	21
HCFU		<i>p.o.</i>	100	50
		<i>p.o.</i>	300	23
		<i>p.o.</i>	30	0
		<i>p.o.</i>	100	31
		<i>p.o.</i>	300	13

45 min. The traces of water evolved were removed under reduced pressure. The resulting viscous **2**¹³) was dissolved in 30 ml of dry acetonitrile (CH₃CN). To this solution, 4-oxopentanoic (levulinic) acid (1.4 g, 12 mmol) was added followed by DCC (2.47 g, 12 mmol) and a catalytic amount of DMAP. The reaction was monitored by thin layer chromatography (TLC). The reaction mixture was stirred at room temperature for 4 h, then filtered to remove dicyclohexylurea and washed with dichloromethane. The organic layer was washed with 1 N HCl (3 times), 2:5% sodium bicarbonate and saturated NaCl solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* afforded a mixture of two major products (2.2 g). The compounds were purified by flash column chromatography on silica gel using methanol and dichloromethane (1:20) as the eluent. The first fraction gave **6k** (0.38 g, 10%) as a viscous oil. The second fraction gave **4k** (1.7 g, 66%) as white crystals. All the reactions were carried out similarly. The reaction time, temperature, solvent, and yield are summarized in Table I. Elemental analysis, IR and ¹H-NMR data are given in Table II.

Carboxylic Acids as Starting Materials—All the carboxylic acids used here were commercially available except for **31** and **3m**, which were synthesized from levulinic acid.

Preparation of 4,4-(Epoxyethanthio)pentanoic Acid (31)—A mixture of levulinic acid (2.9 g, 25 mmol) and 2-mercaptoethanol (1.95 g, 25 mmol) was allowed to react in the presence of boron trifluoride etherate (10 ml) at room temperature.¹⁴⁾ TLC monitoring of the reaction mixture showed that reaction completed within 1 h. After addition of a few drops of methanol to stop the reaction, the mixture was worked up with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude oil was crystallized in hexane-ether, affording **31** as white crystals (4.18 g, 95%). mp 63–64 °C. IR (Nujol): 1680, 1430, 1200, 1040 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.65 (3H, s, CH₃), 2.25 (2H, t, *J* = 7 Hz, CH₂ α to ring), 2.55 (2H, t, *J* = 7 Hz, CH₂COO), 3.0 (2H, t like, CH₂-S of ring), 4.15 (2H, m, CH₂-O of ring), 10.3 (1H, br s, COOH). *Anal.* Calcd for C₇H₁₂O₃S: C, 47.71; H, 6.86. Found: C, 47.94; H, 7.05.

Preparation of 4,4-(Ethylenedithio)pentanoic Acid (3m)—In the same manner as described above, levulinic acid (2.33 g, 20 mmol) and ethane 1,2-dithiol (1.88 g, 20 mmol) were allowed to react for 1 h. After final work-up and evaporation of the solvent, the crude oil was crystallized in ethanol, giving **3m** as white crystals (3.76 g, 98%). mp 52–53 °C. IR (Nujol): 1700, 1440, 1265 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.8 (3H, s, CH₃), 2.2 (2H, t, *J* = 7 Hz, CH₂ α to ring), 2.6 (2H, t, *J* = 7 Hz, CH₂COO), 3.3 (4H, s, CH₂ of ring), 11.55 (1H, s, COOH). *Anal.* Calcd for C₇H₁₂O₂S₂: C, 43.72; H, 6.29. Found: C, 43.67; H, 6.38.

Activity Test—The tumor system and animals used for the evaluation of the antitumor activity of these derivatives were the same as described in our previous publication⁹⁾:

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

where *T* is the average number of days before death in the test group and *C* is the number of days before death in the control group.¹⁵⁾

Acknowledgment The authors wish to thank the Advanced Instrumentation Center for Chemical Analysis, Ehime University, for elemental analysis.

References and Notes

- 5-Fluorouracil Derivatives. XIII. Part XII: S. Ozaki, T. Nagase, H. Tamai, H. Mori, A. Hoshi, and M. Iigo, *Chem. Pharm. Bull.*, **35**, 3894 (1987).
- Postdoctoral Research Fellow (1986–87) of the Ministry of Education, Science and Culture, Japan.
- F. Changlie, M. Caisong, Y. Hui, X. Jianing, D. Qizhu, and Z. Renxi, *Wuhan Daxue Xuebao Ziran Kexueban*, **1984**, 115 [*Chem. Abstr.*, **102**, 6404f (1985)].
- Terumo Corp, Japan. Patent Open 59-204175 (1984) [*Chem. Abstr.*, **102**, 166771b (1985)].
- A. Buur, H. Bundgaard, and E. Falch, *Int. J. Pharm.*, **24**, 43 (1985).
- S. Ozaki, Y. Ike, H. Mizuno, K. Ishikawa, and H. Mori, *Bull. Chem. Soc., Jpn.*, **50**, 2406 (1977).
- S. Ozaki, Y. Watanabe, T. Hoshiko, H. Mizuno, K. Ishikawa, and H. Mori, *Chem. Pharm. Bull.*, **32**, 733 (1984).
- T. Hoshiko, S. Ozaki, Y. Watanabe, T. Ogasawara, S. Yamauchi, K. Fujiwara, A. Hoshi, and M. Iigo, *Chem. Pharm. Bull.*, **33**, 2832 (1985).
- S. Ozaki, Y. Watanabe, T. Hoshiko, T. Nagase, T. Ogasawara, H. Furukawa, A. Uemura, K. Ishikawa, H. Mori, A. Hoshi, M. Iigo, and R. Tokuzen, *Chem. Pharm. Bull.*, **34**, 150 (1986).
- Y. Koyama, *Gan To Kagakuryoho*, **7**, 1181 (1980).
- M. Nakanishi, Y. Tsutanishi, T. Nakamura, I. Hashimoto, Y. Sawata, M. Kawai, T. Okuno, S. Fujisawa, and M. Taneda, *Yakuri To Chiryo*, **8**, 1211 (1980).
- M. Yoshida, H. Murai, and S. Miura, *Gan To Kagakuryoho*, **7**, 1203 (1980).
- The ¹H-NMR spectrum of an acetonitrile solution of **2** showed no peak due to the NH proton in the uracil ring, which suggested that **2** contained not more than about 10% 1- or 3-hydroxymethyl-5-fluorouracil, that is, the purity of **2** was better than 90%. Direct acetylation of **2** with excess acetic anhydride in pyridine gave 1,3-bis(acetoxymethyl)-5-fluorouracil in 68% yield. T. Nagase, H. Tamai, and S. Ozaki, unpublished results.
- L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).
- A. Hoshi, M. Iigo, A. Nakamura, and K. Kuretani, *Chem. Pharm. Bull.*, **26**, 161 (1978).