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Syntheses and Antitumor Activities of 5-(Substituted-methyl)-6-carbamoyluracils

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5-Chloromethyl-6-ethoxycarbonyluracil (**5**) was prepared from furo[3,4-*d*]pyrimidine-2,4,7(1H,3H,5H)-trione (**4**). Reaction of **5** with some nucleophilic reagents such as secondary amines, alcohols and sodium thiolates afforded 5-(substituted-methyl)-6-ethoxycarbonyluracils. By treatment of the corresponding esters with methanolic ammonia or ammonia water, 5-(substituted-methyl)-6-carbamoyluracils were prepared.

The antitumor activities of the newly synthesized compounds were examined against L-1210 cells *in vitro*.

Keywords—halogenation; nucleophilic substitution; pyrrolo[3,4-*d*]pyrimidine; 6-carbamoyluracils; growth inhibition of L-1210 cells

Very many pyrimidine derivatives have been synthesized, and their biological activities as well as chemical properties have been studied. In particular, since its introduction in 1957 by Heidelberger,¹⁾ 5-fluorouracil (5-FU) and its derivatives have been used extensively in cancer chemotherapy.²⁾

In this paper we describe synthetic methods for 5-(substituted-methyl)-6-carbamoyluracils, and present the results of antitumor activity testing of these compounds.

Chemistry

Many reports have been published on the preparation of 5-(substituted-methyl)uracil *via* 5-chloromethyluracil.³⁾ On the other hand, Ross *et al.* reported the preparation of the amides *via* the esters of orotic acid.⁴⁾ Accordingly, the preparation of the title compounds *via* 5-halomethyl-6-alkoxycarbonyluracil was investigated.

5-Halomethyl-6-alkoxycarbonyluracil was prepared as shown in Chart 1. 5-Methylorotic acid (**1**)^{5,6)} was treated with thionyl chloride and methanol to give 6-methoxycarbonyl-5-methyluracil (**2**). Bromine was added to a suspension of **2** in benzene under reflux during irradiation with a high pressure mercury lamp to give 5-bromomethyl-6-methoxycarbonyluracil (**3**) and **1**. The use of absolute benzene and freshly prepared bromine resulted in a better yield.

The intermediate, 5-halomethyl-6-alkoxycarbonyluracil, could be prepared as described above. However, the scale of the photobromination was not more than 0.5 g of **2** and the yield of **3** varied with slight changes in experimental conditions (68.7—26.1%). Thus, we investigated an alternative method to prepare the intermediate.

A mixture of furo[3,4-*d*]pyrimidine-2,4,7(1H,3H,5H)-trione (**4**)⁷⁾ (20 g) and ethanol (2 l), saturated with hydrogen chloride gas, was allowed to stand at room temperature for 2 days, then the mixture was refluxed for 6 hr to give 5-chloromethyl-6-ethoxycarbonyluracil (**5**) in 70.4% yield. However, under the same conditions with methanol, 6-methoxycarbonyl-5-methoxymethyluracil (**7**) was obtained in 77.6% yield. It appears that the reaction proceeded *via* the formation of 5-chloromethyl-6-methoxycarbonyluracil (**6**) as an intermediate to give **7**.

The reaction of **5** with aniline and *p*-chloroaniline finally afforded the lactams **10a** and **10b**. Britikova *et al.* had earlier prepared them directly from **4** and the corresponding amines.⁸⁾ The steps of the present reaction will now be described in detail.

First, the reaction of **5** with 2.5 eq of aniline in ethanol at 0—5° afforded an ester (**8a**) (Chart 2). The infrared (IR) spectrum exhibits absorption bands at 3350 and 1710 cm⁻¹

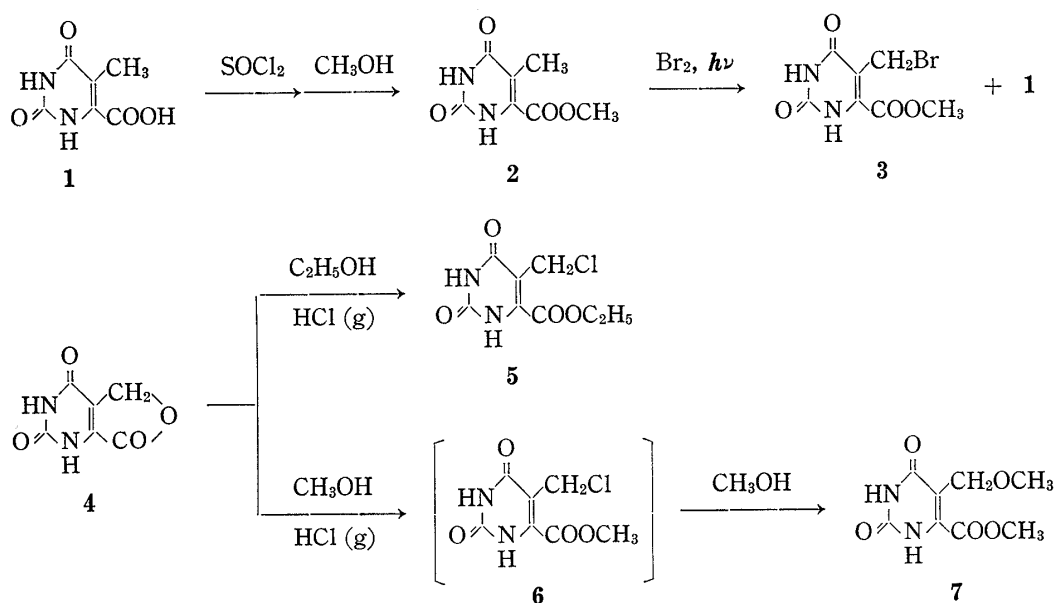


Chart 1

due to a nitrogen-hydrogen bond at the 5-position and a carbonyl group at the 6-position, respectively. Heating of **8a** in ethanol for a few minutes gave a mixture of **8a** and the lactam **10a**⁸⁾ (ca. 3:1), which was recognized from its nuclear magnetic resonance (NMR) spectrum. Heating of **8a** in dimethyl sulfoxide (DMSO) for 1 hr afforded **10a**. The IR spectrum of **10a** shows the absence of a nitrogen-hydrogen bond and the presence of a carbonyl group due to γ -lactam at 1730 cm^{-1} . An M^+ peak (m/e : 243) was observed in the mass spectrum (MS).

On the other hand, the reaction of the crude **8a** with methanolic ammonia afforded an amide (**9a**). The IR spectrum shows a broad carbonyl absorption band at $1670\text{--}1620\text{ cm}^{-1}$. Heating of **9a** in DMSO also gave the lactam **10a**. The similar reaction of **5** with *p*-chloroaniline afforded the lactam (**10b**).⁸⁾

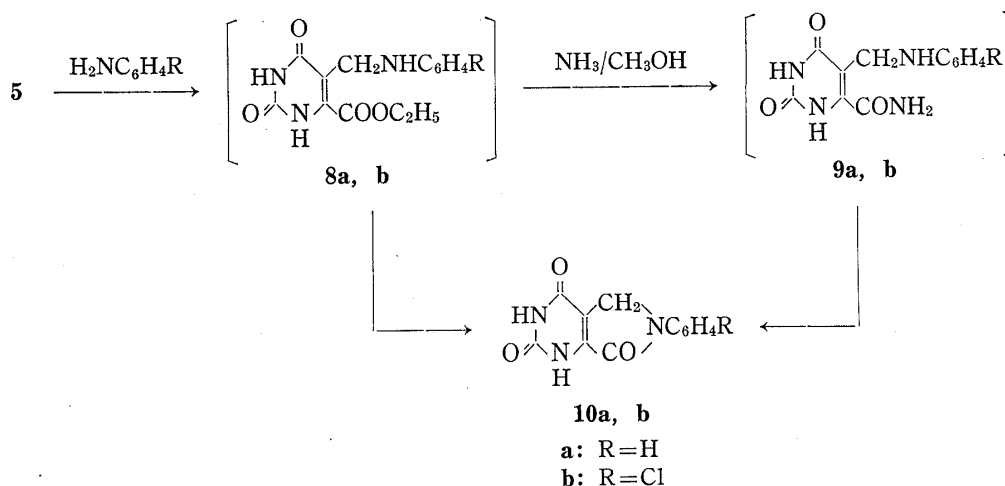


Chart 2

5-(Substituted-methyl)-6-carbamoyluracils (**12a—g**, **14a—h**, **16a—f**) were prepared as shown in Chart 3. The reaction of **5** with secondary amines in ethanol at $0\text{--}5^\circ$ afforded the corresponding esters (**11a—g**). The IR spectra exhibit absorption bands at $1730\text{--}1710\text{ cm}^{-1}$ due to carbonyl groups of the esters. However, the esters were not stable when heated in ethanol for recrystallization. Thus, 5-(substituted-aminomethyl)-6-carbamoyluracils (**12a—g**) were obtained by treatment of the crude **11a—g** with methanolic ammonia.

Refluxing or heating of **5** with alcohols afforded the corresponding esters **13a—h**, which, on treatment with ammonia water, gave 5-alkoxymethyl-6-carbamoyluracils (**14a—h**).

Reaction of **5** with sodium thiolates at room temperature afforded the corresponding esters. The crude 5-propyl and 5-phenylthiomethyl derivatives were heated in methanol to give the methyl esters **15a** and **15d**, respectively. It seems that transesterification was caused by trace amounts of sodium thiolate. On treatment of **15a—f** with ammonia water, 5-alkylthiomethyl-6-carbamoyluracils (**16a—f**) were obtained.

Antitumor Activity

The uracil derivatives described above were tested for antitumor activity against L-1210 cells *in vitro*.

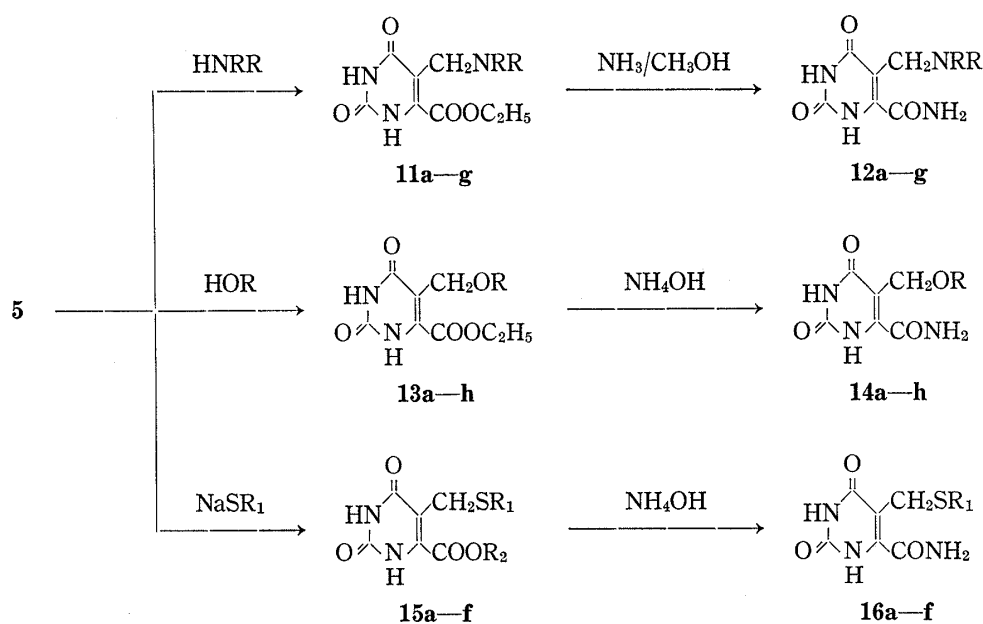
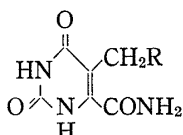


Chart 3

TABLE I. 

Compd. No.	R	Yield (%)	mp(°C) (dec.)	Recryst. solv.	Formula	Analysis(%)		
						Calcd (Found)	C	H N
12a		88.5	213—218	EtOH—H ₂ O	C ₁₁ H ₁₆ N ₄ O ₃	52.37 (52.17)	6.39 6.60	22.21 22.43
12b		81.3	233—240	EtOH—H ₂ O	C ₁₀ H ₁₄ N ₄ O ₃	50.41 (50.32)	5.92 6.11	23.52 23.78
12c		67.7	202—206	EtOH—H ₂ O	C ₁₀ H ₁₅ N ₅ O ₃	47.43 (47.37)	5.97 5.86	27.65 27.63
12d		76.4	234—236	EtOH—H ₂ O	C ₁₁ H ₁₇ N ₅ O ₃	49.43 (49.30)	6.41 6.42	26.20 26.35
12e		84.8	229—232	DMF—EtOH	C ₁₀ H ₁₄ N ₄ O ₄	47.24 (47.35)	5.55 5.68	22.04 21.85
12f		72.0	214—217	EtOH—H ₂ O	C ₈ H ₁₂ N ₄ O ₃	45.28 (45.21)	5.70 5.86	26.40 26.35
12g		95.1	228—234	EtOH—H ₂ O	C ₁₀ H ₁₆ N ₄ O ₃	49.99 (50.17)	6.71 6.78	23.32 23.30

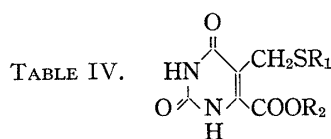
collected with an automatic cell harvester and the radioactivities (cpm) were measured with an auto-gamma scintillation spectrometer.

The incorporation of 5-[¹²⁵I]iodo-2'-deoxyuridine into the tested cells was measured and the percent growth inhibition was calculated by means of the following equation:

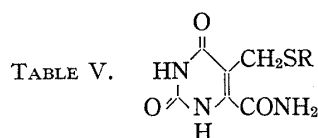
$$\% \text{ growth inhibition} = \left(1 - \frac{\text{cpm}_T}{\text{cpm}_C}\right) \times 100$$

where cpm_T is the radioactivity of the examined compound and cpm_C is that of the control.

6-Carbamoyl-5-(4-chlorophenylthiomethyl)uracil (**16e**) exhibited 42% inhibition at 100 $\mu\text{g}/\text{ml}$. However, other compounds showed no inhibition.



Compd. No.	R ₁	R ₂	Yield (%)	mp(°C)	Recryst. solv.	Formula	Analysis(%)		
							Calcd (Found)	C	H N
15a	CH ₂ CH ₂ CH ₃	CH ₃	65.8	215.5—217.5	MeOH	C ₁₀ H ₁₄ N ₂ O ₄ S	46.50 (46.73)	5.46 5.44	10.85 10.61
15b	CH ₂ (CH ₂) ₂ CH ₃	C ₂ H ₅	69.8	212 —214	MeOH	C ₁₂ H ₁₈ N ₂ O ₄ S	50.33 (50.21)	6.34 6.60	9.78 9.80
15c	CH ₂ COOC ₂ H ₅	C ₂ H ₅	77.6	155 —156.5	EtOH	C ₁₂ H ₁₆ N ₂ O ₆ S	45.56 (45.27)	5.10 5.09	8.86 8.91
15d	C ₆ H ₅	CH ₃	78.5	214.5—216.5	MeOH	C ₁₃ H ₁₂ N ₂ O ₄ S	53.42 (53.15)	4.14 4.10	9.58 9.43
15e	<i>p</i> -C ₆ H ₄ Cl	C ₂ H ₅	87.5	236 —238	EtOH	C ₁₄ H ₁₃ ClN ₂ O ₄ S	49.34 (49.50)	3.85 3.82	8.22 8.16
15f	CH ₂ C ₆ H ₅	C ₂ H ₅	86.7	213 —214.5	MeOH	C ₁₅ H ₁₆ N ₂ O ₄ S	56.24 (56.20)	5.03 5.10	8.74 8.97



Compd. No.	R	Yield (%)	mp(°C) (dec.)	Recryst. solv.	Formula	Analysis(%)		
						Calcd (Found)	C	H N
16a	CH ₂ CH ₂ CH ₃	98.1	283	MeOH-H ₂ O	C ₉ H ₁₃ N ₃ O ₃ S	44.43 (44.16)	5.39 5.36	17.27 17.09
16b	CH ₂ (CH ₂) ₂ CH ₃	95.0	232—235	MeOH-H ₂ O	C ₁₀ H ₁₅ N ₃ O ₃ S	46.68 (46.44)	5.88 5.93	16.33 16.12
16c	CH ₂ CONH ₂	76.0	260	EtOH-H ₂ O	C ₈ H ₁₀ N ₄ O ₄ S	37.21 (37.31)	3.90 4.18	21.64 21.40
16d	C ₆ H ₅	98.6	242	MeOH-H ₂ O	C ₁₂ H ₁₁ N ₃ O ₃ S	51.98 (51.81)	4.00 4.04	15.15 15.19
16e	<i>p</i> -C ₆ H ₄ Cl	79.7	240	MeOH-H ₂ O	C ₁₂ H ₁₀ ClN ₃ O ₃ S	46.23 (46.14)	3.23 3.27	13.48 13.33
16f	CH ₂ C ₆ H ₅	82.2	204—207	MeOH-H ₂ O	C ₁₃ H ₁₃ N ₃ O ₃ S	53.60 (53.52)	4.50 4.41	14.42 14.56

TABLE VI. Growth Inhibition of L-1210 Cells *in Vitro*, % Inhibition

Compd. No.	Concentration ($\mu\text{g/ml}$)			
	3	10	30	100
16e	—	—	3	42
5-FU	-22	-10	13	64

Experimental

All melting points are uncorrected. IR spectra were measured with a Hitachi 215 spectrometer or a Hitachi 260-10 spectrometer. ^1H -NMR spectra were taken at 60 MHz with a Varian A-60 spectrometer or a JEOL JNM-PMX 60 spectrometer. As an internal standard, tetramethylsilane in $\text{DMSO}-d_6$, or 3-(trimethylsilyl)propionic acid sodium salt- d_4 in D_2O was used. Chemical shifts are expressed as δ (ppm) downfield from an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. Mass spectra were measured with a JEOL JMS-01SG-2 mass spectrometer.

6-Methoxycarbonyl-5-methyluracil (2)—A mixture of **1**^{5,6} (1.0 g, 5.9 mmol), thionyl chloride (2.4 g, 20.2 mmol) and N,N -dimethylformamide (1–2 drops) was refluxed for 3 hr with continuous stirring. After cooling, the product was filtered off and washed with benzene. Methanol (30 ml) was added to the crude product and the mixture was refluxed for 2 hr. The reaction mixture was concentrated *in vacuo*. The product was filtered off and recrystallized from methanol to give 0.69 g (63.8%) of **2**: mp 242° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1735. NMR ($\text{DMSO}-d_6$) δ : 1.95 (3H, s), 3.87 (3H, s), 10.70 (1H, br.s), 11.37 (1H, br.s). MS m/e : 184 (M^+). Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.52; H, 4.56; N, 15.17.

5-Bromomethyl-6-methoxycarbonyluracil (3)—Freshly prepared bromine (0.4 g, 5 mmol) was added dropwise to a suspension of **2** (0.5 g, 2.7 mmol) in dry benzene (150 ml) under reflux during irradiation with a high pressure mercury lamp, with stirring. Refluxing, stirring and irradiation were continued for 1 hr. After cooling, the insoluble product **4** was removed by filtration. The filtrate was concentrated *in vacuo*. The precipitates were filtered off and recrystallized from tetrahydrofuran to give 0.49 g (68.7%) of **3**: mp $206\text{--}210^\circ$. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1740, 1710. NMR ($\text{DMSO}-d_6$) δ : 3.92 (3H, s), 4.53 (2H, s), 11.27 (1H, br.s), 11.67 (1H, br.s). MS m/e : 264 (M^++2), 262 (M^+). Anal. Calcd for $\text{C}_7\text{H}_7\text{BrN}_2\text{O}_4$: C, 31.96; H, 2.68; N, 10.65. Found: C, 31.77; H, 2.60; N, 10.78.

5-Chloromethyl-6-ethoxycarbonyluracil (5)—A mixture of **4**⁶ (20 g, 120 mmol) and ethanol (2 l), saturated with hydrogen chloride gas, was allowed to stand at room temperature for 2 days. The mixture was then refluxed for 6 hr and the supernatant solution was decanted off. The residue was **4**. The supernatant was cooled and the resulting precipitates were filtered off and recrystallized from ethyl acetate to give 19.7 g (70.4%) of **5**: mp $210\text{--}211^\circ$. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1735, 1710. NMR ($\text{DMSO}-d_6$) δ : 1.35 (3H, t, $J=7$ Hz), 4.36 (2H, q, $J=7$ Hz), 4.56 (2H, s), 11.21 (1H, br.s), 11.59 (1H, br.s). MS m/e : 234 (M^++2), 232 (M^+). Anal. Calcd for $\text{C}_8\text{H}_9\text{ClN}_2\text{O}_4$: C, 41.31; H, 3.90; N, 12.04. Found: C, 41.53; H, 4.01; N, 12.15.

6-Methoxycarbonyl-5-methoxymethyluracil (7)—A mixture of **4** (0.5 g, 3 mmol) and methanol (40 ml) was saturated with hydrogen chloride gas and allowed to stand overnight at room temperature. The mixture was then refluxed for 2 hr and the insoluble compound **4** was removed by filtration. The filtrate was cooled and the resulting precipitates were recrystallized from methanol to give 0.49 g (77.6%) of **7**: mp 174° (dec.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1740, 1710. NMR ($\text{DMSO}-d_6$) δ : 3.20 (3H, s), 3.88 (3H, s), 4.22 (2H, s), 11.38 (1H, br.s), 11.45 (1H, br.s). MS m/e : 214 (M^+). Anal. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_5$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.76; H, 4.64; N, 13.14.

6-Phenyl-6H-pyrrolo[3,4-*d*]pyrimidine-2,4,7(1H,3H,5H)-trione (10a)—Method A: With continuous stirring, **5** (3 g, 12.9 mmol) was added to a solution of aniline (3 g, 32.3 mmol) in ethanol (100 ml) at $0\text{--}5^\circ$. The mixture was stirred for 2 hr, then the product **8a** was filtered off and heated in DMSO (9 ml) for 1 hr. The precipitates were collected and recrystallized from DMSO-methanol to give 2.6 g (82.9%) of **10a**: mp $>300^\circ$ (lit.⁸) mp $>330^\circ$.

Method B: The crude **8a** (1.4 g, 4.8 mmol) was added to a methanolic solution (70 ml) of ammonia (1 g, 59 mmol) and the mixture was stirred for 2 hr at room temperature. The product **9a** was filtered off and heated in DMSO. After cooling, the precipitates were collected and recrystallized to give 0.87 g (74.6%) of **10a**.

6-(4-Chlorophenyl)-6H-pyrrolo[3,4-*d*]pyrimidine-2,4,7(1H,3H,5H)-trione (10b)—Compound **10b** was obtained from **5** (3 g, 12.9 mmol) according to method A for the preparation of **10a**. Yield: 2.68 g (74.9%). mp $>300^\circ$ (lit.⁸) mp $\sim 300^\circ$.

Compound **10b** was also obtained from the crude **8b** (1.5 g, 4.6 mmol) *via* the amide **8b** according to method B for the preparation of **9a**. Yield: 0.87 g (68.2%).

General Procedure for the Preparation of 5-(Substituted-methyl)-6-alkoxycarbonyluracils (11a–g,

13a—h and 15a—f—Typical Examples: 6-Ethoxycarbonyl-5-piperidinomethyluracil (**11a**): With continuous stirring, **5** (8 g, 34.4 mmol) was added to a solution of piperidine (8 g, 94.1 mmol) in ethanol (120 ml) at 0—5°. The mixture was stirred for 2 hr. The product was filtered off to give 5.6 g (58.3%) of the crude **11a**: mp 221—224°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1710.

The esters **11a—g** were prepared as described above and used in the subsequent reaction without purification. Yields, melting points and IR spectra are given below.

6-Ethoxycarbonyl-5-pyrrolidinomethyluracil (**11b**): Yield: 68.7%. mp 198—205°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1720.

6-Ethoxycarbonyl-5-piperazinomethyluracil (**11c**): Yield: 93.0%. mp 205—210°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1725.

6-Ethoxycarbonyl-5-(N-methylpiperazinomethyl)uracil (**11d**): Yield: 88.3%. mp 208—211°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1720.

6-Ethoxycarbonyl-5-morpholinomethyluracil (**11e**): Yield: 97.0%. mp 211—215°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1730, 1715.

5-Dimethylaminomethyl-6-ethoxycarbonyluracil (**11f**): Yield: 73.5%. mp 190—198°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1730.

5-Diethylaminomethyl-6-ethoxycarbonyluracil (**11g**): Yield: 59.1%. mp 153—156°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1710.

6-Ethoxycarbonyl-5-ethoxymethyluracil (13b)—A mixture of **5** (2.5 g, 10.8 mmol) and ethanol (40 ml) was refluxed for 3 hr. The reaction mixture was concentrated *in vacuo*. The product was filtered off and recrystallized from methanol to give 1.99 g (76.0%) of **13b**: mp 199—201°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1710. NMR (DMSO-*d*₆) δ : 1.07 (3H, t, *J* = 7 Hz), 1.32 (3H, t, *J* = 7 Hz), 3.40 (2H, q, *J* = 7 Hz), 4.25 (2H, s), 4.33 (2H, q, *J* = 7 Hz), 10.34 (1H, br.s), 11.40 (1H, br.s). MS *m/e*: 242 (M⁺).

Data for the esters **13a—f** prepared as described above are listed in Table II. IR, NMR and mass spectral data are given below.

6-Ethoxycarbonyl-5-methoxymethyluracil (**13a**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1710. NMR (DMSO-*d*₆) δ : 1.31 (3H, t, *J* = 7 Hz), 3.18 (3H, s), 4.21 (2H, s), 4.33 (2H, q, *J* = 7 Hz), 11.22 (1H, br.s). MS *m/e*: 228 (M⁺).

6-Ethoxycarbonyl-5-propoxymethyluracil (**13c**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1735, 1710. NMR (DMSO-*d*₆) δ : 0.83 (3H, t, *J* = 7 Hz), 1.31 (3H, t, *J* = 7 Hz), *ca.* 1.5 (2H, m), 3.30 (2H, t, *J* = 7 Hz), 4.24 (2H, s), 4.31 (2H, q, *J* = 7 Hz), 11.22 (1H, br.s), 11.42 (1H, br.s). MS *m/e*: 256 (M⁺).

6-Ethoxycarbonyl-5-isopropoxymethyluracil (**13d**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1740, 1700. NMR (DMSO-*d*₆) δ : 1.03 (6H, d, *J* = 6.2 Hz), 1.30 (3H, t, *J* = 7 Hz), 3.58 (1H, m), 4.23 (2H, s), 4.31 (2H, q, *J* = 7 Hz), 11.17 (1H, br.s), 11.35 (1H, br.s). MS *m/e*: 256 (M⁺).

5-Allyloxymethyl-6-ethoxycarbonyluracil (**13e**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1735, 1710. NMR (DMSO-*d*₆) δ : 1.30 (3H, t, *J* = 7 Hz), 3.91 (2H, m), 4.27 (2H, s), 4.31 (2H, q, *J* = 7 Hz), 5.0—5.4 (2H, m), 5.5—6.3 (1H, m), 11.23 (1H, br.s), 11.42 (1H, br.s). MS *m/e*: 254 (M⁺).

6-Ethoxycarbonyl-5-methoxyethoxymethyluracil (**13f**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1730, 1710. NMR (DMSO-*d*₆) δ : 1.30 (3H, t, *J* = 7 Hz), 3.23 (3H, s), 3.43 (4H, s), 4.28 (2H, s), 4.32 (2H, q, *J* = 7 Hz), 11.20 (1H, br.s), 11.42 (1H, br.s). MS *m/e*: 272 (M⁺).

5-Benzoyloxymethyl-6-ethoxycarbonyluracil (13g)—A mixture of **5** (5.76 g, 24.8 mmol) and benzyl alcohol (200 ml) was heated at 120—140° for 3 hr. The reaction mixture was concentrated *in vacuo*. The product was filtered off and recrystallized from ethyl acetate to give 6.68 g (90.3%) of **13g**: mp 175—176.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1725, 1700. NMR (DMSO-*d*₆) δ : 1.25 (3H, t, *J* = 7 Hz), 4.26 (2H, q, *J* = 7 Hz), 4.35 (2H, s), 4.47 (2H, s), 7.32 (5H, s), 11.27 (1H, br.s), 11.48 (1H, br.s). MS *m/e*: 304 (M⁺).

Data for the esters **13g, h** prepared as described above are listed in Table II. IR, NMR and mass spectral data are given below.

6-Ethoxycarbonyl-5-(2-phenylethoxymethyl)uracil (**13h**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1735, 1710. NMR (DMSO-*d*₆) δ : 1.27 (3H, t, *J* = 7 Hz), 2.77 (2H, t, *J* = 7 Hz), 3.58 (2H, t, *J* = 7 Hz), 4.26 (2H, q, *J* = 7 Hz), 4.32 (2H, s), 7.23 (5H, s), 11.21 (1H, br.s), 11.43 (1H, br.s). MS *m/e*: 318 (M⁺).

5-(4-Chlorophenylthiomethyl)-6-ethoxycarbonyluracil (15e)—A solution of sodium (0.3 g, 12.9 mmol) and 4-chlorothiophenol (1.86 g, 12.9 mmol) in ethanol (90 ml) was refluxed for 1 hr. Compound **5** (3 g, 12.9 mmol) was added to the solution after it had cooled and the mixture was stirred for 5 hr at room temperature. The product was filtered off and recrystallized from ethanol to give 3.84 g (87.5%) of **15f**: mp 236—238°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1725, 1700. NMR (DMSO-*d*₆) δ : 1.25 (3H, t, *J* = 7 Hz), 4.05 (2H, s), 4.15 (2H, q, *J* = 7 Hz), 7.31 (4H, s), 10.88 (1H, br.s), 11.48 (1H, br.s). MS *m/e*: 342 (M⁺ + 2), 340 (M⁺).

Crude 5-propyl and 5-phenylthiomethyl-6-ethoxycarbonyluracil were prepared as described above. Heating of the esters in methanol for recrystallization afforded 5-propyl (**15a**) and 5-phenylthiomethyl-6-methoxycarbonyluracil (**15d**), respectively.

Data for the esters **15a—f** are listed in Table IV. IR, NMR and mass spectral data are given below

6-Methoxycarbonyl-5-propylthiomethyluracil (**15a**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1700. NMR (DMSO-*d*₆) δ : 0.90 (3H, t, *J* = 7 Hz), *ca.* 1.5 (2H, m), 2.47 (2H, t, *J* = 7 Hz), 3.63 (2H, s), 3.88 (3H, s). MS *m/e*: 272 (M⁺).

5-Butylthiomethyl-6-ethoxycarbonyluracil (**15d**): IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1700. NMR (DMSO-*d*₆) δ : 0.85 (3H, m), 1.32 (3H, t, *J* = 7 Hz), 2.47 (2H, m), 3.60 (2H, s), 4.31 (2H, q, *J* = 7 Hz), 10.88 (1H, br.s), 11.43

(1H, br.s). MS m/e : 286 (M^+).

6-Ethoxycarbonyl-5-ethoxycarbonylmethylthiomethyluracil (**15c**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1700. NMR ($\text{DMSO}-d_6$) δ : 1.19 (3H, t, $J=7$ Hz), 1.33 (3H, t, $J=7$ Hz), 3.35 (2H, s), 3.72 (2H, s), 4.09 (2H, q, $J=7$ Hz), 4.34 (2H, q, $J=7$ Hz), 10.95 (1H, br.s), 11.50 (1H, br.s). MS m/e : 316 (M^+).

6-Methoxycarbonyl-5-phenylthiomethyluracil (**15d**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1720. NMR ($\text{DMSO}-d_6$) δ : 3.68 (3H, s), 4.06 (2H, s), 7.32 (5H, s). MS m/e : 292 (M^+).

5-Benzylthiomethyl-6-ethoxycarbonyluracil (**15f**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1730, 1710. NMR ($\text{DMSO}-d_6$) δ : 1.28 (3H, t, $J=7$ Hz), 3.63 (2H, s), 3.78 (2H, s), 4.29 (2H, q, $J=7$ Hz), 7.30 (5H, s), 11.0—11.8 (2H, br). MS m/e : 320 (M^+).

General Procedure for the Preparation of 5-(Substituted-methyl)-6-carbamoyluracil (12a—g, 14a—h and 16a—f)—Typical Examples: 6-Carbamoyl-5-pyrrolidinomethyluracil (**12b**): Crude **14b** (3 g, 11.2 mmol) was added to a methanolic solution (75 ml) of ammonia (1.5 g, 88 mmol) and the mixture was stirred for 1 day at room temperature. The product was filtered off and recrystallized from ethanol-water to give 2.17 g (81.3%) of **15b**: mp 233—240° (dec.). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3400, 3340, 1640—1610. NMR (D_2O) δ : 2.09 (4H, m), 3.41 (4H, m), 4.26 (2H, s). MS m/e : 238 (M^+).

Data for the amides **12a—g** prepared as described above are listed in Table I. IR, NMR and mass spectral data are given below.

6-Carbamoyl-5-piperidinomethyluracil (**12a**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3400, 1675, 1630, 1590. NMR (D_2O) δ : 1.6—2.1 (6H, m), 3.0—3.4 (4H, m), 4.17 (2H, s). MS m/e : 252 (M^+).

6-Carbamoyl-5-piperazinomethyluracil (**12c**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3400—3300, 1680—1600. NMR (D_2O) δ : 2.91 (4H, m), 3.17 (4H, m), 3.72 (2H, s). MS m/e : 155 ($M^+ - \text{C}_5\text{H}_{10}\text{N}_2$).

6-Carbamoyl-5-(N-methylpiperazinomethyl)uracil (**12d**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3200, 1700, 1660. NMR (D_2O) δ : 2.54 (3H, s), 2.98 (8H, s), 3.86 (2H, s). MS m/e : 267 (M^+).

6-Carbamoyl-5-morpholinomethyluracil (**12e**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3200—3080, 1730, 1640. MS m/e : 254 (M^+).

6-Carbamoyl-5-dimethylaminomethyluracil (**12f**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3400, 1670, 1620, 1590. NMR (D_2O) δ : 2.86 (6H, s), 4.18 (2H, s). MS m/e : 212 (M^+).

6-Carbamoyl-5-diethylaminomethyluracil (**12g**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3380, 1660, 1630, 1600. NMR (D_2O) δ : 1.32 (6H, t, $J=7$ Hz), 3.22 (4H, q, $J=7$ Hz), 4.22 (2H, s). MS m/e : 211 ($M^+ - \text{C}_2\text{H}_5$).

5-Allyloxymethyl-6-carbamoyluracil (14e)—A mixture of **13e** (5.3 g, 20.9 mmol) and ammonia water (300 ml) was stirred for 2 days at room temperature. Small amounts of insoluble compounds were filtered off and the filtrate was concentrated *in vacuo*. The precipitates were filtered off and recrystallized from methanol to give 3.64 g (77.9%) of **14e**: mp 173.5—175.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3360, 1750, 1700, 1650. NMR ($\text{DMSO}-d_6$) δ : 3.94 (2H, m), 4.20 (2H, s), 5.0—5.5 (2H, m), 5.5—6.3 (1H, m), 7.8—8.2 (2H, br), 10.7—11.2 (2H, br). MS m/e : 225 (M^+).

Data for the amides **14a—h** and **16a—f** prepared as described above are listed in Tables III and V, respectively. IR, NMR and mass spectral data are given below.

6-Carbamoyl-5-methoxymethyluracil (**14a**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3300, 1700, 1640. NMR ($\text{DMSO}-d_6$) δ : 3.21 (3H, s), 4.13 (2H, s), 7.8—8.2 (2H, br), 11.0—11.3 (2H, br). MS m/e : 199 (M^+).

6-Carbamoyl-5-ethoxymethyluracil (**14b**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3300—3200, 1700—1650. NMR ($\text{DMSO}-d_6$) δ : 1.07 (3H, t, $J=7$ Hz), 3.40 (2H, q, $J=7$ Hz), 4.16 (2H, s), 7.8—8.3 (2H, br), 10.9—11.4 (2H, br). MS m/e : 213 (M^+).

6-Carbamoyl-5-propoxymethyluracil (**14c**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350, 1750, 1690, 1640. NMR ($\text{DMSO}-d_6$) δ : 0.83 (3H, t, $J=7$ Hz), *ca.* 1.5 (2H, m), 3.32 (2H, t, $J=7$ Hz), 4.17 (2H, s), 7.8—8.3 (2H, br), 10.6—11.5 (2H, br). MS m/e : 227 (M^+).

6-Carbamoyl-5-isopropoxymethyluracil (**14d**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3500, 3420, 1750, 1690, 1650. NMR ($\text{DMSO}-d_6$) δ : 1.07 (6H, d, $J=6.2$ Hz), 3.60 (1H, m), 4.17 (2H, s), 7.8—8.2 (2H, br), 10.8—11.3 (2H, br). MS m/e : 227 (M^+).

6-Carbamoyl-5-methoxyethoxymethyluracil (**14f**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350, 1720—1640. NMR ($\text{DMSO}-d_6$) δ : 3.26 (3H, s), 3.48 (4H, s), 4.22 (2H, s), 7.8—8.2 (2H, br), 11.10 (1H, br.s), 11.25 (1H, br.s). MS m/e : 243 (M^+).

5-Benzylloxymethyl-6-carbamoyluracil (**14g**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3360, 1750, 1690, 1650. NMR ($\text{DMSO}-d_6$) δ : 4.27 (2H, s), 4.46 (2H, s), 7.32 (5H, s), 8.00 (1H, br.s), 8.12 (1H, br.s), 11.25 (2H, br.s). MS m/e : 276 ($M^+ + \text{H}$).

6-Carbamoyl-5-(2-phenylethoxymethyl)uracil (**14h**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3500, 3400, 1700. NMR ($\text{DMSO}-d_6$) δ : 2.80 (2H, t, $J=7$ Hz), 3.60 (2H, t, $J=7$ Hz), 4.41 (2H, s), 7.25 (5H, s), 8.00 (2H, br.s), 11.13 (1H, br.s), 11.25 (1H, br.s). MS m/e : 289 (M^+).

6-Carbamoyl-5-propylthiomethyluracil (**16a**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350, 1680—1640. NMR ($\text{DMSO}-d_6$) δ : 0.90 (3H, t, $J=7$ Hz), *ca.* 1.5 (2H, m), 2.49 (2H, t, $J=7$ Hz), 3.41 (2H, s), 7.96 (1H, br.s), 8.16 (1H, br.s), 10.07 (2H, br.s). MS m/e : 243 (M^+).

5-Butylthiomethyl-6-carbamoyluracil (**16b**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1680—1640. NMR ($\text{DMSO}-d_6$) δ : 0.87 (3H, m), 2.48 (2H, m), 3.42 (2H, s), 7.95 (1H, br.s), 8.12 (1H, br.s), 10.95 (1H, br.s), 11.15 (1H, br.s). MS m/e : 257 (M^+).

6-Carbamoyl-5-carbamoylmethylthiomethyluracil (**16c**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3320—3270, 1690—1620. NMR (DMSO- d_6) δ : 3.14 (2H, s), 3.53 (2H, s), 7.03 (1H, br.s), 7.37 (1H, br.s), 8.02 (1H, br.s), 8.25 (1H, br.s), 11.17 (1H, br.s), 11.30 (1H, br.s). MS m/e : 258 (M^+).

6-Carbamoyl-5-phenylthiomethyluracil (**16d**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3375, 1700, 1680, 1650. NMR (DMSO- d_6) δ : 3.95 (2H, s), 7.32 (5H, s), 8.00 (1H, br.s), 8.18 (1H, br.s), 11.17 (1H, br.s), 11.33 (1H, br.s). MS m/e : 277 (M^+).

6-Carbamoyl-5-(4-chlorophenylthiomethyl)uracil (**16e**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350, 1730, 1680, 1650. NMR (DMSO- d_6) δ : 3.94 (2H, s), 7.34 (4H, s), 8.00 (1H, br.s), 8.18 (1H, br.s), 11.22 (1H, br.s), 11.35 (1H, br.s). MS m/e : 313 ($M^+ + 2$), 311 (M^+).

5-Benzylthiomethyl-6-carbamoyluracil (**16f**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350—3230, 1740, 1690, 1650. NMR (DMSO- d_6) δ : 3.41 (2H, s), 3.74 (2H, s), 7.26 (5H, s), 8.00 (1H, br.s), 8.17 (1H, br.s), 11.00 (1H, br.s), 11.13 (1H, br.s). MS m/e : 291 (M^+).

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