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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 decsribed 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}

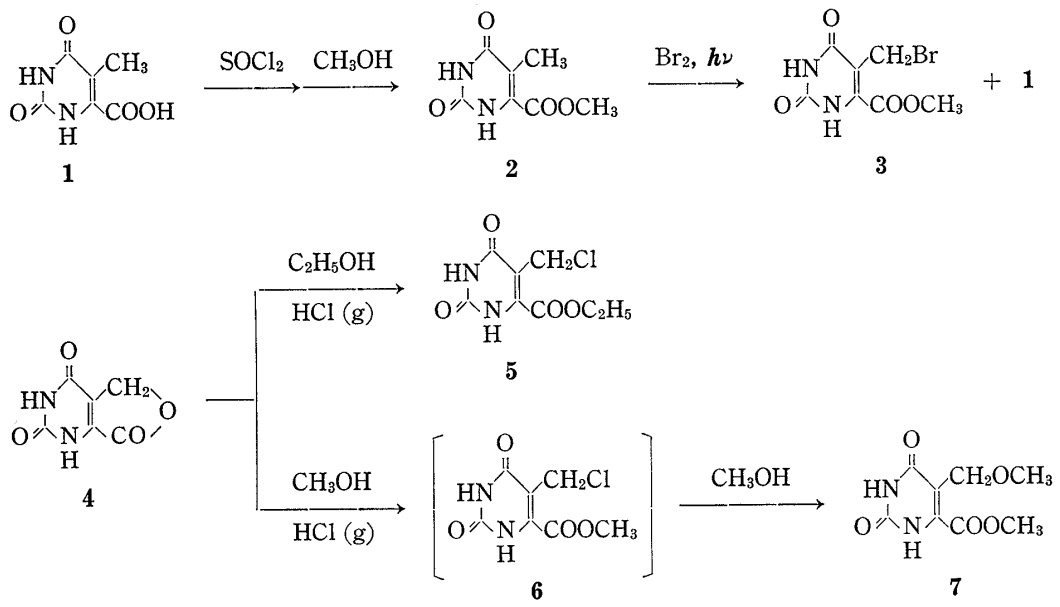


Chart 1

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—1620 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]

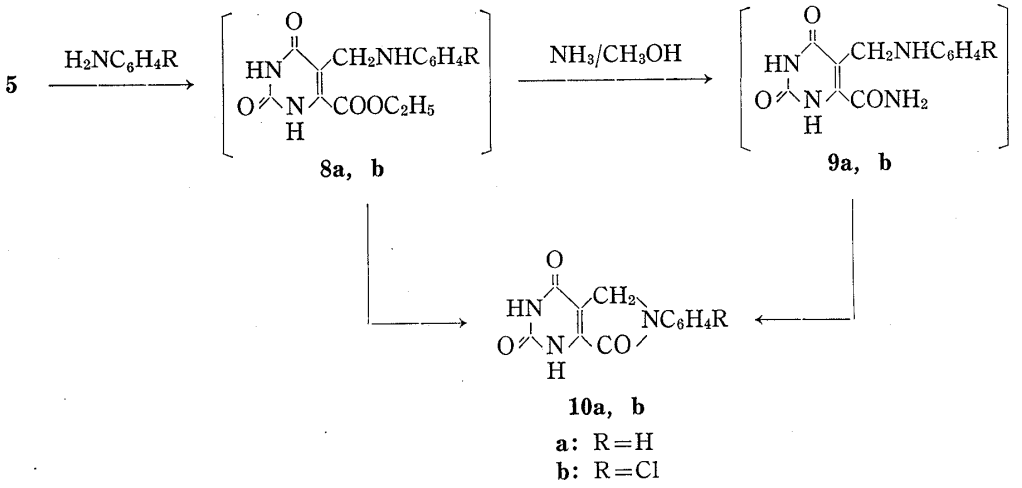


Chart 2

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—5° afforded the corresponding esters (**11a—g**). The IR spectra exhibit absorption bands at 1730—1710 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*.

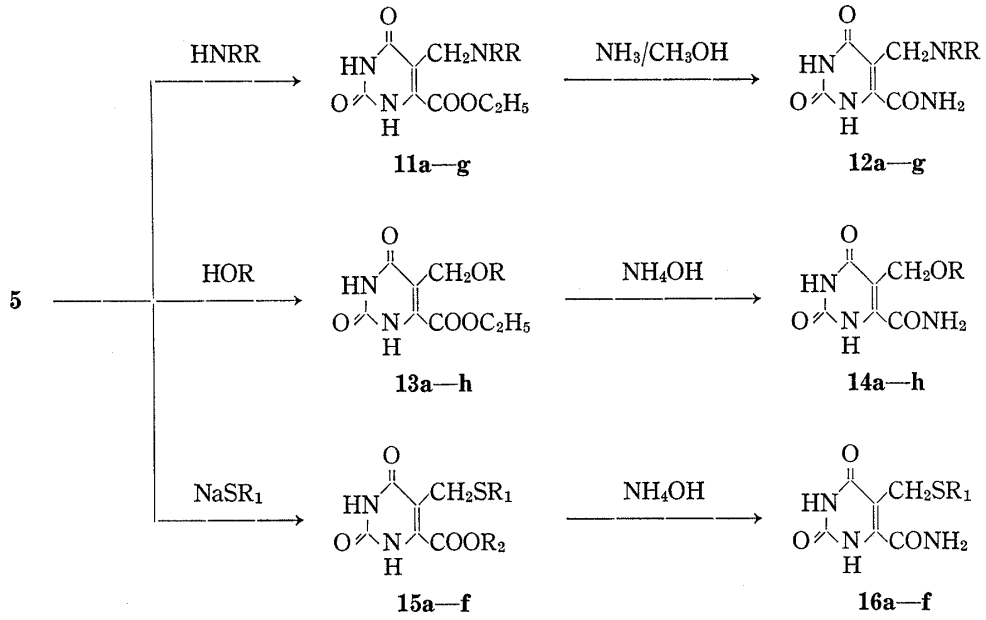
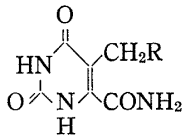


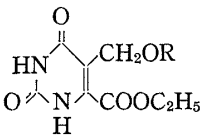
Chart 3

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_2O	$C_{11}H_{16}N_4O_3$	52.37 (52.17	6.39 6.60	22.21 22.43)
12b		81.3	233—240	EtOH–H_2O	$C_{10}H_{14}N_4O_3$	50.41 (50.32	5.92 6.11	23.52 23.78)
12c		67.7	202—206	EtOH–H_2O	$C_{10}H_{15}N_5O_3$	47.43 (47.37	5.97 5.86	27.65 27.63)
12d		76.4	234—236	EtOH–H_2O	$C_{11}H_{17}N_5O_3$	49.43 (49.30	6.41 6.42	26.20 26.35)
12e		84.8	229—232	DMF–EtOH	$C_{10}H_{14}N_4O_4$	47.24 (47.35	5.55 5.68	22.04 21.85)
12f	$N(CH_3)_2$	72.0	214—217	EtOH–H_2O	$C_8H_{12}N_4O_3$	45.28 (45.21	5.70 5.86	26.40 26.35)
12g	$N(C_2H_5)_2$	95.1	228—234	EtOH–H_2O	$C_{10}H_{16}N_4O_3$	49.99 (50.17	6.71 6.78	23.32 23.30)

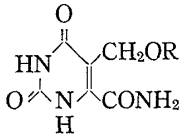
Four samples at concentrations of 3, 10, 30, and 100 μg/ml were prepared in 97.5% saline–2.5% ethanol, and 20 μl of each sample was added to L-1210 cells (1×10^5 cells/180 μl in 10% horse serum). 5-FU was used as an internal standard. After incubation of the medium in a humidified atmosphere of 5% CO_2–95% air for 18 hr at 37°, 5-[^{125}I]iodo-2′-deoxyuridine (0.2 μCi/20 μl) was added. The medium was incubated for a further 6 hr, then L-1210 cells were

Table II.



Compd. No.	R	Yield (%)	mp(°C)	Recryst. solv.	Formula	Analysis(%) Calcd (Found) C	H	N
13a	CH_3	73.8	166 —167 (dec.)	MeOH	$C_9H_{12}N_2O_5$	47.37 (47.63	5.30 5.19	12.28 12.15)
13b	C_2H_5	76.0	199 —201	MeOH	$C_{10}H_{14}N_2O_5$	49.58 (49.64	5.83 5.85	11.56 11.62)
13c	$CH_2CH_2CH_3$	87.1	180 (dec.)	EtOAc	$C_{11}H_{16}N_2O_5$	51.56 (51.54	6.29 6.27	10.93 11.01)
13d	$CH(CH_3)_2$	76.9	179 —181	MeOH	$C_{11}H_{16}N_2O_5$	51.56 (51.34	6.29 6.10	10.93 11.02)
13e	$CH_2CH{=}CH_2$	91.6	166 —169	MeOH	$C_{11}H_{14}N_2O_5$	51.97 (51.75	5.55 5.56	11.02 11.04)
13f	$CH_2CH_2OCH_3$	91.0	171.5—172	EtOAc	$C_{11}H_{16}N_2O_6$	48.53 (48.76	5.92 6.00	10.29 10.47)
13g	$CH_2C_6H_5$	90.3	175 —176.5	EtOAc	$C_{15}H_{16}N_2O_5$	59.21 (59.46	5.30 5.31	9.21 9.32)
13h	$CH_2CH_2C_6H_5$	93.9	178.5—180.5	MeOH	$C_{16}H_{18}N_2O_5$	60.37 (60.26	5.70 5.60	8.80 8.79)

Table III.



Compd. No.	R	Yield (%)	mp(°C)	Recryst. solv.	Formula	Analysis(%) Calcd (Found) C	H	N
14a	CH_3	78.1	220(dec.)	MeOH–H_2O	$C_7H_9N_3O_4$	42.21 (42.44	4.55 4.68	21.10 20.83)
14b	C_2H_5	96.6	223 —228 (dec.)	MeOH–H_2O	$C_8H_{11}N_3O_4$	45.07 (44.93	5.20 5.14	19.71 19.44)
14c	$CH_2CH_2CH_3$	75.2	193.5—195.5	MeOH–H_2O	$C_9H_{13}N_3O_4$	47.57 (47.66	5.77 5.53	18.49 18.58)
14d	$CH(CH_3)_2$	72.0	194.5—197.5 (dec.)	MeOH	$C_9H_{13}N_3O_4$	47.57 (47.32	5.77 5.70	18.49 18.61)
14e	$CH_2CH{=}CH_2$	77.9	173.5—175.5	MeOH	$C_9H_{11}N_3O_4$	48.00 (47.94	4.92 4.78	18.66 18.68)
14f	$CH_2CH_2OCH_3$	79.0	186(dec.)	MeOH–H_2O	$C_9H_{13}N_3O_5$	44.44 (44.41	5.38 5.43	17.28 17.12)
14g	$CH_2C_6H_5$	72.2	220 —227 (dec.)	MeOH	$C_{13}H_{13}N_3O_4$	56.72 (56.97	4.76 4.72	15.27 15.38)
14h	$CH_2CH_2C_6H_5$	63.1	181 —182.5	MeOH	$C_{14}H_{15}N_3O_4$	58.13 (58.09	5.23 5.11	14.53 14.55)

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

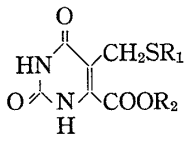
The incorporation of 5-[^{125}I]iodo-2′-deoxyuridine into the tested cells was measured and the percent growth inhibition was calculated by means of the following equation:

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

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

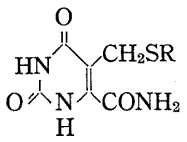
6-Carbamoyl-5-(4-chlorophenylthiomethyl)uracil (**16e**) exhibited 42% inhibition at 100 μg/ml. However, other compounds showed no inhibition.

Table IV.



Compd. No.	R_1	R_2	Yield (%)	mp(°C)	Recryst. solv.	Formula	Analysis(%) Calcd (Found) C	H	N
15a	$CH_2CH_2CH_3$	CH_3	65.8	215.5—217.5	MeOH	$C_{10}H_{14}N_2O_4S$	46.50 (46.73	5.46 5.44	10.85 10.61)
15b	$CH_2(CH_2)_2CH_3$	C_2H_5	69.8	212 —214	MeOH	$C_{12}H_{18}N_2O_4S$	50.33 (50.21	6.34 6.60	9.78 9.80)
15c	$CH_2COOC_2H_5$	C_2H_5	77.6	155 —156.5	EtOH	$C_{12}H_{16}N_2O_6S$	45.56 (45.27	5.10 5.09	8.86 8.91)
15d	C_6H_5	CH_3	78.5	214.5—216.5	MeOH	$C_{13}H_{12}N_2O_4S$	53.42 (53.15	4.14 4.10	9.58 9.43)
15e	*p*-C_6H_4Cl	C_2H_5	87.5	236 —238	EtOH	$C_{14}H_{13}ClN_2O_4S$	49.34 (49.50	3.85 3.82	8.22 8.16)
15f	$CH_2C_6H_5$	C_2H_5	86.7	213 —214.5	MeOH	$C_{15}H_{16}N_2O_4S$	56.24 (56.20	5.03 5.10	8.74 8.97)

Table V.



Compd. No.	R	Yield (%)	mp(°C) (dec.)	Recryst. solv.	Formula	Analysis(%) Calcd (Found) C	H	N
16a	$CH_2CH_2CH_3$	98.1	283	MeOH–H_2O	$C_9H_{13}N_3O_3S$	44.43 (44.16	5.39 5.36	17.27 17.09)
16b	$CH_2(CH_2)_2CH_3$	95.0	232—235	MeOH–H_2O	$C_{10}H_{15}N_3O_3S$	46.68 (46.44	5.88 5.93	16.33 16.12)
16c	CH_2CONH_2	76.0	260	EtOH–H_2O	$C_8H_{10}N_4O_4S$	37.21 (37.31	3.90 4.18	21.64 21.40)
16d	C_6H_5	98.6	242	MeOH–H_2O	$C_{12}H_{11}N_3O_3S$	51.98 (51.81	4.00 4.04	15.15 15.19)
16e	*p*-C_6H_4Cl	79.7	240	MeOH–H_2O	$C_{12}H_{10}ClN_3O_3S$	46.23 (46.14	3.23 3.27	13.48 13.33)
16f	$CH_2C_6H_5$	82.2	204—207	MeOH–H_2O	$C_{13}H_{13}N_3O_3S$	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 (μg/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. ^{1}H-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 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 ν_{max}^{Nujol} cm^{-1}: 1735. NMR (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 $C_7H_8N_2O_4$: 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—210°. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1710. NMR (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 $C_7H_7BrN_2O_4$: 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—211°. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1710. NMR (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 $C_8H_9ClN_2O_4$: 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 ν_{max}^{Nujol} cm^{-1}: 1740, 1710. NMR (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 $C_8H_{10}N_2O_5$: 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—5°. 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° (lit.[8] mp>330°).

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° (lit.[8] mp~300°).

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 ν_{max}^{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 ν_{max}^{Nujol} cm^{-1}: 1720.

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

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

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

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

5-Diethylaminomethyl-6-ethoxycarbonyluracil (**11g**): Yield: 59.1%. mp 153—156°. IR ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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-Benzyloxymethyl-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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{Nujol} cm^{-1}: 1700. NMR (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 ν_{max}^{Nujol} cm^{-1}: 1720. NMR (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 ν_{max}^{Nujol} cm^{-1}: 1730, 1710. NMR (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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ($M^+-C_5H_{10}N_2$).

6-Carbamoyl-5-(N-methylpiperazinomethyl)uracil (**12d**): IR ν_{max}^{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 ν_{max}^{Nujol} cm^{-1}: 3200—3080, 1730, 1640. MS *m/e*: 254 (M^+).

6-Carbamoyl-5-dimethylaminomethyluracil (**12f**): IR ν_{max}^{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 ν_{max}^{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 ($M^+-C_2H_5$).

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 ν_{max}^{Nujol} cm^{-1}: 3360, 1750, 1700, 1650. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3300, 1700, 1640. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3300—3200, 1700—1650. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3350, 1750, 1690, 1640. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3500, 3420, 1750, 1690, 1650. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3350, 1720—1640. NMR (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-Benzyloxymethyl-6-carbamoyluracil (**14g**): IR ν_{max}^{Nujol} cm^{-1}: 3360, 1750, 1690, 1650. NMR (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^++H).

6-Carbamoyl-5-(2-phenylethoxymethyl)uracil (**14h**): IR ν_{max}^{Nujol} cm^{-1}: 3500, 3400, 1700. NMR (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 ν_{max}^{Nujol} cm^{-1}: 3350, 1680—1640. NMR (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 ν_{max}^{Nujol} cm^{-1}: 1680—1640. NMR (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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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 ν_{max}^{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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