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5-Fluorouracil Derivatives. I. The Synthesis of 1-Carbamoyl-5-fluorouracils

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The toxicity and tumor affinity of 5-fluorouracil (**1**) have been modified by the introduction of a carbamoyl group. Carbamoylation by three general methods were studied extensively: (i) The reaction of **1** with isocyanate, (ii) the reaction of 1-chloroformyl-5-fluorouracil with amine, and (iii) the reaction of **1** with carbamoyl chloride. These three methods usually give 1-carbamoyl-5-fluorouracils (**2**). 3-Carbamoyl-5-fluorouracils were not obtained by any method. The **2** substances take a hydrogen-bonded structure in chloroform, a non hydrogen-bonded structure in DMSO at 80 °C, and mixed structures in DMSO at 25 °C. Thirty-six homologues shown by **2** were prepared all of these compounds showed antitumor activity. Of them, 1-hexylcarbamoyl-5-fluorouracil (HCFU) appeared to be the most promising antitumor agent when administered orally in that HCFU retains well balanced lipo- and hydro-philicity, is stable in acid in the stomach, and moreover, decomposed moderately in a tumor. Isocyanate was obtained from the reaction of amine with trichloromethyl chloroformate (TCF) by simply heating these two reagents in toluene; this offers a convenient new method for synthesizing isocyanate from amine. Several new isocyanate were obtained from amino acids.

As the combination of long-standing research on isocyanate chemistry[1] and the synthetic work on 5-fluorouracil derivatives, searching for useful products, the reaction of isocyanate with 5-fluorouracil (**1**) has been studied in detail; it has led to the discovery of the powerful antitumor agents.[2]

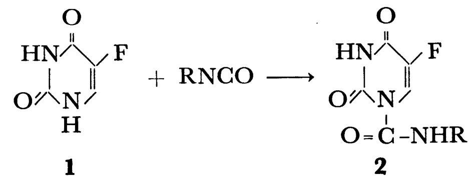
1, though an effective antitumor agent,[3] has a strong toxicity and poor tumor affinity. Chemical modifications of **1** by introducing β-cyanoethyl,[4] 2-tetrahydrofuryl,[5] 2-oxo-3-tetrahydrofuryl,[6] β-amino-β-carboxyethyl,[7] methyl,[8] hydroxy,[9] benzyloxy,[9] 2,3-dihydroxypropyl,[10] acyl,[11] alkyl- and aryl- sulfonyl,[11] and alkoxycarbonylmethyl[12] groups have been reported. However many of these masked compounds have no or only weak activities toward tumors, because the chemical bonds between **1** and the substituents are too strong to undergo biodegradation. Some of the 5-fluorouracil derivatives retaining weakly bonded substituents, though, show no difference in action toward tumors when compared with **1** itself.

In order to adapt the biological activities of **1** for practical purposes, especially for oral administration, hundreds of new structural analogs have been synthesized. The antitumor activities of these compounds were examined at the Pharmacology Division, National Cancer Center Research Institute, Tokyo. Some of the screening results for biological activity have been published.[13,14] In the present paper we wish to report the synthesis of 1-carbamoyl-5-fluorouracils (**2**) in detail.

Although the reaction of uracil and isocyanate has been reported to be sluggish,[15] the treatment of uracil with methyl isocyanate in a dimethyl sulfoxide solution gave 1-methylcarbamoyluracil.[16] We have extensively explored the reactions of **1** with isocyanate, with phosgene and amine, and with carbamoyl chlorides, and have obtained a number of **2** substances by three general synthetic methods.

Results and Discussion

Method 1. The reaction of **1** with isocyanates affords **2**.



Scheme 1.

This reaction was originally carried out in N,N-dimethylformamide. However, our thorough study of the solvent effect revealed that pyridine (Method 1-A) was the best solvent and that the reaction proceeded almost quantitatively. In other solvents, such as N,N-dimethylacetamide (Method 1-B) and dimethyl sulfoxide (Method 1-C), however, the yield does not exceed 70% as is shown in Table 1. The best reaction temperature is 90—100 °C. The best molar ratio of isocyanate/**1** is 1.5. The reaction is catalyzed by organic bases, such as triethylamine, triethylenediamine, and DBU (1,8-diazabicyclo[5.4.0]undecene-7).

This method gives products of the best quality and in good yields as well. 1-Arylcarbamoyl-5-fluorouracil is obtained only by this method. It is known[11] that

TABLE 1. SOLVENT EFFECTS ON THE CONVERSION OF 5-FLUOROURACIL TO 1-HEXYLCARBAMOYL-5-FLUOROURACIL[a]

Solvent	Conversion[b] (%)
Pyridine	99
N,N-Dimethylformamide	70
N,N-Dimethylacetamide	70
Dimethyl sulfoxide	40
Hexamethylphosphoric triamide	60
o-Dichlorobenzene	40
Triethylamine	trace
N,N-Dimethylaniline	60
Quinoline	60
Acetonitrile	70
Nitromethane	70

a) The n-$C_6H_{13}NCO$-to-5-fluorouracil molar ratio was 1.5. The reaction was carried out at 90 °C for 2 h. b) The conversion was measured by comparing the TLC spots of premixed 5-fluorouracil and **22**.

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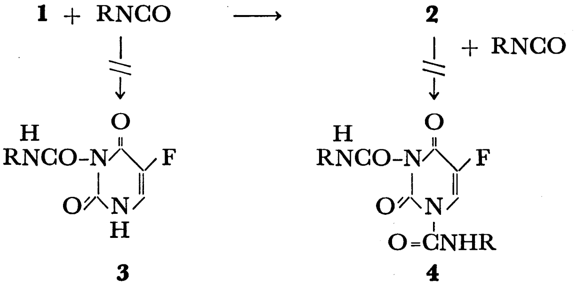
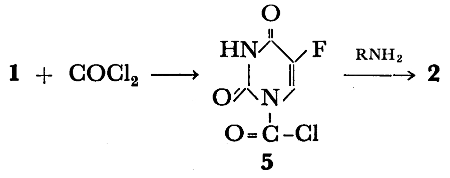
the reaction of **1** with an electrophile like alkyl chloride introduces substituents at the 3- and 1-positions of **1**. However, 3-carbamoyl-substituted 5-fluorouracils (**3** and **4**) were not obtained by the treatment of 5-fluorouracils with isocyanate, even when a higher temperature, a large excess of isocyanate, or a catalyst such as triethylamine was employed. This may result from the acidic character of the proton on the nitrogen at the 3-positions of **1** and **2**, or from the easy dissociation of once-formed carbamoyl groups at the 3-positions of **3** and**4**.



Scheme 2.

Method 2. Phosgene can be condensed with **1**, but the resulting 1-chloroformyl-5-fluorouracil (**5**) is too unstable to be isolated; nevertheless, it is stable enough in a basic solvent such as pyridine at low temperatures. Accordingly, **5** treated with aliphatic amines *in situ* afforded **2**.



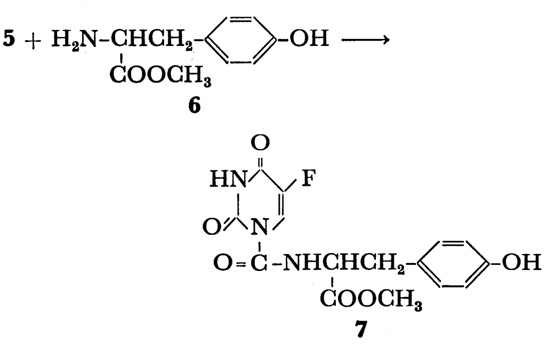
Scheme 3.

On the contrary, aromatic amine does not react with **5**, indicating that a strong basicity is necessary for the amine to react with **5**.

In this reaction, a small amount of triethylamine increases the yield, while excess amines lower the yield, because of the following further reaction:

$$\mathbf{2} + RNH_2 \longrightarrow \mathbf{1} + RNHCONHR$$

Method 2, shown in Scheme 3, is a convenient method to prepare **2**, as amine is more easily available than isocyanate. One more practical advantage is that amines retaining a hydroxy moiety, like thyrosine, **6**, can condense with **5**.

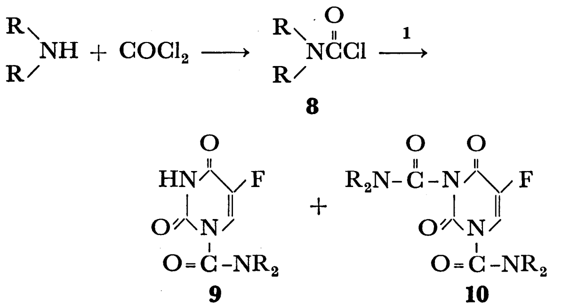


Scheme 4.

The carbamoyl uracil (**7**) can not be obtained by Method 1, because hydroxy isocyanate can not be prepared.

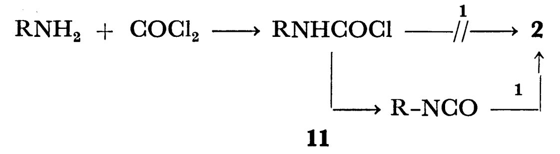
Method 3. Amine and phosgene condense to give carbamoyl chloride. The carbamoyl chloride of secondary amine (**8**) reacted with **1** to give 1-(*N*,*N*-disubstituted carbamoyl)-5-fluorouracil (**9**).

When an excess of carbamoyl chloride (**8**) was employed, 1,3-dicarbamoyl-5-fluorouracil (**10**) was also produced, along with 1-carbamoyl-5-fluorouracil (**9**).



Scheme 5.

The carbamoyl chloride of primary amine (**11**) and **1** do not give **2**, even in the presence of triethylamine at low temperatures, but they do give **2** in low yields at a high temperature (80 °C).



Scheme 6.

The nucleophilicity of **1** is too weak to attack the carbonyl of **11** at low temperatures. At a high temperature (80 °C), **11** decomposes to isocyanate, and eventually the isocyanate reacts with **1** to give **2**.

The structure of **2** was confirmed by elemental analysis and by its infrared and NMR spectra.**

In a polar solvent like dimethyl sulfoxide, the **2** substances take two mixed structures at room temperature, as is shown in Fig. 1 and Table 3. These two structures are presumed to be a hydrogen-bonded[16] **12** and a non hydrogen-bonded structure, **13**.

With an increase in the temperature, **13** predominates over **12**, as polar dimethyl sulfoxide affects the hydrogen bond unfavorably. At 80 °C, for example, 1-hexylcarbamoyl-5-fluorouracil (**22**) mostly exists in the form of

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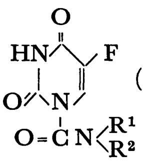
** The position of substituents was clearly distinguished on the basis of UV at varying pH and NMR spectra of 1-alkoxymethyl-, 3-alkoxymethyl-, and 1,3-bis(alkoxymethyl)-5-fluorouracils. The NMR spectra of 1-substituted uracils showed a sharp doublet at around 7.5 ppm due to C_6–H (coupling with F), while non-substituted and 3-monosubstituted uracils gave the corresponding triplets (coupling with F and N_1–H) at around 8 ppm. A fuller account will be given in detail in the third article of this series. The NMR spectrum of **2** showed a doublet due to C_6–H, indicating the 1-carbamoyl structure.

TABLE 2. 1-CARBAMOYL-5-FLUOROURACILS



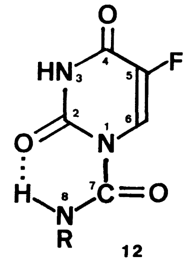
(R^1=H)

Compd	R_2	Synthetic method	Yield %	Mp °C	Molecular formula	Found (Calcd) % C	H	F	N
15	CH_3	1-C	86.1	170	$C_6H_6FN_3O_3$	38.23 (38.51)	3.22 (3.23)	10.10 (10.15)	22.31 (22.46)
16	C_2H_5	1-B	65.1	165	$C_7H_8FN_3O_3$	41.41 (41.80)	4.12 (4.01)	9.46 (9.44)	20.72 (20.89)
17	C_3H_7	1-B	80.1	145	$C_8H_{10}FN_3O_3$	44.61 (44.65)	4.76 (4.65)	8.67 (8.84)	19.81 (19.53)
18	i-C_3H_7	1-B	61.5	145	$C_8H_{10}FN_3O_3$	44.29 (44.65)	4.60 (4.65)	8.98 (8.84)	19.26 (19.53)
19	n-C_4H_9	1-B	72.3	137	$C_9H_{12}FN_3O_3$	47.29 (47.16)	5.32 (5.28)	8.18 (8.29)	18.80 (18.33)
20	t-C_4H_9	1-B	50.2	108	$C_9H_{12}FN_3O_3$	46.99 (47.16)	5.76 (5.28)	8.41 (8.29)	18.78 (18.33)
21	n-C_5H_{11}	1-B	40.2	117	$C_{10}H_{14}FN_3O_3$	49.56 (49.38)	5.81 (5.80)	7.57 (7.81)	17.02 (17.28)
22	n-C_6H_{13}	1-A	95.0	110—111	$C_{11}H_{16}FN_3O_3$	51.19 (51.36)	6.37 (6.23)	7.27 (7.39)	16.60 (16.34)
23	n-C_7H_{15}	1-B	58.4	103	$C_{12}H_{18}FN_3O_3$	53.37 (53.13)	7.02 (6.69)	7.02 (7.00)	15.36 (15.49)
24	n-C_8H_{17}	1-B	53.2	98—100	$C_{13}H_{20}FN_3O_3$	55.12 (54.72)	7.42 (7.07)	6.33 (6.65)	14.34 (14.73)
25	n-$C_{12}H_{25}$	2	60.1	107—108	$C_{17}H_{28}FN_3O_3$	59.20 (59.80)	8.35 (8.27)	5.52 (5.56)	11.92 (12.31)
26	n-$C_{18}H_{37}$	1-B	62.1	107—108	$C_{23}H_{40}FN_3O_3$	65.25 (64.91)	9.81 (9.41)	4.06 (4.46)	9.72 (9.87)
27	cyclo-C_6H_{11}	1-B	55.2	156—157	$C_{11}H_{14}FN_3O_3$	52.14 (51.76)	5.72 (5.49)	7.02 (7.45)	16.17 (16.47)
28	$CH_2C_6H_5$	1-A	91.8	177—178	$C_{12}H_{10}FN_3O_3$	55.45 (55.75)	4.10 (3.83)	7.05 (7.21)	16.30 (15.96)
29	$CH_2CH_2C_6H_5$	1-A	58.9	161	$C_{13}H_{12}FN_3O_3$	56.73 (56.32)	4.48 (4.36)	6.86 (6.85)	15.66 (15.16)
30	CH_2-CH=CH_2	2	31.8	130—131	$C_8H_8FN_3O_3$	44.76 (45.08)	3.57 (3.78)	8.51 (8.91)	19.27 (19.71)
31	CH=CH_2	1-A	70.3	150—160	$C_7H_6FN_3O_3$	41.95 (42.22)	3.03 (3.04)	9.25 (9.54)	20.90 (21.09)
32	COC_6H_5	1-A	28.1	168	$C_{12}H_8FN_3O_4$	52.21 (51.99)	3.21 (2.91)	7.22 (6.85)	14.79 (15.16)
33	C_6H_5	1-C	81.4	280	$C_{11}H_8FN_3O_3$	52.83 (53.02)	3.19 (3.24)	7.64 (7.63)	16.43 (16.86)
34	o-CH_3-C_6H_4	1-C	73.4	280—283	$C_{12}H_{10}FN_3O_3$	55.15 (54.75)	3.97 (3.85)	7.02 (7.22)	15.67 (15.96)
35	o-NO_2-C_6H_4	1-C	46.0	216—242	$C_{11}H_7FN_4O_5$	45.32 (44.91)	2.87 (2.40)	6.03 (5.46)	18.62 (19.04)
36	$(CH_2)_6$[a]	1-A	89.0	172—173	$C_{16}H_{18}F_2N_6O_6$	44.90 (44.87)	4.38 (4.24)	8.39 (8.87)	20.00 (19.61)
37	m-$CH_2C_6H_4CH_2$[b]	1-A	50.2	178—180	$C_{18}H_{14}F_2N_6O_6$	48.22 (47.70)	3.15 (3.40)	8.46 (8.05)	18.51 (18.05)
38	CH_2COOCH_3	1-A	70.5	149—150	$C_8H_8FN_3O_5$	39.19 (39.12)	3.29 (3.27)	7.75 (7.50)	17.14 (16.90)
39	$CH_2CH_2COOC_2H_5$	1-A	86.5	151—153	$C_{10}H_{12}FN_3O_5$	43.96 (44.12)	4.43 (4.38)	6.95 (7.03)	15.38 (15.42)
40	$CHCH_2C_6H_5$ $\overset{\mid}{C}OOCH_3$	1-A	92.1	64— 65	$C_{15}H_{14}FN_3O_5$	53.73 (54.13)	4.21 (4.34)	5.67 (5.61)	12.33 (11.94)
41	$CHCH_2C_6H_5$ $\overset{\mid}{C}OOC_2H_5$	1-A	92.1	55— 56	$C_{16}H_{16}FN_3O_5$	55.01 (55.41)	4.62 (4.92)	5.44 (5.18)	12.03 (12.48)
42	$CHCH_2C_6H_5OH(p)$ $\overset{\mid}{C}OOC_2H_5$	2	25.8	76— 78	$C_{16}H_{16}FN_3O_6$	52.60 (52.90)	4.41 (4.59)	5.00 (4.57)	10.82 (10.50)

Table 2. (Continued)

Compd	R^2	Synthetic method	Yield %	Mp °C	Molecular formula	Found (Calcd) %			
						C	H	F	N
43	$\underset{COOC_2H_5}{CHCH_2CH_2SCH_3}$	1-A	73.2	104—105	$C_{12}H_{16}FN_3O_5S$	43.24 (43.27)	4.84 (4.99)	5.70 (5.69)	12.61 (12.31)
44	$\underset{COOCH_3}{CHCH_2CH(CH_3)_2}$	1-A	87.6	95— 96	$C_{12}H_{16}FN_3O_5$	47.84 (47.92)	5.35 (5.44)	6.31 (5.91)	13.95 (13.94)
45	$\underset{COOCH_3}{CHCH_2CH_2COOCH_3}$	2	78.5	59	$C_{12}H_{14}FN_3O_7$	43.51 (43.51)	4.26 (4.27)	5.73 (5.46)	12.69 (12.52)
46	$R_1=R_2=CH_3$	3	71.1	194—196	$C_7H_8FN_3O_3$	41.80 (41.71)	4.01 (4.13)	9.44 (9.24)	20.89 (20.93)
47	$R_1=R_2=C_2H_5$	3	75.5	157—160	$C_9H_{12}FN_3O_3$	47.16 (47.23)	5.28 (5.27)	8.29 (8.11)	18.33 (18.09)
48	$R_1=R_2=C_6H_5$	3	70.8	256—258	$C_{17}H_{12}FN_3O_3$	62.77 (63.05)	3.72 (3.80)	5.84 (5.96)	12.92 (12.69)
49	$R_1=R_2=CH_2CH_2Cl$	3	43.7	176—177	$C_9H_{10}Cl_2FN_3O_3$	36.26 (36.06)	3.38 (3.36)	6.37 (6.14)	14.09 (13.95)
50	$R_1=R_2=C_6H_{13}$	3	52.8	88	$C_{17}H_{28}FN_3O_3$	59.81 (60.03)	8.27 (7.82)	5.57 (5.30)	12.30 (11.98)
51	1,3-Bis$(C_2H_5)_2$[c]	3	31.0	147—148	$C_{14}H_{21}FN_4O_4$	51.21 (51.11)	6.45 (6.44)	5.80 (5.75)	17.06 (16.87)

a) Prepared from hexamethylene diisocyanate. b) Prepared from *m*-xylene-α,α′-diyl diisocyanate. c) 1,3-Bis(diethylcarbamoyl)-5-fluorouracil.



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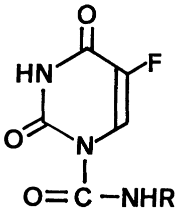

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13. In a poorly solvating chloroform, only the **12** structure is observed at 25 and 60 °C. The ratio of **12** to **13** can be calculated based on the peak-intensity ratio of two doublets at 8.38 ppm (J=8 Hz, C_6–H of **12**) and at 7.70 ppm (J=6 Hz, C_6–H of **13**), or the ratio of two broad triplets at 9.11 ppm (J=6 Hz, N_8–H of **12**) and 5.68 ppm (J=6 Hz, N_8–H of **13**).

In contrast to the fact that the **2** substances decompose gradually in neutral water, they are generally resistant to acid hydrolysis because of their hydrogen bonding. Especially alkylcarbamoyl compounds like **22** are strongly resistant to acid hydrolysis. Indeed, their dormant nature in acid conditions suggests a possible application as oral administrative drugs which can survive acid in the stomach.

1-Alkylcarbamoyl-5-fluorouracil (**2**) can be absorbed into the blood. The lipophilic alkyl group of **2** helps it reach tissues or a tumor, and it moderately decomposes into **1** or other metabolites in tumor cells where the pH is nearly neutral.

The antitumor activities of **2** were evaluated by Hoshi *et al.*[13,14] by oral administration along with two reference compounds, **1** and 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207). The compounds tested in the L-1210 system were methyl-, ethyl-, isopropyl-, phenyl-, hexyl- and cyclohexyl-carbamoyl-5-fluorouracil; the therapeutic ratios ($ILSmax/ILS_{30}$) of these compounds were 1.9, 2.2, 2.3, 1.0, 4.5, and 3.3 respectively, while those of the two reference compounds were 1.7 and 1.0. Among these compounds **22** showed the most effective results. The therapeutic ratio in the C-1498 system of **22** was 11, while those of **1** and FT-207 were 3.3 and 2.5 respectively. **22** was also showed activities toward solid tumors like Nakahara Fukuoka sarcoma and adenocarcinoma-755, and ascites tumors like sarcoma-180A, and was moderately active against Ehrlich ascites carcinoma. This compound had a wider tumor spectrum than **1** and FT-207 upon oral administration.

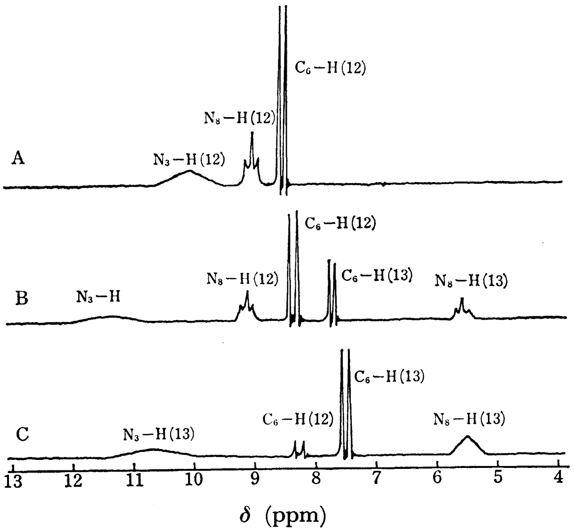

Fig. 1. Partial ^1H NMR spectra of 1-hexylcarbamoyl-5-fluorouracil.

A: In $CDCl_3$ solvent at 25 °C (hydrogen-bonded structure 12),
B: in DMSO-d_6 solvent at 25 °C (60% 12 and 40% 13),
C: in DMSO-d_6 solvent at 80 °C (non hydrogen-bonded structure 13).

TABLE 3. ^{1}H NMR SPECTRAL DATA OF 1-CARBAMOYL-5-FLUOROURACILS

Compd	Carbamoyl groups						Uracil rings				Temp, °C	Solvent
	CH_3	CH_2	$C\underline{H}_nNH$	h,[a] $N\underline{H}C{=}O$	nh,[b] $N\underline{H}C{=}O$	h[c]	N_3-H	h, C_6-H	nh,C_6-H	h(%)		
15			2.52 nh 2.83 h	9.01	5.68	38	11.23	8.37	7.71	41	25	D[e]
15			2.55	—[d]	5.49	0	—	—	7.58	0	80	D
16	1.12		3.30	9.10	5.65	64	11.32	8.37	7.72	67	25	D
17	0.88	1.48	3.14	9.32	5.80	51	11.56	8.50	7.82	44	25	D
17	0.95	1.68	3.38	9.09	—	100	—	8.58	—	100	25	C[f]
18	1.10		3.75	9.02	5.45	41	—	8.38	7.73	43	25	D
19	0.96	1.56	3.45	9.19	—	100	—	8.62	—	100	25	C
20	1.37			9.33	—	100	—	8.48	—	100	25	C
21	0.91	1.47	3.42	9.11	—	100	—	8.63	—	100	25	C
22	0.93	1.47	3.44	9.15	—	100	—	8.62	—	100	25	C
22	0.87	1.28	3.17	9.11	5.68	66	11.20	8.38	7.70	59	25	D
22	0.87	1.28	3.10	—	5.47	0	10.70	8.28	7.50	8	80	D
23	0.89	1.45	3.42	9.15	—	100	—	8.60	—	100	25	C
23	0.88	1.31	3.23	9.21	5.73	73	—	8.47	7.78	67	25	D
24	0.90	1.37	3.34	9.26	—	100	12.44	8.47	—	100	25	C
25	0.90	1.28	3.43	9.12	—	100	—	8.60	—	100	25	C
26	0.88	1.27	3.40	9.00	—	100	—	8.59	—	100	25	C
28			4.55	9.67	—	100	—	8.46	7.75	95	25	D
29		2.70	3.27	—	5.97	0	—	—	7.76	0	25	D+H_2O
30		5.3	4.20	9.72	—	100	—	8.75	—	100	25	P[g]
32				4.33	—	100	12.02	8.31	—	100	25	D
36		1.32	3.30	—	—		—	—	7.78	0	25	D+H_2O
37			4.52	9.65	—	100	12.38	8.47	—	100	25	D
38	3.72, 3.67		4.71, 3.85	9.98	6.60	50	12.00	8.49	7.81	54	25	D
39	1.21	2.56, 4.1	4.2	9.42	6.06	65	11.60	8.46	7.78	72	25	D
40	3.76	3.18	4.85	9.65	—	100	10.14	8.43	—	100	25	C
41	1.41	3.15, 4.15	4.23	9.65	—	100	—	8.43	6.55	95	25	D
42	1.29	3.07, 4.29	4.73	9.45	—	100	—	8.33	—	100	25	C
43	1.33, 2.13	2.4, 4.3	4.75	9.65	—	100	—	8.54	—	100	25	C
44	1.0, 3.82	1.78	4.65	9.75	—	100	11.90	8.50	—	100	25	C
45	2.30	3.76	4.55	9.57	—	100	—	8.50	—	100	25	C
46	2.90, 2.96						—	—	7.96	0	25	C
47	1.18		3.27				—	—	8.15	0	25	C
48							11.85	—	8.45	0	25	D
49		3.80					12.20	—	8.18	0	25	D
50	0.90	1.30	3.30				9.50	—	7.48	0	25	C

a) Hydrogen-bonded. b) Non-hydrogen-bonded. c) (h/h+nh)×100. d) Not detected. e) DMSO-d_6. f) $CDCl_3$. g) Pyridine-d_5.

In one continuing research on antitumor drugs a convenient new method of preparing isocyanate was also found. Isocyanates are obtained by the treatment of amines with trichloromethyl chloroformate (TCF)[17] in toluene at 100—110 °C, followed by distillation. In this reaction, the use of amine hydrochloride is preferable to avoid the formation of 1,3-disubstituted urea. When free amine is used, amine and TFC must be added to the solution so that the TCF is in excess in solution. Otherwise, heating at a high temperature for a long time is necessary for disubstituted ureas to react with TCF. By this method, several new isocyanates, **52**—**55**, were prepared.[18]

Experimental

The melting points were recorded on a Büchi melting-point aparatus and are uncorrected. Most 1-alkylcarbamoyl-5-fluorouracils (**2**) melt instantaneously at 95—170 °C and solidify. This melting point is likely to be overlooked, however. Nevertheless, differential thermal and gravimetric analysis revealed that **2** dissociated to **1** and isocyanates in this melting region, and a loss in weight of the isocyanates was observed. **1** decomposes at 280—283 °C. Therefore, in patents[2] in 1975, we mistakenly observed some decomposition temperatures of **2** to be 280—283 °C. The ^{1}H NMR spectra were recorded on a JEOL-60HL apparatus and the ^{13}C NMR spectra at 15 MHz on a JEOL-FX-60 apparatus. The IR spectra were obtained on a JASCO IR-A-1 apparatus. The mass spectrum was recorded on a Varian CH 7 apparatus. Microanalysis was done by the staff of the Analytical Laboratories of the Mitsui Toatsu Research Center.

*1-Hexylcarbomoyl-5-fluorouracil (**22**) (HCFU). Method 1-A. Reaction in a Pyridine Solution*: Hexyl isocyanate (19.08 g, 0.15 mol) and **1** (13.0 g, 0.1 mol) were heated in 40 ml of pyridine at 90 °C for an hour. The reaction mixture was then cooled to room temperature. About 30 ml of the pyridine were evaporated at 50 °C under reduced pressure. To the resulting residue, 50 ml of ethanol were added at 55 °C. Then the solution was kept at 0—5 °C overnight. Cyrstalline **22** (22.5 g, 87.4%) was thus obtained. As a second crop 2.90 g of product was obtained: mp 110—111 °C.

^{13}C NMR 157.27 (d, $J_{\mathrm{C_4-F}}=1.87$ Hz, C-4), 150.35 (s, C-2), 149.31 (s, C-7), 140.90 (d, $J_{\mathrm{C_5-F}}=16.05$, C-5), 123.43 (d, $J_{\mathrm{C_6-F}}=2.47$ Hz, C-6), 41.52 (s, C-9), 31.38 (s, C-10), 29.11 (s, C-11), 26.51 (s, C-12), 22.55 (s, C-13), 13.97 (s, C-14).

MS *m/e* (rel. intensity) 257 (0.49) (M$^+$), 131 (7.9), 130 (88.4), 128 (1.3), 126 (1.7), 114 (2.0), 113 (1.3), 112 (14.5), 100 (4.9), 99 (70.7), 88 (5.6), 87 (37.4), 86 (2.2), 85 (27.0), 84 (19.8), 83 (1.9), 82 (6.0), 74 (1.3), 71 (3.4), 70 (7.5), 69 (8.6), 68 (1.7), 67 (4.2), 60 (27.0), 59 (8.5), 58 (16.6), 56 (56.2), 55 (49.9), 54 (4.6), 53 (8.0), 51 (2.0), 46 (1.9), 44 (9.5), 43 (35.4), 42 (35.4), 41 (87.4), 40 (7.8), 39 (8.3), 38 (27.0), 37 (2.6), 32 (4.6), 31 (11.4), 30 (11.4), 29 (49.9), 28 (73.8), 27 (43.7), 26 (4.2). IR (KBr) 3320, 3230, 3080, 2920, 1720—1740 (s), 1680, 1660, 1510, 1445, 1340, 1272, 1200, 1090, 1042, 802, 770, 750 cm^{-1}. UV (CHCl$_3$), $\lambda_{\max}$ 258, E 451, $\varepsilon=1.16\times10^4$.

Method 1-B. Reaction in a Dimethylacetamide Solution: Hexyl isocyanate (19.1 g, 0.15 mol), **1** (13.0 g, 0.1 mol) and triethylamine (1.0 g) in 52 ml of *N,N*-dimethylacetamide were heated at 90 °C for 3 h. The reaction mixture was then cooled and stirred into dilute aqueous hydrochloric acid (pH 1; 100 ml). The resulting precipitate was filtered, washed with water, and dried *in vacuo* to yield 21.4 g (83.1%) of crude **22**, which was then recrystallized from ethanol as white crystals.

Method 2. Into a cold (5 °C) solution containing **1** (1.30 g, 0.01 mol) in 40 ml of pyridine, phosgene (2.97 g, 0.03 mol) was bubbled over a 1 h period at 10 °C. Nitrogen gas was passed through to expel the excess phosgene. Hexylamine (1.01 g, 0.01 mol) was then added, and the mixture was stirred 1 h. The resulting pyridine hydrochloride was filtered off, and the reaction mixture was evaporated to dryness. The residue, taken up in 50 ml of chloroform, was washed twice with 30 ml of a dilute hydrochloric acid solution. The chloroform sloution was then dried (Na$_2$SO$_4$) and evaporated to afford **22** (2.05 g, 80.0%).

*1-Phenylcarbamoyl-5-fluorouracil (**33**). Method 1-C. In a Dimethyl Sulfoxide Solution*: To a solution containing **1** (10.4 g, 0.08 mol) in 100 ml of dimethyl sulfoxide, phenyl isocyanate (14.3 g, 0.12 mol) was added, and the mixture was stirred at room temperature for 1 h. When the milky reaction mixture was then filtered, fine precipitates were obtained. The precipitates were suspended in hot ethanol and filtered again to afford **33** (16.2 g, 81.4%); mp 280 °C.

*1-[α-Ethoxycarbonyl-β-(p-hydroxyphenyl)ethylcarbamoyl]-5-fluorouracil (**42**). Method 3.* To a cold pyridine solution containing a 0.04 molar amount of 1-chloroformyl-5-fluorouracil (**5**), a solution of L-thyrosine ethyl ester hydrochloride (9.80 g, 0.04 mol) in triethylamine (12.14 g) was added at 0 °C over a period of 2 h. The pyridine hydrochloride thus formed was filtered off. The filtrate was evaporated to dryness, and the residue, dissolved in 200 ml of chloroform, was washed twice with 200 ml of dilute hydrochloric acid. The chloroform layer was evaporated and column chromatographed on silica gel C-200. Elution with benzene–ethyl acatate (10 : 1) gave 5.10 g (25.8%) of **42**; mp 76.5—78 °C.

*1-Diethylcarbamoyl-5-fluorouracil (**47**). Method 3.* To 1.3 g (0.01 mol) of **1** dissolved in 20 ml of *N,N*-dimethylacetamide was added 0.48 g (0.01 mol) of 50% sodium hydride in mineral oil. Subsequently, diethylcarbamoyl chloride (1.36 g, 0.01 mol) in 5 ml of *N,N*-diethylacetamide was added, drop by drop, at 30 °C. After stirring at 30 °C for 5 h, the reaction mixture was left to stand overnight at room temperature and then filtered; the filtrate was subsequently evaporated *in vacuo*. The chloroform extract of the residue yielded 2.14 g of a crude product which was washed with diethyl ether to afford pure **47** (1.73 g, 75.5%); mp 157—160 °C.

*1,3-Bis(diethylcarbamoyl)-5-fluorouracil (**51**). Method 3.* To **1** (2.6 g, 0.02 mol) in 30 ml of *N,N*-dimethylformamide was added powdered potassium carbonate (3.32 g, 0.024 mol), and then a mixture of diethylcarbamoyl chloride (7.06 g, 0.052 mol) and 20 ml of *N,N*-dimethylformamide. The reaction mixture was heated at 80 °C for 2 h. The product was extracted into chloroform after the removal of the solvent *in vacuo*. The extract was washed with water, dried (Na$_2$SO$_4$), and evaporated to give a viscous oil. The oil was triturated with 5 ml of ethanol, and ether was added to complete the crystallization. The crystal was washed with ether to afford **51** (1.18 g, 31.0%); mp 147—148 °C.

*L-α-Ethoxycarbonyl-β-phenylethyl Isocyanate (**52**).* TCF (16.0 g, 0.07 mol) is added, drop by drop, to a mixture of L-phenylalanine ethyl ester hydrochloride (16.0 g, 0.07 mol) and active carbon (0.1 g) in 200 ml of toluene. The reaction mixture was gradually being heated to 80 °C over a 1 h period, the addition of the TCF being adjusted so as to finish at the time when the temperature reached 80 °C. The reaction was continued for an additional 2 h at 100—110 °C. The subsequent removal of the toluene and distillation of the reaction mixture gave **52** (13.75 g, 89.6%); bp 141—142 °C (5 mm); IR (neat), 2980, 2250(vs), 1735(s), 1208(s), 1197, 1025, 700 cm^{-1}; NMR (neat), 1.12 (3H, t, $J=8$ Hz), 2.95 (2H, d, $J=6$ Hz), 4.09 (2H, q, $J=8$ Hz), 4.0—4.2 (1H, m,) 7.21 (5H, s). Found: C, 65.54; H, 5.91; N, 6.14%. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

*L-α-Ethoxycarbonyl-β-(methylthio)propyl Isocyanate (**53**).* Into a mixture of methionine ethyl ester hydrochloride (14.96 g, 0.07 mol), active carbon (0.01 g), and 200 ml of toluene, TCF (10.4 g, 0.0525 mol) was added dropwise with stirring. Then the reaction mixture was gradually heated up to reflux, and the reflux was continued for 2 h. The subsequent distillation of the reaction mixture gave 7.37 g (51.8%) of **53** as a colorless liquid: bp 133 °C (7 mm); IR (neat), 2995, 2950, 2270(s), 1752(s), 1450, 1225(s), 1040 cm^{-1}; NMR (neat), 1.32(3H, t, $J=8$ Hz), 2—2.2(2H, m), 2.1(3H, s), 2.67(2H, t, $J=7$ Hz), 4.3(2H, q, $J=8$ Hz), 4.2—4.4(1H, m). Found: C, 46.89; H, 6.52; N, 6.66; S, 15.46%. Calcd for $C_8H_{13}NO_3S$: C, 47.27; H, 6.45; N, 6.89; S, 15.74%.

*α-Methoxycarbonyl-β-methylbutyl Isocyanate (**54**).* TCF (19.8 g, 0.1 mol) was added, drop by drop, to a mixture of L-leucine methyl ester hydrochloride (26.62 g, 0.13 mol), active carbon (0.2 g), and toluene (200 ml). The mixture was gradually heated to reflux, and heating at reflux was continued for 2 h. The subsequent distillation of the reaction mixture afforded 15.51 g (69.7%) of **54** as a colorless liquid; bp 74 °C (5 mm); n_D^{25} 1.4322; IR (neat), 3420, 2960, 2270(s), 1755, 1445, 1280, 1220 cm^{-1}; NMR (neat) 0.93(6H, d, J=6 Hz), 1.67 (3H, m), 3.78 (3H, s), 4.05 (1H, t, J=8 Hz). Found: C, 56.61; H, 7.65; N, 7.43%. Calcd for $C_8H_{13}NO_3$: C, 56.31; H, 7.65; N, 8.18%.

*β-(Ethoxycarbonyl)ethyl Isocyanate (**55**).* The treatment of *β*-alanine ethyl ester hydrochloride (15.3 g, 0.1 mol) with TCF (19.8 g, 0.1 mol) in the usual way in **52** afforded 10.2 g (71.2%) of **53** as a colorless liquid; bp 69 °C (8 mm); IR (neat) 3000, 2280, 1750, 1390, 1200 cm^{-1}.

*Phenethyl Isocyanate (**56**).* Into a solution of TCF (19.8 g, 0.1 mol) in 200 ml of toluene, phenethylamine (24.15 g, 0.2 mol) and active carbon (0.1 g) were added, drop by drop, with strring. Then the reaction mixture was gradually heated to 50 °C and TCF (9.9 g, 0.05 mol) was added, drop by drop. The reaction was subsequently continued for 2 h at 100—110 °C. The removal of the solvent and distillation of the residue afforded 25.0 g (85.3%) of **56**: bp 124—126 °C (33 mm).

*Benzyl Isocyanate (**57**).* The treatment of benzylamine (21.4 g, 0.2 mol) with TCF (30.0 g, 0.15 mol) in the same way in was used for **56** afforded 23.0 g (86.4%) of **57**; bp 95 °C (19 mm).

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