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5-Fluorouracil Derivatives. IV.[1] Synthesis of Antitumor-Active Acyloxyalkyl-5-fluorouracils

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The toxicity and tumor affinity of 5-fluorouracil (**1**) have been modified by the introduction of acyloxyalkyl group(s) at the 1-, 3- or 1,3-position(s) of **1**. 1-Acyloxyalkyl-5-fluorouracil (**3**), 3-acyloxyalkyl-5-fluorouracil (**4**) and 1,3-bis(acyloxyalkyl)-5-fluorouracil (**5**) were obtained by three methods: i) the reaction of α-chloroalkyl carboxylate (**2**) with **1**, ii) the reaction of alkylidene diacylate with 2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine, iii) partial hydrolysis of **5**. Compounds **3**, **4** and **5** showed antitumor activity.

Keywords——5-fluorouracil; acyloxyalkyl-5-fluorouracil; antitumor agent; 1-undecanoyloxymethyl-5-fluorouracil

As part of a series of synthetic studies on 5-fluorouracil derivatives aimed at obtaining improved antitumor agents, we have reported the synthesis of 1-carbamoyl-5-fluorouracils.[2]

This time, we wish to report the synthesis of 1-acyloxyalkyl-5-fluorouracils,[3] 3-acyloxyalkyl-5-fluorouracils[4] and 1,3-bis(acyloxyalkyl)-5-fluorouracils (**5**).

Alkyl-substituted 5-fluorouracils such as 1-methyl,[5] 1-pentyl,[6] and 3-pentyl[7]-5-fluorouracils were obtained by the reaction of 5-fluorouracil and alkyl halides. These simple alkyl-substituted 5-fluorouracils have no antitumor activity. Substituted alkyl-5-fluorouracils such as 1-(β-cyanoethyl)-,[8] 1-(2-amino-2-carboxylethyl)-,[9] 1-(2-hydroxyethyl)-,[10] 1,3-bis(2-hydroxyethyl)-,[11] 1-(2,3-dihydroxypropyl)-,[12] 1-glycidyl-,[13] 1-(carboxymethyl)-,[14] 1-(2-tetrahydrofurylmethyl)-[6] 5-fluorouracils were also obtained in a similar way. These substituted alkyl-5-fluorouracils also have no antitumor activity, presumably because the bond between 1-nitrogen of 5-fluorouracil and the α-carbon of the alkyl group in such compounds is too strong to be split in *in vivo* systems. Generation of 5-fluorouracil is essential for antitumor activity.

If ether oxygen is introduced at the α-position of the alkyl group, the bond between nitrogen and carbon becomes labile under hydrolytic conditions. For example, the bond between 1-nitrogen of 5-fluorouracil and carbon of the alkyl group in 1-methoxymethyl-, 1-(α-ethoxyethyl)-, 1-(ethoxymethyl)-,[6] and 1-(2-tetrahydrofuryl)-[15] 5-fluorouracils can be hydrolyzed chemically or enzymatically to 5-fluorouracil. Therefore, these compounds have moderate antitumor activity.

Here we have introduced an acyloxy group instead of an alkoxy group at the α-position of alkyl groups, and strong antitumor activity[16] was obtained with these compounds. α-Acyloxyalkyl-5-fluorouracils have stronger antitumor activity than α-alkoxyalkyl-5-fluorouracils. For example, the increase of life span was 41% when 30 mg/kg of 1-acetoxymethyl-5-fluorouracil was given by intraperitoneal injection in the L-1210 system, whereas the increase of life span was only 6% when 1-methoxymethyl-5-fluorouracil was given under the same conditions.

TABLE I. Acyloxyalkyl-5-fluorouracils

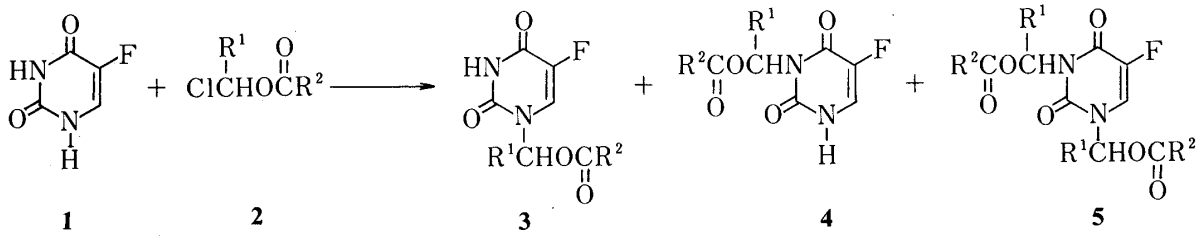
Compd.	Position of substituents	R^1	R^2	Synthetic method	Yield (%)	mp °C (Ref. Ind. n^{25})	Molecular formula	Analysis (%) Found (Calcd)			
								C	H	F	N
8	1	H	CH_3	1	62.0	127—128	$C_7H_7FN_2O_4$	41.86 (41.51	3.51 3.49	9.61 9.40	13.95 13.86)
9	1	H	C_2H_5	1	73.1	105—106	$C_8H_9FN_2O_4$	44.50 (44.45	4.03 4.20	8.39 8.79	12.92 12.96)
10	1	H	C_3H_7	1	86.9	96—98	$C_9H_{11}FN_2O_4$	47.12 (46.96	4.73 4.82	8.08 8.25	12.82 12.17)
11	1	H	C_4H_9	1	77	91—92	$C_{10}H_{13}FN_2O_4$	49.38 (49.18	5.61 5.37	7.61 7.78	11.51 11.47)
12	1	H	C_5H_{11}	1	38.7	95—96	$C_{11}H_{15}FN_2O_4$	50.82 (51.16	5.63 5.85	7.17 7.36	10.42 10.85)
13	1	H	C_6H_{13}	1	82.8	109—110	$C_{12}H_{17}FN_2O_4$	52.69 (52.93	6.24 6.29	6.96 6.98	10.14 10.29)
14	1	H	C_7H_{15}	1	73.6	112—113	$C_{13}H_{19}FN_2O_4$	54.30 (54.54	6.64 6.69	6.78 6.64	9.52 9.78)
15	1	H	C_8H_{17}	1	75.8	111—112	$C_{14}H_{21}FN_2O_4$	56.15 (55.99	7.01 7.05	6.61 6.32	9.06 9.33)
16	1	H	C_9H_{19}	1	68.0	115—116	$C_{15}H_{23}FN_2O_4$	57.00 (57.31	7.50 7.37	6.39 6.04	8.63 8.91)
17	1	H	$C_{10}H_{21}$	1	58.4	93	$C_{16}H_{25}FN_2O_4$	58.30 (58.52	7.35 7.67	5.63 5.79	8.42 8.53)
18	1	H	C_6H_5	1 3	17.1 35.0	183	$C_{12}H_9FN_2O_4$	54.52 (54.55	3.61 3.43	7.05 7.19	10.23 10.60)
19	1	C_3H_7	CH_3	1	38.3	175—175.5	$C_{10}H_{13}FN_2O_4$	48.84 (49.18	5.02 5.37	7.39 7.78	11.26 11.47)

20	1	CH_3	C_4H_9	1	57.0	132	$C_{11}H_{15}FN_2O_4$	50.80 (51.16	5.59 5.85	7.26 7.36	11.22 10.85)
21	1	C_6H_5	CH_3	2	47.8	130	$C_{13}H_{11}FN_2O_4$	56.13 (56.11	4.17 4.00	7.14 6.83	10.52 10.14)
22	3	H	*tert*-C_4H_9	3	20.5	135—137	$C_{10}H_{13}FN_2O_4$	48.85 (49.18	5.06 5.37	7.43 7.78	11.19 11.47)
23	3	H	C_6H_5	3	24.6	188	$C_{12}H_9FN_2O_4$	54.63 (54.55	3.69 3.43	7.44 7.19	10.94 10.60)
24	1,3-Bis	H	CH_3	1	3.2	110—111	$C_{10}H_{11}FN_2O_6$	43.80 (43.53	4.04 4.01	6.93 6.78	10.21 9.99)
25	1,3-Bis	H	C_2H_5	1	33.2	69—70	$C_{12}H_{15}FN_2O_6$	47.38 (47.68	4.97 5.00	5.89 6.29	8.89 9.27)
26	1,3-Bis	H	C_4H_9	1	56	(Oil 1.4830)	$C_{16}H_{23}FN_2O_6$	53.92 (53.62	6.51 6.47	5.11 5.30	7.68 7.82)
27	1,3-Bis	H	*tert*-C_4H_9	1	53.9	113—114	$C_{16}H_{23}FN_2O_6$	54.06 (53.62	6.69 6.47	4.99 5.30	7.72 7.82)
28	1,3-Bis	H	C_5H_{11}	1	88.9	42—44	$C_{18}H_{27}FN_2O_6$	56.21 (55.95	7.23 7.04	4.63 4.91	7.01 7.25)
29	1,3-Bis	H	C_7H_{15}	1	47.1	57—58	$C_{22}H_{35}FN_2O_6$	60.03 (59.71	8.03 7.97	4.09 4.29	6.25 6.33)
30	1,3-Bis	H	$C_{15}H_{31}$	1	15.2	81	$C_{38}H_{67}FN_2O_6$	68.10 (68.43	10.24 10.13	2.65 2.85	4.69 4.20)
31	1,3-Bis	H	C_6H_5	1	35.4	Jelly	$C_{20}H_{15}FN_2O_6$	60.30 (60.15	3.86 3.82	4.77 4.65	7.03 7.01)

The acyloxyalkyl-5-fluorouracils were obtained by three general methods.

Method 1: The Reaction of α-Chloroalkyl Carboxylate (2) with 1 Afforded 3, 4 and 5

This type of reaction was carried out in the presence of a base such as triethylamine in a

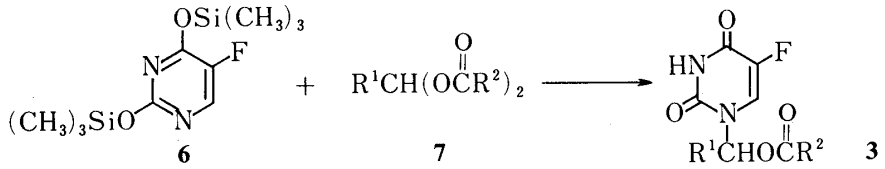


1 2 3 4 5

polar solvent such as *N*,*N*-dimethylformamide or pyridine. When equimolar amounts of **1** and **2** reacted, the products consisted of mostly **3** with very small amounts of **4** and **5**, and about 10—50% of the starting material **1** was recovered. The yield of **3** reached maximum when 1.2—1.3 molar of **2** was used. As the molar ratio of **2** to **1** was increased further, the yield of **5** increased.

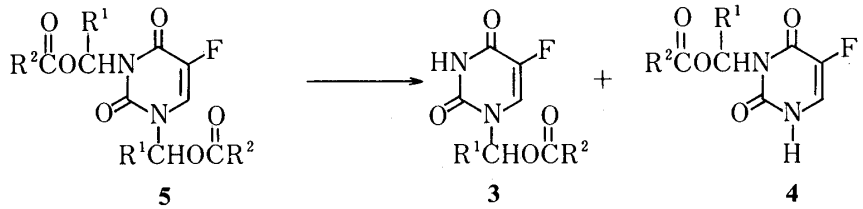
Method 2: The Reaction of 6 with 7 Afforded 3

This reaction was usually carried out in the presence of an acidic catalyst such as tin(IV) chloride, titanium(IV) chloride, or aluminium chloride, as a reaction promoter. The reaction is similar to the reaction[1] of acetal with **6** to afford 1-alkoxyalkyl-5-fluorouracil, 3-alkoxyalkyl-5-fluorouracil and 1,3-bis(alkoxyalkyl)-5-fluorouracil, but the formation of **4** and **5** was so small that they could not be isolated in the present case.



6 7 3

Method 3: Compound 5 was Partially Hydrolyzed to 3 and 4



5 3 4

Acidic or basic aqueous solution was used for hydrolysis, and pH 8—11 was found to be the most favorable for partial hydrolysis. Too strong an acid or base gave the complete hydrolysis product **1**. This reaction was usually conducted at temperatures from 30 to 60 °C, with frequent checking by thin layer chromatography. The ratio of **3** to **4** was around 1. These results contrast with the fact that 1,3-bis(2-tetrahydrofuryl)-5-fluorouracil gives exclusively 1-(2-tetrahydrofuryl)-5-fluorouracil on weak alkaline hydrolysis.[4] Method 3 is the best available to prepare **4** at the present time, because Methods 1 and 2 gave only small amounts of **4**.

Among the 31 products, 1-undecanoyloxymethyl-5-fluorouracil (**17**) seems to be the best antitumor agent, because it has the highest therapeutic ratio (5.8)[16] when administered orally.

TABLE II. ^{1}H-NMR Spectral Data for Acyloxyalkyl-5-fluorouracils

Compd.	–CHR^{1}O	Acyloxy groups R^1		Acyloxy groups R^2			Uracil rings			Solvent (D=DMSO-d_6, C=$CDCl_3$)
		CH_3	CH_2	CH_3	CH_2	$COCH_2R$	N_1–H	N_3–H	C_6–H	
8	5.54					2.04		11.97	8.05 d	D
9	5.63			1.05		2.37		12.05	8.18 d	D
10	5.64			0.92	1.60	2.35		12.02	8.17 d	D
11	5.16			0.93	1.53	2.40		10.12	7.65 d	C
12	5.68			0.93	1.53	2.40		9.85	7.62 d	C
13	5.66			0.89	1.33	2.39		10.03	7.64 d	C
14	5.67			0.90	1.30	2.40		10.21	7.66 d	C
15	5.63			0.88	1.28	2.38		9.97 br	7.61 d	C
16	5.66			0.92	1.31	2.42		9.68 br	7.65 d	C
17	5.63			0.88	1.24	2.38			7.63 d	C
18	5.87			7.4—8.1 (C_6H_5)					8.27 d	D
19	6.83	0.98	1.40			2.11		9.53	7.33 d	D
20	6.75	1.55		0.87	1.55	2.25		11.83	8.16 d	D
21	7.82	7.53 (C_6H_5)				2.22		12.2	7.91 d	D
22	5.75			1.12					7.95 t	D
23	6.0			7.5—8.0 (C_6H_5)			11.25		7.5—8.0	D
24	5,66 5.95					2.08, 2.13			7.62	C
25	5.63, 5.80			1.04		2.1—2.6			8.26 d	C
26	5.65, 5.95			0.7—1.9		2.1—2.6			7.64 d	C
27	5.63, 5.83			1.17, 1.19					7.70 d	C
28	5.63, 5.85			0.9	1.25	2.2			7.64 d	C
29	5.61, 5.90			0.9	1.25	2.0—2.6			7.66 d	C
30	5.71, 6.02			0.87	1.24	2.30			7.71 d	C
31	5.5—6.4			7.4—8.2 (C_6H_5)					7.4—8.2 d	D

Experimental

1-Propionyloxymethyl-5-fluorouracil (9)——Compound **1** (6.50 g, 0.05 mol) was dissolved in 50 ml of dimethylacetamide, then triethylamine (15.18 g, 0.15 mol) was added to the solution. The mixture was treated dropwise with chloromethyl propionate (8.00 g, 0.065 mol) over 30 min. The reaction mixture was stirred for 2 h, allowed to stand overnight and then filtered to remove the precipitated triethylamine hydrochloride. Then, dimethylacetamide was distilled from the filtrate and the residue was applied to a column packed with silica gel. Elution with mixtures (8:2 to 8:1 in mixing ratio) of benzene and ethyl acetate gave **9**. This product was further recrystallized from benzene to afford pure **9** (7.93 g, 73.1%): mp 105—106 °C; IR (KBr); 1725, 1675, 1147 cm^{-1}; NMR (DMSO-d_6): 1.05 (3H, t, J=8 Hz, CH_3), 2.37 (2H, q, J=8 Hz, $COCH_2$), 5.63 (2H, s, OCH_2), 8.18 (1H, d, J=6 Hz, C_6–H), 12.05 (1H, br, NH).

1,3-Bis(pivaloyloxymethyl)-5-fluorouracil (27)——5-Fluorouracil (2.60 g, 0.02 mol) was dissolved in 40 ml of dimethylacetamide, then 1.52 g (0.011 mol) of powdered potassium carbonate was added to this solution. The mixture was treated dropwise with a solution of 6.62 g (0.04 mol) of chloromethyl pivalate in 10 ml of dimethylacetamide over 1 h. The reaction mixture was kept at room temperature for 10 h, then filtered to remove a precipitate. The dimethylacetamide was removed from the filtrate by distillation. The residue was taken up in 30 ml of ether and after filtration to remove insoluble materials, the ethereal filtrate was concentrated to obtain 3.15 g of crude crystals. Recrystallization from ether gave pure **27** (2.12 g, 53.9%): mp 113—114 °C; IR (KBr): 1737, 1685, 1130 cm^{-1}; NMR (CCl_4)δ: 1.17 (9H, s, CH_3), 1.19 (9H, s, CH_3), 5.63 (2H, s, CH_2), 5.83 (2H, s, CH_2) and 7.70 (1H, d, J=6 Hz, C_6–H).

1-(α-Acetoxy-α-phenyl)methyl-5-fluorouracil (21)——2,4-Bis(trimethylsilyloxy)-5-fluoropyrimidine (2.74 g, 0.01 mol) and 2.71 g (0.013 mol) of benzylidine diacetate were dissolved in 20 ml of chloroform, then a solution of 2.0 g of tin(IV) chloride in 10 ml of chloroform was slowly added in a dropwise manner. The chloroform was then removed by distillation and the residue was extracted with water. The extraction residue was dissolved in chloroform and decolorized, and the chloroform was distilled off. The residue was again dissolved in a small amount of chloroform and petroleum ether was added to afford **21** (1.0 g, 47.8%): mp 130 °C; IR (KBr): 1732, 1700 cm^{-1}; NMR (DMSO-d_6) δ: 2.22 (3H, s, CH_3), 7.53 (5H, s, C_6H_5), 7.82 (1H, s, CH), 7.91 (1H, d, J=6 Hz, C_6–H), 12.2 (1H, br,

NH).

1-Benzoyloxymethyl-5-fluorouracil (18) and 3-Benzoyloxymethyl-5-fluorouracil (23)——Compound **31** (4 g, 0.01 mol) was dissolved in mixture of 10 ml of pyridine and 10 ml of water, then a 5% aqueous sodium carbonate solution was slowly added dropwise to the solution under agitation while the pH value of the liquid was maintained at 8—10. The mixture was kept for 4 h at 60 °C to effect alkaline hydrolysis of the starting **31**. The reaction mixture was concentrated under reduced pressure and cooled. Any remaining unreacted **31** (0.35 g, 8.8%) then precipitated and was filtered off. The filtrate was subjected to silica gel column chromatography. Elution with benzene and ethyl acetate (3 : 1 mixing ratio) gave **18** in the first eluate. Recrystallization from benzene gave pure **18** (0.92 g, 34.8%): mp 179—180 °C. This compound was identical with **18** obtained from chloromethyl benzoate and **1** (IR, NMR and mp). **23** (0.65 g, 24.6%) was then obtained in the second eluate: mp 188 °C. IR (KBr): 1702, 1123 cm^{-1}; NMR (DMSO-d_6) δ: 5.99 (2H, s, CH_2), 7.4—8.1 (6H, m, C_6H_5 and C_6–H), 11.23 (1H, br, NH).

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