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3-Alkylcarbonyloxymethyl derivatives of 5-fluorouracil have been synthesized starting with 1-ethyloxycarbonyl-5-fluorouracil. Alkylation of the starting material with alkylcarbonyloxymethyl iodides, generated from the corresponding chlorides by the Finkelstein reaction, in the presence of 1,8-bis(dimethylamino)naphthalene followed by deprotection with 1,1-dimethylethylamine gave good yields (50-60%) of the target derivatives after column chromatography. A 90% yield of 3-acetyloxymethyl-5-fluorouracil was obtained when the corresponding commercially available bromide was used, instead of the *in situ* generated iodide, and the product could be isolated from the crude reaction by crystallization. An alternate path of sequential alkylation of 5-fluorouracil with alkylcarbonyloxymethyl chlorides in the presence of tertiary amines, exhibiting different reactivities towards the chlorides, gave an excellent yield of 1-acetyloxymethyl-3-propionyloxymethyl-5-fluorouracil in the one instance it was attempted, but subsequent deprotection of the 1-position with methylamine gave only a 24% yield of 3-propionyloxymethyl-5-fluorouracil.

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Introduction.

3-Alkylcarbonyloxymethyl derivatives of 5-fluorouracil, **1**, remain attractive synthetic targets because of their potential utility as prodrugs that could enhance the topical delivery of 5-fluorouracil. They are one representative of a broad class of derivatives that function as soft alkyl prodrugs [1]. Enzymatic hydrolysis of the acyl group leaves a hydroxymethyl group on the functional group that had been alkylated, and the hydroxymethyl group undergoes chemical hydrolysis - usually very rapidly - to give the parent drug [2]. Solubility data for the only member of the series that has been characterized - 3-acetyloxymethyl-5-fluorouracil, **2** - showed that it was more lipid and water soluble than 5-fluorouracil [3]; properties that predict that the derivative **2** should permeate the skin faster than 5-fluorouracil itself [4].

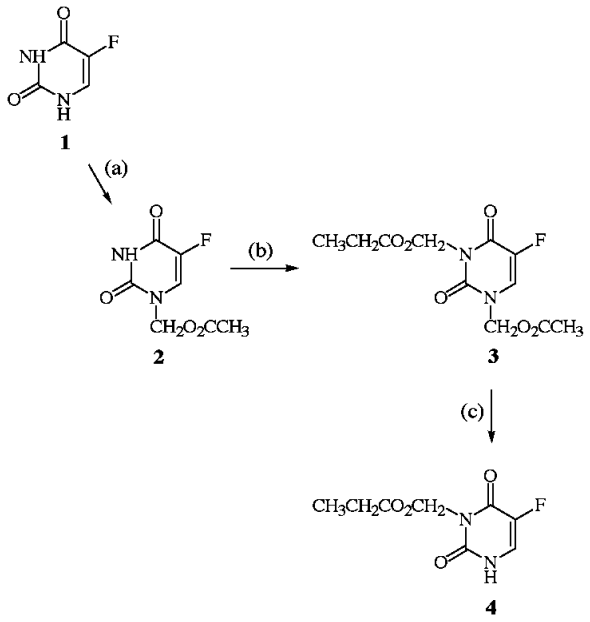
Syntheses of 3-derivatives of 5-fluorouracil are much more difficult than are those of the 1-derivatives. The 1-position is the sterically less hindered and more nucleophilic site (due to its higher pKa value [5]), so it undergoes acylation and alkylation reactions before the 3-position. Thus, protection of the 1-position, alkylation of the 3-position and deprotection of the 1-position is required to synthesize the 3-alkylcarbonyloxymethyl-5-fluorouracil derivatives. In practice most reported syntheses of 3-alkylcarbonyloxymethyl type derivatives of 5-fluorouracil have involved syntheses of symmetrical 1,3-bisalkylcarbonyloxymethyl-5-fluorouracil derivatives and their hydrolyses to give 20-30% yields of the 3-mono derivative from the 1,3-bis derivative in this acyclic series [3,6]. Somewhat higher yields (40-50%) were obtained from the aminolysis of the 1,3-bisphthalidyl-5-fluorouracil derivatives in the corresponding cyclic series [7]. The best yields in the cyclic series (50-94%) were obtained by hydrolysis of 1-acyl-3-phthalidyl-5-fluorouracil derivatives [7,8]; the yields were somewhat lower (35-72%) if based on the starting 1-acyl-5-fluorouracil. However, application of this approach of acylating the 1-position then alkylating the 3-position and hydrolyzing the 1-acyl group of 5-fluorouracil has not been reported for the syntheses of the acyclic series of 3-alkylcarbonyloxymethyl derivatives of 5-fluorouracil.

In this paper the synthesis of acyclic 3-alkylcarbonyloxymethyl-5-fluorouracils from the alkylation of a 1-acyl-5-fluorouracil and the subsequent aminolysis of the 1-acyl group will be reported. In addition, the synthesis of a 3-alkylcarbonyloxymethyl-5-fluorouracil by sequential alkylation of the 1- then the 3-position of 5-fluorouracil and the preferential aminolysis of the 1-alkylcarbonyloxymethyl group will be reported.

Results and Discussion.

The first approach to synthesizing 3-alkylcarbonyloxymethyl-5-fluorouracil derivatives was by preferential aminolysis of a 1,3-bisalkylcarbonyloxymethyl-5-fluouorouracil derivative. Previous utilization of this approach had always started with symmetrical derivatives: the same alkylcarbonyloxymethyl group on both nitrogens. However, it was known that 1-propionyloxymethyl-5-fluorouracil hydrolyzed 25% slower than the 1-acetyloxymethyl derivative; and that the longer alkyl chain members of the series hydrolyzed even slower [9]. Assuming the same degree of steric hindrance to aminolysis as hydrolysis and that the relationships applied in the 3-alkylcarbonyloxymethyl series as well as the 1-series, the synthesis and aminolysis of 1-acetyloxymethyl-3-propionyloxymethyl-5-fluorouracil, **3**, was undertaken to determine the feasibility of using unsymmetrical 1,3-bis derivatives to synthesize 3-mono derivatives (Scheme 1). Synthesis of the intermediate 1-acetyloxymethyl-5-fluorouracil was achieved in excellent yield from the reaction of acetyloxymethyl chloride first with four equivalent of *N*-methylpyrrolidine to form the corresponding quaternary salt, then with

Scheme 1

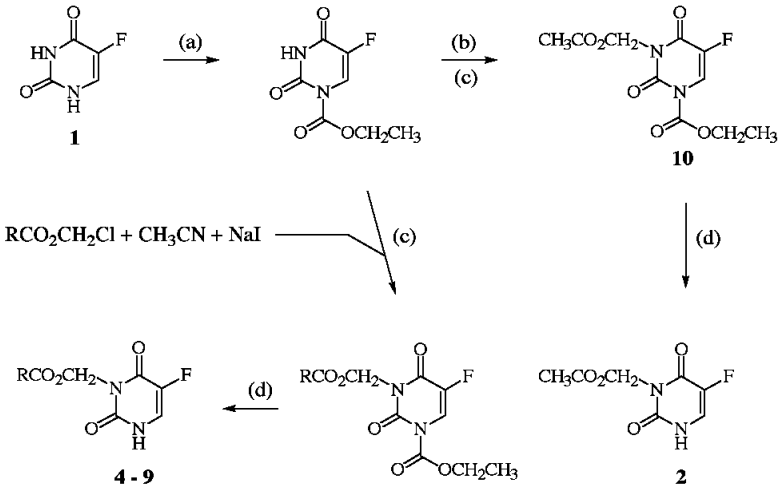


(a) $CH_3CO_2CH_2Cl$, *N*-methylpyrrolidine, CH_3CN
(b) $CH_3CH_2CO_2CH_2Cl$, $(CH_3CH_2)_3N$, CH_3CN
(c) CH_3NH_2, CH_3CN

5-fluorouracil [9]. In contrast to the results of Kamata *et al.* [7], where cyclic arylcarbonyloxymethyl halides (3-bromo- or 3-chlorophthalides) were used, no completely - regio-selective 1-alkylation of 5-fluorouracil was obtained unless the alkyl chloride was first converted to a bulky quaternary salt. Thus, the selectivity in the alkylation reaction is due to the steric bulk of the quaternary salt alkylating agent and the stereoelectronically more hindered nature of the 3-position of 5-fluorouracil.

On the other hand, the second alkylation (alkylation of 1-acetyloxymethyl-5-fluorouracil) had to be accomplished using a non-sterically hindered alkylating agent, so the tertiary amine base that was used in the reaction would ideally not react at all with the alkyl halide. The use of the relatively unreactive propionyloxymethyl chloride, instead of the corresponding bromide or iodide, and an excess of relatively sterically hindered triethylamine, instead of *N*-methylpyrrolidine, were required to give excellent yields of 1-acetyloxymethyl-3-propionyloxymethyl-5-fluorouracil, **3**. Subsequent deprotection of the 1-position required a sterically unhindered amine such as methylamine to give any reaction at all; 1,1-dimethylethylamine gave no apparent aminolysis after 24 hours. The complex mixture that resulted required chromatography to give the desired 3-propionyloxymethyl-5-fluorouracil, **4**, albeit in only 24% crude yield. No 1-acetyloxymethyl-5-fluorouracil was isolated from the aminolysis. Thus, unsymmetrical 1,3-bisalkylcarbonyloxymethyl-5-fluorouracil derivatives can be synthesized in excellent yields, but subsequent aminolysis gives poor yields of the 3-mono derivative in the one example studied. The slightly greater steric hindrance to hydrolysis afforded by the propionyl

Scheme 2



(a) CH_3CH_2OCOCl, $(CH_3CH_2)_3N$, CH_2Cl_2
(b) $CH_3CO_2CH_2Br$, CH_3CN
(c) 1,8 bis(dimethylamino)naphthalene
(d) $(CH_3)_3CNH_2$, CH_2Cl_2

relative to the acetyl group did not give any practical advantage in improved yield of the 3-derivative from the intermediate unsymmetrical 1,3-bis derivative.

The second approach to synthesizing 3-alkylcarbonyloxymethyl-5-fluorouracil derivatives was by preferential aminolysis of 1-acyl-3-alkylcarbonyloxymethyl-5-fluorouracil derivatives. It was known that 1-acyl-3-phthalidyl-5-fluorouracils could be hydrolyzed to give 3-phthalidyl-5-fluorouracils in 50-94% yields. The selectivity of this hydrolysis derived from the fact that the 3-phthalidyl-5-fluorouracil anion (pKa = 8.0)[3] formed during hydrolysis of the 1-acyl group is relatively stable compared to the alkyloxy anion (pKa = 13.1)[10] formed during hydrolytic ring opening of the 3-phthalidyl group. However, it was not known which 1-acyl derivative (1-alkylcarbonyl, 1-arylcarbonyl or 1-alkyloxycarbonyl) would be sufficiently stable under the required alkylation conditions to give good yields of 1-acyl-3-alkylcarbonyloxymethyl-5-fluorouracils. Previously, the analogous cyclic compounds had been obtained by alkylation of 1-alkyloxycarbonyl-5-fluorouracil with 3-bromophthalide and triethylamine [7] or 1-acetyl-5-fluorouracil with 3-bromophthalide and sodium hydride [8]. Thus, any 1-acyl group appeared to be sufficiently stable to be an appropriate choice.

Attempted alkylations of 1-alkylcarbonyl- or 1-alkyloxycarbonyl-5-fluorouracils with alkylcarbonyloxymethyl chlorides in the presence of tertiary amine bases such as triethylamine gave mixtures of 1-mono and 1,3-bis alkylated products. In retrospect this result is not surprising. Since the synthesis of both types of 1-acyl-5-fluorouracil derivative is accomplished using acyl halides and a tertiary amine base, the acylation reaction is reversible in the presence of a tertiary amine because the 5-fluorouracil anion is so stable and hence a good leaving group. Kametani *et al*. [8] observed a similar result from attempts to obtain acylation of the 3-position of 1-acyl-5- fluorouracils to give different acyl groups at the 1- and 3-positions; products with the same acyl group at both positions were obtained. In this case, once the 5-fluorouracil anion is formed it reacts irreversibly with the alkylating agent at the most nucleophilic and least sterically hindered site - the 1-position. The possibility of 3-alkylation was made even less tenable because the alkyl chloride was not very reactive, giving time for the deacylation-alkylation at the 1-position to take place.

On the other hand, the use of a more reactive alkyl bromide or iodide led to a very rapid formation of the quaternary salt even with the relatively sterically hindered triethylamine that subsequently prevented alkylation at the 3-position; only the 1-acylated starting material was recovered. The competing formation of the quaternary salt was apparently not significant in the reaction of 3-bromophthalide and triethylamine with 1-alkyloxycarbonyl-5-fluorouracil [7] because of the additional steric hindrance to the formation of the quaternary salts posed by the phenyl group attached to the same carbon as the bromide. The solution to the problem here was to use the non-nucleophilic, strong base - 1,8-bis(dimethylamino)naphthalene - and an alkyl bromide or iodide in the alkylation of the 1-acyl-5-fluorouracil starting material (Scheme 2).

A 1-alkyloxycarbonyl-5-fluorouracil was chosen as the starting point for the synthesis of 3-alkylcarbonyloxymethyl-5-fluorouracils. A 1-alkyloxycarbonyl group [11] is more stable than 1-alkylcarbonyl [12] or 1-arylcarbonyl groups [13]; and the 1-ethyloxycarbonyl member of the series was chosen because it was the easiest to synthesize and purify in the highest yield (>90%).

Only one alkyl bromide was used - acetyloxymethyl bromide - because it was the only bromide that was commercially available. The remaining alkylations were run using alkylcarbonyloxymethyl iodides generated from the corresponding chlorides using a modification of the Finkelstein reaction [14] but were not isolated; or were generated *in situ* using sodium iodide in a mixed solvent of acetonitrile and dimethyl formamide. The alkylcarbonyloxymethyl chlorides were synthesized from the corresponding acid chlorides and paraformaldehyde in the presence of zinc chloride catalyst without solvent using a modification of the procedure of Neuenschwander and co-workers [15]. They were not purified other than to precipitate the zinc salts with pentane, then filter, wash with aqueous base and concentrate the cooled pentane solutions under reduced pressure. The alkylcarbonyloxymethyl chlorides that were used in the reaction were greater than 80% (and most > 90%) pure based on comparisons of the integrations of the $RCH_2CO_2CH_2Cl$ with the total RCH_2COX type of absorptions in their ^1H nmr spectra: (deuteriochloroform) δ 5.70 (s, 2, $RCH_2CO_2CH_2Cl$) versus δ 2.5- 3.0 (m, 2, RCH_2COX) for X = OCH_2Cl or C1, and R = H or alkyl [9]. The conversions of the chlorides to their corresponding iodides in the modified Finkelstein reaction were followed by the loss of the CO_2CH_2Cl absorption at δ 5.70 and formation of the CO_2CH_2I absorption at δ 5.93 in deuteriochloroform.

The alkylcarbonyloxymethyl bromide or iodide was allowed to react with 1-ethyloxycarbonyl-5-fluorouracil in dry acetonitrile in the presence of 1,8-bis(dimethylamino)naphthalene to give excellent yields of the intermediate 1-ethyloxycarbonyl-3-alkylcarbonyloxymethyl-5-fluorouracils (Scheme 2) as determined by ^1H nmr spectroscopy: (deuteriochloroform) δ 5.90(s, 2, CO_2CH_2N)and δ 7.98(d, J = 6 Hz, 1, C^6-*H*) . However, only in the reaction with the acetyloxymethyl bromide was the intermediate **10** isolated (97% yield), characterized and elemental analysis obtained. Subsequent reaction with 1,1-dimethylethylamine gave 50-60% yields of the corresponding 3-alkylcarbonyloxymethyl-5-fluorouracils, **4** – **9**, after column chromatography, or 90% yield by crystallization in the case of 3-acetyloxymethyl-5-fluorouracil, **2**.

The reaction with the bromide gave a much higher yield primarily because it had been purified before purchase. On the other hand, iodides were generated and used immediately without purification. In addition, the chlorides from which the iodides were generated had not been purified by distillation or chromatography either. Thus, there were numerous side products that were generated in the alkylation reaction with the iodides that were not isolated or characterized. None of the side products appeared to be present in greater than 10% of the crude 3-alkylcarbonyloxymethyl-5-fluorouracil target products.

The structure of the 3-alkylcarbonyloxymethyl derivatives of 5-fluorouracil was confirmed by the fact that the melting points of two of the derivatives (**2** and **9**) are consistent with literature melting points. Also, the ^{1}H nmr spectrum of **2** is consistent with that reported for **2**, in the literature [6].The positions of the C^6-*H* and N-C*H*$_2$O$_2$C absorptions, in the ^{1}H nmr spectra of the other derivatives (**4**-**9**), are identical with those of **2** when run in dimethyl sulfoxide-d$_6$. Finally, the uv spectra of these derivatives undergo a shift in λmax from 266 nm at pH 4.0 to 300 nm at pH 9.1 [13], which is consistent with the shift in λmax previously reported.

Thus, a series of acyclic 3-alkylcarbonyloxymethyl derivatives of 5-fluorouracil (**2**, **4**-**9**) has been synthesized in good yields from the alkylation of 1-alkyloxycarbonyl-5-fluorouracil with an alkylcarbonyloxymethyl bromide or iodide in the presence of 1,8-bis(dimethylamino)naphthlene followed by deprotection with 1,1-dimethylethylamine. An alternate approach involving alkylation of 1-acetyloxymethyl-5-fluorouracil with propionyloxymethyl chloride in the presence of triethylamine gave an excellent yield of 1-acetyloxymethyl-3-propionyloxymethyl-5-fluorouracil, **3**. However, subsequent deprotection of the 1-position gave only a low yield of the desired 3-propionyloxymethyl-5-fluorouracil, **4**.

EXPERIMENTAL

The tlc were run on Brinkman Polygram Sil G/UV 254 plates. The mp were measured in capillary tubes with a Meltemp melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian EM-390 90 MHz spectrometer, while the uv spectra were recorded on Shimadzu UV-265 or 2501 PC spectrophotometers. Microanalyses were obtained from Atlantic Microlabs Inc., Norcross, GA. All of the chemical starting materials and ^{1}H nmr solvents were obtained from Aldrich. The bulk solvents and silica gel for chromatography were from Fisher Scientific.

Synthesis of 3-Acetyloxymethyl-5-fluorouracil (**2**).

To 25 ml of well-stirred, dry acetonitrile was added 5.91 g (0.039 mole) of acetyloxymethyl bromide, 7.89 g (0.037 mole) of 1,8-bis(dimethylamino)naphthalene and 7.03 g (0.037 mole) of 1-ethyloxycarbonyl-5-fluorouracil: mp 126-128°, lit [12] mp 126-128°; ^{1}H nmr (deuteriochloroform): δ 8.0(d, J = 6 Hz, 1, C^6-*H*), 4.47(q, J = 7 Hz, 2, CH$_3$C*H*$_2$O$_2$C) and 1.40(t, J = 7 Hz, 3, C*H*$_3$CH$_2$O$_2$C). After two hours at room temperature the suspension was diluted with 75 ml of ether, allowed to stir for 0.5 hour and filtered. The filtrate was concentrated at the rotary evaporator at 40° until a thick oil was obtained. The intermediate (1-ethyloxycarbonyl-3-acetyloxymethyl-5-fluorouracil, **10**) oil was dissolved in 100 ml of dichloromethane and allowed to react with 2.96 g (0.04 mole) of 1,1-dimethylethylamine for one hour with stirring. Then, over 10 minutes, 300 ml of hexane was added in portions with stirring. The precipitate was filtered, washed with petroleum ether and dried to give **2** as white crystals (6.50 g, 92% yield), mp 160-161°, lit [3] mp 158-159°; tlc (silica gel, ether) Rf 0.20; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 7.89 (d, J = 6 Hz, 1, C^6-*H*), 5.73(s, 2, N-C*H*$_2$O$_2$C) and 2.03(s, 3, C*H*$_3$CO$_2$); uv (acetonitrile): λmax 266 nm (ε 7214 1/mole).

In a similar reaction the intermediate **10** was isolated as white crystals from 12 ml ether and 30 ml petroleum ether (1.92 g, 97% yield), mp 87 - 89°; tlc (silica gel, ether) Rf 0.46; ^{1}H nmr (deuteriochloroform): δ 8.03 (d, J = 6 Hz, 1, C^6-*H*), 5.95 (s, 2, N-C*H*$_2$O$_2$C), 4.50 (q, J = 7 Hz, 2, CH$_3$C*H*$_2$O$_2$C), 2.07(s, 3, C*H*$_3$CO$_2$), and 1.43(t, J = 7 Hz, 3, C*H*$_3$CH$_2$O$_2$C).

Anal. Calcd for C$_{10}$H$_{11}$N$_2$O$_6$F: C, 43.80; H, 4.04; N, 10.22. Found: C, 43,59; H, 4.00; N, 10.46.

General Procedure for the Synthesis of 3-Alkylcarbonyloxymethyl-5-fluorouracil: 3-Propionyloxymethyl-5-fluorouracil (**4**).

To 25 ml of well-stirred, dry acetonitrile was added 2.7 g (0.022 mole) of propionyloxymethyl chloride and 4.00 g (0.027 mole) of anhydrous sodium iodide. The suspension was kept well-stirred and protected from light with an aluminum foil wrap. After 24 hours, the suspension was filtered and the residue was washed twice with 10 ml of dry acetonitrile. The combined filtrates were allowed to react with 3.64 g (0.018 mole) of 1-ethyloxycarbonyl-5-fluorouracil and 4.16 g (0.019 mole) of 1,8-bis(dimethylamino)naphthalene. The reaction mixture became warm to the touch. After 6 hours, the suspension was diluted with 120 ml of ether, stirred for 0.75 hour and filtered. The residue was washed with 20 ml of ether. The combined filtrates were concentrated at the rotary evaporator at 40° to give a dark oil which was primarily the desired intermediate, 1-ethyloxycarbonyl-3-propionyloxymethyl-5-fluorouracil; ^{1}H nmr (deuteriochloroform): δ 8.04 (d, J = 6 Hz, 1, C^6-*H*), 5.97 (s, 2, N-C*H*$_2$O$_2$C), 4.50(q, J = 7 Hz, 2, CH$_3$C*H*$_2$O$_2$C), 2.35(q, J = 8 Hz, 2, CH$_3$C*H*$_2$CO$_2$), 1.45(t, J = 7 Hz, 3, C*H*$_3$CH$_2$O$_2$C)and 1.13(t, J = 8 Hz, 3, C*H*$_3$CH$_2$CO$_2$). The dark oil was dissolved in 20 ml of well-stirred dichloromethane and allowed to react with 1.53 g (0.021 mole) of 1,1-dimethylethylamine; the mixture boiled briefly after mixing. After the mixture had been stirred at room temperature overnight it was adsorbed on 13 g of silica gel and chromatographed on 135 g of silica gel using hexane: acetone 3:1 as the eluent to give **4** as a colorless oil (2.71 g, 70% yield). The oil was crystallized from 1 ml acetone, 35 ml ether and 12 ml of pentane added in 4 ml portions over 24 hours to give **4** as white crystals (2.10 g, 54% yield), mp 93.5-95.5°; tlc (silica gel, ether) Rf 0.24; ^{1}H nmr (deuteriochloroform): δ 7.40(d, J = 6 Hz, 1, C^6-*H*), 5.95(s, 2, N-C*H*$_2$O$_2$C), 2.35(q, J= 8 Hz, 2, CH$_3$C*H*$_2$CO$_2$) and 1.11 (t, J = 8 Hz, 3, C*H*$_3$CH$_2$CO$_2$); uv (acetonitrile): λmax 266 nm (ε 7135 1/mole). A second crop of crystals of **4** was obtained from the filtrate of the first crop (0.23 g, 6% yield), mp 88-91°; tlc (silica gel, ether) Rf 0.24.

Anal. Calcd for $C_8H_9N_2O_4F$: C, 44.45; H, 4.20; N, 12.96. Found: C, 44.36, H, 4.17, N, 12.89.

3-Butyryloxymethyl-5-fluorouracil (**5**).

This compound was obtained as for **4** as white crystals from 20ml ether and 10 ml of pentane (2.08 g, 53% yield), mp 73-75°; tlc (silica gel, ether) Rf 0.26; ^{1}H nmr (deuteriochloroform): δ 7.35 (d, J = 6 Hz, 1, C^6-*H*), 5.97 (s, 2, N-C*H*$_2$O$_2$C), 2.33(t, J = 8 Hz, 2, CH$_2$C*H*$_2$CO$_2$), 1.65 (m, 2, CH$_3$C*H*$_2$CH$_2$CO$_2$) and 0.95 (t, J = 8 Hz, 3, C*H*$_3$CH$_2$CH$_2$CO$_2$); uv (acetonitrile): λmax 266 nm (ε 7196 1/mole). A second crop of crystals of **5** was obtained from the filtrate of the first crop (0.15 g, 4% yield), mp 72-74°; tlc (silica gel, ether) Rf 0.26.

Anal. Calcd for $C_9H_{11}N_2O_4F$: C, 46.70; H, 4.82; N, 12.17. Found: C, 46.86; H, 4.83; N, 12.05.

3-Valeryloxymethyl-5-fluorouracil (**6**).

This compound was obtained as for **4** as white crystals from 14ml ether and 21 ml pentane (1.74 g, 48% yield), mp 93-96°; tlc (silica gel, ether) Rf 0.27; ^{1}H nmr (deuteriochloroform): δ 7.33 (d, J = 6 Hz, 1, C^6-*H*), 5.95 (s, 2, N-C*H*$_2$O$_2$C), 2.33(t, J = 8 Hz, 2, CH$_2$C*H*$_2$CO$_2$), 1.85 - 1.1(m, 4, CH$_3$C*H*$_2$C*H*$_2$CH$_2$CO$_2$) and 0.87 (t, J = 8 Hz, 3, C*H*$_3$CH$_2$CH$_2$); uv (acetonitrile): λmax 266 nm (ε 7144 1/mole). A second crop of crystals of **6** was obtained from the filtrate of the first crop (0.06 g, 2% yield), mp 89-94°; tlc (silica gel, ether) Rf 0.27.

Anal. Calcd for $C_{10}H_{13}N_2O_4F$: C, 49.18; H, 5.37; N, 11.47. Found: C, 49.47; H, 5.39; N, 11.48.

3-Hexanoyloxymethyl-5-fluorouracil (**7**).

This compound was obtained as for **4** as white crystals from 12ml acetone and 40 ml pentane (4.24 g, 50% yield), mp 70-71°; tlc (silica gel, ether) Rf 0.29; ^{1}H nmr (deuteriochloroform): δ 7.33 (d, J = 6 Hz, 1, C^6-*H*), 5.95 (s, 2, N-C*H*$_2$O$_2$C), 2.33(t, J = 8 Hz, 2, CH$_2$C*H*$_2$CO$_2$), 1.9-1.0(m, 6, C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$CO$_2$) and 0.87 (t, J = 8 Hz, 3, C*H*$_3$CH$_2$CH$_2$); uv (acetonitrile): λmax 266 nm (ε 7099 1/mole).

Anal. Calcd for $C_{11}H_{15}N_2O_4F$: C, 51.16; H, 5.85; N, 10.85. Found: C, 51.36; H, 5.84; N, 10.89.

3-Octanoyloxymethyl-5-fluorouracil (**8**).

This compound was obtained as for **4** as a white waxy solid from 5 ml ether and 18 ml pentane (1.66 g, 58% yield), mp 68-70°; tlc (silica gel, ether) Rf 0.32; ^{1}H nmr (deuteriochloroform): δ 7.35 (d, J = 6 Hz, 1, C^6-*H*), 5.95 (s, 2, N-C*H*$_2$O$_2$C), 2.33(t, J = 8 Hz, 2, CH$_2$C*H*$_2$CO$_2$), 1.85-0.7(m, 13, C*H*$_3$ (C*H*$_2$)$_5$); uv (acetonitrile): λmax 266 nm(ε 7128 1/mole). A second crop of crystals of **8** was obtained from the filtrate of the first crop (0.06 g, 2% yield), mp 68-70°; tlc (silica gel, ether) Rf 0.32.

Anal. Calcd for $C_{13}H_{19}N_2O_4F$: C, 54.53; H,6.69; N,9.79. Found: C, 54.67; H, 6.57; N, 9.93.

3-Pivaloyloxymethyl-5-fluorouracil (**9**).

This compound was obtained as for **4** as white crystals from 5 ml ether and 25 ml petroleum ether (0.75 g, 59% yield), mp 130-135°, lit [6] mp 135-137°; tlc (silica gel, ether) Rf 0.30; ^{1}H nmr (deuteriochloroform): δ 7.33 (d, J = 6 Hz, 1, C^6-*H*), 5.93 (s, 2, N-C*H*$_2$O$_2$C), and 1.18 (s, 9, (C*H*$_3$)$_3$C).

General Procedure for the Synthesis of 3-Alkylcarbonyloxymethyl-5-fluorouracil by Alkylation of 1-Acetyloxymethyl-5-fluorouracil: 3-Propionyloxymethyl-5-fluorouracil (**4**).

To 3.05 g (0.015 mole) of 1-acetyloxymethyl-5-fluorouracil [9] in 10 ml of acetonitrile was added propionyloxymethyl chloride [15] (2.64 g, 0.021 mole) and 5.4 g (0.053 mole) of triethylamine. The solution was stirred at room temperature overnight; a precipitate started to form immediately, but the reaction went to completion slowly. The suspension was concentrated at 40° using a rotary evaporator. The residue was partitioned between 200 ml dichloromethane and 10 ml water. The dichloromethane solution was washed with 5 ml of water containing 2 ml of concentrated hydrochloric acid, 5 ml of water, dried over sodium sulfate for 30 minutes, and concentrated to give 4.24 g of an oil that was > 90% 1-acetyloxymethyl-3-propionyloxymethyl-5-fluorouracil, **3**, based on analysis by ^{1}H nmr spectroscopy: (deuteriochloroform): δ 7.52 (d, J = 6 Hz, 1, C^6-*H*), 5.93(s, 2, N^3-C*H*$_2$O$_2$C), 5.63(s, 2, N^1-C*H*$_2$O$_2$C), 2.32(q, J = 8 Hz, 2, CH$_3$C*H*$_2$CO$_2$), 2.12(s, 3, C*H*$_3$CO$_2$) and 1.13(t, J = 8 Hz, 3, C*H*$_3$CH$_2$CO$_2$). The oil was dissolved in 20 ml of acetonitrile and treated on successive days with 1.18 g (0.015 mole), 1.18 g and 0.60 g of 40% aqueous methylamine until all of the 1,3-bis derivative (tlc; silica gel, ethyl acetate; Rf 0.61) was gone. The reaction mixture was adsorbed on 30 g of silica gel and chromatographed on 170 g of silica gel using ethyl acetate and hexanes 1:1 as the eluent to give 0.79 g (24% yield from 1-acetyloxymethyl-5-fluorouracil) of soft white crystals (mp 75-76°) which were one spot on tlc (silica gel, ethyl acetate) Rf 0.50. Recrystallization from acetone and ether gave 0.72 g of fibrous crystals mp 94-96° which were identical with 3-propionyloxymethyl-5-fluorouracil, **4**, obtained by the previous route by mp, tlc, and ^{1}H nmr spectroscopy.

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