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1-Alkylcarbonyl-5-fluorouracil Prodrugs: Synthesis, Thermal and Hydrolytic Stability

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ABSTRACT

Six homologous 1-alkylcarbonyl derivatives of 5-fluorouracil (5-FU) have been synthesized and characterized by ^1H NMR, infrared and UV spectroscopy. The derivatives were found to hydrolyze rapidly in pH 7.1 buffer at 32°C ($t_{1/2}$ = 3–5 min). Although the hydrolysis was found to be catalyzed by hydrated formaldehyde, only 5-FU was observed as a product of the hydrolysis: no 1- or 3-alkylcarbonyloxymethyl products were observed. The 1-alkylcarbonyl derivatives were recovered intact upon heating at 145°C for 1 h, but, upon heating at 205°C for 1 h, 25% of the sample decomposed to 5-FU with the assumed loss of ketene. The 1-alkylcarbonyl derivatives were stable when stored in a desiccator but decomposed to carboxylic acid and 5-FU upon exposure to atmospheric moisture.

INTRODUCTION

5-Fluorouracil (**1**, 5-FU) has been used topically to treat a variety of proliferative disease states since the drug was discovered (1,2). However, in many instances the currently available commercial and extemporaneous formulations have not been effective unless occlusion was used (3) or the skin barrier was compromised, for instance, by abrasion (4). In order to overcome this problem, numerous chemical penetration enhancers have been evaluated (5,6) and many different types of prodrugs (transient chemical modifications) of 5-FU have been synthesized and evaluated in diffusion cell experiments to assess their abilities to enhance the transdermal delivery, or delivery through the skin, of 5-FU (7–10).

Although these prodrug approaches have been successful (3- to 25-fold) in enhancing the transdermal delivery of 5-FU, enhanced dermal delivery, or delivery into the skin, is the more desirable target for prodrugs of 5-FU designed to treat disease states of the skin; and an enhanced ratio of dermal to transdermal delivery of 5-FU, compared to 5-FU itself, is desirable to minimize any systemic side effects of 5-FU. It has been suggested (7) that to achieve the desired results, the prodrug must,

in addition to exhibiting the desired solubility properties, be designed to hydrolyze rapidly to release 5-FU immediately after it partitions into the skin from the vehicle. If the prodrug is too stable, those solubility properties that enhance its partitioning into the skin will also enhance its partitioning through the skin and result in a greater relative increase in transdermal compared to dermal delivery.

The 1-alkylcarbonyl type of derivative of 5-FU has been chosen to test this hypothesis because of its rapid hydrolysis. Only the 1-acetyl derivative has been studied and it exhibited a $t_{1/2}$ of only 6.9 min at 37°C in pH 7.4 buffer (11). In addition, it has been assumed that the members of the 1-alkylcarbonyl type of prodrug will exhibit solubility properties similar to those of the previously studied 1-alkyloxycarbonyl type of prodrug (7): all of the members of the series will be more lipid soluble and one or more of the initial members of the series will be more water soluble than 5-FU, resulting in increased partitioning into the skin. In this paper the synthesis and spectral characterization of a homologous series of 1-alkylcarbonyl derivatives of 5-FU and the evaluation of their hydrolytic and thermal stabilities are reported.

MATERIALS AND METHODS

Melting points (mp) were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental microanalyses were obtained for all novel compounds through Atlantic Microlab Incorporated (Norcross, GA). Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained at 90 MHz on a Varian EM-390 spectrometer. Infrared (IR) spectra were recorded with a Perkin-Elmer 1420 spectrophotometer. Ultraviolet (UV) spectra were obtained with a Cary 210 or Shimadzu UV-265 spectrophotometer. The HPLC system consisted of a Beckman 110A pump, Rheodyne 7125 20 μL loop injector, Lichrosorb (250 × 4.6 mm) 10 μm RP-8 column, Beckman Model 153 fixed-wavelength detector, and a Hewlett Packard 3392A integrator. Differential scanning calorimetric (DSC) analyses in hermetically sealed pans were carried out using a Perkin-Elmer DSC-7 scanning calorimeter, and thermogravimetric analyses (TGA) were performed using a Perkin-Elmer TGA-7 thermogravimetric analyzer, both controlled by a Perkin-Elmer TAC-7 interface and IBM PS/2 Model 50Z microcomputer. 5-FU was purchased from Sigma Chemical Co. All other reagents were obtained from Aldrich Chemical Co.

Synthesis

Preparation of 1-Acyl-5-Fluorouracil: General Procedure

To 0.66 g (0.01 mol) of 85% potassium hydroxide dissolved in methanol (20–50 mL) was added 1.33 g of 5-fluorouracil (0.0102 mol). The methanol suspension was stirred for 30 minutes, and the methanol was evaporated under reduced pressure. The potassium salt was suspended in acetonitrile (25–50 mL), which was evaporated under reduced pressure to remove residual methanol. The salt was resuspended in acetonitrile (25–50 mL), and the suspension was added dropwise over 15 to 30 minutes to a well-stirred, ice-cold acetonitrile (25 mL) solution containing 1.0 to 1.2 equivalents of the appropriate acid chloride. The mixture was stirred at 0°C for 60 minutes. The mixture was filtered, and the residue was washed with acetonitrile (25 mL). The combined acetonitrile solutions were evaporated under reduced pressure, and the solid residue was crystallized from an appropriate solvent or solvent combination.

1-Acetyl-5-fluorouracil (**2**)

Crystallization from dichloromethane gave 0.98 g of **2** (57%): mp 129–130°C (lit. (12) mp 126–127°C); IR (KBr) 1670, 1695, 1725, and 1770 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.73 (*s*, 3H, CH_3) and 8.23 (*d*, J = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.125 × 10^4 L/mol).

1-Propionyl-5-fluorouracil (**3**)

Crystallization from dichloromethane/hexane gave 1.32 g of **3** (71%); mp 130–131°C (lit. (12) mp 124–125°C); IR (KBr) 1695, 1710, and 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.25 (*t*, J = 7 Hz, 3H, CH_3), 3.14 (*q*, J = 7 Hz, 2H, $COCH_2$), and 8.27 (*d*, J = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.141 × 10^4 L/mol).

Anal. Calc. for $C_7H_7FN_2O_3$: C, 45.17; H, 3.79; N, 15.05. Found: C, 45.26; H, 3.83; N, 14.97.

1-Butyryl-5-fluorouracil (**4**)

Crystallization from dichloromethane/hexane gave 0.86 g of **4** (43%): mp 145–146°C; IR (KBr) 1690, 1710, and 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.01 (*t*, J = 7 Hz, 3H, CH_3), 1.77 (*m*, 2H, $COCH_2CH_2$), 3.09 (*t*, J = 7 Hz, 2H, $COCH_2$), and 8.25 (*d*, J = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.168 × 10^4 L/mol).

Anal. Calc. for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; N, 14.00. Found: C, 48.12; H, 4.58; N, 13.91.

1-Valeryl-5-fluorouracil (**5**)

Crystallization from dichloromethane/hexane gave 1.35 g of **5** (63%): mp 120–121°C; IR (KBr) 1695, 1715, and 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.95 (*t*, *J* = 7 Hz, 3H, CH_3), 1.3–1.8 (*m*, 4H, $COCH_2CH_2CH_2$), 3.11 (*t*, *J* = 7 Hz, 3H, $COCH_2$), and 8.24 (*d*, *J* = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.175 × 10^4 L/mol).

Anal. Calc. for $C_9H_{11}FN_2O_3$: C, 50.47; H, 5.18; N, 13.08. Found: C, 50.52; H, 5.23; N, 13.03.

1-Hexanoyl-5-fluorouracil (**6**)

Crystallization from dichloromethane/hexane gave 1.71 g of **6** (75%): mp 101–102°C; IR (KBr) 1690, 1715, and 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.92 (*t*, *J* = 7 Hz, 3H, CH_3), 1.2–1.9 (*m*, 6H, $COCH_2CH_2CH_2CH_2$), 3.09 (*t*, *J* = 7 Hz, 2H, $COCH_2$), and 8.24 (*d*, *J* = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.158 × 10^4 L/mol).

Anal. Calc. for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.69; H, 5.75; N, 12.27.

1-Octanoyl-5-fluorouracil (**7**)

Crystallization from dichloromethane/hexane gave 1.28 g of **7** (50%): mp 83–84°C; IR (KBr) 1685, 1710, and 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.90 (*t*, *J* = 7 Hz, 3H, CH_3), 1.2–1.8 (*m*, 10H, $COCH_2CH_2CH_2CH_2CH_2CH_2$), 3.10 (*t*, *J* = 7 Hz, 2H, $COCH_2$), and 8.23 (*d*, *J* = 7 Hz, 1H, C^6-*H*); UV_{max} (CH_3CN) 261 nm (ε = 1.155 × 10^4 L/mol).

Anal. Calc. for $C_{12}H_{17}FN_2O_3$: C, 56.24; H, 6.69; N, 10.93. Found: C, 56.22, H, 6.73; N, 10.96.

Hydrolysis Experiments

Hydrolysis rates were determined at 32°C in 0.05 M phosphate buffer (pH = 7.1, *I* = 0.12 M). The rates of hydrolysis of 1-acetyl-5-FU (**2**) were also determined in the same buffer with added formaldehyde (3.6 × 10^{-2} M, 1.8 × 10^{-1} M, and 3.6 × 10^{-1} M). The hydrolyses were followed by UV spectroscopy at 266 nm where the absorbance decrease accompanying hydrolysis of the 1-acyl derivatives was maximized. Hydrolyses were initiated by adding 60–75 μL of stock solutions of the derivatives in acetonitrile to 3 mL of buffer prewarmed at 32°C in a thermostated quartz cuvette to give concentrations of **2–7** of 1–2 × 10^{-4} M. Absorbances were recorded at appropriate intervals and pseudo-first-order rate constants were determined from the expression:

$$\ln(A_t - A_\infty) = (A_0 - A_\infty) - kt$$

where A_t is the absorbance at some time = *t*, A_∞ is the absorbance at $t = \infty$, A_0 is the absorbance at $t = 0$, *k* is the pseudo-first-order rate constant, and *t* is the time. The hydrolyses were sufficiently fast to allow experimental determination of A_∞. The slopes, $-k$, of linear plots of $\ln(A_t - A_\infty)$ versus time were determined by linear regression. The half-lives ($t_{1/2}$) were calculated from $t_{1/2} = 0.693/k$. Each hydrolysis reaction was run in triplicate and was followed for a minimum of eight half-lives. The correlation coefficients were ≥ 0.999.

The reaction mixtures from hydrolysis of **2** were also analyzed by HPLC using a mobile phase of 10% methanol, 90% acetate buffer, pH 5.0; a flow rate of 1.0 mL/min; λ_{anal} = 254 nm. The following retention times were found under those conditions: 5-FU, 4.5 min; 1-acetyloxymethyl-5-FU, 11.4 min; 1-acetyl-5-FU, 13.1 min; 3-acetyloxymethyl-5-FU, 15.7 min.

Statistical Analysis

Statistical analysis was accomplished using student's *t*-test. Unless otherwise indicated, statistical significance is for $p < 0.05$.

RESULTS AND DISCUSSION

Synthesis

The 1-alkylcarbonyl-5-FU derivatives were synthesized according to the same general procedure used to synthesize the 1-alkyloxycarbonyl-5-FU derivatives (**7**). The addition of a suspension of the potassium salt of 5-FU in acetonitrile to a solution of the acid chloride in acetonitrile (inverse addition) and the use of a slight excess of 5-FU during salt formation ensured that excess base was not present during the course of the reaction. These conditions were essential for isolation of high yields of pure products and reproducible results. Elemental analyses were obtained for all the new compounds (**4–7**) and for **3**. All the analyses were within acceptable limits (±0.40%).

The structures of the derivatives were based on the published single-crystal x-ray diffraction data for 1-acetyl-5-FU, **2** (13), and on the fact that the ^1H NMR,

IR, and UV spectra of the remainder of the derivatives are essentially identical with those of **2** (see Synthesis above). The single-crystal x-ray diffraction data show that the acetyl group in **2** is attached to the 1-position of 5-FU with the acetyl carbonyl group orientated toward the C^6-H (13). In structurally similar compounds this results in significant deshielding of the affected hydrogens. For **2**, the C^6-H hydrogen absorption is shifted down-field from that in 3-acetyl-5-FU by about 1.0 ppm in $CDCl_3$ because of the orientation of the acetyl carbonyl group (14). Since the ^1H NMR spectra of all the other members of the series exhibit similar shifts of their C^6-H hydrogen absorption, they must also be 1-substituted. The remaining features of the ^1H NMR and IR spectra of the 1-alkylcarbonyl derivatives that differentiate them from the 3-derivatives have been discussed in previous publications (13,14).

Thermolysis

All of the derivatives, when heated at 5°C/min during differential scanning calorimetric (DSC) analyses, exhibited endotherms at approximately the same temperatures as the melting points observed in a capillary apparatus. However, when **2** was held at 132°C for 20 min, then cooled to 40°C before it was analyzed, an endotherm at 126°C instead of 132°C was observed. Similar behavior was observed for **3** where an endotherm was observed at 122°C instead of at 132°C if the sample of **3** was first held at 132°C for 20 min, then cooled to 40°C before it was analyzed. Derivatives **2** and **3** were also the only ones that exhibited broad endotherms starting at about 5°C before the peak in the endotherm. After the preliminary heat treatment, only a single endotherm was observed for **2** and **3** upon DSC analyses. No change in the shape or in the position of the endotherm for **2** or **3** was observed if preheating of the samples was done at 115°C or 120°C, respectively, for 30 min.

Onset of mass loss during the thermogravimetric analysis (TGA) of all the derivatives started at about 170°C except for the 1-octanoyl derivative, **7**, for which mass loss started at about 210°C. Smooth loss of sample mass continued as the temperature was increased at 5°C/min until temperatures of 201, 205, 208, 206, 220 and 240°C for **2, 3, 4, 5, 6,** and **7**, respectively, were reached. At that point there was an abrupt decrease in the rate of mass loss with about 24, 13, 14, 15, 11, and 8%, respectively, of the initial sample masses remaining. Mass loss then continued at a slower rate until complete mass loss occurred at between 240 and 255°C.

The effect of temperature on the 1-alkylcarbonyl-5-FU derivatives was also examined on a larger scale. In one experiment ($n = 2$) a sample of 1-acetyl-5-FU, **2**, was heated for 1 hour at 145°C in a round bottom flask protected from atmospheric moisture with a $CaCl_2$ drying tube. There was no loss of mass during heating and the ^1H NMR and IR spectra of the sample showed no change in the positions or the relative intensities of the absorptions. However, the observed melting point of the heated sample was 122–125°C instead of 129–130°C. The heated sample was recrystallized from dichloromethane to give crystals that exhibited a melting point of 129–130°C and a ^1H NMR spectrum identical with original **2**. Thus, whatever change in **2** that occurs upon heating at 145°C is reversible.

On the other hand, when a sample of **2** was heated at 205°C for 1 hour in a similar experiment, significant decomposition was observed. About 50% of the sample sublimed intact, but the part of the sample that remained at the bottom of the flask contained intact **2** and 5-FU (1:1) by ^1H NMR. Thus, drastic conditions are necessary for thermal decomposition of **2** to occur.

The formation of 5-FU by heating 1-acetyl-5-FU is similar to the previously reported thermal degradation of 7-acyltheophylline derivatives to theophylline (15). By analogy to the thermal decomposition of 1-alkyl-aminocarbonyl-5-FU by loss of alkylisocyanate (8), loss of ketene may be occurring when 1-acetyl-5-FU is heated to give 5-FU.

Hydrolysis

The pH-rate profile for **2** has been reported previously by Buur and Bundgaard (11). The essential features of that profile were a pH independent region from pH 2 to about 8 and a specific base-catalyzed region beyond pH 8. Hydrolysis of the series of 1-alkylcarbonyl derivatives **2–7** was studied in 0.05 M phosphate buffer (pH = 7.1, $I = 0.12$ M) at 32°C. Pseudo-first-order rate constants (k) and half-lives ($t_{1/2}$) are presented in Table 1. The k values for the hydrolyses of these 1-alkylcarbonyl derivatives are much greater (and the corresponding $t_{1/2}$ values are much shorter: 3.1–4.8 min) than those of ester derivatives, which undergo hydrolysis by the usual nucleophilic addition-elimination mechanism under neutral to basic conditions (16) and are controlled by steric effects (17). For example, 1-alkylcarbonyloxymethyl derivatives of 5-FU, where the alkyl group corresponds to those in **2–4**, exhibit $t_{1/2}$ values of 70–140 hours at pH 7.4 and 37°C (18); and a plot of Charton's steric parameter, ν, for the alkyl groups in the

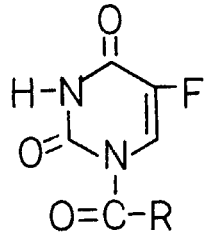
esters against log k_{OH} gives a straight line with $r = 0.999$. However, inspection of the k for the hydrolyses of **2–6** (Table 1) shows that there is no correlation of k with ν for the alkyl groups in **2–6** (Table 1) (19). Similar results were obtained by Buur and Bundgaard (11) in their studies of the hydrolyses of 3-alkylcarbonyl and 1,3-dialkylcarbonyl derivatives of 5-FU.

For esters there is a gradual decrease in k with increasing chain length as more steric bulk is introduced until $R = -CH_2CH_2CH_3$, then k stays relatively constant with further increases. On the other hand, k for $R = -CH_2CH_3$ is greater than that for $R = -CH_3$, then decreases for $R = -CH_2CH_2CH_3$, and stays relatively constant for the remaining alkyl groups in the 1-alkylcarbonyl derivatives. These results suggest that **2–7** are hydrolyzing by an S_N1-like mechanism similar to those observed for acid halides (20) and anhydrides (21). The fact that the k value for $R = -CH_2CH_3$ is greater than for $R = CH_3$ suggests that steric relief from β-methyl interactions is occurring in the transition state for the hydrolyses of the 1-alkylcarbonyl derivatives, which is the opposite of what occurs in the nucleophilic addition-elimination mechanism. Hydrolytic behavior of the 1-alkylcarbonyl derivatives similar to that of acid halides and anhydrides is consistent with the fact that the chemical shifts for the $O{=}CCH_2$-and $O{=}CCH_3$ absorptions in the ^1H NMR of **2–7** are similar to those of acid chlorides (13), suggesting that the anion of 5-FU may exhibit nucleofugicity similar to that of chlorides in these hydrolysis reactions.

Hydrolysis of **2** was also studied in the same buffer with increasing concentrations of formaldehyde added to assess the catalytic role of formaldehyde hydrate that the prodrug would encounter in the receptor phase of diffusion cell experiments (22). These results are also

Table 1

Pseudo-First-Order Rate Constants (k), Half-Lives ($t_{½}$), and Experimental Molar Absorptivities (ε) for Hydrolysis of 1-Acyl Derivatives in 0.05 M Phosphate Buffer (pH = 7.1, I = 0.12 M) at 32°C With and Without Formaldehyde: Charton's Steric Parameters (ν)



Compound R =	Formaldhyde, M	$k(\pm SD)^a$ min^{-1}	$t_{½}$ min	ν^b	$\varepsilon(\pm SD)^c$ L/mol × 10^3
2, CH_3	0	0.143(0.002)	4.8	0.52	6.88(0.22)
2, CH_3	3.6×10^{-2}	0.161(0.008)	4.3		6.84(0.10)
2, CH_3	1.8×10^{-1}	0.219(0.004)	3.2		7.08(0.07)
2, CH_3	3.6×10^{-1}	0.279(0.006)	2.5		7.28(0.02)
3, C_2H_5	0	0.222(0.004)	3.1	0.56	6.64(0.09)
4, C_3H_7	0	0.163(0.003)	4.3	0.68	6.74(0.06)
5, C_4H_9	0	0.169(0.006)	4.1	0.68	6.94(0.04)
6, C_5H_{11}	0	0.173(0.003)	4.0	0.68	7.10(0.07)
7, C_7H_{15}	0	0.183(0.003)	3.8		6.68(0.16)

[a]Mean ± standard deviation for $n = 3$ values.
[b]Charton's steric parameter from reference 19.
[c]From (A_∞)/(prodrug concentration) for each run.

shown in Table 1. It is clear that the hydrolysis rate for **2** is faster in the presence of formaldehyde and the rate is concentration dependent. A plot of the pseudo-first-order rate constants against formaldehyde concentration gives the catalytic rate constant (k_{cat} = 0.375 M^{-1} min^{-1}, r^2 = 0.995) for formaldehyde catalyzed hydrolysis of **2**. Hydrolysis rates for 1-acetyl-5-FU have previously been shown to be general base catalyzed and independent of pH at acidic to neutral pH values (11). Therefore, formaldehyde catalysis is likely due to general base rather than general acid catalysis. Only 5-FU was obtained as a product of the hydrolyses. 1- or 3-Acetyloxymethyl-5-FU, formed during the hydrolysis of 3-acetyl-5-FU in the presence of formaldehyde (13,14), was not observed by HPLC during the hydrolysis of **2** in the presence of formaldehyde.

Besides rapid hydrolysis of the 1-alkylcarbonyl derivatives of 5-FU in water, decomposition of the derivatives to carboxylic acids and 5-FU was also observed in the solid state if the derivatives were not protected from exposure to atmospheric moisture by storage in a vacuum desiccator.

CONCLUSION

The 1-alkylcarbonyl derivatives of 5-FU can be synthesized in reasonable yields using precautions to prevent the presence of excess base during the reactions and taking care to avoid contact with protic solvents such as ethanol that had previously (12) been reported as a crystallization solvent for these types of derivatives. As expected, all of the 1-alkylcarbonyl derivatives hydrolyze very rapidly in buffer by analogy to the reported rapid hydrolysis of N-acylazolides (23). On the other hand, although 1-alkylcarbonyl derivatives undergo rapid hydrolysis, they appear to be thermally stable at least up to 145°C. Thus, the 1-alkylcarbonyl derivatives of 5-FU meet the hypothesized requirement for prodrugs of 5-FU that they must be capable of rapid hydrolysis to selectively enhance dermal delivery, yet must be sufficiently stable, in the absence of protic solvents, to withstand conditions that could occur during formulation processes. Based on these results, the 1-alkylcarbonyl derivatives of 5-FU are likely candidates for development as prodrugs to enhance the dermal delivery of 5-FU.

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