Synthesis of 1- and 3-Arylcarbonyl Derivatives of 5-Fluorouracil

Lolita Caram [1], Mech Doeleman [1], William J. Roberts, Richard J. Prankerd [2], John H. Perrin, William J. Underberg [1], and Kenneth B. Sloan*

Department of Medicinal Chemistry, P.O. Box 100485, University of Florida, Gainesville, FL 32610

Received April 17, 1998

4'-Substituted 1-arylcarbonyl-5-fluorouracil derivatives were synthesized from the reaction of the potassium salt of 5-fluorouracil with one equivalent of aryl acid chloride in acetonitrile. 4'-Substituted 3-arylcarbonyl-5-fluorouracil derivatives were synthesized from the reaction of 5-fluorouracil with **3** equivalents of the aryl acid chloride in pyridine and the subsequent hydrolysis of the 1,3-diarylcarbonyl-5-fluorouracil derivatives *in situ* with a small amount of water. If a large amount of water were used in the second step, the 1,3-diarylcarbonyl-5-fluorouracil precipitated before it hydrolyzed. The melting behaviors of both the 1-arylcarbonyl-5-fluorouracil and 3-arylcarbonyl-5-fluorouracil series suggested that thermal decomposition or rearrangement occurred on heating. The position of the C^6-*H* absorption in the ^1H nmr spectra of 1-arylcarbonyl-5-fluorouracils was 0.14 to 0.23 ppm farther downfield than that of the corresponding 3-arylcarbonyl-5-fluorouracils while that of the 1,3-diarylcarbonyl-5-fluorouracils was even farther downfield. The Rf values of 1-arylcarbonyl-5-fluorouracils were significantly greater (0.23 to 0.41) than those of the corresponding 3-arylcarbonyl-5-fluorouracils, while that of 1,3-diarylcarbonyl-5-fluorouracil was slightly greater than that of 1-arylcarbonyl-5-fluorouracils.

J. Heterocyclic Chem., **36**, 397 (1999).

Introduction.

Recently attempts to synthesize 1-arylcarbonyl derivatives of 5-fluorouracil have been undertaken for the purpose of synthesizing 3-alkylcarbonyloxymethyl derivatives of 5-fluorouracil. The arylcarbonyl derivative was chosen to protect the 1-position of 5-fluorouracil from alkylation to give regiospecific 3-alkylation, *i.e.*, 1-arylcarbonyl-3-alkylcarbonyloxymethyl-5-fluorouracils. 1-Alkylcarbonyl derivatives had proven to be too unstable under a variety of alkylation conditions [3] to give 1-alkylcarbonyl-3-alkylcarbonyloxymethyl-5-fluorouracils, and it was not clear that the analogous 1-alkyloxycarbonyl derivatives, if they were synthesized, would preferentially cleave at the alkyloxycarbonyl carbonyl group to give 3-alkylcarbonyloxymethyl-5-fluorouracils. It was anticipated that the stability of the 1-arylcarbonyl derivative would be intermediate between that of an alkylcarbonyl and an alkyloxycarbonyl derivative.

There are two reports on the synthesis of arylcarbonyl-5-fluorouracil derivatives [4,5], while the most recent report on the synthesis of arylcarbonyl derivatives of uracil and thymidine is by Reese and co-workers [6]. All three articles report the use of an aryl acid halide as the acylating agent, pyridine or triethylamine as the base and dioxane, acetonitrile or pyridine itself as the solvent. The report by Reese and co-workers [6] is straightforward. A slight excess of an aryl acid chloride in acetonitrile-pyridine (10 ml:2 ml) and the corresponding pyrimidine (0.01 mole) gave excellent isolated yields of the 1-derivatives, 2.2 equivalents of aryl acid chloride in acetonitrile-pyridine (10 ml:4 ml) gave the 1,3-derivatives and mild hydrolysis of the 1,3-derivatives gave the corresponding 3-derivatives.

On the other hand, an earlier report by Tada [4] on the synthesis of 1-arylcarbonyl derivatives of 5-fluorouracil is inconsistent with the report by Reese and co-workers. Tada reports the use of 2 equivalents of aryl acid chloride with an excess (5 equivalents) of triethylamine as base in dioxane gave 1-arylcarbonyl-5-fluorouracil: conditions reported by Reese and coworkers to give 1,3-derivatives [6]. The crude reaction mixture, which was not characterized by Tada, was subsequently recrystallized from ethanol to give 1-arylcarbonyl-5-fluorouracils; conditions later reported by Kametani *et al.* [5] to give hydrolysis of the 1-acetyl group from a 1,3-diacyl-5-fluorouracil derivative to give a 3-acyl-5-fluorouracil derivative. Thus, it was not clear what Tada had isolated but it seemed possible that they were actually 3-arylcarbonyl-5-fluorouracil derivatives.

Kametani *et al.* [5] also reported that the reaction of 3 equivalents of aryl acid chloride with 5-fluorouracil and 20 equivalents of triethylamine in dioxane gave 1,3-diarylcarbonyl-5-fluorouracils after evaporation of solvent, admixture of that residue with water and extraction with benzene. On the other hand, Kametani *et al.* [5] reported that the reaction of 3 equivalents of aryl acid chloride with 5-fluorouracil in pyridine gave 3-arylcarbonyl-5-fluorouracil after the reaction mixture was poured into water and extracted with benzene. Thus, there are also some apparent internal inconsistencies in the report by Kametani *et al.* on the synthesis of 3-mono- and 1,3-diarylcarbonyl-5-fluorouracil derivatives.

In this paper, previous reports on the synthesis of 1- and 3-arylcarbonyl and 1,3-diarylcarbonyl-5-fluorouracil derivatives have been reexamined and the synthesis of 4'-substituted 1- and 3-arylcarbonyl-5-fluorouracil derivatives will be reported.

Results and Discussion.

Previously, 1-alkylcarbonyl derivatives of 5-fluorouracil had been synthesized from the reaction of the potassium salt of 5-fluorouracil with the corresponding acid chloride

in acetone or acetonitrile [7]. The structure of the product from this reaction had been shown by X-ray crystallography [8] to be the 1-acyl product, as opposed to the possible 2- or 3-acyl products, so the same procedure was used here to synthesize the 1-(4'-substituted arylcarbonyl)-5-fluorouracil derivatives **2-6**. The 1-arylcarbonyl-5-fluorouracil derivatives were obtained in moderate yields and no attempt was made to maximize them.

When the synthetic procedure described by Tada [4] was repeated using benzoyl chloride, a pure product was not isolated. However, tlc (silica gel, ether) analysis of the crude material that was isolated suggested that it was primarily the corresponding 3-arylcarbonyl-5-fluorouracil. In addition, when samples of 1-arylcarbonyl-5-fluorouracils where the 4'-substituent was H (**2**), NO_2 (**4**) or OCH_3 (**6**) were recrystallized from absolute ethanol, **2** partially decomposed and **4** completely decomposed to 5-fluorouracil while **6** was recovered intact. These results are consistent with the failure to isolate 1-arylcarbonyl-5-fluorouracil products using the Tada procedure previously reported by Lucey *et al.* [9]. No attempt was made to apply the procedures reported by Reese and co-workers for uracil [6] to the synthesis of 1-arylcarbonyl-5-fluorouracils, but based on these results such an attempt should be successful except for the more reactive 4'-NO_2 and 4'-Cl substituted derivatives [6].

The ir and uv spectra of **2-6** were consistent with the assigned 1-arylcarbonyl structure and the uv spectrum of **2** was identical with that reported by Lucey *et al.* [9]. The positions of the AB quartets in the ^1H nmr spectra of **3-6** were analogous to the AB quartets in the spectra of the corresponding acid chlorides except that the doublet assigned to the 2- and 6-protons in **2-6** were shifted slightly upfield (0.10 to 0.17 ppm); the 3- and 5-protons were in about the same positions as they were in the acid chlorides. The C^6-*H* absorptions in **2-6** were all shifted downfield compared to the C^6-*H* absorption in 5-fluorouracil which is considered diagnostic of the carbonyl group in the 1-arylcarbonyl being oriented towards the C^6-*H* in other series of 1-acyl derivates of 5-fluorouracil [7,10-12].

On the other hand, it was difficult to obtain reproducible mp of the 1-arylcarbonyl derivatives. In Table 1 are the mp and yields of 1-arylcarbonyl-5-fluorouracils reported by Tada [4]. Based on the failure here and elsewhere [9] to reproduce the results of Tada, perhaps those mp should be questioned. However, although the mp obtained here using a variety of instruments gave somewhat different mp, they were not totally inconsistent with those reported by Tada except for **3**. In Table 1 are reported the baseline extrapolated fusion temperatures from the endotherms obtained by dsc analyses of **2-6** run at 2°/minute in hermetically sealed sample pans, mp obtained from an Electrothermal 9300 digital capillary apparatus run at 2°/minute starting at 140° and mp obtained using a simple, well-stirred paraffin oil bath. All the 1-arylcarbonyl derivatives displayed some shrinking and a small degree of pre-melting which could also be seen in the dsc tracings. The most consistent mp were obtained when the rate of temperature increase was carefully controlled. Values for mp could be as much as 5-12° higher if the rate of temperature increase was not controlled to ≤2°/minute. The fact that the mp were not reproducible from method to method may be because the 1-arylcarbonyl-5-fluorouracil compounds were not thermally stable at temperatures up to their melting points. When mp samples were cooled and reheated, the samples did not melt by 200°.

The 3-arylcarbonyl-5-fluorouracil derivatives were synthesized following the general procedure described by Kametani *et al.* [5] but modified by the insight provided by the work of Reese and co-workers [6]. It seemed obvious from the work of Reese and co-workers that the initial products of the procedure described by Kametani *et al.* [5] were the 1,3-diarylcarbonyl-5-fluorouracil derivatives and that the subsequent workup with water resulted in the hydrolysis of the 1,3-diarylcarbonyl-5-fluorouracils to the 3-arylcarbonyl-5-fluorouracils. However, Kametani did not define the amount of water added during the workup procedure, and the key to the success of converting 1,3-diarylcarbonyl-5-fluorouracils to 3-arylcarbonyl-5-fluorouracils was not to use too much water. If too much water were added to the pyridine solution, 1,3-diarylcarbonyl-5-fluorouracils precipitated before they underwent hydrolysis so that a mixture of 1,3-diarylcarbonyl-5-fluorouracil and 3-arylcarbonyl-5-fluorouracil formed, the exact composition of which depended on how much water had been added. For most of the reactions it was essential to maintain a clear solution after the addition of water (<30 ml) so that all of the 1,3-diarylcarbonyl-5-fluorouracils hydrolyzed to 3-arylcarbonyl-5-fluorouracils. It was not possible to obtain a clear solution from the reaction of 4-nitrobenzoyl chloride with 5-fluorouracil even using as little as 2.5 ml of water in the hydrolytic workup. A suspension formed from the beginning of the reaction because of the poor solubility of the 1,3-diarylcarbonyl-5-fluorouracil (and eventually the 3-arylcarbonyl-5-fluorouracil) in the reaction mixture.

The mp of **7** was consistent with that reported for **7** by Kametani *et al.* [5]. All of the 3-arylcarbonyl-5-fluorouracils exhibited mp followed by resolidification suggesting that they underwent thermal rearrangement. This behavior is similar to that previously described for some of the 3-alkylcarbonyl-5-fluorouracil derivatives [13]. The dsc tracings observed for the 3-arylcarbonyl-5-fluorouracils were also similar to those previously reported for the 3-alkylcarbonyl-5-fluorouracils; an endotherm followed by an immediate exotherm. The endotherms obtained by dsc are consistent with the mp obtained using the Electrothermal 9300 and a well-stirred paraffin oil bath (Table 1).

The ir and uv spectra of **7-11** were consistent with the assigned 3-arylcarbonyl-5-fluorouracil structure and the

Table 1

4'-Substituent	Literature [4] Capillary mp °C (% yield)	Calorimetry Endotherm °C	Digital Capillary mp °C	Paraffin Bath Capillary mp °C [a]
	1-Arylcarbonyl-5-fluorouracil			
H	170-172 (43)	174	172.4-174.3	171.9-173.9
Cl	185-186 (35)	155	152.2-154.4	153.1-156.1
NO_2	182-183 (53)	193	185.5-189.2	185.0 dec
CH_3	198-199 (49)	192	186.1-188.0	188.7-189.7
OCH_3	200-201 (49)	197	184.8-187.0	191.8-192.4
	3-Arylcarbonyl-5-fluorouracil			
H	170-172 (85) [5]	155	152.9-154.6	159.8 dec
Cl			158.2-162.5	
NO_2		170	169.5-171.4	169.8 dec
CH_3		169	170.4-171.0	172.4 dec
OCH_3		167	163.4-165.9	166.1 dec

[a] It is difficult to dlefine the upper temperature for the melting ranges of those compounds which are denoted by dec, as partial resolidification occurred and remelt did not occur until about 210-220°. For these compounds, it was not possible to tell where melting of the compound was complete, and only the temperature where melting began is given. For the 1-(4'-nitrobenzoyl) compound, the decomposition is supported by the appearance of additional thermal events in the dsc.

uv spectrum of **7** was identical with that reported by Lucey *et al.* [9]. The position of the C^6-*H* absorption in the ^1H nmr spectra of **7-11** (δ 7.97 to 8.06) was consistent with that reported by Kametani *et al.* [5] for the 2'-methyl substituted 3-arylcarbonyl derivative (δ 8.02). The position of the C^6-*H* absorption is very dependent on the solvent used so the comparison had to be made with the spectrum of a 3-arylcarbonyl derivative run in dimethyl-d_6 sulfoxide. The positions of the AB quartets in the ^1H nmr spectra of **8, 10** and **11** were analogous to the positions in the ^1H nmr spectra of the corresponding acid chloride except that the sets of doublets assigned to the 2- and 6-protons and the 3- and 5-protons were both shifted slightly downfield.

The one example of a 1,3-diarylcarbonyl-5-fluorouracil (**12**) was synthesized according to the general procedure of Kametani *et al.* [5] to confirm the effect of the amount of water used in the workup of the reaction mixture on the product isolated. In this example, enough cold water (100 ml) was used to cause **12** to precipitate immediately. A low yield of **12** was obtained using this procedure that exhibited the same mp as that reported by Kametani *et al.* for **12**. The tlc (silica gel, ether) of **12** was one component that exhibited an Rf only slightly higher than that of **2** (0.44 versus 0.40). The position of the absorption due to the C^6-*H* in the ^1H nmr was much farther downfield (δ 8.53) than that due to the C^6-*H* for 1-arylcarbonyl-(δ 8.14-8.26) or for 3-arylcarbonyl-5-fluorouracils (δ 7.97 to 8.06) in dimethyl-d_6 sulfoxide.

Thus, series of 1-arylcarbonyl- and 3-arylcarbonyl-5-fluorouracil derivatives have been synthesized which exhibit ^1H nmr, ir and uv spectra consistent with their respective assigned structures. The previous report [4] on the synthesis of the 1-arylcarbonyl series is not consistent with these results or others [9]; the use of ethanol as a recrystallization solvent for 1-arylcarbonyl-5-fluorouracil is particularly problematic. The previous report [5] on the synthesis of 3-arylcarbonyl- and 1,3-diarylcarbonyl-5-fluorouracil derivatives is reproducible if the amount of water used in the workup is taken into account for the two different types of derivatives.

EXPERIMENTAL

The tlc were run on Brinkman Polygram Sil G/UV 254 plates. The mp were measured in capillary tubes with the following instruments: (i) a well-stirred paraffin oil bath using a calibrated thermometer (Buchi, Flawil, Switzerland); and (ii) an Electrothermal 9300 digital apparatus. The fusion temperature was also determined with a Perkin-Elmer DSC-7 differential scanning calorimeter (dsc) controlled by a Perkin-Elmer TAC-7 interface and a KT Technology IBM-compatible microcomputer (80386 CPU, 4 Mb RAM; Perkin-Elmer DSC-7 software, version 3.1; calibrated for temperature against indium and tin standards). The ^1H nmr spectra were recorded on a Varian EM-390 90 MHZ spectrometer while the uv and ir spectra were recorded on a Shimadzu UV-160U and a Perkin-Elmer 1420 ratio recording spectrophotometer, respectively. Microanalyses were obtained from Atlantic Microlab Inc., Norcross, GA. All of the chemical starting materials and ^1H nmr solvents were obtained from Aldrich. The bulk solvents were obtained from Fisher Scientific.

General procedure for the Synthesis of 1-Arylcarbonyl-5-fluorouracil Derivatives.

To 0.69 g (0.0105 mole) of 85% potassium hydroxide dissolved in 50 ml of methanol was added 1.37 g (0.0105 mole) of 5-fluorouracil. The suspension was stirred at room temperature for 20 minutes. The suspension was concentrated at 50° using a rotary evaporator. The residue was resuspended in 50 ml of acetonitrile and stirred at room temperature for 30 minutes. The suspension was concentrated at 40° using a rotary evaporator to remove residual water, then that residue was resuspended in 50 ml of acetonitrile with stirring at room temperature for 30 minutes. The suspension of the potassium salt of 5-fluorouracil in acetonitrile was added portion-wise over 20 minutes to 0.01 mole of the aryl acid chloride in 50 ml of acetonitrile cooled with an ice bath. The reaction mixture was stirred at room temperature for 3 hours then filtered by gravity. The filtrate was concentrated at 40° using a rotary evaporator. The residue was suspended in hot dichloromethane (150 to 600 ml depending on the derivative) and filtered by gravity while the suspension was still warm. The dichloromethane solution was concentrated at 30° using a rotary evaporator until only about 10 to 30 ml remained. The suspension was cooled then filtered by vacuum. The residue was washed with dichloromethane and briefly air dried to give the desired product. The filtrate was further concentrated to give a second fraction of the desired product.

1-Benzoyl-5-fluorouracil (**2**).

This compound was obtained as white crystals in 60% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.20 (d, J = 6 Hz, 1, C^6-*H*), 7.9-7.3 (m, 5, C_6H_5), 12 (m, 1, N*H*); ir (potassium bromide): ν 3190 (NH amide, broad), 3060 (NH amide, broad), 1740 (C=C)) cm^{-1}; uv (acetonitrile): λmax 260 nm (ε 12900 l/mole) 271 nm (ε 13100 l/mole); tlc (silica gel, ether) Rf 0.40.

Anal. Calcd. for $C_{11}H_7FN_2O_3$; C, 56.41; H, 3.02; N, 11.96. Found: C, 56.22; H, 2.98; N. 11.86.

1-(4'-Chlorobenzoyl)-5-fluorouracil (**3**).

This compound was obtained as white crystals in 51% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, J = 6 Hz, 1, C^6-*H*), 7.63 (ABq, Δν = 25.5 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3270 (NH amide, broad), 3180 (NH amide, broad), 1740 (C=O) cm^{-1}; uv (acetonitrile): λmax 214 nm (shoulder, ε 17520 l/mole), 267 nm (ε 16450 l/mole); tlc (silica gel, ether) Rf 0.60.

Anal. Calcd. for $C_{11}H_6ClFN_2O_3$ (0.33 CH_2Cl_2): C, 45.83; H, 2.26; N. 9.44. Found: C, 46.14; H, 2.26; N, 9.47.

1-(4'-Nitrobenzoyl)-5-fluorouracil (**4**).

This compound was obtained as light yellow crystals in 52% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.25 (d, J = 6 Hz, 1, C^6-*H*), 8.10 (ABq, Δν = 25.5 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3180 (NH amide, broad), 3050 (NH amide, broad), 1730-1700 (C=O) cm^{-1}; uv (acetonitrile): λmax 213 nm (shoulder, ε 15400 l/mole), 270 nm (ε 18970 l/mole); tlc (silica gel, ether) Rf 0.49.

Anal. Calcd. for $C_{11}H_6FN_3O_5$: C, 47.32; H, 2.17; N, 15.05. Found: C, 47.44; H, 2.14; N, 14.92.

1-(4'-Methylbenzoyl)-5-fluorouracil (**5**).

This compound was obtained as white crystals in 49% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.14 (d, J = 6 Hz, 1, C^6-*H*), 7.47 (ABq, Δν = 38 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3180 (NH amide, broad), 3050 (NH amide, broad), 1730-1700 (C=O) cm^{-1}; uv (acetonitrile): λmax 214 nm (shoulder, ε 18100 l/mole), 271 nm (ε 18100 l/mole); tlc (silica gel, ether) Rf 0.53.

Anal. Calcd for $C_{12}H_9FN_2O_3$: C, 58.07; H, 3.65; N, 11.29. Found: C, 58.11; H, 3.64; N, 11.22.

1-(4'-Methoxybenzoyl)-5-fluorouracil (**6**).

This compound was obtained as white crystals in 34% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.14 (d, J = 6 Hz, 1, C^6-*H*), 7.39 (ABq, Δν = 73 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3160-3140 (NH amide), 3040 NH amide, broad), 1733 (C=O) cm^{-1}; uv (acetonitrile): λmax 226 nm (ε 12630 l/mole), 277 nm (shoulder, ε 14820 l/mole), 295 nm (ε 19100 l/mole); tlc (silica gel, ether) Rf 0.37.

Anal. Calcd. for $C_{12}H_9FN_2O_4$: C, 54.55; H, 3.43; N, 10.61. Found: C, 54.28; H, 3.40; N, 10.45.

General Procedure for the Syntheses of 3-Arylcarbonyl-5-fluorouracil Derivatives.

5-Fluorouracil (1.3 g, 0.01 mole) in 24 ml of pyridine was added to a well-stirred solution of the appropriate aryl acid chloride (0.03 mole) in 6 ml of pyridine at room temperature. The mixture was stirred for one to three hours, then water (2.5 to 30 ml, depending on the derivative) was added to hydrolyze the 1,3-diarylcarbonyl-5-fluorouracil derivative that had been formed. The reaction mixture, which was usually a clear solution, was stirred at room temperature for 30 minutes, then diluted with 100 ml of water containing 5 ml of concentrated aqueous hydrogen chloride. If a suspension formed after the addition of 100 ml of water, the solid was filtered and dissolved in dichloromethane (200 to 500 ml). The dichloromethane solution was dried over sodium sulfate and concentrated to 10 to 30 ml at 40° using a rotary evaporator. The precipitate from the dichloromethane solution was filtered and that residue was washed with dichloromethane and air-dried to give the desired product. The dichloromethane filtrate was further concentrated to give a second fraction of the desired product. The aqueous-pyridine filtrate could also be extracted with dichloromethane and processed as below to give more of the desired derivative. If a suspension did not form after the addition of 100 ml of water, the aqueous-pyridine solution was extracted 2 to 3 times with 100 ml of dichloromethane. The combined dichloromethane extracts were washed with water (20 ml), dried over sodium sulfate and concentrated at 40° using a rotary evaporator. The oily concentrate was triturated with ether (10 to 30 ml) then filtered to give the desired derivative.

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

This compound was obtained as white crystals in 40% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.06 (d, J = 6 Hz, 1, C^6-*H*), 8.1-7.4 (m, 5, C_6H_5), 12 (m, 1, N*H*); ir (potassium bromide): ν 3190 (NH amide, broad), 3090 (NH amide, broad), 1770 (C=O) cm^{-1}; uv (acetonitrile): λmax 253 nm (ε 18450 l/mole), 272 nm (shoulder, ε 7570 l/mole); tlc (silica gel, ether) Rf 0.17.

Anal. Calcd. for $C_{11}H_7FN_2O_3$: C, 56.41; H 3.02; N, 11.96. Found: C, 56.13; H, 2.98; N, 11.90.

3-(4'-Chlorobenzoyl)-5-fluorouracil (**8**).

This compound was obtained as white crystals in 27% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.00 (d, J = 6 Hz, 1, C^6-*H*), 7.82 (ABq, Δν = 36.4 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3190 (NH amide, broad), 3095 (NH amide, broad), 1760 (C=O) cm^{-1}; uv (acetonitrile): λmax 209 nm (shoulder, ε 19200 l/mole), 261 nm (ε 24400); tlc (silica gel, ether) Rf 0.19.

Anal. Calcd. for $C_{11}H_6ClFN_2O_3$: C, 49.18; H, 2.27; N, 10.43. Found: C, 49.25; H, 2.22; N, 10.39.

3-(4'-Nitrobenzoyl)-5-fluorouracil (**9**).

This compound was obtained as light yellow crystals in 47% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.30 (s, 4, C_6H_4), 8.03 (d, J = 6 Hz, 1, C^6-*H*), 12 (m, 1, N*H*); ir (potassium bromide): ν 3230 (NH amide, broad), 3180 (NH amide, broad), 1765 (C=O) cm^{-1}; uv (acetonitrile): λmax 265 nm (ε 21260 l/mole); 303 nm (shoulder, ε 3960); tlc (silica gel, ether) Rf 0.17.

Anal. Calcd. for $C_{11}H_6FN_3O_5$: C, 47.32; H, 2.17; N, 15.05. Found: C, 47.44; H, 2.21; N, 15.06.

3-(4'-Methylbenzoyl)-5-fluorouracil (**10**).

This compound was obtained as white crystals in 53% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.97 (d, J = 6 Hz, 1, C^6-*H*), 7.60 (ABq, Δν = 44 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3200-3185 (NH amide, broad), 3100 (NH amide, broad), 1770 (C=O) cm^{-1}; uv (acetonitrile): λmax 209 nm (shoulder, ε 19800 l/mole), 263 nm (ε 22470 l/mole); tlc (silica gel, ether) Rf 0.22.

Anal. Calcd. for $C_{12}H_9FN_2O_3$: C, 58.07; H, 3.65; N, 11.29. Found: C, 58.15; H, 3.60; N, 11.36.

3-(4'-Methoxybenzoyl)-5-fluorouracil (**11**).

This compound was obtained as white crystals in 21% yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.97 (d, J = 6 Hz, 1, C^6-*H*), 7.48 (ABq, Δν = 75 Hz, J = 9 Hz, 4, C_6H_4), 12 (m, 1, N*H*); ir (potassium bromide): ν 3180 (NH amide, broad), 3080 (NH amide, broad), 1745 (C=O) cm^{-1}; uv (acetonitrile): λmax (ε 12340 l/mole), 238 nm (ε 21000 l/mole); tlc (silica gel, ether) Rf 0.14.

Anal. Calcd for $C_{12}H_9FN_2O_4$: C, 54.55; H, 3.43; N, 10.61. Found: C, 54.49; H, 3.43; N, 10.50.

Synthesis of 1,3-Dibenzoyl-5-fluorouracil (**12**).

5-Fluorouracil (1.3 g, 0.01 mole) dissolved in 24 ml of pyridine was added to 4.2 g (0.03 mole) of benzoyl chloride in 6 ml of pyridine. The mixture was stirred for 1 hour at room temperature then it was poured into 100 ml of vigorously stirred ice-cold water. This mixture was stirred for 15 minutes while a yellow-tan precipitate formed on the sides of the container. The clear pyridine-water solution was decanted. The solid was dissolved in 150 ml of benzene. The benzene solution was washed with 100 ml of water, dried over sodium sulfate, and concentrated at 40° using a rotary evaporator to give 2.14 g of waxy yellow solid. The solid was dissolved in 3 ml of dichloromethane. The dichloromethane solution was diluted with 50 ml of ether and allowed to crystallize over night. The crystals were filtered, washed with ether and briefly air-dried to give 1.05 g of the product as white crystals in 30% yield; mp 162-166°, lit [5] mp 169-171°; ^{1}H nmr (dimethyl-d_6 sulfoxide) δ 8.53 (d, J = 6 Hz, 1, C^6-*H*), 8.3-7.35 (m, 10, C_6H_5); tlc (silica gel, ether) Rf 0.44.

Acknowledgment.

This work was supported by NIH grant R15 CA 67230 and by Dr. Saal van Zwanenbergsticking, Oss, The Netherlands.

REFERENCES AND NOTES

[1] Department of Pharmaceutical Analysis, University of Utrecht, Utrecht, The Netherlands.

[2] School of Pharmacy, University of Queensland, St. Lucia, Queensland, Australia 4072.

[3] K. B. Sloan, unpublished work.

[4] M. Tada, *Chem. Letters,* 129 (1975).

[5] T. Kametani, K, Kigasawa, M. Hiiragi, K Wakisaka, S. Haga, Y. Nagamatsu, H. Sugi, K Fukawa, O. Irino, T. Yamamoto, N. Nishimura, A. Taguchi, T. Okaka and M. Nakayama, *J. Med. Chem.,* **23**, 1324 (1980).

[6] K. A. Cruickshank, J. Jiricny and C. B. Reese, *Tetrahedron Letters,* **25**, 681 (1984).

[7] H. D. Beall, R. J. Prankerd and K B. Sloan, *Drug Dev. Ind. Pharm.,* **22**, 85 (1996).

[8] H. D. Beall, R. J. Prankerd, L J. Todara and K. B. Sloan, *Pharm. Res.,* **10**, 905 (1993).

[9] N. M. Lucey, J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin Trans. 1.,* 795 (1990).

[10] S. Ozaki, Y. Ike, H. Mizuno, K Ishikawa. and H. Mori, *Bull. Chem. Soc. Japan.,* **50**, 2406 (1977).

[11] K. B. Sloan, J. J. Getz, H. D. Beall and R. J. Prankerd, *Int. J. Pharm.,* **93**, 27 (1993).

[12] H. D. Beall, R. J. Prankerd and K. B. Sloan, *Int. J. Pharm.,* **111**, 223 (1994).

[13] H. D. Beall, R. J. Prankerd and K. B. Sloan, *Drug Dev. Ind. Pharm.,* **23**, 517 (1997).