Synthesis of 5-Substituted Uracil Derivatives†

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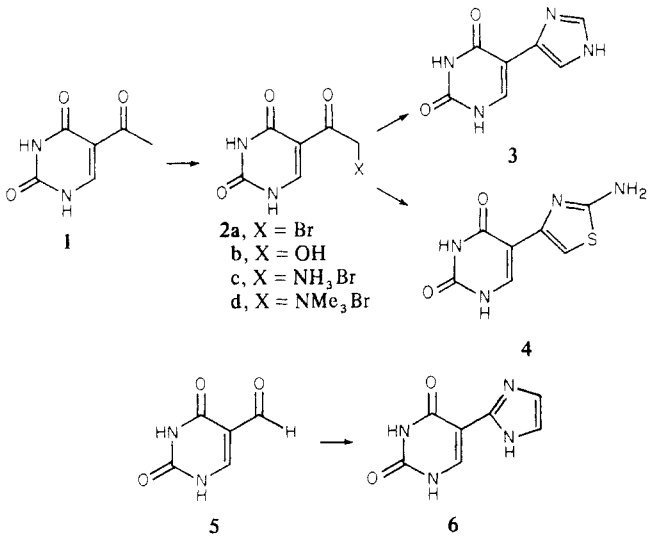
The synthesis of a series of 5-substituted uracil derivatives is described. 5-Bromoacetyluracil (**2a**) was converted to the glycolyl (**2b**), glycyl (**2c**), *N,N*-dimethylglycyl (**2d**), 4-imidazolyl (**3**), and 2-amino-4-thiazolyl (**4**) derivatives. 5-Formyluracil (**5**) was used in the preparation of the 2-imidazolyl (**6**), the 3-acrylic acid (**7b**), the ester (**7a**), and the 3-*N,N*-dimethylacrylamide (**8**) derivatives. A Mannich reaction converted 5-acetyluracil to the amino ketone **9** which was reduced to give the 3-dimethylamino-1-propanol derivative **10**. Compounds **2b**, **d**, **3**, **4**, **6**, and **7b** failed to inhibit the growth of *Escherichia coli* B and *Staphylococcus aureus*.

Nucleoside derivatives of 5-substituted uracil have been explored for their potential application as antiviral agents and in the treatment of tumors. Of particular interest are agents designed to inhibit thymidylate synthetase.[1] Several 5-substituted uracils were prepared in this study as the first phase of a program in the synthesis of new 2'-deoxy ribonucleosides as potential inhibitors of this enzyme.

Recent reports on the synthesis of 5-substituted uracils are the aminoacyl derivatives reported by Ivanovics and coworkers,[2] an unusual aminobutylaminomethyl derivative of uracil isolated from a bacteriophage,[3] and Fissekis and Sweet[4] described the preparation of 5-vinyluracil and the chemistry of 5-(2-hydroxyalkyl)uracil derivatives.

The synthesis of the 5-(imidazol-4-yl)uracil, compound **3**, started with 5-acetyluracil (**1**).[5] Bromination of **1** in acetic acid gave 5-bromoacetyluracil (**2a**) in high yield. The reactivity of the halide was examined and the half-life in water determined. At reflux temperatures the half-life for hydrolysis of **2a** to 5-glycolyluracil (**2b**) was less than 30 min.

The glycyl derivatives, 5-glycyluracil (**2c**) and 5-trimethylammoniumacetyluracil bromide (**2d**), were obtained from **2a** by treatment with liquid ammonia or dimethylamine followed by methyl bromide. A solution of **2a** in formamide heated to 140° for 1 hr gave 5-(imidazol-4-yl)uracil (**3**). Treatment of **2a** with urea or guanidine did not give the desired aminoimidazole; there was no detectable reaction at room temperature and at elevated temperatures hydrolysis to the glycolyl product **2b** occurred. In contrast, thiourea reacted with **2a** to give the 5-(2-amino-4-thiazolyl)uracil (**4**).



Difficulties were encountered in the preparation of the 5-(imidazol-2-yl)uracil (**6**). The initial attempt, a classical imidazole synthesis,[6] was by treatment of **5** with aqueous ammonia and glyoxal; the desired product could not be obtained. Considering the report[7] that nitriles and ethylenediamine salts give imidazolines which can be dehydrogenated[8] to imidazoles led us to try this reaction with 5-cyanouracil.[9] Formation of the oxime of **5** followed by dehydration using acetic anhydride gave 5-cyanouracil. Condensation of 5-cyanouracil with ethylenediamine mono-*p*-toluenesulfonate at 170° failed to give any product. The nitrile did not dissolve in the fused amine salt and was recovered intact. Successful condensations of this type have used nitriles that are in solution at the reaction temperature. Compound **6** was obtained in low yield using the formyl compound **5** and glyoxal in liquid ammonia.

A target compound in this study was the 5-(3-dimethylamino-1-propenyl)uracil. Two routes for the synthesis of this compound were unsuccessful. The first attempt was to synthesize the acrylamide **8** which would be reduced by hydride reduction. 5-Formyluracil (**5**) was converted, in low yield, to ethyl *trans*-3-(5-uracilyl)-propenate (**7a**) by treatment with the Wittig reagent, carbethoxymethylidenetriphenylphosphorane, in Me_2SO.

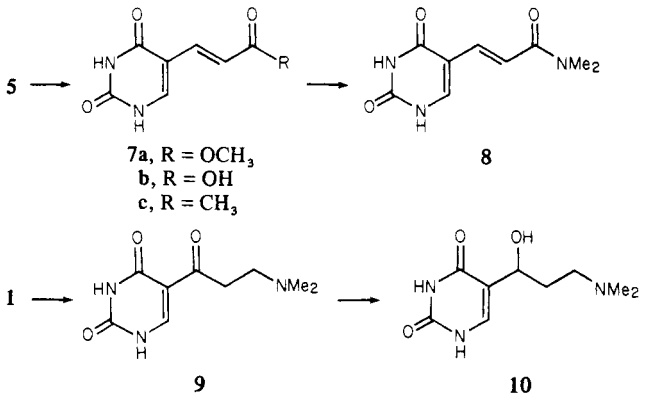
The reactivity of **5** under conditions of the aldol condensation was examined with acetone using sodium hydroxide or piperidine as the catalyst. Both methods gave reasonable yields of 1-(5-uracilyl)buten-3-one (**7c**). Therefore, an alternate method to *trans*-3-(5-uracilyl)-propenoic acid, base-catalyzed condensation of **5** with malonic acid followed by decarboxylation and esterification of the acid **7b**, gave a much improved yield of **7a**. Fissekis and Sweet[4] recently reported the formation of **7b** by the same route. Both routes gave the trans compound as determined by the coupling constants of the olefinic protons. Formation of *N,N*-dimethyl *trans*-3-(5-uracilyl)propenamide (**8**) was accomplished by treatment of a pyridine solution of the acid **7b** with dicyclohexylcarbodiimide followed by the addition of dimethylamine.

The final step in the sequence, reduction of the amide carbonyl, was unsuccessful. The bis(trimethylsilyl) ether of **8** could not be reduced to the amine using lithium aluminum hydride in ether, tetrahydrofuran, or *N*-methylmorpholine and sodium borohydride in pyridine.[10] Sodium bis(2-methoxyethoxy)aluminum hydride in benzene also failed to give the desired amine.

A final attempt to prepare the amine was by dehydration of the alcohol **10**. 5-Acetyluracil (**1**) was treated with dimethylamine hydrochloride and paraformaldehyde to give the Mannich product 5-*N,N*-dimethyl-β-alanyluracil (**9**). Reduction of the ketone **9** with an alkaline solution of sodium borohydride, a procedure adapted from the work of Evans and coworkers,[11] gave 1-(5-uracilyl)-3-dimethylaminopropanol (**10**). The feasibility of the dehydration reaction was based on the synthesis of 5-vinyluracil by dehydration of 5-α-hydroxyethyluracil. The initial attempts using 80% formic acid at reflux for 15 min did not cause any reaction. Other attempted dehydrations

† Dedicated to Edward E. Smissman, Chairman of this Department from 1960 until his death on July 14, 1974.

using 20% sulfuric acid in acetic acid,[12] dimethyl sulfoxide, hexamethylphosphoramide,[13] and finally phosphorus oxychloride in pyridine[14] also were unsuccessful.



The analysis of these compounds for their inhibitory effect on the target enzyme, thymidylate synthetase, is not feasible since the nucleotide is required for in vitro testing. Preliminary biological results were obtained on the effects of these compounds on inhibiting the growth of microorganisms. Compounds **2b,d** and **4** at a concentration of 1×10^{-3} *M* and compounds **3**, **6**, and **7b** at a concentration of 1×10^{-4} *M* failed to inhibit the growth of *Escherichia coli* B and *Staphylococcus aureus* in broth culture.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were measured with a Beckmann IR33, uv spectra with a Cary 14 recording spectrophotometer, mass spectra with a Varian CH-5 or a Finnegan 1015 mass spectrometer, and NMR spectra with a Varian Model A-60 or T-60. Microanalyses were obtained from an F & M 185 or a Hewlett-Packard 185B and are within ±0.4% of theory except where otherwise noted. Qualitative TLC was run on silica gel with chloroform–95% ethanol (3:1) as eluent. Qualitative and preparative paper chromatograms were resolved using 2-propanol–aqueous ammonia–water (7:1:2).

5-Bromoacetyluracil (2a). A solution of 7.8 g (50 mmol, 1) of 5-acetyluracil[5] in 50 ml of glacial acetic acid was stirred at room temperature while a solution of 8.0 g (50 mmol) of bromine in 25 ml of glacial acetic acid was added dropwise. After the suspension was decolorized to a pale yellow (about 16 hr; slight heating from the stirring motor accelerates the reaction), it was cooled almost to the freezing point and filtered. The white powder was washed with ether and dried under vacuum to yield 11.08 g (95%) of the desired product **2a**: mp 241–244° dec; ^{1}H NMR (Me_2SO-d_6) δ 4.68 (2, s, CH_2Br), 8.17 (1, s, H-6); uv $\lambda_{max}^{pH\ 1}$ 285 nm (ε 14100). Anal. ($C_6H_5BrN_2O_3$) C, H, N.

5-Glycolyluracil (2b). 5-Bromoacetyluracil (**2a**, 1.0 g, 4.3 mmol) in 25 ml of water was heated at reflux until TLC indicated that no starting material remained (about 5 hr). Filtration of the cooled solution yielded 303 mg (42%) of yellow powder. Two recrystallizations from water afforded 154 mg (21%) of small colorless needles, identified as 5-glycolyluracil (**2b**): mp 265–268° dec; ^{1}H NMR (Me_2SO-d_6) δ 4.60 (2, s, CH_2OH), 8.12 (1, s, H-6); ir (KBr) 3490 cm^{-1}. Anal. ($C_6H_6N_2O_4$) C, H, N.

5-Glycyluracil Hydrobromide Hemihydrate (2c). About 10 ml (500 mmol) of ammonia was condensed into a flask cooled in a dry ice–acetone bath and protected by a nitrogen bubbler. With rapid stirring, 5-bromoacetyluracil (**2a**, 700 mg, 3 mmol) was added in small portions, and the resulting solution was stirred an additional 30 min. The cooling bath was removed, the ammonia allowed to distill, and the red solid residue swept with a stream of nitrogen until the smell of ammonia could no longer be detected. The solid was boiled to dissolve in 75 ml of 0.1 *N* HBr and treated with charcoal; the solution was filtered and evaporated to dryness. The white solid was triturated in 200 ml of acetone to remove potential ammonium bromide contaminant and recrystallized from 95% ethanol to yield 72 mg (10%) of pale tan needles and plates: mp 292–295° dec (darkens at 200°); ^{1}H NMR (Me_2SO-d_6) δ 4.32 (2, s, CH_2), 8.33 (1, s, H-6), 7.0–9.5 (3, very br s, exchangeable, $^+NH_3$); uv $\lambda_{max}^{pH\ 1}$ 285 nm (ε 12500), 230.5 (10090). Anal. ($C_6H_8BrN_3O_3 \cdot 0.5H_2O$) C, H, N.

5-Trimethylammoniumacetyluracil Bromide (2d). A stirred, cooled (5°) suspension of 1.0 g (4.3 mmol) of 5-bromoacetyluracil (**2a**) in 8 ml of methanol was prepared and protected by a nitrogen bubbler and a rubber septum. Trimethylamine solution (25% in methanol, 1.2 g, 5 mmol) was added via a syringe; stirring was continued in the cold for 60 min and overnight at room temperature. The suspension was then chilled and filtered, and the solid was recrystallized from 0.3 *N* HBr in methanol, filtered, and air-dried to yield 392 mg (31%) of **2d** as a white powder: mp 211–213° dec (softens at 197–199°); ^{1}H NMR (CF_3CO_2H) δ 3.50 [9, s, $N(CH_3)_3$], 5.07 (2, s, CH_2), 8.73 (1, s, H-6); $\lambda_{max}^{pH\ 1}$ 286.5 nm (ε 13100). Anal. ($C_9H_{14}BrN_3O_3 \cdot 0.5H_2O$) C, H, N.

5-(Imidazol-4-yl)uracil (3). A suspension of 930 ml (4 mmol) of 5-bromoacetyluracil (**2a**) in 10 ml of freshly distilled formamide was stirred under nitrogen while heating over 60 min to 140°. The solid dissolved almost completely, and the solution was maintained at 140° for an additional 60 min. Most of the solvent was removed at high vacuum; the residue was washed successively with ether (3 × 25 ml) and 95% ethanol (2 × 10 ml) and filtered to yield 800 mg of a tan powder. This was recrystallized from 60 ml of 1% aqueous $NaHCO_3$ to yield 90 mg of tan flowers which did not melt below 315° (sinters at 270°): uv $\lambda_{max}^{pH\ 1}$ 283 nm (ε 8900), 232.5 (11100). Anal. ($C_7H_6N_4O_2$) C, H, N.

5-(2-Amino-4-thiazolyl)uracil Hydrobromide (4). A suspension of 5-bromoacetyluracil (**2a**, 2.0 g, 8.58 mmol) and thiourea (646 mg, 8.5 mmol) in 15 ml of water was stirred overnight at room temperature. The water was removed by evaporation and the residue recrystallized from 0.1 *N* HBr to yield 2.19 g (89%) of **4** as a pale yellow powder which does not melt below 310°: ^{1}H NMR (Me_2SO-d_6) δ 7.19 (1, s, C=CHS), 8.00 (1, d, *J* = 6 Hz, H-6), 8.76 (3, br, s, $^+NH_3$); uv $\lambda_{max}^{pH\ 1}$ 303 nm (ε 5160), 246 (12430). Anal. ($C_7H_7BrN_4O_2S$) C, H, N.

5-Formyluracil (5). This synthesis was adapted from Trahanovsky, Young, and Brown.[15] A slurry of 3.55 g (25 mmol) of 5-hydroxymethyluracil (prepared by the method of Cline, Fink, and Fink)[16] in 55 ml of water was stirred vigorously and 55 ml of 1 *N* ceric ammonium nitrate solution (a 10% excess) added in one portion. Stirring was continued while the suspension was heated on a hot plate to 60°; then heating was discontinued and the reaction allowed to cool. After chilling in a refrigerator, 1.52 g (44%) of a white powder could be filtered from the pale yellow solvent: mp 304–306° dec (darkens at 280°) (lit.[17] 305° dec). Anal. ($C_5H_4N_2O_3$) C, H, N.

5-(Imidazol-2-yl)uracil (6). A 25-ml three-neck flask containing 1.4 g (10 mmol) of 5-formyluracil (**5**) and a stirring bar was fitted with two dry ice condensers and a rubber septum and cooled in a dry ice bath. Approximately 10 ml (500 mmol) of ammonia was condensed into the flask, and the resulting slurry was stirred for 30 min. Then, 4.8 g of 30% aqueous glyoxal solution (25 mmol) was added via a syringe and stirred for an additional 5 hr. The cooling bath was removed, and the ammonia was allowed to distill. The residue, a yellow-pink powder, was suspended in 10 ml of methanol and filtered. Recrystallization from water afforded 130 mg (7%) of **6** as white plates and needles: mp 312–320° dec; uv $\lambda_{max}^{pH\ 1}$ 294 nm (ε 9720), 240 (7960). Anal. ($C_7H_6N_4O_2$) C, H, N.

Ethyl *trans*-3-(5-Uracilyl)propenate (7a). Using a method adapted from Wiley,[18] a solution of 202 mg (1.44 mmol) of 5-formyluracil (**5**) and 1.00 g (2.87 mmol) of carbethoxymethylidenetriphenylphosphorane in 20 ml of dry Me_2SO was heated on a steam bath overnight, protected with nitrogen. About 15 ml of Me_2SO was removed by vacuum distillation and the residue diluted with 25 ml of water. The resulting milky brown suspension, after standing overnight, deposited pale tan needles and a brown oil adhering to the reaction vessel. The solvent and needles (identified as triphenylphosphine oxide) were decanted, and the oil was recrystallized twice from 95% ethanol (once with charcoal), two crops being recovered totaling 84 mg (28%) of short white needles: mp 215–219° dec; ^{1}H NMR (Me_2SO-d_6) δ 1.23 (3, t, *J* = 7 Hz, OCH_2CH_3), 4.16 (2, q, *J* = 7 Hz, OCH_2CH_3), 6.85 (1, d, *J* = 16 Hz, CH=CHCO$_2$Et), 7.40 (1, d, *J* = 16 Hz,

CH=CHCO$_2$Et), 8.01 (1, s, H-6); uv $\lambda_{max}^{pH\ 1}$ 297 nm (ϵ 20000). Anal. ($C_9H_{10}N_2O_4$) C, H, N.

trans-**3-(5-Uracilyl)propenoic Acid (7b).** A solution of 2.00 g (1.43 mmol) of 5-formyluracil (**5**), 2.91 g (2.8 mmol) of malonic acid, and 0.25 ml of piperidine in 35 ml of dry pyridine was heated on a steam bath for 1 hr and then at reflux in an oil bath for 20 min. After cooling, the yellow solution was diluted with 50 ml of water and extracted repeatedly with ether until the volume of the aqueous phase remained constant. Upon final extraction, a copious yellow precipitate appeared. This phase was acidified to pH 2 with HCl and reextracted with ether to remove unreacted malonic acid. The yellow powder was filtered and recrystallized from water to yield 2.60 g (84%) of white powder: mp 283–284° dec (lit.[4] 283–284°); ^{1}H NMR (Me$_2$SO-d_6) δ 6.95 (1, d, J = 16 Hz, CH=C*H*CO$_2$H), 7.33 (1, d, J = 16 Hz, C*H*=CHCO$_2$H), 7.95 (1, d, J = 6 Hz, coalesced to singlet on addition of D$_2$O, H-6); uv $\lambda_{max}^{pH\ 1}$ 297 nm (ϵ 16320), 268 (13800). Anal. ($C_7H_6N_2O_4$) C, H, N.

1-(5-Uracilyl)buten-3-one (7c). A suspension of 1.0 g (7 mmol) of 5-formyluracil (**5**) in 10 ml of water containing 1.14 g of acetone was stirred at 25° while 3.1 ml of 10% sodium hydroxide was added slowly over 90 min. The yellow solution was heated to 50° for 12 hr after which TLC indicated about 70% reaction. An additional 1.8 ml of acetone was added in 0.3-ml aliquots over a 6-hr period while heating was continued. After cooling to 2°, cold hydrochloric acid was added to give a pH of 2 and the solid was separated and recrystallized twice from acetic acid to give 200 mg of product (16%): mp 276–277°; uv (0.1 *M* HCl) λ_{max} 309 nm (ϵ 13900); uv (0.1 *M* NaOH) λ_{max} 287 nm (ϵ 4730), 355 (2140). Anal. ($C_8H_8N_2O_3$) H, N; C: calcd, 53.33; found, 52.86.

The product (**7c**) could be obtained in higher yield using an excess of acetone, 5-formyluracil (**5**), and piperidine in equimolar amounts in acetic acid as the solvent. After 40 hr of reflux the cooled solution was filtered to give a 65% yield of crude product. After recrystallization 35% of pure product was obtained.

Dimethyl *trans*-3-(5-Uracilyl)propenamide (8). A three-neck flask was fitted with a rubber septum and two dry ice condensers and provision made for flushing with nitrogen. *trans*-3-(5-Uracilyl)acrylic acid[4] (**7b**, 360 mg, 2.0 mmol) and 6 ml of pyridine were added. A solution of 1.0 g (4.9 mmol) of dicyclohexylcarbodiimide in 6 ml of pyridine then was introduced via a syringe and the reaction stirred at room temperature for 2 hr. The flask was cooled in an ice bath, and 10–15 drops of dimethylamine was condensed into the mixture. After the ice melted, the reaction was stirred at room temperature overnight. After 0.1 ml of water (more than that needed to react with the excess DCC) was added, the suspension was stirred an additional 30 min. The suspension was chilled and filtered to remove dicyclohexylurea. The filtrate was diluted with an equal volume of water and the pyridine removed by partitioning into ether. The aqueous layer was evaporated almost to dryness and neutralized with HCl, and the residue was recrystallized from 0.1 *M* phosphate buffer at pH 8 (to keep unreacted acid in solution). The yield of white microcrystalline material was 140 mg (34%): mp 312–314° dec; uv $\lambda_{max}^{pH\ 1}$ 297 nm (ϵ 16000), 278 (13400). Anal. ($C_9H_{11}N_3O_3$) C, H, N.

5-*N*,*N*-Dimethyl-β-alanyluracil Hydrochloride (9). 5-Acetyluracil (7.8 g, 50 mmol, **1**), paraformaldehyde (1.5 g, 50 mmol), and dimethylamine hydrochloride (4.25 g, 52 mmol) were placed in a 500-ml flask with 250 ml of water and 0.5 ml of HCl. The mixture was heated at reflux and monitored by TLC. After 2 days, an additional 0.50-g (17 mmol) portion of paraformaldehyde was added, and at 3 days the reaction had gone to completion. A small amount of insoluble matter was filtered from the hot solution, and the filtrate was evaporated at reduced pressure to a viscous yellow oil. Crystallization was induced by shaking with methanol, and recrystallization from 0.1 *N* HCl afforded 4.3 g (41%) of slightly off-white powder: mp 279–285° dec; uv $\lambda_{max}^{pH\ 1}$ 287 nm (ϵ 10000), 230 (7500). Anal. ($C_9H_{14}ClN_3O_3$) C, H, N.

1-(5-Uracilyl)-3-dimethylaminopropanol Hydrochloride (10). The Mannich base **9** was reduced by a procedure adapted from Evans et al.;[11] the ketone **9** (1.06 g, 5.0 mmol) was dissolved in 60 ml of 0.1 *N* NaOH in an Erlenmeyer flask wrapped in aluminum foil. Sodium borohydride (0.7 g, 74 mequiv) and a stirring bar were added, the flask was capped with aluminum foil, and the reaction stirred at room temperature for 24 hr, when an aliquot analyzed by uv indicated complete reaction. Excess reducing agent was destroyed and the solution neutralized by addition of Dowex-50 (H^+ form). The resin was filtered and washed with 3 × 50 ml of 0.1 *N* HCl. The combined washings and filtrate were evaporated to dryness on a steam bath, and the residue was suspended in 100 ml of methanol. This was allowed to evaporate to dryness on a steam bath, and sequential suspension and evaporation was carried out a total of six times. The remaining product, a tan powder largely insoluble in hot methanol, was recrystallized from 0.1 *N* HCl to yield 480 mg (45%) of a white powder: mp 258–261° dec; uv $\lambda_{max}^{pH\ 1}$ 264 nm (ϵ 9600). Anal. ($C_9H_{16}ClN_3O_3$) C, H, N.

Growth Inhibition Studies. The compounds to be tested were dissolved in sterile nutrient broth media at a concentration of 1×10^{-3} *M* for compounds **2b**, **2d**, and **4**. Due to limited solubility compounds **3**, **6**, and **7b** were studied at 1×10^{-4} *M*. A 2% inoculum of a stock culture of *E. coli* B or *Staph. aureus* was added to each inhibitor solution. After incubation for 20 hr at 37°C the samples were examined for turbidity at 500 nm. Controls on the *E. coli* were 0.60 OD and for *Staph. aureus* were 0.25 OD. All of the compounds examined failed to inhibit growth; the samples in all cases were at least 90% of the controls.

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