1-Acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (7).[2]—A mixture of 3.2 g (0.01 mol) of 1-acetyl-7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine, 60 ml of methylene chloride, and 4 ml of (0.044 mol) of phosphorus oxychloride was stirred at room temperature for 3 hr. The usual hydrolytic work-up left 2.7 g of residue which was chromatographed on 90 g of silica gel with ethyl acetate. Crystallization of the evaporated clean fractions from ethyl acetate–hexane yielded 1.4 g (47%) of product, mp 164–166° (some starting material was eluated first).

6-Chloro-1-methyl-4-phenylcarbamoyl-1,2,3,4-tetrahydroquinoxaline (8).—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1.5 g (0.0125 mol) of phenyl isocyanate, and 40 ml of toluene was refluxed for 24 hr. The crystals which separated from the cooled reaction mixture were collected by filtration and recrystallized twice from ethyl acetate–ethanol to yield 1.2 g (40%) of **8**: mp 190–192°; nmr (DMSO-*d*) δ 2.89 (s, 3, NCH_3), 3.1–4 (m, 4, C_2 H, C_3 H), 8.85 (s, 1, NH); uv max 227–228 mμ (ϵ 24,300), 244–246 (20,800), 273–274 (17,900); ir (KBr) 3250 (NH), 1640 cm^{-1} (NC=O).

Anal. Calcd for $C_{16}H_{16}ClN_3O$: C, 63.68; H, 5.34; N, 13.92. Found: C, 63.48; H, 5.39; N, 14.01.

The original filtrate was extracted three times with 1 *N* hydrochloric acid. The combined extracts were made alkaline with ammonia and extracted with benzene. The dried and evaporated extracts left a yellow oil which was chromatographed on 40 g of silica gel with ethyl acetate. The known 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (0.18 g, 6.6%) was obtained, melting point and mixture melting point with an authentic sample,[3] 97–99°.

7-Chloro-2,3-dihydro-1,3-dimethyl-5-phenyl-1*H*-1,4-benzodiazepine (2c).—A mixture of 5 g (0.0165 mol) of 7-chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**), 2.5 g (0.045 mol) of potassium hydroxide, and 50 ml of ethanol was refluxed for 24 hr. The solvent was removed under reduced pressure and the residue was distributed between benzene and water. The organic layer was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride–petroleum ether gave 3.1 g (66%) of product, mp 102–104°.

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02. Found: C, 71.90; H, 6.24.

By the same procedure the known compounds **2a**[3] and **2b**[3] were obtained from **1a**[2] and **1b** in 93 and 72% yield, respectively.

Registry No.—**1b**, 28121-71-3; **1c**, 28199-16-8; **1d**, 28199-17-9; **2c**, 28199-18-0; **3b**, 28199-19-1; **3b** benzoyl, 28199-20-4; **3c**, 28199-21-5; **3c** *p*-chlorobenzoyl, 28199-22-6; **3d**, 28199-23-7; **3d** HCl, 28199-24-8; **4b**, 28199-25-9; **5**, 28199-26-0; **6**, 1803-97-0; **7**, 1803-95-8; **8**, 28199-28-2; **9c**, 28199-29-3; **9d**, 28199-30-6.

Acknowledgment.—We wish to thank the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, Dr. Toome for the uv spectra, and Mr. S. Traiman for the ir spectra.

Pyrimidines. XI. The Conversion of 5-Hydroxyuracils into 6-Alkyluracils *via* Claisen Rearrangements[1]

BRIAN A. OTTER,* AVIVA TAUBE, AND JACK J. FOX

Division of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021

Received October 2, 1970

Approaches to the synthesis of 6-carbon-substituted pyrimidine nucleosides from 5-hydroxypyrimidine nucleosides have been investigated using N-alkylated 5-hydroxyuracils as model compounds. 5-Allyl ethers of hydroxyuracils readily undergo Claisen rearrangement at ~120° to give the 6-allyl-5-hydroxyuracils in very high yield. These rearrangements proceed by a normal intramolecular Claisen mechanism. Under more drastic conditions (207°), 5-allylamino-1,3-dimethyluracil undergoes an amino-Claisen rearrangement to 6-allyl-5-amino-1,3-dimethyluracil. 5-Benzyloxy-1,3-dimethyluracil undergoes a different type of rearrangement at 207° to give 6-benzyl-1,3-dimethyl-5-hydroxyuracil. Direct electrophilic attack at C-6 of 5-hydroxyuracils is demonstrated with the hydroxymethylation of 1-methyl-5-hydroxyuracil. Two methods for removal of a pyrimidine 5-hydroxyl group are given. Thus hydrogenolysis of the 5-tetrazolyl ether of 1,3-dimethyl-6-propyl-5-hydroxyuracil and treatment of 1,3-dimethyl-5-mesyloxy-6-propyldihydrouracil with 1,5-diazobicyclo[5.4.0]-undecene-5 (DBU) both afford 1,3-dimethyl-6-propyluracil. The synthesis of 5-allyloxyuridine and subsequent Claisen rearrangement to give 6-allyl-5-hydroxyuridine is described.

Orotidylic acid (the 5′-phosphate ester of 6-carboxyuridine) plays an important role in the biosynthesis of the nucleotide components of ribonucleic acid. Synthetic pyrimidine nucleosides bearing a carbon substituent at C-6 are of interest because of their structural similarity to orotidylic acid, and it is possible that compounds of this class may interfere with nucleic acid metabolism. However, 6-carbon-substituted nucleosides are not easily prepared and the first examples of synthetic compounds of this type were described only recently.[2,3] These compounds, the 6-methyl and 5,6-dimethyl analogs of uridine and cytidine, were prepared in low yield by use of conventional procedures involving the initial condensation of suitable 6-methylcytosines with halogeno sugars.

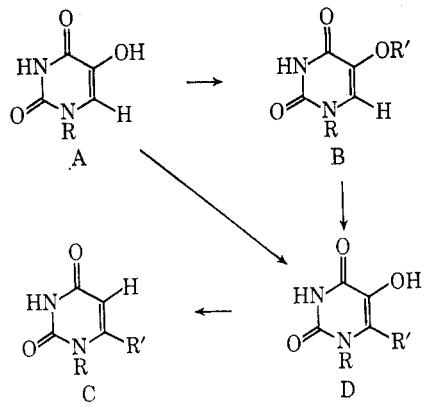
An alternative approach to the synthesis of 6-substituted nucleosides, namely substitution of C-6 of a *preformed* nucleoside, is shown in Scheme I, which illustrates two possible methods for converting a 5-hydroxyuracil A into a 6-carbon substituted uracil C. One route involves the rearrangement of suitable 5-hydroxyuracil ethers B to give the isomeric 6-substituted 5-hydroxyuracils D. The other route involves the formation of compounds D by direct attack of a carbon electrophile at C-6 of A. Removal of the 5-hydroxyl group of D would then effect an overall synthesis of C from A. We have now investigated these general approaches and the results obtained using N-alkylated 5-hydroxyuracils as models form the subject of this paper.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478), and by a Postdoctoral Fellowship (to A. T.) from the Westchester Division of the American Cancer Society.

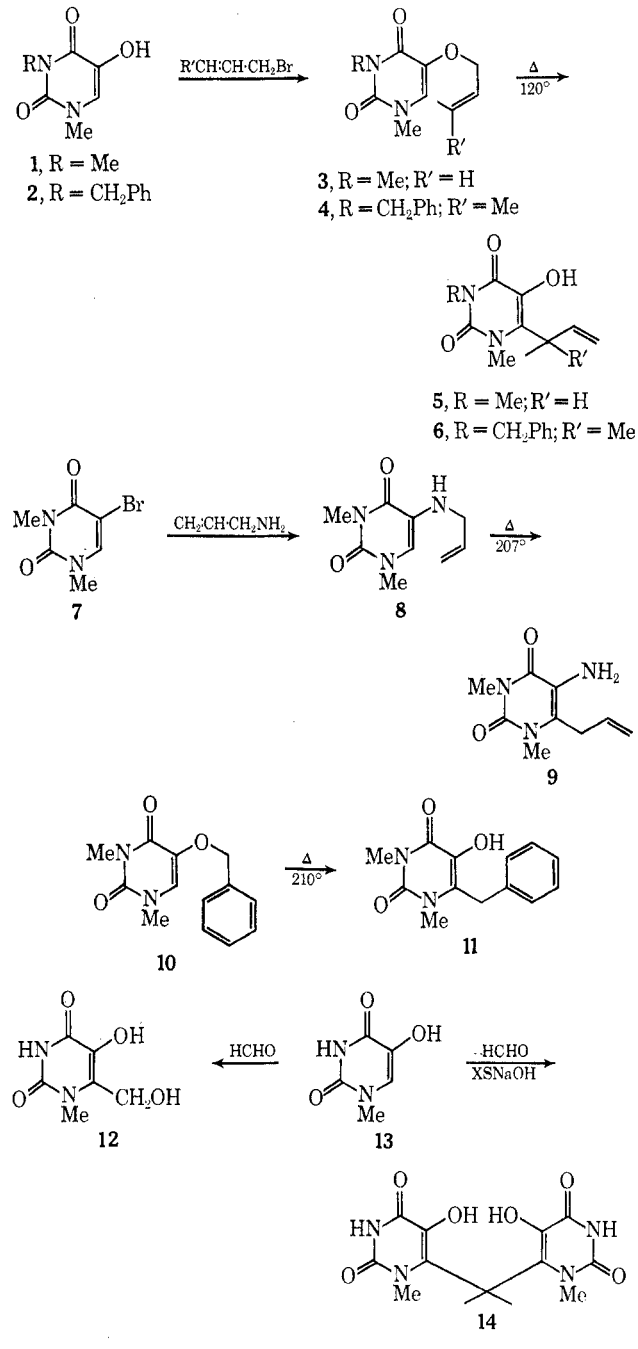
(2) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968).

(3) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 2316 (1968).

SCHEME I



SCHEME II



An obvious choice for the reaction B → D in Scheme I is the Claisen rearrangement of a 5-allyloxyuracil.[4] Such a compound (**3**, Scheme II) was easily prepared by treatment of the sodium salt of 1,3-dimethyl-5-hydroxyuracil (**1**) with allyl bromide in methanol. Rearrangement of the allyl ether **3** occurred readily at 120°. Moreover, the product **5** was formed in quantitative yield within a 10-min period. The structure of **5** was evident from the uv spectrum, and from the nmr spectrum, which shows absence of a C-6 proton but presence of the 5-hydroxyl and 6-allyl protons. The 5-crotyloxy ether **4** was prepared from **2** and rearranged at 125° to test for the inversion of the allyl group that is characteristic of the ortho-Claisen rearrangement. The nmr spectrum of the product **6** shows the presence of the 6-methylallyl group, thereby confirming that inversion had taken place. Pyrolysis of a mixture of ethers **3** and **4** afforded only **5** and **6**; the absence of crossover products means that these reactions proceed by the normal intramolecular mechanism established for the ortho-Claisen rearrangement.[5]

It is clear from examination of the experimental conditions used to effect a large number of Claisen rearrangements,[5a] that the ethers **3** and **4** rearrange with unusual ease. This suggested that the corresponding 5-allylamino compounds might also rearrange[6] and led us to examine the pyrolysis of 1,3-dimethyl-5-allylaminouracil (**8**). As expected, compound **8** is much more stable than the allyl ether **3**, and temperatures of at least 200° are required for rearrangement to take place at a reasonable rate. In refluxing tetralin (207°) compound **8** underwent partial rearrangement and, after a 12-hr period, the 6-allyl-5-aminouracil (**9**) was isolated in 24% yield.

The benzyloxyuracil **10** does not undergo the Claisen rearrangement, even though a 1,5-diene system is present. Instead, **10** partially rearranges when heated without solvent at 210° for 3 hr to give 6-benzyl-1,3-dimethyl-5-hydroxyuracil (**11**) in 20% yield. When **10** was refluxed in tetralin for 16 hr, the rearrangement product (**11**) was obtained in 30% yield. That compound **11** contains a 6-benzyl group, rather than a 6-*o*-tolyl group resulting from Claisen rearrangement, is clear from the nmr spectrum which shows a methylene rather than a *C*-methyl resonance. This rearrangement is analogous to the thermal conversion of phenylbenzyl ether[7] into *o*- and *p*-benzylphenol, a reaction that is thought to involve an intermolecular, free-radical mechanism.

Previous studies have shown that 5-hydroxyuracils are susceptible to direct electrophilic substitution at C-6. For example, 5-hydroxyuracil itself undergoes nitrosation,[8a] diazo coupling,[8b] and Mannich reactions[9]

(4) (a) Although Claisen rearrangements of 2-allyloxy-[4b] and 4-allyloxypyrimidines[4c] have been studied previously, no examples of the rearrangement of 5-allyloxypyrimidines had been reported prior to the present study. For a review of Claisen rearrangments in pyrimidines and other N-heterocyclic systems, see B. S. Thyagarajan, *Advan. Heterocycl. Chem.*, **8**, 143 (1967). (b) J. K. Elwood and J. W. Gates, *J. Org. Chem.*, **32**, 2956 (1967). (c) H. J. Minnemeyer, P. B. Clarke, and H. Tieckelmann, *ibid.*, **31**, 406 (1966).

(5) For reviews, see (a) D. S. Tarbell, *Org. React.*, **2**, 1 (1944); (b) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968).

(6) Relatively few amino-Claisen rearrangements are known. Some examples are given in ref 5b.

(7) F. M. Elkobaisi and W. J. Hickinbottom, *J. Chem. Soc.*, 1873 (1959); *ibid.*, 1286 (1960).

(8) (a) D. Davidson and M. T. Bogert, *Proc. Nat. Acad. Sci. U. S.*, **18**, 490 (1932); (b) M. T. Bogert and D. Davidson, *ibid.*, **18**, 215 (1932).

(9) D. E. O'Brien, R. H. Springer, and C. C. Cheng, *J. Heterocycl. Chem.*, **3**, 115 (1966).

to give 6-substituted products. More recently, we have shown[10] that isopropylidene-5-hydroxyuridine and 1,3-dimethyl-5- hydroxyuracil undergo base-catalyzed exchange of H-6 for deuterium. This reaction, and presumably the examples above, involves ionization of the 5-hydroxyl group to give a mesomeric anion in which C-6 has sufficient carbanion character to react with electrophiles.[10]

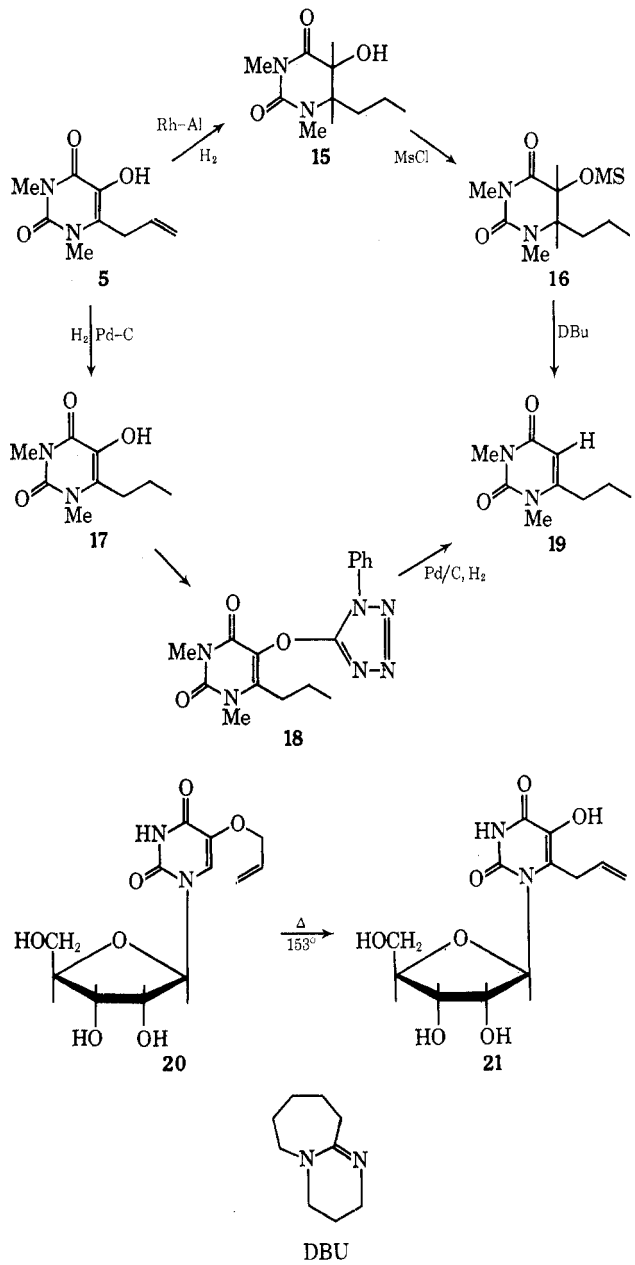
A further example of electrophilic substitution, namely hydroxymethylation, is shown in Scheme II. Thus treatment of the sodium salt of 1-methyl-5-hydroxyuracil (**13**) with an excess of aqueous formaldehyde affords the 6-hydroxymethyluracil **12** in 61% yield. Treatment of **13** with formaldehyde in the presence of an excess of sodium hydroxide results in the formation of the methylene-bridged compound **14**. The structure of **14** was apparent from the nmr spectrum, which shows ureide, hydroxyl, methylene, and methyl signals with intensities in the ratio 1:1:1:3. This type of diarylation reaction is frequently encountered during the hydroxymethylation of phenols.[11]

The final step (D → C) in Scheme I, involving removal of the 5-hydroxyl group from a 6-substituted 5-hydroxyuracil, was accomplished by using the two methods shown in Scheme III. These procedures are illustrated with 6-allyl-1,3-dimethyl-5-hydroxyuracil (**5**), but in principle they should be applicable to a variety of 6-substituted uracils. Hydrogenation of compound **5** over rhodium–alumina catalyst, followed by mesylation of the resulting dihydrouracil (**15**) afforded the 5-mesyl ester **16**. Treatment of **16** with 1,5-diazobicyclo[5.4.0]undecene-5 (DBU)[12] in refluxing tetrahydrofuran then gave 1,3-dimethyl-6-propyluracil (**19**, 48% yield) together with small amounts of two unidentified products. The structure of **19** was confirmed by comparison with authentic material prepared from 2-thio-6-propyluracil according to the method described by Burckhalter and Scarborough.[13]

The alternative synthesis of compound **19** shown in Scheme III is an extension of the procedure developed by Musliner and Gates[14] for removal of phenolic hydroxyl groups. As applied to the 5-hydroxy-6-propyluracil **17**, this method readily affords **19** in a high state of purity. Thus, condensation of **17** with 1-phenyl-5-chlorotetrazole in acetone in the presence of potassium carbonate afforded the 1-phenyltetrazolyl ether **18**. Hydrogenolysis of **18** with palladium/charcoal then gave 1,3-dimethyl-6-propyluracil (**19**) in more than 50% yield. These transformations appear to be the first examples of the replacement of a 5-hydroxyl group of a pyrimidine by hydrogen.

Preliminary studies on the extension of the above procedures to the nucleoside series have shown that 5-allyloxyuridine (**20**) can be prepared by selective allylation of 5-hydroxyuridine, and that **20** undergoes Claisen rearrangement in refluxing dimethylformamide to give the 6-allyl nucleoside **21** in excellent yield. The conversion of **21** into a series of 6-substituted pyrimidine nucleosides is currently being investigated.

SCHEME III



Experimental Section

General Procedures.—Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent (unless otherwise stated) and tetramethylsilane as internal reference. First-order values are given for coupling constants (hertz) and chemical shifts. Ultraviolet spectra were measured on Cary Model 15 and Unicam SP 500 spectrometers. Evaporations were carried out under reduced pressure. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

5-Allyloxy-1,3-dimethyluracil (3).—Allyl bromide (8.6 ml, 0.1 mol) was added to a solution of **1** (7.8 g, 0.05 mol) in methanol (250 ml) containing 1.15 g (0.05 g-atom) of sodium. The solution was refluxed for 1 hr, cooled, and evaporated to dryness. The residue was partitioned between water and chloroform (three 50-ml portions), and the chloroform solution was dried (sodium sulfate) and concentrated to a syrup which crystallized from ethyl acetate to give 8 g (82%) of **3**: mp 103–104°; uv $\lambda_{max}^{pH\ 1-14}$ 281 mμ; nmr δ 7.50 s (1, H-6), 6.02 14-line m, width 37 Hz (1,

(10) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(11) For a review, see H. Schnell and H. Krimm, *Angew. Chem., Int. Ed. Engl.*, **2**, 373 (1963).

(12) This reagent was introduced for the dehydrohalogenation of bromoalkanes by H. Oediger and Fr. Möller, *ibid.*, **6**, 76 (1967).

(13) J. H. Burckhalter and H. C. Scarborough, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 545 (1955).

(14) W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

-CH=), 5.47 m, 5.31 m, 5.17 m (2, $=CH_2$), 4.39 m (2, OCH_2), 3.27 s (3, NCH_3), and 3.17 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.93; H, 6.04; N, 14.23.

3-Benzyl-5-crotyloxy-1-methyluracil (4).—To 100 ml of methanol containing 460 mg (20 mg-atoms) of sodium was added 2.32 g (10 mmol) of compound **2**.[10] Technical grade crotyl bromide (2.6 g, ~20 mmol) was added and the solution was refluxed for 3 hr. The solution was concentrated to dryness and the residue was dissolved in benzene. The benzene solution was washed successively with dilute NaOH and water, dried, and concentrated to give a white solid (1.73 g, 60%) with mp 78–81°. Recrystallization from benzene–petroleum ether (bp 30–60°) gave pure **4**: mp 81–83°; uv $\lambda_{max}^{pH\ 1-14}$ 283 mμ; nmr δ 7.45 s (1, H-6), 7.21 s (5, phenyl), 5.67 m (2, CH=CH), 4.98 s (2, CH_2Ph), 4.28 m (2, OCH_2), 3.27 s (3, NCH_3), and 1.67 ppm m (3, CCH_3).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.14; H, 6.24; N, 9.61.

6-Allyl-1,3-dimethyl-5-hydroxyuracil (5).—Compound **3** (1 g) was melted and kept at 120° for 10 min. During this time, uv examination (pH ~10) of samples showed rapid loss of absorption at 281 mμ and appearance of a new peak at 316 mμ. Crystallization of the cooled melt from benzene–petroleum ether afforded 960 mg (96%) of **5**: mp 104–106°; uv $\lambda_{max}^{pH\ 1}$ 287 mμ; $\lambda_{max}^{pH\ 12}$ 316 mμ; nmr δ 8.40 s (1, 5 OH), 5.93 m (1, CH=), 5.22 m, 5.06 m, 4.95 m (2, $=CH_2$), 3.45 m (2, CH_2), 3.30 s (3, NCH_3), and 3.22 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.10; H, 6.12; N, 14.22.

3-Benzyl-5-hydroxy-1-methyl-6-methylallyluracil (6).—Pyrolysis of 180 mg (6.3 mmol) of **4** at 125° for 20 min, and crystallization of the melt from benzene–petroleum ether afforded 175 mg (97%) of **6**: mp 118–120°; uv $\lambda_{max}^{pH\ 1}$ 288 mμ; $\lambda_{max}^{pH\ 12}$ 319 mμ; nmr δ 8.39 s (1, 5 OH), 7.25 s (5, phenyl), 6.11 8-line m (1, CH=), four-proton group with 5.02 s (CH_2Ph) overlapping high-field part of multiplet pair at 5.20 and ~4.97 ($=CH_2$), 3.99 m (1, $CHCH_3$), 3.31 s (3, NCH_3), and 1.39 ppm d (3, CCH_3, J_{H,CH_3} = 7.0 Hz).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.85; H, 6.19; N, 9.55.

Mixed Pyrolysis of 3 and 4.—A mixture containing 196 mg (1 mmol) of **3** and 286 mg (1 mmol) of **4** was melted and kept at 125° for 20 min. Tlc of the melt on silica gel G_{254} (Merck) in benzene–ethyl acetate (4:1 v.v) revealed only two components. Fractionation of the mixture on a column containing 25 g of silica gel G, using the above solvent system, afforded 270 mg (95%) of **6** and 192 mg (98%) of **5**. Identification of **5** and **6** was made on the basis of mixture melting points and comparison of uv and nmr spectra with those of **5** and **6** prepared as above.

1,3-Dimethyl-5-allylaminouracil (8).—A solution of 8 g of 1,3-dimethyl-5-bromouracil (**7**) in 80 ml of freshly distilled allylamine (bp 56°) was refluxed for 5 hr. The solution was evaporated to dryness and the solid residue was partitioned between water and dichloromethane. The organic layer was dried over sodium sulfate and concentrated to a syrup which crystallized readily from hot ethyl acetate. The yield of **8**, mp 107–109°, was 5.3 g (70%). The analytical sample was obtained by sublimation *in vacuo* at 110°: uv $\lambda_{max}^{pH\ 1}$ 270 mμ; $\lambda_{max}^{pH\ 7-14}$ 302 mμ; nmr δ 6.65 s (1, H-6), 5.95 m (1, CH=), 5.38 m, 5.23 m, 5.08 m (2, $=CH_2$), 4.60 broad t (1, NH, $J_{NH,CH}$ = 6 Hz), 3.64 m (2, NCH_2), 3.35 s (3, NCH_3), and 3.30 ppm s (3, NCH_3).

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.31; H, 6.57; N, 21.55.

6-Allyl-5-amino-1,3-dimethyluracil (9).—A solution of **8** (500 mg) in 5 ml of tetralin was refluxed for 12 hr. The solution was decanted from a small amount of tarry material, diluted with benzene (5 ml), and extracted with 0.01 *N* HCl (three 10-ml portions). The aqueous layer was neutralized with NaOH and extracted with chloroform. The chloroform solution was dried (sodium sulfate), concentrated to a small volume, and applied to two thick layer plates (20 × 20 cm with 30 g of Merck silica gel P_{254}). The plates were developed in ethyl acetate and the appropriate zones were removed and extracted with hot ethanol. Concentration of the combined extracts afforded a yellow syrup which crystallized spontaneously. The yield of **9** was 122 mg (24%): nmr δ 5.91 m, width 38 Hz (1, CH=), 5.22 m, 5.04 m, 4.95 m (2, $=CH_2$), 3.97 broad peak (2, NH_2), 3.40 m (2, CH_2), 3.29 s (3, NCH_3), and 3.21 ppm s (3, NCH_3). The picrate salt was prepared by addition of ethanolic picric acid to an ethanol solution of **9**. Recrystallization of the yellow solid from aqueous ethanol afforded the hemihydrate, mp 159–161°. The nmr spectrum of the picrate confirmed the presence of 0.5 H_2O of crystallization.

Anal. Calcd for $C_{15}H_{16}N_6O_9 \cdot 0.5H_2O$: C, 41.57; H, 3.95; N, 19.39. Found: C, 41.65; H, 3.81; N, 19.36.

5-Benzyloxy-1,3-dimethyluracil (10).—Benzyl chloride (2.3 ml, 20 mmol) was added to a solution of **1** (1.56, 10 mmol) in methanol (50 ml) containing 40 ml of 0.25 *N* NaOH (10 mmol). The mixture was refluxed for 5 hr and then concentrated to ~30 ml. The solid that precipitated was removed and crystallized from benzene–petroleum ether to give 2.16 g (88%) of **10**: mp 95–97°; uv $\lambda_{max}^{pH\ 1-14}$ 281 mμ; nmr δ 7.51 s (1, H-6), 7.34 s (5, phenyl), 4.87 s (2, CH_2Ph), 3.25 s (3, NCH_3), and 3.17 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.04; H, 5.67; N, 11.14.

6-Benzyl-1,3-dimethyl-5-hydroxyuracil (11). Method A.—Compound **10** (500 mg) was heated at 210° for 3 hr. A solution of the melt in ethanol was passed through a column containing ~10 ml of Dowex 1 (OH^-, equilibrated with ethanol). The column was washed with 50% ethanol until the effluent showed no uv absorption (fraction 1) and then with 1 *N* ammonium bicarbonate in 50% ethanol until the effluent failed to give a blue color with ferric chloride (fraction 2). Concentration of fraction 1 afforded 270 mg of slightly impure starting material. Fraction 2 was concentrated to half-volume, neutralized, and extracted with dichloromethane. Evaporation of the dried dichloromethane solution afforded a syrup which crystallized from aqueous methanol. The yield of **11**, mp 180–181°, was 102 mg (20%): uv $\lambda_{max}^{pH\ 1}$ 287 mμ; $\lambda_{max}^{pH\ 14}$ 316; nmr δ 8.47 s (1, 5 OH), 7.23 s (5, phenyl), 4.09 s (2, CH_2Ph), 3.24 s (3, NCH_3), and 3.15 ppm s (3, NCH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.41; H, 5.78; N, 11.64.

Method B.—A solution of 984 mg (4 mmol) of **10** in 10 ml of tetralin was refluxed for 16 hr. The dark brown solution was extracted with dilute NaOH and the aqueous alkaline solution was neutralized with HCl. Extraction with chloroform, followed by evaporation of the chloroform solution to dryness and crystallization of the residue from benzene–petroleum ether gave 300 mg (30.5%) of pure **11**, mp and mmp 180–181°.

6-Hydroxymethyl-5-hydroxy-1-methyluracil (12).—Sodium hydroxide (10 ml of 1 *N* solution) and aqueous formaldehyde (2 ml of ~37% solution, ~25 mmol) were added to a suspension of 1-methyl-5-hydroxyuracil (**13**) (1.42 g, 10 mmol) in 88 ml of water. The solution was kept at 50° for 1 hr, cooled, and passed through a column containing 30 ml of Dowex 50 (H^+). The column was washed with water until samples of the effluent failed to give a blue color with ferric chloride. Concentration of the effluent to ~10 ml, and cooling at 5°, afforded two crops of colorless crystals (1.05 g, 61%) with mp 195–196° eff: uv $\lambda_{max}^{pH\ 1}$ 289 mμ; $\lambda_{max}^{pH\ 10}$ 318 and 241 mμ; $\lambda_{max}^{pH\ 14}$ 313 and 245 mμ; nmr δ 11.45 broad s (1, NH), 8.43 s (1, 5 OH), 5.35 t (1, CH_2OH, $J_{H,OH}$ = 5.0 Hz), 4.46 d (2, CH_2), and 3.32 ppm s (3, NCH_3).

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.86; H, 4.79; N, 16.02.

6,6′-Methylenebis(1-methyl-5-hydroxyuracil) (14).—1-Methyl-5-hydroxyuracil (**13**) (710 mg, 5 mmol) was dissolved in 50 ml of 1 *N* NaOH (50 mmol); aqueous formaldehyde (2 ml of ~37% solution, ~25 mmol) was added and the solution was heated at 50° for 3 hr. Acidification of the cooled solution with concentrated HCl resulted in the formation of a white, crystalline solid which was collected and washed successively with water, ethanol, and ether. The yield of **14** was 350 mg (47%): mp >305°; uv $\lambda_{max}^{pH\ 1}$ 292 mμ; $\lambda_{max}^{pH\ 10}$ 327 and 242 mμ; $\lambda_{max}^{pH\ 14}$ 322 and 245 mμ; nmr singlets at δ 11.35 (broad, NH), 8.58 (broad, OH), 3.98 (CH_2), and 3.15 ppm (NCH_3 + H_2O) with intensities in the ratio of 1:1:1:3.5. Removal of the water, NH, and OH peaks by addition of D_2O revealed methylene and *N*-methyl peaks with relative intensities of 1:3.

Anal. Calcd for $C_{11}H_{12}N_4O_6 \cdot 0.5H_2O$: C, 43.28; H, 4.29; N, 18.35. Found: C, 43.51; H, 4.22; N, 18.40.

1,3-Dimethyl-5-hydroxy-6-propyl-5,6-dihydrouracil (15).—A solution of **5** (1.96 g, 10 mmol) in ethanol (75 ml) was shaken with 5% rhodium-on-alumina catalyst (~50 mg) under hydrogen in a Parr apparatus for 17 hr. The catalyst was removed and the filtrate concentrated to a colorless syrup which was crystallized from benzene–petroleum ether. The yield of **15**, mp 95–98°, was 1.92 g (96%): nmr δ 5.80 broad peak (1, OH), 4.45 d (1, H-5, $J_{5,6}$ = 6.5 Hz), ~3.5 broad m (1, H-6), 3.0 s (6, *N*-methyls),

~1.4 broad band (4, CH_2CH_2), and ~0.9 ppm broad band (3, CCH_3).

Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 53.53; H, 7.78; N, 13.75.

1,3-Dimethyl-5-mesyloxy-6-propyl-5,6-dihydrouracil (16).—Mesyl chloride (0.8 ml, 10 mmol) was added dropwise to a solution of **15** (1 g, 5 mmol) in pyridine (15 ml) at 0° and the mixture was kept at room temperature for 17 hr. The dark solution was poured into ice-cold water and the gummy precipitate was extracted into ether. The ether layer was washed with 10% HCl and then with water, dried over potassium carbonate–sodium sulfate, and evaporated to dryness. Trituration of the syrupy residue with petroleum ether, with cooling in an acetone–Dry Ice bath, afforded solid material (1.23 g, 83%), mp 97–100°. Recrystallization from chloroform–petroleum ether did not change the melting point.

Anal. Calcd for $C_{10}H_{18}N_2O_5S$: C, 43.15; H, 6.52; N, 10.06. Found: C, 43.07; H, 6.39; N, 9.94.

1,3-Dimethyl-5-hydroxy-6-propyluracil (17).—Compound **5** (1.2 g, 6 mmol) was hydrogenated at atmospheric pressure in 30 ml of ethanol with 10% palladium/charcoal catalyst. Uptake of 6 mmol of hydrogen was complete within 5 min. The catalyst was removed and the filtrate evaporated to a solid which crystallized from ethyl acetate in quantitative yield: mp 95–97°; uv $\lambda_{max}^{pH\ 1}$ 285 mμ; $\lambda_{max}^{pH\ 14}$ 315 and 247 mμ; nmr ($CDCl_3$) δ 6.27 s (1, 5 OH), 3.43 s (6, *N*-methyls), 2.70 m (2, allylic CH_2), 1.65 m (2, CH_2), and 1.05 ppm t (3, CCH_3).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.47; H, 6.99; N, 14.00.

1,3-Dimethyl-6-propyl-5-(1-phenyltetrazolyloxy)uracil (18).—Compound **17** (990 mg, 5 mmol) and 1-phenyl-5-chlorotetrazole (903 mg, 5 mmol)[15] were dissolved in 50 ml of dry acetone. Potassium carbonate (1.38 g, 10 mmol) was added and the mixture was stirred and refluxed overnight. The cooled mixture was filtered and the filtrate was evaporated to dryness. Crystallization of the residue from hot methanol afforded 1.45 g (85%) of **18**: mp 143–145°; uv $\lambda_{max}^{pH\ 1-14}$ 265 mμ; nmr ($CDCl_3$) δ ~7.6 m (5, phenyl), 3.46 s (3, NCH_3), 3.34 s (3, NCH_3), 2.66 m (2, allylic CH_2), 1.70 m (2, CH_2), and 1.00 ppm t (3, CCH_3).

Anal. Calcd for $C_{16}H_{18}N_6O_3$: C, 56.13; H, 5.30; N, 24.55. Found: C, 55.96; H, 5.25; N, 24.59.

1,3-Dimethyl-6-propyluracil (19). Method A.—A mixture of 1.03 g (3 mmol) of **18** and 210 mg of 10% palladium/charcoal in 250 ml of ethanol was shaken under hydrogen at atmospheric pressure for 7 hr. The catalyst was removed and the solution was concentrated to dryness. The crude syrup was added to a column of silica gel G (30 g, Merck) and eluted with chloroform–methanol (10:1 v/v). Concentration of the appropriate fractions afforded (in order of elution) 260 mg (48%) of **19**, 80 mg of a mixture of **19** and 1-phenyltetrazolone, and 449 mg (92.5%) of pure 1-phenyltetrazolone, mp 185–188° (lit.[16] 187°). Compound **19** (mp and mmp 60–61°) showed ir, uv ($\lambda_{max}^{pH\ 1-14}$ 268 mμ), and nmr spectra [($CDCl_3$) δ 5.53 s (1, H-5), 3.43 s (3, NCH_3), 3.35 s (3, NCH_3), 2.52 t (2, allylic CH_2), 1.67 sextet (2, CH_2), and 1.06 ppm t (3, CCH_3)] identical with those of authentic[13] **19**.

Method B.—A solution of 1,5-diazobicyclo[5.4.0]undecene-5 (1.7 ml, 11 mmol)[15] in 25 ml of tetrahydrofuran was added dropwise, under a nitrogen atmosphere, to a solution of **16** (2.78 g, 10 mmol) in 25 ml of tetrahydrofuran. The yellow solution was refluxed for 48 hr and then concentrated to dryness. The residue was extracted with benzene and the benzene solution was washed successively with cold, dilute sulfuric acid and water. Evaporation of the dried solution afforded a syrup which contained (tlc on Merck aluminum oxide HF_{254}, chloroform–methanol, 4:1) three uv-absorbing compounds. The syrup was fractionated on 100 g of basic alumina (Bio-Rad AG 10). Elution with chloroform afforded fractions from which 200 mg of unidentified material, mp 108–112°, was obtained. Elution with chloroform–methanol (4:1 v/v) then afforded 870 mg (48%) of **19** which was identified by comparison with **19** prepared as above, and with authentic material.[13] Continued elution with chloroform–methanol afforded **19** admixed with an unidentified compound. A sample (120 mg) of this unknown compound, obtained from the final fractions, had mp 126–129° after recrystallization of ethyl acetate–petroleum ether.

5-Allyloxyuridine (20).—Allylbromide (15 ml, 0.17 mol) was added to a solution of 5-hydroxyuridine (15.6 g, 0.06 mol) in 500 ml of 50% methanol containing 60 ml of 1 *N* NaOH (0.06 mol). The mixture was stirred at room temperature for 3 hr and the white solid (which began to precipitate after ~20 min) was removed and dried in air. Tlc (dichloromethane–methanol, 5:1 v/v) showed that the solid (11.8 g, 66%, mp 184–185°) contained only trace amounts of starting material. Recrystallization from boiling water afforded **20** with unchanged melting point: uv $\lambda_{max}^{pH\ 1}$ 279 mμ; λ_{min} 246 mμ; $\lambda_{max}^{pH\ 10}$ 276 mμ; λ_{min} 251 mμ; nmr δ 11.32 s (1, NH), 7.66 s (1, H-6), 6.3–5.7 m (2, H-1′ and $=CH_2$), 5.6–4.8 m (5, $=CH_2$ and 2′,3′,5′-hydroxyls), 4.35 m (1, OCH_2), 4.2–3.8 m (3, H-2′, H-3′, H-4′), and 3.63 ppm m (2, H-5′, H-5′). Removal of hydroxyl signals by addition of D_2O revealed $=CH_2$ as a multiplet with components at 5.50 m, 5.27 m, and 5.20 ppm m.

Anal. Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.81; H, 5.20, N, 9.24.

6-Allyl-5-hydroxyuridine (21).—A sample of compound **20** (1.85 g) was dissolved in 20 ml of near-boiling dimethylformamide and the solution was refluxed for 10 min. The pale-yellow solution was evaporated (50°, oil pump) to a syrup from which DMF was removed by codistillation with xylene. Tlc (dichloromethane–methanol, 5:1 v/v) of the dry syrup (1.8 g) showed the presence of **21** and very small amounts of 5-hydroxyuridine, formed presumably by cleavage of the allyloxy group of **20**. Crystallization of the syrup from ~5 ml of 85% ethanol took place slowly to give 1.5 g (79%) (in two crops) of **21** as the hemihydrate: mp 121–125°; uv $\lambda_{max}^{pH\ 1}$ 281 mμ; $\lambda_{max}^{pH\ 10}$ 312 mμ; $\lambda_{max}^{pH\ 14}$ 310, sh 255 mμ; nmr δ 11.47 s (1, NH), 8.47 s (1, OH), 5.55–6.2 (1, m, CH=), 4.8–5.4 m (5, H-1′, 2′-OH, 3′-OH, and $=CH_2$), 4.6 m (2, 5′-OH and H-2′), 4.10 q (1, H-3′), and 3.85 – 3.30 ppm m (6, CH_2, H-4′, H-5′, H-5′, and $^1/_2H_2O$). Removal of OH signals by addition of D_2O revealed signals at δ 5.33 d (H-1′, $J_{1'2'}$ = 4.5 Hz), 5.27 m, 5.08 m, 4.95 m ($=CH_2$), and 4.60 ppm m (H-2′).

Anal. Calcd for $C_{12}H_{16}N_2O_7 \cdot 0.5H_2O$: C, 46.60; H, 5.54; N, 9.06. Found: C, 46.48; H, 5.42; N, 8.82.

Registry No.—**3**, 28199-38-4; **4**, 28199-39-5; **5**, 28199-40-8; **6**, 28199-41-9; **8**, 28199-42-0; **9**, 28199-43-1; **9** picrate, 28199-44-2; **10**, 28199-45-3; **11**, 28199-46-4; **12**, 28199-47-5; **14**, 28199-48-6; **15**, 28199-49-7; **16**, 28199-50-0; **17**, 28199-51-1; **18**, 28199-52-2; **19**, 28267-45-0; **20**, 28192-74-7; **21**, 28192-75-8.

(15) Aldrich Chemical Co., Inc.

(16) O. Dimroth and G. de Montmollin, *Ber.*, **43**, 2904 (1910).