M solution of triethylamine (0.10 mL). The mixture was kept at room temperature while samples were taken and examined (TLC, systems C and D) from time to time. For comparison, a similarly treated solution of compound **5** was used. For **7**, a half conversion time (to **8**) of about 24 h was observed, as judged from the intensities of the spots on TLC under UV. For compound **5**, a $t_{1/2}$ of about 400 h was found.[1] The elimination of α-hydroxyacetophenone was confirmed by TLC on comparison with an authentic sample. Also, both the aminosuccinimide derivative **8** and the α-hydroxyacetophenone were isolated by chromatography on a column of silica gel. Crystallization from ether yielded a sample of **8**, mp 190–192 °C, which gave the expected NMR ($CDCl_3$) spectrum.[14] The α-hydroxyacetophenone was identified by its melting point (86–87 °C) and NMR spectrum.

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**Registry No.**—**1**, 66515-54-6; **2**, 66515-61-5; **2** (Cs salt), 66515-60-4; **4**, 66515-55-7; **5**, 66515-58-0; **6** (Cs salt), 66515-57-9; **7**, 66515-59-1; **8**, 66515-56-8; α-hydroxyacetophenone, 582-24-1.

## References and Notes

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(10) A sample of compound **2** was dissolved in both phases of the solvent system *n*-butanol–pyridine–acetic acid–water (4:2:1:7) and left to stand at room temperature. Gradually the aminosuccinimide derivative **4** formed. In one week, about a third of the starting material was converted. This agrees with the observation made earlier in this laboratory with the antibiotic amphomycin: M. Bodanszky, G. F. Sigler, and A. Bodanszky, *J. Am. Chem. Soc.*, **95**, 2352 (1973).
(11) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973); also cf. ref 3.
(12) The formation of a small amount (2.4%) of aminosuccinyl derivative detected by Yang and Merrifield (ref 3) could also be due to the brief exposure to basic conditions in the chain-lengthening process rather than to the treatment with strong acids in the final stages of solid phase peptide synthesis. If this is indeed the case, then repeated exposures to base in the building of long chains might become the source of major byproduct formation.
(13) To a solution of compound **1** (1 mmol) in DMF (1 mL) was added triethylamine (1 mmol). After one day at room temperature, the ring closure was complete as shown on TLC. The solvent was removed in vacuo and the residue crystallized by trituration with ether. In the NMR spectrum ($CDCl_3$; $Me_4Si$ as an internal reference on a Varian A 60 instrument) the following signals were observed: δ 8.17 (s, NH of naphthylamide), 7.23–7.86 (7 H, naphthalene), 5.73 (d, NH peptide bond), 4.40 (s, $CH_2$ of glycine), 4.16 (m, α-CH of aspartic acid), 3.00 (m, $CH_2$ of aspartic acid), 1.42 (s, $(CH_3)_3$).
(14) In this rigid compound, the coupling constant for the doublet of the α-CH of valine (δ 4.50) is conspicuously large (9 Hz), as are the coupling constants for the two doublets of the nonequivalent $CH_3$ protons of this amino acid (δ 0.98 and 1.17, $J_1$ = 6 Hz and $J_2$ = 17 Hz). These values are much higher than the corresponding signals of the phenacyl derivative (two doublets at δ 0.80 and 1.90, $J_1$ = 2 Hz and $J_2$ = 7 Hz).

## 1,3-Dialkyluracils as a Source of Formyl Acetate for Synthesis[1]

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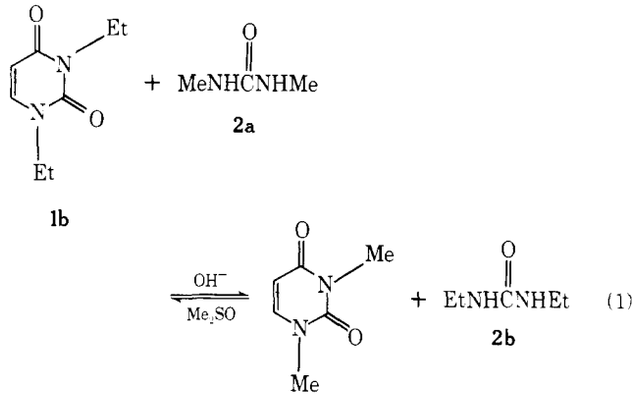
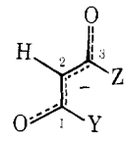
1,3-Dialkyluracils (**1**) can be used as a source of formyl acetate for the synthesis of monosubstituted uracils, for the preparation of **1** with *N*-alkyl groups different from the original ones, or for the synthesis of 2-alkyl- and 2-(dialkylamino)uracils. The favored course for these reactions involves substitution in an enolate anion intermediate.

It was shown recently[2] that 1,3-diethyluracil (**1b**) reacts with 1,3-dimethylurea (**2a**) in dimethyl sulfoxide ($Me_2SO$) solution in the presence of tetramethylammonium hydroxide (TMAH) to give a partial conversion to 1,3-dimethyluracil (**1a**) and 1,3-diethylurea (**2b**) (eq 1).




(1)

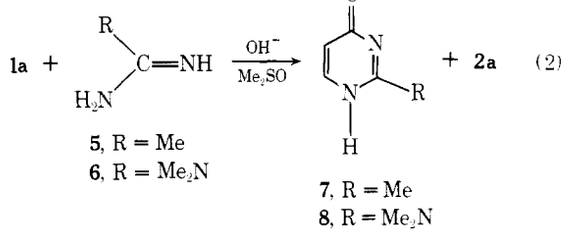
A mechanism was suggested for this reaction which involved condensation of the urea with the enolate anion (**3a**; Y = H,




**3**

Z = RNC(O)NHR) derived from **1**. An alternative one involved direct addition of the urea to C-4 or C-6 of **1**.

The conditions required for such a reaction to take place now have been further delineated and the scope of the reaction has been extended. First, the reaction *requires* hydroxide as the base and $Me_2SO$ as the solvent. It does not take place (TLC) with ethoxide as the base and ethanol or ethanol–$Me_2SO$ (2:3) as the solvents, or with hydroxide as the base and water as the solvent. Second, only a catalytic amount of TMAH is necessary for the reaction of **1** with *N,N'*-dialkylureas. Third, essentially quantitative conversions of **1a**, **1b**, and 1,3-dimethylthymine to the corresponding 1- and 3-monomethyl derivatives result from the reactions of these substrates with *N*-methylurea (**4**) in the presence of an equivalent of TMAH. The requirement for 1 equiv of base in these reactions is due to the fact that the products are formed as the anions, rather than neutral molecules. Fourth, reactions analogous to eq 1 occur with acetamidine (**5**) or *N,N*-dimethylguanidine (**6**) substituted for the urea[3] (eq 2). The yield




(2)

of product, 4-hydroxy-2-methylpyrimidine (**7**), in the reaction with **5** is 39%, with a recovery of 29% of **1a**. This compares favorably with the reported yield of 33% by total synthesis.[4] The product of the reaction of **6** is 2-(dimethylamino)-4-hydroxypyrimidine. Finally, a number of modifications of

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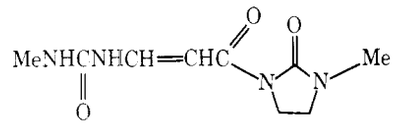
reaction 1 were tried which did not yield the expected products. These were **1a** plus urea, *N*-methylthiourea, or *S*-benzylisothiourea, 1-methyluracil plus **2a**, and 1-methylcytosine plus **4**.

The fact that the type of reaction discussed here occurs only under conditions where enolate anion formation has been observed[2,5] strongly suggests that the mechanism involves this intermediate, with the reactive center being at C-1 or C-3. On the other hand, the former possibility apparently is ruled out by the fact that no reaction product, e.g., A, was obtained



A

corresponding to attack of 4 on C-1 of the enolate (**3b**; Y = H, Z = 1-methylimidazolidone-3) prepared from 3-(β-chloroethyl)-1-methyluracil plus TMAH in $Me_2SO$.[5]

## Experimental Section

$^1H$ NMR spectra were obtained on a Varian A-60A spectrometer at room temperature using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. A Cary 14 spectrophotometer was used to obtain UV spectra. Mass spectra were obtained on a Varian M-66 mass spectrometer at an ionizing potential of 70 eV, an ionizing current of 30 μA, a resolution of ~1200, and with perfluorokerosene as a standard.

Thin-layer chromatography was performed on Analtech silica gel G thin-layer plates containing fluorescent indicator (Analtech, Inc., Newark, Del.). Preparative chromatography (dry column) was performed on silica gel Woelm (ICN, Cleveland, Ohio). The progress of such chromatography was monitored by TLC. High-pressure liquid chromatography (LC) was performed using a Waters ALC 202 liquid chromatograph with a Corasil I column (Waters Associates, Inc., Framingham, Mass.), 4 ft × 0.125 in.

Melting points are corrected.

**Reaction of 1,3-Diethyluracil (1b) with 1,3-Dimethylurea (2a).** Compounds **1b** (80 mg, 0.48 mmol) and **2a** (40 mg, 0.46 mmol) were dissolved in 2.5 mL of $Me_2SO$ and 2.5 mL of 0.1 N TMAH (0.25 mmol) in $Me_2SO$ was added. After 1 h the reaction mixture was treated with 200 μL of glacial acetic acid and it was desalted by passing the mixture through 3 g of silica gel. The silica gel was washed with 25 mL of AcOEt to elute all UV-containing materials. The solvents were evaporated in vacuo and the residue was dissolved in 10 mL of absolute EtOH. The UV spectrum indicated 79% of the original chromophore was present. LC analysis with 5% EtOH in *n*-hexane showed 51% conversion to **1a**.

Repetition of the above experiment, at the same dilution, using 1 mL of 0.1 N TMAH (0.10 mmol) gave 84% of the original chromophore. LC analysis showed this mixture contained 48% of **1a**.

**Reactions of 1,3-Dimethyluracil (1a), 1,3-Diethyluracil (1b), and 1,3-Dimethylthymine with *N*-Methylurea (4).** Compounds **1b** (80 mg, 0.48 mmol) and **4** (40 mg, 0.54 mmol) were combined and treated with 5 mL of 0.1 N TMAH (0.50 mmol) in $Me_2SO$. After 1 h the reaction mixture was treated with 0.2 mL of glacial acetic acid and it was desalted as described above. The residue, after evaporation of $Me_2SO$ and AcOEt, was dissolved in absolute EtOH. UV indicated 80% retention of the chromophore and LC showed that the material was a mixture of 22% **1b**, 35% 3-methyluracil, and 42% 1-methyluracil. The ethanol was evaporated and the residue was dissolved in 1 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer contained the starting material. Neutralization of the basic aqueous layer, followed by evaporation, afforded a mixture of the two monomethyluracils. This was confirmed by $^1H$ NMR.

When **1a** was subjected to the same reaction conditions, 96% conversion to 1- and 3-methyluracils was observed. With 0.3 equiv of base, only 15% of a mixture of the two isomers was obtained in 1 h.

When 1,3-dimethylthymine was subjected to the same reaction conditions as **1b** for 1 h, complete conversion to a mixture of 1- and 3-methylthymine was observed. The two isomers were obtained in a ratio of 38:62, but which one was more abundant is not known.

**Reaction of 1,3-Dimethyluracil (1a) with Acetamidine (5). 4-Hydroxy-2-methylpyrimidine (7).** Compounds **1a** (210 mg, 1.50 mmol) and **5** hydrochloride (160 mg, 1.69 mmol) were dissolved in 10 mL of $Me_2SO$. TMAH was added in two portions (280 mg, 1.54 mmol each) and the reaction mixture was shaken vigorously. After 2 h, TLC indicated some starting material was still present. An additional 90 mg (0.77 mmol) of TMAH was added and the reaction mixture was stirred at room temperature for 24 h. It then was desalted on 10 g of silica gel and the solvents were evaporated in vacuo. The residue was dissolved in 10 mL of $CHCl_3$ and extracted with 2 × 10 mL of $H_2O$. The $CHCl_3$ layer contained 60 mg (29%) of **1a**. UV analysis of the aqueous extracts indicated that 36% of **7** was present. The material was chromatographed on an anion-exchange column [Rexyn AG 1($OH^-$)]. After washing the column with water, the UV-absorbing material was released from the column by acidification with HCl. Evaporation afforded a solid which had mp 260–265 °C and gave a positive test with silver nitrate. This solid was dissolved in absolute EtOH and $NaHCO_3$ was added until $CO_2$ evolution ceased. The solid was removed by filtration and the filtrate was evaporated in vacuo. The residue was recrystallized from MeOH to give pure **7**: mp 211–213 °C (lit.[4] mp 212.5–213 °C); $^1H$ NMR ($D_2O$) δ 2.77 (s, 3, $CH_3$), 6.72 (d, 1, $J$ = 8 Hz, H-5), and 7.55 (d, 1, $J$ = 8 Hz, H-6); $M^+$· 110 (98).

**Reaction of 1,3-Dimethyluracil (1a) with *N,N*-Dimethylguanidine (6). 2-(Dimethylamino)-4-hydroxypyrimidine (8).** Compounds **1a** (210 mg, 1.50 mmol) and **6** hydrochloride (250 mg, 2.00 mmol) were dissolved in 10 mL of $Me_2SO$ and 660 mg (3.65 mmol) of TMAH was added. The reaction mixture was stirred at room temperature. After 7 days the reaction mixture was desalted on 10 g of silica gel. The residue obtained after evaporation of solvents was dissolved in 10 mL of $CHCl_3$ and extracted with 3 × 10 mL of $H_2O$. The $CHCl_3$ layer afforded 60 mg (26%) of **1a**. The aqueous extracts were concentrated in vacuo to 10 mL and poured on to an anion-exchange column [Rexyn AG 1($OH^-$)]. The initial washes with water afforded ~13% more **1a**. Acidification with HCl caused the release of the remaining UV-absorbing material, $\lambda_{max}$ (0.1 N HCl) 262 nm and $\lambda_{max}$ (0.1 N NaOH) 280 nm. Evaporation afforded 110 mg (41%) of **8** as the hydrochloride, which was dissolved in absolute EtOH and treated with aqueous $NaHCO_3$ until $CO_2$ evolution ceased. The solution was concentrated in vacuo and filtered to remove NaCl. The filtrate was evaporated in vacuo and the residue was crystallized from water to give pure **8**: mp 175–177 °C (lit.[6] mp 175.5–176.5 °C); $^1H$ NMR ($CDCl_3$) δ 3.19 (s, 6, $CH_3$), 5.69 (d, 1, $J$ = 6.5 Hz, H-5) and 7.72 (d, 1, $J$ = 6.5 Hz, H-6); $M^+$· 139 (100).

**Registry No.**—**1a**, 874-14-6; **1b**, 22390-04-1; **2a**, 96-31-1; **4**, 598-50-5; **5** HCl, 124-42-5; **6** HCl, 22583-29-5; **7**, 19875-04-8; **8**, 1635-28-5; **8** HCl, 66575-45-9; 1,3-dimethylthymine, 4401-71-2; 3-methyluracil, 608-34-4; 1-methyluracil, 614-77-0.

## References and Notes

(1) The authors are indebted to two anonymous donors for their generosity in providing partial support for this investigation. Additional support was provided by a Biomedical Sciences Support Grant from the General Research Support Branch, Division of Research Resources, Bureau of Health Professions Education and Manpower Training, National Institutes of Health.
(2) E. G. Lovett and D. Lipkin, *J. Org. Chem.*, **42**, 2574 (1977). See also K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **43**, 1193 (1978).
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# A New Convenient Synthesis of Bridgehead Substituted Norbornenes[1]

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Bridgehead substituted norbornenes, while being simple compounds in appearance, are synthesized only with difficulty. To date the syntheses of these compounds have involved a Wagner–Meerwein type rearrangement step. For example, the bridgehead methoxycarbonylnorbornene (**4**; Scheme I) has been prepared from *exo*-2-bromo-*endo*-2-methoxycarbonylnorbornane.[2] The bridgehead chloronorbornene has

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