The Role of Michael Adducts in Pyrimidine Chemistry. Reactions of 3-(β-Methanesulfonyloxyethyl)-1-methyluracil with Bases[1,2]

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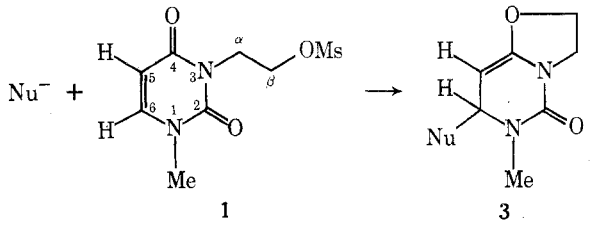
The reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with hydroxide in DMSO and DMSO-d_6 were investigated in an attempt to trap a Michael adduct. In spite of the demonstrated ease of formation, under a variety of conditions, of a product containing an oxazoline ring, the principal product was a malonsemialdehyde-substituted imidazolidone. This resulted from the addition of hydroxide at C-6 of the mesyl ester and subsequent cleavage between N-1 and C-6 of the pyrimidine ring. The course of the reaction was elucidated by the characterization of derivatives and then degradation of one of these. The results of the reactions between hydroxide and ester in deuterated media support the carbanion mechanism for exchange at C-6 of the mesylate and elucidate the nature of a competing pathway involving Michael addition. Finally, the reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with alcohols and amines were studied to complete the comparison with the behavior of the isomeric salt, N^3,O^4-ethylene-1-methyluracilium mesylate.

Michael additions have been suggested as intermediate steps in a variety of phenomena involving pyrimidines. These are the formation of $O^6,5'$-cyclonucleosides from 5-halopyrimidine nucleosides;[3] deuterium exchange at C-5 and C-6 in basic media;[4] the mode of action of thymidylate synthetase;[5] bisulfite addition;[6] nucleophilic addition to 5-nitropyrimidines;[7] alkaline degradation of methylated pyrimidine nucleosides;[8] and 5'-thiol additions.[9] To determine the role, if any, of Michael-type additions in these phenomena, the reactions of 3-(β-mesyloxyethyl)-1-methyluracil (1), other than those in which the initial step is conversion of 1 to N^3,O^4-ethylene-1-methyluracilium mesylate (2),[2] were explored. This ester, 1, has the potential of forming an adduct which then is stabilized by intramolecular conversion to a 6-substituted N^3,O^4-ethylene-1-methyl-O^4,6-dihydrouracil (3), i.e. (Nu = nucleophile)



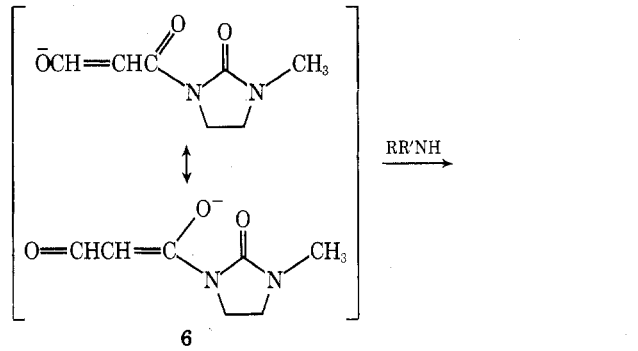
1 3

The emphasis in this paper is on reactions of 1 with hydroxide ion in DMSO. With this same base and solvent, 1,3-dimethyluracil has been reported to undergo rapid H-6 exchange,[4f] while 5-halopyrimidine nucleosides have been converted to $O^6,5'$-cyclonucleosides.[3] Alternative mechanisms, other than ones involving the formation of Michael adducts, have been suggested for these two latter reactions.[4e,f,3a]

Results and Discussion

A number of complexities were to be avoided in investigating the reactions of 1 with hydroxide in DMSO. This mesyl ester, as has been previously noted,[2] reacts slowly with DMSO to form *O*-[β-(1-methyluracil-3)ethyl]-*S*-dimethylsulfoxonium mesylate (4). This salt is converted rapidly by the addition of base to 3-(β-hydroxyethyl)-1-methyluracil (5), which would also be obtained by direct displacement of the mesyl group of 1 by hydroxide ion or via the cyclic salt 2 plus hydroxide. These reactions are irrelevant with respect to the reactions to be discussed here. Furthermore, the degradation of 5 in basic media also is in the same category.[2] In order to minimize the effect of these competing reactions, the solutions of base were usually added to the solid ester 1. This makes reactions where the base is not intended to be in excess actually have an excess initially and introduces some problems with reproducibility. The results are least complicated with a large excess of base or a catalytic amount of base.

When a twofold excess of tetramethylammonium hydroxide pentahydrate (TMAH) in DMSO was added to a sample of the solid ester 1, not 5, but a new product (6),[10] was formed rapidly which could be fully characterized only as enamine derivatives (7). Support for the structure of 7 is

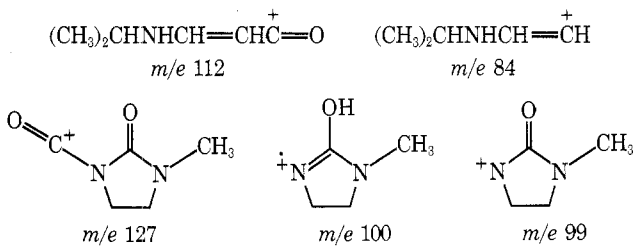


6

7a, R = Me_2CH; R' = H
b, R = R' = Et

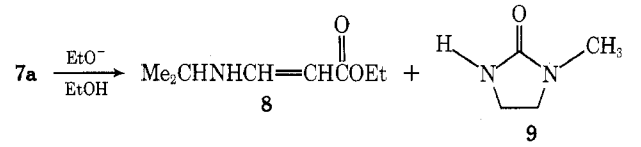
provided by the spectroscopic data. The relatively long wavelength uv absorption of 7 in neutral or alkaline solution is similar to that of enamine ketones. The shift of the maximum of 7 to a much shorter wavelength in acid solution must be due to N-, rather than O-, protonation.[11] The infrared spectra of 7 have two absorption bands (~1648 and ~1705 cm^{-1}) corresponding to those characteristic of 1-acetyl-3-methylimidazolidone (1670 and 1730 cm^{-1}).[12] In addition, however, the two compounds have another absorption (~1555 cm^{-1}) characteristic of enamino ketones (1535–1574 cm^{-1}).[13] The ^1H NMR spectrum provides further support for the assigned structure. In 7 the protons of the methylene group adjacent to the NMe group absorb at ca. δ 3.3 (DMSO-d_6) and those adjacent to the nitrogen atom flanked by two carbonyl groups absorb at ca. δ 3.7. These assignments are based on the fact that the methylene protons in 1-methylimidazolidone absorb at δ 3.45, while those in 1,3-diacetylimidazolidone are at δ 3.83.[12] The ^1H NMR data also demonstrate that in **7b** the trans isomer

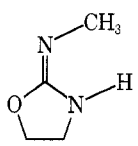
is the stable one in both chloroform and DMSO solutions. The compound **7a**, by contrast, is present as the trans isomer in DMSO, but in chloroform it exists mainly (>95%) as the cis isomer. This presumably is due to the formation of an intramolecular hydrogen bond between the NH group and the exocyclic carbonyl.[14] The mass spectra gave added confirmation to the structure written for **7**. Abundant ions corresponding to the following proposed structures are observed for **7a**. The diethylamino derivative, **7b**, gave an analogous series of abundant ions.



abundant ions.

Chemical evidence for the structures assigned to **7** includes a positive Ehrlich's test[15] (orange color) with **7a**, but not with **7b**. This is indicative of an active methylene group in the tautomer of **7a**. Degradation of **7a** with ethoxide in ethanol afforded an enamino ester (**8**) and 1-methylimidazolidone (**9**). The latter was identical with a sample prepared by an unequivocal route and ruled out the possibility that **9** is the isomeric 2-(methylamino)-2-oxazolidine.[16]

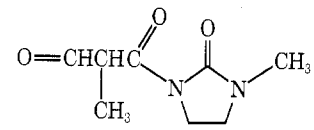




Compound **8** was isolated as a colorless oil which darkened on standing at room temperature for a few days.[17] It too gave a positive Ehrlich's test, as expected. Spectral data for **8** are in good agreement with those of Huisgen.[14]

Enolate anion **6**, a malonsemialdehyde derivative, must be the precursor of enamines **7a** and **7b**. Both chemical and physical evidence support this assumption. On electrophoresis at pH 9.2 **6** migrated toward the anode, indicating a negatively charged species. The uv absorption of **6** in alkaline solution (λ_{max} 290 nm) and the fact that this absorption disappears on acidification, as well as a positive Ehrlich's test (orange), is indicative of an active methylene group.[15] By comparison, thio esters of malonsemialdehyde have λ_{max} ca. 299 nm.[18] The sulfur atom probably has a bathochromic effect on this absorption,[19] but then the substituted urea residue in **6** also may have a bathochromic effect.[20] The difference in λ_{max} for **7** and **8** also may be due, in part, to the same effect. The ^{1}H NMR data provide additional support for the structure of **6**. The marked downfield shift of the absorption of H-6 (the γ carbon atom of the malonsemialdehyde side chain[10]), relative to the corresponding proton in **7** or **8**, probably is due to the fact that **6** is to be represented by the two principal resonance structures depicted.

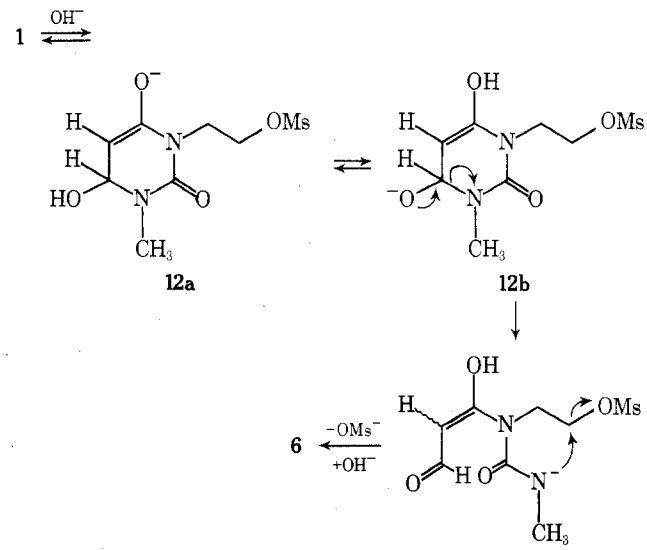
Extraction of an acidified solution of **6** yielded a compound (**10**) in which H-6 was even further downfield (in the typical aldehyde region). In addition, other changes in the ^{1}H NMR spectrum are consistent with the conversion of the enolate **6** to the corresponding aldehyde **10**. Furthermore, upon methylation of **6** with methyl iodide, presumably the homolog of **10** (**11**) was obtained. In **11** the H-5



11

resonance is a quartet (J_{5,CH_3} = 7.5 Hz), which is further split by coupling to H-6 ($J_{5,6}$ = 1 Hz). The H-6 resonance of **11**, which is at the same δ as in **10**, is now a doublet rather than a triplet with $J_{5,6}$ < 1 Hz. Except for the *C*-methyl group, the other absorptions are essentially the same as in **10**. The mass spectral fragmentation pattern of **11** is related to that of **7**. This lends further support to the structures proposed for **6** and **10**.

A reasonable course for the formation of **6** from **1** is as follows.



Two essential features of this scheme are that initial attack by hydroxide ion takes place at C-6 and that opening of the pyrimidine ring involves *the breaking of the bond between N-1 and C-6*. In contrast to expectations, the final product is a substituted imidazolidone, a cyclic urea derivative, rather than the anticipated compound, **3**. Furthermore, in light of the demonstrated ease of formation of an oxazoline from **1**,[2] the formation of a cyclic urea, **6**, also was surprising. A possible explanation for this observation is that ionization of the added hydroxyl in **12a**, accompanied by protonation of the C-4 oxygen to give **12b**, makes O-4 less nucleophilic.

Many examples are known of the degradation of substituted uracils by means of aqueous hydroxide[21] to acyclic ureas[4b,8,22] or substituted 2-oxo-4-imidazolines.[3b] By contrast with the reaction leading to the formation of **6**, these reactions take place by the Michael addition of water or an alcohol to the 5,6 double bond of the pyrimidine followed by cleavage of the bond *between N-3 and C-4* in the resulting 5,6-dihydrouracil derivative. This is a well-documented course for the alkaline degradation of substituted 5,6-dihydrouracils.[23]

As mentioned above, cleavage of the pyrimidine ring between N-1 and C-6 leads to the formation of an enolate. The formation of aldehyde intermediates in the alkaline degradation of pyrimidine derivatives has been suggested previously by two groups. Kondo et al. have found that N^3-methyl-2′,3′-*O*-isopropylideneuridine was converted by means of aqueous alkali to 3-methylurea riboside.[8] They have suggested that here too a 5,6-dihydrouracil was

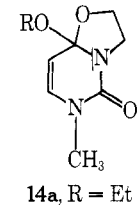
formed as an intermediate and that subsequently this was degraded to the final product through the breaking of the bond between N-1 and C-6 before the bond between N-3 and C-4 was broken. The data provided by these authors may not be in agreement with this suggestion. They observed a transient ^{1}H NMR absorption at 8.29 ppm which has been assigned to an aldehydic proton. This is in disagreement with the value given for the C-6 proton of **6** (δ 9.10), but in good agreement with the value (δ 8.44) suggested by Cushley et al.[4b] for the ^{1}H NMR signal due to the vinylic proton of an α,β-unsaturated 5-deuterated ureido acid, $D_2NC(O)N(R)CH{=}CDCO_2H$. Lozeron et al.[24] found that 5-fluoro-6-hydroxy-5,6-dihydrouracil was unstable in alkali and decomposed to form urea and, probably, α-fluoro-α-formylacetic acid. The data provided by both groups are insufficient to indicate which of the two bonds, that between N-1 and C-6 or between N-3 and C-4, was cleaved first.

In order to determine whether or not an intermediate such as **12** plays a role in C-6 exchange, three experiments were performed in which a solution of TMAH in DMSO-d_6 was added to mesyl ester **1**. The reaction mixtures were too dilute to permit direct observation by ^{1}H NMR. Analyses were performed on the end products and no rates were obtained. In one experiment the ratio of base to mesyl ester was 1:4. The mixture of **1**, **2**, **4**, and **5** which remained after the base was consumed was converted by a combination of hydrolysis and methanolysis to a mixture of **5** and 3-(β-methoxyethyl)-1-methyluracil.[2] Both of these products contained ca. 10–15% deuterium at C-6, but less than 5% at C-5. The fact that the methyl ether was deuterated confirms that exchange had occurred on the mesyl ester or on **4**, and not on **5** after its formation or on **2**.[2] A 1:1 ratio was used in the second experiment. The reaction mixture contained the enolate **6** in a yield of 40% based on the uv spectrum. It also contained **5** and possibly its acetate, 3-(β-acetoxyethyl)-1-methyluracil (**13**). Substitution of deuterium at both C-5 and C-6 of **5** and **13** was found to have taken place to the extent of ca. 10–15%.[25] The third experiment was one in which a 4.6:1 ratio of base to **1** was used. It was found that **6**, the principal identifiable product, this time contained 60% deuterium at C-6 and less than 5% at C-5. By contrast with the results of these experiments in DMSO, reaction of **1** with 0.4 *N* NaOD in D_2O resulted in unlabeled **5**.

These observations are consistent with the notion that there is competition between two primary reactions, i.e., carbanion formation at C-6 of the mesyl ester **1** and addition of hydroxide at this carbon atom to form **12**. At low base ratios the predominant reaction is carbanion formation leading to deuterium exchange. The equilibrium giving rise to the hydroxyl adduct **12** is unfavorable because the hydroxide ion concentration is low. This equilibrium is favored only when sufficient base is present to ionize the added hydroxyl. The reaction leading to the formation of **5** is not pertinent here. The second experiment with the higher base ratio indicates that the competition between carbanion formation and formation of **12** favors the latter. That adduct formation has become significant was substantiated by the fact that exchange at C-5, as well as C-6, is observed and that **6** is a reaction product. Exchange at C-5 takes place through the addition of hydroxide ion at C-6 and a proton at C-5.[4] Finally, in the third experiment with a large excess of base, the C-6 adduct **12** is stabilized by formation of the anion and it then can undergo further reaction to form **6**. There is also sufficient base to allow substantial carbanion formation at C-6. The latter reaction is obviously faster than the former. As a consequence, **6** is formed with a large amount of deuterium at C-6. Even though addition at C-6 has become an important reaction, there is no appreciable amount of substitution of deuterium at C-5 because the highly basic medium is deficient in available deuterium ions.

A more detailed examination of the products from the 1:1 experiment helped to identify the fate of **6** in the absence of excess base. After concentrating the reaction mixture, no absorptions due to the vinyl protons in **6** could be found in the complex ^{1}H NMR spectrum of the crude reaction mixture. This might have been due to the fact that little **6** was present at this point. Compound **6** decomposes quite rapidly except in very basic media. On the other hand, these protons may not have been detected because they already had been replaced by deuterium. The C-5 protons could have been exchanged for deuterium during the concentration of the reaction mixture, which was no longer strongly basic. Work-up of the residue afforded a 14% yield of **13**. The acetyl group of this compound contained 72% deuterium while C-5 and C-6 contained approximately equal amounts (ca. 15%). That the reagent for the acetylation of **5** present in the concentrate was not the acetic acid-h_4 used to neutralize the crude product was confirmed by isolating the same product, **13**, from a reaction mixture acidified with trifluoroacetic acid. The acetylating agent also could not have been 1-acetyl-3-methylimidazolidone. This was demonstrated by carrying out a reaction of **5** with this reagent under the same conditions which were used for the reaction of **1** with TMAH. The yield of **13** was negligible (1%). In all likelihood, **13** with the deuterated acetyl group was formed by reaction of **5** with **6**, or its keto tautomer, to give the formylacetate ester of **5**. This could then decompose in the deuterated medium to give **13** and formate.

Under neutral or basic conditions, addition of an alcohol at C-6 of **1** might be expected to lead to a stable adduct. However, alcohols solvolyzed **1** to a 3-(β-alkoxyethyl)-1-methyluracil.[2] The alcoholysis proceeded via **2** as an intermediate (uv), rather than by direct solvolysis of the ester. The mesyl ester **1** reacted slowly with alcoholic alkoxide solutions to form a compound (**14**) which resulted from addition at C-4 rather than C-6, probably again by way of **2**. A



14a, R = Et
b, R = Me

reasonable explanation for the formation of a C-4 adduct from alkoxide involves initial formation of the sought-for C-6 adduct, which then reacts at C-4 and expels the C-6 alkoxide. An analogous rationalization has been discussed previously.[2]

In a further experiment with alkoxides, the mesyl ester **1** was treated with sodium methoxide in methanol-*O*-*d*. Although an adduct, **14b**, was formed, there was no deuterium incorporation at C-5 or C-6. This demonstrates that addition of methoxide at C-4 of **1** is a more rapid reaction than exchange. On the other hand, as a basis of comparison, 1,3-dimethyluracil does undergo exchange with the same base and in the same solvent. It was found that there was incorporation of 73% deuterium at C-5 and 16% at C-6 in this uracil derivative.

In order to make more complete a comparison of the chemistry of the mesyl ester **1** and the uracilium cation **2**,

the reactions of 1 with amines were investigated. Isopropylamine reacted with 1 to give two products: 86% of 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine and 14% of 3-(β-isopropylaminoethyl)-1-methyluracil. The latter probably arises by direct substitution of the mesyl group and the former via 2. By contrast, 2 plus the amine yielded only the first of these products.[2] Pyridine slowly converted 1 to the quaternary salt, [β-(1-methyluracil-3)ethyl]pyridinium mesylate. The only example of the ability of 1 to form an adduct at C-6, other than its reaction with hydroxide to yield 6, was the reaction with diethylamine. Two products were obtained: *trans*-2-(β-diethylaminoethenyl)-Δ^2-oxazoline (74%) and 3-(β-diethylaminoethyl)-1-methyluracil (26%). The latter probably arose by direct displacement of the mesyl group of 1 and the former via 2. Again, by contrast, an additional product was obtained in the corresponding reaction of 2.[2]

In conclusion, we have observed only two examples of products arising from Michael additions to 1: the reactions of hydroxide and diethylamine. The former contrasts with the reaction of 2 with hydroxide to give 5. In both examples, the products observed resulted from a cleavage of the bond between N-1 and C-6. While the diethylamine reaction gave rise to an oxazoline as the principal product, the reaction of 1 with hydroxide unexpectedly resulted in the formation of a cyclic urea derivative. Furthermore, our results confirm the carbanion mechanism for C-6 exchange in 1 and demonstrate a highly competitive pathway involving the formation of Michael adducts by the reaction of hydroxide ion with 1 at C-6. These latter intermediates are relevant to an addition–elimination mechanism for cyclonucleoside formation.[3a]

Further studies of the behavior of substituted pyrimidines in basic media are in progress in order to determine the generality of the type of reaction which was observed with 1, i.e., a step in which the first bond-breaking reaction in the pyrimidine ring is cleavage of the bond between N-1 and C-6.

Experimental Section

^{1}H NMR spectra were obtained on a Varian A-60 spectrometer at room temperature using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. A Cary 14, a Beckman DU, and a Perkin-Elmer 457 grating infrared spectrophotometer were used to obtain uv and ir 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 ca. 2200, and with perfluorokerosene as a standard.

VPC was done on a 24 × 0.25 in. o.d. aluminum column packed with 1% SE-30 (Applied Science Laboratories, State College, Pa.) on ANAKROM AS, 40–50 mesh (Analabs, North Haven, Conn.). Column temperatures ranged from 110 to 155° with helium flow rates of 85–100 ml/min. Thin layer chromatography was performed on Analtech silica gel G thin layer plates containing fluorescent indicator (Analtech, Inc., Newark, Del.) and Chrom AR 500 sheets (Mallinckrodt, St. Louis, Mo.) Preparative chromatography (dry column) was performed on silica gel Woelm (Waters Associates, Inc., Framingham, Mass.).

Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of 1 with Excess Tetramethylammonium Hydroxide in DMSO. Enolate Anion of N^1-(Formylacetyl)-N^3-methylimidazolidone (6). TMAH (2.0 g, 11 mmol) was added to 100 ml of DMSO, warmed to 80°, and filtered. This solution was approximately 0.1 *N*. Mesyl ester 1 (0.84 g, 3.39 mmol) was added to this solution at room temperature. The mixture turned bright red instantaneously. Paper electrophoresis of an aliquot in 0.05 *M* sodium borate (pH 9.2) demonstrated the presence of a uv-absorbing species (orange Ehrlich's test) which migrated 2.7 cm toward the anode. Barbituric acid migrated 3.5 cm while 5 did not migrate at all under the same conditions. Aliquots of the DMSO solution had λ_{max} 293 nm (ε ~19,000),[26] λ_{min} 246 nm (ε 3700) in 95% EtOH; λ_{max} 290 nm (ε ~20,000), λ_{min} 244 nm (ε 6300) in 0.1 *N* NaOH; no λ_{max} in 0.1 *N* HCl. The reaction mixture was concentrated in vacuo at 40° to a semisolid: ^{1}H NMR (DMSO-d_6) δ 9.10 (d, 1, J = 10 Hz, H-6), 5.50 (d, 1, J = 10 Hz, H-5), 4.00 and 3.43 (m, 4, CH_2CH_2), and 2.55 ppm (s, 3, NCH_3);[27] on acidification of this solution H-6 shifted to δ 9.67 (t, 1, J = 1 Hz) and H-5 to 3.96 ppm (d, 2, J = 1 Hz).

Attempts to isolate the enolate anion by crystallization, or charcoal or ion exchange chromatography, were unsuccessful. It was stable, however, in alkaline solution for days. It proved possible, however, to isolate N^1-(formylacetyl)-N^3-methylimidazolidone (10), the aldehyde corresponding to the enolate anion 6. Compound 1 (220 mg, 0.89 mmol) was added to 25 ml of 0.1 *N* TMAH in DMSO (2.5 mmol). The λ_{max} of an aliquot of this solution was 290 nm in 0.1 *N* NaOH and the optical density (based on ε 20,000) corresponded to 61% conversion to enolate anion 6. The solution was evaporated in vacuo and water was added to the residue. The mixture was neutralized with acetic acid and extracted with 1,2-dichloroethane. An assay of the organic extracts (uv) showed that 72% of the optical density was still present. A residue remained on evaporation of the solvent in vacuo: ^{1}H NMR ($CDCl_3$) δ 9.75 (t, 1, $J_{5,6}$ = 1 Hz, CH=O), 4.02 (d, 2, $J_{5,6}$ = 1 Hz, CH_2CH=O), 3.87 and 3.48 (m, 4, CH_2CH_2) and 2.87 ppm (s, 3, NCH_3).

Once again, 6 was prepared from 1 (220 mg, 0.89 mmol) and 25 ml of 0.1 *N* TMAH (2.5 mmol) in DMSO. The DMSO was removed in vacuo and 10 ml of MeOH was added to the residue. Methyl iodide (2 ml, 32 mmol) was added and the reaction mixture was allowed to stand at room temperature overnight. TLC (AcOEt) indicated four uv-absorbing components, two of which were major. The fastest moving component, which was obtained pure by VPC, is assigned structure 11: mass spectrum m/e (rel intensity) 184 (7), 170 (7), 156 (100), 127 (23), 101 (26), 100 (79), 99 (100), and 84 (44). Column chromatography on silica gel (AcOEt) afforded 65 mg (40%) of 11: ^{1}H NMR ($CDCl_3$) δ 9.72 (d, 1, $J_{5,6}$ = 1 Hz, CH=O), 4.71 (d of q, 1, $J_{5,6}$ = 1, $J_{CH_3,H}$ = 7.5 Hz, H-5), 3.90 and 3.41 (m, 4, CH_2CH_2), 2.88 (s, 3, NCH_3), and 1.35 ppm (d, 3, $J_{CH_3,H}$ = 7.5 Hz, CH_3CH).

Conversion of Enolate Anion 6 to N^1-(β-Isopropylaminoacrylyl)-N^3-methylimidazolidone (7a). The enolate anion 6, prepared as above from 3.39 mmol of 1, was dissolved in 10 ml of MeOH. Isopropylamine (1 ml, 11.7 mmol) and 0.8 ml of glacial AcOH (14.1 mmol) were added. The mixture, now neutral, was evaporated in vacuo and 20 ml of $CHCl_3$ was added to the residue. The solids were removed by filtration and washed with 2 × 10 ml of $CHCl_3$. The combined $CHCl_3$ washes were extracted with water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.47 g of crude product. TLC (AcOEt) of the aqueous extracts showed two uv-absorbing materials, the faster moving one of which gave a pink Ehrlich's test. The $CHCl_3$ layer gave a spot at the origin and halfway up the plate. The latter (7a) gave an orange Ehrlich's test. The $CHCl_3$-soluble material was chromatographed on 12 g of silica gel with $CHCl_3$ as the solvent. Fractions 5–23 (3 ml) afforded 355 mg (50%) of 7a. An analytical sample was obtained from $CHCl_3$–Et_2O: mp 109.5–112.5°; ir (Nujol) 3220 (m), 1700 (s), 1655 (s), 1545 (s), 1332 (w), 1270 (s), 1230 (s), 1170 (w), 1040 (w), 1000 (w), 805 (w), 735 (w), and 705 cm^{-1} (m); uv (95% EtOH) λ_{max} 302 nm (ε 30,200) and 229 (7700), λ_{min} 255 nm (ε 1400); uv (0.1 *N* NaOH) λ_{max} 305 nm (ε 31,500), λ_{min} 258 nm (ε 2100); uv (0.1 *N* HCl) λ_{max} 222 nm (ε 12,800), λ_{min} 208 nm (ε 8500); ^{1}H NMR ($CDCl_3$) δ 7.00 (m, 1, $J_{NH,H-6}$ = 13 Hz, NH), 6.78 (d of d, 1, $J_{NH,H-6}$ = 13, $J_{5,6}$ = 8 Hz, H-6), 6.03 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 3.85 and 3.33 [m, 5, CH_2CH_2 and $(CH_3)_2CH$], 2.82 (s, 3, NCH_3), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; ^{1}H NMR (DMSO-d_6) 7.46 (d of d, 1, $J_{NH,H-6}$ = 9 Hz, $J_{5,6}$ = 13 Hz, H-6), 7.02 (m, 1, $J_{NH,H-6}$ = 9 Hz, NH), 6.03 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.68 and 3.30 [m, 5, CH_2CH_2 and $(CH_3)_2CH$], and 1.10 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; mass spectrum m/e (rel intensity) 211 (100), 196 (8), 142 (7), 127 (19), 113 (23), 112 (96), 110 (13), 100 (29), 99 (21), 98 (21), 96 (68), 84 (54), and 70 (70).

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.84; H, 8.15; N, 19.87.

Conversion of Enolate Anion 6 to N^1-(β-Diethylaminoacrylyl)-N^3-methylimidazolidone (7b). The enolate anion 6, prepared as described above starting with 0.875 g of 1, was dissolved in 13 ml of MeOH. To this solution was added 2.3 ml (22.4 mmol) of diethylamine and 1 ml (17.6 mmol) of glacial AcOH at 0°. It then was stored at 10° for 2 days. The residue obtained after evaporation was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ layer after drying ($MgSO_4$) and evaporation afforded 0.49 g of ma-

terial (62%) which crystallized, but by TLC (AcOEt) contained a fast-moving major component and two minor ones. Chromatography on silica gel G with $CHCl_3$ (fractions 5–24, 3 ml) afforded 380 mg (48%) of **7b**. An analytical sample was obtained from C_6H_6–petroleum ether: mp 134–135.5°; ir (Nujol) 1710 (s), 1640 (s), 1565 (s), 1380–1350 (s), 1320 (m), 1220 (s), 1180 (sh), 1135 (m), 1085 (m), 1047 (m), 1007 (w), 800 (s), 758 (w), and 730 cm^{-1} (w); uv (95% EtOH) λ_{max} 308 nm (ϵ 34,100) and 230 (8100), λ_{min} 260 nm (ϵ 800); uv (0.1 *N* NaOH) λ_{max} 315 nm (ϵ 37,000), λ_{min} 262 nm (ϵ 600); uv (0.1 *N* HCl) λ_{max} 222 nm (ϵ 12,800), λ_{min} 209 nm (ϵ 8000); ^1H NMR ($CDCl_3$) δ 7.67 (d, 1, $J_{5,6}$ = 13 Hz, H-6), 6.30 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.88 and 3.33 (m, 4, CH_2CH_2), 3.27 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.85 (s, 3, NCH_3), and 1.17 ppm (t, 6, J_{Et} = 7 Hz, CH_3CH_2); ^1H NMR (DMSO-d_6) δ 7.49 (d, 1, $J_{5,6}$ = 13 Hz, H-6), 6.17 (d, 1, $J_{5,6}$ = 13 Hz, H-5), 3.70 and 3.32 (m, 4, CH_2CH_2), 3.23 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.73 (s, 3, NCH_3), and 1.11 ppm (t, 6, J_{Et} = 7 Hz, CH_3CH_2); mass spectrum *m/e* (rel intensity) 225 (84), 210 (5), 196 (7), 142 (5), 127 (41), 126 (100), 125 (21), 124 (8), 113 (12), 110 (11), 108 (10), 101 (13), 100 (19), 99 (22), 98 (60), 97 (8), 96 (26), 84 (10), and 82 (16).

Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.80; H, 8.53; N, 18.52.

Degradation of 7a with Ethoxide in Ethanol to Ethyl β-Isopropylaminoacrylate (8) and *N*-Methylimidazolidone (9). Compound **7a** (130 mg, 0.618 mmol) was dissolved in 10 ml of 0.275 *N* EtONa in EtOH (2.75 mmol) and refluxed for 2 hr. TLC (AcOEt) indicated complete conversion to two new products, one with uv absorption and giving a pink Ehrlich's test (faster moving), the other with no uv absorption and giving a yellow Ehrlich's test. The reaction mixture was evaporated to dryness and the residue, which was dissolved in Et_2O, was extracted with water. Only the uv-absorbing product remained in the Et_2O. Evaporation after drying ($MgSO_4$) afforded 55 mg of a sweet-smelling, colorless oil, **8**: ir ($CHCl_3$) 3560 (m), 2980 (s), 1660 (s), 1600 (s), 1390 (w), and 1050 cm^{-1} (m); for a sample purified by vpc, uv (100% EtOH λ_{max} 281 nm (ϵ 19,400); uv (0.1 *N* NaOH) λ_{max} 278 nm (ϵ 24,200), λ_{min} 238 nm (ϵ 2000); no λ_{max} in 0.1 *N* HCl; ^1H NMR ($CDCl_3$) of a 1:1 mixture of cis and trans isomers δ 7.65 (m, 1, NH), 7.33 (d of d, 0.5, $J_{5,6}$ = 13.5, $J_{NH,H-6}$ = 9 Hz, H-6, trans), 6.89 (d of d, 0.5, $J_{5,6}$ = 8, $J_{NH,H-6}$ = 13 Hz, H-6, cis), 4.52 (d, 0.5, $J_{5,6}$ = 13.5 Hz, H-5, trans), 4.33 (d, 0.5, $J_{5,6}$ = 8 Hz, H-5, cis), 4.12 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.55 [septet, 1, $J_{i\text{-}Pr}$ = 6.5 Hz, $CH(CH_3)_2$], 1.27 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; ^1H NMR (DMSO-d_6) of a 84% cis:16% trans mixture δ 7.65 (m, 1, NH), 6.67 (d of d, 1, $J_{5,6}$ = 8, $J_{NH,H-6}$ = 13 Hz, H-6, *cis*; $J_{5,6}$ = 13.5, $J_{NH,H-6}$ = 9 Hz, H-6, trans), 4.46 (d, 0.84, $J_{5,6}$ = 8 Hz, H-5, cis), 4.71 (d, 0.16, $J_{5,6}$ = 13.5 Hz, H-5, trans), 4.12 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.55 [septet, 1, $J_{i\text{-}Pr}$ = 6.5 Hz, $CH(CH_3)_2$], 1.25 (t, 3, J_{Et} = 7 Hz, CH_3CH_2), and 1.22 ppm [d, 6, $J_{i\text{-}Pr}$ = 6.5 Hz, $(CH_3)_2CH$]; mass spectrum *m/e* (rel intensity) 157 (41), 142 (31), 128 (31), 112 (34), 110 (16), 96 (100), and 70 (56). On standing in air at room temperature for several days, **8** darkened.[17]

The uv-transparent product, **9**, was obtained by evaporation of the aqueous extracts. Crystallization from toluene afforded a solid: mp 112–114°; mmp with an authentic sample of *N*-methylimidazolidone, 111.5–114°;[28] ir (Nujol) 3220 (s), 1660 (s), 1505 (m), 1410 (m), 1377 (s), 1285 (m), 1260 (m), 1090 cm^{-1} (m); ^1H NMR (DMSO-d_6) δ 6.20 (broad, 1, NH), 3.24 (m, 4, CH_2CH_2), and 2.60 ppm (s, 3, NCH_3).

Reaction of 1 with a Catalytic Amount of Tetramethylammonium Hydroxide in DMSO-d_6. A solution of 1.4 ml (0.16 mmol) of 0.11 *N* TMAH in DMSO-d_6 was added to 135 mg (0.542 mmol) of **1** dissolved in 600 μl of DMSO-d_6. After 2 hr, water was added to the reaction mixture, which was now neutral. The reaction mixture was evaporated to dryness in vacuo and then 10 ml of MeOH was added to the residue. After 3 days, this mixture was evaporated to dryness and the resulting residue was chromatographed on 8 g of silica gel (AcOEt). Two components were isolated: 20 mg (20%) of 3-(β-methoxyethyl)-1-methyluracil (fractions 7–38, 3 ml) and 67 mg (73%) of **5** (fractions 49–56, 3 ml). Both compounds contained approximately 10–15% deuterium at C-6 and less than 5% at C-5 (^1H NMR).

Reaction of 1 with 1 Equiv of TMAH in DMSO-d_6. A solution of TMAH (210 mg, 1.16 mmol) in 10 g of DMSO-d_6 was added to **1** (280 mg, 1.13 mmol) and the mixture was shaken vigorously for several minutes until all solids dissolved. The uv spectrum of an aliquot in 0.1 *N* NaOH had λ_{max} 280 nm. Based on the absorbance at 290 nm, the yield of enolate **6** was ca. 40%. The reaction mixture was concentrated in vacuo and the ^1H NMR spectrum of the residue showed only vinyl hydrogens like those of **5** and **13**, i.e., no enolate anion vinyl hydrogens. The H-5 and H-6 hydrogens had undergone ca. 10–15% exchange. The DMSO-d_6, which was used as the solvent in obtaining the ^1H NMR spectrum, was evaporated again and the residue was dissolved in 5 ml of MeOH. It was treated with 300 μl (2.91 mmol) of diethylamine and 100 μl (1.76 mmol) of glacial AcOH. TLC (AcOEt) showed a fast-moving component in addition to **5** and **7b**. The mixture was evaporated and the residue was taken up in $CHCl_3$ and extracted with water. The water layer contained most of the **5**, while the $CHCl_3$ contained the remaining two components. Chromatography on silica gel ($CHCl_3$ followed by AcOEt) afforded 15 mg of **13** (14%), which was identical by TLC with authentic material.[2] The ^1H NMR spectrum confirmed its identity. Added confirmation was obtained from a mass spectrum on a sample which was purified by VPC. Both sets of spectra showed that the acetyl group was 72% deuterated. The β-acetoxyethyl derivative **13** also was obtained in a similar reaction in nondeuterated solvent in which the reaction mixture was acidified with trifluoroacetic acid.

Reaction of 1 with Excess TMAH in DMSO-d_6. A 0.12 *N* solution of TMAH in DMSO-d_6 (8.9 ml, 1.06 mmol), prepared as described above, was added to **1** (57.6 mg, 0.23 mmol) dissolved in 0.6 ml of DMSO-d_6. The uv spectrum of an aliquot in 0.1 *N* NaOH had λ_{max} 290 nm and the absorbance corresponded to ca. 68% conversion to enolate anion **6**. The reaction mixture was evaporated in vacuo to dryness and the orange semisolid residue was redissolved in DMSO-d_6. The ^1H NMR spectrum showed 68% deuterium at C-6 and less than 5% at C-5.

Reaction of 1 with NaOD in D_2O. Compound **1** (87 mg, 0.35 mmol) was added to a solution of 200 μl of D_2O and 200 μl (0.155 mmol) of 0.775 *N* sodium deuteroxide in D_2O. The sample did not dissolve completely. A portion of the solution was transferred to a ^1H NMR tube. The spectrum obtained within 5 min was that of **5** only. No exchange of H-5 or H-6 was observed.

Attempted Preparation of 3-(β-Acetoxyethyl)-1-methyluracil (13) from 5 and 1-Acetyl-3-methylimidazolidone. 1-Acetyl-3-methylimidazolidone (70 mg, 0.5 mmol), prepared from methylimidazolidone according to Roberts,[12] and compound **5** (85 mg, 0.5 mmol) were dissolved in 1 ml of DMSO and 3 ml of 0.15 *N* TMAH solution (0.45 mmol) in DMSO was added. The solution turned yellow immediately. The reaction mixture was evaporated in vacuo and the residue was taken up in AcOEt. TLC (AcOEt) indicated a trace of **13** and a large amount of **5**. The AcOEt solution was extracted with water, dried ($MgSO_4$), and evaporated in vacuo. The residue, 12 mg, was chromatographed on Chrom AR 500 (AcOEt). The two uv-absorbing bands were cut out and eluted with methanol. One corresponded to 1% of **13** and the other to 10% of **5** (uv). The aqueous extracts contained an additional 70% of **5** (uv).

Methanolysis of 1. 3-(β-Methoxyethyl)-1-methyluracil. The mesyl ester **1** (68 mg, 0.27 mmol) was dissolved in 25 ml of dry MeOH. The uv spectrum was recorded periodically. The optical density at 267 nm decreased by 25% in 5.5 hr and a shoulder appeared at 290 nm. It reached a maximum value in 9 hr. The shoulder then steadily decreased and the optical density at 267 nm increased to a constant value. The reaction mixture was evaporated in vacuo after 8 days. $CHCl_3$ was added to the residue and the mixture was extracted with 10 ml of 1 *N* NaOH and then 10 ml of water. The $CHCl_3$ extract (dried with $MgSO_4$) afforded 48 mg (96%) of a crystalline solid on evaporation: mp 95.5–97°; mmp with 3-(β-methoxyethyl)-1-methyluracil, 96–97.5°.[2]

Ethanolysis of 1. 3-(β-Ethoxyethyl)-1-methyluracil. Compound **1** (318 mg, 1.24 mmol) was added to 10 ml of absolute EtOH. The solid dissolved as the reaction proceeded. After 6 days the solvent was evaporated in vacuo and the residue was dissolved in $CHCl_3$. TLC (AcOEt) indicated a fast-moving major new product, in addition to **5** and β-(1-methyluracil-3)ethyl ether[29] (slowest moving component). The $CHCl_3$ was washed with 2 × 10 ml of 1 *N* NaOH, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on 12 g of silica gel with AcOEt as eluent. Fractions 3–10 (3 ml) contained 174 mg (71%) of 3-(β-ethoxyethyl)-1-methyluracil. After evaporation of the AcOEt, the residue was sublimed at 60° ($2.5–5 \times 10^{-2}$ mm): mp 50–51.5°; ir ($CHCl_3$) 1711 (s), 1662 (s), 1630 (sh), 1485 (m), 1451 (s), 1438 (m), 1390 (s), 1380 (w), 1350 (s), 1325 (w), 1140 (s), 1120 (s), 1020 (w), and 955 cm^{-1} (w); uv (95% EtOH) λ_{max} 267 nm (ϵ 8200) and 207 (8200), λ_{min} 234 nm (ϵ 1800); uv (0.1 *N* NaOH) λ_{max} 267 nm (ϵ 8300), λ_{min} 236 nm (ϵ 1900); uv (0.1 *N* HCl) λ_{max} 267 nm (ϵ 8200), λ_{min} 235 nm (ϵ 1400); ^1H NMR ($CDCl_3$) δ 7.18 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.70 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.17 and 3.69 (m, 4, CH_2CH_2), 3.54 (q, 2, J_{Et} = 7 Hz, CH_3CH_2), 3.39 (s, 3, CH_3N), and 1.15 ppm (t, 3, J_{Et} = 7 Hz,

CH_2CH_3); mass spectrum *m/e* (rel intensity) 198 (6), 169 (8), 154 (30), 153 (23), 152 (28), 139 (16), 128 (17), 127 (100), 126 (42), 96 (7), 84 (35), 83 (28), 82 (49), 72 (44), and 70 (15).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.70; H, 7.11; N, 13.94.

Preparation of β-(1-Methyluracil-3)ethyl Ether. N^3,O^4-Ethylene-1-methyluracilium mesylate[2] (190 mg, 0.775 mmol) and 130 mg (0.775 mmol) of **5** were dissolved in 2 ml of MeCN and allowed to stand at room temperature for 2 weeks. TLC (1:1 AcOEt–EtOH) indicated that some salt was still present. The reaction mixture was refluxed for 4 hr. It then was evaporated in vacuo and $CHCl_3$ was added to the residue. The $CHCl_3$ solution was extracted with 1 *N* NaOH, dried ($MgSO_4$), and evaporated in vacuo. Chromatography on 8 g of silica gel (AcOEt followed by AcOEt plus EtOH) afforded 62 mg (26%) of the product. An analytical sample was obtained from 1:1 $CHCl_3$–hexane: mp 154–156°; ir ($CHCl_3$) 1712 (s), 1665 (s), 1450 (m), 1387 (w), 1383 (w), 1190 (m), 1180 (w), 1140 (w), and 1078 cm^{-1} (m); uv (95% EtOH) λ_{max} 267 nm (ε 15,100) and 206 (14,400), λ_{min} 234 nm (ε 3200); uv (0.1 *N* NaOH) 267 nm (ε 15,500), λ_{min} 240 nm (ε 5400); uv (0.1 *N* HCl) λ_{max} 267 nm (ε 15,200), λ_{min} 235 nm (ε 3200); ^1H NMR ($CDCl_3$) 7.09 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.82 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.15 and 3.71 (m, 4, CH_2CH_2), and 3.37 ppm (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) 322 (5), 169 (13), 154 (43), 153 (100), 152 (74), 151 (8), 140 (5), 127 (37), 126 (23), 96 (15), 84 (32), 82 (27), and 70 (35).

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.20; H, 5.80; N, 17.45.

Reaction of 1 with Ethoxide–Ethanol. 4-Ethoxy-N^3,O^4-ethylene-1-methyl-3,4-dihydrouracil (14a). Mesyl ester 1 (245 mg, 0.99 mmol) was added to 25.8 ml of absolute EtOH containing 0.99 mmol of sodium ethoxide. After 24 hr a solid precipitate ($MeSO_3Na$) was present. Approximately 26% of the original uv chromophore remained and a new maximum was observed at 235 nm. When an aliquot of this solution was acidified with 1 *N* HCl, the λ_{max} shifted to 290 nm, that of the cyclic salt **2**. Filtration followed by evaporation of a portion of the solution afforded a residue which could not be crystallized. Attempts to chromatograph the material on silica gel afforded **5**. The ^1H NMR spectrum was identical with that of **14a** prepared from **2**.[2]

Reaction of 1 with Sodium Methoxide in Methanol-*O*-*d*. Compound 1 (250 mg, 1.0 mmol) was added to a solution of 20 ml of MeOD and 1.2 ml of 0.83 *N* sodium methoxide (1.0 mmol) in MeOD. The ester dissolved over a period of 30 min. The λ_{max} at 267 nm slowly decreased and the absorbance increased at 235 nm. After 22 hr, the solution was evaporated in vacuo and the residue was dissolved in absolute EtOH and filtered to remove sodium methanesulfonate. Evaporation in vacuo afforded 240 mg of material whose ^1H NMR spectrum in $CDCl_3$ indicated equal amounts of two kinds of products, **14**[30] and **5**,[31] both of which contained less than 5% deuterium at C-5 and C-6.

Reaction of 1,3-Dimethyluracil with Sodium Methoxide in Methanol-*O*-*d*. 1,3-Dimethyluracil (50 mg, 0.357 mmol) and 1 ml (0.83 mmol) of the above solution of sodium methoxide in MeOD were combined and allowed to stand at room temperature for 22 hr. Neutralization with glacial AcOH and evaporation in vacuo afforded a solid residue of 1,3-dimethyluracil. The ^1H NMR spectrum showed 73% deuterium at C-5 and 16% at C-6.

Reaction of 1 with Diethylamine. *trans*-2-(β-diethylaminoethenyl)-Δ²-oxazoline and 3-(β-Diethylaminoethyl)-1-methyluracil. Compound 1 (60 mg, 0.242 mmol) was dissolved in 300 μl of MeCN and 100 μl (0.97 mmol) of diethylamine. The solution turned yellow immediately. The reaction was complete after 5 days (TLC, 10% Et_3N in AcOEt) at room temperature. The reaction mixture was evaporated in vacuo. $CHCl_3$ was added to the residue and the solution was extracted with 2 × 5 ml of 1 *N* HCl. The $CHCl_3$ layer (dried with $MgSO_4$) on evaporation afforded 12 mg (38%) of *N,N*-diethyl-*N'*-methylurea. The acid extracts were made alkaline with 1 *N* NaOH and extracted with 3 × 15 ml of $CHCl_3$. The $CHCl_3$ layer (dried with $MgSO_4$) afforded 49 mg of oil which was 74% oxazoline[2] and 26% β-diethylamino derivative[2] (^1H NMR). Chromatography on Chrom AR 500 sheets with 2.5% Et_3N–MeCN was used to separate the components in order to obtain pure samples for uv spectra. These spectra confirmed the structure assignments.[2]

Reaction of 1 with Isopropylamine. 3-(β-Hydroxyethyl)-1-methyl-N^4-isopropylcytosine and 3-(β-Isopropylaminoethyl)-1-methyluracil. Ester 1 (66 mg, 0.27 mmol) was dissolved in 300 μl of MeCN and 100 μl (1.18 mmol) of isopropylamine. The reaction was complete after 5 days at room temperature (TLC, 10% Et_3N in AcOEt). $CHCl_3$ was added to the residue obtained after evaporation of the reaction mixture in vacuo. The resulting $CHCl_3$ solution was extracted with 3 × 15 ml of 1 *N* HCl. The organic layer contained less than 5 mg of **5** (TLC). The acidic extracts were made alkaline with 1 *N* NaOH and extracted with 3 × 15 ml of $CHCl_3$. After drying ($MgSO_4$), the $CHCl_3$ washings on evaporation afforded 42 mg (77%) of two components which were separated on Chrom AR 500 sheets (2.5% Et_3N in MeCN). The faster moving component (86%) was identical in all respects with 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine prepared from **2**.[2] The slower moving component (14%) had uv max (95% EtOH, 0.1 *N* HCl, and 0.1 *N* NaOH) 268 nm; ^1H NMR ($CDCl_3$) δ 7.17 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.70 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 3.39 (s, 3, CH_3N), 2.86 [septet, 1, $J_{Me,H}$ = 6 Hz, $(CH_3)_2CH$], and 1.03 ppm [d, 6, $J_{Me,H}$ = 6 Hz, $(CH_3)_2CH$]; the remaining lines for the ethylene group and the NH were presumed to be under absorptions due to the other component.[32] These data are in agreement with the assigned structure, 3-(β-isopropylaminoethyl)-1-methyluracil, and with the data for the related compound, 3-(β-diethylaminoethyl)-1-methyluracil.

Reaction of 1 with Pyridine. [β-(1-Methyluracil-3)ethyl]pyridinium Mesylate. The mesyl ester 1 (360 mg, 1.45 mmol) was dissolved in 2 ml of pyridine and allowed to stand overnight. Electrophoresis (Millipore strip) in 0.05 *M* phosphate buffer (pH 7), with Methyl Green and **5** as markers, indicated almost total conversion to a positively charged species. The product and the dye moved 3.2 cm, while **5** did not migrate. Ether was added to the crystals which had appeared in the reaction flask. The product was collected by filtration (267 mg, 56%) and washed with ether. No attempt was made to recover the remainder from the filtrate. The product was hygroscopic. An analytical sample was obtained from absolute EtOH–Et_2O: mp 157–158°; ir (Nujol) 3020 (w), 3060 (w), 1710 (s), 1660 (s), 1495 (s), 1380 (m), 1360 (m), 1345 (m), 1320 (w), 1260 (w), 1200 (s), 1080 (m), 1065 (w), 1045 (m), 1015 (w), 990 (w), 845 (w), and 775 cm^{-1} (m); uv (95% EtOH) λ_{max} 261 nm (ε 11,400) and 207 (12,400), shoulder 265 (11,000), λ_{min} 237 nm (ε 3500); uv (0.1 *N* NaOH) λ_{max} 260 nm (ε 11,400), shoulder 266 (11,000), λ_{min} 237 nm (ε 3500); uv (0.1 *N* HCl) 261 nm (ε 11,000), shoulder 265 (10,700), λ_{min} 235 nm (ε 2500); ^1H NMR (D_2O) 8.88 and 8.58 (m, 5, aromatic protons), 7.60 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 5.77 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 4.88 and 4.62 (m, 4, CH_2CH_2), 3.35 (s, 3, NCH_3), and 2.80 ppm (s, 3, $CH_3SO_3^-$).

Anal. Calcd for $C_{13}H_{17}N_3O_5S$: C, 47.71; H, 5.24; N, 12.84; S, 9.77. Found: C, 47.53; H, 5.33; N, 12.74; S, 9.58.

Registry No.—**1**, 54931-79-2; **5**, 1127-64-6; **6** tautomer 1, 54931-80-5; **6** tautomer 2, 54931-81-6; **7a**, 54931-82-7; **7b**, 54931-83-8; *cis*-**8**, 54931-84-9; *trans*-**8**, 54931-85-0; **9**, 694-32-6; **11**, 54931-86-1; 3-(β-Methoxyethyl)-1-methyluracil, 54931-87-2; 3-(β-ethoxyethyl)-1-methyluracil, 54931-88-3; β-(1-methyluracil-3) ethyl ether, 54931-89-4; N^3,O^4-ethylene-1-methyluracilium mesylate, 54931-91-8; *trans*-2-(β-diethylaminoethenyl)-Δ²-oxazoline, 54931-92-9; 3-(β-diethylaminoethyl)-1-methyluracil, 54931-93-0; 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine, 54931-94-1; 3-(β-isopropylaminoethyl)-1-methyluracil, 54931-95-2; [β-(1-methyluracil-3)ethyl]pyridinium mesylate, 54931-97-4.

References and Notes

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(25) These measurements are subject to considerable error because of the complexity of the reaction mixture.
(26) The extinction coefficients were estimated by assuming 100% conversion to enolate anion.
(27) The sample also contains tetramethylammonium cations, mesylate anions, and DMSO-h_6. Although it integrates correctly, this resonance may not be due to the NCH_3 group. This resonance could be hidden under one of the others.
(28) *N*-Methylimidazolidone was prepared from imidazolidone by reaction with sodium hydride and methyl iodide in dimethylformamide. It was crystallized from toluene, mp 112–113.5°. A. N. Smirnov and I. F. Spasskaya found mp 114° from CCl_4 [*Zh. Obshch. Khim.*, **35**, 178 (1965)] and A. M. Fusco, G. J. Del Franco, and E. J. Aranaff report mp 116–116.5° for a vacuum-sublimed sample [*J. Org. Chem.*, **31**, 313 (1966)].
(29) These latter two were probably present in the starting material, which had been exposed to air several times prior to use.
(30) This product consists of both **14a** and **14b** (^{1}H NMR). Apparently **14a** was produced by a facile exchange which took place when absolute ethanol was added to the crude reaction mixture.
(31) In all likelihood **5** was formed by the action of adventitiotious moisture on the reaction mixture. An alternative, however, is that this came about by the action of methoxide on **14b**, a reaction reported by S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964).
(32) The ^{1}H NMR spectrum was obtained on a mixture of the two products.

Trapping of Thiaziridinimines with Heterocumulenes[1]

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N-Sulfonyliminothiaziridines (e.g., **2**), generated by thermolysis of 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (e.g., **1**) react with ketenes, isocyanates, carbodiimides, and isothiocyanates to give five-membered heterocyclic compounds (**6**, **7**, **8**, and **9**) in good yields. Structure assignment was essentially based on independent synthesis and on comparison of the ^{13}C NMR data with those of pertinent model compounds from the chemical literature.

Recently, we reported that thiaziridinimines or their ring-opened dipolar species are formed as intermediates in the synthesis of sulfonylcarbodiimides by thermal decomposition of 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (e.g., **1** → **2** → **3**).[2] Although **2** was too unstable to be isolated, it could be efficiently trapped with unsaturated systems. Thus, enamines and ynamines produced 4-aminothiazolidines (e.g., **4**) and 4-aminothiazolines (e.g., **5**), respectively. Keto-stabilized phosphorus ylides also trapped the thiaziridinimines to give thiazolines by loss of tertiary phosphine oxides.[2]

Since 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines are readily obtained in good yields from the reaction of sulfonyl isothiocyanates with alkyl azides at room temperature,[2] their decomposition in the presence of unsaturated systems provides a new entry into synthetic heterocyclic chemistry. The present phase of our work involves the use of heterocumulenes as trapping reagents for **2**.

Reaction Products. When 1-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**) was decomposed at 60–80° in the presence of ketenes, isocyanates, carbodiimides, and isothiocyanates, compounds **6**, **7**, **8**, and **9** were obtained in reasonably good yields. The results are summarized in Table I.

The NMR spectra of the crude reaction mixtures indicated that single products were formed in all cases, except for the reaction of diphenylketene with **1**, which gave **10** (9%, mp 221–223°, C=N at 1525 cm^{-1}) and **11** (16%, mp 234–238°, C=N at 1535 cm^{-1}) in addition to **6a** (major product). Compound **10** results from cycloaddition of **2** with **3** (formed as side product) and compound **11** is formally the cycloaddition product of **2** with tosyl isothiocyanate. We assume that tosyl isothiocyanate is formed in this