hedron Lett., 349 (1967); (f) M. Jones, Jr., J. Am. Chem. Soc., 89, 4236 (1967).
(6) W. von E. Doering, Zh. Vses. Khim. Ova., 7, 308 (1962); W. von E. Doering and W. R. Roth, Tetrahedron, 19, 715 (1963).
(7) Monosubstituted derivatives: (a) G. Schröder, R. Merényi, and J. F. M. Oth, Tetrahedron Lett., 773 (1964); (b) J. F. M. Oth, R. Merényi, J. Nielsen, and G. Schröder, Chem. Ber., 98, 3385 (1965); (c) J. F. M. Oth, R. Merényi, H. Röttele, and G. Schröder, Tetrahedron Lett., 3941 (1968); (d) J. F. M. Oth, E. Machens, H. Röttele, and G. Schröder, Justus Liebigs Ann. Chem., 745, 112 (1971); (e) C. Hoogzand, J. Nielsen, and J. F. M. Oth, Tetrahedron Lett., 2287 (1970).
(8) Disubstituted derivatives: (a) U. Kruerke, Angew. Chem., Int. Ed. Engl., 6, 79 (1967); Angew. Chem., 79, 55 (1967); (b) E. Vogel, W. Grimme, W. Meckel, H. J. Riebel, and J. F. M. Oth, Angew. Chem., Int. Ed. Engl., 5, 590 (1966); Angew. Chem., 78, 599 (1966); (c) H. Röttele, P. Nikoloff, J. F. M. Oth, and G. Schröder, Chem. Ber., 102, 3367 (1969).
(9) G. Schröder, J. F. M. Oth, and R. Merényi, Angew. Chem., 77, 774 (1965); Angew. Chem., Int. Ed. Engl., 4, 752 (1965); (b) G. Schröder and J. F. M. Oth, Angew. Chem., 79, 458 (1967); Angew. Chem., Int. Ed. Engl., 6, 414 (1967).
(10) In bullvalene, two different olefinic positions can in principle be juxtaposed to the reactive center.
(11) (a) L. A. Paquette and G. V. Meehan, J. Am. Chem. Soc., 92, 3039 (1970); (b) L. A. Paquette and G. H. Birnberg, ibid., 94, 164 (1972); (c) S. J. Cristol, G. C. Schloemer, D. R. James, and L. A. Paquette, J. Org. Chem., 37, 3852 (1972).
(12) Our study of the various possible semibullvalenylcarbinyl cations is nearing completion and will be reported elsewhere.
(13) H. O. House and W. F. Fischer, Jr., J. Org. Chem., 34, 3626 (1967).
(14) Schröder and Oth have independently prepared alcohol 3a. When we learned of their detailed ^{1}H NMR investigation of this bullvalene derivative (private communication), efforts of a similar type were discontinued here.
(15) H.-P. Löffler and G. Schröder, Angew. Chem., Int. Ed. Engl., 7, 736 (1968); Angew. Chem., 80, 758 (1968).
(16) See, for example, G. Schröder, U. Prange, B. Putze, J. Thio, and J. F. M. Oth, Chem. Ber., 104, 3406 (1971); L. A. Paquette and M. J. Broadhurst, J. Org. Chem., 38, 1886 (1973).
(17) R. Merényi, J. F. M. Oth, and G. Schröder, Chem. Ber., 97, 3150 (1964).
(18) (a) D. W. Adamson and J. Kenner, J. Chem. Soc., 286 (1935); (b) G. L. Closs and W. A. Böll, Angew. Chem., Int. Ed. Engl., 2, 399 (1963); Angew. Chem., 75, 640 (1963); (c) G. L. Closs, L. E. Closs, and W. A. Böll, J. Am. Chem. Soc., 85, 3796 (1963); (d) R. K. Bertlett and T. S. Stevens, J. Chem. Soc. C, 1964 (1967); (e) C. D. Hurd and S. C. Lui, J. Am. Chem. Soc., 57, 2656 (1935); (f) D. Y. Curtin and S. M. Gerber, ibid., 74, 4052 (1952).
(19) M. R. Willicott, J. F. M. Oth, J. Thio, G. Plinke, and G. Schröder, Tetrahedron Lett., 1579 (1971).
(20) R. L. Shriner, R. C. Fuson, and R. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th ed, Wiley, New York, N.Y., 1967, p 321.

N^3,O^4-Ethylene-1-methyluracilium Methanesulfonate. A Uracil-Derived Heteronuclear Stabilized Cation[1]

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The preparation and properties of N^3,O^4-ethylene-1-methyluracilium methanesulfonate, a heteronuclear stabilized cation, and its interconversions with 3-(β-methanesulfonyloxyethyl)-1-methyluracil were studied. The former was shown to have three sites for reactions with nucleophilic reagents: the β carbon of the ethylene moiety and C-4 and C-6 of the pyrimidine ring. Products resulting from attack at the β position were observed with DMSO, water, alcohols, benzoate, chloride, diethylamine, and pyridine. A strong rate dependence on solvent was noted with chloride ions. Products resulting from attack at C-4 were observed with water, hydroxide, alcohols, alkoxide, and isopropylamine. Diethylamine was the only reagent which led to a product resulting from attack at C-6 of the cation. Oxygen-18 experiments verified the sites at which the uracilium salt reacted with hydroxide and water. Although the N^3,O^4-ethylene-1-methyluracilium cation bears a net positive charge, deuterium exchange reactions were not observed. Mechanisms are proposed to account for the products of the various reactions which were investigated.

N^3,O^4-Ethylene-1-methyluracilium mesylate (**1**, Scheme I) was isolated during the course of the synthesis of 3-(β-mesyloxyethyl)-1-methyluracil[2] (**2**). This uracilium salt is an exceptionally stable member of the class of compounds referred to as heteronuclear stabilized cations.[3,4] Two examples of resonance-stabilized cations having the pyrimidine nucleus have been observed, but only in solution.[5]

Delocalization of the positive charge over several atoms of cation **1** enhances stability and provides multiple sites for chemical reactions. Furthermore, one of its resonance structures is analogous to that postulated as a rationalization for the carbanion mechanism of H-6 exchange in pyrimidines.[6]

In most cases where salts of heteronuclear stabilized cations have been isolated, the anions have been nonnucleophilic species such as ClO_4^-, BF_4^-, or SbF_6^-. By contrast, the anionic portion of salt **1** is sufficiently nucleophilic under certain circumstances to enable the salt to revert to its covalent isomer.

Results and Discussion

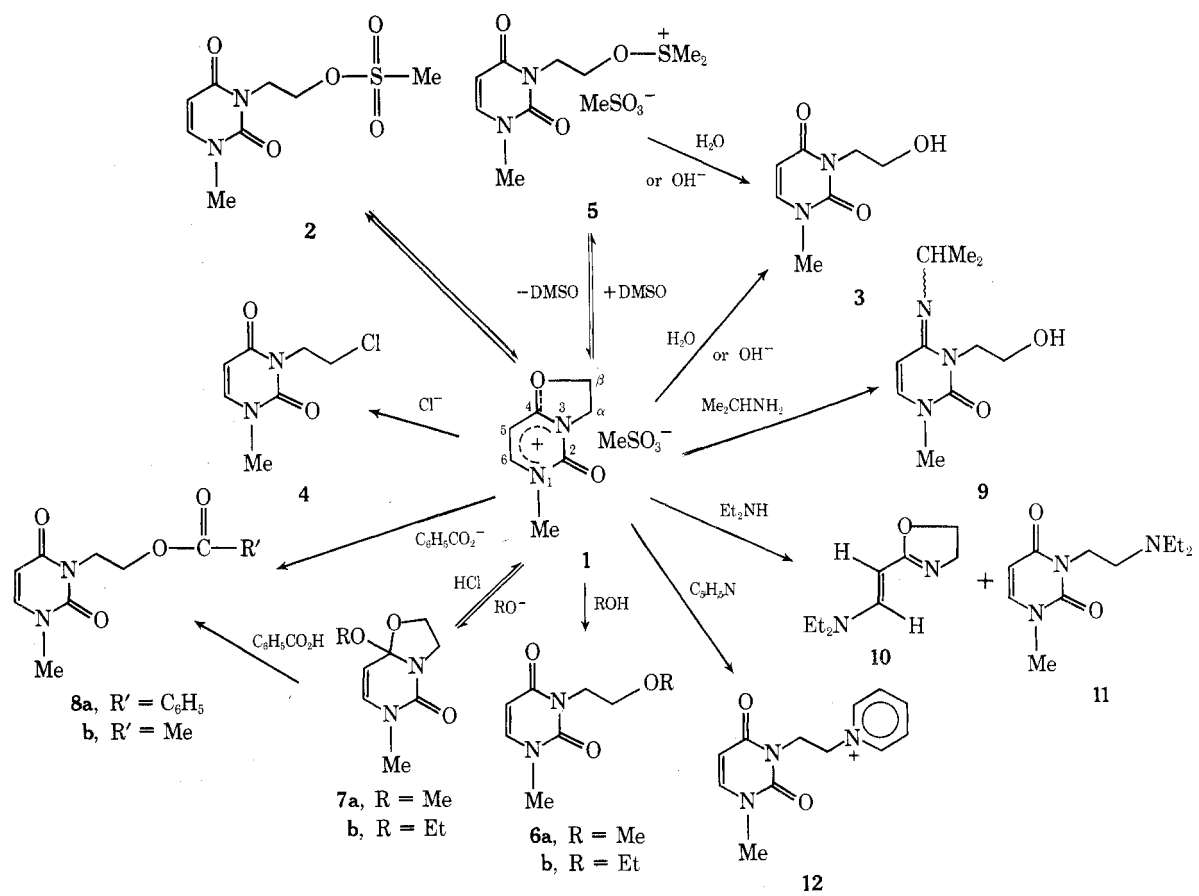
3-(β-Hydroxyethyl)-1-methyluracil (**3**) was obtained in high yield by a three-step synthesis starting with 2,4-diethoxypyrimidine.[7] Mesylation of **3** gave a 90% yield of ester **2** and a small amount of 3-(β-chloroethyl)-1-methyluracil (**4**). The structure assigned to **2** is supported by the ultraviolet absorption spectrum, which is essentially identical with that of **3**[8] and of 1,3-dimethyluracil.[9] The infrared spectrum of compound **2** is that of a typical 1,3-disubstituted uracil: ν (C_2=O) 1700, ν (C_4=O) 1660, ν (C=C) 1620 cm^{-1} and absorptions due to uracil nucleus vibrations at 1415–1440 and 1450–1490 cm^{-1}.[10] In fact, the infrared spectra of all of the compounds (**2, 3, 4, 6, 8, 11,** and **12**) which have the uracil nucleus exhibit these characteristic absorption bands. In general, these compounds also absorb in regions characteristic of the functional groups which are substituents on the N-3 ethyl side chain; e.g., compound **2** absorbs at 1185 and 1345 cm^{-1}.[11] The ^{1}H NMR resonances of H-5, H-6, and NCH_3 in ester **2** are essentially the same as those in **3**, while the methylene resonances are shifted downfield, as expected. The resonance due to the protons in the methanesulfonyl group is in the same region as that of other methanesulfonate esters.[12] The ester was soluble and relatively stable in nonpolar solvents (e.g., chloroform, ethyl acetate, and acetone) and it migrated like a covalent compound in thin layer chromatography on silica gel.

Table I
Ultraviolet Absorption Spectra

Compd	95% EtOH		0.1 N HCl		0.1 N NaOH	
	λ_{max}	λ_{min}	λ_{max}	λ_{min}	λ_{max}	λ_{min}
1	290 (9.9)[a,b]	247 (0.7)[b]	288 (9.8)	245 (0.9)		
	202 (11.5)[b]					
2[c]	267 (7.2)	232 (2.0)				
	207 (7.0)					
3	267 (8.3)	234 (1.8)	267 (8.3)	235 (1.3)	267 (8.3)	236 (1.7)
	207 (7.9)					
4	267 (8.6)	234 (1.6)	267 (8.4)	234 (1.3)	267 (8.6)	236 (1.8)
	207 (8.4)					
5[d]	270 (7.3)					
6a	267 (8.3)	230 (1.9)	267 (8.3)	235 (1.7)	267 (8.3)	237 (2.2)
	206 (8.4)					
7b[e]	235 (6.5)	226 (6.3)				
8a	267 (9.2)	247 (5.4)	267 (9.3)	250 (6.2)	267 (9.2)	245 (4.8)
	228 (14.0)	212 (11.5)	230 (13.1)	214 (10.8)		
8b	266 (8.5)	233 (1.7)	267 (8.5)	235 (1.6)	267 (8.5)	237 (2.3)
	206 (8.4)					
9	285 (7.8)	250 (2.4)	292 (13.1)	255 (2.8)	285 (7.8)	254 (3.0)
	225 (10.8)	206 (6.7)				
10	287 (25.6)	240 (1.8)	296 (38.0)	245 (0.05)	285 (19.5)	238 (0.4)
11	267 (8.4)	224 (2.1)	268 (9.1)	234 (1.6)	267 (8.7)	239 (2.5)
12	261 (11.4)	265 sh (11.0)	261 (11.0)	265 sh (10.7)	260 (11.4)	266 sh (11.0)
	207 (12.4)	237 (3.5)		235 (2.5)		237 (3.5)

[a] λ in nanometers, ε × 10^{-3} in parentheses. [b] MeCN. [c] Absolute EtOH. [d] DMSO. These data are for an equilibrium mixture of 1, 2, and 5. The molar extinction coefficient is corrected for the content of 1 and 2. [e] Absolute EtOH. The molar extinction coefficients are calculated on the assumption of quantitative conversion of 1 to 7.

Scheme I



The ester 2 was unstable at room temperature, both neat and in solution in polar solvents such as water or alcohol.[2] It rearranged readily to a new compound (1), whose salt-like nature soon became evident. Electrophoresis in acetate buffer, pH 4.6,[13] demonstrated that the uv-absorbing moiety of 1 was positively charged. The salt-like nature of 1

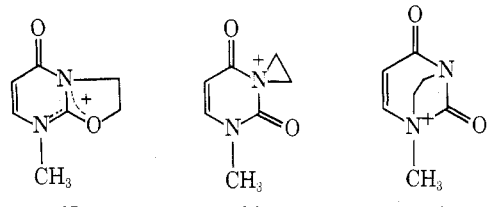
Table II
^{1}H NMR Spectra[a]

Compd	Solvent	H-6 (d)	H-5 (d)	$J_{5,6}$	$C_\alpha H_2$–$C_\beta H_2$[b]		$J_{\alpha,\beta}$	NMe (s)	Other
1	DMSO-d_6	8.83	6.83	8	5.20	4.40	9.5	3.59	2.32 (s, 3, $CH_3SO_3^-$)
	D_2O	8.60	6.65	8	5.32	4.57		3.69	2.79 (s, 3, $CH_3SO_3^-$)
	CF_3COOH	8.45	6.55	8	5.37	4.68		3.80	3.15 (s, 3, $CH_3SO_3^-$)[c]
2	DMSO-d_6	7.70	5.68	8	4.35	4.18	6	3.30	3.13 (s, 3, CH_3SO_3)
	D_2O	7.62	5.87	8	4.58	4.32		3.40	3.17 (s, 3, CH_3SO_3)
	$CDCl_3$	7.18	5.89	8	4.46	4.35		3.40	3.02 (s, 3, CH_3SO_3)
3	DMSO-d_6	7.65	5.65	8	3.92	3.48	6	3.28	4.68 (broad, 1, OH)
	$CDCl_3$	7.17	5.75	8	4.22	3.90		3.40	3.87 (broad, 1, OH)
4	$CDCl_3$	7.22	5.82	8	4.15	3.71		3.37	
5	DMSO-h_6	7.75	5.72	8	4.48	4.17	6	3.33	2.32 (s, 3, $CH_3SO_3^-$), 3.30 [s, 6, $(CH_3)_2S$]
6a	DMSO-d_6	7.66	5.64	8	4.00	3.47	6	3.23 or 3.29	3.29 or 3.23 (s, 3, CH_3O)
	$CDCl_3$	7.19	5.72	8	4.19	3.64		3.40 or 3.38	3.38 or 3.40 (s, 3, CH_3O)
7b	DMSO-d_6	6.60	5.11	8	3.97			3.05	3.26 (q, 2, J_{Et} = 7, CH_3CH_2O), 1.07 (t, 3, J_{Et} = 7, CH_3CH_2O)
	$CDCl_3$	6.34	5.12	8	4.08			3.17	3.35 (q, 2, J_{Et} = 7, CH_3CH_2O), 1.16 (t, 3, J_{Et} = 7, CH_3CH_2O)
8a	$CDCl_3$	7.13	5.68	8	4.38	4.54	6	3.34	8.00 and 7.43 (m, 5, aromatic protons)
8b	$CDCl_3$	7.20	5.72	8	4.28			3.40	3.61 (s, 3, CH_3CO)
9	$CDCl_3$	6.75	5.75	8	4.28	3.83	4.5	3.30	5.17 (m, 1, OH), 3.57 [septet, 1, $J_{i\text{-}Pr}$ = 6.5, $NCH(CH_3)_2$], 1.14 [d, 6, $J_{i\text{-}Pr}$ = 6.5, $(CH_3)_2CHN$]
10[d]	$CDCl_3$	7.17	4.70	13.5	4.19	3.82	9		3.17 (q, 4, J_{Et} = 7.5, CH_3CH_2N), 1.15 (t, 6, J_{Et} = 7.5, CH_3CH_2N)
11	$CDCl_3$	7.21	5.68	8	4.05	2.70		3.39	2.61 (q, 4, J_{Et} = 7, CH_3CH_2N), 1.04 (t, 6, J_{Et} = 7, CH_3CH_2N),
12[e]	D_2O	7.60	5.77	8	4.88	4.62	5	3.35	8.58 and 8.88 (m, 5, aromatic protons), 2.80 (s, 3, $CH_3SO_3^-$)

[a] Chemical shifts are in parts per million from TMS or DSS; multiplicity is in parentheses; coupling constants are in hertz; integration is correct for assignments. [b] The definite assignment of the α and β protons can be made only in the case of **3**, where hydroxyl coupling is observed. The others could be interchanged. The spectra of these protons consists of a set of multiplets which are symmetrical and can best be described as an A_2B_2 pattern. The A_2B_2 pattern fits best for those structures in which the ethylene group is part of a ring. However, even in the nonring compounds, the spectra are not complex enough to be AA'BB' systems. Therefore, the chemical shifts given are for the approximate position of the highest line in the multiplet, assumed to be line 4. The coupling constant $J_{\alpha\beta}$ is one-half the difference between lines 2 and 7. See J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, pp 347-351. [c] The methyl protons of CH_3SO_3H in CF_3COOH have δ 3.25 ppm. [d] The numbering system used for designating the atoms in **1** was retained for the purpose of simplification and ease of comparison. [e] See ref 2.

also was evident on thin layer chromatography on silica gel and by its insolubility in nonpolar solvents and solubility in polar solvents. Confirmation of the structure was provided by spectroscopic data. The cation has a λ_{max} at 290 nm, as contrasted with a λ_{max} of 267 nm for the ester **2**, indicating an extended conjugated system. Analogous resonant cations[5] also exhibit long-wavelength maxima. The infrared spectrum of **1** in the region 1600–1800 cm^{-1} differs considerably from that of a typical 1,3-disubstituted uracil. The major changes are the absence of an absorption at ca. 1660 cm^{-1}, corresponding to ν (C_4=O), and the appearance of a band at 1605 cm^{-1}, corresponding to the structural element –O–C$^+$–NCH$_3$.[14] The absorption due to ν (C=C) is still unchanged at 1619 cm^{-1} and that corresponding to ν (C_2=O) has shifted to 1751 cm^{-1}. The ^{1}H NMR absorptions of the cation portion of the salt are shifted to lower field relative to the corresponding resonances of the mesyl ester **2**, as expected for a positively charged species. The mesyl resonance is shifted upfield to δ 2.32, a value corresponding to that of mesylate anion.[15] Finally, the reaction of **4** with silver tetrafluoroborate in acetonitrile[3b] produces the same cation **1**.

Alternative positively charged cyclic structures for cation **1** include the following.



13 **14** **15**

Crystal structure data for uracil and 1-methyluracil show that the bond between C-4 and O-4 is longer than the one between C-2 and O-2,[16] and therefore compound **1** is a more likely product than **13**. In fact, of the four structures illustrated for the uracilium cation (**1**, **13**, **14**,[17] and **15**), the one in Scheme I is the most resonance stabilized; the positive charge in it is more delocalized than in the others. This argument in support of the assigned structure is analogous to the explanation given for the stability of the cation derived by monoprotonation of uracil on O-4 relative to the one derived by protonation on O-2.[18] Finally, structures **13**, **14**, and **15** are inconsistent with the uv, ^{1}H NMR, and chemical data.

Although the cation **1** was prepared by the thermolysis of **2**, the two compounds were found to be interconvertible.

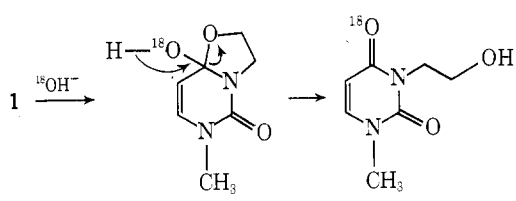
When the cation was heated in the solid probe of the mass spectrometer, only the mass spectrum of **2** was observed. Further, in contrast to the behavior of **2** in polar solvents (vide supra), **1** on solution in acetonitrile at room temperature equilibrated to a mixture containing **2** and **1**. The reaction, **2** to **1**, is merely an intramolecular nucleophilic substitution of the mesylate anion by the oxygen atom on C-4, while the reverse is an SN2 reaction of mesylate anion at the β carbon atom of the ethylene moiety. The former resembles the conversion of 5-(2-methanesulfonyloxyethyl)-uracil to 2*H*,3*H*,5(7)*H*-furano[2,3]pyrimidin-6-one.[5b]

The earlier expectation that there would be multiple reaction sites in cation **1** was borne out by further study of its behavior toward a variety of reagents. The ester **2** and salt **1** both reacted with DMSO at room temperature to give an equilibrium mixture containing 21% **2**, 16% **1**, and 63% of a new cation to which we assign the structure of a dimethylsulfoxonium salt (**5**). Equilibrium was reached in about 4 hr from the salt and 20 hr from the ester (^{1}H NMR). On evaporation of the DMSO solution, **5** reverted to **1**. This regeneration of **1** on evaporation of the DMSO was confirmed by means of both ^{1}H NMR and uv spectroscopy. Compound **3** was obtained quantitatively on the addition of water or a catalytic amount of aqueous sodium hydroxide to the DMSO solution of the equilibrium mixture.

Although **5** could not be isolated, the ^{1}H NMR data in DMSO support the suggested structure. The chemical shifts assigned to **5** have values similar to those of the mesyl ester **2**, except for the resonance due to the mesyl group. This is in the same position as in mesylate anion. In addition, a new six-proton singlet is observed at δ 3.30.[19] The changes in the uv spectrum which take place on solution of **1** in DMSO also support the proposed structure.

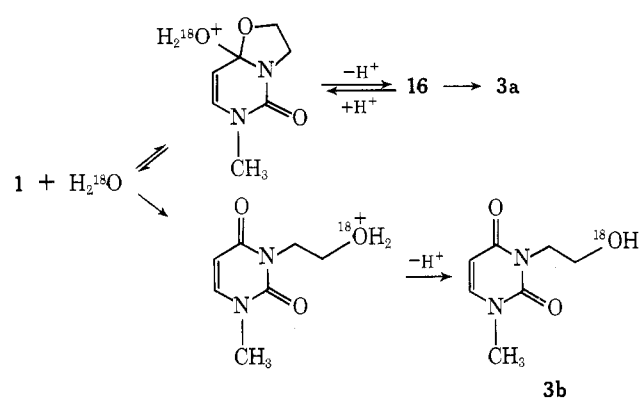
The cation **1** was stable at low pH values, but it reacted rapidly in alkaline solutions to give **3**. When **1** was treated with Na^{18}OH in $H_2{}^{18}O$, the labeled **3** contained all of the ^{18}O in the C-4 carbonyl group. The solvolysis in $H_2{}^{18}O$ yielded **3** containing only one atom of ^{18}O; one-half the molecules of **3** were labeled in O-4 and the other half were labeled in the β-OH group.[20]

The results with Na^{18}OH are best explained by a mechanism such as shown.



16 3a

A mechanism for the aqueous solvolysis which explains the observed distribution of the ^{18}O label is as follows.



3b

As the reaction progresses, the medium becomes more acidic. The equilibria between **1** and **16** shift in favor of **1** and thus suppress incorporation of ^{18}O in the C-4 carbonyl. Substitution in the β position, to give **3b**, then becomes more important.

In agreement with the Na^{18}OH experiment, cation **1** reacted with alcoholic alkoxide solutions[21] to form an addition compound (**7**), behavior analogous to the mode of formation of the dimethyl acetal of dimethylformamide, $(CH_3)_2NCH(OCH_3)_2$.[22] Formation of **7** was instantaneous and quantitative. Spectroscopic evidence confirmed the structure assigned to the product resulting from the addition of ethoxide at C-4. The uv maximum of **7b** is at 235 nm (ϵ 6500), in agreement with values reported for 2-oxo-4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidine and its N-3 methyl derivative.[23] The ^{1}H NMR spectrum has resonances for both H-5 and H-6, with J = 8 Hz, shifted upfield relative to the corresponding resonances in **2**, **3**, **4**, and **6**, as expected.[24] Absorptions corresponding to the ethoxyl group also are present.

Chemical evidence supporting the structure assigned to **7** includes the fact that it reverted immediately and quantitatively to the uracilium cation **1** when an alcoholic solution of it was acidified with a strong acid, such as hydrochloric acid. On the other hand, addition of benzoic acid to an alcoholic solution of **7** resulted in the formation of 3-(β-benzoxyethyl)-1-methyluracil (**8a**) in 80% yield. The first step in both of these reactions involves protonation of **7**, followed by loss of ROH to give cation **1**. In the case of benzoic acid, the benzoate ion then reacts further with this cation, a reaction similar in character to the reaction of benzoic acid with the dimethyl acetal of dimethylformamide.[25] The fact that ethyl benzoate was not formed indicates that the cyclic cation is more stable than the alternative acyclic one. Reaction of uracilium ion **1** with sodium benzoate in DMF gave rise to the same ester, **8a**.

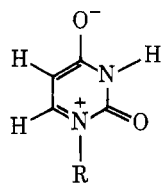
Methanol slowly solvolyzed **1** to 3-(β-methoxyethyl)-1-methyluracil (**6a**), whose structure is evident from the spectral data. The formation of this product was not surprising in view of the results of the $H_2{}^{18}O$ experiment. The analogy between hydrolysis and alcoholysis of **1** is reinforced by another experiment. On solution of **1** in absolute ethanol, 20–25% of it was converted to **7b**. This observation is in accord with the series of reactions proposed above for the aqueous solvolysis.

As implied previously, the uracilium ion **1** is quite stable in aqueous hydrochloric acid. In acetonitrile, however, **1** reacted rapidly with lithium or tetraethylammonium chloride to form the β chloride **4**. That the rate enhancement is solvent dependent was demonstrated by the reaction of **1** with aqueous hydrochloric acid in acetonitrile, again a fast reaction compared to aqueous hydrochloric acid itself.[26] This marked difference in rates could be due to little or no pairing of **1** with chloride ion in water compared to acetonitrile and/or to the fact that chloride ion is much less solvated in acetonitrile than in aqueous solution.

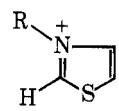
As in ordinary water, at room temperature the uracilium cation **1** was solvolyzed slowly (10% in 3 hr) in D_2O to **3**. No deuterium exchange at C-5 or C-6 of either the starting material or the product was observed. Even in 0.5 *N* sodium deuteroxide no exchange was observed at these positions during the conversion of **1** to **3**. In methanol-*O*-*d*–methoxide, the C-4 adduct **7a** formed instantly. On removal of the methanol-*O*-*d* by distillation, the adduct was converted to **3**. This product also did not contain deuterium.

These results appear surprising at first. Rabi and Fox[6b] have provided support for the suggestion that H-6 exchange in various uracil derivatives takes place through the

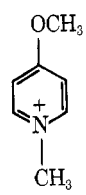
intermediacy of a C-6 carbanion. A resonance structure such as shown presumably accounts for the acidity of H-6



in these systems.[6a] The uracilium cation **1**, with a net positive charge, might have been expected to have a more acidic H-6 than a species with a net charge of zero. Breslow, in thiamine analogs of the type shown, has found exchange of



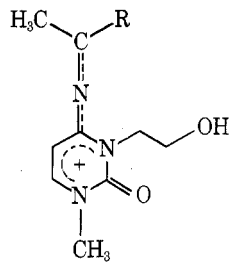
the C-2 hydrogen to occur in D_2O at room temperature in a few hours.[27] Beak et al. have reported that some pyridinium salts, such as shown, exchange C-2 and C-6 hydrogen



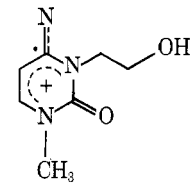
atoms in methoxide–methanol-*O*-*d* in 15 min at room temperature.[28] The uracilium cation, instead, preferentially reacts with hydroxide and methoxide ions at C-4 to give electrically neutral products. The D_2O reaction, on the other hand, demonstrates that the C-6 hydrogen in **1** is not as acidic as the C-2 hydrogen of thiamine analogs.

Reaction of **1** with 1 equiv of tetramethylammonium hydroxide pentahydrate in DMSO-d_6 gave **3** containing ca. 15% deuterium at C-6 and less than 5% at C-5. A similar experiment with **3** led to 50% degradation of starting material,[9,29] but recovered **3** contained 100% deuterium at C-6 and 67% at C-5. The exchange observed with **1** occurred in all likelihood after conversion to **3.**

The reactions of the cyclic salt **1** with amines led to products which were markedly dependent on whether the amine was primary, secondary, or tertiary. Isopropylamine gave solely the product resulting from attack at C-4, 3-(β-hydroxyethyl)-1-methyl-N^4-isopropylcytosine (**9**). Spectroscopic data are the basis for the structure assigned to this compound. Comparison of the uv spectral characteristics of **9** with the values for N^3,N^4-bis(β-hydroxyethyl)-1-methylcytosine,[30] 1,3-dimethylcytosine,[31] and 3-methylcytidine[5a] show substantial agreement. These compounds exist in the N^4-imino, rather than amino, forms. Further, an important characteristic of the infrared spectra of cytosine derivatives which have a double bond between C-4 and its exocyclic nitrogen has been noted by Brown et al. Such compounds have two absorption bands in the region 1650–1700 cm^{-1}. By contrast, compounds having a single bond between these two atoms have only a single absorption in this region.[32] Compound **9** also has two absorption bands in this region. The ^1H NMR and mass spectra also are in agreement with the assigned structure for **9.** Although a peak corresponding to the molecular ion was not found in the latter spectrum, the three ions of *m/e* 210, 196, and 168 lend further support to this structure. These may be represented by the resonance-stabilized structures below.

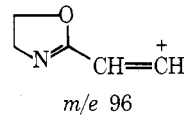


R = H, *m/e* 196
R = CH_3, *m/e* 210

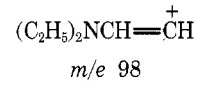


m/e 168

Diethylamine plus **1** afforded three uv-absorbing bases: 61% of *trans*-2-(β-diethylaminoethyl)-Δ^2-oxazoline (**10**); 27% of 3-(β-diethylaminoethyl)-1-methyluracil (**11**); and 12% of a compound to which the structure shown is tentatively assigned.[33] In addition, *N*,*N*-diethyl-*N'*-methylurea was isolated from the reaction mixture in 62% yield. The uv data for **10** agree with that of dienamines derived from α,β-unsaturated ketones.[34] The similarity in the wavelengths of the maxima and minima of the uv spectra of **9** and **10,** and their variation with changes in solvent, is corroborative structural evidence, since the chromophore in both of these is the structural element N—C=C—C=N. The infrared spectrum of **10** is also in agreement with the spectra reported for 2-methyl- and 2-ethyl-Δ^2-oxazoline[35] and with a characteristic frequency (1647–1652 cm^{-1}) reported for 2-aryl-Δ^2-oxazolines.[36] The ^1H NMR data lend added support to the structure given for **10;** in particular, the data demonstrate that the compound has the trans configuration. The mass spectrum is in agreement with the assigned structure too. The principal ions observed are the molecular ion and two other ions which are of structural significance. These may be represented as shown.

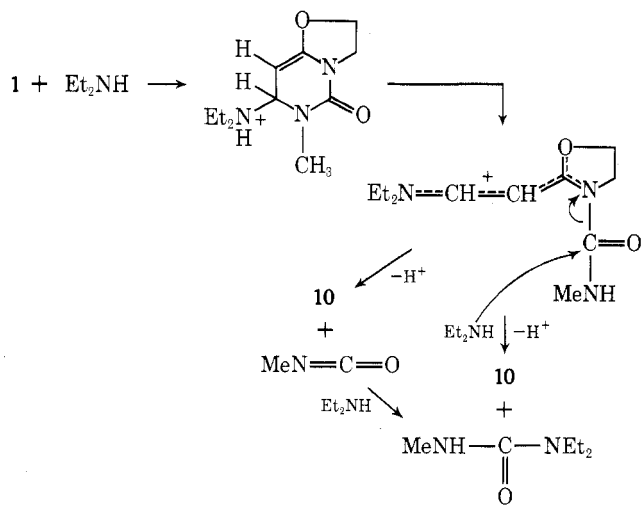


m/e 96



m/e 98

The reaction leading to **10,** the only clear-cut example of C-6 addition, involves initial attack of diethylamine at C-6 followed by ring opening between N-1 and C-6. Next, two pathways may lead to the final products. A similar reaction



has been observed with 3-methyl-4-thiouracil and dimethylamine, but it required much more drastic conditions (155°, 60 hr).[37]

The uracilium salt **1**, when dissolved in pyridine, was converted to [β-(1-methyluracil-3)ethyl]pyridinium mesylate (**12**). The basis for the assignment of structures to **11** and **12** is evident from the spectral data.

The uracilium cation **1** appears to be the first resonance-stabilized cation which has been demonstrated to have more than two reactive centers toward nucleophiles, i.e., C-4, C-6, and the β position. For this reason, if no other, its chemistry is more complex than that of the numerous heteronuclear stabilized cations which have been described in the literature.[3] The β-substitution products can be formed in two ways: direct attack at the β position or attack at C-4 followed by expulsion of the β-hydroxyethyl group. The β products are undoubtedly the most stable final products, since the α,β-conjugated system is regenerated in them. In only one case (diethylamine) the product results from attack at C-6. The absence of C-6 adducts with other nucleophiles is probably due to the fact that they would contain a ketene-*N,O*-acetal group. It has been reported that this functional group is extremely susceptible to nucleophilic attack.[14] By analogy, were C-6 adducts of cation **1** to be formed, they would be rapidly converted by further reaction with nucleophiles to C-4 addition products.

The nucleophiles which were examined fall into two groups: those which are electrically neutral and those which are anions. Both groups are each to be further divided into two subgroups. With one of these, whether electrically neutral or negatively charged, the bond initially formed at C-4 or C-6 is preserved in the final product. With the other subgroup, the final product is the result of nucleophilic substitution on the β carbon. The electrically neutral reagents which fall in the first subgroup mentioned are water, alcohols, isopropylamine, and diethylamine; those in the second are DMSO, pyridine and, once again, water and alcohols. With the latter, the equilibria involving the formation of an adduct from **1** and the nucleophile presumably is not favored. Instead, a relatively slow nucleophilic attack at the β position predominates. Of the anionic reagents, the first subgroup consists of hydroxide and alkoxide ions; the second includes mesylate, benzoate, and chloride ions. The first step in these anionic reactions takes advantage of coulombic attraction to form an ion pair which is then converted to a covalent adduct at C-4. The interaction of **1** with alkoxide is the only reaction in which the initial product was stable enough to be detected. The hydroxide ion adduct loses a proton and regains a conjugated carbonyl group. The others undergo an intramolecular conversion to the β-substituted product. These steps are analogous to those reported for the conversion of 2-methyl-*cis*-4,5-tetramethylene-1,3-dioxolenium cation by means of acetate to *cis*-1,2-acetoxycyclohexane.[38]

It is of interest to compare the chemistry of the uracilium cation **1** with the oxazolinium cations of Tomalia and Paige.[3b] By analogy with the results of these authors, solvolysis of cation **1** would involve initial attack of the nucleophile at C-4 and eventual cleavage of the bond between C-4 and N-3. No examples of this type of behavior were found. A further comparison of cation **1** with the *N,O*-trimethylenephthalimidium cation (**17**) of Hünig[3a] is desirable too. The principal differences between cations **1** and **17** lie in their solvolytic behavior. Cation **1** is converted by alcohols to **6**, whereas if its behavior paralleled that of **17** the product would have been **3**. In addition, the ^{18}O experiments with cation **1** clearly demonstrate that its reaction with water leads to a mixture of **3** labeled at O-4 and **3** labeled at the β-OH group, in contrast to the prediction of Hünig. The reaction of a secondary amine, diethylamine, with cation **1** also is quite different in character from the reaction of piperidine with **17**. Both amines form adducts with the respective cations, but since diethylamine is more sterically hindered than piperidine, and an alternative position is available in **1** for adduct formation, the diethylamine adds to C-6 rather than C-4. The initial adduct from piperidine and **17** loses a proton to form a stable product, while the adduct from diethylamine and **1** undergoes much more complex transformations to yield a stable end product. The behavior of pyridine and halide ion toward **1** is analogous to that observed by Hünig for their reactions with **17**.

Experimental Section

^1H 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, and 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 He 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.). Preparative chromatography (dry column) was performed on silica gel Woelm (Waters Associates, Inc., Framingham, Mass.).

Uv and ^1H NMR data for compounds **1–12** are summarized in Tables I and II, respectively. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Melting points are uncorrected.

3-(β-Hydroxyethyl)-1-methyluracil (3). 2,4-Diethoxypyrimidine, prepared from uracil via the dichloride,[39] was methylated with methyl iodide and hydrolyzed to give 1-methyluracil.[7a] 1-Methyluracil (6.33 g, 50.2 mmol), ethylene carbonate (4.8 g, 57.1 mmol), and potassium carbonate (100 mg, 0.72 mmol) were heated to reflux in dimethylformamide for 75 min.[7b] The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue, crystallized from absolute EtOH, afforded 8.16 g (95%) of **3**: mp 138.5–140° (lit.[40] mp 136.5–138.5°); TLC, AcOEt; ir ($CHCl_3$) 3450 (m), 3000 (m), 1710 (s), 1660 (s), 1635 (s), 1455 (s), 1435 (m), 1390 (m), 1360 (w), 1335 (m), 1210 (m), 1155 (w), 1120 (w), 1015 (w), and 965 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 140 (22), 139 (14), 128 (13), 127 (100), 84 (27), 83 (31), and 82 (58).

3-(β-Mesyloxyethyl)-1-methyluracil (2). All materials were thoroughly dried and cooled to 0–10°. All operations were carried out in this temperature range. Compound **3** (1.7 g, 10 mmol) was dissolved in 100 ml of MeCN plus 6 ml (43.2 mmol) of triethylamine in a three-necked flask fitted with addition funnel, drying tube, and thermometer. Mesyl chloride (2 ml, 25.8 mmol) in 25 ml of MeCN was added slowly to the stirred reaction mixture. It is important to keep the temperature below 10°. The reaction mixture was stirred for an additional 30 min and then filtered to remove triethylamine hydrochloride. The filtrate was concentrated in vacuo to a thick oil. AcOEt was added and the solution was filtered again to remove triethylamine hydrochloride. The filtrate was evaporated in vacuo to a small volume and 2 g of silica gel was added. This mixture next was added to a column containing 25 g of silica gel and then was eluted with AcOEt. Fractions (3 ml) 12–14 contained 0.45 g of **2** plus **4** and 15–57 contained 2.24 g (91%) of **2**. The latter crystallized on evaporation of solvent. It appeared to soften at 48°, became liquid at 53°, then resolidified and melted at 105–112°. Crystalline samples liquefied when stored at room temperature overnight, but were stable for at least 30 days if stored below 10°: ir ($CHCl_3$) 1715 (s), 1665 (s), 1645 (sh), 1450 (m), 1435 (w), 1385 (m), 1355 (m), 1345 (s), 1185 (s), 1135 (w), 1078 (w), 1000 (m) and 965 cm^{-1} (m).

Ester **2** dissolved unchanged (^1H NMR) in $CDCl_3$, acetone-d_6, and pyridine-d_5.

3-(β-Chloroethyl)-1-methyluracil (4). The fractions from two

preparations of 2 (from 16.9 mmol of 3) which contained 4 were combined and chromatographed on 21 g of silica gel with AcOEt as eluent. Fractions (3 ml) 3–6 contained a single component weighing 220 mg (7%). Crystallization from MeOH–Et_2O afforded 160 mg of 4: mp 93–94.5°; ir ($CHCl_3$) 3000 (w), 1702 (s), 1665 (s), 1638 (m), 1450 (s), 1439 (m), 1390 (m), 1370 (w), 1348 (m), 1321 (w), and 1000 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 190 (28), 188 (85), 153 (100), 139 (22), 127 (20), 126 (94), 84 (46), 83 (31), and 82 (60).

Anal. Calcd for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81; N, 14.85; Cl, 18.79. Found: C, 44.50; H, 4.59; N, 14.81; Cl, 18.79.

N^3,O^4-Ethylene-1-methyluracilium Mesylate (1). The ester 2 (1.115 g) was heated in vacuo at 81° for 4 hr. The compound melted and bubbled at approximately 70–73° and then solidified. The solid was broken up and washed with 3 × 5 ml of dry MeCN and dried in vacuo at 60–65° to afford 0.780 g of product (70%): mp 122.5–125°; ir (MeCN) 1751 (s), 1619 (s) and 1605 cm^{-1} (s); mass spectrum[41] *m/e* (rel intensity) 248 (10) ($M\cdot^+$), 170 (14), 169 (100) ($M\cdot^+ - CH_3SO_2$), 153 (18), 152 (6), 151 (11), 139 (34), 127 (14), 126 (15), 96 (6), 84 (49), 83 (23), 82 (51), 79 (17), and 70 (6).

Anal. Calcd for $C_8H_{12}N_2O_5S$: C, 38.72; H, 4.87; N, 11.29; S, 12.89. Found: C, 38.50; H, 5.08; N, 11.20; S, 13.05.

Salt 1 was soluble in H_2O and DMSO (vide infra). It dissolved unchanged in DMF and CF_3CO_2H; it was slightly soluble in MeCN and EtOH; and it was insoluble in $CHCl_3$ and AcOEt. On electrophoresis at pH 4.6 (paper, 0.05 *M* acetate buffer) 1 migrated 4 cm toward the cathode, whereas 3 did not move at all.

Although the filtrate contained 1 and 2 (TLC, AcOEt; R_f of 1 0), attempts to recover more 1 from it were unsuccessful. The reason for this became apparent when pure 1 (19.70 mg, 7.95×10^{-2} mmol) was dissolved in 25 ml of MeCN. An aliquot of this solution, diluted with more MeCN, had λ_{max} 290 nm. After 4 hr at room temperature, the optical density at 290 nm had decreased and a shoulder appeared at 267 nm. This spectrum remained constant and represented 64% of 1 and 36% of 2. After 24 hr another aliquot was removed and diluted with 0.1 *N* HCl. The λ_{max} of this solution slowly reached a constant absorbance at 288 nm, corresponding to complete regeneration of 1. The finite equilibrium between 1 and 2 also was evident from an ir spectrum in MeCN. In addition to the bands characteristic of 1, there were strong absorptions at 1716, 1668, and 1655 cm^{-1} (sh) corresponding to 2.

Reaction of 4 with Silver Tetrafluoroborate. Compound 4 (178 mg, 0.94 mmol) was dissolved in 4 ml of MeCN and anhydrous $AgBF_4$ (0.6 g, 3.0 mmol) was added. After 3 days the absorbance at 290 nm corresponded to a 75% yield of the cation of 1. TLC of the reaction mixture in AcOEt showed a spot at the origin and a spot with the same R_f as starting material. The solution was filtered and concentrated in vacuo. The crude residue, recrystallized from MeCN–1,2-dichloroethane, afforded 132 mg (59%) of the tetrafluoroborate of the cation of 1: mp 156–159°; ir (MeCN) 1751 (s), 1621 (s), and 1606 cm^{-1} (s); ^1H NMR (D_2O) δ 8.59 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 6.62 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 5.30 and 4.59 (m, 4, NCH_2CH_2O), and 3.68 (s, 3, NCH_3). The sample turned dark on standing, an indication of contamination by silver ion.

O-[β-(1-Methyluracil-3)ethyl]-S-dimethylsulfoxonium Mesylate (5). Attempts to obtain the ^1H NMR spectra of the mesyl ester 2 and the cyclic cation 1 in DMSO-d_6 indicated that both were transformed to a third product. Starting with 2, equilibrium was reached in ca. 20 hr; with 1 it took ca. 5 hr. At equilibrium the ^1H NMR spectrum showed the new compound 5 to be 63% of the total, 2 21%, and 1 16%. In an attempt to prepare and isolate 5, a sample of 1 (255 mg) was dissolved in 2 ml of DMSO-h_6 with gentle warming. The λ_{max} of an aliquot of this solution in absolute EtOH had shifted from 290 to 265 nm, suggesting conversion to 5. The solvent was evaporated in vacuo and a ^1H NMR spectrum of a portion of the residue was obtained in DMSO-d_6. This spectrum was identical with that obtained by dissolving 1 in DMSO-d_6, i.e., no dimethylsulfoxonium absorption was observed. Spectra in CF_3CO_2H and D_2O of other portions of the residue confirmed that 5 had reverted to 1 on evaporation of the DMSO. When 1 was dissolved in DMSO-h_6, the ^1H NMR spectrum showed a new line for the dimethylsulfoxonium group at 3.30 ppm. The uv spectrum of an equilibrated solution of 1 in DMSO had λ_{max} 270 nm (ϵ ~7300).[42] Evaporation of this solution, followed by dissolution of the residue in absolute EtOH, showed increased absorbance at 290 nm, the λ_{max} of 1, further confirming reversal of formation of 5 on removal of DMSO.

Addition of D_2O or NaOD to equilibrated DMSO-d_6 solutions of 1 resulted in formation of 3 which contained less than 5% deuterium.

3-(β-Acetoxyethyl)-1-methyluracil (8b). Compound 3 (340 mg, 2.00 mmol) was added to 2 ml of pyridine containing 300 μl (3 mmol) of Ac_2O. The mixture was warmed briefly to achieve solution and then allowed to stand at room temperature overnight. TLC (AcOEt) indicated complete conversion to a new product. The reaction mixture was evaporated in vacuo, treated with water, and evaporated again. The residue, which resisted all attempts at crystallization, was chromatographed on 12 g of silica gel (AcOEt). The solvent was removed in vacuo from fractions (3 ml) 7–30, which contained the product: ir ($CHCl_3$) 3000 (m), 1740 (s), 1715 (s), 1655 (s), 1640 (sh), 1450 (m), 1435 (w), 1390 (m), 1375 (m), 1360 (w), 1350 (m), 1240 (s), 1140 (w), 1080 (w), 1065 (w), and 1025 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 212 (16), 169 (46), 153 (10), 152 (49), 151 (22), 140 (51), 139 (20), 128 (17), 127 (100), 84 (28), 83 (44), and 82 (49).

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.81; H, 5.81; N, 13.31.

Reaction of 1 with $Na^{18}OH$. $H_2{}^{18}O$ (250 μl, 14% ^{18}O by mass spectrometry) was placed in a vial and weighed. The vial and contents were cooled in an ice bath and a small piece of sodium was added. After the vigorous hydrogen evolution ceased, the vial was weighed. The weight of sodium was ca. 13 mg (0.56 mmol). Compound 1 (36.4 mg, 0.15 mmol) was placed in a second vial and the $Na^{18}OH$ solution was injected into it. The vial was shaken vigorously for 5 min and then 30 μl (0.53 mmol) of glacial AcOH was added. The solution was evaporated in vacuo and the residue was chromatographed on 8 g of silica with 1:1 AcOEt–EtOH. The product, 22 mg (93%) of 3, was dissolved in EtOH and this solution was divided into two equal parts. One part, after evaporation in vacuo, was treated with 200 μl (2.1 mmol) of Ac_2O in 1 ml of pyridine for 14 hr. TLC (AcOEt) indicated complete conversion to 8b. The solvent and excess reagent were evaporated in vacuo and the residue was dissolved in 300 μl of $CHCl_3$. VPC of a 20-μl aliquot yielded a pure sample of 8b which was used for mass spectrometric analysis. The isotopic composition was measured on the molecular ion and was found to contain 12% ^{18}O. The remaining portion of 3 was dissolved in 2 ml of 1,2-dichloroethane and treated with 50 μl (8.35×10^{-2} mmol) of thionyl chloride for 14 hr. TLC (AcOEt) indicated complete conversion to 4. The reaction mixture was evaporated in vacuo and the residue was dissolved in 300 μl of $CHCl_3$. VPC of a 20-μl aliquot yielded a pure sample which was used for mass spectrometric analysis. The isotopic composition was measured on the molecular ion and was found to be 12% ^{18}O.

Solvolysis of 1 with $H_2{}^{18}O$. Uracilium mesylate 1 (39.8 mg, 0.160 mmol) was placed in an airtight vial and 125 μl of $H_2{}^{18}O$ (14% ^{18}O) was injected. The solution was allowed to stand at room temperature for 8 days. An aliquot of the solution diluted with absolute EtOH had λ_{max} 267 nm and very little optical density at 290 nm. The remainder of the solution also was diluted with EtOH and then evaporated in vacuo. The residue was chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. The product, 27 mg (100%) of 3, was dissolved in EtOH and divided into two equal parts. One portion was converted to 8b and the other to 4, as described above. Samples for mass spectrometry were obtained by VPC. The acetate 8b contained 12% ^{18}O and the chloride 4 contained 6% ^{18}O.

Reaction of 1 with Ethanolic Ethoxide. 4-Ethoxy-N^3,O^4-ethylene-1-methyl-3,4-dihydrouracil (7b). Compound 1 (460 mg, 1.86 mmol) was added to 250 ml of ice-cold absolute EtOH and 8 ml of freshly prepared 0.236 *N* EtONa in EtOH (1.89 mmol) was added. Within 75 min, a finely divided solid separated and the λ_{max} of the solution had shifted from 267 to 235 nm. When an aliquot of this solution was acidified with 1 *N* HCl, λ_{max} changed back to 290 nm, a value characteristic of 1. Filtration of the main portion of the solution and concentration of the filtrate in vacuo afforded a residue, 7b, which could not be crystallized. Attempts to chromatograph the residue yielded 3. VPC of a portion of the residue led to isolation of 6b, which was characterized by TLC (AcOEt) and mass spectroscopy.[2]

Reaction of 7b with Benzoic Acid. 3-(β-Benzoxyethyl)-1-methyluracil (8a). To 10 ml (0.171 mmol) of an ethanolic solution of 7b was added benzoic acid (21 mg, 0.172 mmol). When a sample of the mixture was subjected to TLC (AcOEt) immediately after mixing, a new component was found. The residue obtained on evaporation of the reaction mixture in vacuo was dissolved in $CHCl_3$ and this solution was extracted with 1 *N* NaOH. It was dried ($MgSO_4$) and then evaporated in vacuo to give 37 mg (79%) of 8a. An analytical sample was obtained from $CHCl_3$–petroleum ether: mp 142–144°; ir ($CHCl_3$) 1710 (s), 1665 (s), 1601 (w), 1450 (m), 1435 (w), 1385 (w), 1355 (w), 1350 (w), 1320 (w), 1280 (s), 1120 (m), and 1030 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 274 (8),

232 (10), 231 (78), 169 (21), 153 (18), 152 (64), 151 (20), 139 (7), 127 (8), 126 (8), 106 (23), 105 (100), 84 (16), 83 (15), 82 (36), and 77 (39).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.19; H, 5.09; N, 10.25. Found: C, 61.31; H, 5.14; N, 10.21.

Reaction of 1 with Sodium Benzoate. Compound 1 (24.2 mg, 9.77×10^{-2} mmol) and sodium benzoate (17.2 mg, 0.12 mmol) were dissolved in 1 ml of DMF. TLC (AcOEt) indicated complete conversion to **8a** within 0.5 hr. The reaction mixture, after evaporation to dryness, was dissolved in $CHCl_3$ and this solution was washed with water. The $CHCl_3$ layer was dried ($MgSO_4$) and after evaporation afforded 20 mg (75%) of **8a** identical with that obtained above.

Alcoholysis of 1. 3-(β-Methoxyethyl)-1-methyluracil (6a). A solution of the uracilium salt 1 (244 mg, 0.983 mmol) in 100 ml of dry MeOH was allowed to stand at room temperature. The λ_{max} shifted from 290 nm to a constant absorbance at 267 nm in 5 days. The solution was evaporated in vacuo and the residue was dissolved in 1,2-dichlorethane, washed (5% $NaHCO_3$), dried ($MgSO_4$), and concentrated in vacuo until crystallization began. The crude weight of product was 155 mg (86%). An analytical sample of **6a** was crystallized from AcOEt–petroleum ether: mp 97–98°; ir ($CHCl_3$) 1710 (s), 1665 (s), 1640 (sh), 1480 (m), 1450 (s), 1435 (m), 1390 (s), 1350 (m), 1320 (w), 1160 (w), 1140 (m), 1120 (m), 1020 (w), and 980 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 184 (12), 153 (6), 151 (20), 141 (6), 139 (14), 128 (9), 127 (100), 126 (25), 84 (19), 83 (13), and 82 (63).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 51.99; H, 6.68; N, 15.10.

The uv spectrum of a solution of 1 (5.75 mg, 2.32×10^{-2} mmol) in 250 ml of absolute EtOH was measured within a few minutes of its preparation. The absorbance at 290 nm was found to be 20–25% lower than it would have been in MeCN or 0.1 *N* HCl and a shoulder was noted at *ca.* 235 nm. This absorption corresponds to that observed for **7b.** On acidification with 1 *N* HCl the absorbance increased at the λ_{max} for 1 and the shoulder disappeared.

Reaction of 1 with Ionic Chlorides. Stock solutions of 1 (7.35 mg, 2.96×10^{-2} mmol) and tetraethylammonium chloride (14.55 mg, 8.8×10^{-2} mmol), each in 10 ml of MeCN, were prepared. The solution of 1 (200 μl, 5.92×10^{-3} mmol) and 100 μl (8.8×10^{-3} mmol) of the chloride solution were added to a 10-ml volumetric flask containing MeCN and then diluted to the mark. The uv spectrum was recorded immediately; it showed a shoulder at 290 nm and a λ_{max} at 264 nm. The shoulder at 290 nm continued to decrease as the λ_{max} at 264 nm increased. After 20 min the reaction was complete.

A 200-μl aliquot (5.92×10^{-3} mmol) of the stock solution of 1 was diluted to 100 ml with 0.1 *N* HCl and the uv spectrum was obtained. The λ_{max} was at 288 nm (ε 9800) and after 3 hr it still had 97% of the original absorbance. After 48 hr the λ_{max} had shifted to 280 nm and after 5 days a shoulder was still present at 290 nm, but the λ_{max} was at 269 nm.[26]

A 200-μl aliquot (5.92×10^{-3} mmol) of the stock solution of 1 was added to 1 ml of 1 *N* HCl and MeCN was added to the mark. The uv spectrum was obtained immediately; it showed a shoulder at 290 nm and a λ_{max} at 270 nm.[26]

Lithium chloride (5.70 mg, 0.134 mmol) was added to the remainder of the stock solution of 1 (2.88×10^{-2} mmol). The solution became cloudy immediately and a new, finely divided solid separated. The lithium chloride did not dissolve completely. TLC (AcOEt) showed complete conversion of 1 to **4.**

Conversion of 2 to 1 in D_2O Solution. A 30-mg sample of **2** was dissolved in D_2O containing 1% DSS (w/w). The ^1H NMR spectrum obtained within 5 min showed ca. 55% of **2** and 45% of **1.** In 18 min the spectrum showed 100% conversion of **2** to **1.** At the end of 3 hr ca. 10% hydrolysis to **3** had occurred. Less than 5% exchange had taken place for H-5 or H-6 in 1 and **3.**

Reaction of 1 with NaOD in D_2O. To 30 mg (0.121 mmol) of 1 was added 200 μl (0.155 mmol) of 0.775 *N* NaOD and 100 μl of D_2O containing DSS. The ^1H NMR spectrum was that of **3** and showed less than 5% exchange for H-5 or H-6.

Reaction of 1 with MeONa–MeOD. Compound 1 (36.25 mg, 0.146 mmol) was added to 25 ml of MeOD. A 200-μl portion of 0.83 *N* MeONa in MeOD (0.166 mmol) was added. The λ_{max} of an aliquot was 237 nm. The MeOD was distilled off until ca. 5 ml remained. The residue was diluted with ether and filtered to remove sodium mesylate. TLC (AcOEt) indicated a single product with R_f equal to that of **3.**[43] Evaporation of the solution in vacuo left a white, crystalline solid. It was dissolved in absolute EtOH and the uv spectrum showed a λ_{max} at 267 nm corresponding to a 99% yield of **3.** The structure was confirmed by the ^1H NMR spectrum, which showed less than 5% deuterium incorporation at C-5 or C-6.

Reaction of 1 with Tetramethylammonium Hydroxide Pentahydrate in DMSO-d_6. Tetramethylammonium hydroxide pentahydrate (ca. 150 mg) was added to 6 ml of DMSO-d_6 and warmed on a steam bath. The solution was cooled to room temperature, filtered, and titrated with standard acid. The normality was ca. 0.144. Compound 1 (104 mg, 0.419 mmol) was placed in a 10-ml volumetric flask and 2.8 ml (0.403 mmol) of this solution was added. The reaction mixture was shaken vigorously for 4 min. The solid uracilium salt dissolved and a new solid separated. Water was added and the reaction mixture was diluted to 10 ml. The uv absorption spectrum had a λ_{max} at 267 nm corresponding to an 86% yield of **3.** The mixture was evaporated in vacuo and chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. The ^1H NMR spectrum in D_2O confirmed that the compound was **3** with 15% deuterium at C-6 and less than 5% at C-5.

Reaction of 3 with Tetramethylammonium Hydroxide Pentahydrate in DMSO-d_6. Compound **3** (36.5 mg, 0.214 mmol) was placed in a 10-ml volumetric flask and 1.65 ml (0.237 mmol) of the above 0.144 *N* tetramethylammonium hydroxide solution were added. The mixture was shaken vigorously for 4 min and then 250 μl (0.25 mmol) of 1 *N* HCl was added. Next the flask was diluted to the mark with water. The uv spectrum indicated that 54% of the initial chromophore was present. The solution was evaporated in vacuo and the residue was chromatographed on 8 g of silica gel with 1:1 AcOEt–EtOH. Fractions 1–4 (3 ml) contained 46% (uv) of **3** (TLC, AcOEt). The ^1H NMR spectrum in D_2O showed that H-6 had exchanged completely and H-5 was 67% exchanged.

Reaction of 1 with Isopropylamine. 3-(β-Hydroxyethyl)-1-methyl-N^4-isopropylcytosine (9). Compound 1 (220 mg, 0.889 mmol) was added to 2 ml (23.3 mmol) of isopropylamine at room temperature. An exothermic reaction ensued and the solution boiled. The reaction mixture was evaporated in vacuo. The residue was dissolved in $CHCl_3$ and extracted with 10 ml of 0.1 *N* NaOH, dried ($MgSO_4$), and evaporated in vacuo. The residue, 184 mg (98%), was chromatographed on 7.5 g of silica gel with AcOEt to give 146 mg (78%) of material which resisted crystallization. A sample distilled in vacuo at 95–110° (5×10^{-2} mm) crystallized: mp 57–60°;[44] ir ($CHCl_3$) 2985 (w), 1690 (m), 1661 (s), 1601 (s), 1445 (m), 1431 (m), 1391 (m), 1381 (w), 1361 (m), 1340 (m), 1180 (m), 1040 (w), 980 (w), and 950 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 210 (7), 196 (46), 194 (9), 188 (7), 181 (12), 169 (32), 168 (100), 166 (22), 153 (28), 152 (60), 150 (15), 139 (10), 127 (11), 126 (53), 125 (29), 124 (16), 111 (25), 109 (17), 84 (12), 83 (14), 82 (25), and 81 (14).

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.78; H, 8.05; N, 20.10.

Reaction of 1 with Diethylamine. *trans*-2-(β-Diethylaminoethenyl)-Δ^2-oxazoline (10) and 3-(β-Diethylaminoethyl)-1-methyluracil (11). Uracilium salt 1 (238 mg, 0.96 mmol) was added to 2 ml (19.5 mmol) of diethylamine. An exothermic reaction ensued; the solution boiled and separated into two layers. After 2 hr the reaction mixture was evaporated in vacuo. The residue was dissolved in $CHCl_3$ and extracted with 3×10 ml of 1 *N* HCl. The $CHCl_3$ layer, after drying ($MgSO_4$) and evaporation, afforded 78 mg (62%) of an oil, *N,N*-diethyl-*N'*-methylurea:[45] ^1H NMR ($CDCl_3$) δ 3.92 (broad, 1, NH), 3.30 (q, 4, J_{Et} = 7 Hz, CH_3CH_2), 2.82 (s, 3, CH_3N–), and 1.15 (t, 6, J_{Et} = 7 Hz, CH_3CH_2). The acid extract was made alkaline with 1 *N* NaOH and extracted with 3×20 ml of $CHCl_3$. These extracts, after drying ($MgSO_4$) and evaporation, afforded 188 mg of an oil which contained three products (^1H NMR) in the ratio of 12, 27, and 61%. Chromatography on 30 g of silica gel (2.5% Et_3N in MeCN) separated two minor components (50 mg) from the major component (80 mg). An analytical sample of the major component, **10,** was purified by VPC: ir (film) 2980 (m), 2940 (m), 2900 (sh), 2880 (m), 1640 (s), 1470 (m), 1420 (s), 1370 (s), 1330 (w), 1265 (s), 1200 (m), 1125 (s), 1103 (sh), 1085 (w), 1040 (w), 1010 (s), 960 (s), 940 (w), 910 (w), 839 (m), and 785 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 168 (100), 153 (8), 140 (11), 139 (99), 138 (16), 137 (12), 125 (13), 112 (11), 111 (11), 110 (9), 98 (17), 96 (21), and 95 (17).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.91; H, 9.58; N, 16.81.

This compound was unstable in air and darkened quickly. Attempts to form a maleic anhydride adduct resulted in an exothermic reaction. The reaction mixture turned red, then brown, and finally to a black, carbon-like substance.[46]

The mixture of the two minor components obtained above was separated on analytical TLC plates (10% Et_3N–AcOEt). The slow-

er moving component was scraped from the plates and eluted from the silica gel with the same solvent. An analytical sample of **11** was obtained from the 35 mg (16%) of crude material by VPC: ir ($CHCl_3$) 2980 (m), 2940 (m), 2820 (m), 1712 (s), 1665 (s), 1635 (s), 1451 (s), 1440 (m), 1421 (w), 1390 (m), 1380 (m), 1355 (m), 1325 (w), 1181 (w), 1142 (m), and 1012 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 225 (7), 196 (4), 182 (4), 168 (13), 154 (27), 153 (24), 138 (6), 110 (28), 87 (21), 86 (100), 84 (15), and 82 (11).

Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.48; H, 8.49; N, 18.40.

For the third component: ^1H NMR ($CDCl_3$) δ 3.30 (s, 3, CH_3), ~3.84 and 4.30 (m, 4, CH_2CH_2), 5.76 (d, 1, $J_{5,6}$ = 8 Hz, H-5), and 6.81 (d, 1, $J_{5,6}$ = 8 Hz, H-6). After long standing on a TLC plate, the R_f of this component decreased to that of **3**.

Another sample of the two minor components (70 mg) was dissolved in 250 μl of Ac_2O. The solution was warmed briefly and then chromatographed on analytical TLC plates as described above. Compound **11** (52 mg) was unchanged. The ^1H NMR spectrum of the other component ($CDCl_3$) was δ 2.00 (s, 3, CH_3CO), 3.27 (s, 3, CH_3N), 4.34 (m, 4, CH_2CH_2), 5.69 (d, 1, $J_{5,6}$ = 8 Hz, H-5), and 6.67 (d, 1, $J_{5,6}$ = 8 Hz, H-6); uv max (95% EtOH) 280 nm (broad);[33] mass spectrum *m/e* (rel intensity) 212 (7), 196 (41), 180 (52), 169 (21), 155 (26), 154 (100), 153 (47), 152 (54), 140 (29), 139 (16), 138 (40), 127 (63), 125 (44), 123 (85), 111 (21), 87 (23), 83 (32), 82 (36), 81 (25), and 69 (21). A sample of acetylated material stored in a ^1H NMR tube for ca. 6 weeks, and from which the solvent had evaporated, was 50% transformed to **8b**.

Reaction of 1 with Pyridine. β-(1-Methyluracil-3)ethylpyridinium Mesylate (12). Compound **1** (30 mg, 0.121 mmol) was added to 300 μl of pyridine-d_5 and warmed briefly in an oil bath at 110°. The salt dissolved. The ^1H NMR spectrum was obtained and showed complete conversion to **12**, which had been fully characterized from a preparation starting with **2**.[2]

Registry No.—**1**, 54931-91-8; 1 BF_4, 54932-15-9; **2**, 54931-79-2; **3**, 1127-64-6; **4**, 54932-16-0; **5**, 54932-18-2; **6a**, 54931-87-2; **7b**, 54932-19-3; **8a**, 54932-20-6; **8b**, 54932-21-7; **9**, 54931-94-1; **10**, 54931-92-9; **11**, 54931-93-0; **12**, 54931-97-4; 1-methyluracil, 615-77-0; ethylene carbonate, 96-49-1; mesyl chloride, 124-63-0; silver tetrafluoroborate, 14104-20-2; ethanol, 64-17-5; benzoic acid, 65-85-0; isopropylamine, 75-31-0; diethylamine, 109-89-7.

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) The synthesis of **2** was undertaken in connection with studies related to the role of Michael adducts in pyrimidine chemistry. See following paper in this issue: E. G. Lovett and D. Lipkin, *J. Org. Chem.*, **40**, 1722 (1975).

(3) See, for example, (a) S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964); (b) D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, **38**, 422 (1973).

(4) Such compounds have been referred to also as ambident cations.[3a] This is a contradiction in terms if one takes into account the derivation of the word "ambident". It would be preferable to refer to such cations as dicoilate, tricoilate, etc., words which are derived from the Greek word "koilos" meaning "hollow".

(5) (a) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963); (b) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).

(6) (a) C. T. Cori, Ph.D. Thesis, Washington University, St. Louis, Mo., 1970, p 113; (b) J. A. Rabi and J. J. Fox, *J. Am. Chem. Soc.*, **95**, 1628 (1973).

(7) (a) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001 (1930); (b) M. Pyrstaš and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 1054 (1962).

(8) Spectral data for all of the compounds are presented in Tables I and II.

(9) The values λ_{max} (pH 1–14) 266 nm (ϵ 8900) have been reported for this compound by D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

(10) (a) R. N. Lacey and W. R. Ward, *J. Chem. Soc.*, 2134 (1958); (b) C. L. Angell, *ibid.*, 504 (1961).

(11) Methyl methanesulfonate has two characteristic absorption bands at 1176 and 1355 cm^{-1}. See J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1970, Spectrum 403F.

(12) The ^1H NMR resonance of the CH_3SO_3 group of ethyl methanesulfonate in DMSO-d_6 is at δ 3.10 ppm.

(13) Electrophoreses could not be run at a higher pH because of the instability of the compound.

(14) A. I. Meyers and N. Nazarenko, *J. Am. Chem. Soc.*, **94**, 3243 (1972).

(15) In sodium methanesulfonate the ^1H NMR absorption in DMSO-d_6 is at δ 2.38 ppm. In addition, as expected, there are two absorption bands in the infrared spectrum (1060 and 1200 cm^{-1}) characteristic of the sodium alkanesulfonates (~1064 and ~1198 cm^{-1}). See ref 11, Spectra 400C, D, and E.

(16) D. W. Green, F. S. Mathews, and A. Rich, *J. Biol. Chem.*, **237**, 3573 (1962); R. F. Stewart and L. H. Jensen, *Acta Crystallogr.*, **23**, 1102 (1967).

(17) This may be an unstable intermediate in the formation of **1**, but this possibility is of no concern here. See J. L. Wong and D. O. Helton, *J. Chem. Soc., Chem. Commun.*, 352 (1973).

(18) R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970).

(19) The CH_3S resonance in $(CH_3)_2S^+$–$OCH_3BF_4^-$ (DMSO-d_6), corresponding to six protons, is found at δ 3.28 ppm.

(20) The analysis could not be performed on **3** itself because in this compound the β oxygen could not be distinguished from O-4 by mass spectrometry. The analyses were performed on two derivatives, the β acetate (**8b**), which contains both oxygen atoms, and the β chloride (**4**), which contains only O-4.

(21) Note that the methoxyl derivative was unstable and was converted to **3** when an attempt was made to isolate it.

(22) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

(23) G. Ziguener, E. Fuchs, and W. Galatik, *Monatsh. Chem.*, **97**, 43 (1966).

(24) For example, the vinyl resonances in crotyl alcohol are at ca. 5.7 ppm compared to 6.13 and 6.87 ppm for the corresponding resonances in crotonaldehyde. See N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog", Varian Associates, Palo Alto, Calif., 1962, Spectra 414 and 60, respectively.

(25) H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **48**, 1746 (1965).

(26) It is not known whether in the presence of water the product is **4** or **3**.

(27) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).

(28) P. Beak and J. Bonham, *J. Am. Chem. Soc.*, **87**, 3365 (1965); P. Beak and E. M. Monroe, *J. Org. Chem.*, **34**, 589 (1969).

(29) C. Janion and D. Shugar, *Acta Biochim. Pol.*, **7**, 309 (1960); J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966); Y. Kondo, J.-L. Fourrey, and B. Witkop, *J. Am. Chem. Soc.*, **93**, 3527 (1971).

(30) H. Mizuno, H. Okuyama, H. Hayatsu, and T. Ukita [*Chem. Pharm. Bull.*, **12**, 1240 (1964)] have reported λ_{max} 285 nm (ϵ 7750) for the neutral species and λ_{max} 291 nm (ϵ 12,700) for the protonated species.

(31) G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 855, (1955); P. Brooks and P. D. Lawley, *ibid.*, 1348 (1962).

(32) D. M. Brown, M. J. E. Hewlins, and P. Schell, *J. Chem. Soc. C*, 1925 (1968). The two absorption bands for their compounds VI, VII, XII, and XV occur at 1658–1664 and 1681–1695 cm^{-1}.

(33) This assignment of structure is reasonable even though the uv spectrum of this compound disagrees with the uv spectral data reported for 2-imino-1,3-oxazines,[10a] which have ϵ ca. 2000. Our sample may have been contaminated with a small amount of **10**, which has ϵ 25,600. Lacey and Ward also state that the oxazines can be isomerized to the corresponding uracils. This is in agreement with our observations on this compound and its acetate.

(34) The values λ_{max} 270–280 nm (ϵ 19,000–26,000) have been reported by S. H. Malhotra in "Enamines: Synthesis, Structure, and Reactions", A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 42.

(35) Reference 11, Spectra 364F and G.

(36) S. Hünig and L. Geldern, *Chem. Ber.*, **96**, 3105 (1963).

(37) K. A. Watanabe, H. A. Friedman, R. J. Cushley, and J. J. Fox, *J. Org. Chem.*, **31**, 2942 (1966).

(38) C. B. Anderson, E. C. Friedrich, and S. Winstein, *Tetrahedron Lett.*, 2037 (1963).

(39) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930).

(40) T. Ukita, H. Okuyama, and J. Hayatsu, *Chem. Pharm. Bull.*, **11**, 1399 (1963).

(41) Presumably this is the spectrum of the covalent mesyl ester **2**. It is unlikely that the ionic compound **1** would volatilize as such at the probe temperature which was used.

(42) This value has been corrected for the equilibrium amounts of **1** and **2** present.

(43) Compound **7a** either has the same R_f as **3** or is converted to it by the TLC plate. No solvent system succeeded in separating them.

(44) Recrystallization did not improve the melting point. This melting range is probably due to the fact that the compound is a mixture of *E* and *Z* isomers.

(45) I. Ježo, K. Babor, and Z. Votický, *Chem. Zvesti*, **6**, 273 (1952); *Chem. Abstr.*, **48**, 8177*h* (1954).

(46) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellman, *Angew. Chem., Int. Ed. Engl.*, **5**, 875 (1966).