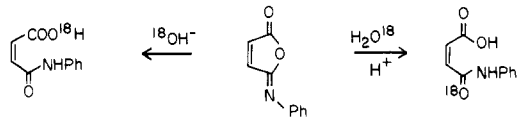
Scheme III



H (Scheme II), which should be further solvolyzed to G. Hydrolysis of G to phenylpyruvic acid is attributable to contact with trace water either in the methanolysis step or in the workup process. In acidic hydrolysis, attack of water at the imine carbon of protonated **1a** would produce (*Z*)-α-(acetylamino)cinnamic acid in the place of H, and this product is not easily converted to G.

In summary, lack of the reactivity of **2** under acidic conditions, results of the Hammett plots obtained for **1a-f**, and methanolysis products of **1a** indicate that the carbonyl carbon of the oxazolin-5-one derivatives is the site of nucleophilic attack under basic conditions, while the imine carbon is the site under acidic conditions. The hydrolysis of *N*-phenylmaleisoimide may be cited as an analogue of the present reaction. As summarized in Scheme III, the carbonyl carbon and the imine carbon were the reaction sites under basic and acidic conditions, respectively, in the hydrolysis of *N*-phenylmaleisoimide.[15]

Acknowledgment. This work was supported by the Basic Science Research Institute Program (1984), Ministry of Education, Republic of Korea.

Registry No. (*Z*)-**1a**, 38879-46-8; (*Z*)-**1b**, 66949-13-1; (*Z*)-**1c**, 94929-80-3; (*Z*)-**1d**, 93634-55-0; (*Z*)-**1e**, 93634-54-9; (*Z*)-**1f**, 71198-72-6; (*Z*)-**2**, 17606-70-1; PhCHO, 100-52-7; *p*-$NO_2C_6H_4CHO$, 555-16-8; *p*-NCC_6H_4CHO, 105-07-7; *p*-ClC_6H_4CHO, 104-88-1; *p*-MeC_6H_4CHO, 104-87-0; *p*-$MeOC_6H_4CHO$, 123-11-5; (*Z*)-PhCH=C(CO_2H)NHAc, 55065-02-6; (*Z*)-PhCH=C(CO_2H)-NHC(O)Ph, 26348-47-0; (*Z*)-PhCH=C(CO_2Me)NHAc, 60676-51-9; *N*-acetylglycine, 543-24-8.

(15) Sauers, C. K. *Tetrahedron Lett.* **1970**, 1149.

Elimination Reactions of α-Substituted Thymines Derived from Tautomeric Heterocyclic Thiols and Selenols

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Received August 27, 1984

Tautomeric heterocyclic thiols are readily alkylated by 5-(halomethyl)uracils, giving both S- and N-substituted products. S derivatives such as **19** undergo rapid elimination of thiolate anion in base, whereas the isomeric 6-substituted uracil derivatives such as **3** show no elimination. Kinetic and ^{13}C NMR studies are consistent with an elimination mechanism involving heterocyclic quinone methide intermediates, which can arise from the 5-substituted uracil derivatives but not from the 6-substituted series. The proposed mechanism is further supported by studies of the pH dependency of the elimination reaction and of the effect of substitution in the uracil ring (see Table I and Scheme II). N-Substituted (thione) derivatives such as **36** also undergo base-catalyzed elimination, but at rates some 10^5 to 10^6 times slower than those for the corresponding S derivatives when the uracil is unsubstituted on nitrogen. The high sensitivity of elimination rate to changes in the leaving group atom is attributed to a transition state in which the connecting methylene group has considerable carbocation character (see Scheme VI). Analogous derivatives (such as **42**) of tautomeric heterocyclic selenols have also been prepared, and their elimination kinetics further support this interpretation.

The importance of uracil and its derivatives as constituents of nucleic acids and related biological systems has led to extensive studies of the chemistry of pyrimidine derivatives bearing oxygen functions.[1] One interesting aspect of this chemistry concerns the relationship between uracil, thymine, and 5-(hydroxymethyl)uracil (**23**) derivatives[2] (Scheme IV). Kinetic studies[3,4] of the solvolysis of esters and *p*-nitrophenyl ethers derived from **23** suggest involvement of heterocyclic quinone methide species **20** and **21**; intermediacy of **20** has also been invoked[5] to explain the reaction of the corresponding Mannich bases[6] with aniline. A number of 5-(thiomethyl)uracil derivatives have been described,[7] but the possibility of solvolysis involving quinone methide species in this series appears not to have been addressed. Our interest in protective groups for heterocyclic thiols and photographically useful materials[8] led us to investigate the chemistry of the thioethers derived from alkylation by 5-(chloromethyl)uracils. We report here our findings, which not only demonstrate that such thioethers undergo base-catalyzed elimination of thiolate anions but also provide strong evidence for a mechanism involving heterocyclic quinone methide species.

Results and Discussion

Thioethers Derived from 1-Phenyl-1,2,3,4-tetrazole-5-thiol and 5- and 6-(Chloromethyl)uracils. 5-

† Principle Author. Deceased January 19, 1984.

(1) Brown, D. J. "The Pyrimidines"; New York, 1962; pp 256-258. See also: "The Pyrmidines", Supplement I, Wiley: New York, 1970, pp 193-198. Bradshaw, T. K.; Hutchinson, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.

(2) For further discussions related to the possible biological implications of these relationships see: Green, M.; Barner, H. D.; Cohen, S. S. *J. Biol. Chem.* **1957**, *228*, 621. Kallen, R. G.; Simons, M.; Marmur, J. *J. Mol. Biol.* **1962**, *5*, 248. Charlton, P. A.; Young, D. W. *Chem. Commun. J. Chem. Soc.* **1980**, 614.

(3) Pogolotti, A. L.; Santi, D. V. *Biochemistry* **1974**, *13*, 456.

(4) Santi, D. V.; Pogolotti, A. L. *J. Heterocycl. Chem.* **1971**, *8*, 265.

(5) Asherson, J. L.; Bilgic, O.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 522.

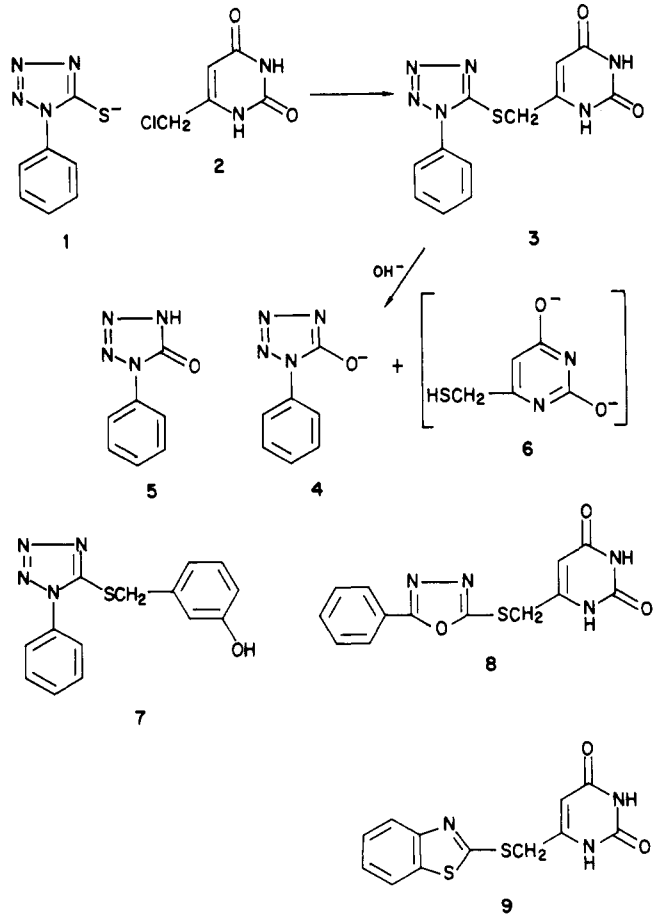
(6) Burckhalter, J. H.; Seiwald, R. J.; Scarborough, H. C. *J. Am. Chem. Soc.* **1960**, *82*, 991. Delia, Scovill, W. D.; Munslow, Burckhalter, J. H. *J. Med. Chem.* **1976**, *19*, 344.

(7) Giner-Sorolla, A.; Medrek, L. *J. Med. Chem.* **1966**, *9*, 97.

(8) Bartels-Keith, J. R.; Puttick, A. J. U.S. Pat. 4350754 and 4442290.

0022-3263/85/1950-0980$01.50/0

Scheme I



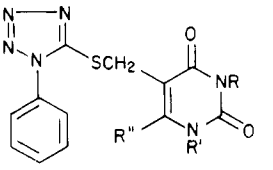
(Chloromethyl)uracil reacts readily with 1-phenyl-1,2,3,4-tetrazole-5-thiolate anion (1) under mild conditions to give the thioether **19**, which undergoes exceedingly rapid elimination of anion **1** in base. In 0.25 N KOH in 30% aqueous acetonitrile at 22 °C the pseudo- first-order rate constant k' was 146 s^{-1}, corresponding to a half-life of 4.7 ms. This result was in accord with our expectation that **19** would undergo an elimination reaction involving the intermediacy of a heterocyclic quinone methide species **22** (Scheme IV) analogous to the homocyclic quinone methide species proposed by Taylor, Grasshof, and Pluhar[9] to explain the rapid base-induced solvolysis of thioethers.

In an effort to throw some light on the fate of the proposed intermediate **22**, we examined the ^{13}C NMR spectrum of a solution of thioether **19** in 2.5 N sodium hydroxide. Under these conditions, lines due to **1** are observed together with a number of broader, weaker lines in roughly the expected positions for anionic species derived from a 5-substituted uracil. A similar pattern of lines is seen in the ^{13}C NMR spectrum of 5-(hydroxymethyl)uracil (**23**) in 2.5 N sodium hydroxide, whereas in Me_2SO-d_6 this compound gives the expected five sharp lines in the ^{13}C NMR spectrum. The dianion of 5-(hydroxymethyl)uracil might be expected to result from the attack of hydroxide ion on the quinone methide **22**, but the weak ^{13}C NMR signals shown by both alkaline solutions suggest polymeric products, or, possibly, a dynamic equilibrium involving several ionic species.

Similar results were obtained when **19** was dissolved in 0.96 N tetrabutylammonium hydroxide in methanol. The presence of a line at 67.2 ppm suggests trapping of the reactive intermediate **22** by methoxide ion.

(9) Taylor, L. D.; Grasshof, J. M.; Pluhar, M. *J. Org. Chem.* **1978**, *43*, 1197.

Table I. Effect of Substitution on Pseudo-First-Order Elimination Rate Constant k' (s^{-1}; 0.25 N KOH in 30% Acetonitrile–Water at 22 °C) for 19 and Its Derivatives



	R	R′	R″	k'
19	H	H	H	146
24	CH_3	H	H	0.86
25	n-C_4H_9	H	H	1.46
26	H	CH_3	H	$<5 \times 10^{-5}$
27	CH_3	CH_3	H	$<5 \times 10^{-5}$
28	H	H	CH_3	608

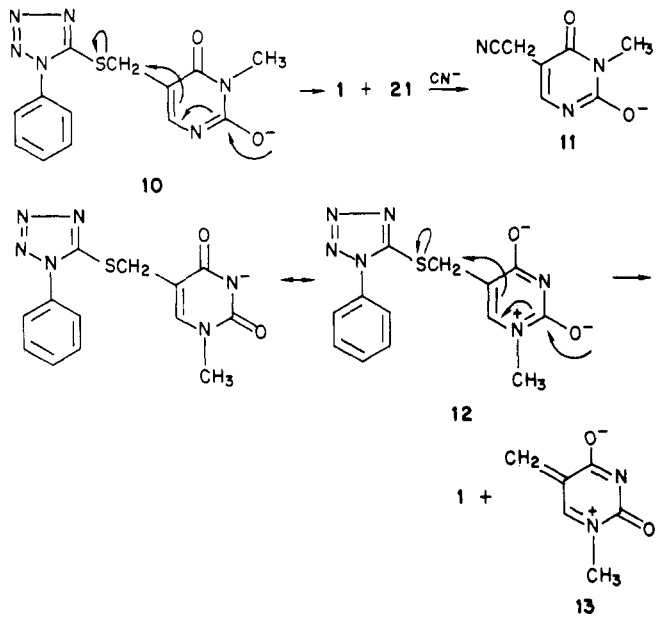
In contrast, the isomeric thioether **3**, readily prepared from anion **1** and 6-(chloromethyl)uracil (**2**), did not undergo base-catalyzed elimination. The ^{13}C NMR spectrum of a solution of **3** in 0.96 N tetrabutylammonium hydroxide in methanol showed the expected lines for an intact anionic species (Scheme I). After standing for 24 h, however, the sample showed new lines, due to slow attack by hydroxide ion at the tetrazole C-5 to give the anion **4** of 1-phenyl-5-1*H*-tetrazolone (**5**). The free tetrazolone was isolated on acidification. The other expected reaction product **6** apparently underwent further decomposition and was not isolated. This behavior is reminiscent of that of the *m*-hydroxybenzyl thioether **7** described by Taylor, Grasshof, and Pluhar,[9] and it is significant that it is impossible to derive a quinone methide elimination product from either **3** or **7**. The analogous 1,3,4-oxadiazole derivative **8** behaved like **3**, while **9** was stable in 2.5 N sodium hydroxide at room temperature.

Returning to thioether **19**, we next attempted to trap the quinone methide intermediate using an excess of cyanide ion. We theorized that while cyanide should add readily to a species such as **22**, the resulting adduct should be stable in alkali. 2.5 N Sodium hydroxide was added to a sample of **19** which had been overlaid with a fivefold molar excess of solid sodium cyanide. The ^{13}C NMR spectrum of the resulting solution again showed evidence of complete elimination, but in this case additional lines were observed. Single-frequency off-resonance decoupling (SFORD) showed that these lines were due respectively to two nonprotonated carbons and to a methylene group. Spectra of models indicate that the observed chemical shifts are consistent with formation of 5-(cyanomethyl)-uracil anion or a related species.

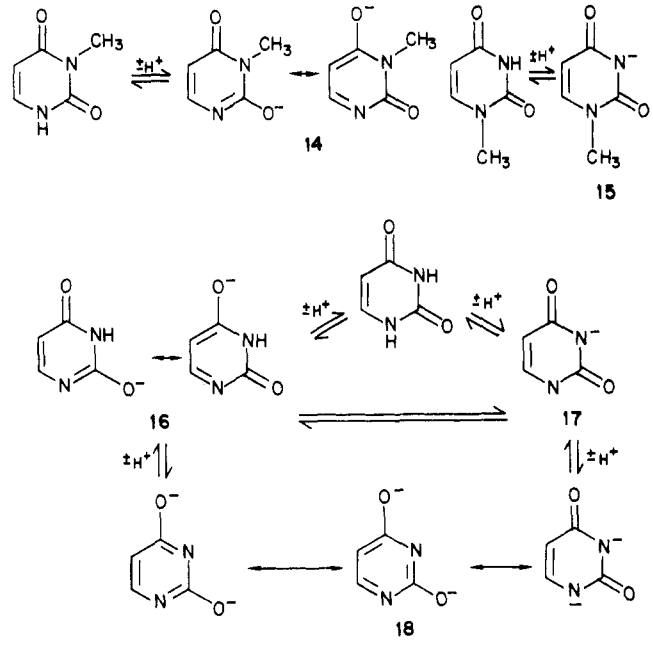
Thioether **19** also reacted readily with sodium borohydride in DMF-diglyme–water at room temperature; isolation furnished 1-phenyl-2-tetrazoline-5-thione and thymine. The formation of thymine is consistent with the trapping of a quinone methide species such as **20** with hydride ion. Santi and Pogolotti[4] reported the production of thymine on similar borohydride reduction of 5-[(4-nitrophenoxy)methyl]uracil. There is thus considerable support for the postulated intermediacy of quinone methide species in solvolyses of this type.

Thioethers Derived from Substituted 5-(Chloromethyl)uracils. The study of analogues of **19** bearing N substituents is summarized in Table I. Thioethers **24**, **25**, **26**, **27**, and **28** were prepared from the known substituted uracils. **24** underwent elimination, though at a rate about 170 times slower than that for **19**. **25** behaved similarly, but neither **26** nor **27** showed elimination at an observable rate under the conditions we employed. On the other

Scheme II



Scheme III

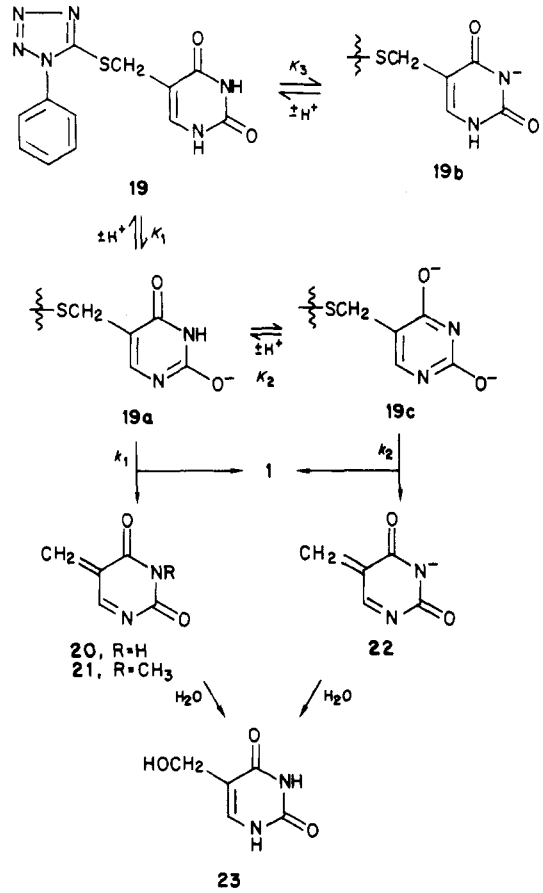


hand, substitution on C-6 of the uracil ring (**28**) led to a modest increase in rate, suggesting some degree of steric acceleration or stabilization of an incipient carbocation by the electron-releasing methyl group.

These findings, too, are consistent with the intermediacy of heterocyclic quinone methide species (see Scheme II). When N-3 is substituted, rapid elimination can still occur, since the anion **10** can proceed to the neutral intermediate **21**. An in fact **24** on treatment with sodium hydroxide in the presence of an excess of cyanide ion gave a solution whose ^{13}C NMR spectrum was consistent with the presence of the cyanomethyl derivative **11** and suggestive of the intermediacy of **21**. Substitution of N-1, in contrast, gives a structure which is much less favorable for elimination. Reaction should proceed only slowly, if at all. Even though formation of a mesoionic quinone methide species **13** is theoretically possible, the redistribution of charge necessary to reach it implies a high-energy pathway. These findings essentially rule out alternative mechanisms such as S_N2 displacement of thiolate anion by hydroxide, since they demonstrate that ready elimination can occur only when the uracil moiety can be deprotonated at the 1-NH site.

But we must still account for the large difference in reactivity between **19** and **24**. The concentration of KOH normally used in our studies (0.25 N) corresponds to a pH of 13.4. Uracil itself is a weak dibasic acid with pK_a values of 9.72 and 14.16.[10] For thymine the corresponding values are 10.04 and 14.65,[11] and for 3-methyluracil a pK_a value of 10.00 has been reported.[12] For **19**, these values imply a mixture of monoanion and dianion in 0.25 N KOH and suggest the possibility that both species may be undergoing elimination. For the 3-methyl analogue **24**, of course, the reactive species must be the monoanion. Studies of pH dependence of rate for these compounds have helped to clarify the various processes involved, but before discussing these results it would be helpful to consider the proton equilibria of uracils in more detail.

Scheme IV



On the basis of UV studies Nakanishi and his co-workers[12] deduced that 3-methyluracil gives rise to conjugated oxygen anion **14**, whereas 1-methyluracil gives nitrogen anion **15** in which the negative charge is stabilized by the two adjacent carbonyls (see Scheme III). Uracil itself gives rise to an equilibrium mixture of two monoanions, **16** and **17**, corresponding to **14** and **15**, respectively. More recently, DeMember and Wallace[10] have studied the proton equilibria of uracil by ^{13}C NMR. Their results confirm the symmetrical distribution of charge implied by the foregoing

(10) DeMember, J. R.; Wallace, F. A. *J. Am. Chem. Soc.* **1975**, *97*, 6240.
(11) Shugar, D.; Fox, J. J. *Biochim. Biophys. Acta* **1952**, *9*, 199. Reexamination of their UV spectral data furnished the pK_a values quoted.
(12) Nakanishi, K.; Suzuki, N.; Yamazaki, F. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 53.

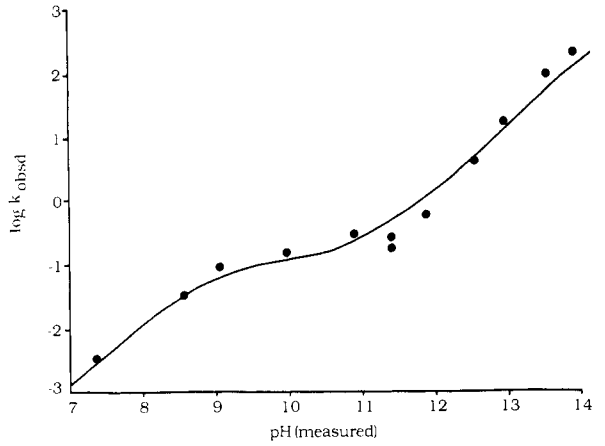


Figure 1. pH dependence of elimination for **19** (30% acetonitrile–water at 22 °C): circles represent experimental values of log k_{obsd} (s^{-1}): solid line represents computed curve for best fit using eq 1.

scheme for the monoanion. In addition, they provide strong evidence for extensive delocalization—and hence aromaticity—for the dianion **18**, here represented by three canonical structures.

On this basis we propose the following scheme for the elimination reactions of **19** (Scheme IV). Of the two possible monoanionic species, one is an oxygen anion (**19a**) formed by deprotonation at N-1 (dissociation constant K_1), which can undergo elimination (rate constant k_1) like the analogous 3-methyl-substituted **24**. The other is a *nitrogen* anion (**19b**) formed by deprotonation at N-3 (dissociation constant k_3), which, like the analogous 1-methyl-substituted **26**, should not readily undergo elimination. Further dissociation (constant K_2) leads to the dianion **19c**, for which k_2 is the elimination rate constant. If **19a** and **19c** are the only species undergoing reaction, then the observed rate k_{obsd} should be related to the hydrogen ion activity {H} by the derived relationship 1.

$$k_{obsd} = \frac{k_1K_1\{H\} + k_2K_1K_2}{\{H\}^2 + (K_1 + K_3)\{H\} + K_1K_2} \quad (1)$$

In Figure 1 are shown the data for the pH dependence of elimination for **19**, together with the computed curve for best fit using eq 1. The latter yields the following values for the constants: k_1, 0.35 s^{-1}; k_2, 5000 s^{-1}; pK_1, 9.4; pK_2, 15.1; and pK_3, 9.1. Thus, the very rapid elimination observed for **19** in 0.25 N KOH in 30% acetonitrile–water is due primarily to the dianion, even though dissociation to this species has proceeded only to a modest extent. The much lower rate constant (k_1) observed for the monoanion should be compared with the pseudo-first-order rate constant ($k' = 0.86$ s^{-1}) observed for **24** in 0.25 N KOH in 30% acetonitrile–water.

The pH dependence of elimination for **24** was consistent with the proposed mechanism (Scheme II), though deviations from simple pseudo-first-order kinetics were observed below pH 12, precluding generation of a satisfactory pH dependence curve. Passage of nitrogen through the solutions before running the experiments resulted in a closer approximation to pseudo-first-order kinetics, suggesting that the observed deviations might be dependent on the presence of oxygen. The pH dependence of elimination for the 1,3,4-oxadiazole derivative **33** (see Table II) showed similar characteristics. Further analysis of the data was attempted, but a satisfactory fit to a coherent mechanistic scheme could not be achieved. However, when a similar study of pH dependence of elimination for **33** was carried out in oxygen-free 0.25 N KOH in 2% acetonitrile–water, and absorbance measured at 320 nm, deviations from pseudo-first-order kinetics were greatly reduced, and an acceptable fit of the observed data to an A → B → C scheme was obtained by using eq 2, where k is

$$\text{for A} \rightarrow \text{B}, \; k_{obsd} = \frac{kK}{\{H\} + K} \quad (2)$$

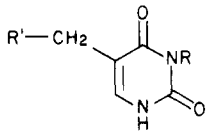
the unimolecular rate constant and K the dissociation constant for deprotonation of the substrate, and eq 3,

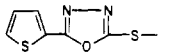
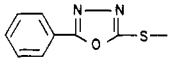
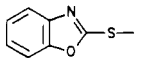
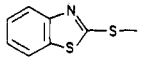
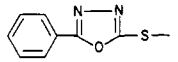
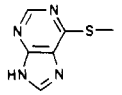
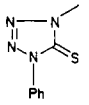
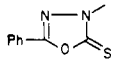
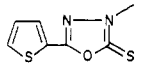
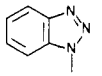
$$\text{for B} \rightarrow \text{C}, \; k_{obsd} = k''\{OH\}^n \quad (3)$$

where k'' is the bimolecular rate constant for reaction of a labile intermediate with hydroxide ion and {OH} the hydroxide ion activity.

In Figure 2 are shown the data for the pH dependence of both reactions, together with the computed curves for best fit using eq 2 and 3. The slower reaction (A → B; Figure 2a) corresponds to elimination of the 1,3,4-oxadiazole-2-thiolate anion (cf. Scheme IV), while the faster reaction (B → C, Figure 2b) is believed to be due to solvolysis of the quinone methide intermediate **21**, although the value of n was approximately 0.45, suggesting that other reactions, including readdition of thiolate anion to **21**, may also be involved.

Table II. The Effect of Leaving Group. Pseudo-First-Order Rate Constants k' (s^{-1}; 0.25 N KOH in 30% Acetonitrile–Water at 22 °C)



	R′	R	k′
29		H	636
30		H	395
31		H	631
32		H	10.2
33		CH_3	4.31
34		H	$<5 \times 10^{-5}$
35		H	0.0089
36		H	0.000 77
37		H	0.000 639
38		H	0.000 16
39		CH_3	0.000 458
40		H	no elimination

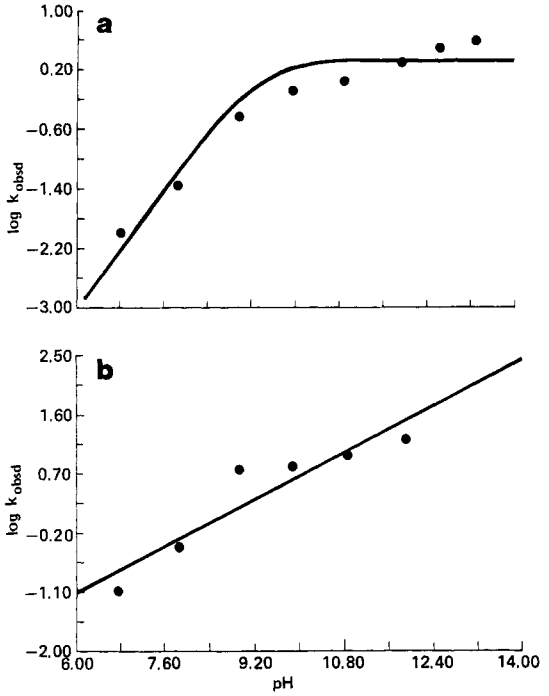


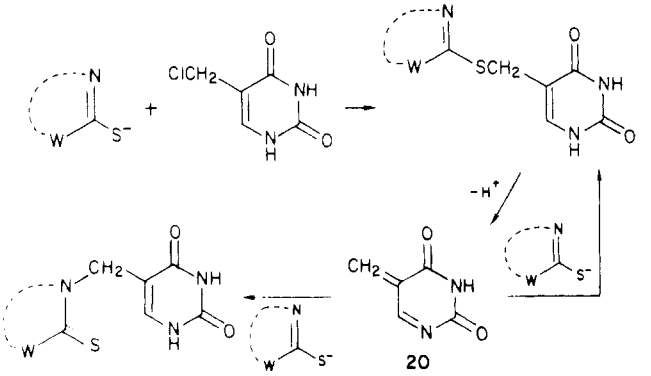
Figure 2. pH dependence of elimination for **33** (oxygen-free 2% acetonitrile–water at 22 °C): Circles represent experimental values of log k_{obsd} (s^{-1}), (a) A → B reaction (elimination); solid line represents computed curve for best fit using eq 2, (b) B → C reaction. Solid line represents best straight line on basis of eq 3.

These observations suggest that molecular oxygen reacts with the quinone methide species **21**. Although rapid destruction of **21** would be expected at high hydroxide ion concentrations, the lifetime of **21** at pH 12 and below may be sufficient to permit observation of other reactions of this species. UV absorption studies[13] of some isolable quinone methides suggest that at an observing wavelength of 300 nm the kinetic measurements could be responsive to reactions of quinone methide species as well as to the elimination of thiolate anion. The UV absorption of **33** permits kinetic observations at 320 nm, a wavelength expected to be less sensitive to the presence of quinone methide species. In addition, the use of 2% acetonitrile–water as solvent might be expected to result in lower concentrations of molecular oxygen. In contrast, the pseudo-first-order kinetics uniformly observed in the pH dependence studies for **19** imply extremely short lifetimes for the quinone methide species **20** and **22** at all pH values.

The large difference in elimination rate between the dianion of **19** and the monoanions of **19** and **24** may be attributed to the following factors: (1) charge repulsion in the dianion, and (2) a higher degree of delocalization in the dianion as compared to the monoanions, which possess a conjugated but nonaromatic ring system. This latter consideration has important implications for the structure of the transition state, a point to which we shall return later.

Temperature–rate studies, carried out in 0.25 N KOH in 30% acetonitrile–water, furnished linear plots for both **19** and **24**. For **19**, activation parameters were calculated from a plot of log k' against $1/T$ for three reactions carried out from 15.4 to 24.6 °C and took into account variation of pK_2 and K_w with temperature, giving $\Delta H^{\ddagger}$ = 26.3 kcal/mol and $\Delta S^{\ddagger}$ = 17.8 eu. These values refer to k_2, since

Scheme V



the contribution of k_1 to the observed rate in this medium is essentially negligible. For **24**, dissociation to form the anion is complete in 0.25 N KOH, so that no correction for proton equilibria was required, and calculated values were $\Delta H^{\ddagger}$, 19.3 kcal/mol, and $\Delta S^{\ddagger}$, 8.9 eu. These values strongly support unimolecular elimination of the anion as the rate-determining step for both the dianion of **19** and the monoanion of **24**.

Thioethers Derived from Heterocyclic Thiols Other Than Tetrazoles. Synthesis and study of similar uracil derivatives containing a wide variety of heterocyclic thiol residues suggests that this elimination reaction is a general one, though there is considerable variation in rates (Table II). Although some differences in rate may merely reflect small variations in the second ionization constant, and hence the active mass of the dianion, the range of variation observed suggests considerable sensitivity of rate to the structure of the heterocyclic thiol residue. The anomalously low rates of **34** and **35** are illustrative (Table II). That these materials are indeed S derivatives (thioethers) and not N derivatives (thiones) is shown by their ^{13}C NMR spectra. Earlier work in our laboratory[14] has shown the diagnostic value of ^{13}C NMR for studies of S vs. N substitution in derivatives of tautomeric heterocyclic thiols. The carbon attached to sulfur absorbs at consistently higher field for the S derivative than for the corresponding N derivative, even though the chemical shifts observed vary considerably among different heterocyclic systems. Since the starting thiols generally exist in solution as their thione tautomers, structural assignment is usually straightforward. In addition, the methylene group absorbs in the region 26–30 ppm for S derivatives but near 45 ppm for N derivatives.

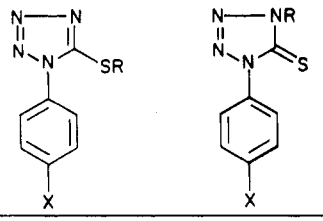
It is significant, however, that **34** and **35** possess additional acidic functions on the heterocyclic thiol residue. Deprotonation at these sites would be expected to inhibit elimination, since the elimination product should be a dianion. The magnitude of this effect should depend on the position of the additional acidic site relative to that of the thioether function, and this expectation is confirmed by the higher reactivity observed for **35** as compared to **34**.

N-Substituted Derivatives of Heterocyclic Thiols. We have also studied derivatives of heterocyclic thiols where the uracil moiety is attached to nitrogen. The structures of these N-substituted derivatives were unambiguously confirmed by their ^{13}C NMR spectra. While the tendency to form such N derivatives varies considerably with the nature of the starting heterocyclic thiol, formation of the N derivative is generally favored by vigorous reaction

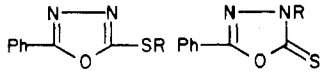
(13) Pospisek, J.; Pisova, M.; Soucek, M. *Collect. Czech. Chem. Commun.* **1975**, *40* 142.

(14) Bartels-Keith, J. R.; Burgess, M. T.; J. M. Stevenson, J. M. *J. Org. Chem.* **1977**, *42*, 3725.

Table III. Michael Adducts of Heterocyclic Thiols: Pseudo-First-Order Elimination Rate Constants for S (k'_S) and N Isomers (k'_N) (s^{-1}; 0.25 N KOH in 30% Acetonitrile–Water at 22 °C)



R	X	k'_S	k'_N	k'_S/k'_N
$CH_2CH_2COCH_3$	H	2.21	0.64	3.5
$CH_2CH_2COCH_3$	SO_2NH_2	2.14	0.70	3.1
$CH_2CH_2SO_2CH_3$	SO_2NH_2	0.74	0.016	46



R	k'_S	k'_N	k'_S/k'_N
$CH_2CH_2SO_2Ph$	2.52	0.010	250

conditions and also by the presence of an excess of base or thiolate anion. It is possible that the initial product is the kinetically favored S derivative, which subsequently undergoes base-catalyzed rearrangement to the thermodynamically favored N derivative. Formation and subsequent capture of a quinone methide intermediate such as **20** may well be involved (see Scheme V).

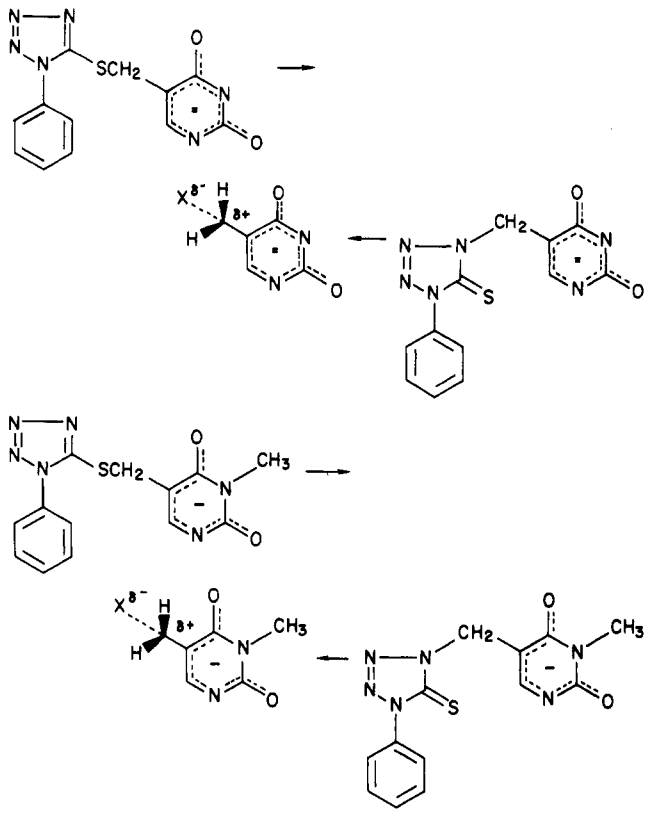
These N derivatives exhibited surprising kinetic behavior, elimination rates being 10^5–10^6 times slower than those of the corresponding S isomers when the uracil ring is unsubstituted in the 3-position (Table II). The presence of a 3-methyl group results in a smaller ratio of rates—about 2000; but this is still larger than is generally observed for S and N Michael adducts[15] of similar thiols (ratios in the range 3–250) (Table III). Nevertheless a ^{13}C NMR study of the solvolysis of **36** in a NaOH/NaCN medium gave results similar to those obtained for **19** (see above) and consistent with the same mechanism. In line with these findings, **40** showed no elimination of benzotriazole anion in our experimental system.

Leaving Group Ability and the Transition State. The extensive investigations of Stirling and his collaborators[16] show that leaving group ability (or nucleofugality) varies in general according to the group (in the periodic table[26]) of the connecting atom, decreasing in the order group 16 (VI) (O, S, Se) > 15 (V) (N, P) > 14 (IV) (C). They also show the absence of a simple relationship of leaving group ability to the pK_a of that group's conjugate acid. But of special significance for our present purposes is Stirling's discussion of the sensitivity of various mechanistic pathways to changes in leaving-group ability.

Comparison of isomeric S and N derivatives of heterocyclic thiols has the advantage that the leaving group—the thiolate anion—is the same in both reactions, thus providing a direct comparison of the effects of different connecting atoms on leaving group ability. While it is not surprising that the S isomer undergoes elimination faster than the N isomer, the ratio of elimination rates actually observed, k'_S/k'_N, depends on the sensitivity of the elimination pathway to changes in leaving-group ability, and this in turn depends on the structure of the transition state.

Elimination reactions of S and N Michael adducts of heterocyclic thiols appear to proceed by an E1cB mechanism,[17] in which reversible deprotonation leads to the conjugate base, which in turn collapses to alkene and leaving group (X). For such reactions Stirling's data[16] imply relatively little C–X bond extension in the transition state. The sensitivity of the elimination rate should be negligible in the absence of C–X bond extension [$(E1cB)_I$ mechanism] but may be appreciable if a small degree of C–X bond extension occurs [$(E1cB)_R$ mechanism]. The observed rates for S and N Michael adducts (Table III) are consistent with this general description, suggesting reaction pathways intermediate between the $(E1cB)_I$ and $(E1cB)_R$ cases.

Scheme VI



If we extend this reasoning to the uracil derivatives in our present study, it would follow that for these materials the C–X bond extension in the transition state should be considerable in order to account for the large values of k'_S/k'_N observed. We suggest that this bond extension is the result of the 5-methylene group, acquiring a partial positive charge which is stabilized by the adjacent electron-rich delocalized system of the uracil ring (see Scheme VI). For the highly delocalized dianion in **19** and **36** this effect should be large. For the 3-methyl-substituted **24** and **39**, for which the monoanion is a less extensively delocalized system, the effect should be smaller but still appreciable. The observed values of k'_S/k'_N for **19** and **36** and for **24** and **39** are in accord with this interpretation.

There is precedent for the stabilization of an incipient (or actual) carbocation by an adjacent delocalized system in the ready solvolysis of benzyl halides, particularly those bearing electron-releasing substituents in the ortho or para position, e.g., *p*-methoxybenzyl chloride.[18] Indeed, this ability of the uracil ring to stabilize a carbocation attached

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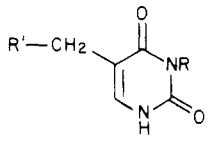
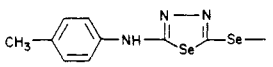
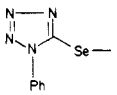
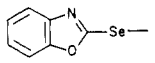
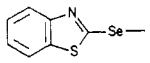
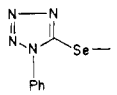
(16) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.
(17) For discussions of the classification of alkene-forming elimination reactions, see: Saunders, W. H. *Acc. Chem. Res.* **1976**, *9*, 19. Aleskerov, M. A.; Yufit, S. S.; Kucherov, V. F. *Usp. Khim.* **1978**, *47*, 235. Bartsch, R. A.; Zavada, J. *Chem. Rev.* **1980**, *80*, 453.
(18) Altscher, S.; Baltzly, R.; Blackman, S. W. *J. Am. Chem. Soc.* **1952**, *74*, 3649.

Table IV. Pseudo-First-Order Elimination Rate Constants for Selenoethers (k', s^{-1}; 0.25 N KOH in 30% Acetonitrile–Water at 22 °C)



	R'	R	k'
41		H	0.014
42		H	139[a]
43		H	940
44		H	172
45		CH_3	4.5

[a] Measured in 0.022 N KOH in 30% acetonitrile–water; the rate found corresponds to an extrapolated value of 1580 s^{-1} in 0.25 N KOH.

to the 5-position may also account for the high reactivity of 5-(chloromethyl)uracil as an alkylating agent.

Selenoethers Derived from 5-(Chloromethyl)uracils and Heterocyclic Selenols. The 1,3,4-selenadiazole derivative **41** showed surprisingly slow elimination ($k' = 0.014\ s^{-1}$ in 0.25 N KOH in 50% aqueous ethanol). The observed rate suggests that the NH group attached to the selenadiazole ring may be just acidic enough to inhibit formation of the selenolate ion—an effect analogous to that already noted for derivatives of thiols bearing additional ionizable groups.

In view of the limited availability of this and related selenols and the problems involved in handling them, we turned our attention to sequences in which the isolation of free selenols could be avoided (See Experimental Section). For these selenoethers (see Table IV) elimination is about an order of magnitude faster than that for their thioether analogues, **42** showing the fastest elimination so far seen in this series. This rate enhancement is consistent with the interpretation put forward earlier, since the weaker C–Se bond (relative to the C–S bond) should further increase bond extension in the transition state.

Experimental Section

Except as noted, all kinetic measurements were carried out in 0.25 N KOH in 30% acetonitrile–water at 22 °C, the course of the reaction being followed by UV. For fast reactions such as that of **19** a Durrum stopped-flow apparatus was employed, while slow ($t_{1/2} > 10$ min) reactions were followed on a Cary 14 spectrophotometer. Although the measured absorbances were clearly due to the UV absorption of several species, values of rate constants were reproducible to within ±5% except for some of the fastest reactions ($k' > 500\ s^{-1}$). In all cases quoted values of k' represent the average of at least three determinations. The course of reactions was further checked by acid-quenching aliquots of the reaction mixture at various intervals and analyzing their composition by TLC. The structure and purity of each compound synthesized was determined by ^{13}C NMR (Varian CFT 20), ^1H NMR (Varian EM-390), IR (Perkin-Elmer 727), and UV (Cary 14). Total microanalysis on all compounds synthesized was performed by Galbraith Laboratories, Inc., Knoxville TN. All recorded melting points are uncorrected.

5-[[(1-Phenyl-1,2,3,4-tetrazol-5-yl)thio]methyl]uracil (19). 5-(Chloromethyl)uracil[19] (2.0 g, 0.0125 mol) was added under nitrogen to a stirred solution of sodium 1-phenyl-1,2,3,4-tetrazole-5-thiolate (2.5 g, 0.0125 mol) in dimethylformamide (DMF, 25 mL). Stirring was continued for 10 min, after which the mixture was poured into ice water (150 mL) containing acetic acid (1 mL). The resulting precipitate was collected, washed first with water and then with methanol, and dried in air, giving a product with mp 215–216 °C dec (3.05 g, 81%). A similar procedure was used to prepare the following compounds: **24**, 92%, mp 223–224 °C; **26**, 95%, mp 193–194 °C; **27**, 19%, mp 197 °C; **28**, 73%, mp 208 °C; **30**, 53%, mp 299–300 °C; **33**, 82%, mp 257–259 °C.

6-[[(1-Phenyl-1,2,3,4-tetrazol-5-yl)thio]methyl]uracil (3). A mixture of sodium 1-phenyl-1,2,3,4-tetrazole-5-thiolate (4.0 g, 0.020 mol), 6-(chloromethyl)uracil (3.2 g, 0.020 mol), and ethanol (2B; 100 mL) was stirred under reflux in an atmosphere of dry nitrogen for 16 h. The resulting mixture was poured into ice water (300 mL), and the pale yellow solid was collected, washed with water, and dried in air, mp 203–204 °C dec (5.0 g, 83%).

When dry DMF (20 mL) was used as the solvent in place of ethanol, the same quantities of reactants on warming (steam bath) for 0.75 h and subsequent precipitation into ice water (200 mL) gave a product, mp 200–202 °C dec (4.6 g, 76%), identical (IR spectrum) with the foregoing material. The two products when combined and recrystallized from a mixture of 2-propanol (50 mL) and 2-methoxyethanol (70 mL) gave material with mp 212–214 °C dec (6.1 g, 50%). A similar procedure (DMF) was used to prepare the following compounds: **8**, 60%, mp 264–265 °C; **9**, 64%, mp 290–292 °C.

3-*n*-Butyl-5-[[(1-phenyl-1,2,3,4-tetrazol-5-yl)thio]methyl]uracil (25). Paraformaldehyde (1.0 g, 0.033 mol) was added with stirring to a mixture of 3-*n*-butyluracil (1.7 g, 0.010 mol) and hydrobromic acid (10 mL, 48%), and the mixture was heated at 60 °C for 15 min. The resulting orange solution was stirred for a further 4 h at room temperature and then evaporated to dryness overnight in a stream of nitrogen. The oily residue was taken up in DMF (20 mL), and sodium 1-phenyl-1,2,3,4-tetrazole-5-thiolate (2.0 g, 0.010 mol) was added. The mixture was then stirred in an atmosphere of nitrogen for 15 min, after which it was poured into ice water (100 mL) and the supernatant decanted. The residual gum crystallized after standing for 1 month. Recrystallization from 2-propanol gave a pale yellow product, mp 140–143 °C (1.22 g).

5-[[[5-(2-Thienyl)-1,3,4-oxadiazol-2-yl]thio]methyl]uracil (29). A mixture of 5-(2-thienyl)-1,3,4-oxadiazole-2-thiol[25] (0.92 g, 0.0050 mol), sodium methoxide (0.31 g, 0.0057 mol), and DMF (10 mL) was stirred at 80 °C under nitrogen for 5 min. To the resulting clear yellow solution was added 5-(chloromethyl)uracil (0.80 g, 0.0050 mol), and stirring was continued for a further 30 min at 80 °C. The resulting mixture was poured into ice water (100 mL) with stirring, and the solid was collected and washed successively with water, methanol, and ether, and air-dried. The product had mp 297–298 °C dec (1.29 g, 84%). A similar procedure was used to prepare the following compounds: **31**, 31%, mp 310–313 °C; **32**, 38%, mp 290–300 °C; **34**, 84%, mp 252–260 °C; **35**, 88%, mp 283–286 °C.

5-[(1-Phenyl-5-thioxo-2-tetrazolin-4-yl)methyl]uracil (36). A mixture of 5-(chloromethyl)uracil (3.0 g, 0.019 mol), sodium 1-phenyl-1,2,3,4-tetrazole-5-thiolate (9.0 g; 0.045 mol), sodium methoxide (0.1 g), and DMF (100 mL) was stirred under nitrogen at 80–90 °C for 4 h, and the mixture was treated with ice water (50 mL), giving a solid which was collected, washed with water, and dried in air. The crude product, mp 213–217 °C dec, on

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(24) Pfleiderer, W.; Schundehutte, K.-H. *Liebigs Ann. Chem.* **1958**, *612*, 158.
(25) Turilli, O.; Gandino, M. *Ann. Chim.* (Rome) **1963**, *53*, 1685; *Chem. Abstr.* **1964**, *60*, 13245c.
(26) The group notation is being changed in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is being eliminated because of wide confusion. Group I becomes groups 1 and 11, group II becomes groups 2 and 12, group III becomes groups 3 and 13, etc.

recrystallization from 2-methoxyethanol–water mixture, gave a crystalline product, mp 234 °C dec (2.6 g, 45% based on 5-(chloromethyl)uracil). The following compounds were prepared in a similar manner: (**37**, 54%, mp 294–297 °C; **38**, 75%, mp 286–288 °C; **39**, 52%, 223 °C.

5-[(1,2,3-Benzotriazol-1-yl)methyl]uracil (40). 5-(Chloromethyl)uracil (1.0 g, 0.0062 mol), 1,2,3-benzotriazole (0.8 g, 0.0067 mol), and triethylamine (0.65 g; 0.0065 mol) were dissolved in dry DMF (20 mL), and the resulting clear solution was stirred at 65 °C (oil bath). Solid appeared after 5 min. After 1 h the mixture was cooled and the solid (triethylamine hydrochloride) collected. The filtrate on dilution with ether (250 mL) gave a slightly sticky solid which was collected and recrystallized from water (100 mL), giving a product with mp 268–269 °C (0.20 g).

5-[[[5-(*p*-Toluidino)-1,3,4-selenadiazol-2-yl]seleno]methyl]uracil (41). All operations were performed in an atmosphere of nitrogen and in subdued light. Due to the toxicity of possible volatile selenium byproducts, a well-ventilated hood was used. A solution of 5-(*p*-toluidino)-1,3,4-3*H*-selenadiazoline-2-selone[13] (158.6 mg, 0.50 mmol) in DMF (1 mL) was filtered through Celite into a stirred suspension of sodium methoxide (27.0 mg, 0.50 mmol) in DMF (1 mL). The Celite pad was washed with additional DMF (1 mL) and the washings were also added to the foregoing suspension. Stirring was continued for 30 min, after which the resulting clear orange-yellow solution was syringed dropwise into a stirred solution of 5-(chloromethyl)uracil (80.3 mg, 0.50 mmol) in DMF (2 mL) at 0 °C (ice bath) during 10 min. Stirring at 0 °C was continued for an additional 5 min, after which the reaction mixture was added dropwise to deaerated water (40 mL). The resulting solid was collected, washed thoroughly with water, and dried under vacuum, giving the hemihydrate of **41** as a pale yellow solid (192.0 mg, 85%), mp 230–232 °C dec.

5-[[(1-Phenyl-1,2,3,4-tetrazol-5-yl)seleno]methyl]uracil (42). All operations were performed in an atmosphere of nitrogen and in subdued light. 5-Chloro-1-phenyl-1,2,3,4-tetrazole (1.8 g, 0.010 mol) was added to a vigorously stirred suspension of finely divided sodium selenide (1.25 g, 0.010 mol) in DMF (25 mL), and the mixture was stirred at 100–110 °C for 1 h. The mixture was then cooled (ice–salt bath) and 5-(chloromethyl)uracil (1.6 g, 0.010 mol) added. The resulting pale yellow suspension was stirred for 15 min and then poured into ice water (150 mL) containing acetic acid (2 mL). The yellow solid was collected, washed with water and then with methanol, and dried in vacuo, mp 180–181 °C dec (2.4 g, 68%). A similar procedure was used to prepare the following compounds: **43**, 47%, mp 285–286 °C; **44**, 77%, mp 266–267 °C; **45**, 44% mp 187–188 °C.

5-(Chloromethyl)-3-methyluracil. A mixture of 3-methyluracil[22] (12.6 g, 0.10 mol), paraformaldehyde (4.4 g, 0.15 mol), and concentrated hydrochloric acid (75 mL) was warmed on the steam bath for 15 min. A clear solution was obtained at first, but later a thick precipitate formed. Hydrogen chloride was bubbled in for 2 min, after which the hot mixture was stirred for a further 5 min and then chilled and diluted with ice water (200 mL). The product was collected, washed sparingly with ice water followed by acetone, and dried in air. The product (11.9 g, 68%) had mp 248–249 °C dec (lit.[4] mp 239.5–241.5 °C).

3-*n*-Butyl-5-carboxyuracil. 3-*n*-Butyl-5-carbethoxyuracil[22] (5.0 g, 0.021 mol) was added to a solution of sodium hydroxide (5.0 g, 0.125 mol) in water (100 mL), and the yellow solution was stirred under reflux in an atmosphere of nitrogen for 30 min. The resulting colorless solution was cooled and acidified with concentrated hydrochloric acid (15 mL), giving a solid which was collected, washed with water, and dried, and then had mp 188–189 °C (3.9 g, 88%).

3-*n*-Butyluracil. 3-*n*-Butyl-5-carboxyuracil (3.4 g, 0.016 mol) was heated at 250 °C (Woods metal bath) under nitrogen for 15 min. The solid melted with evolution of carbon dioxide, giving (after cooling under nitrogen) pale yellow crystalline material, mp 163–164 °C (2.6 g, 96%).

5-(Hydroxymethyl)-1-methyluracil. 5-(Hydroxymethyl)-uracil (as hydrate containing 0.25 mol of H_2O, 7.3 g, 0.050 mol), 1,1,1,3,3,3-hexamethyldisilazane (50 g, 0.31 mol), and chlorotrimethylsilane (1 mL) were stirred together under reflux in an atmosphere of dry nitrogen for 4 h. The resulting solution was cooled and iodomethane (114 g, 0.80 mol) added, after which stirring under reflux was continued for a further 18 h. After removal of volatile reagents at 80 °C under reduced pressure, the yellow residue was cooled (ice bath) and ice water (50 mL) added cautiously during 10 min. After addition of acetic acid (25 mL), the yellow suspension was concentrated to about 30 mL at 60 °C under reduced pressure. The residual mixture was chilled and the solid collected, washed with water, and dried in air. It had mp 311–312 °C (3.6 g, 46%).[23]

5-(Chloromethyl)-1-methyluracil. 5-(Hydroxymethyl)-1-methyluracil (0.5 g, 0.0032 mol) was stirred in ethanol (95%, 10 mL) while hydrogen chloride was passed in for 2 min. The mixture, which had become warm, was stirred for a further 8 min, after which the solvent was removed in a stream of nitrogen. The resulting pale yellow solid, mp 197–200 °C dec (0.5 g, 90%) was used without further purification.

5-(Chloromethyl)-6-methyluracil. 5-(Hydroxymethyl)-6-methyluracil (60.0 g, 0.38 mol) was added to concentrated hydrochloric acid (300 mL) with rapid stirring. A milky emulsion formed initially but quickly gave way to a dense precipitate. After 30 min the mixture was chilled in an ice bath, and the solid was collected, washed with ice water and then with acetone, and air-dried, giving a product with mp 348–350 °C dec (54.2 g, 81%).

Acknowledgment. We thank Ms. Jean B. Rogers for the preparation of **40**, Dr. Roger A. Boggs for providing 3-methyluracil in quantity, Mr. Wade T. Hunt, Jr., and Ms. Nancy M. Sofen for technical assistance, and Drs. Maynard Chen, Kenneth L. Norland, and Lloyd D. Taylor for helpful discussions.

Registry No. **3**, 4433-40-3; **8**·Na^+, 15052-19-4; **8** (thiol), 86-93-1; **9**, 3590-48-5; **10**, 84345-57-3; **17**, 18592-13-7; **18**, 94820-33-4; **23**, 94820-34-5; **24**, 94820-44-7; **30**, 84345-58-4; **31**, 94820-35-6; **32**, 94820-36-7; **33**, 94820-37-8; **34**, 84389-04-8; **44**, 84345-68-6; **45**, 84345-64-2; **46**, 84345-71-1; **47**, 84345-70-0; **48**, 84345-61-9; **49**, 94820-38-9; **50**, 84389-05-9; **51**, 84345-62-0; **52**, 84345-65-3; **53**, 94820-39-0; **54**, 84345-63-1; **55**, 94820-40-3; **57**, 63528-62-1; **59**, 84345-73-3; **60**, 14210-25-4; **62**, 84345-76-6; **63**, 84345-81-3; **64**, 84345-75-5; **65**, 84345-84-6; potassium 5-phenyl-1,3,4-oxadiazole-2-thiolate, 63467-41-4; 5-phenyl-1,3,4-oxadiazole-2-thione potassium salt, 63467-41-4; benzothiazole-2-thiol, 149-30-4; sodium benzothiazole-2-thiolate, 2492-26-4; 5-(chloromethyl)-3-methyluracil, 32079-00-8; 3-methyluracil, 608-34-4; 3-*n*-butyl-5-carboxyuracil, 94820-41-4; 3-*n*-butyl-5-carbethoxyuracil, 94820-42-5; 3-*n*-butyluracil, 28289-95-4; 5-(hydroxymethyl)-1-methyluracil, 21579-17-9; 5-(chloromethyl)-1-methyluracil, 94820-43-6; 1,3-dimethyluracil, 874-14-6; 5-(chloromethyl)-1,3-dimethyluracil, 32079-06-4; 5-(chloromethyl)-6-methyluracil, 66947-91-9; 5-(hydroxymethyl)-6-methyluracil, 147-61-5; 5-(2′-thienyl)-1,3,4-oxadiazole-2-thiol, 10551-15-2; sodium benzoxazole-2-thiolate, 15091-70-0; sodium 1,2,4-1*H*-triazole-3-thiolate, 61631-61-6; sodium 9*H*-purine-6-thiolate, 1194-62-3; 4,5-dihydro-1-phenyl-1*H*-1,2,3,4-tetrazole-5-thione sodium salt, 15052-19-4; 5-(2′-thienyl)-3*H*-1,3,4-oxadiazole-2-thione, 10551-15-2; 1*H*-benzotriazole, 95-14-7; 2-chlorobenzoxazole, 615-18-9; 2-chlorobenzothiazole, 615-20-3; 5-[(3-oxobutyl)thio]-1-phenyl-1,2,3,4-tetrazole, 13137-99-0; 5-[(3-oxobutyl)thio]-1-(4-sulfamoylphenyl)-1,2,3,4-tetrazole, 83936-34-9; 5-[[2-(methylsulfonyl)ethyl]thio]-1-(4-sulfamoylphenyl)-1,2,3,4-tetrazole, 83936-32-7; 5-phenyl-2-[[2-(phenylsulfonyl)ethyl]thio]-1,3,4-oxadiazole, 94820-47-0; 4,5-dihydro-1-(3-oxobutyl)-4-phenyl-1*H*-1,2,3,4-tetrazole-5-thione, 58408-33-6; 4,5-dihydro-1-(3-oxobutyl)-4-(4-sulfamoylphenyl)-1*H*-1,2,3,4-tetrazole-5-thione, 94820-45-8; 4,5-dihydro-1-[2-(phenylsulfonyl)ethyl]-4-(4-sulfamoylphenyl)-1*H*-1,2,3,4-tetrazole-5-thione, 94820-46-9; 5-phenyl-3-[2-(phenylsulfonyl)ethyl]-3*H*-1,3,4-oxadiazole-2-thione, 94820-48-1.

Supplementary Material Available: The unabridged original version of this article (87 pages). Ordering information is given on any current masthead page.