Extrusion of Sulfur from [(Acylmethyl)thio]pyrimidinones[1]

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Thermally mediated sulfur extrusion from 4-(phenacylthio)-2(1*H*)-pyrimidinones occurs rapidly in solution at 125 °C to yield 4(3*H*)-(benzoylmethenyl)-2(1*H*)-pyrimidinones. 4-(Acetonylthio)-2(1*H*)-pyrimidinone, however, rearranges via an episulfide intermediate to 4(3*H*)-(α-acetyl-α-mercaptomethenyl)-2(1*H*)-pyrimidinone. Adjacent 3- or 5-methyl substituents in the pyrimidine ring assist sulfur extrusion. No reaction occurs in the absence of a 2-oxo function or on replacement of it by a 2-amino group. On the other hand, 2-amino-4-[(1-methylacetonyl)thio]-6(1*H*)-pyrimidinone cyclizes very readily to 2-amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one. 2-(Phenacylthio)-4(3*H*)-pyrimidinones lose sulfur at about one-seventh the rate of the 4-phenacylthio isomers. No thermally mediated reaction occurs with 2-(acetonylthio)-4-pyrimidinones under the conditions described here.

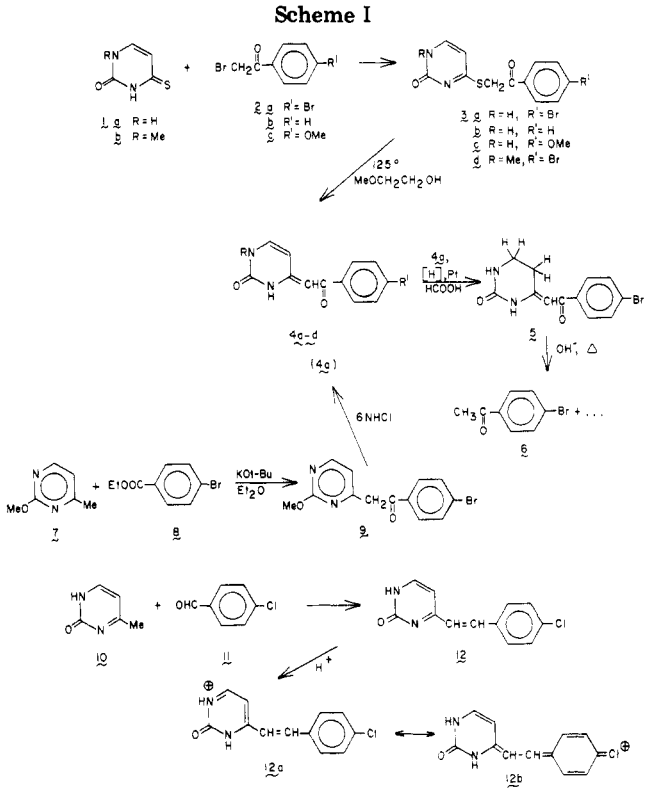
This paper describes an unexpectedly facile thermally mediated sulfur extrusion from certain 2- and 4-[(acylmethyl)thio]pyrimidinones. We had found previously that related 4-(phenacylthio)pyrimidines containing 2,6-diamino or 2-amino-6-hydroxy substituents cyclized to thieno[2,3-*d*]pyrimidines or to thiazolo[3,2-*c*]pyrimidinium salts, depending on the conditions and the nature of the side-chain substituents.[2]

There is considerable literature on sulfur-extrusion reactions.[3-6] The Eschenmoser corrin synthesis[7-9] via a sulfide-contraction reaction has stimulated recent reports of related syntheses from several laboratories.[10] The method normally uses triphenylphosphine and derivatives and/or a base to assist in the desulfurization.

The work reported here is restricted to a study of sulfur extrusion from pyrimidines by thermal means alone; our purpose was to determine substituent effects and tautomeric forms of intermediates and products as related to reaction requirements.

Our initial observation was the ready loss of sulfur from 4-[(4-bromophenacyl)thio]-2(1*H*)-pyrimidinone (**3a**) to produce a bright yellow compound which proved to be 4(3*H*)-[(4-bromobenzoyl)methenyl]-2(1*H*)-pyrimidinone (**4a**, Scheme I). This occurred upon mere recrystallization of **3a** from β-methoxyethanol (bp 125 °C). The identity of **4a** was not immediately obvious, although the analysis showed a simple loss of sulfur. The NMR spectrum had no methylene signals, and the UV spectrum exhibited strong conjugation, with very high absorption in the 375–400-nm region. Figure 1A provides UV spectra of **4a**, which are to be compared with those of its sulfide precursor **3a** (Figure 1B). Compound **4a** was too insoluble in water for accurate pK_a determinations. However, the more soluble phenyl analogue **4b** had a dissociation constant of −0.7 for monoprotonation and two overlapping constants (loss of one and two protons) in the pH 12–13 region, in contrast to 0.8 (monoprotonation) and 9.6 (one proton loss) for its sulfide precursor **3b**. The pK_a value of **3b** for loss of two protons was above 12 and was not determined.

Scheme I



Katritzky and co-workers[11] investigated tautomeric forms of 2- and 4-phenacylpyridines, their methiodides, and corresponding anhydro bases. They concluded that the anhydro bases existed as 2- and 4-(benzoylmethenyl)-1,2-dihydro-1-methylpyridines from their very high UV absorption near 400 nm; the nonmethylated derivatives had low absorption in this region and were considered to be mixtures of tautomeric forms, including the enol and a small amount of the methenyl form. von Phillipsborn[12] postulated the presence of the structural

(1) This paper was presented in part at the 1st International Congress of Heterocyclic Chemistry, Albuquerque, NM, June, 1967; *Angew. Chem. (Nachr. Chem. Techn.)* **1967**, *15*, 319.
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(12) von Phillipsborn, W.; Stierlin, H.; Traber, W. In "Pteridine Chemistry"; Pfleiderer, W., Taylor, E. C., Eds.; Pergamon Press: London, 1964; p 169 ff.

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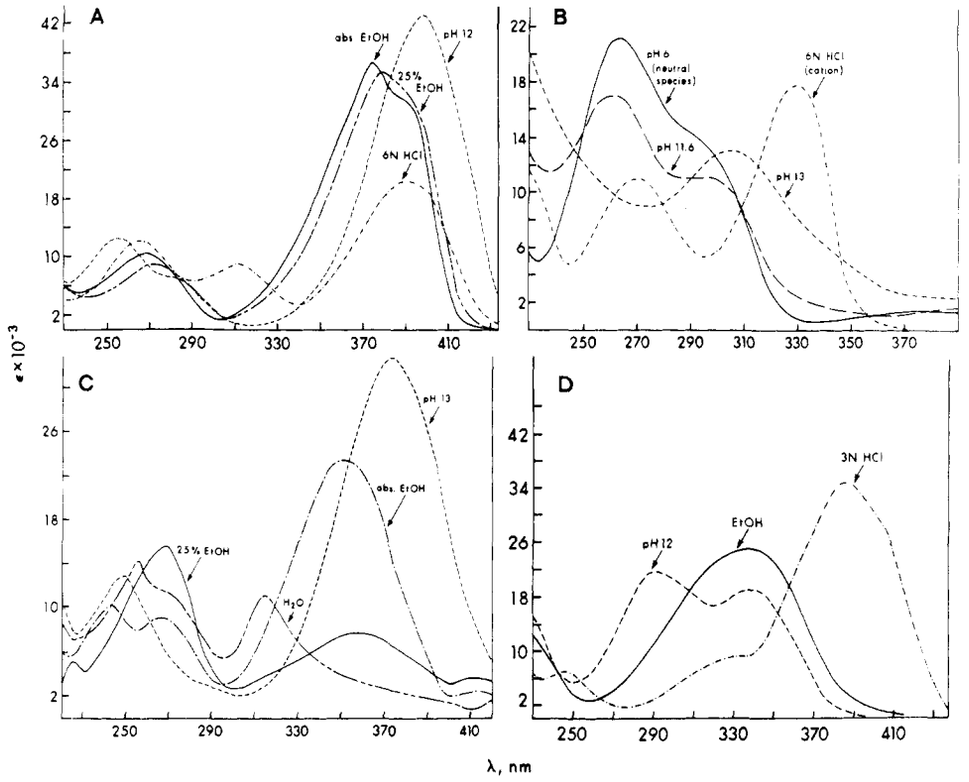


Figure 1. (A) UV spectra of **4a** as a cation (6 N HCl), as a neutral species in absolute EtOH and in 25% EtOH, and as a partial anion (pH 12). (B) UV spectra of **3a** as a cation (6 N HCl), as a neutral species (pH 6), as a monoanion (pH 11.6), and as a partial dianion (pH 13). (C) UV spectra of **9** as the neutral species in water, 25% EtOH, and absolute EtOH and as the partial anionic species at pH 13 (0.1 N NaOH). (D) UV spectra of **12** as a cationic species (3 N HCl), as a neutral species in EtOH, and as an anion (pH 12).

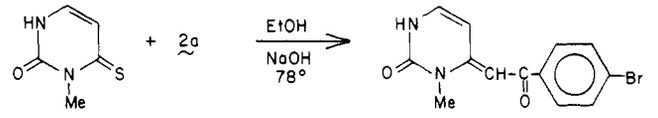
element =CHCOR in 7-acetonylxanthopterin and erythropterin from similar data. On the basis of these analogies, structure **4** seemed plausible here.

Structural proof was obtained by independent synthesis and by UV studies of model compounds. Condensation of **7** with **8** produced 2-methoxy-4-(4-bromophenacyl)pyrimidine (**9**, Scheme I). Hydrolysis of the 2-methoxy substituent produced **4a**, identical with the sulfur-extrusion product.

Figure 1C depicts the UV spectra of **9** as the neutral species in three mediums: water, 25% ethanol, and absolute ethanol. Note that in water the spectrum below 290 nm resembles that of the phenacyl sulfide **3a** (Figure 1B); the 315-nm absorption suggests the presence of some enol. The solvent change moves this peak out to 350 nm and greatly increases the intensity, which is consistent with a keto–enol shift. No further long-wavelength change occurred in diglyme. The NMR spectrum in Me_2SO showed the presence of a keto–enol mixture (see the Experimental Section). A comparison of the ethanolic UV spectrum with that of **4a** (Figure 1A) shows that the latter has a much more pronounced long-wavelength absorption in the 370–390-nm region, which is consistent with a third tautomeric form—a ketomethene. A low-absorption band at 410–420 nm suggests that **9** contains a small amount of the ketomethenyl tautomer in solution.[11] In alkali both compounds exhibit very strong long-wavelength absorption; **4a**, which forms a dianion, has the greater resonance capabilities and the stronger band.

4-(*p*-Chlorostyryl)-2(1*H*)-pyrimidinone (**12**), prepared as a model for an enol, had a long-wavelength maximum at 330 nm in ethanol (Figure 1D); an additional hydroxyl function (cf. **9**, Figure 1C) might be expected to produce a bathochromic shift through additional resonance capabilities. The protonated species of **12**, however, again exhibited high absorption in the 400-nm region, a result which can be explained by resonating forms **12a** and **12b**. Compound **4a** can undergo a similar resonance involving the benzene ring, through the electron-withdrawing keto oxygen.

Scheme II



13 14

Catalytic reduction of **4a** produced a dihydro derivative (**5**) which had no dissociation constant between 1 and 13, on the basis of the lack of change in its UV spectrum. The NMR spectrum showed adjacent methylene groups and a vinyl proton, consistent with **5** (Scheme I). The compound was unstable in alkali; *p*-bromoacetophenone (**6**) was isolated as a cleavage product.

To test whether the nature of the tautomeric structure of **3** influenced the extrusion of sulfur, we investigated some methylated derivatives (Table I). 1-Methyl-4-thiouracil (**1b**)[13] was converted to **3d**; its UV spectrum was practically identical with that of the parent nonmethylated analogue **3a**, suggesting that the amide proton of the latter is probably on N-1 rather than N-3. The methyl group had no influence on the course of sulfur extrusion; **4d** was produced. 3-Methyl-4-thiouracil (**13**),[14] however, produced a sulfur-extrusion product (**14**) directly upon brief warming with **2a** in ethanol (Scheme II). The neighboring methyl

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Table I. Pyrimidyl Sulfides

compd	pyrimidine substituents 2	4	other	recryst solvent[a]	mp, °C	formula	Anal.[b]	thermal reaction[c]
3a[d]	=O	$SCH_2COC_6H_4$-4-Br		A	185-187 dec	$C_{12}H_9BrN_2O_2S$	C, H, N, S	+
3b[e]	=O	$SCH_2COC_6H_5$		B	180 dec	$C_{12}H_{10}N_2O_2S$	C, H, N, S	+
3c	=O	$SCH_2COC_6H_4$-4-OCH_3		A	150 dec	$C_{13}H_{12}N_2O_3S$	C, H, N, S	+
3d[f]	=O	$SCH_2COC_6H_4$-4-Br	1-CH_3	A	170-174 dec	$C_{13}H_{11}BrN_2O_2S$	C, H, N, S	+
15a	=O	SCH_2COCH_3	5-CH_3	B	162-165 dec	$C_8H_{10}N_2O_2S$	C, H, N	+
15b[g]	=O	SCH_2COCH_3		C	150-151	$C_7H_8N_2O_2S$	C, H, N, S	R
21a	$SCH_2COC_6H_5$	=O		A	165-167	$C_{12}H_{10}N_2O_2S$	C, H, N, S	+
21b	$SCH_2COC_6H_4$-4-Br	=O		A	180 dec	$C_{12}H_9BrN_2O_2S$	C, H, N, S	+
21c[h]	SCH_2COCH_3	=O		B	161-162	$C_7H_8N_2O_2S$	C, H, N, S	–
27		$SCH_2COC_6H_4$-4-Br		B	128-129	$C_{12}H_9BrN_2OS$	C, H, N, S	–
28[i]	NH_2	$SCH_2COC_6H_4$-4-Br		B	173-174	$C_{12}H_{10}BrN_3OS$	C, H, N, S	–
29	NH_2	$SCH_2COC_6H_4$-4-Br	6-(=O)	E	252-257 dec	$C_{12}H_{10}BrN_3O_2S$	C, H, N	–
30	NH_2	SCH_2COCH_3	6-NH_2	B	146-147	$C_7H_{10}N_4OS$	C, H, N	C
31[j]	AcNH	$SCH_2COC_6H_4$-4-Br	6-AcNH	E	237-241	$C_{16}H_{15}BrN_4O_3S$	C, H, N	–
32[k]	=O	$SC(CH_3)_2COCH_3$		D	143-146	$C_9H_{12}N_2O_2S$	C, H, N	–
33[l]	=O	$SCH_2COC(CH_3)_3$		B	133-135	$C_{10}H_{14}N_2O_2S$	C, H, N	+
34[m]	=O	$SCH_2COOC_2H_5$		B	163.5-164	$C_8H_{10}N_2O_3S$	C, H, N, S	–
35	NH_2	SCH_2COOH		C	255-270 dec	$C_6H_7N_3O_2S$	C, H, N[n]	–
36	=O	$SCH_2C_6H_4$-4-NO_2		B	194-197 dec	$C_{11}H_9N_3O_3S$	C, H, N	–

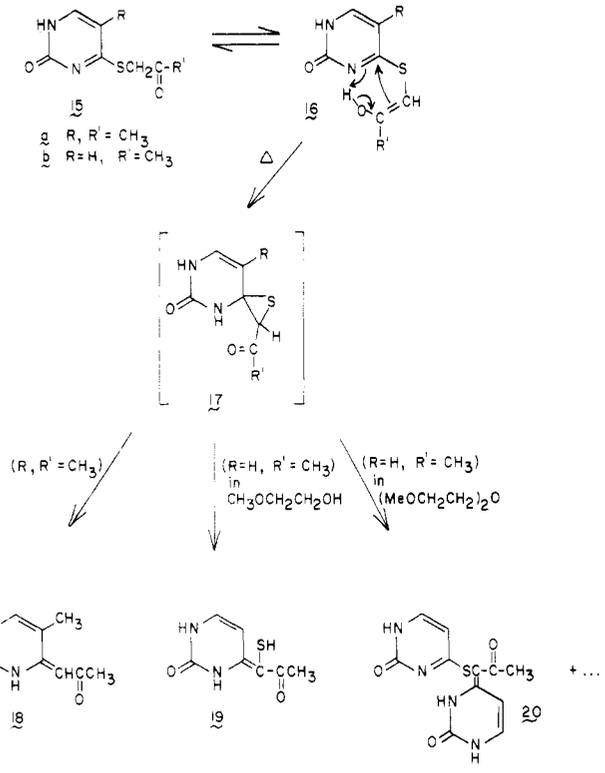
[a] A, EtOH/H_2O; B, EtOH; C, H_2O; D, EtOAc; E, DMF. [b] Satisfactory analytical data (±0.4% for C, H, N, and S as noted) were reported for all new compounds listed in the table except as indicated in the footnotes. [c] Compounds were heated for a maximum of 3 h in β-methoxyethanol at 125 °C or in some cases to 160 °C in DMF (see text). Symbols: +, extrudes S; –, no reaction; R, rearrangement; C, ring closure. [d] See Experimental Section for preparation. [e] UV (cation, 4.25 N HCl) λ_{max} 256 nm (ε 7720), 330 (17 300); (neutral species, pH 5.2, acetate) 252 nm (ε 15 000), 295 (11 350); (pH 9.65) 250 nm (ε 15 300), 298 (10 500); (pH 13, 0.1 N NaOH) 250 nm (sh, ε 11 600), 303 (11 800); (2 N NaOH) 307 nm (ε 14 400); pK_a (25 °C, proton gain) = 0.82 ± 0.1; pK_a (one proton loss) = 9.6 ± 0.1; pK_a (two proton loss) ≈ 12.9. [f] UV (neutral species, pH 4 and 9 identical) λ_{max} 262.5 nm (ε 21 900), 298 (14 900). [g] NMR (TFA) δ 2.22 (s, 3, Me), 3.92 (s, 2, CH_2), 6.93 (d, 1, Pyr, J = 7 Hz), 8.27 (d, 1, Pyr, J = 7 Hz); (Me_2SO-$_6$) δ 2.25 (s, 3, Me), 4.08 (s, 2, CH_2), 6.34 (d, 1, J = 7 Hz), 7.65 (d, 1, J = 7 Hz), 7.65 (d, 1, J = 7 Hz), 11.45 (br s, 1, NH); UV (neutral species, pH 6) λ_{max} 206 nm (ε 14 150), 222.5 (sh, 6630), 267.5 (7200), 297 (9650), 332.5 (sh, 625); (cation, 0.6 N HCl) 220 nm (ε 4700), 267.5 (2240), 324 (17 250); (anion, 0.01 N NaOH) 222.5 nm (ε 14 150), 244 (sh, 5500), 300 (9020); pK_a (proton gain) = 2.22 ± 0.03; pK_a (proton loss) = 9.63 ± 0.03 (20 °C); IR (KBr) 1721 (s), 1669 (s), 1618 (s), 1429 (s), 1364 (m) cm^{-1}. [h] NMR (TFA) δ 2.10 (s, 3, Me), 4.02 (s, 2, CH_2), 6.79 (d, 1, Pyr, J = 7 Hz), 8.11 (d, 1, Pyr, J = 7 Hz). [i] NMR (Me_2SO-d_6) δ 4.77 (s, 2, CH_2), 6.52 (s, 2, NH_2), 6.55 (d, 1, Pyr, J = 5 Hz), 7.75 (d, 2, Ar, J = 8 Hz), 7.95 (d, 1, Pyr, J = 5 Hz), 8.02 (s, 2, Ar, J = 8 Hz). [j] NMR (Me_2SO-d_6) δ 2.12 (s, 3, MeCONH), 2.15 (s, 3, MeCONH), 4.90 (s, 2, CH_2), 7.65 (s, 1, Pyr), 7.81 (s, 2, Ar, J = 6 Hz), 7.95 (d, 2, Ar, J = 6 Hz), 10.05 and 10.52 (2 br s, 2 NHAc). [k] NMR (Me_2SO-d_6) δ 1.53 (s, 6, Me), 2.27 (s, 3, Me), 6.28 (d, 1, Pyr, J = 6.5 Hz), 7.68 (d, 1, Pyr, J = 6.5 Hz), 11.5 (br s, 1, NH); UV (neutral species, pH 6) λ_{max} 222 nm (sh, ε 6600), 264 (sh, 5100), 300 (8900), 308 (sh, 8400), 332 (sh, 4500); (cation, 0.1 N HCl) λ_{max} 219 nm (ε 4800), 271 (1800), 329 (18 700); pK_a (proton gain) = 3.49 ± 0.01 (20 °C); the compound is unstable in alkali; IR 1710 (s), 1645 (s), 1615 (s) cm^{-1}. Reaction of the compound with NH_2OH at pH 6.5 produced 4(3*H*)-oximino-2(1*H*)-pyrimidinone (Brown, D. M.; Schell, P. *J. Chem. Soc.* **1965**, 208). [l] NMR (Me_2SO-d_6) δ 1.20 (s, 9, Me), 4.32 (s, 2, CH_2), 6.32 (d, 1, Pyr, J = 7 Hz), 7.62 (d, 1, Pyr, J = 7 Hz), 11.45 (br s, 1, NH). [m] NMR (Me_2SO-d_6) δ 1.20 (t, 3, CH_2CH_3, J = 7 Hz), 3.50 (br s, 2, NH, 0.5 H_2O), 4.02 (s, 2, CH_2), 4.14 (q, 2, CH_2CH_3, J = 7 Hz), 6.34 (d, 1, Pyr, J = 7 Hz), 7.65 (d, 1, Pyr, J = 7 Hz). [n] Anal. Calcd: N, 22.69. Found: N, 22.23.

group evidently has a strong steric influence in assisting sulfur extrusion.

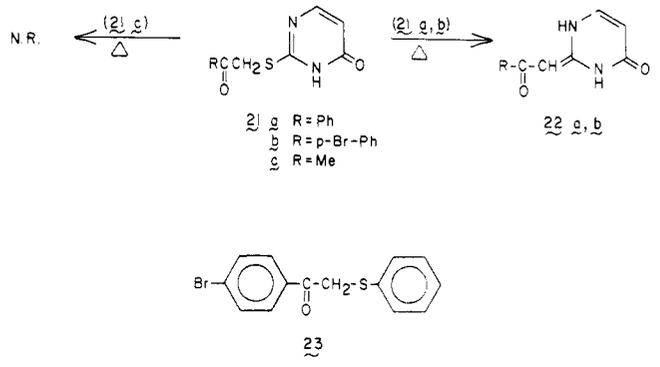
To explore the effect of a neighboring methyl group further, we prepared 5-methyl-4-(acetonylthio)-2(1*H*)-pyrimidinone (**15a**) from 4-thiothymine. This compound could be recrystallized from ethanol without change, in contrast to the above case (Scheme II); however, heating in β-methoxyethanol at 125 °C produced a sulfur-extrusion product in 50% yield, along with a 50% yield of elemental sulfur (Scheme III). Product **18** had a UV spectrum similar in character to those of the phenacyl derivatives, except that the long-wavelength maximum was now between 370 and 380 nm and of somewhat lower intensity, as would be expected with the decreased conjugation. The NMR spectra also indicated the acetylmethenyl tautomer.

The 5-methyl group of **15a** proved to have a very important steric effect in aiding sulfur removal. The analogous compound without the 5-methyl substituent (**15b**) underwent a thermally mediated reaction to give a yellow product with a UV spectrum very similar to that of **18**; however, the elemental analysis was the same as that of the starting material. The change in UV spectrum over 6 pH units indicated the presence of two ionizable groups between pH 6 and 12, which were calculated to have pK_a values of 8.2 and 9.5. This can be explained by rearrangement of **15b** via an episulfide (**17**) which then cleaved only the original C–S bond to give **19**, in the absence of a 5-substituent. Compound **19** would have one more ion-

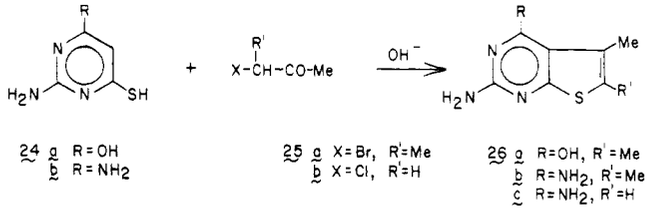
Scheme III



Scheme IV



Scheme V



izable group in the appropriate pH range than would **18**. The NMR spectra (**19**, Experimental Section) are consistent with this conclusion.

Further evidence for this structure was obtained by changing the solvent for the thermal reaction. In diglyme, a mixture of products was obtained, from which was isolated a product with an analysis and physical properties consistent with **20**. This could be formed from **19** by attack of the sulfhydryl group on the 4-carbon of the original sulfide, **15b**.

It is possible that sulfur extrusion from the [(acylmethyl)thio]pyrimidinones would be assisted by the formation of an H-bonded enol form of the acylmethylene function (**16**) as a general case. The 4-carbon of such a structure might be expected to be electron deficient and to readily undergo attack by the electron-rich methenyl group, forming an intermediate episulfide. Homolytic fission to yield a six-membered, H-bonded structure, accompanied by sulfur extrusion under the influence of thermal energy, should then occur readily. The assignment of the amide proton of **3a** to N-1, rather than N-3, from spectral comparisons with **3d** assisted in this argument. Obviously this explanation does not fit the case of the 3-methyl derivative **13**. However, a common driving force for S extrusion from these nonaromatic amide-type compounds does not seem essential. Eschenmoser indeed reached the same conclusion.[9] The steric effect of the methyl group in the latter case may provide an alternative means for accomplishing the same result.

In all of the above extrusion reactions, other products were present in the reaction mixture. Normally the product of sulfur extrusion crystallized out as a single component when β-methoxyethanol was used as the solvent. Usually a mixture of evil-smelling oils was left in solution, probably the result of cleavage of the side chain to produce thioacetone and analogous compounds plus uracil and other degradation products. An attempt to study the kinetics of the reaction of **3b** in β-methoxyethanol at 94 °C gave very erratic results which indicated the sequential formation of at least two products absorbing in the 350–390-nm range, followed by gradual decomposition. This fits the picture of an episulfide which breaks one or both C–S bonds to form an (acylmethenyl)pyrimidinone as the preferred tautomer of the product.

Phenacylthio derivatives prepared from 2-thiouracil (**21a,b**, Scheme IV) also extruded sulfur to give **22a** and **22b**, but at a slower rate, estimated to be about one-seventh that for a 4-substituted derivative in a single comparable reaction. 2-(Acetonylthio)-4(3*H*)-pyrimidinone (**21c**) proved resistant to thermally mediated sulfur extrusion. Only the starting material was recovered. The products of these reactions would have less conjugating capability than do the 4-methenyl derivatives, which may explain the lower reactivity.

A nonpyrimidyl sulfide (**23**, Scheme IV), in which the pyrimidinone moiety of **3a** is replaced by a benzene ring, was stable under the conditions of the thermal reaction. This was likewise true on replacement by 4-pyrimidyl and 2-amino-4-pyrimidyl functions (**27** and **28**, Table I). Lack of reaction of these aromatic systems is not surprising, since there would be considerably less likelihood of these forming nonaromatic episulfide intermediates as well as acylmethenyl products. The presence of an appropriate amide function in the pyrimidine ring is then suggested as a requirement.

An inappropriate pyrimidinone function is represented by the intermediate 6-mercaptoisocytosine (**24a**); its sulfides would have to exist as the 4-hydroxypyrimidine tautomers in order for an episulfide or acylmethenyl derivative to form. In the actual event, **24a** reacts with 3-bromo-2-butanone (**25a**) to form a thieno[2,3-*d*]pyrimidine (**26a**, Scheme V). Reaction with **2a** yields a sulfide (**29**, Table I) which is stable in refluxing DMF. It was previously found that the presence of an aromatic ring attached to the carbonyl function in the side chain causes cyclization to occur with extreme difficulty.[2] 2,4-Diamino-6-mercaptopyrimidine (**24b**) likewise yielded thieno[2,3-*d*]pyrimidines with aliphatic halo ketones (Scheme V). A sulfide (**30**, Table I) was isolated by operation under very mild conditions (40 °C). An acetylated derivative (**31**) did not react in any way.

Compound **32** (Table I), a *gem*-dimethyl derivative which lacks α-protons, does not undergo a thermal reaction at 125 °C. This compound, of course, cannot form an

episulfide. The *tert*-butyl ketone **33** (Table I) decomposed to an evil-smelling mixture. Ester **34** and acid **35** (Table I) did not extrude sulfur under our conditions.

The requirement for a ketone function in the α position of the sulfide side chain was tested by substitution with the electron-withdrawing *p*-nitrobenzyl group (**36**, Table I); this compound was stable in refluxing DMF.

In the monocyclic pyrimidine series then (as far as we have tested it), the thermally mediated extrusion of sulfur from acylmethyl sulfide derivatives is limited to certain 4- and 2-pyrimidinones which can occur as appropriate nonaromatic tautomers and which can form episulfide intermediates and acylmethenyl derivatives. An *o*-alkyl substituent assists the extrusion. The utility of this reaction can no doubt be extended by the addition of reagents to assist in the desulfurization. We have found our reaction to be useful for preparing nucleoside analogues; this will be reported in a future paper. A recent publication by Vorbrueggen[15] describes similar reactions.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60, XL-100, and T-60 spectrophotometers; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Ultraviolet absorption spectra (UV) were recorded on Cary 13 and 118 spectrophotometers. Infrared spectra (IR) were obtained on a Beckman IR4 or a Perkin-Elmer 267 grating spectrophotometer and are reported in reciprocal centimeters. Melting points were measured on a Thomas-Hoover apparatus and are corrected.

Elemental microanalyses were performed by Samuel Blackman and Stuart Hurlbert and their staffs in this laboratory and by Atlantic Microlab, Inc.

[(Acylmethyl)thio]pyrimidines. General Method. The mercaptopyrimidine was normally dissolved in an equivalent amount of 1–2 N NaOH, and the α-halo ketone was dissolved separately in sufficient ethanol so that when the two solutions were heated on the steam bath and then poured together, the halo ketone did not precipitate. Normally a clear solution formed upon mixing; the product soon precipitated. Heating was continued for about 10 min, or until the solution was no longer alkaline, followed by cooling and isolation of the product. Yields were normally greater than 60%. The products were usually recrystallized from ethanol with a minimum of heating. These are described in Table I. Examples are provided below.

4-[(4-Bromophenacyl)thio]-2(1*H*)-pyrimidinone (3a). 4-Thiouracil (**1a**; 3.2 g, 25 mmol) was dissolved in a mixture of 12.5 mL of 2 N NaOH and 10 mL of EtOH on a steam bath and poured into a warm solution of 6.95 g (25 mmol) of **2a** in 60 mL of absolute EtOH. A clear yellow solution formed. After about 2 min a crystalline precipitate separated. The mixture was heated 15 min longer on the steam bath and chilled, and the white crystals were isolated: 6.8 g (84%); mp 185–187 °C dec (EtOH/H_2O); NMR (TFA) δ 4.70 (s, 2), 7.08, 8.32 (d, 2, J = 7 Hz), 7.71 (s, 4); NMR (Me_2SO-d_6) δ 4.77 (s, 2), 6.37 (d, 1, J = 7 Hz), 7.66 (d, 1, J = 7 Hz), 7.73 (d, 2, J = 8.5 Hz), 8.00 (d, 2, J = 8.5 Hz), 11.5 (br, 1); UV (neutral species, pH 6, acetate) λ_{max} 263 nm (ϵ 21 200), 290 (sh, 14 300); (monocation, 6 N HCl) 270 nm (ϵ 11 000), 330 (17 900); (monoanion, pH 11.6) 261 nm (ϵ 17 400), 295 (12 500), 400 (1790); (partial dianion, pH 13) 305 nm (ϵ 13 200); pK_a (proton gain) ≈0.8 (±0.1); pK_a (proton loss) ≈ 9.7 (±0.1); IR (KBr) 1667 (s), 1616 (s).

4-[(1,1-Dimethylacetonyl)thio]-1(1*H*)-pyrimidinone (32). Compound **1a** (3.2 g, 0.024 mol) was treated with 3-bromo-3-methyl-2-butanone in the manner of **3a** above. After 2 h the solution was chilled; the weight of the precipitate was 0.85 g (Na salt of **1a**). The filtrate was evaporated, yielding an oily solid which was extracted with Et_2O, followed by aqueous $NaHCO_3$–EtOAc mixtures. The Et_2O- and EtOAc-soluble fractions were combined and purified by chromatography on silica gel (EtOAc–MeOH, 19:1). The initial fractions contained a red oil, followed by **1a**, and then a white crystalline fraction (**32**): 2.2 g; mp 143–146 °C (EtOAc). This product showed no chemical change upon being heated for 2 h in β-methoxyethanol (125 °C).

4(3*H*)-[(4-Bromobenzoyl)methenyl]-2(1*H*)-pyrimidinone (4a). Method A. By Sulfur Extrusion from 1a. A mixture of 6.4 g (50 mmol) of **1a**, 2.7 g (50 mmol) of NaOMe, and 100 mL of $(CH_2OH)_2$ was heated with stirring until a clear solution was formed (100 °C). Compound **2a** (13.9 g, 50 mmol) was then added with stirring. A heavy precipitate formed. The temperature was raised to the point where the precipitate dissolved (120 °C). The solution then rapidly became cloudy, and a precipitate soon formed. After 30 min, the mixture was cooled to 0 °C, and the yellow crystalline precipitate was isolated and washed well with glycol, EtOH, and Et_2O to give 6.9 g (dry weight, 47%) of **4a**. The filtrate had a strong sulfurous odor. Compound **4a** was quite insoluble in EtOH and Me_2CO but could be recrystallized easily from β-methoxyethanol (1 g/32 mL) or DMF; mp 300–303 °C dec. The NMR spectrum in TFA showed no methylene signals but was difficult to interpret because of apparent hidden peaks, all of which were in the δ 5–9 region. However, in *N*-methylpyrrolidone good separation of peaks was obtained above δ 4 as follows: δ 4.56 and 5.07 (2 br s totaling 1 H), 6.22 (s, 1), 6.01 and 7.38 (d, 2, J = 7 Hz), 7.68 and 7.96 (d, 4 Ar, J = 8.5 Hz); UV see Figure 1A; IR (KBr) 1701 (s), 1667 (s). Anal. Calcd for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.10; Br, 27.26; N, 9.56. Found: C, 49.27; H, 3.05; Br, 27.36; N, 9.58. The substance contained no sulfur.

Method B. By Sulfur Extrusion from 3a. A 6.8-g portion (20 mmol) of **3a** was mixed with 150 mL of β-methoxyethanol in an Erlenmeyer flask and heated to the boil (125 °C). The resultant clear solution became increasingly yellow with time, and a small amount of H_2S was evolved. After 30 min, the solution was treated with charcoal (Darco G-60), clarified, and chilled, yielding bright yellow crystals, which were isolated and washed well with EtOH and Et_2O to give 2.26 g of product. The UV spectra were identical with those of **4a** by method A. Upon addition of water to the filtrate, an additional yellow precipitate formed (3.08 g) which contained some Et_2O-soluble material. The insoluble fraction contained only about 30% of **4a**, as judged from the long-wavelength UV maximum. When the mixture was heated for an additional 30 min in β-methoxyethanol, the resultant precipitate (1.64 g) was now identical with **4a**; total yield 53%. The residue consisted of a mixture of degradation products.

The reaction was repeated by using 500 mg of **3a** in 8 mL of DMF at 125 °C. A 49% yield of **4a** crystallized on chilling of the DMF solution. Again, the filtrate yielded a mixture. When the reaction was carried out in diglyme, no precipitate separated on chilling, and a complex mixture was obtained upon addition of water.

Method C. From 2-Methoxy-4-methylpyrimidine (7). Compound **7**[16] (24.2 mmol) was treated with ethyl 4-bromobenzoate (**8**) by the procedure of Pfleiderer and Mosthaf[17] to produce **2-methoxy-4-(4-bromophenacyl)pyrimidine (9)**: 26% recrystallized (rx); mp 158–160 °C (absolute EtOH). The NMR spectrum in Me_2SO indicated the presence of a 1:1.4 keto–enol mixture: NMR (8% in Me_2SO-d_6, 60 °C, Varian XL-100); keto tautomer δ 3.869 (s, 3, OMe), 4.497 (s, 2, CH_2), 7.120 and 8.532 (d, 2 Pyr-5, Pyr-6, J = 5.0 Hz), 7.656 and 7.960 (d, 4, Ar); (enol tautomer) δ 3.990 (s, 3, OMe), 6.910 (s, 1, CH=), 6.910 and 8.431 (d, 2, Pyr-5, Pyr-6, J = 5.4 Hz), 7.737 and 7.823 (d, 4, Ar), 14.6 (br s, 1, OH); UV see Figure 1C; IR (KBr) 1634 (s); ($CHCl_3$) 1684 (w), 1631 (m). Anal. Calcd for $C_{13}H_{11}BrN_2O_2$: C, 50.83; H, 3.61; N, 9.12. Found: C, 50.71; H, 3.82; N, 9.15.

Compound **9** was heated on the steam bath with 1 mL of 95% EtOH and 1 mL of concentrated HCl for 1.5 h. The initial clear solution soon deposited a yellow crystalline precipitate. Water was added and the precipitate collected and recrystallized from β-methoxyethanol. It was then identical in all respects with **4a** by methods A and B.

4(3*H*)-(Benzoylmethenyl)-2(1*H*)-pyrimidinone (4b). This compound was prepared from **3b** by method B: 64%; mp 276–278 °C (β-methoxyethanol); UV (neutral species, pH 2, 5, 11.5) λ_{max} 262 nm (ϵ 7290), 375 (34 700), 390 (sh, 30 600); (95% EtOH) 260

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nm (ε 7600), 355 (sh, 24 400), 371 (33 000), 386 (27 700); (Et_2O) 257 nm (ε 7350), 352.5 (sh, 25 300), 367 (31 800), 386 (24 100); (cation, 8 N HCl) 251 nm (ε 9800), 310 (8050), 388 (17 900); (approximate anion, 0.1 N NaOH), 250 nm (ε 9350), 280 (5150), 395 (40 000); (partial dianion, 2 N NaOH) 245 nm (sh, ε 8550), 282 (5050), 390 (29 500); pK_a (proton gain) ≈ −0.70; pK_a (proton loss), two overlapping pK_a's in strong alkali, one between 11.5 and 13 and one above 13. The substance was not very stable in alkali, and the endpoint was above the useful aqueous range. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.84; H, 4.85; N, 12.86.

An attempt was made to study the kinetics of the S-extrusion reaction. Thirteen milligrams of **3b** was dissolved in 100 mL of β-methoxyethanol (20 °C); 3-mL aliquots were placed in 10-mL "Color-break" ampules, and the ampules were sealed and placed in a constant-temperature bath at 94.2 ± 0.1 °C. Samples were removed at intervals and quenched in an ice bath. One-milliliter samples were removed and diluted to 10 mL in EtOH for optical density readings. These data indicate the occurrence of more than one sequential reaction, followed by erratic decomposition. Similar data were obtained with **3a**.

4(3*H*)-[(4-Methoxybenzoyl)methenyl]-2(1*H*)-pyrimidinone (4c). This compound was prepared from **3c** by method B for **4a**: yield 73%; mp 276–278 °C (β-methoxyethanol). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.63; H, 4.92; N, 11.34.

1-Methyl-4(3*H*)-[(4-bromobenzoyl)methenyl]-2-pyrimidinone (4d). Compound **3d** (100 mg) was boiled in β-methoxyethanol for 20 min; a yellow solution formed which yielded shiny orange-yellow plates on cooling of the mixture: 62 mg; mp 236–237 °C (EtOH); UV (EtOH) λ_{max} 268 nm (ε 10 000), 381 (36 800), 395 (sh, 32 600); (6 N HCl) 265 nm (ε 12 600), 315 (10 250), 395 (14 600). Anal. Calcd for $C_{13}H_{11}BrN_2O_2$: C, 50.83; H, 3.61; N, 9.12. Found: C, 50.89; H, 3.35; N, 9.14.

3-Methyl-4(1*H*)-[(4-bromobenzoyl)methenyl]-2-pyrimidinone (14). Compound **13**[14] (0.122 g, 0.9 mmol) was dissolved in 0.4 mL of warm EtOH containing 0.9 mL of 1 N NaOH, and this was mixed with a warm solution of 0.249 g (0.9 mmol) of **2a** in 2 mL of EtOH. The initial clear orange solution soon deposited a solid. After 10 min at 72 °C the solution, now neutral, was chilled. The yellow precipitate was isolated and washed well with cold EtOH and Et_2O: 0.076 g; mp 258–260 °C; NMR (Me_2SO-d_6) δ 3.35 (s, 3, NMe), 5.93 (s, 1, =CHCO), 7.14 (t, 1, Pyr-6, J = 8 Hz), 7.76 (m, 4, Ar), 7.77 (d, 1, Pyr-5, J = 8 Hz), 11.0 (br, 1, NH); UV (pH 6 acetate) λ_{max} 270 nm (ε 10 900), 380 (30 600); (6 N HCl) 267 nm (ε 16 400), 316 (10 850), 390 (3380); (0.1 N NaOH) 257 nm (ε 16 700), 285 (sh, 5000), 400 (35 500). Anal. Calcd for $C_{13}H_{11}BrN_2O_2$: C, 50.83; H, 3.61; N, 9.12. Found: C, 50.34; H, 3.50; N, 8.84.

2(1*H*)-(Benzoylmethenyl)-4(3*H*)-pyrimidinone (22a). A 10-g sample of **21a** was heated at the boil in 200 mL of β-methoxyethanol for 2.5 h. After 1.5 h a precipitate began to separate. This was isolated after the mixture was chilled (yield 6.3 g). A white impurity was removed upon recrystallization from β-methoxyethanol: weight of purified **22a** 3.7 g (42.5%); mp 224 °C dec. This reaction was slower than the reactions with the corresponding 4-(phenacylthio)pyrimidinone derivatives. When **21a** was heated for 40 min, only 15% of **22a** was obtained: NMR (Me_2SO-d_6) δ 5.70 (d, 1, Pyr H, J = 10 Hz), 5.77 (s, 1 CH=, exch D_2O), 7.43–7.84 (m, 5, Ar), 7.65 (d, 1, Pyr H, J = 10 Hz, decoupled), 11.55 (br s, 1, NH), 13.7 (br s, NH); UV (neutral species, pH 3) λ_{max} 225 nm (ε 13 700), 245 (11 400), 350 (27 700); (cation, 6 N HCl) 227.5 nm (ε 12 000), 253 (14 300), 335 (6800); (monoanion, pH 10, 12) 238 nm (ε 13 200), 292.5 (sh, 5140), 357 (21 500); pK_a (proton gain) ≈ 0.64, as estimated from the midpoint of a plot of log (α/1 − α) vs. H_0; the slope was 1.62, indicating that the compound was not a Hammett base;[18] pK_a (proton loss) = 7.99 ± 0.03 (20 °C). The UV spectrum did not change between pH 10 and 12. No spectral determinations were carried out in more alkaline media. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.34; H, 4.67; N, 13.16.

2(1*H*)-[(4-Bromobenzoyl)methenyl]-4(3*H*)-pyrimidinone (22b). Sulfur extrusion from **21b** was accomplished as from **21a** above: recrystallized yield 33% (β-methoxyethanol, 1 g of **22b**/234 mL); mp 301 °C dec. Anal. Calcd for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.10; N, 9.56. Found: C, 49.20; H, 3.08; N, 9.59.

4(3*H*)-(Acetylmethenyl)-5-methyl-2(1*H*)-pyrimidinone (18). A 1-g portion of **15a** was heated with 10 mL of β-methoxyethanol at the boil for 20 min; the resultant red-orange solution was chilled, and the yellow precipitate was isolated and washed with EtOH and Et_2O. This wash dissolved some bright yellow material, leaving a light cream precipitate (117 mg) which after further extraction with EtOH weighed 75 mg; mp 113 °C. This proved by analysis to be elemental sulfur (47%) (Anal. Found: S, 97.0; C, H, N, 0.0). The addition of 5 mL of water to the β-methoxyethanol filtrate yielded a light yellow precipitate (498 mg) which yielded 335 mg of **18** (40%) after recrystallization from 70% EtOH: mp 202 °C; UV (cation, 6 N HCl) λ_{max} 235 nm (ε 3720), 297 (3075), 340 (sh, 9500), 360 (sh, 16 020), 372 (19 400); (neutral species, pH 6) 260 nm (ε 4680), 337.5 (sh, 20 000), 350.5 (24 800), 364 (19 000); (anion, 0.1 N NaOH) 257.5 nm (sh, ε 6800), 272 (8520), 378 (33 600); pK_a (proton loss) = 10.0 ± 0.1 (20 °C); pK_a (proton gain) ≈ 0.1 ± 0.1 (due to large medium shifts in strong acid, this value could not be obtained with precision); IR (KBr) 1715 (s), 1669 (s). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.80; H, 6.12; N, 16.89; S, 0.3.

Thermal Rearrangement of 4-(Acetonylthio)-2(1*H*)-pyrimidinone (15b). (A) In β-Methoxyethanol. 4(3*H*)-(α-Acetyl-α-mercaptomethenyl)-2(1*H*)-pyrimidinone (19). A 2-g sample of **15b** was heated in the same manner as for **15a**. Upon the addition of 10 mL of water to the hot solution, a yellow precipitate formed (**19**) which was isolated after the mixture was chilled: 0.30 g; mp 262–263 °C dec (β-methoxyethanol); UV (pH 1–6) λ_{max} 265 nm (ε 5250), 320 (sh, 6620), 370 (10 280); (pH 13) 272.5 nm (ε 6540), 325 (sh, 5460), 376 (15 620) [between pH 6 and 12 there was a constant increase in intensity of the long-wavelength maximum, with no isosbestic points—rather, there was constant shift, indicating two overlapping pK_a values; these were calculated from a plot of optical density at 375 nm vs. pH by use of the Thamer equation;[19] this gave pK_a values of 8.18 and 9.49 for ionization of the mercaptan and pyrimidinone functions]; NMR (Me_2SO-d_6) δ 2.39 (s, 3), 6.27 (d, 1, J = 7.5 Hz), 7.44 (d, 1, J = 7.5 Hz), 11.45 (br, 1, exch D_2O), 13.62 (br, 1, exch D_2O), accounting for 7 H; IR (KBr) 2551 (w), 1721 (s), 1650 (s). Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21; S, 17.41. Found: C, 45.78; H, 3.81; N, 15.00; S, 17.63.

(B) In Diglyme. 4(3*H*)-[α-[(2(1*H*)-Oxo-4-pyrimidyl)thio]-α-acetylmethenyl]-2(1*H*)-pyrimidinone (20). Experiment A was repeated in diglyme at 125 °C; **15b** dissolved upon heating, but a heavy precipitate soon separated. After 20 min the mixture was chilled to give a precipitate, 1.06 g. This was extracted with hot EtOH and H_2O, in which very little dissolved, followed by 2 N HCl. A shiny yellow insoluble fraction weighed 0.17 g. The soluble fraction was neutralized with ammonia to give **20**: 0.36 g; decomposes above 250 °C (DMF); NMR (Me_2SO-d_6) δ 2.24 (s, 3, MeCO), 6.22 (d, 2, Pyr, J = 7 Hz), 7.48 (d, 1, Pyr, J = 7 Hz), 7.67 (d, 1, Pyr, J = 7 Hz), 11.58 (br s, 2, NH), 13.88 (br s, 1, NH). Anal. Calcd for $C_{11}H_{10}N_4O_3S$: C, 47.47; H, 3.62; N, 19.68; S, 11.52. Found: C, 47.02; H, 3.74; N, 19.81; S, 11.26.

4-(*p*-Chlorostyryl)-2(1*H*)-pyrimidinone (12). 4-Methyl-2-(1*H*)-pyrimidinone (**10**) was treated with *p*-chlorobenzaldehyde according to the method of Brown and Kon[20] to yield **12**: 22%; mp 301–302 °C (β-methoxyethanol); UV see Figure 1D. Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.90; Cl, 15.24; N, 12.04. Found: C, 61.88; H, 4.04; N, 12.02; Cl, 15.27.

4-[(4-Bromobenzoyl)methenyl]-5,6-dihydro-2(1*H*)-pyrimidinone (5). Compound **4a** (2.93 g, 10 mmol) in 100 mL of slightly warm 98–100% HCOOH was reduced in a Parr apparatus with freshly prepared PtO catalyst. Some of the starting material crystallized at room temperature but redissolved as the reduction commenced; the reduction time was 15 min/mol of H_2. The solution was clarified and diluted with 6 volumes of water, which produced a cream precipitate: 2.47 g; mp 261.5–264 °C (β-methoxyethanol); NMR (TFA) δ 2.97 (t, 2, J = 7 Hz), 3.70 (t, 2,

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J = 7 Hz), 6.26 (s, 1), 7.72 (s, 4); (Me_2SO-d_6) δ 2.72 (t, 2, J = 7 Hz), 3.24 (quintet, 3, J = 7 Hz), 6.09 (s, 1), 7.08, 7.30 (br, total 1), 7.63, 7.88 (d, 4, J = 7 Hz), 9.20 (br, 1) (H_2O present); UV (same between pH 1 and 12) λ_{max} 268 nm (ϵ 8700), 327 (25 400), at pH 12 a rapid decay with an increase in low λ_{max} values, after 10 min (100 °C) λ_{max} 258 nm, 320–330 (very small); IR (KBr) 1701 (s), 1642 (s). Anal. Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.83; H, 3.76; N, 9.49. Found: C, 48.89; H, 4.05; N, 9.49.

Degradation of the above product by heating 200 mg with 14 mL of 0.1 N NaOH plus 10 mL of EtOH on a steam bath for 30 min produced an oil which solidified on cooling: 60 mg; mp 49.5–50.5 °C; NMR (CCl_4) δ 2.51 (s, 3), 7.55, 7.79 (d, 4, J = 9 Hz); UV (EtOH) λ_{max} 256–257 nm (ϵ 17 600, calcd for mol wt 198). The analysis was confirmatory for ***p*-bromoacetophenone (6)**. Anal. Calcd for C_8H_7BrO: C, 48.51; H, 3.56. Found: C, 48.69; H, 3.87. A mixture of other fragments was obtained, which were not characterized.

ω-(Phenylthio)-*p*-bromoacetophenone (23). Thiophenol (2.75 g, 0.025 mol) was treated with **2a** by the general procedure for pyrimidyl sulfides; there was obtained 7.44 g (97%) of **23**, mp 52–55 °C (EtOH). Anal. Calcd for $C_{14}H_{11}BrOS$: Br, 26.01; S, 10.44. Found: Br, 26.17; S, 10.59.

2-Amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (26a). This compound was prepared from 6-mercaptoisocytosine (**24a**) by the method described for **26b** below on a 0.04-mol scale: weight of crude product 4 g (51%); the compound did not melt below 320 °C (dilute EtOH); NMR (Me_2SO-d_6) δ 2.21 (s, 3, Me), 2.26 (s, 3, Me), 6.34 (br s, 2, NH_2), 10.70 (br s, 1, NH). Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.62; N, 21.53. Found: C, 48.84; H, 4.53; N, 21.33.

2,4-Diamino-5,6-dimethylthieno[2,3-*d*]pyrimidine (26b). A mixture of 5.66 g (0.04 mol) of **24b**, 2.16 g (0.04 mol) of NaOMe, 6.04 g (0.04 mol) of **25a**, and 50 mL of $(CH_2OH)_2$ was heated on a steam bath for 1 h. When the mixture cooled, crystals separated; these were isolated and washed with water: 6.5 g (84%); mp 127–129 °C (EtOH); NMR (Me_2SO-d_6) δ 2.24 (s, 3, Me), 2.29 (s, 3, Me), 5.84 (br s, 2, NH_2), 6.29 (br s, 2, NH_2). Anal. Calcd for $C_8H_{10}N_4S$: C, 49.49; H, 5.56; N, 28.85. Found: C, 49.46; H, 5.25; N, 28.63.

2,4-Diamino-5-methylthieno[2,3-*d*]pyrimidine (26c). The method used for **26b** was used with **25b** as the halo ketone, except that the mixture was heated for 4 h: crude yield 44%; mp 210–212 °C (absolute EtOH); NMR (Me_2SO-d_6) δ 2.405 (d, 3, Me, J = 1 Hz), 5.94 (br s, 2, NH_2), 6.37 (br s, 2, NH_2), 6.495 (d, H-6, J = 1 Hz, decoupled at 2.405 ppm). Anal. Calcd for $C_7H_8N_4S \cdot 0.2H_2O$: C, 45.84; H, 4.61; N, 30.48; S, 17.44. Found: C, 45.70; H, 4.43; N, 30.52; S, 17.52.

When this reaction was carried out in water at 40 °C for 45 min with 1 equiv of alkali, the sulfide **30** was obtained (see Table I).

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Registry No. **1a**, 591-28-6; **1b**, 15184-02-8; **2a**, 99-73-0; **2b**, 70-11-1; **2c**, 2632-13-5; **3a**, 74195-29-2; **3b**, 74195-30-5; **3c**, 74195-31-6; **3d**, 74203-17-1; **4a**, 74195-32-7; **4b**, 74195-33-8; **4c**, 74195-34-9; **4d**, 74195-35-0; **5**, 74195-36-1; **6**, 99-90-1; **7**, 14001-60-6; **8**, 5798-75-4; **9**, 74195-37-2; **10**, 15231-48-8; **11**, 104-88-1; **12**, 74195-38-3; **13**, 33268-02-9; **14**, 74195-39-4; **15a**, 74195-40-7; **15b**, 74195-41-8; **18**, 74195-42-9; **19**, 74195-43-0; **20**, 74195-44-1; **21a**, 17649-29-5; **21b**, 74195-45-2; **21c**, 17649-28-4; **22a**, 74195-46-3; **22b**, 74195-47-4; **23**, 27047-19-4; **24a**, 6973-81-5; **24b**, 56-08-6; **25a**, 814-75-5; **25b**, 78-95-5; **26a**, 74195-48-5; **26b**, 74195-49-6; **26c**, 74195-50-9; **27**, 74195-51-0; **28**, 74195-52-1; **29**, 74195-53-2; **30**, 21863-73-0; **31**, 74195-54-3; **32**, 74195-55-4; **33**, 74195-56-5; **34**, 74195-57-6; **35**, 74195-58-7; **36**, 74195-59-8; 3-bromo-3-methyl-2-butanone, 2648-71-7; thiophenol, 108-98-5.

Lewis Acid Promoted Reactions of Diazocarbonyl Compounds. 3.[1a] Synthesis of Oxazoles from Nitriles through Intermediate β-Imidatoalkenediazonium Salts

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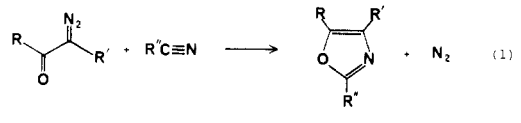
Lewis acid promoted reactions of α-diazocarbonyl compounds with nitriles provide a general method for the production of oxazoles in high isolated yields. The generality of this method is evaluated by the effectiveness of oxazole formation in surveys of Lewis acids, diazocarbonyl compounds, and nitriles. Because of the relative absence of α-halogenation products in reactions performed with $BF_3 \cdot Et_2O$, this Lewis acid is preferred when the nitrile is employed as the reaction solvent. Reactions of diazo ketones in nitrile solvents generally result in higher oxazole yields (70–99%) than do reactions of ethyl diazoacetate (26–31%). When these transformations are performed at or below room temperature, at least 1 equiv of the Lewis acid is required, although catalytic activity is observed in reactions performed at 65 °C. In $BF_3 \cdot Et_2O$ promoted reactions, a minimum tenfold molar excess of nitrile is required for optimum oxazole production, although use of SbF_5 results in high yields of oxazoles even when only a threefold excess of the nitrile is employed. The mechanism for oxazole formation is established as involving initial activation of the nitrile through association with the Lewis acid, followed by attack of the nitrilium complex at the carbonyl oxygen of the diazocarbonyl compound and internal displacement of nitrogen. Although Lewis acid association with the diazocarbonyl compound is the more favorable process in reactions performed with equivalent amounts of nitrile and diazocarbonyl compound, only equilibrium association of the Lewis acid with the nitrile effectively leads to oxazole formation.

Diazocarbonyl compounds react with nitriles under diverse reaction conditions to produce oxazoles (eq 1).[2]



(1)

Thermal decomposition of diazocarbonyl compounds in nitrile solvents at temperatures normally exceeding 100

(1) (a) For papers 1 and 2 see ref 8 and 17. (b) Camille and Henry Dreyfus Foundation Undergraduate Student-Scholar at Hope College, 1979–1980. (c) National Science Foundation Undergraduate Research Participant, Summer, 1977.

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