Intermediates in the Hantzsch Thiazole Synthesis

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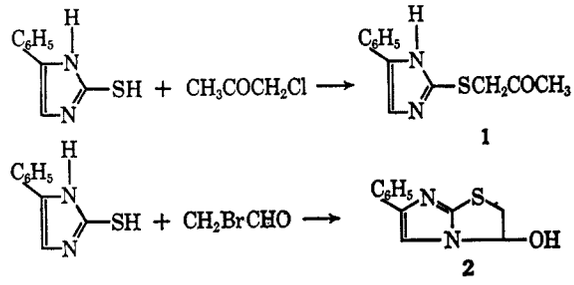
The reaction of N-methyl-*p*-dimethylaminothiobenzamide (**3**) with a number of α-halo ketones and one α-halo-aldehyde gave stable 4-hydroxythiazolinium salts (**4**) which could be subsequently dehydrated to the thiazolium salts (**5**). When the intermediates were also substituted in the 5 position, both possible diastereoisomeric forms were detected by nmr spectroscopy. The effects of acidification and temperature variation on the nmr spectra indicated that the diastereoisomeric 4-hydroxythiazolinium salts are in dynamic equilibrium *via* the open-chain α-thio ketone.

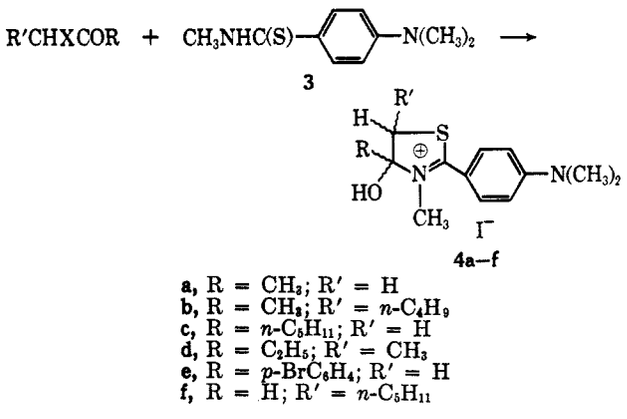
The reaction of a thioamide or a thiourea with an α-halocarbonyl compound in the Hantzsch synthesis usually proceeds smoothly to yield the desired thiazole.[1] Although the reaction has been postulated to be stepwise, reports of the isolation of intermediates in this reaction have been infrequent. In some early examples[2] intermediates of varying stability were isolated by working at low temperatures. These substances were characterized solely by elemental analysis (before the advent of spectroscopic techniques) and were always assumed to be the open-chain α-thio ketones (for example, see ref 3).

Recently, Kochergin and Shchukina[4] isolated an intermediate from the reaction of chloroacetone with 2-mercapto-4-phenylimidazole which was shown by both chemical evidence and ir spectroscopy to be 2-acetonylmercapto-4-phenylimidazole (**1**). However, the analogous reaction[5] between bromoacetaldehyde and 2-mercapto-4-phenylimidazole unexpectedly afforded the cyclized intermediate 2,3-dihydro-3-hydroxyimidazo[2,1-*b*]thiazole (**2**). Both **1** and **2** could be dehydrated in acidic media to the corresponding thiazole derivatives.



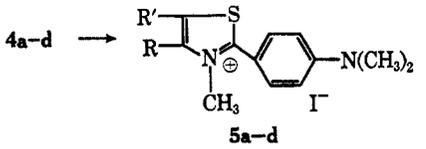
In a series of papers by Murav'eva and Shchukina,[6] the isolation of hydroxythiazolines from the reaction between α-halo ketones and a variety of thioureas is reported. The use of a reagent bearing a basic center or the addition of a base to the reaction mixture was recognized as necessary to prevent the acid-catalyzed elimination of the elements of water from the intermediates. Since the publication of this work, a number of similar intermediates have been isolated from analogous reactions.[7,8] It is interesting to note that in each of these cases[3-8] only one intermediate, either the α-thio ketone or the hydroxythiazoline, was isolated from the reaction mixture.

In the present work, the reaction of N-methyl-*p*-dimethylaminothiobenzamide (**3**) with a number of α-halo ketones and one α-halo aldehyde was found to give stable 4-hydroxy-2-thiazolinium derivatives **4a–f**, which were isolated as the iodide salts.



a, R = CH_3; R′ = H
b, R = CH_3; R′ = *n*-C_4H_9
c, R = *n*-C_5H_{11}; R′ = H
d, R = C_2H_5; R′ = CH_3
e, R = *p*-BrC_6H_4; R′ = H
f, R = H; R′ = *n*-C_5H_{11}

The 4-hydroxy-2-thiazolinium salts were stable in neutral and basic media, but they could be dehydrated to the thiazolium salts **5a–d** by treatment with methanolic hydrogen chloride. Dehydration could also be accomplished, although less conveniently, by treatment with methanesulfonyl chloride containing sulfur dioxide in the presence of collidine.[9]



The reaction of **3** with 3-bromo-2-pentanone yielded a mixture of the intermediate (**4d**) and the thiazolium

(1) R. H. Wiley, D. C. England, and L. L. Behr, *Org. Reactions*, **6**, 367 (1951).

(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 496.

(3) A. R. Todd, F. Bergel, and Karimullah, *Ber.*, **69B**, 217 (1936).

(4) P. M. Kochergin and M. N. Shchukina, *J. Gen. Chem. USSR*, **26**, 483 (1956).

(5) P. M. Kochergin and M. N. Shchukina, *ibid.*, **26**, 3233 (1956).

(6) (a) K. M. Murav'eva and M. N. Shchukina, *Zh. Obshch. Khim.*, **30**, 2327 (1960); *Chem. Abstr.*, **55**, 9376*a* (1961). (b) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2334 (1960); *Chem. Abstr.*, **55**, 9376*g* (1961). (c) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2340 (1960); *Chem. Abstr.*, **55**, 9377*b* (1961). (d) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2344 (1960); *Chem. Abstr.*, **55**, 9377*e* (1961). (e) K. M. Murav'eva and M. N. Shchukina, *Dokl. Akad. Nauk SSSR*, **126**, 1274 (1959); *Chem. Abstr.*, **54**, 498*g* (1960).

(7) A. Takamizawa, K. Hirai, T. Ishiba, and Y. Matsumoto, *Chem. Pharm. Bull. Jap.*, **15**, 731 (1967).

(8) B. M. Regan, F. T. Galysh, and R. N. Morris, *J. Med. Chem.*, **10**, 649 (1967).

(9) G. G. Hazen and D. W. Rosenberg, *J. Org. Chem.*, **29**, 1930 (1964).

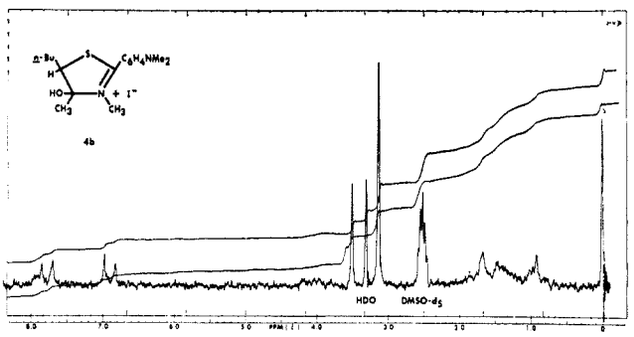


Figure 1.—The nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at 60 MHz in DMSO-d_6.

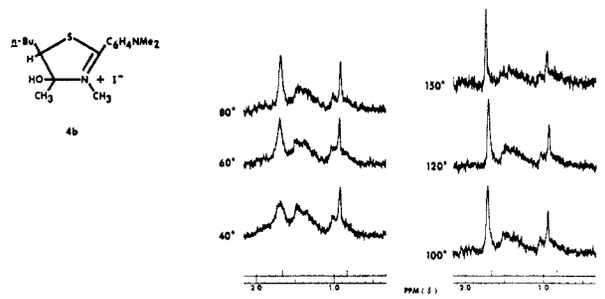


Figure 2.—The partial 60-MHz nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at various temperatures in DMSO-d_6.

salt (**5d**). The mixture was readily resolved by crystallization.

The importance of the quaternary nitrogen in stabilizing the intermediates was shown by the fact that replacement of **3** by *p*-dimethylaminothiobenzamide in the reaction with 3-bromo-2-heptanone resulted in a normal Hantzsch reaction with no evidence of formation of a stable intermediate.

The cyclic nature of the intermediates was established by means of nmr and ir spectra, and, in those cases where diastereomers were possible, both forms were detected and the existence of a dynamic equilibrium between them, *via* the open-chain keto form, could be observed. The absence of carbonyl and NH absorptions coupled with the presence of hydrogen-bonded –OH bands in the ir spectrum indicated the cyclized rather than the open-chain structure for the intermediates. The nmr spectrum of **4b** in dimethyl sulfoxide-d_6 (DMSO-d_6) (Figure 1) showed, in addition to the expected aromatic, *n*-butyl and N-methyl resonances, a broadened singlet at δ 1.67 (relative area 3) assigned to the ring methyl, and a multiplet at 4.17 (relative area 1) assigned to the ring methine group. The chemical shift of the methyl group was inconsistent with an acetyl moiety and thus excluded the ketonic structure. The –OH proton was not visible owing to exchange with the D_2O present in the solvent.

Attention was focused on the broadening of the 4-methyl peak in **4b**. A variable-temperature experiment was performed on this compound with the results shown in Figure 2. The broad methyl peak sharpened with increasing temperature until at 150°, the peak had the same width at half-height exhibited by other sharp singlets in the spectrum. No other peaks were affected by the increase in temperature.

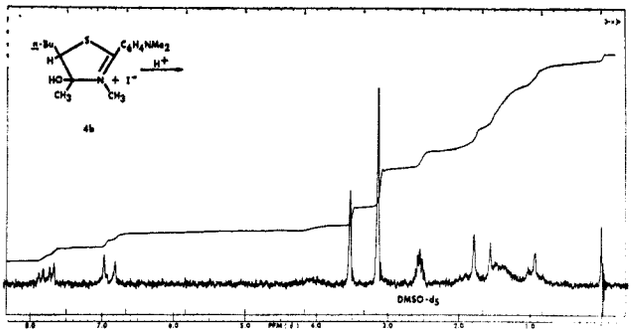


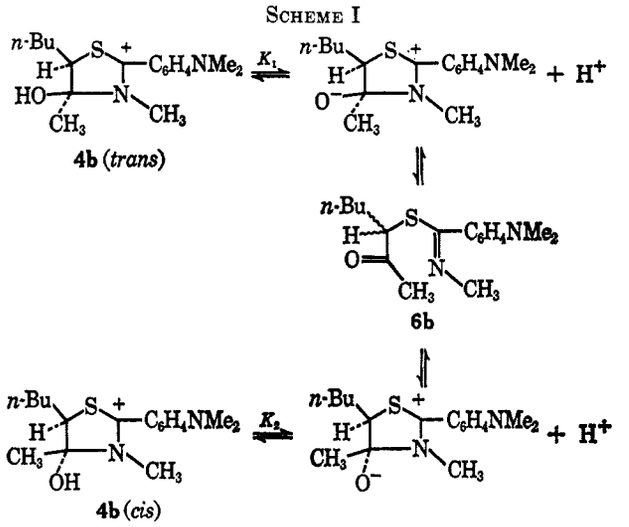
Figure 3.—The nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at 60 MHz in DMSO-d_6 after the addition of 1 drop of trifluoroacetic acid.

The effect on the nmr spectrum of adding trifluoroacetic acid to a solution of **4b** in DMSO-d_6 is shown in Figure 3. The most striking change observed in the spectrum after acidification was the appearance of two separate methyl singlets at δ 1.57 and 1.80 symmetrically located about the position of the broad singlet which was present before acidification.

The sharpening of the methyl peak indicated an equilibrium which affected the environment of this group. The addition of acid effectively retarded the rate of the equilibrium responsible for the original broadening, and allowed the observation of the individual species participating.

These observations may be accounted for by the equilibria outlined in Scheme I.

SCHEME I



The equilibrium between *cis* **4b** and *trans* **4b** (*cis* and *trans* are defined with reference to the orientations of the 4-methyl and 5-*n*-butyl groups), which proceeds *via* the open-chain ketone **6b**, is sufficiently slow on the nmr time scale to cause broadening of the 4-methyl signal in untreated DMSO-d_6 solution. Raising the temperature of the sample increases the rate of equilibration, thereby sharpening the methyl signal. In the proposed scheme, the addition of acid is postulated to shift the equilibria (K_1 and K_2) to the left and thus to retard the interconversion of the two isomers. The 4-methyl signals of both *cis* **4b** and *trans* **4b** are therefore detectable in the nmr spectrum. Since the chemical shift of the dimethylamino group does not change after

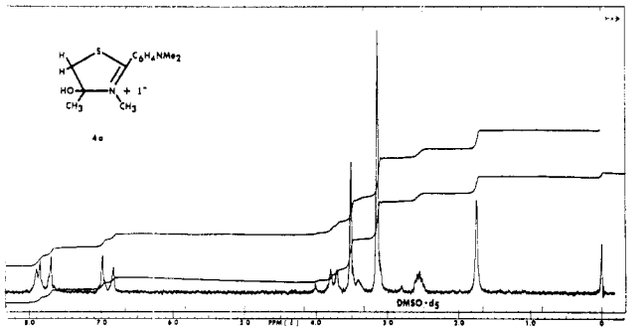
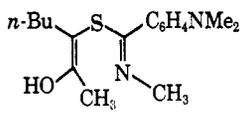


Figure 4.—The 60-MHz nmr spectrum of 2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4a**) in DMSO-d_6.

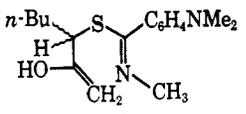
the addition of trifluoroacetic acid, **4b** is not protonated in this medium. This is probably a consequence of unfavorable resonance interaction in the conjugate acid of **4b**.

Further evidence in agreement with the proposed explanation was obtained by examining the nmr spectrum (Figure 4) of the simple analog **4a**. The absorption of the 4-methyl group at δ 1.75 appeared as a sharp singlet which was uneffected by either temperature variation or acidification. The slow equilibrium between enantiomers was evidenced in the room temperature spectrum by the appearance of the absorption of the C-5 methylene protons as an AB quartet centered at δ 3.75 which coalesced when the spectrum was determined at 110°.

Nmr evidence rules out the possibility that **4b** may be an enol form (**7b** or **8b**) of the ketone **6b**.



7b



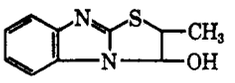
8b

Although enolization of carbonyl groups causes a paramagnetic shift of vicinal methyl groups,[10] the magnitude of such a shift (δ +0.17) is not sufficient to account for the observed shift of δ +0.41 from the normal acetyl resonance. In addition, the proton involved in the enolization would be rapidly exchangeable with D_2O; however, no evidence of the rapid exchange of the proton at C-5 was found.[11] No vinyl proton resonance was observed in the nmr spectrum of any compounds in the present series. Further, the AB quartet of the C-5 methylene protons in compound **4a** is consistent only with the cyclic 4-hydroxy compound. Finally, the nmr spectrum of the structurally related 3-methylmercapto-2-heptanone (prepared by treating 3-bromo-2-heptanone with sodium methyl mercaptide) gave no evidence of enolization.

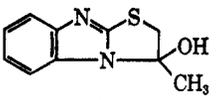
The existence of equilibria of the kind outlined in Scheme I may account for the acid-catalyzed rearrangements of 2-imino-3-phenyl-4-thiazolines to 2-anilinothiazoles observed by Murav'eva and Shchukina,[6c] since the 2-anilinothiazoles can readily arise from the authors on the rearrangement of 4-hydroxy-2-acyliminothiazolidines[6d,e] induced by acetylation agents may also be accounted for by the intermediacy of an open-chain compound.

In the work described by Fefer and King[12] a series of *para*-substituted phenacyl halides was condensed with 2-thioimidazolidine and the resulting intermediates were isolated. The Hammett σ values of the substituent on the phenacyl halides were correlated with the presence or absence of carbonyl absorption in the ir spectra of the reactive intermediates. The authors postulated that these results were evidence of enolization induced by unfavorable resonance interactions. The present work, however, shows that enolization of ketonic intermediates of this type is not demonstrable. The results of Fefer and King may be more adequately explained by the proposed equilibria between open-chain and cyclic intermediates.

Alper and Taurins[13] have recently described the preparation, chemical properties, and nmr spectra of 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**9**) and the 3-methyl analog (**10**) along with other related compounds. On the basis of the nmr



9



10

spectrum in DMSO-d_6 acidified with trifluoroacetic acid, **9** was shown to be a mixture of the *cis*- and *trans*-alcohols, which could not be separated by thin layer chromatography. The nmr spectrum of **10** indicated that in solution the cyclic structure and the tautomeric open-chain α-mercapto ketone are present in a 1:2 ratio.

The nmr spectra of **9** and **10** in DMSO-d_6, in the absence of acid, were investigated in these laboratories to determine whether equilibria were involved similar to those in the present work.[14] The nmr spectrum of **9** exhibited a significant temperature dependence, and at 180°, the pair of methyl doublets of the diastereomeric alcohols coalesced to a single doublet. Complete coalescence of the C-2 and C-3 protons did not occur even at 190°. This is not unexpected because the methyl doublets have a smaller chemical-shift difference ($\Delta\delta$ = 0.02) than either the C-2 or C-3 protons ($\Delta\delta$ = 0.48, and 0.17, respectively), and the coalescence temperature is a function of the lifetimes of the protons at both sites and the chemical shift differences between these sites.[15] The nmr spectrum of **10** was also temperature dependent as the AB quartet and singlet arising from the C-2 methylene protons of the cyclic and open-chain forms coalesced to a single sharp resonance at 150°. The same behavior was noted for the methyl signals of both isomers. These results are consistent with those obtained with our compounds, and support the proposal that the hydroxythiazoline open-chain form. The observations by the same

(10) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 91.

(11) The proton at C-5 did exchange after prolonged standing in DMSO-d_6/D_2O solution, but this is thought to be due to the proximity of the ring sulfur. See P. Beak and E. McLeister, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. P127.

(12) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

(13) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).

(14) We are indebted to Dr. A. Taurins for kindly supplying us with these samples.

(15) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 218.

intermediates in the Hantzsch synthesis are in equilibrium with the corresponding α-thio ketones.

Experimental Section

Melting points were determined using a Thomas–Hoover apparatus and are corrected. Nmr spectra were obtained on Varian A-60 and HA-100 spectrometers. Tetramethylsilane (δ 0) was used as an internal reference standard. Ir spectra were determined in potassium bromide using a Beckman IR-8 spectrophotometer.

4-Hydroxy-2-thiazolinium Salts (4a–e). 3,4-Dimethyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-2-thiazolinium Iodide (4a).—A suspension of N-methyl-4-dimethylaminophenylthiobenzamide[16] (**3**) (6.0 g, 0.03 mol) in methanol (25 ml) containing chloroacetone (4.5 g, 0.05 mol) was shaken at room temperature for 6 days. The solution was evaporated and the residue was partitioned between water (75 ml) and ether (50 ml). Addition of excess potassium iodide (15 g) to the aqueous layer gave the product as the iodide salt: yield 10.3 g (90%); mp 157–158° (recrystallization from ethanol–ether raised this to 164°); ν_{max} 3170 (OH), 1605 (C=N).

When the reaction was performed at 100° for 1 hr in dimethylformamide, the same product was obtained in 80% yield.

Anal. Calcd for $C_{13}H_{19}IN_2OS$: C, 41.27; H, 5.06; I, 33.55; N, 7.41; O, 4.23; S, 8.48. Found: C, 41.09; H, 5.11; I, 33.27; N, 7.60; O, 4.29; S, 8.40.

5-*n*-Butyl-3,4-dimethyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-2-thiazolinium Iodide (4b).—The thioamide (**3**) was shaken with 3-bromo-2-heptanone in methanol as described above and the iodide salt, mp 130–133°, was obtained in 78% yield (recrystallization from methanol–ether raised the melting point to 134–135°): ν_{max} 3180 (OH), 1605 (C=N).

When the reaction was performed in refluxing ethanol a less pure product was formed.

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.01; H, 6.27; N, 6.45. Found: C, 47.37; H, 6.20; N, 6.59.

4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4c).—1-Bromo-2-heptanone (6.5 g, 0.033 mol) was added to a suspension of **3** (6.0 g, 0.03 mol) in 25 ml of methanol. The temperature rose spontaneously to 50° and the solution was allowed to stand for 2 days. The methanol was evaporated and the residue was dissolved in water. The aqueous solution was neutralized with ammonium hydroxide and treated with excess potassium iodide: yield 11.1 g (85%); mp 145° (from methanol–ether); ν_{max} 3150 (OH), 1604 (C=N).

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.01; H, 6.27; I, 29.22; N, 6.45; O, 3.68; S, 7.28. Found: C, 47.26; H, 6.28; I, 29.49; N, 6.38; O, 3.70; S, 7.44.

3,5-Dimethyl-2-(*p*-dimethylaminophenyl)-4-ethyl-4-hydroxy-2-thiazolinium Iodide (4d) and 3,5-Dimethyl-2-(*p*-dimethylaminophenyl)-4-ethylthiazolium Iodide (5d).—A solution of **3** (44.7 g, 0.23 mol) and 2-bromo-3-pentanone (58.8 g, 0.36 mol) in ethanol (150 ml) was refluxed for 4 hr. The ethanol was evaporated and the residue was dissolved in water. The solution was neutralized to pH 7 and potassium iodide (57 g) was added to precipitate a mixture of the thiazolinium and thiazolium salts (90 g). The mixture was crystallized from chloroform–ether and methanol–ethyl acetate to give the less soluble thiazolium salt (**5d**): mp 198–200°; yield 25 g, 28%; ν_{max} 1610 (C=N).

Anal. Calcd for $C_{15}H_{21}IN_2S$: C, 46.39; H, 5.45; I, 32.68; N, 7.22; S, 8.26. Found: C, 46.22; H, 5.46; I, 32.64; N, 7.23; S, 8.16.

The 4-hydroxy-2-thiazolinium salt (**4d**) was obtained from the mother liquors: yield 9 g (9%); mp 148–150° (from methanol–ether); ν_{max} 3190 (OH), 1610 (C=N).

Anal. Calcd for $C_{15}H_{23}IN_2OS$: C, 44.34; H, 5.70; N, 6.90. Found: C, 44.78; H, 5.61; N, 7.04.

4-(*p*-Bromophenyl)-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4e).—A solution of *p*-bromophenacyl bromide (2.8 g, 0.01 mol) and **3** (1.9 g, 0.01 mol) in dimethylformamide (10 ml) was heated at 100° for 40 min. The solution was evaporated and the residue was extracted with hot water. The product separated on addition of potassium iodide: yield 1.5 g (32%); mp 164–165° (from methanol); ν_{max} 3160 (OH), 1612 (C=N).

Anal. Calcd for $C_{18}H_{20}BrIN_2OS$: C, 41.63; H, 3.88; Br, 15.39; I, 24.44; N, 5.40. Found: C, 41.65; H, 4.11; Br, 15.23; I, 24.42; N, 5.42.

5-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4f).—A solution of **3** (6.0 g, 0.02 mol) and α-bromoheptaldehyde (6.0 g, 0.02 mol) was refluxed in methanol (50 ml) for 5 hr. The solution was evaporated and the residue was dissolved in water. The aqueous solution was washed with ether, neutralized with ammonia, and treated with potassium iodide (5 g). The thiazolinium salt melted at 108–115° after recrystallization from methanol–ether: yield 4.5 g (54%); ν_{max} 3200 (OH), 1602 (C=N).

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.00; H, 6.27; I, 29.22; N, 6.45. Found: C, 46.95; H, 6.07; I, 29.04; N, 6.65.

Dehydration of the 4-Hydroxy-2-thiazolinium Salts. 2-(*p*-Dimethylaminophenyl)-3,4-dimethylthiazolium Iodide (5a).—2-(*p*-Dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (7.7 g, 0.02 mol) was dissolved in 100 ml of saturated methanolic hydrogen chloride and the solution was allowed to stand for 1 day. The methanol was evaporated and the residue was dissolved in water and filtered clear. The filtrate was neutralized with ammonium hydroxide and an excess of potassium iodide was added to give the thiazolium salt: mp 212–213° (from ethanol–ether); yield 4.3 g (63%); ν_{max} 1605 (C=N).

Anal. Calcd for $C_{13}H_{17}IN_2S$: C, 43.34; H, 4.76; N, 7.78. Found: C, 43.28; H, 5.05; N, 7.81.

5-*n*-Butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethylthiazolium Iodide (5b).—The dehydration of the 4-hydroxy compound was performed by refluxing for 20 min in methanolic hydrogen chloride. The solution was evaporated, the residue was dissolved in water, and the aqueous solution was neutralized with ammonium hydroxide. Addition of potassium iodide caused the precipitation of the product: mp 119–120° (from methanol–ethyl acetate); yield 70%; ν_{max} 1594 (C=N).

Anal. Calcd for $C_{17}H_{25}IN_2S$: C, 49.04; H, 6.05; I, 30.48; N, 6.73; S, 7.70. Found: C, 49.34; H, 6.30; I, 30.77; N, 6.59; S, 7.86.

4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-3-methylthiazolium Iodide (5c).—4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium iodide (0.47 g, 0.002 mol) was dissolved in dimethylformamide (5 ml) containing 1.6 ml of collidine. Methanesulfonyl chloride (0.8 ml) containing 4% sulfur dioxide was added in portions at 20–25°, and the mixture was allowed to stand for 1 hr. Dilution with water gave a brown solid which was crystallized from methanol–ethyl acetate to give 0.8 g, mp 123–130°. The analytical sample obtained by repeated recrystallization from the same solvents had mp 134°, ν_{max} 1600 (C=N).

Anal. Calcd for $C_{17}H_{25}IN_2S$: C, 49.04; H, 6.05; I, 30.48; N, 6.73; S, 7.70. Found: C, 48.99; H, 6.31; I, 30.43; N, 6.71; S, 7.44.

3-Methylthio-2-heptanone.—Methanethiol (2.4 g, 0.05 mol) was added to a solution of sodium ethoxide (from 1.2 g of sodium) in 40 ml of ethanol. 3-Bromo-2-heptanone (10.0 g, 0.05 mol) was added dropwise with stirring, and the mixture was refluxed for 2 hr. The precipitated sodium bromide was removed by filtration, and the filtrate was fractionated to yield 2-methylthio-2-heptanone: bp 72–75° (20 mm); ν_{max} (in chloroform) 1700 (C=O).

Anal. Calcd for $C_8H_{16}OS$: C, 59.96; H, 10.06; O, 9.98; S, 20.00. Found: C, 59.92; H, 10.21; O, 9.70; S, 20.23.

5-*n*-Butyl-2-(4-dimethylaminophenyl)-4-methylthiazole.—A solution of 3-bromo-2-heptanone (3.9 g, 0.02 mol) and *p*-dimethylaminothiobenzamide (3.6 g, 0.02 mol) in *n*-butyl alcohol (20 ml) was heated at 100° for 2 hr. The solution was evaporated and the residue was crystallized from ether, giving the thiazole hydrobromide, mp 160–165° dec. The salt was dissolved in water and basified, giving the free base: mp 50–51.5° (from petroleum ether; ν_{max} 1608 (C=N). Recrystallization from petroleum ether (bp 30–60°) raised the melting point to 50–51.5°.

Anal. Calcd for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21; S, 11.68. Found: C, 69.75; H, 8.23; N, 10.41; S, 11.65.

Registry No.—**4a**, 17790-29-3; **4b** (*trans*), 17796-66-6; **4b** (*cis*), 17797-05-6; **4c**, 17790-30-6; **4d**, 17790-31-7; **4e**, 17790-32-8; **4f**, 17790-33-9; **5a**, 17790-34-0; **5b**, 17790-35-1; **5c**, 17790-36-2; **5d**, 17790-37-3; 3-methylthio-2-heptanone, 17790-38-4; 5-*n*-butyl-2-(4-dimethylaminophenyl)-4-methylthiazole, 17790-39-5;

(16) D. L. Garmaise, C. H. Chambers, and R. C. McCrae, submitted for publication.

5-*n*-butyl-2-(4-dimethylaminophenyl)-4-methylthiazole hydrobromide, 17790-40-8.

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A One-Step Synthesis of 5-Hydroxy-1,3-benzoxathiol-2-ones from Quinones and Thiourea

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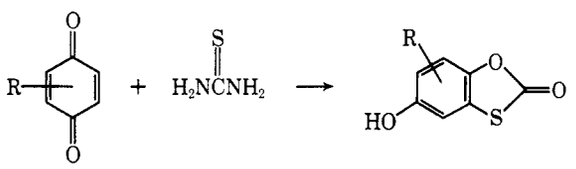
A wide variety of 5-hydroxy-1,3-benzoxathiol-2-ones were prepared in excellent yields by a one-step synthesis from readily available quinones and thiourea. Depending on the nature of the substituents and the reaction conditions, the intermediate S-(2,5-dihydroxyaryl)thiouronium salts and 5-hydroxy-2-imino-1,3-benzoxathioles could also be readily isolated. Reactions of thiourea with unsubstituted, disubstituted, or trisubstituted quinone gave only one end product. However, monosubstituted quinones gave one or more of the three possible isomeric end products, the 4-, 6-, and 7-substituted 5-hydroxy-1,3-benzoxathiol-2-ones. The directive influence of the substituent groups on the addition of thiourea and their effect on the ease of cyclization of the resulting thiouronium salts are described.

Although several methods have been reported in the literature[1,2] for the synthesis of 5-hydroxy-1,3-benzoxathiol-2-ones, these methods are, in general, characterized by low yields or by cumbersome preparative procedures.

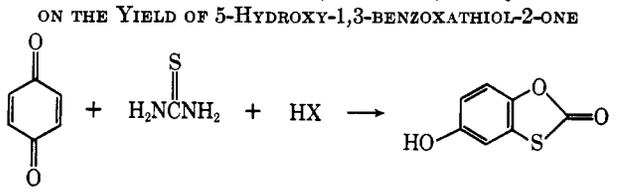
In this paper we describe a method whereby a wide variety of 5-hydroxy-1,3-benzoxathiol-2-ones can be prepared rapidly and in excellent yields by a one-step synthesis from readily available quinones and thiourea.



In general, the procedure consists in mixing a solution of thiourea in aqueous hydrochloric acid with a solution of a quinone in glacial acetic acid and heating for 1 hr on a steam bath. The product, which crystallizes from solution on cooling, is essentially pure. As can be seen from Table I, the reaction is best run with a large excess of thiourea and aqueous hydrochloric acid. Good results are also obtained with sulfuric or trifluoroacetic acid. When a weak acid such as acetic acid is used, the yield is considerably lower, and the product is generally contaminated with colored impurities which are difficult to separate. No product is formed in the absence of acid.

These observations strongly suggest that the reaction involves a 1,4 addition of thiourea to the protonated quinone, giving first an intermediate S-(2,5-dihydroxyaryl)thiouronium salt (**1**), which cyclizes to a second intermediate, 5-hydroxy-2-imino-1,3-benzoxathiole (**2**). This, in turn, is hydrolyzed to the final 5-hydroxy-1,3-benzoxathiol-2-one (**3**) (Scheme I). The formation of each intermediate, and the final product, during the course of the reaction can be readily detected and followed by thin layer chromatography (tlc). Several of the thiouronium salts (Table II) and imino salt were isolated and characterized. Upon being heated in strong aqueous acid, they were rapidly and quantitatively converted into the corresponding products.

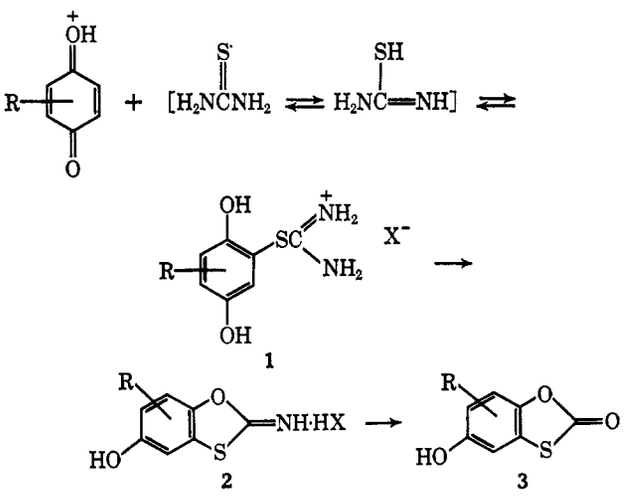
TABLE I
EFFECTS OF AMOUNT OF ACIDS, THIOUREA, AND QUINONES ON THE YIELD OF 5-HYDROXY-1,3-BENZOXATHIOL-2-ONE



Acid	Molar ratio	Benzoquinone[a] molar ratio	Thiourea[b] molar ratio	Yield, %
...	...	1.0	1.5	0
HCl	3.0	1.0	1.5	92
HCl	1.0	1.0	1.5	60
HCl	0.5	1.0	1.5	21
HCl	3.0	2.0	1.0	10
H_2SO_4	3.0	1.0	1.5	94
CF_3CO_2H	10.0	1.0	1.5	85
HOAc	10.0	1.0	1.5	45

[a] Solution in HOAc. [b] Solution in aqueous 2 *N* HCl or H_2SO_4

SCHEME I



(1) H. Burton and S. B. David, *J. Chem. Soc.*, 2193 (1952).
(2) H. Fiedler, *Chem. Ber.*, **95**, 1771 (1962).