When triketone **1** was treated with acetic anhydride but no boron fluoride, only **1** was recovered upon subsequent treatment with sodium acetate solution.

Conversion of Acylpyrone 4a to Acylpyridone 5a.—To a solution of 1.02 g of acylpyrone **4a** in 25 ml of 95% ethanol, was added commercial anhydrous liquid ammonia until the flask grew cold. The solution was evaporated to dryness, and the entire process was repeated. The remaining oil solidified on treatment with a small amount of acetone to afford 0.74 g (73%) of 2-methyl-3-benzoyl-6-phenyl-4(1H)-pyridone (**5a**), mp 267–269°.

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.89; H, 5.22; N, 4.86.

Acetylation and Cyclization of 1-Phenyl-1,3,5-hexanetrione (19) to Form Acylpyrone 21a.—This reaction of triketone **19**[2] was effected essentially as described for the acetylation of triketone **1**. After neutralization with excess sodium acetate solution, the layers were separated and the 1,2-dichloroethane layer was dried (magnesium sulfate). The solvent was removed and the residue was recrystallized from 95% ethanol to give 2-methyl-3-acetyl-6-phenyl-4*H*-pyran-4-one (**21a**) in 52% yield; it melted at 137–141° and at 147–148° after recrystallization from 95% ethanol.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.58; H, 5.50.

Conversion of Acylpyrone 21a to Acylpyridone 22a.—A solution of 1.0 g of acylpyrone **21a** in 25 ml of 95% ethanol was treated with anhydrous liquid ammonia essentially as described above for that of **4a** to afford 0.15 g (16%) of 2-methyl-3-acetyl-6-phenyl-4(1H)-pyridone (**22a**), mp 207–210°, and 214–214.5° after recrystallization from acetone.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.90; H, 5.88; N, 6.41.

Acetylation and Cyclization of *o*-Hydroxybenzoylacetone (23) to Form Chromone 25.—This reaction was effected essentially as described for triketone **1** employing 4.0 g (0.0225 mole) of hydroxy β-diketone **23**[14] and 7.0 g (0.068 mole) of acetic anhydride in 75 ml of 1,2-dichloroethane. After stirring for 18 hr, the reaction mixture was decomposed with a solution of 18.5 g of sodium acetate trihydrate in 50 ml of water, and the 1,2-dichloroethane was removed by distillation until the vapor temperature reached 90°. The remaining mixture was refluxed for 1 hr and then cooled overnight to precipitate 2.15 g of crude product (mp 75–80°), a thin layer chromatogram of which showed a single component with no starting material present. Two recrystallizations from cyclohexane afforded 2.0 g (approximately 50%) of 2-methyl-3-acetylchromone (**25**), mp 89–90° (lit.[12] mp 89°); a mixture melting point with starting compound **23** (mp 95°) was only 68–75°. The product failed to give an enol test with ethanolic ferric chloride; its structure was supported by its nmr spectrum.

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.36; H, 4.86.

When the reaction was repeated essentially as described above except for the absence of boron fluoride, only the starting hydroxy β-diketone (**23**) was recovered.

Registry No.—Acetic anhydride, 108-24-7; boron fluoride, 7637-07-2; **4a**, 10037-16-8; **5a**, 10037-17-9; **21a**, 10037-18-0; **22a**, 10037-19-1; **25**, 10037-20-4; **2**, 1029-94-3; **7**, 1004-36-0; **6**, 1013-99-6.

(14) C. G. Badcock, F. M. Dean, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 903 (1950).

Chain Tautomerism of Thiazolidines[1]

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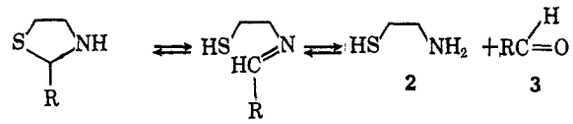
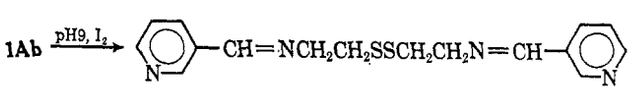
A novel reaction of 2-phenylthiazolidine (**1Aa**) with mercaptoacetic ester (**4a**) or acid (**4b**) to form a thiazolidone (**5**) is described. By alkylation of the thiazolidine (**1Aa**) under alkaline conditions, imino sulfides (**7**) are obtained. Oxidation of **1Ac** by bubbling oxygen through a dimethyl sulfoxide (DMSO) solution constitutes a new oxidation of thiazolidines to disulfides in a neutral medium. These reactions extend this previously limited area of chain-tautomeric thiazolidine chemistry. Prelminary work suggests that these reactions are catalyzed by acidic or basic conditions analogous to the ring–chain tautomerism (mutarotation) of sugars.

Our interest in the chain-tautomeric chemical behavior of iminothiophenes[3] suggested examination of a system, for which the nitrogen function in relation to sulfur is incorporated in a heterocyclic ring, rather than being an exocyclic imino group. Thiazolidines **1A** offer such a situation, and indeed their chain-tautomeric ramifications have been recognized.[4] For the most part, however, the chemistry of thiazolidines has not characterized an intact chain tautomer (**1B**) but rather the aminothiol (**2**) and carbonyl (**3**) precursors of thiazolidine **1A**, as derivatives.[5] Only recently has a disulfide corresponding to **1Bb** been observed.[6]



1Aa, R = C_6H_5
b, R = 3-C_5H_4N
c, R = *p*-ClC_6H_4



We wish now to report several new examples of chain-tautomeric thiazolidine chemistry, which significantly extend this area of dual product formation, consistent with chain tautomer **1B**. In past investigations of the stability or dual reactivity of **1A** emphasis has been on the incipient thiol function of **1B**. A novel aspect of the current investigation is concerned with the imino function. The discovery by Troutman and Long[7] that ethyl mercaptoacetate (**4a**) reacts with alkylamine-derived Schiff bases to form thiazolidones prompted us to attempt the interception of **1B** through its imino function in such a reaction. Conditions

(1) Presented before the 21st Annual Northwest Regional Meeting, Vancouver, B. C., Canada, June 1966. For Paper III on Tautomerism see G. W. Stacy, T. E. Wollner, and T. R. Oakes, *J. Heterocyclic Chem.*, **3**, 51 (1966).

(2) From the Ph.D. Thesis of P. L. Strong, Washington State University, June 1965. National Defense Education Act Fellow, 1961–1964.

(3) (a) G. W. Stacy, A. J. Papa, F. W. Villaescusa, and S. C. Ray, *J. Org. Chem.*, **29**, 607 (1964); (b) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *ibid.*, **30**, 4074 (1965).

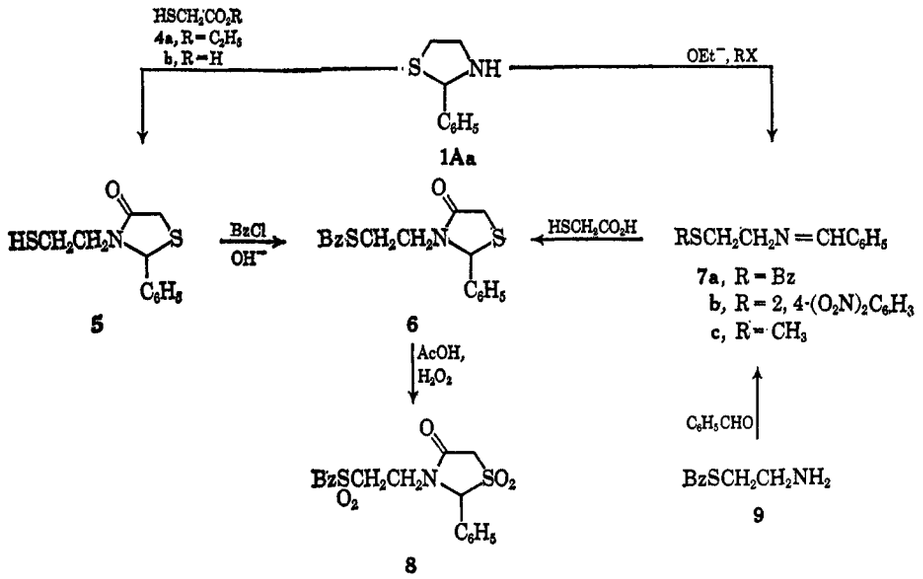
(4) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 701.

(5) S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).

(6) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **27**, 2452 (1962).

(7) H. D. Troutman and L. M. Long, *J. Am. Chem. Soc.*, **70**, 3436 (1948).

SCHEME I

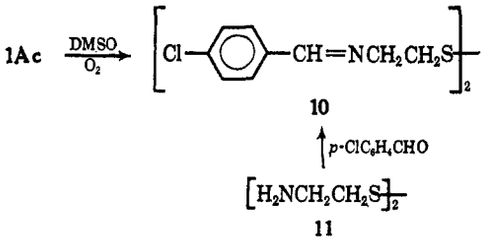


involved heating 2-phenylthiazolidine (**1Aa**) with ethyl mercaptoacetate (**4a**) at 100–110°. Although the anticipated product was immediately isolated, initial success was limited. A 3-day reaction period was required, and then only a 15% yield of thiazolidone **5** was obtained. However, if the reaction was carried out with the corresponding acid (**4b**) in benzene, and if the water formed by condensation of the amino and carboxyl functions was removed by azeotropic distillation,[8] the yield was substantially increased to 75%. Although the foregoing was the procedure of choice, the question of possible acidic catalysis of ring opening of **1Aa** by acid **4b** was of interest. Qualitative exploration suggests that this is the case, for if ester **4a** is employed under conditions identical with the initial experiment with 1 equiv of acetic acid added, the reaction time is shortened (10 hr) and the yield improved (53%).

The structure of **5** was confirmed by spectroscopic evidence. A molecular weight determination and a triplet at δ 1.30 in the nmr spectrum were in agreement with a thiol group (rather than a disulfide). Chemical characterization followed from the alkylation of **5** to sulfide **6**, which in turn was oxidized to a disulfone (**8**).

The alkylation of thiazolidines to chain-related products has been implied in prior work, but the S-alkyl derivatives corresponding to an intact chain tautomer **1B** were not isolated.[5] We have now observed, however, that the S-benzyl chain derivative (**7a**) is readily formed by benzyl chloride alkylation of 2-phenylthiazolidine (**1Aa**) is alkaline absolute ethanol. The identity of **7a** was established by a strong infrared band at 1640 cm^{-1} corresponding to the imino group and by the alternative formation of **7a** from 2-(benzylthio)-ethylamine (**9**) and benzaldehyde. Of particular interest was the fact that **7a** by reaction with mercaptoacetic acid (**4b**) was converted to benzylthiothiazolidone **6**, resulting in intersection of two series of chain-related products. In similar fashion, a crystalline sulfide (**7b**) was formed by the reaction of **1A** with 2,4-dinitrochlorobenzene (see Scheme I).

Although like Johnston and Gallagher,[6] we found that under alkaline conditions oxidation to a disulfide (**10**) readily occurred (72% yield; hydrogen peroxide employed rather than iodine), it was significant to explore this oxidation under neutral conditions wherein the opening of the ring could not be facilitated by either acidic or basic considerations (**1** → **15**). Since Yiannios and Karabinos[9] had observed that dimethyl sulfoxide smoothly oxidizes thiols to disulfides, **1Ac** was treated in a similar manner. Oxidation occurred, but interestingly only, if in addition to the DMSO, oxygen



was bubbled through the solution over a 2-day period. 2-(*p*-Chlorophenyl)thiazolidine (**1Ac**) was employed for experimental convenience, as disulfide **10** was a nicely crystalline product in contrast to the parent phenyl derivative. For comparison, **10** was alternatively prepared from 2,2′-dithiobisethylamine (**11**) and *p*-chlorobenzaldehyde.

Classically, the formation of products which can be related to both members of the tautomeric system is viewed as a tautomeric ramification, regardless of the precise mechanistic details by which the products are actually formed.[10a] We recommend this point of view, implied in the title of this paper, because of its value in product identification and anticipation. Although such dual-product formation is an intriguing facet of tautomerism, all modern practitioners in the field recognize that reactivity and product formation are seldom admissible evidence for the reality of a tautomer itself, while physical evidence is persuasive.[10b]

In the present instance, for example, despite chain-tautomeric chemistry, spectroscopic evidence argues

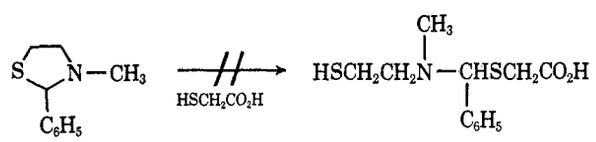
(8) A. R. Surrey, *J. Am. Soc. Chem.*, **69**, 2911 (1947).

(9) C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).

(10) (a) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1960, p 666; (b) A. R. Katritzky and J. M. Lagouski, "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 321.

against the existence of chain tautomer **1Ba** within concentrations detectable. The nmr spectrum of **1A** compares well with that of 3-methyl-2-phenylthiazolidine (**12**) and does not show the singlet at δ 8.11 assignable to the imino proton of **7c**. Similarly, the ultraviolet spectrum of **1A** closely resembles that of **12** and is different from **7c** under neutral conditions.[11] In their thiazolidine studies, Bergmann and Kaluszyner[12] found no infrared bands indicative of the imino or thiol groups of **1B**,[13] and we concur in these findings. Our ultraviolet absorption spectra also agree with those of the aforementioned authors.[12]

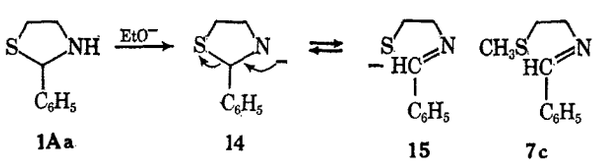
Although reaction of thiazolidines with mercaptoacetic acid (or ester) has been established, interception of **1B** *via* an imino group is not necessarily indicated. An alternative explanation involves nucleophilic displacement by the thiol group on C-2 of the thiazolidine ring, and even lack of reactivity of mercaptoacetic acid (**4b**) with 3-methyl-2-phenylthiazolidine (**12**) (where the N-methyl group makes impossible opening of the ring to the chain tautomer) to from **13** fails to



12 **13**

rule out this possibility. This is so as it can be argued that for the proposed displacement to succeed, concerted condensation heterocyclization must also be possible, and, of course, for **12** this is blocked by the same methyl group which precludes chain tautomerism.

However, definitive evidence for chain tautomerization (alkylation and oxidation to a disulfide) under basic conditions has been obtained. Here, ring opening presumably would be facilitated by the formation of a mercaptide anion (**15**). This is borne out by the



1Aa **14** **15** **7c**

ultraviolet spectrum in alkaline ethanol, as the absorption peak at 245 mμ common to **7c**[14] appears, strongly suggesting the presence of **15**.

The indications of acidic and basic catalysis in the chain tautomerism of thiazolidines is reminiscent of mutarotation of glucose.[15]

Experimental Section

All melting points are corrected; boiling points at reduced pressures are uncorrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on Beckman IR-5 and IR-8 spectrophotometers and on a Perkin-Elmer Infracord with sodium chloride optics throughout; the spectra of liquids were run as neat films. The nmr spectra were determined with a Varian A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal reference. The chemical shifts in parts per million (ppm) are followed in parentheses by the splitting pattern with the symbols cm = complex multiplet, q = quartet, and d = doublet, and singlets being otherwise assumed; the number of protons found by integration is then indicated. Glpc was carried out by an Aerograph 1520.

Reaction of 2-Phenylthiazolidine (1Aa) with Mercaptoacetic Ester (4a) or Acid (4b) to Form 3-(2-Mercaptoethyl)-2-phenyl-4-thiazolidinone (5). A. Ester 4a.—A mixture of 5.00 g (0.030 mole) of 2-phenylthiazolidine[16] (**1Aa**) and 4.00 g (0.033 mole) of ethyl mercaptoacetate (**4a**) was heated at 100–110° for 3 days (nitrogen). The resulting oil was dissolved in 100 ml of ether and washed with 10% hydrochloric acid (three 50-ml portions) and with water (three 50-ml portions). The ether solution was dried over anhydrous magnesium sulfate and the ether was removed (aspirator). The residual oil was distilled (micromolecular still) to give 1.08 g (15%) of thiazolidone as a colorless, viscous oil, identical (by infrared spectrum) with that obtained in B.

B. Acid 4b in Benzene.—A solution of 3.28 g (0.020 mole) of 2-phenylthiazolidine (**1Aa**) and 2.02 g (0.022 mole) of mercaptoacetic acid (**4b**) in 10 ml of anhydrous benzene was heated under reflux (nitrogen) until the theoretical amount (0.36 ml) of water was collected (5 hr). After the benzene was removed under reduced pressure (aspirator), the residual oil was distilled (micromolecular still) with the distilling flask maintained at a temperature of 220° (0.1 mm) to yield 3.59 g (75%) of a pale yellow, viscous oil: $n^{25}D$ 1.6130; $\nu_{max}^{CHCl_3}$ 1690 (s, CON), 2580 cm^{-1} (w, SH); δ 7.27 (cm, C_6H_5), 5.67 (SC*H*C_6H_5N), 3.12 (SCH_2CO), 2.33–3.00 (cm, NCH_2CH_2S), 1.30 (t, J = 7 cps, SH), ratio 5:1:2:4:1.

Anal. Calcd for $C_{11}H_{13}NOS_2$: C, 55.19; H, 5.47; S, 26.79; mol wt, 239.4. Found: C, 54.97; H, 5.64; S, 26.43; mol wt, 250.0.

C. Acid 4b (Neat).—A mixture of 5.00 g (0.030 mole) of **1Aa** and 3.00 g (0.033 mole) of mercaptoacetic acid (**4b**) was heated at 100–110° (nitrogen) for 10 hr. The resulting oil was dissolved in 100 ml of ether and washed with 10% hydrochloric acid (three 25-ml portions) and with saturated sodium bicarbonate solution (three 25-ml portions). The ether solution was dried over anhydrous magnesium sulfate and the ether was evaporated (aspirator). The residue was distilled to yield 2.20 g (30%) of **5**.

D. Ethyl Mercaptoacetate (4a) Catalyzed by Acetic Acid.—A solution of 5.00 g (0.030 mole) of **1Aa**, 4.00 g (0.033 mole) of ethyl mercaptoacetate (**4a**), and 1.80 g (0.030 mole) of acetic acid was heated at 100–110° for 10 hr. Ether (50 ml) was added, the the orange solution was washed with 10% hydrochloric acid (three 25-ml portions) and with saturated sodium bicarbonate solution (three 25-ml portions). The ether solution was processed in the usual way to give 4.39 g of orange oil; molecular distillation yielded 3.80 g (53%) of **5**. Samples of thiazolidone **5** obtained from all procedures were shown to be identical by their infrared absorption spectra.

3-[(2-Benzylthio)ethyl]-2-phenyl-4-thiazolidinone (6). A. From 3-(2-Mercaptoethyl)-2-phenyl-4-thiazolidinone (5).—A solution of 1.00 g (4.0 mmoles) of **5** and 3 ml of 2 *N* sodium hydroxide in 20 ml of absolute ethanol was added dropwise with stirring to 500 mg (4.0 mmole) of benzyl chloride in 15 ml of absolute ethanol (nitrogen). After the mixture had been stirred for 19 hr and the ethanol was removed under reduced pressure (aspirator), the residue was dissolved in 100 ml of ether. The ether solution was washed with water (two 50-ml portions) and was dried over anhydrous magnesium sulfate. The ether was removed by distillation to give 1.21 g of a yellow oil, which was distilled (micromolecular still) with a temperature of the distilling head at 270° (0.1 mm) to give 730 mg (56%) of pale

(11) G. Hesse and G. Ludwig [*Ann.*, **632**, 158 (1960)] on the basis of ultraviolet evidence have claimed that voruscharine, an African arrow poison, exists to the extent of about 1% chain tautomer of the type **1B** in neutral or acidic solution.

(12) E. D. Bergmann and A. Kaluszyner, *Rec. Trav. Chim.*, **78**, 289 (1959).

(13) However, it was observed that the corresponding six-membered heterocycle from 3-aminopropanethiol showed infrared evidence for a chain tautomer: E. D. Bergmann and A. Kaluszyner, *ibid.*, **78**, 327 (1959).

(14) For N-benzylidenemethylamine, λ_{max}^{EtOH} 247 mμ (ϵ 17,000) is reported by H. Ley and W. Wingchen, *Ber.*, **67**, 501 (1934); J. Meisenheimer and A. Dorner, *Ann.*, **502**, 158 (1933).

(15) (a) C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, **74**, 2534, 2538 (1952); (b) T. M. Lowry, *J. Chem. Soc.*, 2554 (1927); (c) J. N. Brønsted and E. A. Guggenheim, *J. Am. Chem. Soc.*, **49**, 2554 (1927).

(16) 2-Phenylthiazolidine was prepared in quantitative yield, mp 108–109°, recrystallized from hexane mp 109–110°, by the procedure of I. R. Schmolka and P. E. Spoerri, *ibid.*, **79**, 4716 (1957) (lit. 78% yield, mp 108.3–108.8°). We found the following spectroscopic data: ν_{max}^{KBr} 3215 (s, N–H), 1598 (w, C_6H_5), 1090 (s), 1160 (s), 1185 cm^{-1} (s, thiazolidine ring); δ^{CDCl_3} 7.18–7.56 (cm, C_6H_5), 5.53 [SCH(C_6H_5)N], 2.85–3.75 (cm, SCH_2CH_2N), 1.93 (N–H), ratio 5:1:4:1.

yellow, viscous oil: $n^{25}D$ 1.6219; $\nu_{max}^{CHCl_3}$ 1692 cm^{-1} (s, CON); δ 7.10–7.25 (cm, C_6H_5), 5.54 [$NCH(C_6H_5)S$], 3.54 ($C_6H_5CH_2$), 3.54 (SCH_2CO), 3.14–3.97 (cm, SCH_2CH_2N), ratio 10:1:2:2:4.

Anal. Calcd for $C_{18}H_{19}NOS_2$: C, 65.61; H, 5.81; S, 19.46. Found: C, 65.87; H, 5.87; S, 19.62.

B. From N-Benzylidene-2-(benzylthio)ethylamine (7a).—A solution of 3.00 g (0.012 mole) of **7a** (as described in the sequel) and 1.10 g (0.012 mole) of mercaptoacetic acid (**4b**) in 10 ml of anhydrous benzene was heated under reflux (nitrogen) and then the theoretical amount (0.2 ml) of water was collected (5 hr). The benzene solution was washed with saturated sodium bicarbonate solution (two 10-ml portions), with 10% hydrochloric acid (10 ml), and with water (three 10-ml portions). The benzene was dried over anhydrous magnesium sulfate and was then evaporated at reduced pressure (aspirator) to give 3.85 g of a crude product as a colorless oil, which was distilled (molecular still) at a bath temperature of 270° (0.1 mm) to give 3.31 g (84%) of **6**. The infrared spectrum of the substance was identical with that of the material obtained from **5**.

3-[(2-Benzylthio)ethyl]-2-phenyl-4-thiazolidinone Disulfone (8).—By the procedure of Bordwell and Albisetti,[17] 5 ml of 30% hydrogen peroxide was added to a solution of 1.00 g (0.003 mole) of **6** in 5 ml of acetic anhydride and 5 ml of glacial acetic acid. The mixture was heated under reflux for 1 hr and cooled; 20 ml of cold water was added slowly to produce a precipitate, which upon filtration gave 540 mg of a white solid, mp 137–141°. Recrystallization from ethanol gave 468 mg (35%) of **8** as colorless crystals: mp 143–144°; ν_{max}^{KBr} 1710 (s, CON), 1335 (s), 1128 cm^{-1} (s, SO_2).

Anal. Calcd for $C_{18}H_{19}NO_5S_2$: C, 54.94; H, 4.87; S, 16.30. Found: C, 54.99; H, 4.93; S, 16.30.

N-Benzylidene-2-(benzylthio)ethylamine (7a). A. From 2-Phenylthiazolidine (1Aa).—A solution, prepared by dissolving 280 mg (0.012 g-atom) of sodium and 2.00 g (0.012 mole) of **1Aa** in 50 ml of absolute ethanol, was added dropwise with stirring (nitrogen) to 1.50 g (0.012 mole) of benzyl chloride in 40 ml of absolute ethanol over a period of 1.25 hr. The resulting mixture was stirred for 2 days at room temperature, and the solution was filtered. The ethanol was then evaporated under reduced pressure, and 2.00 g of crude residue was distilled to give 1.61 g (53%) of a colorless oil: bp 124–125° (0.1 mm); $n^{25}D$ 1.6058, d^{25}_4 1.1505, $\nu_{max}^{CHCl_3}$ 1640 cm^{-1} (s, C=N).

Anal. Calcd for $C_{16}H_{17}NS$: C, 75.24; H, 6.71; S, 12.56. Found: C, 75.13; H, 6.76; S, 12.73.

B. From 2-(Benzylthio)ethylamine (9).—A solution of 5.98 g (0.036 mole) of S-benzyl-2-aminoethanethiol (**9**)[18] and 3.82 g (0.036 mole) of benzaldehyde in 25 ml of anhydrous benzene was heated under reflux until the theoretical amount of water (0.5 ml) was collected by azeotropic distillation (2 hr). The benzene solution was evaporated under reduced pressure (aspirator), and residual oil was distilled to give 8.55 g (93%) of the product, bp 124–125° (0.1 mm), which had an infrared absorption spectrum identical with that of the substance prepared by the preceding method.

2-(*p*-Chlorophenyl)thiazolidine (1Ac).—The substance was prepared from 21.2 g (0.15 mole) of *p*-chlorobenzaldehyde and 11.4 g (0.10 mole) of 2-mercaptoethylamine hydrochloride by the general method in a 72% yield: mp 101–102° (lit.[12] mp 102–103°, 53% yield); ν_{max}^{KBr} 1600 (m, C_6H_5), 1188 (s), 1167 (m), 1090 cm^{-1} (s, thiazolidine ring).

N-(*p*-Chlorobenzylidene)-2-aminodithioethane. A. Alkaline Hydrogen Peroxide.—To a mixture of 2.00 g (0.01 mole) of **1Ac** and 20 ml of absolute ethanol was added 0.23 g (0.01 g-atom) of sodium in small pieces. The opaque solution was stirred and cooled in an ice bath during the dropwise addition of 1.5 ml of 30% hydrogen peroxide solution within 1 min. After 5 min the mixture was filtered and cooled to give 1.43 g (72%) of **10** as white crystals, mp 85–86°. The infrared absorption spectrum was identical with that of the material prepared in C.

B. Dimethyl Sulfoxide–Oxygen.—A stream of oxygen was slowly bubbled through a solution of 1.00 g (5.0 mmole) of **1Ac** in 5 ml of DMSO, which was heated at 85–95° for 2 days. The DMSO was removed under reduced pressure (0.1 mm), and the residue was poured into 50 ml of water, after which the aqueous mixture was extracted with ether (three 50-ml portions). After the solution was dried over magnesium sulfate and the solvent was removed (aspirator), 1.10 g of a yellow residue was obtained, mp 50–63°, which was recrystallized from *n*-hexane to yield 580 mg (58%) of pale yellow crystals, mp 82–84°. The infrared absorption spectra were identical with that of the material described in C.

C. From 2,2′-Dithiobisethylamine (11) and *p*-Chlorobenzaldehyde.—To a solution of 500 mg (3.54 mmoles) of *p*-chlorobenzaldehyde and 3 ml of ethanol was added 404 mg (2.66 mmoles) of 2,2′-dithiobisethylamine (**11**).[19] The mixture was swirled for several minutes, filtered, and allowed to stand at room temperature for 0.5 hr; 590 mg of a white, crystalline precipitate was removed by filtration, mp 70–78°. This was twice recrystallized from ethanol to give 330 mg (67%): mp 85–86°; $\nu_{max}^{CHCl_3}$ 1652 cm^{-1} (s, C=N); δ 8.18 (CH=N), 7.17–7.73 (cm, C_6H_5), 3.18 (t, NCH_2), 2.95 (t, SCH_2), ratio 1:4:2:2.

Anal. Calcd for $C_{18}H_{18}Cl_2N_2S_2$: C, 54.40; H, 4.56; Cl, 17.84. Found: C, 54.68; H, 4.48; Cl, 18.01.

3-Methyl-2-phenylthiazolidine (12).—To 3.00 g (0.033 mole) of 2-(methylamino)ethanethiol[20] was added 3.50 g (0.033 mole) of benzaldehyde. A vigorous exothermic reaction occurred, and after standing for 1 hr, the product was distilled. After a forerun of 1.53 g [bp 50–86° (0.07 mm), $n^{25}D$ 1.5760], the product was collected: 2.82 g (48%), bp 86–87° (0.07 mm); $n^{25}D$ 1.5803 [lit.[12] bp 135–136° (9 mm), $n^{25}D$ 1.5807]; $\nu_{max}^{CHCl_3}$ 1212 (s), 1193 (s), 1130 (s), 1075 cm^{-1} (s, thiazolidine ring); λ_{max}^{EtOH} 201 mμ (ϵ 69,000), 258 mμ (ϵ 28,000); δ^{neat} 7.07–7.66 (cm, C_6H_5), 4.86 [s, $SCH(C_6H_5)N$], 2.41–3.32 (cm, SCH_2CH_2N), 2.12 (s, NCH_3), ratio 5:1:4:3.

Attempted Formation of 13 by Reaction of 3-Methyl-2-phenylthiazolidine (12) with Mercaptoacetic Acid (4b).—A solution of 1.50 g (8.39 mmoles) of 3-methyl-2-phenylthiazolidine (**12**) and 702 mg (8.56 mmoles) of mercaptoacetic acid (**4b**) in 5 ml of benzene was heated for 18 hr in the same manner that had been employed for the formation of **5**. A 5-ml sample of the mixture was analyzed by gas chromatography on a 15% Carbowax 20 M Chromium W column at 150°, and by comparison with retention times of known substances the sample was shown to contain only the initial reactants.

The benzene solution was washed with 10% sodium carbonate solution (three 10-ml portions), washed with water (two 10-ml portions), and dried over anhydrous magnesium sulfate. After removal of benzene a recovery of 1.26 g (84%) of **12** was obtained; identification was made by glpc and infrared spectrum.

1-Methylthio-2-(N-benzylidene)aminoethane (7c).—A slurry of 2.00 g (0.012 mole) of 2-phenylthiazolidine in 50 ml of ethanol was added to a solution of 280 mg of sodium (0.012 g-atom) in 50 ml of absolute ethanol (nitrogen). After the mixture had been stirred for 15 min, 1.71 g (0.012 mole) of methyl iodide was added and stirring was continued overnight. Sodium iodide was removed by filtration and the filtrate was worked up in the usual manner, 1.80 g of a pale yellow residue was obtained; this was distilled to yield 1.36 g (36%) of **7c**: bp 129–132° (3.8 mm); $n^{25}D$ 1.5773; ν_{max}^{neat} 1645 cm^{-1} (s, C=N); λ_{max}^{EtOH} 246 mμ (ϵ 33,500), 203 mμ (ϵ 63,000); δ^{neat} 8.11 (s, N=CH), 7.10–7.90 (cm, C_6H_5), 3.69 (t, J = 6.8 cps, NCH_2), 2.70 (t, J = 6.9 cps, SCH_2), 1.98 (s, SCH_3), ratio 1:5:2:2:3.

Anal. Calcd for $C_{10}H_{13}NS$: C, 66.98; H, 7.30; S, 17.88. Found: C, 66.73; H, 7.47; S, 18.05.

Ultraviolet Spectrum of 2-Phenylthiazolidine (1Aa) in Alkaline Solution.—The ultraviolet spectrum of 2-phenylthiazolidine (**1Aa**) in 95% ethanol gave λ_{max} 201 mμ (ϵ 30,000). However, if 2-phenylthiazolidine (3.39×10^{-5} *M*) in 95% ethanolic solution of sodium hydroxide (9.12×10^{-5} *M*) was allowed to stand for 17 hr, a prominent absorption band at 245 mμ (ϵ 13,000) gradually appeared; based on ϵ 33,500 for **7c**, **15** is present at a concentration of 1.39×10^{-1} *M* in equilibrium with 2.00×10^{-5} *M* of the 2-phenylthiazolidine (**1Aa**).

2-(2,4-Dinitrophenylthio)-2-(N-benzylidene)aminoethane (7b).—To a solution of 2.00 g (0.012 mole) of **1Aa** and 280 mg (0.012 g-atom) of sodium in 50 ml of absolute ethanol was added 2.45 g (0.012 mole) of 2,4-dinitrochlorobenzene in 40 ml of absolute ethanol (nitrogen). After work-up, 3.15 g of crude product was obtained and was recrystallized from 30 ml of ethyl

(17) F. G. Bordwell and C. H. Albisetti, Jr., *J. Am. Chem. Soc.*, **70**, 1558 (1948).

(18) Prepared by the method of J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 800 (1952), in 72% yield, bp 89–91° (0.1 mm) [lit. bp 100° (0.8 mm), D. B. Reisner, *J. Am. Chem. Soc.*, **78**, 5102 (1956)].

(19) Crude 2,2′-dithiobisethylamine (**11**) was prepared in quantitative yield by the method of A. H. Nathan and M. T. Bogert, *ibid.*, **63**, 2361 (1941).

(20) This substance was prepared by reduction of thialzolidine by lithium aluminum hydride in a 70% yield: E. L. Eliel, E. W. Della, and M. M. Rogic, *J. Org. Chem.*, **27**, 4712 (1962).

acetate to which 20 ml of hexane was added to yield 2.33 g (59%) of yellow crystals: mp 82–82.5°; ν_{max}^{KBr} 1654 (m, C=N), 1535 (s), 1352 cm^{-1} (s, NO_2).

Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.36; H, 3.95; N, 12.68. Found: C, 54.50; H, 4.08; N, 12.45.

Registry No.—**1Aa**, 4569-82-8; **5**, 7782-02-7; **6**, 7738-96-7; **8**, 7738-97-8; **7a**, 7738-98-9; **1Ac**, 7738-99-0; **10**, 7739-00-6; **12**, 7739-01-7; **7c**, 7739-02-8; **7b**, 7739-03-9.

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The Oxidation of Organic Divalent Sulfur by Iodine. I. Alternative Pathways for Thiols as Determined by Structure[1]

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While many water-soluble thiols are oxidized terminally to disulfides by iodine in aqueous potassium iodide, thiols which have a free β-carboxyl group are strongly inclined to further oxidation, apparently without going through the disulfide stage, and the ratio of higher oxidation product to disulfide increases with increasing initial dilution of the thiol. For 3-mercaptopropionic acid, mercaptosuccinic acid, and *o*-mercaptobenzoic acid the higher oxidation products are the corresponding sulfonic acids. For cysteine the higher oxidation product is 3-sulfinoalanine, the corresponding sulfinic acid. *o*-Mercaptobenzoic acid gives particularly high ratios of sulfonic acid to disulfide since the latter is unusually sensitive to further oxidation. It is suggested that a sulfenyl iodide is first formed in all cases, and that this intermediate is either attacked by thiol to give disulfide, or undergoes an intramolecular displacement reaction to form a five-membered cyclic intermediate which undergoes hydrolysis and further oxidation.

It has long been known that water-soluble thiols are rapidly oxidized by iodine in aqueous potassium iodide to disulfides, which are then resistant to further oxidation by small concentrations of iodine over a wide range of temperature and pH. Klason[2] first used the reaction as the basis for a quantitative procedure for the determination of thiols, but occasional reports have appeared of the overoxidation of certain thiols, *i.e.*, of the consumption of more than 1 equiv of iodine per mole of thiol. Dowler[3] reported that cysteine is not oxidized to cystine with iodine, "... provided but a small amount of cysteine is present and further provided that cysteine is added to the solution of iodine" (rather than *vice versa*). Bierich and Kalle[4] observed that the apparent SH values as determined iodometrically for solutions of cysteine and of reduced glutathione of known concentrations agreed approximately with the theoretical when sodium nitroprusside was used as indicator, but when starch was used as indicator consumptions of iodine were greater, the extent of the difference increasing with decreasing initial concentration of cysteine. Shinohara[5] demonstrated the much slower but ultimately complete oxidation of cystine to cysteic acid by the use of a large excess of iodine, but Lavine[6] has shown that cystine is completely resistant to iodine in water at 25–30°, provided the concentration of HI is molar or higher.

Lucas and King[7] made a study of the influences of several factors on the oxidation of a number of thiols by aqueous iodine. While their data on the effects of temperature and of pH are very interesting, the results are not definitive since they failed to realize that initial concentration is the overriding factor in those cases where the thiol is sensitive to overoxidation. They did demonstrate clearly, however, that individual thiols differ quite markedly in their behavior toward iodine. Simonsen[8] did realize the primary importance of concentration, insofar as cysteine is concerned, and attempted, though unsuccessfully, to isolate cysteinesulfinic acid (3-sulfinoalanine) as a reaction product. More recently Larrouquere[9] has studied the reaction of iodine with several thiols, but substantially all of the work was done with solutions of one initial concentration (0.005 *M* RSH).

Tables I and II give the experimental evidence for the two empirical generalizations: that initial concentration of thiol is of primary importance in determining the degree of overoxidation observed with a given thiol, and that thiols vary greatly in their susceptibility to overoxidation. The 12 thiols examined in the present study are easily divided into two groups: (A) those rather resistant to overoxidation, and (B) those highly susceptible to it. All of the members of group A could be satisfactorily assayed iodometrically in 0.01 *M* solution, but with further dilution each exhibits a small but significant degree of overoxidation. Even under the forcing conditions of inverted addition, however, the highest observed value (2.20) is far from the maximal value of 6, which would correspond to oxidation to sulfonic acid. The members of group B, though they differ among themselves, are all quite prone to overoxidation, even without resort to inverted addition.

There appear, then, to be two distinct, but closely related questions of chemical interest here. First,

(1) Presented at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 14, 1966. Based on the M.S. dissertation of M. Y. Oester.

(2) P. Klason, *Ber.*, **14**, 409 (1881); **39**, 738 (1906).

(3) V. B. Dowler, *Proc. Am. Soc. Biol. Chem.*, **XXII**, XXXVIII (1928); with *J. Biol. Chem.*, **78** (1928).

(4) R. Bierich and K. Kalle, *Z. Physiol. Chem.*, **175**, 115 (1928).

(5) K. Shinohara, *J. Biol. Chem.*, **96**, 285 (1932).

(6) T. F. Lavine, *ibid.*, **109**, 141 (1935).

(7) C. C. Lucas and E. J. King, *Biochem. J.*, **26**, 2076 (1932).

(8) D. G. Simonsen, *J. Biol. Chem.*, **101**, 35 (1933).

(9) J. Larrouquere, *Ann. Chim.* (Paris), **6**, 733 (1961).