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Some Thiazinethiols and their Intermediate Compounds[1]

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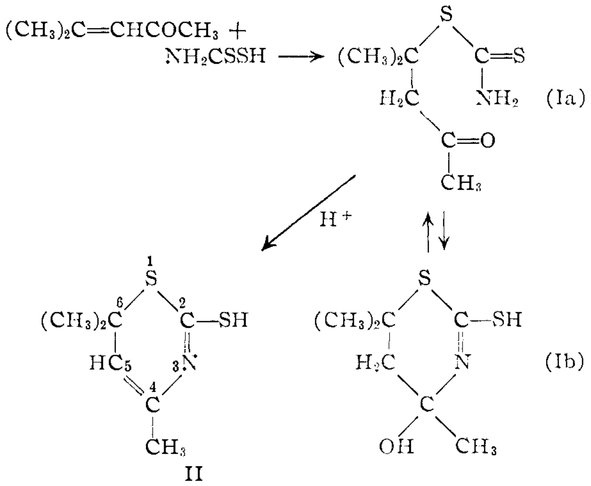
Substituted thiazine-2-thiols were prepared by treating dithiocarbamic acid with α,β-unsaturated ketones. When mesityl oxide was employed, a stable addition compound was first formed; this intermediate cyclized, with loss of water, in the presence of excess acid to form 4,6,6-trimethyl-6H-1,3-thiazine-2-thiol. Upon heating with sulfuric acid, this thiazinethiol dimerized, and an elucidation of the structure of the dimer so formed is presented. Benzalacetone and benzalacetophenone behaved similarly on interaction with dithiocarbamic acid. Crotonaldehyde and methyl acrylate, as examples of α,β-unsaturated aldehydes and esters, reacted to give well-defined addition compounds. Cyclization gave thiazines which showed certain structural variations from those obtained with α,β-unsaturated ketones.

The synthesis of 6H-1,3-thiazine-2-thiols, with the exception of a somewhat related bicyclic 4,5-benzo-6H-1,3-thiazine-2-thiol, has not been reported. This compound was prepared by Paal and Commerell[2] by treating *o*-aminobenzyl alcohol with carbon bisulfide. In connection with studies on vulcanization accelerators, a new synthesis[3] for 6H-1,3-thiazine-2-thiols was developed which involves the addition of dithiocarbamic acid to α,β-unsaturated compounds. A convenient route to this class of compounds is offered by the synthesis described in this paper.

Addition of dithiocarbamic acid to mesityl oxide gives a high yield of 1,1-dimethyl-3-oxobutyl dithiocarbamate (Ia). Ultraviolet absorption indicates that in the crystalline state this compound exists primarily in the cyclic form (Ib) since the absorption curve is essentially the same as that for the dihydrothiazine (IV). The strong absorption in infrared for hydroxyl and the lack of carbonyl are further evidence for the ring structure. A similar examination of certain other intermediates (V, VI and IX) shows that they follow the same pattern, and indicates that they also exist chiefly in the cyclic form in the crystalline state. In acid solution, spontaneous cyclization with loss of water occurs to give 4,6,6-trimethyl-6H-1,3-thiazine-2-thiol (II). The intermediate I can be isolated, however, from reactions in which an excess of acid is avoided. In general it was more convenient to liberate dithiocarbamic acid from its salt in the presence of the unsaturated ketone. Equally satisfactory results were obtained by adding the ketone to the liberated acid at 0°.

The thiazine (II) is only weakly acidic (pK_A about 10.9) but it is soluble and stable in excess aqueous sodium hydroxide. The zinc and lead salts are prepared readily from such alkaline solutions. Oxidation with ammonium persulfate, and other oxidizing agents, gives the disulfide as an unstable liquid which reverts to II and tars on standing. A sulfenamide prepared by oxidation in the presence of cyclohexylamine is similarly unstable. The 2,4-dinitrophenyl derivative, prepared by reaction of an alkaline solution and 2,4-dinitrochlorobenzene, is a stable, crystalline solid.



When II was heated with sulfuric acid, a dimer[4] (III) was obtained from which it was not possible to regenerate II. This dimer is dibasic and stable in aqueous sodium hydroxide solution; these properties exclude dimerization by linking at either the sulfur or nitrogen. Structure determination by means of ultraviolet absorption[5] showed that the maximum at 314 mμ for II (Table I) was reproduced in III but at approximately half the intensity. This suggested that half the dimer molecule had the same structure as II. Examination of curves for reference compounds revealed that the absorption peak for 4,4,6-trimethyl-4,5-dihydro-4H-1,3-thiazine-2-thiol (IV) occurred at about 288 mμ which is nearly the same wave length as the second absorption peak for III. The agreement of the absorption curve for III with that for a mixture of equal parts of II and IV was so close as to leave little doubt that the structure of the dimer is as represented in formula III. Exact agreement would not be expected since the position of the methyl groups in IV is different from those in II, and because the 5-position in the II portion of the dimer can be considered as being substituted. Addition of the proton at the 5-position with bond formation at the 4-position was preferred. Exam-

TABLE I

Compound	Spectrum λmax., mμ	$\epsilon \times 10^{-3}$	λmin., mμ	$\epsilon \times 10^{-3}$
I	289	72	241	41
II	314	71		
III	290	49	243	22
IV	288	74	241	40
Equal parts of II and IV	290	56	240	23

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[1] A portion of this work was presented at the XIIth International Congress of Pure and Applied Chemistry, New York, 1951.

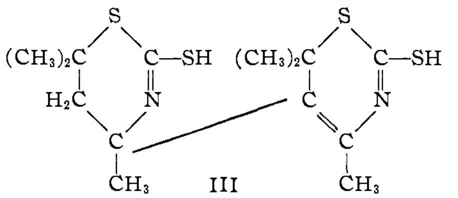
[2] C. Paal and O. Commerell, *Ber.*, **27**, 2427 (1894).

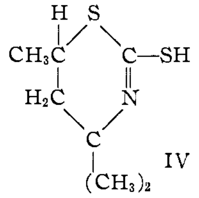
[3] J. E. Jansen, U. S. Patents 2,440,095 and 2,568,633.

[4] F. Swedish, U. S. Patent 2,439,828.

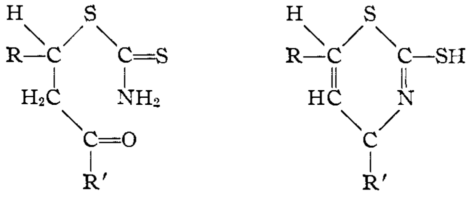
[5] We are indebted to (Mrs.) Laura Schaefgen for the experimental work and interpretation of this portion of the investigation.

ination of models indicated sufficient steric hindrance to make the attachment of the group at the 5-position unlikely. Further evidence for the structure of III was the observation that it was not possible to form a dimer from IV.


III

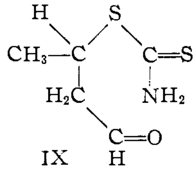

IV

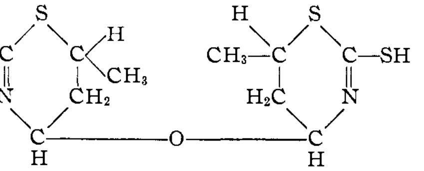
The reactions of benzalacetophenone and benzalacetone with dithiocarbamic acid were investigated. Both ketones gave reactions which followed the same general course as that described for mesityl oxide. Stable intermediates, 1,3-diphenyl-3-oxopropyl dithiocarbamate (V) and 1-phenyl-3-oxobutyl dithiocarbamate (VII), respectively, were isolated and characterized. Cyclization of these intermediates was effected in the presence of acid to give the corresponding thiazines, 4,6-diphenyl-6H-1,3-thiazine-2-thiol (VI) and 4-methyl-6-phenyl-6H-1,3-thiazine-2-thiol (VIII).



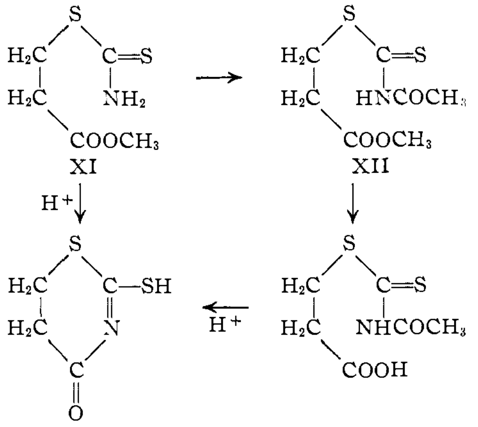
	R	R'
V, VI	C_6H_5	C_6H_5
VII, VIII	C_6H_5	CH_3

With crotonaldehyde, 2-dithiocarbamylbutyraldehyde (IX) was readily formed. Attempts to form the expected thiazine by loss of water from IX gave what appears to be an ether which has been tentatively assigned formula X. The difference in ease of loss of water as compared to the ketone addition product I may be attributable to the fact that the cyclic intermediate in the case of IX has the properties of a secondary alcohol rather than those of tertiary alcohol in I.


IX


X

Addition of methyl acrylate to a suspension of dithiocarbamic acid in water gave methyl 3-dithiocarbamylpropionate (XI). Unlike the corresponding acid,[6] this ester was not cyclized to 4,5-dihydro-2-thiol-6H-1,3-thiazine-4-one (XIV) with acetic anhydride containing a trace of sulfuric acid; instead the amide XII was formed. On warming with sulfuric acid, XI was converted to XIV. Under these conditions, the ester was probably hydrolyzed to the acid before ring closure occurred. The amide XII was soluble in dilute sodium hydroxide but on acidification the acid XIII was recovered, indicating that XII is not a cyclic compound. Compound XIII was also converted to XIV by warming with aqueous sulfuric acid.


XI XII XIV XIII

Experimental[7]

1,1-Dimethyl-3-oxobutyl Dithiocarbamate (I) and 4,6,6-Trimethyl-6H-1,3-thiazine-2-thiol (II).—Mesityl oxide (410 g., 3.64 moles) was added to a solution of 370 g. of hydrochloric acid in 500 ml. of water with stirring. The temperature was held at 15–20° with cooling. To this solution was added (45 minutes) 100 g. (3.64 moles) of a 40% aqueous solution of ammonium dithiocarbamate,[8] with stirring and cooling, to maintain the temperature at 8 to 12°. The product separated as a thick, yellow paste and, after stirring and warming to room temperature, 600 ml. of hexane was added to the mixture. Fine crystals of I which separated were filtered, washed with water, and dried to give 395 g. (63%); after recrystallization from benzene, the m.p. was 128 to 129°.

Anal. Calcd. for $C_7H_{13}NOS_2$: C, 43.94; H, 6.85; N, 7.33; S, 33.95. Found: C, 43.90; H, 6.90; N, 7.40; S, 33.43.

The hexane layer in the filtrate was separated and on standing crystals of II were deposited. The crude product weighed 59 g. (9.5%); after recrystallization from ether-hexane, the m.p. was 96 to 97°.

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.51; H, 6.40; N, 8.08; S, 37.00; –SH (by iodine oxidation to the disulfide), 19. Found: C, 48.57; H, 6.50; N, 8.10; S, 37.07; –SH, 19.

When this experiment was repeated using 425 g. (20% excess) of hydrochloric acid, there was obtained 565 g. (91%) of II which melted at 94 to 96°.

The Dimer of II (III).—One hundred grams of II was suspended in 125 g. of 65% sulfuric acid, and this mixture was stirred and maintained at 60 to 65° for 20 minutes. Upon dilution with one liter of cold water and continued stirring, the tan-colored paste solidified to give a fine dispersion of crystalline product. This was filtered, washed and dried

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[6] T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **70**, 1001 (1948).

[7] All melting points are uncorrected.

[8] R. A. Mathes, "Inorganic Syntheses," Vol. 3, McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 48.

to give 97 g. (97%) of III melting at 206 to 207° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{22}N_2S_4$: C, 48.50; H, 6.40; N, 8.09; S, 37.01; mol. wt., 346. Found: C, 48.55; H, 6.42; N, 8.11; S, 37.07; mol. wt. (Rast), 342.

4,4,6-Trimethyl-4,5-dihydro-4H-1,3-thiazine-2-thiol (IV).—The preparation was carried out as described by Kahan.[9] After recrystallization from ethanol, the product melted at 181 to 182°.

Anal. Calcd. for $C_7H_{13}NS_2$: C, 47.96; H, 7.47; N, 7.99; S, 36.58. Found: C, 48.00; H, 7.36; N, 8.06; S, 36.43.

1,3-Diphenyl-3-oxopropyl Dithiocarbamate (V) and 4,6-Diphenyl-6H-1,3-thiazine-2-thiol (VI).—Hydrochloric acid (38 ml., 0.45 mole) was slowly added with stirring to 62.4 g. (0.3 mole) of benzalacetophenone dissolved in 100 ml. of ethanol at a temperature of 12°. To this mixture, there was added 39.6 g. (0.36 mole) of ammonium dithiocarbamate as a 37% aqueous solution, at a temperature of 30 to 35°. The yellow-colored precipitate was filtered, washed with water and dried to give 85 g. (94%) of crude product. After extraction with boiling hexane to remove residual benzalacetophenone and recrystallization from benzene, the purified compound melted at 150 to 151°.

Anal. Calcd. for $C_{16}H_{15}NOS_2$: C, 63.73; H, 5.02; N, 4.65; S, 21.29. Found: C, 64.03; H, 5.10; N, 4.54; S, 21.72.

To 5 g. of V, there was added 25 ml. of acetic anhydride containing 2 drops of sulfuric acid. The solid material dissolved with stirring and the temperature rose to 35°. The yellow, crystalline material (VI) which precipitated on cooling was filtered, washed with hexane and dried to give 4 g. (87%) of crude product. After purification by recrystallization from ethanol, the compound melted at 125 to 125.5°.

Anal. Calcd. for $C_{16}H_{13}NS_2$: C, 67.81; H, 4.62; N, 4.94; S, 22.63; mol. wt., 283. Found: C, 67.88; H, 4.74; N, 4.97; S, 22.52; mol. wt., 287.

1-Phenyl-3-oxobutyl Dithiocarbamate (VII) and 4-Methyl-6-phenyl-6H-1,3-thiazine-2-thiol (VIII).—Hydrochloric acid (25 ml., 0.3 mole) was slowly added (15 minutes) to 24 g. (0.22 mole) of ammonium dithiocarbamate as a 20% aqueous solution at a temperature of −5°. To the resulting slurry of dithiocarbamic acid, there was slowly added (40 minutes) at a temperature of −5°, 29.2 g. (0.2 mole) of benzalacetone dissolved in 25 ml. of ethanol. The oily material which precipitated was filtered and was washed repeatedly with hexane, then with ether, to remove residual benzalacetone. The crude product weighed 33 g. (75%); after recrystallization from benzene, the m.p. was 123 to 124°.

Anal. Calcd. for $C_{11}H_{13}NOS_2$: C, 55.21; H, 5.47; N, 5.86; S, 26.77; mol. wt., 239. Found: C, 55.27; H, 5.55; N, 5.86; S, 26.71; mol. wt., 244.

The preparation of VIII was performed by the same method described for V. From 5 g. of VII there was obtained 4.5 g. (100%) of product melting at 145° after purification by recrystallization from isopropyl acetate.

Anal. Calcd. for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.00; N, 6.32; S, 28.99; mol. wt., 221. Found: C, 59.55; H, 4.96; N, 6.32; S, 28.88; mol. wt., 226.

2-Dithiocarbamylbutyraldehyde (IX).—A solution of 35 g. (0.32 mole) of ammonium dithiocarbamate in 175 ml. of water was acidified by adding 38 ml. of hydrochloric acid diluted with 38 ml. of water. Both solutions were precooled to −5°, and the temperature was maintained at −5° throughout the addition (20 minutes), which was carried out with good stirring. The resulting slurry of solid dithiocarbamic acid was held at 0° during the addition (15 minutes) of 21 g. (0.3 mole) of crotonaldehyde. After stirring at 0° for 1.5 hours, the mixture was allowed to warm to room temperature, and the suspended pasty mass slowly solidified. The solid was filtered, washed three times with water, and once with ethanol, and dried. The weight was 24.2 g. (49.5%); after purification by recrystallization from water; the m.p. was 115 to 116°.

Anal. Calcd. for $C_5H_9NOS_2$: C, 36.77; H, 5.56; N, 8.58; S, 39.29. Found: C, 36.82; H, 5.61; N, 8.58; S, 39.35.

4,4′-Bis-(4,5-dihydro-6-methyl-6H-1,3-thiazine-2-thiol) Ether (X).—A suspension of 20 g. of IX in 75 ml. of 25% sulfuric acid was stirred at 75° for 10 minutes. The pale yellow product was filtered, washed with water and dried to give 17 g. (90%) of X. Purification was effected by acid precipitation from a solution in 10% sodium hydroxide, followed by recrystallization from ethanol. The analytical sample melted at 200 to 201°.

Anal. Calcd. for $C_{10}H_{16}N_2OS_4$: C, 38.91; H, 5.22; N, 9.08; S, 41.57. Found: C, 39.15; H, 5.35; N, 8.94; S, 41.79.

Methyl 3-Dithiocarbamylpropionate (XI).—To a suspension of dithiocarbamic acid, prepared from 110 g. (1 mole) of ammonium dithiocarbamate in 135 ml. of water as previously described under IX, there was added 86 g. (1 mole) of methyl acrylate. The addition, which required 30 minutes, was carried out with good stirring while maintaining the temperature at −5°. After stirring at −5° for an additional hour, the mixture was allowed to warm to room temperature. The oil layer was separated after 2 hours, and after washing with water and drying at 50° under reduced pressure, the oil crystallized. There was obtained 110 g. (61%) of crude product. Purification was effected by recrystallization from benzene–hexane to give an analytical sample which melted at 68.5–69.5°.

Anal. Calcd. for $C_5H_9NO_2S_2$: C, 33.48; H, 5.06; N, 7.82; S, 35.78. Found: C, 33.66; H, 5.11; N, 7.66; S, 36.38.

Methyl 3-(N-Acetyldithiocarbamyl)-propionate (XII).—A suspension of 19 g. of XI in 50 ml. of acetic anhydride containing 1 g. of sulfuric acid was stirred and heated to 60°. The resulting clear, red solution when cooled to 10° deposited fine, needle crystals which were filtered, washed with benzene and dried. There was obtained 15.5 g. (70%) of product which melted at 112 to 113° after recrystallization from benzene.

Anal. Calcd. for $C_7H_{11}NO_3S_2$: C, 37.98; H, 5.01; N, 6.33; S, 28.99. Found: C, 38.09; H, 5.09; N, 6.42; S, 29.12.

3-(N-Acetyldithiocarbamyl)-propionic Acid (XIII).—A solution of 18 g. of XII in 50 ml. of 10% sodium hydroxide was warmed to 50°, then cooled and acidified with hydrochloric acid. The precipitate which formed was filtered, washed with cold water, and dried to give 4 g. (25%) of crude product melting at 177 to 178°, after recrystallization from water.

Anal. Calcd. for $C_6H_9NO_3S_2$: C, 34.75; H, 4.39; N, 6.76; S, 30.95. Found: C, 34.76; H, 4.39; N, 6.75; S, 30.95.

4,5-Dihydro-2-thio-6H-1,3-thiazine-4-one (XIV).—A suspension of 120 g. of XI in 500 g. of 50% sulfuric acid was heated at 80° for one hour with stirring. Ice (500 g.) was added to the resulting mixture of oil and water, and the yellow solid which precipitated was filtered, washed with cold water, and dried. There was obtained 54 g. (66%) of product with m.p. 119 to 120° after recrystallization from benzene.

Anal. Calcd. for $C_4H_5NOS_2$: C, 32.61; H, 3.42; N, 9.52; S, 43.56. Found: C, 32.91; H, 3.52; N, 9.66; S, 43.82.

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(9) M. Kakan, *Ber.*, **30**, 1318 (1897). Reported m.p. 180°.