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Thiazolethiols and their Derivatives

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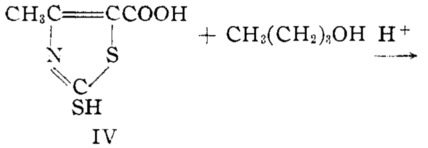
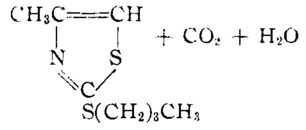
5-Carbomethoxy-4-methyl-2-thiazolethiol, 5-carbethoxy-4-methyl-2-thiazolethiol and 2-mercapto-4-methyl-5-thiazolyl methyl ketone have been prepared. The corresponding disulfides, zinc salts and sulfenamides were also synthesized. An unexpected reaction encountered was the decarboxylation of 2-mercapto-4-methyl-5-thiazolecarboxylic acid to give 2-(butylmercapto)-4-methylthiazole when treated with butyl alcohol under acidic conditions.

Thiazolethiols and their derivatives containing substituents, other than hydrocarbon radicals, in the 5-position have been prepared only in a limited number of examples. 5-Carbethoxy-4-methyl-2-thiazolethiol[1a,b] (II) has been prepared by the reaction of ethyl α-chloroacetoacetate with ammonium dithiocarbamate. Saponification of II gave 2-mercapto-4-methyl-5-thiazolecarboxylic acid[1a] (IV).

Ammonium dithiocarbamate reacted with methyl α-chloroacetoacetate and 3-chloro-2,4-pentanedione to form 5-carbomethoxy-4-methyl-2-thiazolethiol (I) and 2-mercapto-4-methyl-5-thiazolyl methyl ketone (III), respectively. Saponification of I gave IV. Reaction of IV with *n*-butyl alcohol did not yield the expected product, 5-carbobutoxy-4-methyl-2-thiazolethiol, but instead 2-(butylmercapto)-4-methylthiazole (VIII) was obtained. The reaction may be represented as

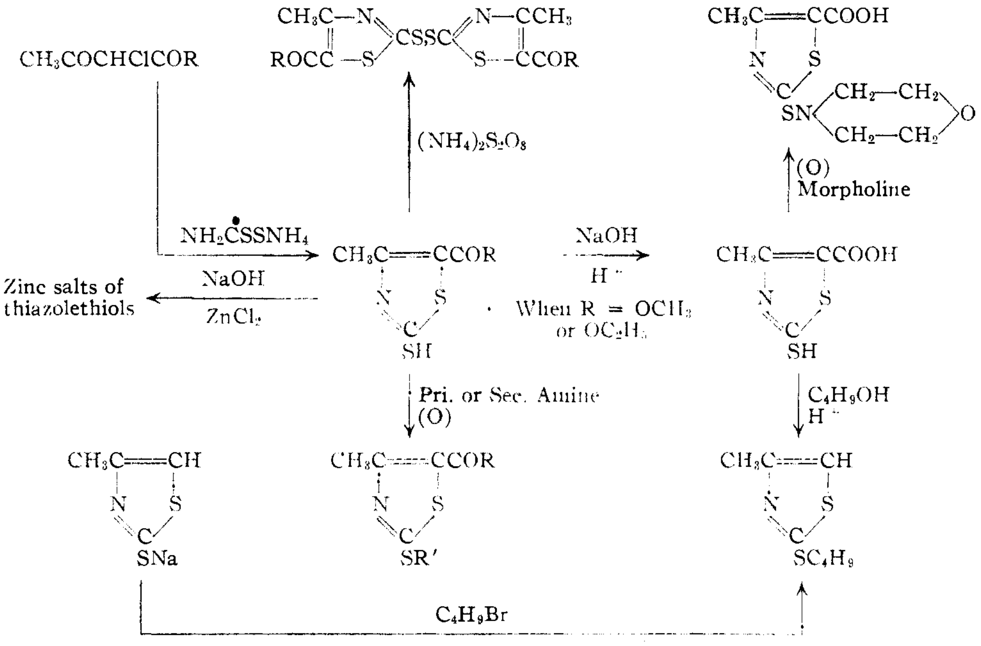


IV



VIII

This same product VIII was obtained by the reaction of *n*-butyl bromide with sodium salt of 4-methyl-2-thiazolethiol.



R = OCH_3, OC_2H_5 or CH_3 except where otherwise indicated
R' = $(CH_3)_2CHNH$, $(C_2H_5)_2N$, $C_6H_{11}NH$ or morpholinyl

The thiazolethiols I, II and III reacted with 30% aqueous solution of ammonium persulfate to form 2,2'-dithiobis-(5-carbomethoxy-4-methylthiazole) (V), 2,2'-dithiobis-(5-carbethoxy-4-methylthiazole) (VI) and 2,2'-dithiobis-(5-acetyl-4-methylthiazole) (VII), respectively.

The zinc salts of the thiazolethiols IX, X and XI were prepared by the reaction of an aqueous solution of the sodium salts of I, II and III with zinc chloride solution.

The thiazolesulfenamides XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI and XXII were prepared by the oxidative condensation of a primary or secondary amine with I, II, III and IV. The thiazolesulfenamides are in general rather unstable compounds which decompose upon standing to the disulfide and ammonium thiazolyl mercaptide. The stability of the thiazolesulfen-

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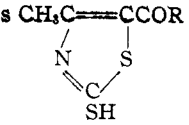
(1) (a) A. Miolati, *Gazz. chim. ital.*, **231**, 575 (1893); (b) T. G. Levi, *ibid.* **61**, 719 (1931).

TABLE I

THIAZOLETHIOLS



No.	R	Yield, % crude	M.p., °C. Obtained	M.p., °C. Reported	Empirical formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found
I	OCH_3	73.4	179–180[a]	..	$C_6H_7NO_2S_2$	7.40	7.45	33.88	33.70
II	OC_2H_5	75.0	151–152[a]	150[1,b]	$C_7H_9NO_2S_2$	6.89	6.92	31.54	31.30
III	CH_3	74.4	210–211[b]	..	$C_6H_7NOS_2$	8.09	8.00	37.01	37.30

[a] Recrystallization from benzene. [b] Recrystallization from ethyl alcohol.

TABLE II

DISULFIDES

No.	R	Yield, % crude	M.p., °C.[a]	Empirical formula	Mol. wt. Calcd.	Mol. wt. Found	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found
V	OCH_3	94.5	88–89	$C_{12}H_{12}N_2O_4S_4$	376.5	374.9	7.44	7.50	34.06	34.30
VI	OC_2H_5	98.0	120–121	$C_{14}H_{16}N_2O_4S_4$	404.5	403.5	6.93	6.81	31.70	31.68
VII	CH_3	99.0	92–93	$C_{12}H_{12}N_2O_2S_4$	344.5	342.0	8.13	8.09	37.23	37.22

[a] Recrystallization from ethyl alcohol.

TABLE III

ZINC SALTS OF THIAZOLETHIOL

No.	R	Yield, % crude	M.p., °C.	Empirical formula	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	Zn, % Calcd.	Zn, % Found
IX	OCH_3	95.0	123–133	$C_{12}H_{12}N_2O_4S_4Zn$	6.34	5.96	29.02	29.20	14.79	14.80
X	OC_2H_5	99.0	104–110	$C_{14}H_{16}N_2O_4S_4Zn$	5.96	5.90	27.29	27.99	13.91	13.91
XI	CH_3	76.0	147–155	$C_{12}H_{12}N_2O_2S_4Zn$	6.84	6.61	31.29	31.27	15.95	16.16

amide was found to depend upon the nature of the amine from which it was derived. The thiazolesulfenamides prepared from morpholine or cyclohexylamine were found to be more stable under ordinary conditions.

Experimental[2]

Alkyl α-Chloroacetoacetate and 3-Chloro-2,4-pentanedione.—Methyl α-chloroacetoacetate, ethyl α-chloroacetoacetate and 3-chloro-2,4-pentanedione were obtained by reaction of methyl acetoacetate, ethyl acetoacetate and 2,4-pentanedione with sulfuryl chloride.[3,4]

Thiazolethiols I, II and III.—The reaction was carried out in a manner similar to that described by Mathes.[5]

Alkyl α-chloroacetoacetate or 3-chloro-2,4-pentanedione (1 mole) was added to a stirred solution containing 110 g. (1 mole) of ammonium dithiocarbamate in 990 g. of water. Immediately an exothermic reaction set in and a precipitate formed. The reaction mixture was stirred for eight hours and allowed to stand for an additional eight hours. The precipitate was filtered, washed with water until the washings were neutral to litmus and dried at 50°. The data are summarized in Table I.

2-Mercapto-4-methyl-5-thiazolecarboxylic Acid (IV).—A solution containing 1 mole of either I or II, 320 g. (2 moles) of 25% aqueous sodium hydroxide solution and 800 ml. of water was stirred at 60–70° for two hours. After cooling to 15°, the solution was made acidic with concd. hydrochloric acid, the precipitate was filtered, washed with water until free of acid, and dried at 50°. The product, a light yellow solid, m.p. 200–203°, was obtained in 79–83% yield. After recrystallization from benzene, it melted at 211–212° (reported m.p. 211–212°[1a]).

Anal. Calcd. for $C_5H_5NO_2S_2$: N, 7.99; S, 36.59. Found: N, 8.21; S, 36.10.

Disulfides V, VI and VIII.—To an agitated suspension of 0.40 mole of either I, II or III in 500 ml. of water was added dropwise 238 ml. (0.44 mole) of a 30% aqueous solution of ammonium persulfate over a 30-minute period at 25–30°. After stirring for two hours longer, the precipitate was filtered and dried at 50°. The data are summarized in Table II.

2-(Butylmercapto)-4-methylthiazole (VIII). Procedure A.—A solution containing 69 g. (0.39 mole) of IV, 290 g. (3.9 moles) of *n*-butyl alcohol and 5 g. of concd. sulfuric acid was heated at 115–116° for two days. The water, 6 ml., was allowed to distil off as formed. The excess *n*-butyl alcohol was removed by distillation. Vacuum distillation of the residue through a four-foot Vigreux type column yielded an amber colored liquid (45 g., 61.6%), b.p. 83–84° (1 mm.), $n^{25}D$ 1.5460.

Anal. Calcd. for $C_8H_{13}NS_2$: H, 6.99; N, 7.48; S, 34.24; mol. wt., 187.3. Found: H, 6.98; N, 7.37; S, 34.16; mol. wt., 188.0.

Procedure B.—To a solution containing 163 g. (1.24 moles) of 4-methyl-2-thiazolethiol, 69.5 g. (1.24 moles) of potassium hydroxide and 800 ml. of ethyl alcohol, 171 g. (1.24 moles) of *n*-butyl bromide was added dropwise with agitation. The reaction mixture was heated under reflux for three hours and was filtered to remove potassium bromide. The ethyl alcohol was removed by evaporation and distillation of the residue yielded an amber colored liquid (106 g., 45.6%), b.p. 83–84° (1 mm.), $n^{25}D$ 1.5464.

Anal. Calcd. for $C_8H_{13}NS_2$: N, 7.48; S, 34.24. Found: N, 7.51; S, 33.99.

Zinc Salts of the Thiazoles IX, X and XI.—To a solution of 0.40 mole of either I, II or III in 160 g. (0.40 mole) of 10% aqueous sodium hydroxide and 800 ml. of water, was added, with agitation, a solution containing 27.4 g. (0.20 mole) of zinc chloride in 1160 ml. of water. The reaction mixture was stirred for one hour, the resulting precipitate filtered, washed with water until the washings were neutral to litmus and dried at 50°. The data are summarized in Table III.

Thiazolesulfenamides XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI and XXII. Procedure A. XVIII, XIX, XX, XXI, and XXII.—This reaction was carried out in a manner similar to that described by Cooper[6] except with modification as shown below. To a cooled aqueous solution containing 0.25 mole of III or IV, 170 g. of water and 40 g.

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(2) All melting points were taken upon a Fisher–Johns block and are uncorrected.

(3) E. R. Buchman and E. M. Richardson, THIS JOURNAL, **61**, 891 (1939).

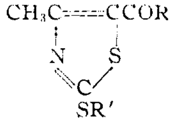
(4) E. R. Buchman and E. M. Richardson, *ibid.*, **67**, 395 (1945).

(5) R. A. Mathes, U. S. Patent 2,186,421.

(6) R. H. Cooper, U. S. Patent 2,339,002.

TABLE IV

THIAZOLESULFENAMIDES



No.	R	R′	Procedure	Yield, % crude	Mole ratio amine to thiazole	M.p., °C.	Empirical formula	N, %		S, %	
								Calcd.	Found	Calcd.	Found
XII	OCH_3	C_4H_8NO[a]	B	38.0	10:1	123–124	$C_{10}H_{14}N_2O_3S_2$	10.21	10.00	23.38	23.50
			D	78.5	1.1:1	123–124[b]	$C_{10}H_{14}N_2O_3S_2$	10.21	10.37	...	...
XIII	OCH_3	$C_6H_{11}NH$	B	65.5	10:1	55–57	$C_{12}H_{18}N_2O_2S_2$	9.78	9.89	22.39	22.62
XIV	OCH_3	$(CH_3)_2CHNH$	B	49.1	10:1	57–58	$C_9H_{14}N_2O_2S_2$	11.37	11.50	26.03	25.78
XV	OCH_3	$(C_2H_5)_2N$	B	54.5	10:1	39	$C_{10}H_{16}N_2O_2S_2$	10.76	11.00	24.63	24.49
XVI	OC_2H_5	$(CH_3)_2CHNH$	B	48.0	10:1	Oil	$C_{10}H_{16}N_2O_2S_2$	...	...	24.63	24.10
XVII	OC_2H_5	C_4H_8NO[a]	B	66.0	10:1	53–54	$C_{11}H_{16}N_2O_3S_2$	9.71	9.77	22.23	22.49
			C	76.0	...	53–54	$C_{11}H_{16}N_2O_3S_2$	9.71	9.70	...	...
XVIII	CH_3	$C_6H_{11}NH$	A	69.8	4:1	114–115	$C_{12}H_{18}N_2OS_2$	10.36	10.39	23.72	23.27
XIX	CH_3	$(C_2H_5)_2N$	A	41.0	4:1	Oil	$C_{10}H_{16}N_2OS_2$	11.46	11.52	26.24	26.31
XX	CH_3	$(CH_3)_2CHNH$	A	69.5	4:1	50–52	$C_9H_{14}N_2OS_2$	12.16	11.97	27.84	27.72
XXI	CH_3	C_4H_8NO[a]	A	86.7	3:1	116–117	$C_{10}H_{14}N_2O_2S_2$	10.84	11.08	24.82	24.47
			B	55.0	10:1	116–117	$C_{10}H_{14}N_2O_2S_2$	10.84	11.10	24.82	24.71
XXII	OH	C_4H_8NO[a]	A	12.3	3:1	56–57	$C_9H_{12}N_2O_3S_2$	10.76	10.34	24.63	24.75

[a] Morpholinyl. [b] Recrystallization from ethyl alcohol.

(0.25 mole) of 25% aqueous sodium hydroxide solution, 1 mole of amine was added with agitation at such a rate that the reaction mixture did not exceed a temperature of 27°. The mixture was cooled to 13° and 42 ml. of 25% sulfuric acid added dropwise at 13–15° in 20 minutes. To this mixture, at 13–20°, was added, drop by drop, with stirring in two hours, 170 ml. (15 g./100 ml.) of aqueous sodium hypochlorite solution. The excess sodium hypochlorite was destroyed by the addition of 1 g. of sodium sulfite. For XVIII, XXI and XXII the reaction mixture was cooled to 10°, the precipitate was filtered, washed with water until free of chloride and dried at room temperature.

For XIX and XX, the reaction mixture was extracted with 500 ml. of ethyl ether, the ether extract washed with water until the washings were neutral to litmus, dried over sodium sulfate and the ether removed *in vacuo*.

Procedure B. XII, XIII, XIV, XV, XVI, XVII and XXI.—To an aqueous solution containing 0.12 mole of either I, II or III, 9.6 g. (0.24 mole) of sodium hydroxide in 200 ml. of water and 1.2 moles of the amine, was added, drop by drop, with stirring in 2.5 hours, 30.6 g. of iodine dissolved in 400 ml. of water containing 40 g. of potassium iodide. For all thiazolesulfenamides except XIII and XVI, the precipitate was filtered, washed with water until free from alkali, and air-dried at room temperature.

For XIII and XVI, the reaction mixture was extracted with 500 ml. of ethyl ether, the ether extract washed with water until washings were neutral to litmus, dried over sodium sulfate and and ether removed *in vacuo*.

Procedure C. XVII.—To a solution containing 39 g. (0.096 mole) of VI and 1200 ml. of heptane at 50°, 19.2 g. (0.22 mole) of morpholine was added. The reaction mixture was heated at 50° for one hour. After cooling to 25°, the morpholine salt of **II** was recovered by filtration. The filtrate was successively washed with 2% aqueous sodium hydroxide solution and water until the washings were neutral to litmus and the heptane removed *in vacuo* at 35–40°. After cooling the residue to 10°, a precipitate formed which was filtered, washed with water and air-dried at room temperature.

Procedure D. XII.—To an aqueous slurry containing 50 g. (0.26 mole) of I, 150 g. of water and 24.8 g. (0.29 mole) of morpholine at 50–52°, was added, drop by drop, with stirring in 50 minutes, 160 ml. (14.6 g./100 ml.) of aqueous sodium hypochlorite solution. After cooling to 10°, the precipitate was filtered, washed with water until free of chloride and air-dried at room temperature. The product, a white solid, m.p. 100–105°, was obtained in 78.5% yield. After recrystallization from ethyl alcohol, it melted at 123–124°.

The data for thiazolesulfenamides are summarized in Table IV.

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NITRO, WEST VIRGINIA