

SYNTHESIS OF DERIVATIVES OF 4,5-DIMETHYL-2-MERCAPTOTHIAZOLE

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Thiazoles, particularly 2-mercaptobenzothiazole, and certain derivatives of these compounds, have found wide application as accelerators for the vulcanization of rubber. This investigation had for its purpose the synthesis of a series of derivatives of 4,5-dimethyl-2-mercaptothiazole to determine the effect of different substituents on the properties of rubber vulcanizates. A comparison of the activity of these compounds as vulcanization accelerators will be reported elsewhere.

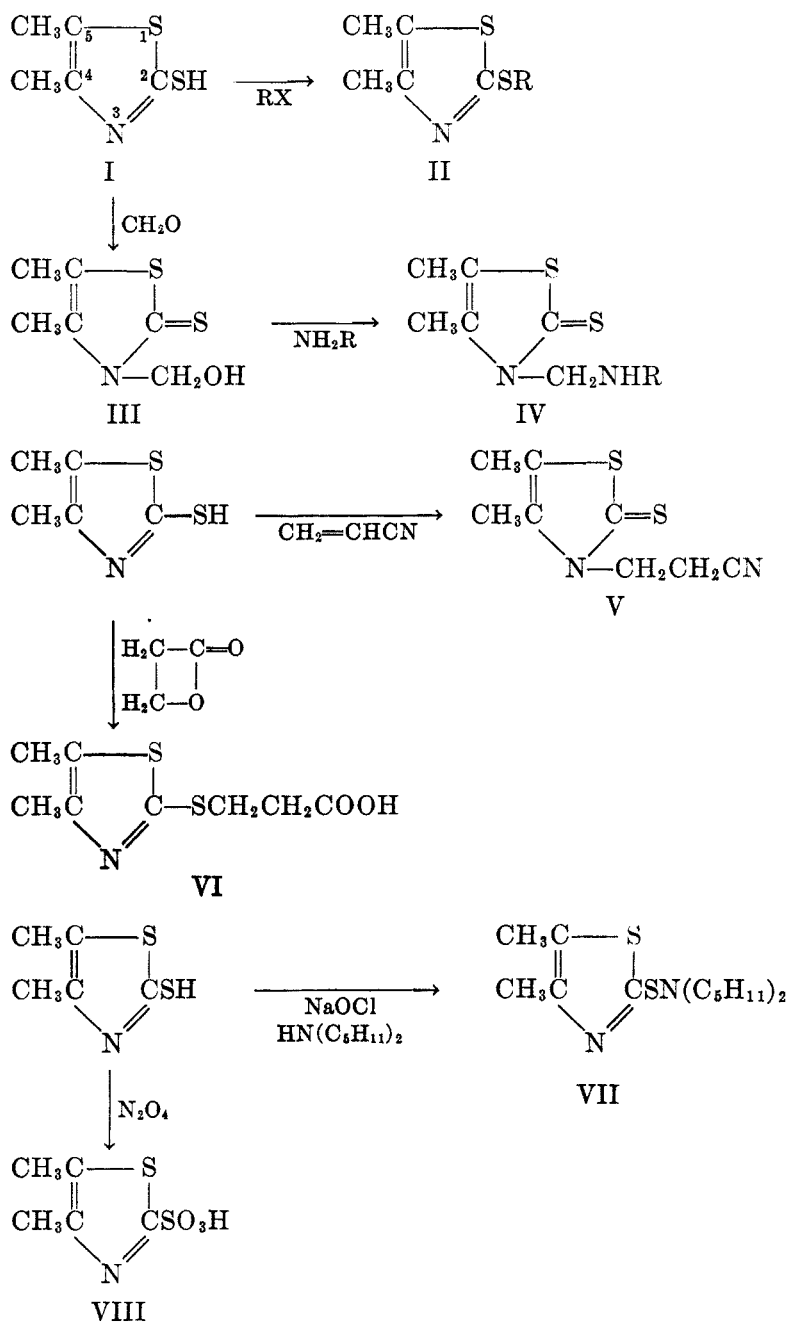
Derivatives prepared from the parent 4,5-dimethyl-2-mercaptothiazole (I) in this study can be broadly classified into several groups. Members of the largest class (II) were synthesized by reacting the sodium salt of 4,5-dimethyl-2-mercaptothiazole, either in water solution or as the anhydrous sodium salt, with the following halogenated reagents: *n*-butyl bromide, benzyl chloride, 1,4-dichlorobutane, 2-chloroethylamine, 2,4-dinitrochlorobenzene, chloroacetone, chloroacetamide, benzoyl chloride, phthalyl chloride, furoyl chloride, *o*-nitrobenzenesulfonyl chloride, and 2-chloro-6-nitrobenzothiazole. The lead, magnesium, and zinc salts of I were similarly prepared from water-soluble salts of the corresponding metals.

The hydroxymethyl derivative (III) was obtained by reacting I with formaldehyde and this compound was further condensed with amines to form aminomethyl derivatives (IV). While three members of this class, compounds derived from *p*-phenylenediamine, *n*-butylamine, and *o*-toluidine were isolated, only the one derived from the latter amine was stable to recrystallization. Under the experimental conditions employed, attempts to prepare similar derivatives from diethylamine, cyclohexylamine, and *n*-amylamine were unsuccessful.

Acrylonitrile reacted with I to produce the cyanoethyl derivative (V), while with β -propiolactone a high yield of the substituted propionic acid (VI) was obtained. A member of the sulfenamide class (VII) was prepared from diamylamine.

Oxidations were performed to produce the previously described 4,5-dimethylthiazole and the disulfide, 2,2'-dithiobis-(4,5-dimethylthiazole) (1). The sulfonic acid (VIII) was obtained by oxidation of I with nitrogen tetroxide under mild reaction conditions.

Unpublished results of ultraviolet absorption studies performed in these laboratories show that the substituting radical in compounds III, IV, and V is attached to the nitrogen rather than to the sulfur of the thiol group. In the preparation of these derivatives, I apparently reacted in a different form, possibly as a tautomer, from that shown structurally. 4,5-Dimethyl-2-mercaptothiazole, in other reactions described in this paper, reacts in a manner to support



the structure given (I). A similar relationship for the derivative of 2-mercapto-benzothiazole corresponding to V has previously been reported (2).

EXPERIMENTAL¹

Ammonium dithiocarbamate (3). A solution of 152 g. (2 moles) of carbon disulfide and 1,000 ml. of dry isopropyl acetate was vigorously agitated in a reaction flask. Ammonia (68 g., 4 moles) was introduced in a gaseous form below the liquid surface while maintaining the reaction mixture at 20–30°. The pale yellow, rather unstable product which precipitated was recovered by filtration, and after drying rapidly at room temperature (203 g.), was stored in a refrigerator. An alternative method was to add water to the slurry of ammonium dithiocarbamate in isopropyl acetate and recover the product as a water solution. A water solution of ammonium dithiocarbamate, which should also be stored in a refrigerator, is more stable than the dry product.

4,5-Dimethyl-2-mercaptothiazole (I). This compound (4) was prepared by reacting ammonium dithiocarbamate with a mixture of 3-chloro-2-butanone and 1-chloro-2-butanone which was obtained by the chlorination of 2-butanone. To a solution of 121 g. (1.1 moles) of ammonium dithiocarbamate in 500 ml. of water there was rapidly added 106.5 g. (1 mole) of mixed monochlorobutanones. The reaction mixture was agitated vigorously, the temperature rose to about 90°, and a finely divided solid precipitated. The product weighed 123 g. (85% yield). The mixture of 4,5-dimethyl-2-mercaptothiazole and 4-ethyl-2-mercaptothiazole resulting from this reaction was extracted with sodium carbonate to dissolve the latter compound. 4,5-Dimethyl-2-mercaptothiazole, which represented about 80% of the mixture, was recovered by filtration. As further purification it was extracted twice with benzene to give 4,5-dimethyl-2-mercaptothiazole melting at 162–163° (1).

Anhydrous sodium salt of 4,5-dimethyl-2-mercaptothiazole (IX). Twelve grams (0.5 mole) of sodium metal was slowly added to 500 ml. of ethanol. To the solution of sodium ethoxide was added 72.5 g. (0.5 mole) of I. Ethanol was removed from the resulting solution by evaporation and the salt was stored under anhydrous conditions.

4,5-Dimethyl-2-n-butylmercaptothiazole. To 83.5 g. (0.5 mole) of IX dissolved in 400 ml. of ethanol, 68.5 g. (0.5 mole) of *n*-butylbromide was added dropwise, with agitation. The reaction mixture was heated under reflux for 2 hours and was filtered to remove sodium bromide. After evaporation of ethanol, 85 g. of the liquid product was recovered.

4,5-Dimethyl-2-benzylmercaptothiazole. A solution of 33.4 g. (0.2 mole) of IX in 300 ml. of methanol was heated under reflux with 25.2 g. (0.2 mole) of benzylchloride for 1 hour. Sodium chloride was removed, and after concentrating the filtrate, there was obtained 37 g. of the liquid product.

4,5-Dimethyl-2-(4-chlorobutylmercapto)thiazole. A solution consisting of 83.5 g. (0.5 mole) of IX, 32 g. (0.25 mole) of 1,4-dichlorobutane, and 350 ml. of ethanol was heated under reflux for 2 hours. The reaction mixture was filtered and ethanol was evaporated from the filtrate to yield 50 g. of the liquid product.

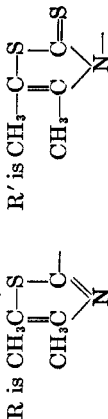
3-β-Cyanoethyl-4,5-dimethyl-2-thiono-4-thiazoline. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added dropwise, with agitation, 26.5 g. (0.5 mole) of acrylonitrile. After stirring for 11 hours at room temperature, the crude product was 21 g. of crystalline material. This compound was purified by recrystallization from ethanol.

4,5-Dimethyl-2-(2-aminoethylmercapto)thiazole (5). Seventy-two and one-half grams (0.5 mole) of I, dissolved in 400 ml. of 10% aqueous sodium hydroxide, was added to 58 g. (0.5 mole) of 2-chloroethylamine hydrochloride dissolved in 100 ml. of water. The agitated solution was heated at 85° for 30 minutes and 58 g. of the liquid product was recovered by extraction with ether.

4,5-Dimethyl-2-(2,4-dinitrophenylmercapto)thiazole. Eighty-one grams (0.4 mole) of 2,4-dinitrochlorobenzene was dissolved in 400 ml. of ethanol and with agitation, was added at 30–35° to a solution of 58 g. (0.4 mole) of I in 200 ml. of 8% sodium hydroxide. The yellow,

¹ All melting points and boiling points reported are uncorrected.

TABLE I
DERIVATIVES OF 4,5-DIMETHYL-2-MERCAPTOTHIAZOLE



DERIVATIVE	YIELD, ^a %	M.P. OR B.P., ^c °C.	EMPIRICAL FORMULA	C, %		H, %		N, %		S, %		MOL. WT.	
				Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
RS(CH ₃) ₂ CH ₃ ^f	84	101	C ₉ H ₁₃ NS ₂	53.73	53.67	7.46	7.48	6.97	7.06	31.84	31.94	201	207
RSCH ₂ CH ₃ ^d	79	173-176	C ₁₂ H ₁₃ NS ₂	61.27	61.10	5.54	5.63	5.96	6.04	27.23	27.32	235	232
RS(CH ₃) ₂ Cl ^e	85	115-116	C ₉ H ₁₄ ClNS ₂	45.86	45.59	5.06	6.02	5.96	6.00	27.15	27.18	235	231
R'(CH ₃) ₂ CN	22	158-159	C ₇ H ₁₀ N ₂ S ₂	48.48	48.44	5.06	5.08	14.14	14.06	32.32	32.32	198	203
RS(CH ₃) ₂ NH ₂ ^f	61	115-117	C ₇ H ₁₂ N ₂ S ₂	44.68	44.67	6.38	6.42	14.90	14.97	34.04	34.04	188	193
RSC ₂ H ₅ -2,4-(NO ₂) ₂	97	150-151	C ₁₁ H ₉ N ₃ O ₄ S ₂	42.44	42.15	2.89	2.87	13.50	13.39	20.57	20.46	311	307
R'CH ₂ OH	89	75-78	C ₇ H ₁₀ NOS ₂	41.15	41.25	5.14	5.18	8.00	8.08	36.57	36.64	175	175
RS(CH ₃) ₂ COOH	85	66-67	C ₈ H ₁₁ N ₂ O ₂ S ₂	44.24	44.24	5.07	5.13	6.46	6.48	29.49	29.50	217	219
RSCH ₂ COCH ₃	91	105-106	C ₁₄ H ₁₅ N ₅ O ₄ S ₂ ^g	44.09	44.07	3.93	3.94	18.38	18.49	16.80	16.87	381	386
RSCH ₂ CONH ₂	71	98-99	C ₇ H ₁₀ N ₂ OS	41.54	41.56	4.98	5.04	13.86	13.88	31.71	31.76	202	207
R'CH ₂ NHC ₆ H ₅ -o-CH ₃	90	98-99	C ₁₃ H ₁₆ N ₂ O ₂ S ₂	59.07	59.12	6.10	6.00	10.60	10.61	24.23	24.34	264	269
RSCOC ₆ H ₅	99	62-63	C ₁₂ H ₁₁ NOS ₂	57.83	57.66	4.42	4.51	5.63	5.68	25.70	25.83	249	247
(RSCO) ₂ -1,2-C ₆ H ₄	87	118-119	C ₁₈ H ₁₆ N ₂ O ₂ S ₄	51.43	51.39	3.81	3.81	6.67	6.66	30.47	30.56	420	408
RSCOC:CHCH:CHO	94	90-91	C ₁₀ H ₉ NO ₂ S ₂	50.19	50.26	3.79	3.68	5.86	5.81			300	281
RSN(C ₆ H ₁₁) ₂ ^f	70	138-140	C ₁₄ H ₂₃ N ₂ S ₂	59.94	58.62	9.39	9.21	9.34	9.84	21.33	22.46	300	281
RSSC ₆ H ₄ -o-NO ₂	89	81-82	C ₁₁ H ₁₀ N ₂ O ₂ S ₃	44.29	44.27	3.36	3.45	9.39	9.43	32.23	32.26	298	301
RSY ^h	77	128-129	C ₁₂ H ₉ N ₄ O ₂ S ₃	44.56	44.60	2.80	2.79	12.99	12.87	29.77	29.82	323	325
RSO ₂ H	76	260-263	C ₈ H ₇ NO ₂ S ₂	31.09	31.16	3.62	3.76	7.25	7.25	33.17	33.17	193	188
RSSR ^h	92	51-52											
RH ^h	60	83-84											
(RS) ₂ Pb	96		C ₁₀ H ₁₂ N ₂ PbS ₄					41.81				41.50	
(RS) ₂ Mg	87		C ₁₀ H ₁₂ MgN ₂ S ₄					7.78				7.57	
(RS) ₂ Zn	95		C ₁₀ H ₁₂ N ₂ ZnS ₄					18.48				18.59	

^a Yields are based on crude products. ^b Data are for analytical samples. ^c Distilled at 1.0 mm.; ^d Distilled at 6.0 mm.; ^e ⁿ_D 1.5461. ^f Distilled at 0.4 mm.; ^g ⁿ_D 1.5958. ^h Distilled at 2 mm. As the material was not very stable to distillation, unsuccessful efforts were made to prepare a derivative such as the picrate and the methiodide for purposes of identification. ⁱ Y represents the 6-nitrobenzothiazole nucleus. ^j Reported (1) m.p. 51.5°. ^k Distilled at 61 mm. Reported (1) b.p. 81-83° at 59 mm.

crystalline precipitate weighed 120 g., m.p. 145–147°. This compound was purified by recrystallization from ethanol.

3-Hydroxymethyl-4,5-dimethyl-2-thiono-4-thiazoline. One hundred forty-five grams (1 mole) of I and 410 g. (5 moles) of 37% formaldehyde were agitated and heated together at 93–95° for 2 hours. The resulting solution was cooled to 50° and was diluted with 300 ml. of water. The solid precipitated after cooling the mixture to 10°; yield 155 g.

β-(4,5-Dimethyl-2-thiazolyl)mercaptopropionic acid. To a solution of 145 g. (1 mole) of I in 200 ml. of 20% aqueous sodium hydroxide was added, with agitation, 72 g. (1 mole) of β-propiolactone at 20–30°. The mixture was agitated for 30 minutes and was then acidified at 20° with 37% hydrochloric acid. The white, crystalline product (185 g.) was purified by recrystallization from benzene.

4,5-Dimethyl-2-acetylmercaptothiazole. To a stirred solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide was added 46.3 g. (0.5 mole) of chloroacetone at 35–45°. After agitating for 1 hour, 92 g. of the brown-colored liquid product was separated from the water. Decomposition resulted when an attempt was made to distill this product under reduced pressure. The *2,4-dinitrophenylhydrazone* derivative melted at 160–161° after recrystallization from methanol.

4,5-Dimethyl-2-carbamylmethylmercaptothiazole. A solution consisting of 83.5 g. (0.5 mole) of IX and 46.8 g. (0.5 mole) of chloroacetamide in 300 ml. of ethanol was agitated and heated under reflux for 5 hours. After filtering, alcohol was eliminated from the filtrate by evaporation. The crude product, 73 g., was recovered as buff-colored crystals, m.p. 99–108°. This compound was purified by recrystallization from ethanol.

3-o-Toluidinomethyl-4,5-dimethyl-2-thiono-4-thiazoline. To a solution of 72.5 g. (0.5 mole) of I and 20 g. (0.5 mole) of sodium hydroxide in 250 ml. of water was added, with agitation, 41 g. (0.5 mole) of 37% formaldehyde at 10°. This solution was cooled to 5–10° and 71.8 g. (0.5 mole) of *o*-toluidine hydrochloride was added with stirring. The precipitate which first formed was gummy but crystallization took place after agitating for 2 hours. Water was decanted from the reaction mixture, the solid product was dissolved in ethanol and after concentration of this solution, 119 g. of the white crystalline product, m.p. 103–105°, was obtained. As recrystallization resulted in decomposition, with the recovery of I, purification was effected by repeated extraction with ether.

4,5-Dimethyl-2-benzoylmercaptothiazole. To a suspension of 33.4 g. (0.2 mole) of IX in 300 ml. of benzene was added 28 g. (0.2 mole) of benzoyl chloride. The solution which formed was heated under reflux for 1 hour. Sodium chloride was removed and the filtrate was concentrated; yield, 49 g. of solid. Purification was effected by recrystallization from hexane.

Phthaloyl bis-(4,5-dimethylthiazole-2-sulfide). To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide was added, with agitation, 51 g. (0.25 mole) of phthalyl chloride at 30–35°. The precipitate which first formed was gummy but crystallized upon continued stirring; yield, 91 g. of crude material, m.p. 98–103°. Purification was effected by crystallization from ethanol.

4,5-Dimethyl-2-(2-furoyl)mercaptothiazole. To a suspension of 41.8 g. (0.25 mole) of IX in 300 ml. of benzene there was slowly added 32.7 g. (0.25 mole) of furoyl chloride. The reaction mixture was heated at 65–70° for 1 hour. After cooling to room temperature, sodium chloride was removed and the filtrate was concentrated; yield 56 g. of solid. Purification was effected by recrystallization from ether.

N-Diamyl-4,5-dimethyl-2-thiazolesulfenamide. A mixture of 145 g. (1 mole) of I, 157 g. (1 mole) of the diamylamine (mixed isomers), and 600 ml. of water was agitated while slowly adding 1,320 ml. of 8.5% aqueous sodium hypochlorite (1.5 mole) at 30–40°. After stirring for 1 hour, the brown liquid was separated from water to give 210 g. of crude product.

2-(o-Nitrophenyldithio)-4,5-dimethylthiazole. Forty-eight grams (0.25 mole) of *o*-nitrobenzenesulfonyl chloride was dissolved in 450 ml. of methanol and was added, with agitation, to a solution of 36.3 g. (0.25 mole) of I in 400 ml. of 2.5% aqueous sodium hydroxide

at 25–30°. The product, which first formed as a brown liquid, crystallized after stirring for 16 hours; yield 66 g., m. p. 80–83°. This compound was purified by recrystallization from ether.

6-Nitrobenzothiazole-4,5-dimethylthiazole-2,2'-monosulfide. Twenty-nine grams (0.2 mole) of I was dissolved in a solution of 8.5 g. (0.21 mole) of sodium hydroxide, 10 ml. of water, and 400 ml. of methanol. To this solution was added 43 g. (0.2 mole) of 2-chloro-6-nitrobenzothiazole and the mixture was heated under reflux for 45 minutes. A yellow, crystalline material was formed, yield, 50 g. of crude product, m.p. 118–120°. Purification was effected by crystallization from ether and ethanol.

4,5-Dimethylthiazole-2-sulfonic acid. Seventy-eight grams (0.85 mole) of nitrogen tetroxide vapor was passed into an agitated solution of 72.5 g. (0.5 mole) of I in 500 ml. of chloroform at 0–5°. The mixture was stirred for 45 minutes and was allowed to come to room temperature. The crude product (77 g., m.p. 260–263°) was obtained by filtration and by evaporation of the chloroform filtrate. Purification was effected by recrystallization from ethanol.

2,2'-Dithiobis-(4,5-dimethylthiazole) (6). A fine suspension of 72.5 g. (0.5 mole) of I in 250 ml. of water was prepared. To this agitated slurry was added 138 ml. (0.55 mole) of a 30% aqueous solution of ammonium persulfate in 30 minutes at 25–30°. Filtration yielded 66 g. of a buff-colored crystalline material, m.p. 46–48°, which was purified by recrystallization from hexane.

4,5-Dimethylthiazole. One hundred and six grams (0.8 mole) of I and 480 g. of 37% hydrochloric acid were agitated and while heating at 65–70°, 272 g. (2.4 moles) of hydrogen peroxide was added. After heating the mixture to 80° for 15 minutes, it was cooled to room temperature and 200 g. of barium chloride in 600 ml. of water was added. The precipitated barium sulfate was removed and the filtrate was concentrated under reduced pressure to about one-tenth of the original volume. The filtrate was neutralized with sodium hydroxide and the crude liquid product which separated was extracted with ether. After removing the ether there was obtained 57 g.

Lead salt. To an agitated solution of 72.5 g. (0.5 mole) of I, 20 g. (0.5 mole) of sodium hydroxide, and 1,200 ml. of water was added 82.8 g. (0.25 mole) of lead nitrate dissolved in 500 ml. of water. The yellow precipitate was recovered by filtration; yield 120 g.

Magnesium salt. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added, with agitation, a solution of 61.7 g. (0.25 mole) of magnesium sulfate in 600 ml. of water. The white precipitate amounted to 68 g.

Zinc salt. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added, with agitation, a solution of 34 g. (0.25 mole) of zinc chloride in 900 ml. of water; white precipitate, yield 84 g.

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SUMMARY

Methods for the synthesis and purification of twenty-three derivatives of 4,5-dimethyl-2-mercaptothiazole have been described. The sodium salt was reacted with acid chlorides and with halogenated members of the following classes of organic compounds: hydrocarbons, ketones, amides, and alkylamines. Heavy metal and alkaline earth salts were formed from water-soluble salts of the corresponding metals. 4,5-Dimethyl-2-mercaptothiazole reacted with formaldehyde to form a hydroxymethyl derivative which was further condensed with amines to form aminomethyl derivatives. The reaction with β -propiolactone

produced a thiazolyl substituted β -mercaptopropionic acid, and with acrylonitrile, a cyanoethyl derivative. Oxidation with nitrogen tetroxide, under mild conditions, gave the sulfonic acid.

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