

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, NITRO RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Derivatives of Ethyl 2-Mercapto-4-thiazoleacetate and Rhodanine

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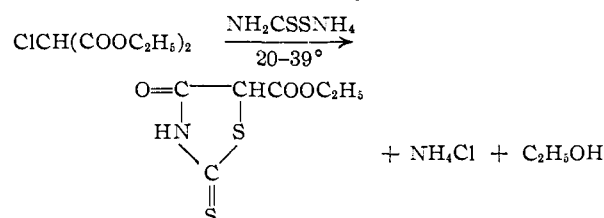
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Ammonium dithiocarbamate and ethyl γ -chloroacetoacetate reacted at 19–44° to give ethyl (thiocarbamoylthio)-acetoacetate. At 90–100°, the same reactants gave ethyl 2-mercapto-4-thiazoleacetate. Saponification of the thiazoleacetate gave 2-mercapto-4-thiazoleacetic acid. The following derivatives of the thiazoleacetate were prepared: zinc and cadmium salts, diethyl 2,2'-dithiobis-(4-thiazoleacetate), 2,2'-dithiobis-(4-thiazoleacetic acid), ethyl 2-(*N,N*-diethylthiocarbamoylthio)-4-thiazoleacetate, 2,4,6-tris-(4-carbomethoxymethyl-2-thiazolylthio)-*s*-triazine, and ethyl 2-(chloroalkenyl or alkynylthio)-4-thiazoleacetates. Two interesting results encountered were: (1) the reaction of diethyl chloromalonate with ammonium dithiocarbamate at 20–39° and 70–80° gave 5-carbomethoxyrhodanine and rhodanine, respectively; and (2) the reaction of 2-mercapto-4-thiazoleacetic acid with butyl alcohol under acidic conditions gave butyl 2-(butylthio)-4-thiazoleacetate.

Since some of the alkyl 2-mercapto-4-methyl-5-thiazolecarboxylates and their derivatives are excellent accelerators for the vulcanization of rubber,^{1,2} it was desirable to prepare the unknown thiazolethiols containing substituents other than alkyl radicals in the 4-position, in particular: (1) ethyl 2-mercapto-4-thiazoleacetate and its derivatives; (2) ethyl 4-ethoxy-2-mercapto-4-thiazolecarboxylate, and to determine the effect of the 4-position substituent on the accelerator activity. This evaluation will be reported in another paper.

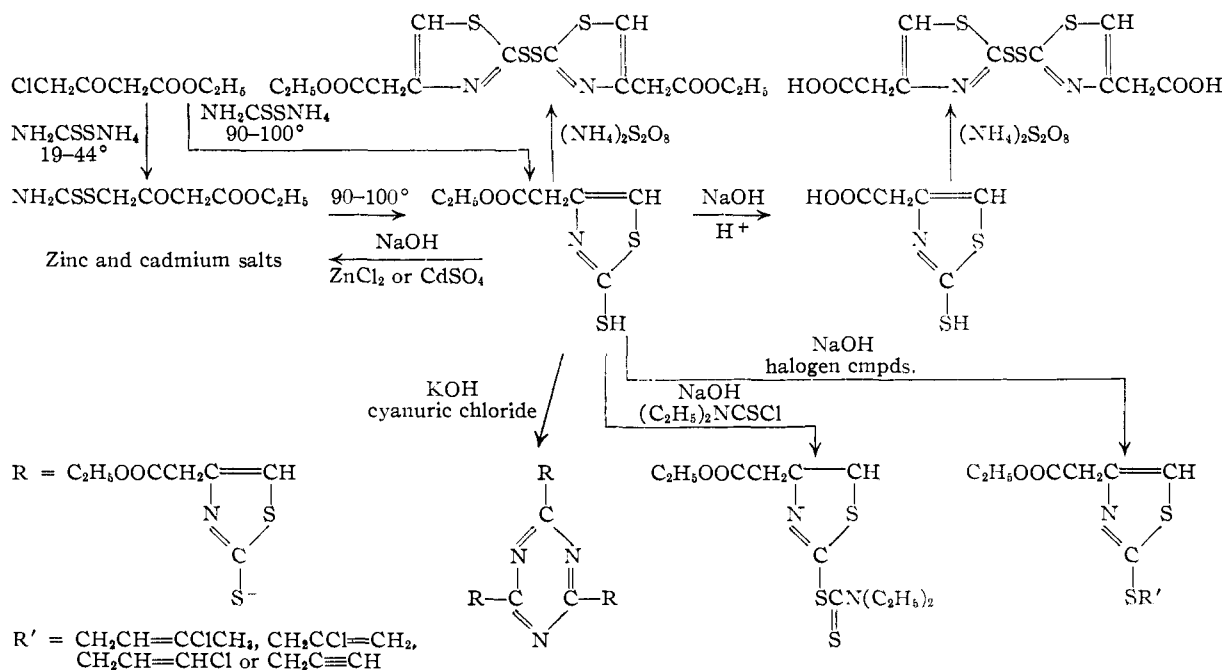
An aqueous solution of ammonium dithiocarbamate reacted with ethyl γ -chloroacetoacetate at 19–44° to form ethyl (thiocarbamoylthio)-acetoacetate; at 90–100°, ethyl 2-mercapto-4-thiazoleacetate was obtained. The same product was prepared by heating a stirred water suspension of ethyl (thiocarbamoylthio)-acetoacetate at 90–100°. Saponification of the thiazoleacetate gave 2-mercapto-4-thiazoleacetic acid.

20–39° did not yield the desired ethyl 4-ethoxy-2-mercapto-5-thiazolecarboxylate, but instead the tautomeric 5-carbomethoxyrhodanine, which at 70–80° is saponified and decarboxylated to rhodanine.



The reaction of 2-mercapto-4-thiazoleacetic acid with butyl alcohol under acidic conditions gave butyl 2-(butylthio)-4-thiazoleacetate; 2-mercapto-4-methyl-5-thiazolecarboxylic acid under the same conditions is decarboxylated to give 2-(butylthio)-4-methylthiazole.¹

The zinc and cadmium salts of ethyl 2-mercapto-



The reaction of diethyl chloromalonate with an aqueous solution of ammonium dithiocarbamate at

4-thiazoleacetate were prepared by the reaction of an aqueous solution of the sodium salt of the thiazoleacetate with a zinc chloride or cadmium sulfate solution.

Ethyl 2-mercapto-4-thiazoleacetate and 2-mer-

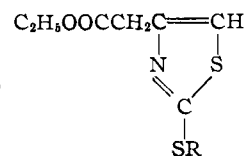
(1) J. J. D'Amico, *THIS JOURNAL*, **75**, 102 (1953).

(2) K. E. Creed, Jr., J. J. D'Amico, M. W. Harman and R. O. Zerbe, *Ind. Eng. Chem.*, **46**, 808 (1953).

TABLE I

ETHYL 2-(CHLOROALKENYL OR ALKYNYLTHIO)-4-THIAZOLEACETATES (OILS No M.P.)

R	Yield, % crude	Empirical formula	Nitrogen, %		Sulfur, %		Chlorine, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH ₂ CH=CClCH ₂	67.5	C ₁₁ H ₁₄ ClNO ₂ S ₂	21.98	21.98	12.15	11.83
CH ₂ CCl=CH ₂	59.1	C ₁₀ H ₁₂ ClNO ₂ S ₂	5.04	5.02	23.08	23.09	12.76	12.46
CH ₂ CH=CHCl	64.9	C ₁₀ H ₁₀ ClNO ₂ S ₂	5.04	4.90	23.08	22.84
CH ₂ C≡CH	49.8	C ₁₀ H ₁₁ NO ₂ S ₂	5.80	5.67	26.57	26.33



capto-4-thiazoleacetic acid reacted with a 30% aqueous solution of ammonium persulfate to form diethyl 2,2'-dithiobis-(4-thiazoleacetate) and 2,2'-dithiobis-(4-thiazoleacetic acid), respectively.

Ethyl 2-(N,N-diethylthiocarbamoylthio)-4-thiazoleacetate was prepared by the reaction of the sodium salt of ethyl 2-mercapto-4-thiazoleacetate with N,N-diethylthiocarbamoyl chloride.

The reaction of the potassium salt of ethyl 2-mercapto-4-thiazoleacetate with cyanuric chloride gave the desired 2,4,6-tris-(4-carbomethoxymethyl-2-thiazolylthio)-s-triazine.

The ethyl 2-(chloroalkenyl or alkynylthio)-4-thiazoleacetates were prepared by treating the sodium salt of ethyl 2-mercapto-4-thiazoleacetate with the following compounds: 1,3-dichloro-2-butene, 2,3-dichloro-1-propene, 1,3-dichloropropene and 3-bromo-1-propyne.

Experimental³

Ethyl (Thiocarbamoylthio)-acetoacetate.—To a stirred solution containing 87 g. (0.79 mole) of ammonium dithiocarbamate in 790 g. of water was added 130 g. (0.79 mole) of ethyl γ -chloroacetoacetate⁴; the temperature rose immediately from 19 to 44°. The reaction mixture was stirred for 24 hours and cooled to 3°. The precipitate was filtered, washed with cold water until the washings were free of chloride and air-dried at room temperature. The product, a tan colored solid, m.p. 73–75°, was obtained in 80.1% yield, m.p. after recrystallization from benzene 74–75°.

Anal. Calcd. for C₇H₁₁NO₃S₂: N, 6.33; S, 28.98. Found: N, 6.32; S, 29.20.

Ethyl 2-Mercapto-4-thiazoleacetate. Procedure A.—When after the 24-hour reaction period, the stirred reaction mixture was heated at 90–100° for two hours, a tan colored solid, m.p. 135–138°, was obtained in 95.1% yield, m.p. after recrystallization from benzene 139–140°.

Anal. Calcd. for C₇H₉NO₂S₂: N, 6.89; S, 31.54. Found: N, 7.01; S, 31.70.

Procedure B.—A stirred suspension containing 140 g. (0.63 mole) of ethyl (thiocarbamoylthio)-acetoacetate and 500 ml. of water was heated at 90–100° for two hours. After cooling to 5°, the solid was filtered and air-dried at 50°. The product, m.p. 135–139°, was obtained in 93.2% yield. After recrystallization from benzene, the m.p. was 139–140°. The mixed melting point of the two recrystallized products showed no depression.

2-Mercapto-4-thiazoleacetic Acid.—A solution containing 50.8 g. (0.25 mole) of ethyl 2-mercapto-4-thiazoleacetate, 80 g. (0.5 mole) of 25% aqueous sodium hydroxide and 200 ml. of water was stirred at 70–80° for three hours. After cooling to 15°, the solution was made acidic with concentrated hydrochloric acid, the precipitate was filtered, washed with water until free of acid and dried at 50°. The product, a tan colored solid, m.p. 156–157° dec., was obtained in 84% yield.

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

(4) J. F. Hamel, *Bull. soc. chim. France*, [4] 29, 390 (1921).

Anal. Calcd. for C₈H₉NO₂S₂: N, 7.99; S, 36.60. Found: N, 8.08; S, 36.63.

5-Carbethoxyrhodanine.—To a stirred solution containing 110 g. (1.0 mole) of ammonium dithiocarbamate in 800 ml. of water was added 194.6 g. (1.0 mole) of diethyl chloromalonate⁵; the temperature rose immediately from 20 to 39°. The reaction mixture was stirred at 20–25° for two days and allowed to stand at 0–10° for an additional two days. The precipitate was filtered, washed with water until the washings were neutral to litmus and dried at 50°. The product, a yellow colored solid, m.p. 82–84°, was obtained in 42.5% yield. After recrystallization from dilute ethyl alcohol, it melted at 85–86°.

Anal. Calcd. for C₈H₇NO₃S₂: H, 3.44; N, 6.83; S, 31.24. Found: H, 3.60; N, 6.84; S, 31.24.

Rhodanine.—This procedure was similar to that described above except after the addition of diethyl chloromalonate, the reaction mixture was stirred at 25–30° for three hours, then heated at 70–80° for 16 hours. After cooling to 0°, the precipitate was filtered, washed with water until the wash water was neutral to litmus and dried at 50°. The product, a light yellow colored solid, m.p. 150–160°, was obtained in 50% yield. After recrystallization from acetic acid, it melted at 166–167°. A mixed melting point with authentic rhodanine was not depressed.

Anal. Calcd. for C₈H₃NOS₂: N, 10.52; H, 2.27; mol. wt., 133.2. Found: N, 10.31; H, 2.39; mol. wt., 132.0°.

Butyl 2-(Butylthio)-4-thiazoleacetate.—A solution containing 48 g. (0.27 mole) of 2-mercapto-4-thiazoleacetic acid, 203 g. (2.7 moles) of butyl alcohol and 5 g. of concentrated sulfuric acid was heated at 115–120° for two days. The water, 9.5 ml., was allowed to distill off as formed. After cooling to room temperature, the reaction mixture was washed with two 500-ml. portions of 2% aqueous sodium bicarbonate solution, then with water until the wash water was neutral to litmus and dried over sodium sulfate. The excess butyl alcohol was removed by distillation. Vacuum distillation of the residue through a 4-foot Vigreux-type column yielded an amber colored liquid (49 g., 62.2%), b.p. 166–168° (1 mm.), *n*_D²⁰ 1.5200.

Anal. Calcd. for C₁₃H₂₁NO₂S₂: C, 54.32; H, 7.36; N, 4.87; S, 22.31. Found: C, 54.58; H, 7.62; N, 4.79; S, 22.57.

Zinc and Cadmium Salts of Ethyl 2-Mercapto-4-thiazoleacetate.—To a solution containing 24 g. (0.24 mole) of ethyl 2-mercapto-4-thiazoleacetate, 38.4 g. (0.24 mole) of 25% aqueous sodium hydroxide and 800 ml. of water was added with agitation, 16.4 g. (0.12 mole) of zinc chloride or 30.8 g. (0.12 mole) of cadmium sulfate (3CdSO₄·8H₂O) dissolved in 800 ml. of water. The reaction mixture was stirred for one hour, the resulting precipitate was filtered, washed with water until the washings were neutral to litmus and dried at 50°. The zinc salt, a white solid, m.p. 78–86°, and the cadmium salt, a white solid, m.p. 170–180°, were obtained in yields of 90.7 and 95.1%, respectively.

Anal. Calcd. for C₁₄H₁₈N₂O₄S₄Zn: N, 5.96; S, 27.29; Zn, 13.91. Found: N, 5.97; S, 26.96; Zn, 13.41. Calcd. for C₁₄H₁₈CdN₂O₄S₄: N, 5.42; S, 24.81; Cd, 21.74. Found: N, 5.25; S, 24.45; Cd, 22.30.

Diethyl 2,2'-Dithiobis-(4-thiazoleacetate) and 2,2'-Dithiobis-(4-thiazoleacetic Acid).—To an agitated suspension of 0.25 mole of ethyl 2-mercapto-4-thiazoleacetate or 2-

(5) M. O. Forster and R. Muller, *J. Chem. Soc.*, 97, 136 (1910).

mercapto-4-thiazoleacetic acid in 300 ml. of water was added dropwise a solution containing 63 g. (0.275 mole) of ammonium persulfate in 147 ml. of water over a 30-minute period at 25–30°. The reaction mixture was stirred for two additional hours.

For the ester, the upper aqueous layer was decanted, and the lower layer was dissolved in 400 ml. of ethyl ether. The ether solution was washed with 200 ml. of 2% aqueous sodium hydroxide, then with water until the washings were neutral to litmus, dried over sodium sulfate, and ether removed *in vacuo*. The product, a tan colored solid, m.p. 32–33°, was obtained in 65.4% yield.

For the acid, the precipitate was filtered and dried at 50°. The product, a tan colored solid, m.p. 150–151° dec., was obtained in 95.6% yield.

Anal. Calcd. for the ester $C_{14}H_{16}N_2O_4S_4$: N, 6.93; S, 31.70. Found: N, 7.03; S, 31.77. Calcd. for the acid $C_{10}H_8N_2O_4S_4$: N, 8.04; S, 36.81. Found: N, 7.88; S, 36.53.

Ethyl 2-(N,N-Diethylthiocarbamoylthio)-4-thiazoleacetate.—To a stirred solution containing 50.8 g. (0.25 mole) of ethyl 2-mercapto-4-thiazoleacetate, 10 g. (0.25 mole) of sodium hydroxide and 500 ml. of acetone was added dropwise 38 g. (0.25 mole) of N,N-diethylthiocarbamoyl chloride⁶ dissolved in 200 ml. of acetone at 28–32° over a 10-minute period. The reaction mixture was stirred for four hours. The sodium chloride was collected by filtration, and the acetone removed *in vacuo*. The residue was dissolved in 500 ml. of ethyl ether, the ether solution was washed with 200 ml. of 2% aqueous sodium hydroxide, then with water until the washings were neutral to litmus, dried over sodium sulfate and the ether removed *in vacuo*. The product, a dark amber colored oil, was obtained in 84.3% yield.

Anal. Calcd. for $C_{18}H_{18}N_2O_2S_3$: N, 8.80; S, 30.20. Found: N, 8.69; S, 29.84.

2,4,6-Tris-(4-carbomethoxymethyl-2-thiazolylthio)-s-triazine.—To a stirred solution containing 50.9 g. (0.25 mole) of ethyl 2-mercapto-4-thiazoleacetate, 14 g. (0.25 mole) of potassium hydroxide and 400 ml. of acetone was added

(6) Kindly supplied by Sharples Chemicals, Inc., Philadelphia, Penna.

15.4 g. (0.083 mole) of cyanuric chloride⁷ dissolved in 100 ml. of acetone. An exothermic reaction set in, causing the temperature to rise from 25 to 42°. The stirred reaction mixture was heated at 55–56° for five hours and after cooling to room temperature the potassium chloride was removed by filtration. Upon removal of the acetone *in vacuo*, the desired product was obtained as a resinous solid in a yield of 88%.

Anal. Calcd. for $C_{24}H_{24}N_6O_6S_6$: N, 12.27. Found: N, 12.10.

Ethyl 2-(Chloroalkenyl or alkynylthio)-4-thiazoleacetates.—A 0.25-mole solution of the potassium salt of ethyl 2-mercapto-4-thiazoleacetate was prepared by dissolving the thiazoleacetate and potassium hydroxide in 300 ml. of acetone and 10 g. of water. To this stirred solution, 0.25 mole of either 1,3-dichloro-2-butene,⁸ 2,3-dichloro-1-propene,⁹ 1,3-dichloropropene⁹ or 3-bromo-1-propyne¹⁰ was added. Immediately, an exothermic reaction set in, the temperature rising from 25 to about 50°. The stirred reaction mixture was heated at 55–56° for six hours, cooled to room temperature, and filtered to remove the potassium chloride. The acetone was removed *in vacuo*. The residues were dissolved in 500 ml. of ethyl ether and washed with water until the washings were neutral to litmus, dried over sodium sulfate and the ether removed *in vacuo*. The data are summarized in Table I.

Acknowledgment.—The writers wish to acknowledge their indebtedness to Messrs. R. O. Zerbe and J. M. Hildebrand for assistance during the course of this investigation. Grateful acknowledgment also is made for the analyses by Mr. E. E. Null.

(7) Kindly supplied by American Cyanamid Company, New York, N. Y.

(8) Kindly furnished by E. I. du Pont de Nemours and Company, Wilmington, Del.

(9) Kindly supplied by Shell Chemical Corporation, Emeryville, Calif.

(10) Kindly furnished by General Aniline and Film Corporation, New York, N. Y.

NITRO, WEST VIRGINIA

NOTES

Nucleophilic Displacement in the Biphenyl Series

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4-Bromo-4'-nitro-, 4-bromo-2'-nitro- and 2-bromo-4'-nitrobiphenyl are unreactive toward piperidine in a typical nucleophilic displacement reaction, while under the same experimental conditions displacement of bromine in 4-bromo-3-nitrobiphenyl proceeds practically to completion.² From the unreactivity of the bromine in the heteronuclear biphenyl derivatives, Campbell, *et al.*, concluded that the activating effect of the nitro group was not transmitted from one ring into the other, and that the two rings in biphenyl act independently of each other, a view prevalent at that time.

(1) Taken in part from M.A. theses submitted to the Chemistry Department of Bryn Mawr College, June, 1950 (T.M.R.) and June, 1953 (B.N.).

(2) N. Campbell, W. Anderson and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

Since then it has been shown that substituent effects can be transmitted through the biphenyl system, and that substituents affect the dissociation constants of biphenylcarboxylic acids and the rates of hydrolysis of their esters across the biphenyl system qualitatively in the same way as they affect the corresponding reactions in the benzene series, but that transmission in biphenyl is quantitatively less than in the benzene series.³ In the light of these results, it seemed that the conclusion drawn from the unreactivity of the bromine in the aforementioned biphenyl derivatives was not justified, because under the same conditions 4-bromo-biphenyl was also completely unreactive. The only permissible generalization is that the transmission of the effect of the 4'-nitro group must be less than in the benzene series.

In order to bring the biphenyl derivatives up to the level of reactivity, a nitro group was introduced *ortho* to the bromine, as has been done before in

(3) E. Berliner and E. A. Blouiniers, *THIS JOURNAL*, **73**, 2479 (1951); E. Berliner and I. H. Liu, *ibid.* **75**, 2417 (1953).