their helpful counsel through the entire program of research relating to antimalarials. The compounds, all prepared in this Institute, were the result of patience as well as skill on the part of many, who are indicated in references. The careful spectrophotometric studies have been due, in the main, to Mrs. E. Faulkner, Mrs. M. Becker, Mrs. K. Grant and Miss J. Gould. We are further indebted to Mrs. B. Beecher for her patient and meticulous efforts in plotting the curves.

Summary

The ultraviolet absorption spectra of thirty-five substituted quinolines have been reported.

Fifteen out of the sixteen possible bz-halo-3-methyl-4-(4'-diethylamino-1'-methylbutylamino)-quinolines have been studied and the influence of halo-substitution has been discussed critically.

Spectral changes due to the influence of the methyl or propyl groups in the 3- position, as well as the influence of the methyl group in position 2 has been pointed out.

The 4-diethylamino-1-methylbutylamino side chain has been replaced by eight other side chains and the resulting spectra have been discussed.

Finally the influence of *p*H on the resonance of these substituted quinolines has been investigated and compared with other data reported in the literature.

RENSSELAER, N. Y. RECEIVED MARCH 16, 1948

[CONTRIBUTION FROM THE CAROTHERS RESEARCH LABORATORY, RAYON TECHNICAL DIVISION, E. I. DU PONT DE NEMOURS & CO., INC.]

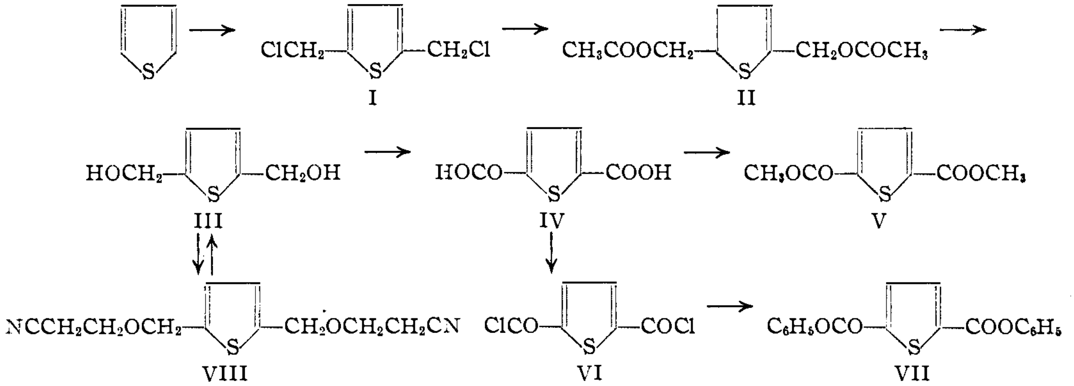
2,5-bis-(Chloromethyl)-thiophene and Some of its Derivatives

BY JOHN M. GRIFFING AND L. FRANK SALISBURY

Introduction

In the course of investigations of linear condensation polymers a number of difunctional intermediates containing the thiophene nucleus have been prepared. All were based on the intermediate, 2,5-bis-(chloromethyl)-thiophene, I, for which a simple method of preparation was developed. The preparation and properties of the new compounds are described in this paper.

The addition of thiophene to a mixture of formalin and strong hydrochloric acid in the absence of other catalysts gave I, together with some of the monofunctional derivative, 2-chloromethylthiophene, which has previously been described by Blicke and Zienty.[1] Treatment of I with potassium acetate in glacial acetic acid gave the diacetate, II, which was hydrolyzed to the glycol, III, not isolated in this instance, but oxidized directly to the dicarboxylic acid, IV. The diacid was converted to a dimethyl ester, V, the melting point (148.5–149.5°) of which corresponded to that of the dimethyl ester of thiophene-2,5-dicarboxylic acid (146–147°) reported by R. Bonz[2] who prepared the acid by a sodium amalgam condensation of 2,5-dibromothiophene and ethyl chlorocarbonate and esterified its silver salt with methyl iodide. The 2,3 isomer melts at 60°,[3] while the 2,4 isomer melts at 120–121°.[4] The positions on the thiophene nucleus occupied by the original chloromethyl groups are thus demonstrated, it having been shown that monochloromethylation occurs at the 2 position.[1] That the second chloromethyl group should enter the 5 position of thiophene is in agreement with observed reactions of thiophenes substituted in the 2 position by an electron donor.



Fusion of thiophene-2,5-dicarbonyl chloride, VI (from IV and thionyl chloride), with phenol

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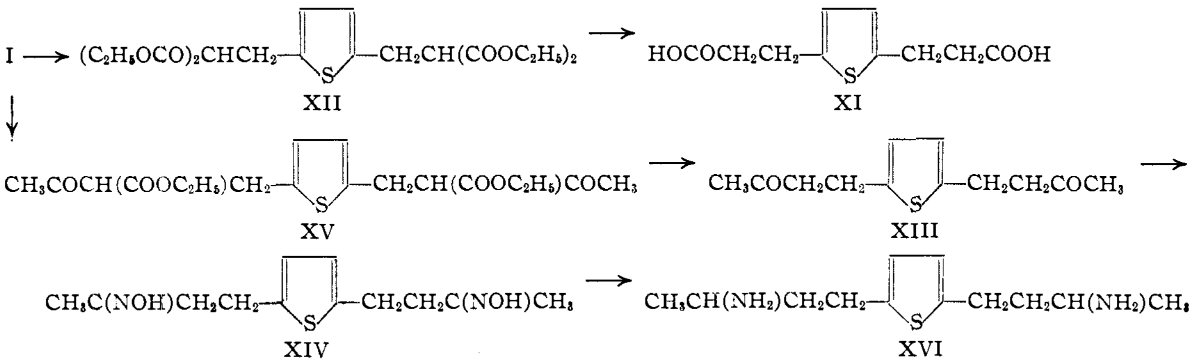
[1] F. F. Blicke and M. F. Zienty, THIS JOURNAL, 63, 2945 (1941).

[2] R. Bonz, *Ber.*, 18, 2305–2307 (1885).

[3] W. Grünewald, *ibid.*, 20, 2585–2587 (1887).

[4] N. Zelinsky, *ibid.*, 20, 2017–2035 (1887).



gave the corresponding diphenyl ester, VII. The glycol, III, was isolated from II by alcoholysis. The glycol, III, with acrylonitrile gave the diadduct, VIII, which on hydrogenation using Raney cobalt catalyst was cleaved to the original glycol, III. Similar catalytic cleavage of benzyl ethers has been reported.[5]

Alkylation of malonic ester with I gave the tetraethyl ester of 2,5-bis-(2′,2′-dicarboxyethyl)-thiophene, XII, which, on hydrolysis and decarboxylation was converted to 2,5-bis-(2′-carboxyethyl)-thiophene, XI. A similar reaction utilizing acetoacetic ester led, by way of the alkylation product, XV, to thiophene-2,5-bis-(1′-butan-3′-one), XIII. Reduction of the dioxime, XIV, of this ketone gave 2,5-bis-(3′-aminobutyl)-thiophene, XVI.

Although attempts to convert I to other products in aqueous alkaline media usually led to resin formation, replacement reactions in anhydrous organic solvents were often succesful. The conversion of I to 2,5-bis-(ethoxymethyl)-thiophene, IX, and 2,5-bis-(hydroxyethoxymethyl)-thiophene, X, using excess of the dry alcohol as solvent in each case are examples.

2,5-bis-(Chloromethyl)-thiophene is a lachrymator and vesicant. It polymerizes at room temperature, a property which necessitates its storage in the cold.

Experimental

Thiophene was obtained from the Socony-Vacuum Oil Company. A fraction boiling at 84°, n^{20}_D 1.5288, was employed.

2,5-bis-(Chloromethyl)-thiophene (I).—A stream of dry hydrogen chloride was added to a stirred solution of 2040 ml. (28.05 moles) of formalin (37%) and 500 ml. of concd. hydrochloric acid (sp. gr. of the mixture, 1.115), allowing the temperature to rise to 50–60°, until the solution was saturated (sp. gr., 1.185). The mixture was then cooled to 30°, whereupon 700 g. (8.33 moles) of thiophene was added dropwise with stirring. After the mixture had been stirred for twenty minutes, the oily lower layer was siphoned off and washed with five 500-ml. portions of cold water. The oil was refrigerated overnight, and filtered using Filter-cel to remove some paraformaldehyde. When seeded with previously prepared crystals, the cold oil solidified to a mass of pale tan crystals. The yield of crude I was 1200 g. (78.8%). It was used without further purification for the large-scale preparation of the diacetate (II) described later. Its b.p. was 106–108° (5 mm.) and 122–124° (11 mm.), n^{25}_D 1.5842 (super-cooled liquid), m.p. 36–37° after recrystallization from purified petroleum ether.

Anal. Calcd. for $C_6H_6SCl_2$: S, 17.70; Cl, 39.17. Found: S, 17.62, 17.62, 17.54; Cl, 39.37, 39.11, 39.11.

2,5-bis-(Acetoxymethyl)-thiophene (II).—Following a procedure of Gattermann and Wieland,[6] 238 g. (1.31 moles) of I was added to a stirred suspension of powdered fused potassium acetate (278 g., 2.83 moles) in glacial acetic acid at 60°. Stirring was continued for five hours at 60°, and the reaction mixture was allowed to stand sixteen hours at room temperature. Precipitated potassium chloride was removed by filtration and the filtrate concentrated *in vacuo* on a hot water-bath. The residue was washed with cold water, neutralized with excess potassium carbonate and extracted with ether. The extract was distilled giving 219 g. (73%) of II, b.p. 140–142° (2 mm.).

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.28; S, 14.0. Found: C, 52.9; H, 5.37; S, 13.2, 13.1.

2,5-bis-(Hydroxymethyl)-thiophene (III).—To a solution prepared by reaction of 10 g. of sodium with 3 l. of absolute ethanol, 400 g. (1.75 moles) of II was added. The reaction mixture was shaken well and allowed to stand at room temperature sixty hours, then concentrated *in vacuo*. The residue was redissolved in ethanol (1 l.), reconcentrated, and finally slurried with 15 g. of ammonium chloride and filtered. The viscous filtrate on distillation gave 140 g. (56%) of water-white oil, b.p. 162–166° (0.25 mm.), n^{25}_D 1.5690.

Anal. Calcd. for $C_6H_8O_2S$: C, 50.0; H, 5.55. Found: C, 49.87, 49.67; H, 5.90, 5.95.

Thiophene-2,5-Dicarboxylic Acid (IV).—Vacuum distilled II (700 g., 3.07 moles) was treated with potassium hydroxide (700 g., 12.5 moles) in 8 l. of water, the solution being maintained at about 35°. The mixture was stirred four hours, and allowed to stand overnight. The flask was immersed in an ice-bath and the contents cooled below 15°, whereupon 1380–1400 g. (8.86 moles) of pulverized potassium permanganate was added in small portions over a seven-hour period, while the temperature was held below 15°. Excess permanganate was destroyed with ethyl alcohol, and the manganese dioxide removed by filtration and washed with 6 l. of hot water. IV was obtained in 91.5% yield from the combined filtrates by acidification with concd. hydrochloric acid.

A portion of the product was sublimed under vacuum (0.0001 mm.) to give a white powder, which was converted to the dimethyl ester (V) with diazomethane in the usual manner. The ester was recrystallized from methanol using Darco, m.p. 148.5–149.5°.

Anal. Calcd. for $C_8H_8O_4S$: C, 48.03; H, 4.03. Found: C, 48.13, 48.19; H, 4.10, 4.07.

The neutral equivalent of IV recovered from the dimethyl ester by saponification, acidification and recrystallization from water was 86.0; calcd., 86.08. Larger amounts of V were made from the acid and methanol in dioxane–toluene–dry hydrogen chloride mixture.

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[5] W. P. Utermohlen, Jr., THIS JOURNAL, **67**, 1505 (1945).

[6] Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," 24th ed., Macmillan and Co., London, 1943, p. 114.

Thiophene-2,5-Diacid Chloride (VI).—The method employed was adapted from a synthesis of terephthaloyl chloride.[7] A suspension of IV (42.5 g., 0.25 mole) in 400 ml. of benzene containing 39 g. (0.49 mole) of pyridine was heated to reflux while thionyl chloride (58.5 g., 0.49 mole) in 100 ml. of benzene was added dropwise with stirring. The reaction mixture was heated at reflux for six hours and allowed to stand overnight at room temperature. The benzene solution was filtered and the pyridine hydrochloride extracted with 300 ml. of hot benzene. The filtrates were combined, concentrated, and the product distilled, b.p. 102–103° (2 mm.). It solidified in the receiver to a white, crystalline mass, 38 g. (72.5% yield). In a second experiment using a longer reflux period (twelve hours) an 89% yield of distilled VI was obtained, m.p. 45–46°, after crystallization from a benzene–heptane mixture.

Anal. Calcd. for $C_6H_2O_2Cl_2S$: Cl, 33.9; S, 15.3. Found: Cl, 33.5; S, 15.4, 15.6.

Diphenyl Ester of Thiophene-2,5-dicarboxylic Acid (VII).—Phenol (25 g., 0.27 mole) and VI (26 g., 0.12 mole) were heated in an oil-bath, raising the temperature over a two-hour period to 200°. This temperature was maintained for an additional hour whereupon the ester was heated at 240° for one-half hour under a water pump vacuum to remove excess phenol. The residue (quantitative yield) solidified to a pale tan solid. It was recrystallized from ethyl alcohol, m.p. 136–137°.

Anal. Calcd. for $C_{18}H_{12}O_4S$: C, 66.7; H, 3.74; S, 9.89. Found: C, 66.8, 67.0; H, 3.89, 3.86; S, 10.1, 10.1.

2,5-bis-(β-Cyanoethoxymethyl)-thiophene (VIII).—The procedure outlined for the isolation of III was in part repeated using 5 g. of sodium and 100 g. (0.439 mole) of II. The residue from the second concentration was taken up in 500 ml. of dry dioxane and at 30°[8] an excess of acrylonitrile was added slowly. Stirring was continued at 45° for six hours and then at room temperature for sixteen hours. The dioxane and excess acrylonitrile were removed *in vacuo* and the residue added to cold water, neutralized with ammonium chloride, and extracted with chloroform. The extract, on distillation, gave 35 g. of VIII (32% from II), b.p. 210–212° (0.45 mm.).

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: S, 12.8. Found: S, 12.3, 12.3.

Catalytic hydrogenation of VIII at 125°, using Raney cobalt–cobalt on kieselguhr catalyst under an initial hydrogen pressure of 2,500 p.s.i., resulted in cleavage of the ether linkage. The recovered glycol was characterized by conversion to II.

2,5-bis-(Ethoxymethyl)-thiophene (IX).—Sodium (10 g., 0.44 mole) was dissolved in 400 ml. of absolute ethanol, and 30 g. (0.166 mole) of I was added to the stirred solution at 60°. Stirring was continued for sixteen hours. Sodium chloride was filtered out and the alcohol solution concentrated *in vacuo*. The residue was taken up in 200 ml. of water and extracted with ether, from which 33 g. (77%) of IX was obtained which boiled at 124–126° (12–13 mm.).

Anal. Calcd. for $C_{10}H_{16}O_2S$: S, 16.0. Found: S, 14.5, 14.3.

2,5-bis-(β-Hydroxyethoxymethyl)-thiophene (X).—Thirty grams of I was added to a solution prepared from 7.63 g. of sodium and 200 ml. of ethylene glycol. The solution was warmed to 50° for six hours and allowed to stand at room temperature for thirty-six hours. Excess ethylene glycol was removed *in vacuo*, the residue was taken up in hot benzene, filtered free of sodium chloride, and the extract distilled giving 23.5 g. (61%) of X, b.p. 210–220° (1 mm.).

Anal. Calcd. for $C_{10}H_{26}O_4S$: S, 13.8. Found: S, 12.4, 12.3.

2,5-bis-(2′-Carboxyethyl)-thiophene (XI).—To a solution prepared from 46 g. (2 moles) of sodium and 1000 ml. of absolute ethanol, 500 g. (3.12 moles) of freshly distilled diethyl malonate was added. The reaction vessel was cooled while 175 g. (0.97 mole) of purified I was added in small portions with stirring. The suspension warmed spontaneously during the addition and required external cooling. It was cooled to room temperature and allowed to stand for forty hours. The suspension was heated to 75° for two hours, cooled and filtered using Filter-cel. The salt was washed thoroughly with alcohol, and the combined filtrates concentrated *in vacuo*. The residue was extracted with one pound of purified ether, and washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, and water. The dried extract was concentrated, removing the excess malonic ester *in vacuo*. The tetraethyl ester of 2,5-bis-(2′,2′-dicarboxyethyl)-thiophene (XII) boiled at 220–230° (0.2–0.5 mm. and weighed 110 g. (26.6%). A large residue indicated that some higher boiling product was formed. XII was redistilled at 163–165° (0.0001 mm.); 103 g., $n^{25}\text{D}$ 1.4840.

Anal. Calcd. for $C_{20}H_{28}O_8S$: C, 56.1; H, 6.59. Found: C, 55.8, 55.1, 55.9; H, 6.70, 6.40, 6.45.

Seventy-five grams of XII was treated with 50 ml. of absolute ethanol, 250 ml. of water, and 50 g. of sodium hydroxide. The solution was boiled for two hours, allowing the alcohol to evaporate. Water was added to bring the volume to 500 ml. and concd. hydrochloric acid added to *p*H 2. Boiling with reflux was maintained for twenty-four hours. After the solution had been concentrated to a volume of 300 ml. and cooled, pale tan crystals of XI separated (30 g., 75%). The acid was recrystallized repeatedly from boiling water using Darco, m.p. 165–167°.

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.29; neut. equiv., 114.1. Found: C, 52.57, 52.54; H, 5.47, 5.27; neut. equiv., 115.4.

Thiophene-2,5-bis-(1′-butan-3′-one) (XIII) and its Dioxime (XIV).—To a finely divided suspension of 60 g. (2.6 moles) of sodium in 1000 ml. of hot, dry dioxane, 400 g. (3.08 moles) of freshly distilled acetoacetic ester was added at such a rate that a gentle reflux of the solvent was maintained. Stirring was continued until the sodium had disappeared, whereupon 181 g. (1 mole) of I was added in small portions. The reaction mixture was stirred until cool, allowed to stand at room temperature for forty hours, stirred at 60° for two hours, cooled and filtered using Filter-Cel. The filtrate was concentrated under reduced pressure. The cooled residue was extracted with ether, and the extract was washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, and water. The residue from the dried ether extract was distilled, giving 120 g. (32.6%) of the diethyl ester of thiophene-2,5-bis-(1′-butan-2′-carboxy-3′-one) (XV), b.p. 225–230° (0.5 mm.); XV was redistilled at 158–160° (0.0001 mm.); $n^{25}\text{D}$ 1.5032.

Anal. Calcd. for $C_{18}H_{24}O_6S$: C, 58.9; H, 6.56; S, 8.69. Found: C, 59.04, 59.16; H, 6.51, 6.72; S, 8.33, 8.32.

To a cold solution of 40 g. (1 mole) of sodium hydroxide in 800 ml. of water, 110 g. (0.3 mole) of XV was added. After the mixture had been stirred for four hours, 90 ml. of concd. hydrochloric acid was added. The mixture was boiled with reflux for twenty minutes, cooled and the organic layer separated. The aqueous layer was extracted with three 300-ml. portions of ether, and the combined extracts together with the original oil were washed with dilute sodium bicarbonate and water and dried. The product (XIII), after a second distillation, amounted to 38 g. (57%), b.p. 128–130° (0.001 mm.); $n^{26}\text{D}$ 1.5192.

Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.2; H, 7.2; S, 14.25. Found: C, 64.67, 64.20, 64.14; H, 7.33, 7.49, 7.33; S, 13.9, 13.8.

A mixture of 300 ml. of absolute ethanol, 60 ml. of pyridine, 25 g. (0.36 mole) of hydroxylamine hydrochloride, and 34 g. (0.15 mole) of XIII was boiled with reflux for twenty hours. The residue after removal of the ethanol was poured into 700 ml. of ice-water. An oil separated which deposited crystals on standing. Recrystallization from 35% ethanol gave white crystals of XIV, m.p. 86–

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(7) P. Carré and D. Libermann, *Compt. rend.*, **199**, 1422 (1934).

(8) F. C. Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944).

87°, together with some lower melting product, possibly geometric isomers.

Anal. Calcd. for $C_{12}H_{18}N_2O_2S$: C, 56.7; H, 7.10. Found: C, 56.82, 57.20, 57.17; H, 7.08, 7.15, 7.18.

2,5-bis-(3′-Aminobutyl)-thiophene (XVI).—The dioxime XIV (14 g.) was hydrogenated (1500 p.s.i.) in methanol at 80° using 10 g. of Raney nickel catalyst. The product was filtered from the catalyst, which was rinsed with purified dioxane, and the filtrate and washings combined. The product (XVI) boiled at 133–135° (2 mm.), yield, 6 g.

Anal. Calcd. for $C_{12}H_{22}N_2S$: N, 12.38. Found: N, 12.29, 12.02.

Acknowledgment.—The analytical data reported here were determined by the Analytical Division, Chemical Department, E I. du Pont de Nemours & Co., Inc.

Summary

The preparation and properties of 2,5-bis-(chloromethyl)-thiophene and a number of compounds derived therefrom are described.

RECEIVED APRIL 20, 1948

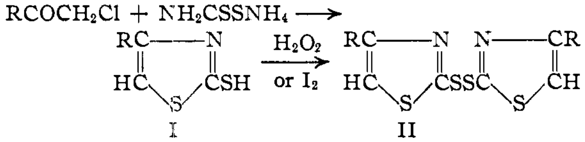
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

The Preparation of Certain Mercaptothiazoles and Thiazyl Disulfides[1]

BY JOHN J. RITTER AND H. SOKOL

During the early stages of the Government Synthetic Rubber Program the need was felt for an elucidation of the mechanism of modifier action in the emulsion copolymerization of butadiene and styrene to produce GR-S. Several recent publications[2] have described the use of *n*-dodecyl mercaptan, thioglycolic acid, ethyl thioglycolate and diisopropyl xanthogen disulfide as modifiers and the effect of such modifiers in controlling polymer molecular weight has been demonstrated. In connection with this program it was thought desirable to synthesize certain other types of mercaptans and disulfides for evaluation as modifiers. This paper describes the preparation of a series of 2-mercaptothiazoles (I) and bis-(thiazyl-2) disulfides (II); the testing of these compounds for modifier activity was performed elsewhere.

Miolati,[3] Levi[4] and Buchman[5] have previously described the preparation of 4-methyl-, 4-ethyl-, 4-carbethoxymethyl-, 4-phenyl- and 4,5-dimethyl-2-mercaptothiazoles by the condensation of the corresponding halomethyl ketones with ammonium dithiocarbamate. The disulfides were obtained by oxidation with hydrogen peroxide or iodine. In a more recent investigation,[6] done in association with this project, there were prepared 4-dodecyl- and 4-tetradecyl-2-mercaptothiazoles.



I II

Using this same general reaction we have prepared a series of 2-mercaptothiazoles and bis-(thiazyl-2) disulfides bearing in the 4-position *n*-alkyl and *p*-substituted aryl substituents. *n*-Alkyl chloromethyl ketones were conveniently prepared in excellent yields (Table I) from the corresponding acid chlorides and ethereal diazomethane followed by treatment with dry hydrogen chloride. *p*-Alkylphenacyl chlorides were synthesized from alkylbenzenes and chloroacetyl chloride in the presence of an aluminum chloride catalyst. Both types of chloromethyl ketones were found to react readily at room temperature with ammonium dithiocarbamate. These condensations were carried out by slowly adding the chloromethyl ketone to a 50% molar excess of the dithiocarbamate in order to prevent the formation of 2-ketonylthiothiazoles. The 2-mercaptothiazoles were readily crystallized and melted sharply. They were found to be insoluble in cold 10% hydrochloric acid and potassium hydroxide solutions. Treatment with boiling 10% potassium hydroxide solution generally caused decomposition with the formation of ammonia. Attempts to form hydrochlorides of these mercaptothiazoles by saturation of their ethereal solutions with dry hydrogen chloride were unsuccessful; nor did they appear to form picrates readily. Although they gave insoluble salts by treatment with lead acetate and mercuric chloride, the compositions of these precipitates were not uniform and they could not be used for characterization. The reaction of 5% silver nitrate solution with an alcohol–pyridine solution of the mercaptothiazole occurred quantitatively to precipitate the silver salt of the mercaptothiazole and liberate an equivalent quantity of nitric acid. Titration of the nitric acid with 0.1 *N* sodium hydroxide served as an accurate and convenient method for the determination of per cent. mercaptan.[7] The silver salts thus produced,

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[1] Abstracted from a portion of the thesis submitted by H. Sokol to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This work was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Snyder, Stewart, Allen and Dearborn, THIS JOURNAL, **68**, 1422 (1946); Wall, Banes and Sands, *ibid.*, **68**, 1429 (1946).

(3) Miolati, *Gazz. chim. ital.*, **23**, I, 575 (1893).

(4) Levi, *ibid.*, **61**, 719 (1931).

(5) Buchman, Reims and Sargent, *J. Org. Chem.*, **6**, 764 (1941).

(6) Bunnett and Tarbell, THIS JOURNAL, **67**, 1945 (1945).

(7) Private communication to Office of Rubber Reserve, Reconstruction Finance Corp., by Willard P. Tyler, B. F. Goodrich Company, Research Laboratories.