that minoxidil, not 2,4-diamino-6-piperidinopyrimidine, was released from the glucuronide.

It appears that, as with monkey urine, a single glucuronide best explains the results with human urine. In addition to minoxidil, the glucuronide of minoxidil, and the very polar minoxidil-related material in human urine, small (less than 3%) amounts of 2,4-diamino-6-(4′-hydroxypiperidino)pyrimidine 3-oxide and, in a few samples, traces of 2,4-diamino-6-piperidinopyrimidine were found. The more mobile component of the very polar zone of radioactivity corresponded to the migration of the carboxy metabolites of minoxidil. The urinary metabolite profile for the human is based on the results reported by Gottlieb *et al.* (2) modified by our chromatographic results with human and monkey urine containing the glucuronide of minoxidil as discussed.

The urinary metabolite profile for minoxidil in the human is compared to those in the rat, dog, and monkey in Fig. 1. This comparison shows that each species, including the human, excreted substantially the same metabolites but in quite different relative amounts. The monkey and human exhibited similar metabolite profiles, whereas the dog and rat were quantitatively different from each other and from the monkey and human. Thus, of the three animal species studied, the monkey is most like the human in its biotransformation and disposition (1) of minoxidil.

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[x] To whom inquiries should be directed.

Antiradiation Compounds XV: Condensations of Carbon Disulfide with Amino, Chloro, Cyanomethyl, and Sulfonamido Heterocycles

WILLIAM O. FOYE [x], JOEL M. KAUFFMAN, JOSEPH J. LANZILLO, and EDWARD F. LaSALA

Abstract □ Condensations of carbon disulfide were carried out with amino, chloro, and diamino heterocycles to give condensed ring thiazoline-2-thiones and imidazoline-2-thiones, with cyanomethyl heterocycles to give dithio acid derivatives, and with heterocyclic sulfonamides to give sulfonyldithiocarbamates. Of several examples tested, pyrido[3,2-*d*]thiazoline-2-thione, disodium 2-(5-chloro-2-thienyl)-3,3-dimercaptoacrylonitrile, triethylammonium 4-sulfamoylphenyldithiocarbamate, ammonium β-phenethyldithiocarbamate, and methyl *N*-(thiophene-2-sulfonyl)dithiocarbamate, only the last-named compound showed any radiation protection for mice. Several compounds gave negative tests for antimalarial activity.

Keyphrases □ Antiradiation compounds—condensations of carbon disulfide with amino, chloro, cyanomethyl, and sulfonamido heterocycles □ Carbon disulfide—condensation products with amino, chloro, cyanomethyl, and sulfonamido heterocycles, potential antiradiation agents □ Heterocycles (amino, chloro, cyanomethyl, and sulfonamido)—condensation products with carbon disulfide, antiradiation activity

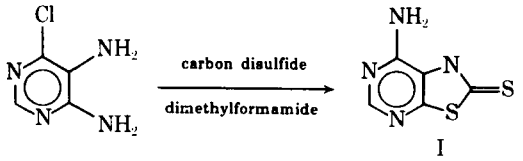
Condensation products of carbon disulfide with amines (1, 2) and mercaptans (3), as well as with active methylenes adjacent to cyano groups (4), have all shown some degree of protection for animals against ionizing radiation. With the dithiocarbamates, the presence of heterocyclic rings, particularly when strongly basic (5), provided greater protective properties. In the case of the dimercaptoacrylonitriles derived from active methylene compounds, the presence of heterocyclic rings on the carbon alpha to the dimercapto acid function generally resulted in hygroscopic products and sometimes compounds of low stability.

The attempt accordingly has been made to obtain condensation products of carbon disulfide with heterocyclic rings that have greater stability and also a mercapto group two or three atoms distant from a basic nitrogen or heteroatom, to provide an analogy with the more protective aliphatic mercapto amines.

DISCUSSION

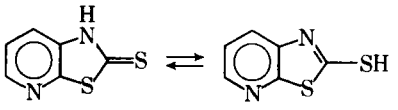
Condensations with Amino and Chloro Heterocycles—The finding (6) that 4-chloro-5,6-diaminopyrimidine gave a thiazoline-2-thione (I) with replacement of amino and chloro groups and not the imidazoline-2-thione prompted a trial of this reaction on several suitably substituted heterocycles (Scheme I).

The pyridine analog (II) was prepared previously by Yamamoto and Takahashi (7), who reported a decomposition point of 294° and stated no percentage yield. Their product was obtained from 2-chloro-3-nitropyridine, sodium sulfide, hydrogen sulfide, and carbon disulfide; sulfide reduction of the nitro group was involved. In the present research, II was obtained in 73% yield, mp 310–314° dec., from 3-amino-2-chloropyridine and carbon disulfide, with dimethylformamide as the solvent.



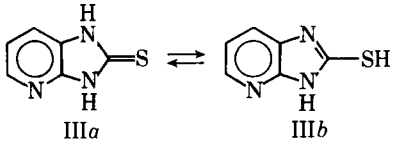
I

Scheme I



IIa IIb

Scheme II



IIIa IIIb

Scheme III

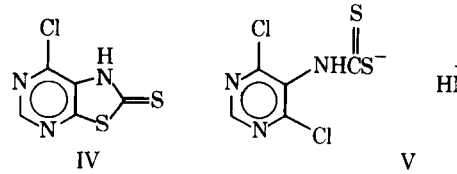
Most evidence indicates that 2-mercaptothiazole (8) and 2-mercaptobenzothiazole (9) are present in neutral media mainly as the thiones (8). The pyridine derivative has a melting point 150° higher than the benzo analog, dissolves instantly in cold, aqueous alkali, and is insoluble in cold, dilute, mineral acid. This behavior can be explained by the existence in neutral media of the thione form as a hydrogen-bonded dimer, in equilibrium with a small amount of thiol (II*b*) (Scheme II).

A broad, intense IR absorption band at 2650–2900 cm^{-1} supports the existence of the hydrogen-bonded dimer with a significant amount of proton transfer, as postulated for 2-mercaptobenzothiazole (10). Absorption at 2550 cm^{-1} also indicates the presence of thiol. The UV absorption in dimethylformamide was identical to that for 2-mercaptobenzothiazole.

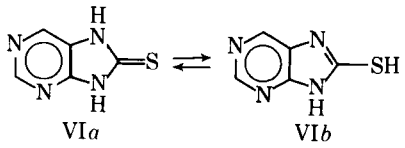
Reaction of 4-amino-3-bromopyridine with carbon disulfide in dimethylformamide failed to give the isomeric pyrido[4,3-*d*]thiazoline-2-thione. Pyrido[2,3-*c*]imidazoline-2-thione (III), however, was synthesized from 2,3-diaminopyridine and carbon disulfide in ethanol; a melting point of "over 300°" had previously been reported for this compound (11). By recrystallizing the product from dimethylformamide and propanol, a melting point of 326–330° dec. was obtained. The IR absorption at 2700–2900 cm^{-1}, as well as the high melting point, again indicated that the hydrogen-bonded dimeric thione was the predominant form of the compound. A small absorption band at 2600 cm^{-1} and solubility in alkali indicated some thiol form (III*b*) (Scheme III).

Condensation of carbon disulfide with 5-amino-4,6-dichloropyrimidine did not give the expected thiazoline-2-thione (IV) but the dithiocarbamate salt (V) instead. Reaction of 4,5-diaminopyrimidine with carbon disulfide, however, gave a 35% yield of purine-8-thiol (VI) (Scheme IV). Previous syntheses of this compound from pyrimidine and thiourea (12) and from purine and sulfur (13) are known. The IR absorption of this compound between 2700 and 2900 cm^{-1} was complex, and its breadth was characteristic of that of the hydrogen-bonded dimeric thione of 2-mercaptobenzothiazole (10). An IR absorption band at 2550 cm^{-1} also indicated the presence of some of the thiol form. Reaction of 2-amino-3-chloropyrazine with carbon disulfide in dimethylformamide at 110° for 22 hr gave only a small amount of orange solid, mp 380° dec., which was not characterized.

Condensations with Cyanomethyl Heterocycles—One attempt to obtain more stable heterocyclic-substituted dimercaptoacrylonitriles involved the use of heterocycles with electron-attracting substituents. 2-Chloro-5-cyanomethylthiophene was prepared from 2-chlorothiophene *via* chloromethylation, and condensation with carbon disulfide was carried out in the presence of sodium hydride. Although the reaction was carried out in anhydrous ether, a hydrated product (VII) was obtained, similar to previous compounds of this type (4). Attempts to prepare the corresponding phenyl and sulfonamido derivatives failed; the electron-withdrawing effects of the substituents apparently deactivated the rings to chloromethylation.

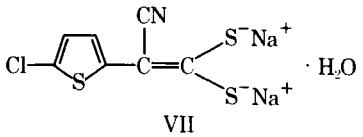


IV V



VIa VIb

Scheme IV



VII

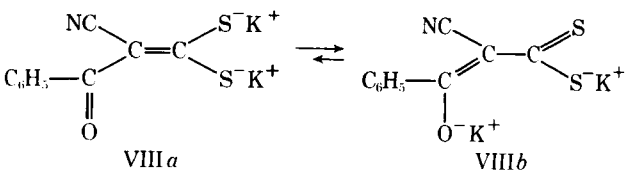
The carbon disulfide condensation product from benzoylacetonitrile (4) was found to be more stable than the condensation products having aromatic rings attached directly to the cyanomethyl group, apparently due to extension of conjugation and shifting of a negative charge from sulfur to the more electronegative oxygen (VIII) (Scheme V). The IR absorption did not show the presence of a carbonyl group, indicating VIIIb to be the predominant form. Condensation of 2-furoylacetonitrile with carbon disulfide and sodium methoxide gave the monothio anion (IX). The IR absorption showed the presence of hydroxy and cyano groups, carbon–carbon unsaturation, and carbon–sulfur unsaturation. When potassium hydroxide was used as the base, an unidentifiable water-soluble red salt was obtained.

Condensation of 2-thenoylacetonitrile with carbon disulfide in the presence of potassium hydroxide, however, gave the dithio dianion (X). The IR absorption showed the presence of the cyano group, carbon–carbon unsaturation, and carbon–sulfur unsaturation but no evidence of a carbonyl group, analogous to the product from benzoylacetonitrile. Neither IX nor X was obtained in a hydrated or solvated form.

Condensations with Sulfonamides—Gompper and Hägele (14) first described the reaction of sulfonamides with carbon disulfide and alkali to give *N*-sulfonylimidodithiocarbonates (XI). These compounds were not isolated but could be converted to derivatives such as mono- or diethers or *N*-sulfonyldithiourethanes (XII) (Scheme VI).

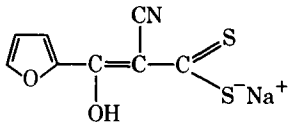
Attempts were made to prepare the *N*-sulfonylimidodithiocarbonates and thioesters of N^4-acetylsulfanilamide, thiazole-2-sulfonamide, benzothiazole-2-sulfonamide, 4-phenylthiazole-2-sulfonamide, and thiophene-2-sulfonamide. Only the thiophene-2-sulfonamide gave products that could be characterized. These compounds were the *N*-sulfonylimidodithiocarbonate (XIII) and the methyl ester of the sulfonyl dithiocarbamate (XIV).

Treatment of sulfanilamide with carbon disulfide and alkali gave 4-sulfamoylphenyldithiocarbamate (XV); both the potassium and triethylammonium salts were isolated. Evidence for the attack of carbon disulfide at the aromatic amine rather than at the sulfonamide nitrogen was found by an IR absorption peak for C=S, the presence of only one cation in the product, and the failure of carbon disulfide to react with N^4-acetylsulfanilamide. Attempts to prepare an *N*-sulfonylimidodithiocarbonate monothioester of XV were also unsuccessful.

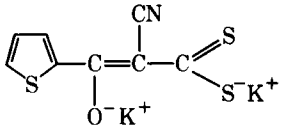


VIIIa VIIIb

Scheme V



IX



X

RESULTS[1]

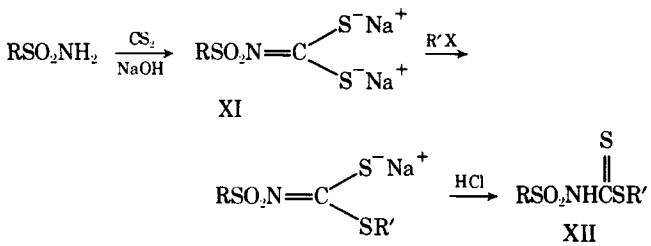
Tests were carried out in mice (groups of six) *versus* 825 rads (X-rays), with an observation period of 30 days. The compounds were administered intraperitoneally in a carboxymethylcellulose–polysorbate vehicle at dose levels of 80–400 mg/kg. Compounds II, VII, and XV and ammonium β-phenethyldithiocarbamate, which had been previously prepared (15), were inactive. Compound XIV provided slight protection (17% survival) in this test at a dose of 400 mg/kg ip.

Several compounds were also screened for antimalarial activity in mice infected with *Plasmodium berghei*, according to the method of Osdene *et al.* (16), and in *Aedes aegypti* infected with *Plasmodium gallinaceum*, according to the method of Gerberg *et al.* (17). In the former test, II, XIV, and XV were listed as inactive; XV, however, showed a test/control survival ratio of 2.2 at a dose of 640 mg/kg. In the latter test, XIV, XV, and ammonium β-phenethyldithiocarbamate were inactive.

On the basis of the radiation-protective test results reported here and in previous papers (4, 18), it may be concluded that compounds with thiol anions or potential thiol anions, capable of rapid hydrogen atom transfer, may be radiation protective without the presence of a strongly basic nitrogen in the molecule. Nevertheless, the presence of an electron-rich heterocyclic ring system or other group capable of binding to DNA or other essential macromolecules appears to be required in the absence of a strongly basic nitrogen. However, by far the most potent of the basic thiol radiation-protective compounds do contain strongly basic amine functions (19).

EXPERIMENTAL[2]

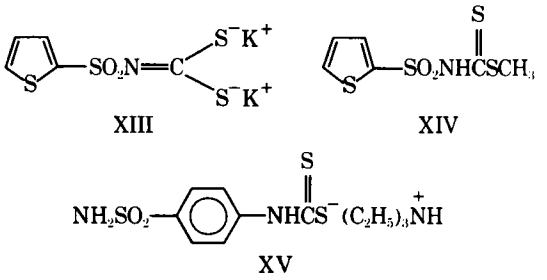
Pyrido[3,2-*d*]thiazoline-2-thione (II)—A mixture of 3-amino-2-chloropyridine[3] (6.43 g, 0.05 mole), carbon disulfide (50 ml), and dimethylformamide (50 ml) was heated at reflux for 47 hr, cooled, and evaporated at 50° and 50 mm pressure to remove excess carbon disulfide. The solution was poured into 300 ml of ice and water with stirring. The precipitate was dried to give 7.2 g of tan powder,



XI

XII

Scheme VI



XIII XIV XV

mp 304–306° dec., and recrystallized from a mixture of 40 ml of dimethylformamide and 100 ml of 1-propanol.

The first crop of tan crystals weighed 5.8 g (69%), mp 310–314° dec. The compound was soluble in acetone and cold dilute sodium hydroxide solution and insoluble in water and hot 8% sulfuric acid. Recrystallization from dimethylformamide–propanol and drying at 100°/0.3 mm gave the analytical sample of off-white spars, mp 312–315° dec. [lit. (7) mp 294°]; IR ν_{max} (KBr): 2650–2900 (NH), 2550 (SH), and 1040 (C=S) cm^{-1}; UV λ_{max} (dimethylformamide): 265 nm.

Anal.—Calc. for $C_6H_4N_2S_2$: C, 42.8; H, 2.4; N, 16.6; S, 38.1. Found: C, 43.0; H, 2.3; N, 16.4; S, 37.8.

Pyrido[2,3-*d*]imidazoline-2-thione (III)—The procedure of Petrow and Saper (11) gave an 89% yield of product, mp 326–330° [lit. (11) mp >300°]. Recrystallization of 9.1 g from a mixture of 40 ml of dimethylformamide and 100 ml of 1-propanol gave 6.9 g (76%), mp 326–330°; IR ν_{max} (KBr): 2700–2900 (NH), 2550 (SH), and 1200 (C=S) cm^{-1}.

Anal.—Calc. for $C_6H_5N_3S$: C, 47.7; H, 3.3; N, 27.8; S, 21.2. Found: C, 48.1; H, 3.4; N, 27.5; S, 21.0.

4,6-Dichloro-5-aminopyrimidinium 4,6-Dichloropyrimidine-5-dithiocarbamate (V)—A mixture of 4,6-dichloro-5-aminopyridine[4] (0.82 g, 0.005 mole), carbon disulfide (5 ml), and dimethyl sulfoxide (5 ml) was heated at reflux for 5 days, freed of carbon disulfide by evaporation, and diluted with 30 ml of water. The yellow powder that separated was dried at 125°/3 mm for 3 hr, giving 0.2 g, mp 239–242° dec.

Anal.—Calc. for $C_9H_6Cl_4N_6S_2$: C, 26.8; H, 1.5; N, 20.8; S, 15.9. Found: C, 27.2; H, 1.4; N, 21.2; S, 16.1.

Purine-8-thiol (VI)—A mixture of 4,5-diaminopyrimidine[5] (4.7 g, 0.043 mole), carbon disulfide (10 ml), and 95% ethanol (50 ml) was heated at reflux for 70 hr. Hydrogen sulfide was liberated, and product separated during the reaction. Addition of 10 ml of water and chilling in an ice bath gave a tan solid. This product was washed with 30% ethanol, dried at 130°/3 mm for 3 hr, and recrystallized from 150 ml of water, yielding 2.3 g (35%) of light-yellow spars, mp 312–318° dec. [lit. (12) mp 268° dec. and (13) mp 295–297° dec.]; IR ν_{max} (KBr): 2700–2900 (NH) and 1200 (C=S) cm^{-1}.

The compound was soluble in cold, dilute sodium hydroxide solution, cold, dilute sulfuric acid, dimethylformamide, and hot 1-propanol.

Anal.—Calc. for $C_5H_4N_4S$: C, 39.4; H, 2.7; N, 36.8; S, 21.0. Found: C, 39.6; H, 3.0; N, 36.4; S, 20.6.

Disodium 2-(5-Chloro-2-thienyl)-3,3-dimercaptoacrylonitrile Hydrate (VII)—Sodium hydride[6] (1.05 g, 0.025 mole, 57% in petroleum ether) was washed three times with anhydrous ether and suspended in ether (12 ml). To this mixture was added carbon disulfide (0.8 ml, 0.013 mole) and 2-chloro-5-cyanomethylthiophene (20) (2 g, 0.013 mole) dropwise during 20 min. The reaction mixture was stirred at room temperature for 7 days.

The precipitate was filtered and washed with anhydrous ether to give a 60% yield of a green powder, mp >360°; IR ν_{max} (KBr): 3450 (OH), 2160 (C≡N), and 1625 (C=C) cm^{-1}.

Anal.—Calc. for $C_7H_2NNa_2S_3 \cdot H_2O$: C, 28.40; H, 1.35; N, 4.75. Found: C, 27.98; H, 1.67; N, 4.50.

Sodium 2-Furoylacetonitrile-2-dithiocarboxylate (IX)—2-Furoylacetonitrile (21) (1 g, 0.0074 mole) and sodium methoxide (0.4 g, 0.0074 mole) were suspended in anhydrous benzene (15 ml) and heated at reflux for 1 hr. Heating was stopped, and carbon di-

[1] Antiradiation screening of several compounds was carried out at the Walter Reed Army Institute of Research. Results were reported through the courtesy of Capt. Gene Withrow.

[2] Melting points were determined in capillaries with a Mel-Temp melting-point block and are corrected. IR absorption spectra were obtained with a Perkin-Elmer model 137 B spectrophotometer with sodium chloride optics. UV absorption spectra were obtained with a Beckman DB-GT spectrophotometer. Elemental analyses were done by Dr. F. B. Strauss, Oxford, England, or by Dr. Carol K. Fitz, Carlisle, Mass. TLC was carried out using silica gel, and products were detected by exposure to iodine vapor.

[3] Aldrich Chemical Co.

[4] Cyclo Chemicals.

[5] K & K Chemicals.

[6] Metal Hydrides, Inc.

sulfide (0.56 g, 0.0074 mole) in methanol (5 ml) was added to the warm mixture. An additional 0.4 g of sodium methoxide was added, and stirring and refluxing were continued for 0.5 hr. The yellow precipitate was filtered, washed with anhydrous ether, and dried *in vacuo*, giving 0.9 g (90%) of yellow powder, mp 275–278°; IR ν_{max} (KBr): 3500 (OH), 2190 (C≡N), 1592 (C=C), and 1015 (C=S) cm^{-1}.

Anal.—Calc. for $C_8H_4NNaO_2S_2$: C, 41.20; H, 1.72; N, 6.01. Found: C, 41.52; H, 2.08; N, 6.29.

Dipotassium 2-(2-Thenoyl)-3,3-dimercaptoacrylonitrile (X)—Potassium hydroxide (0.47 g, 0.007 mole), dissolved in 10 ml of absolute ethanol, was added to a solution of thenoylacetonitrile (21) (0.5 g, 0.0035 mole) and carbon disulfide (0.22 ml, 0.0035 mole) in 10 ml of dry benzene and 5 ml of absolute ethanol. The mixture was stirred at room temperature for 4 days, filtered, and washed with ether, giving a 50% yield of brown powder, mp 208–210°; IR ν_{max} (KBr): 3450 (OH), 2198 (C≡N), 1640 (C=C), and 1000 (C=S) cm^{-1}.

Anal.—Calc. for $C_8H_3K_2NOS_3$: C, 31.70; H, 0.99; N, 4.63; S, 31.70. Found: C, 31.27; H, 1.38; N, 4.75; S, 31.40.

Triethylammonium 4-Sulfamoylphenyldithiocarbamate (XV)—To a solution of 1.72 g (0.01 mole) of sulfanilamide in 20.8 ml of triethylamine were added 10.5 ml (0.15 mole) of carbon disulfide and 60 ml of absolute ethanol. The solution was stirred for 6 hr at room temperature, allowed to stand overnight, and filtered. The product was washed with absolute ethanol and ether, giving 2.65 g (75%) of yellow crystals, mp 138–141°; IR ν_{max} (KBr): 990 (C=S) cm^{-1}.

Anal.—Calc for $C_{13}H_{23}N_3O_2S_3$: C, 44.70; H, 6.59; N, 12.03; S, 27.51. Found: C, 44.67; H, 6.77; N, 12.00; S, 27.91.

Potassium 4-Sulfamoylphenyldithiocarbamate—The potassium salt was prepared from sulfanilamide (1.72 g, 0.01 mole), dimethylformamide (5 ml), absolute ethanol (20 ml), and carbon disulfide (10.5 ml, 0.15 mole) in a manner similar to that described for XV. A yield of 2.25 g (71%) was obtained, mp 219° dec.

Anal.—Calc. for $C_7H_7KN_2O_2S_3$: C, 29.37; H, 2.45; N, 9.79; S, 33.60. Found: C, 29.58; H, 2.71; N, 10.00; S, 33.66.

Dipotassium Thiophene-2-sulfonylimidodithiocarbonate (XIII)—A solution of 1.63 g (0.01 mole) of thiophene-2-sulfonamide (22) in 20 ml of absolute ethanol was mixed with 10.5 ml (0.15 mole) of carbon disulfide and 8 ml of ethanol containing 0.03 mole of potassium hydroxide. The mixture was stirred overnight at room temperature, and the precipitate was washed with absolute ethanol, dry ether, and acetone, giving 1.5 g (47%) of hygroscopic yellow powder, mp 202–204° dec.

Anal.—Calc. for $C_5H_3K_2NO_2S_4$: C, 19.05; H, 0.95; N, 4.44; S, 40.64. Found: C, 18.63; H, 2.06; N, 4.05; S, 41.03.

Methyl *N*-(Thiophene-2-sulfonyl)dithiocarbamate (XIV)—A solution of 3.26 g (0.02 mole) of thiophene-2-sulfonamide (22) in 15 ml of dimethylformamide was treated with 1.2 ml of sodium hydroxide solution (16 g in 20 ml of water) and 0.7 ml (0.01 mole) of carbon disulfide with stirring. After 10 min, 0.6 ml of sodium hydroxide solution and 0.35 ml (0.005 mole) of carbon disulfide were added, and this addition was repeated 10 min later.

After being stirred for an additional 10 min, the solution was placed in an ice bath and treated with 1.1 ml (0.02 mole) of methyl iodide; the resulting solution was stirred for 2 hr and poured into 50 ml of water. Hydrochloric acid (concentrated) was added dropwise to the point of disappearance of turbidity, and the red oil which separated was isolated and shaken with several 50-ml portions of water. The resulting crystals were collected and recrystallized from benzene with a small amount of petroleum ether, giving 1.2 g (24%), mp 104–105°; IR ν_{max} (KBr): 1050 (C=S) cm^{-1}.

Anal.—Calc. for $C_6H_7NO_2S_4$: C, 28.42; H, 2.78; N, 5.53; S, 50.63. Found: C, 28.76; H, 3.01; N, 5.70; S, 51.02.

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