Pyridinium- and Quinolinium-2-dithioacetic Acid Zwitterions: Antiradiation and Anticancer Activities

WILLIAM O. FOYE ˣ, YEUN JAI LEE, KIRIT A. SHAH, and JOEL M. KAUFFMAN

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Abstract □ Pyridinium-, quinolinium-, and one pyrimidinium-2-dithioacetic acid zwitterions were prepared by condensation of the *N*-methyl heterocyclic anhydro bases with carbon disulfide. Reaction of the 2-methylpyridine methiodide anhydro base with carbon disulfide resulted in replacement of the 2-methyl group to give the 1-methylpyridinium-2-dithioacetic acid zwitterion. The 1,6-dimethylquinolinium-2-dithioacetic acid zwitterion showed appreciable anticancer activity against P-388 lymphocytic leukemia in mice, but the other zwitterions tested showed no activity. No antiradiation activity was found for 1-methylpyridinium-2-dithioacetic acid zwitterion.

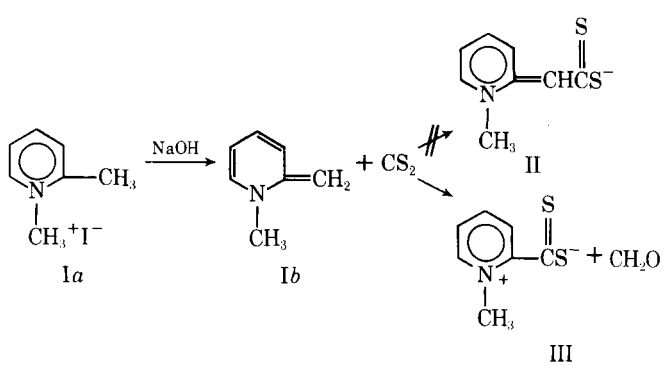
Keyphrases □ Dithioacetic acids, pyridinium and quinolinium—zwitterions synthesized, antitumor and antiradiation activity evaluated □ Zwitterions—pyridinium- and quinolinium-2-dithioacetic acids synthesized, antitumor and antiradiation activity evaluated □ Antitumor activity—various pyridinium- and quinolinium-2-dithioacetic acids evaluated in mice □ Antiradiation activity—1-methylpyridinium-2-dithioacetic acid evaluated in mice □ Structure–activity relationships—various pyridinium- and quinolinium-2-dithioacetic acids evaluated for antitumor and antiradiation activity

Condensation of carbon disulfide with active methylene groups is a method for preparing dithio acids (1). Dithio acid dianions prepared from several cyanomethylene-substituted compounds (2), in particular *N*-cyanoacetylpyrrolidine (3), had appreciable radiation-protective properties. Dithio acids and esters derived from pyridinium ylids also were radiation protective in both mice and bacteria (4).

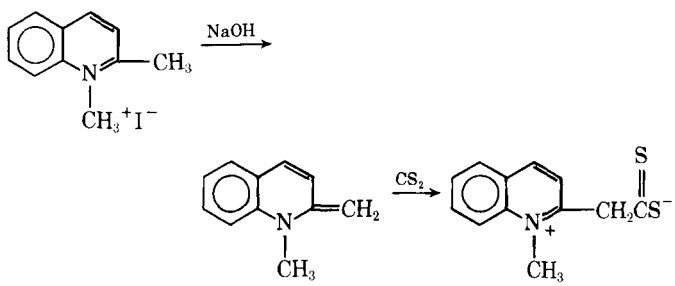
Antileukemia tests were performed for some dithio acid dianions; although positive activity was not found, it is considered that radiation-protective compounds that may act as DNA-complexing agents should have anticancer potential as well (3). Therefore, synthesis of other dithio acids, particularly those with nitrogen-containing heterocycles, was undertaken to prepare potential antiradiation and anticancer agents.

DISCUSSION

Anhydro bases derived from quaternary pyridinium and quinolinium salts by alkaline treatment react with carbon disulfide to form dithio acids (5, 6). With 2-methylpyridine methiodide (I*a*), carbon disulfide condensation with the anhydro base (I*b*) took place with elimination of the 2-methyl group to give the 1-methylpyridinium-2-dithiocarboxylic acid zwitterion (III, Scheme I). Reaction of I*b* with carbon disulfide was first observed by Schneider *et al.* (7), who obtained a product melting at 186° for which they claimed Structure II.



Scheme I



Scheme II

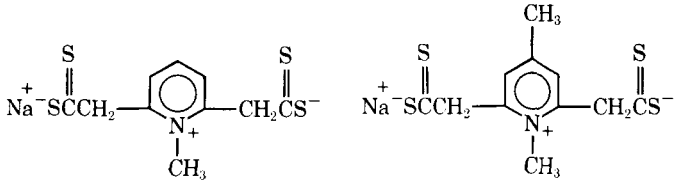
A solution of I*b* was obtained in 20% alkali, and repetition of their reaction in a two-phase aqueous ether system or in a homogeneous aqueous dioxane solution gave an orange product, mp 247–249°. Analytical data did not support Schneider's structure, and NMR analysis showed the complete loss of the C-methyl protons. Both the product and I*a* showed four aromatic ring protons and a singlet for *N*-methyl protons (δ 4.37 ppm in I*a* and 4.11 ppm in the product); only I*a* showed C-methyl protons (δ 2.94 ppm).

Both elemental analysis and NMR data support Structure III for the product, the 1-methylpyridinium-2-dithiocarboxylic acid zwitterion. Mass spectral peaks also corresponded to those expected from III rather than from II. Peaks were observed from measurement at 100, 170, and 235° at *m/e* 76 (CS_2^+), 78, 79 (pyridine$^+$), 92, 93 (*N*-methylpyridine$^+$), 192 (S_6^+), 224 (S_7^+), 256 (S_8^+), and 51 and 148 (polymerized acetylene). No peak was observed at either *m/e* 183 (Structure II) or 169 (Structure III) because of loss of carbon disulfide.

The only other product detected in the reaction was a small quantity of yellow crystals at the interface of the two-phase reaction. Heating this material in dimethylformamide or recrystallization from ethanol converted it to III. Gompper *et al.* (8) found that Schneider's product (II) could be obtained at −30° in acetonitrile.

The same procedure carried out with quinaldine methiodide, however, resulted in the formation of the quinaldinium-2-dithioacetic acid zwitterion (IV, Scheme II) without loss of the 2-methyl group, probably because of greater stability of the quinaldinium anhydro base.

Although condensation of carbon disulfide with the methyl groups of 2,6-dimethylpyridine (2,6-lutidine) and 2-methylquinoline has been claimed to give salts of dithio acids (9), neither 2-methylpyridine, 2,6-lutidine, nor 2,4,6-collidine would react with carbon disulfide in the presence of various concentrations of base. Conversion to the methiodides, however, produced more active methyl groups which did condense with carbon disulfide. The products from 2,6-lutidine and 2,4,6-collidine were the sodium salts of 1-methylpyridinium-2,6-bis(dithioacetic acid) (V) and 1,4-dimethylpyridinium-2,6-bis(dithioacetic acid) (VI) zwitterions, respectively.



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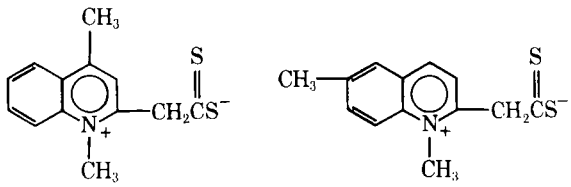


VII VIII

Substitution of the 2- and 6-methyl groups in each compound was confirmed by NMR analysis. 2,6-Lutidine methiodide and V showed three aromatic ring protons (δ 8.10 ppm) and a three-proton singlet (δ 4.20 ppm) for the *N*-methyl. 2,6-Lutidine methiodide also showed a six-proton singlet (δ 3.00 ppm) for the C-methyls, and V showed a four-proton singlet at δ 3.00 ppm.

2,4,6-Collidine methiodide and VI showed two aromatic ring protons (δ 8.10 ppm) and a three-proton singlet (δ 4.20 ppm) for the *N*-methyl. 2,4,6-Collidine methiodide also showed a six-proton singlet (δ 2.82 ppm) for the 2- and 6-methyls and a three-proton singlet (δ 2.50 ppm) for the 4-methyl group. Compound VI showed a three-proton singlet (δ 2.50 ppm) for the 4-methyl but a four-proton singlet (δ 2.85 ppm) for the 2- and 6-methyls.

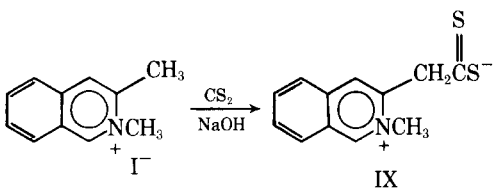
Condensation of carbon disulfide also occurred with the methiodides of 4-methylquinaldine and 6-methylquinaldine. In both cases, the 2-dithioacetic acid zwitterion (VII and VIII, respectively) was obtained; no bis(dithioacetic acid) was observed. This result is supported by the fact that 4-methylquinaldine condenses with benzaldehyde in the presence of alkali only on the 2-methyl group (10). NMR data could not be obtained because of the insolubility of these compounds.

3-Methylisoquinolinium methiodide underwent condensation with carbon disulfide and alkali to give the expected 2-methylisoquinolinium-3-dithioacetic acid zwitterion (IX, Scheme III).

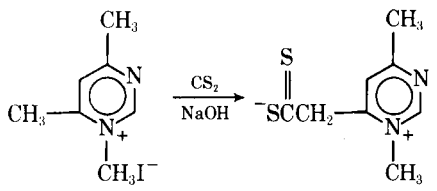
4,6-Dimethylpyrimidine methiodide also condensed with carbon disulfide to give a mono(dithioacetic acid). On the basis of previous results, anhydro base formation can be assumed to occur on the methyl adjacent to the *N*-methyl group; therefore, the product is 1,4-dimethylpyrimidinium-6-dithioacetic acid zwitterion (X, Scheme IV).

Antiradiation testing[1] was carried out with III in mice at several dosage levels up to 100 mg/kg ip and up to 400 mg/kg po. Radiation dosage was 849 rads of γ-radiation (from a ^{137}Cs-source); no protection of the mice was observed. Details of the testing procedure were described previously (3).

Anticancer screening was done[2] using either L-1210 lymphoid leukemia or P-388 lymphocytic leukemia. Compounds III, VI, and IX were essentially inactive; details regarding dose, tumor system, and survival are listed in Table I. Compound VI, however, showed positive activity in mice with P-388 lymphocytic leukemia, comparable to that from mercaptopurine. Details of the testing procedures were described previously (3).



Scheme III



Scheme IV

[1] Antiradiation testing was carried out at the Walter Reed Army Institute of Research. Results were made available through the courtesy of Dr. Marie M. Grenan.

[2] Anticancer screening was carried out by the Division of Cancer Treatment, National Cancer Institute, in accordance with their protocol (11).

Table I—Antitumor Activities in Mice

Compound	Tumor[a]	Dose, mg/kg	Animal Weight Difference (T − C), g	Survival (T/C), %
III	LE	25	−1.8	102
	PS	25	−0.3	95
VI	LE	87.5	−0.4	105
VIII	PS	50	−2.3	126
	PS	100	−1.3	140
IX	PS	100	−1.4	99
6-Mercaptopurine	LE	80	−1.9	156
	LE	160	−3.3	144

[a] LE refers to L-1210 lymphoid leukemia; PS refers to P-388 lymphocytic leukemia.

Antimalarial screening of two compounds was carried out[3] using the blood schizonticidal test in mice infected with *Plasmodium berghei* KBG 173 malaria, according to the procedure of Osdene *et al.* (12). Compounds VII and IX showed essentially no activity at dose levels of 40, 160, and 640 mg/kg.

The antileukemic activity of VIII possibly could be regarded as due to the loss of carbon disulfide, by reversal of the aldol-like condensation, leaving a reactive carbanion which might function similarly to the alkylating agents. Since none of the related structures showed appreciable antileukemic effects and would be expected to undergo the loss of carbon disulfide with similar ease or difficulty, it can be assumed at present that the activity is a function of the dithiocarboxylic acid structure. No previous examples of anticancer activity by dithio acids are known.

EXPERIMENTAL[4]

2-Methylpyridine Methiodide—2-Methylpyridine (20 ml, 0.204 mole) and methyl iodide (16 ml, 0.258 mole) in 125 ml of absolute ethanol were refluxed for 3 hr. Cooling at 5° produced colorless crystals that were recrystallized from absolute ethanol, mp 220–225° [lit. (13) mp 224°]; NMR (dimethyl sulfoxide-d_6): δ 2.94 (s, 3H, 2-CH_3), 4.40 (s, 3H, NCH_3), and 7.9–8.4 (m, 4H, ring H) ppm.

1-Methylpyridinium-2-dithiocarboxylic Acid Zwitterion (III)—To a solution of 2-methylpyridine methiodide (4 g, 0.0163 mole), carbon disulfide (10 ml, 0.166 mole), dioxane (20 ml), and water (10 ml) was added 30 ml of 20% aqueous sodium hydroxide during 0.5 hr at room temperature. The resulting red solution was stirred overnight at room temperature. The red precipitate was filtered, washed with hot water, and dried, giving a 33% yield of orange-brown crystals, mp 247–249°; IR (KBr): 1320 (C=S) and 925 (C=S) cm^{-1}; NMR (dimethyl sulfoxide-d_6); δ 4.4 (s, 3H, NCH_3) and 7.9–8.4 (m, 4H, ring H) ppm; mass spectrum: *m/e* 76 (CS^{+2}), 78, 79 (pyridine$^+$), 92, 93 (*N*-methylpyridine$^+$), 192 (S_6^+), 224 (S_7^+), 256 (S_8^+), and 51 and 148 (polymerized acetylene).

Anal.—Calc. for $C_7H_7NS_2$: C, 49.80; H, 4.14; N, 8.29; S, 37.80. Found: C, 50.08; H, 4.05; N, 8.20; S, 37.50.

GC of the reaction mixture was carried out at 100°, using nitrogen as the carrier with 8% dinonyl phthalate on Chromosorb W and 8% Carbowax 1540 on Chromosorb W columns. A sample was removed from the reaction mixture 15 min after the start of the reaction; it was injected in a solution of either ethanol or methanol. The retention time of one peak was identical to that obtained with 37% formaldehyde solution; the only other peaks were attributable to the alcohol, carbon disulfide, and water.

1-Methylquinolinium-2-dithoacetic Acid Zwitterion (IV)—To a solution of 1-methylquinaldinium iodide (14) (4.85 g, 0.017 mole), dioxane (20 ml), water (10 ml), and carbon disulfide (10 ml, 0.166 mole) was added rapidly 30 ml of saturated sodium hydroxide. A thick red paste formed immediately; an additional 5 ml of water was added, and the mixture was stirred overnight at room temperature. The red solid was filtered and washed with water, mp 185–187°; IR (KBr): 1305 (C=S) and

[3] Antimalarial screening was carried out at the University of Miami; results were made available by the Walter Reed Army Institute of Research.

[4] Melting points were determined with a Mel-Temp capillary melting-point block and are uncorrected. IR spectra were obtained using a Perkin-Elmer model 137B spectrophotometer. NMR spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained on a Consolidated Electrodynamics Corp. model 21-110 spectrometer. TLC was carried out using silica gel, and products were detected by exposure to iodine vapor. Elemental analyses were done by F. B. Strauss, Oxford, England, or by Carol K. Fitz, Carlisle, Mass. Organic reagents were obtained from Aldrich Chemical Co. and Fisher Scientific Co.

920 (C=S) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 2.55 (s, 2H, 2-CH_2), 4.4 (s, 3H, NCH_3), and 7.9–8.4 (m, 6H, ring H) ppm.

Anal.—Calc. for $C_{12}H_{11}NS_2$: C, 61.80; H, 4.72; N, 6.01; S, 27.46. Found: C, 62.14; H, 4.77; N, 6.20; S, 27.10.

2,6-Dimethylpyridine Methiodide—2,6-Dimethylpyridine (40 ml, 0.37 mole) and methyl iodide (32 ml, 0.32 mole) were added to 250 ml of absolute ethanol. The resulting solution was refluxed for 3 hr and cooled at 5°. The white crystals were recrystallized from absolute ethanol, mp 240–242°; NMR (dimethyl sulfoxide-d_6): δ 3.00 (s, 6H, CH_3), 4.20 (s, 3H, NCH_3), and 8.10 (m, 3H, aromatic H) ppm.

Anal.—Calc. for $C_8H_{12}IN$: C, 38.55; H, 4.81; N, 5.62. Found: C, 38.19; H, 4.97; N, 5.64.

Sodium 1-Methylpyridinium-2,6-bis(dithioacetate) Zwitterion (V)—To a solution of 2,6-dimethylpyridine methiodide (4 g, 0.02 mole), water (10 ml), dioxane (20 ml), and carbon disulfide (10 ml, 0.166 mole) was added 30 ml of 20% sodium hydroxide over 0.5 hr at room temperature. The solution was stirred overnight. A red precipitate was filtered, washed with hot water, and dried in a desiccator, mp 249–250°; IR (KBr): 1335 (C=S) and 935 (C=S) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 3.00 (s, 4H, CCH_2), 4.20 (s, 3H, NCH_3), and 8.10 (m, 3H, aromatic H) ppm.

Anal.—Calc. for $C_{10}H_{11}NNaS_4$: C, 40.65; H, 3.41; N, 4.74. Found: C, 41.04; H, 3.46; N, 4.93.

2,4,6-Trimethylpyridine Methiodide—2,4,6-Trimethylpyridine (40 ml, 0.32 mole) and methyl iodide (32 ml, 0.32 mole) were added to 250 ml of absolute ethanol. The resulting solution was refluxed for 3 hr and cooled at 5°. The white crystals were recrystallized from absolute ethanol, mp 209–210°; NMR (dimethyl sulfoxide-d_6): δ 2.50 (s, 3H, 4-CH_3), 2.82 (s, 6H, 2- and 6-CH_3), 4.20 (s, 3H, NCH_3), and 8.10 (s, 2H, aromatic H) ppm.

Anal.—Calc. for $C_9H_{14}IN$: C, 41.06; H, 5.32; N, 5.32. Found: C, 40.95; H, 5.36; N, 5.07.

Sodium 1,4-Dimethylpyridinium-2,6-bis(dithioacetate) Zwitterion (VI)—To a solution of 2,4,6-trimethylpyridine methiodide (4 g, 0.02 mole), water (10 ml), dioxane (20 ml), and carbon disulfide (10 ml, 0.166 mole) was added 30 ml of 20% sodium hydroxide over 0.5 hr at room temperature. The solution was stirred overnight. A red precipitate was filtered, washed with hot water, and dried in a desiccator, mp 188–190°; IR (KBr): 1300 (C=S) and 920 (C=S) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 2.50 (s, 3H, 4-CH_3), 2.85 (s, 4H, 2- and 6-CH_2), 4.20 (s, 3H, NCH_3), and 8.10 (s, 2H, aromatic H) ppm.

Anal.—Calc. for $C_{11}H_{12}NNaS_4$: C, 42.69; H, 3.91; N, 4.53. Found: C, 42.45; H, 3.91; N, 4.85.

1,4-Dimethylquinaldinium Iodide—4-Methylquinaldine (25 g, 0.159 mole) and methyl iodide (10 ml, 0.159 mole) were added to 130 ml of butanol. The resulting solution was refluxed for 4 hr and allowed to stand at 5°. The yellow crystals were filtered and recrystallized from propanol, mp 267–268° [lit. (15) mp 263–265°]; NMR (dimethyl sulfoxide-d_6): δ 2.85 (s, 3H, 4-CH_3), 3.00 (d, 3H, 2-CH_3), and 4.40 (s, 3H, NCH_3) ppm.

1,4-Dimethylquinolinium-2-dithioacetic Acid Zwitterion (VII)—To a solution of 1,4-dimethylquinaldinium iodide (5.38 g, 0.017 mole), water (10 ml), dioxane (20 ml), and carbon disulfide (10 ml, 0.166 mole) was added rapidly 30 ml of 30% sodium hydroxide. A thick red paste was formed, and 5 ml of water was added; the mixture was stirred overnight at room temperature. Then the mixture was filtered and washed with hot water and carbon disulfide to give a dark-red powder (2 g, 50% yield), mp 165–167°; IR (KBr): 1300 (C=S) and 920 (C=S) cm^{-1}.

Anal.—Calc. for $C_{13}H_{13}NS_2$: C, 63.15; H, 4.7; N, 5.6; S, 25.9. Found: C, 63.3; H, 5.0; N, 5.6; S, 26.3.

1,6-Dimethylquinaldinium Iodide—To 150 ml of butanol, 6-methylquinaldine (10.05 g, 0.064 mole) and methyl iodide (4 ml, 0.064 mole) were added rapidly. The solution was refluxed for 4 hr, and the resulting mixture was cooled at 5° overnight. Yellow needles were isolated and recrystallized from propanol, mp 251–252° [lit. (16) mp 236–237°]; NMR (dimethyl sulfoxide-d_6): δ 2.55 (s, 3H, 6-CH_3), 3.15 (s, 3H, 2-CH_3), and 4.50 (s, 3H, NCH_3) ppm.

1,6-Dimethylquinolinium-2-dithioacetic Acid Zwitterion (VIII)—To a solution of 1,6-dimethylquinaldinium iodide (3.90 g, 0.013 mole), water (10 ml), dioxane (20 ml), and carbon disulfide (10 ml, 0.166 mole) was added rapidly 30 ml of 30% sodium hydroxide. A dark-red precipitate formed immediately; 5 ml of water was added, and the mixture was stirred overnight at room temperature. The mixture was filtered and washed with hot water and carbon disulfide to give a dark-red powder (1.8 g, 60% yield), mp 191–192°; IR (KBr): 1300 (C=S) and 920 (C=S) cm^{-1}.

Anal.—Calc. for $C_{13}H_{13}NS_2$: C, 63.15; H, 4.7; N, 5.6; S, 25.9. Found: C, 62.9; H, 5.0; N, 5.5; S, 25.6.

2,3-Dimethylisoquinolinium Iodide—3-Methylisoquinoline (36.95 g, 0.258 mole) and methyl iodide (16 ml, 0.258 mole) in 175 ml of butanol were refluxed with stirring for 4 hr and cooled overnight at 5°. The yellow needles were filtered and recrystallized from absolute ethanol, mp 224–225° [lit. (27) mp 219°]; NMR (dimethyl sulfoxide-d_6): δ 2.75 (s, 3H, 3-CH_3) and 4.40 (s, 3H, NCH_3) ppm.

2-Methylisoquinolinium-3-dithioacetic Acid Zwitterion (IX)—To 2,3-dimethylisoquinolinium iodide (4.85 g, 0.017 mole), water (10 ml), dioxane (20 ml), and carbon disulfide (10 ml, 0.166 mole) was added rapidly 30 ml of 30% sodium hydroxide. An orange solid precipitated, 5 ml of water was added, and the mixture was stirred overnight at room temperature. The precipitate was filtered and washed with hot water and carbon disulfide, giving 1.1 g (30% yield) of orange powder, mp 246–250°; IR (KBr): 1020 (C=S) cm^{-1}.

Anal.—Calc. for $C_{12}H_{11}NS_2$: C, 61.8; H, 4.7; N, 6.0; S, 27.4. Found: C, 61.5; H, 4.6; N, 5.8; S, 27.1.

1,4,6-Trimethylpyrimidinium Iodide—4,6-Dimethylpyrimidine (10 g, 0.092 mole) and methyl iodide (6 ml, 0.092 mole) in 100 ml of methanol were refluxed for 3 hr and cooled overnight at 5°. The pale-yellow crystals were filtered and recrystallized from water and methanol–ethyl acetate to give 6 g (40% yield), mp 250–252°; NMR (dimethyl sulfoxide-d_6): δ 2.75 (d, 6H, 4-,6-CH_3), 4.25 (s, 3H, NCH_3), and 8.40 (s, 2H, aromatic H) ppm.

Anal.—Calc. for $C_7H_{11}IN_2$: C, 33.6; H, 4.4; N, 11.2. Found: C, 33.7; H, 4.4; N, 11.0.

1,4-Dimethylpyrimidinium-6-dithioacetic Acid Zwitterion (X)—To a solution of 1,4,6-trimethylpyrimidinium iodide (2.5 g, 0.01 mole), water (5 ml), dioxane (20 ml), and carbon disulfide (5 ml, 0.084 mole) was added rapidly 20 ml of 30% sodium hydroxide. A dark-red solid precipitated, 5 ml of water was added, and the mixture was stirred overnight at room temperature. The product was filtered and washed with water and carbon disulfide, giving 160 mg (10% yield) of dark-red powder, mp 186–187°; IR (KBr): 1300 (C=S) and 865 (C=S) cm^{-1}.

Anal.—Calc. for $C_8H_{10}N_2S_2$: C, 48.5; H, 5.0; N, 14.1. Found: C, 48.8; H, 4.6; N, 13.9.

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