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Keyphrases

Molluscicides—structure, activity relationship
 Snails, *Schistosoma mansoni* infection—analysis
 Peroxidase activity—*p*-phenylenediamine oxidation

Colorimetric analysis—spectrophotometer
 Catalase activity—hydrogen peroxide decomposition
 UV spectrophotometry—analysis

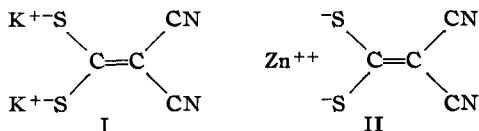
Antiradiation Compounds X. Derivatives of 3,3-Dimercaptoacrylonitrile

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The dipotassium salt of 2-cyano-3,3-dimercaptoacrylonitrile was found to give fair protection to mice *versus* X-rays. Derivatives prepared for further radioprotective evaluation include dialkyl thioethers, metal complexes, and fused heterocyclic dithioles. A series of 3,3-dimercaptoacrylonitriles bearing aromatic and heterocyclic rings was also obtained from the condensation of arylacetonitriles with carbon disulfide in the presence of alkoxide ion. Of these various derivatives, the zinc complex and the benzoyl derivative showed some radioprotective properties.

CONDENSATIONS of carbon disulfide with certain amines and mercaptans have given dithiocarbamates (1, 2) and trithiocarbonates (3) with radioprotective activity. In order to determine whether nonbasic compounds, unrelated to the 2-mercaptoethylamine structure, having a dithio acid group may have radioprotective properties, condensations of a number of active methylene compounds with carbon disulfide have been carried out. Some of the products obtained have been examined for radiation protection in mice. Radiation protection of animals by dithio acids has not been previously reported.

Reaction of malononitrile with carbon disulfide is known to give the dipotassium salt of 2-cyano-3,3-dimercaptoacrylonitrile (4) (I). Brown's procedure was repeated, utilizing potassium hydroxide in 95% ethanol,



to give a product melting at 313–316° (dec) (m.p. previously listed as > 250°) with loss of water below 300°. Analysis indicated a monohydrate, and the

infrared absorption spectrum showed the presence of water and C≡N, C=C, and C—S bonds (960 and 872 cm.⁻¹) (5). A trihydrate of the sodium salt of this compound has been reported by Soderback (6). Antiradiation tests carried out at the Walter Reed Army Institute of Research¹ showed this compound to give fair protection to mice *versus* 825 r (X-rays) at a dose level of 350–700 mg./kg. Accordingly, derivatives of this compound have been prepared as well as analogs in which one of the cyano groups was replaced, primarily by aromatic rings.

A zinc complex (II) was obtained as the hemihydrate which was much less water soluble than the potassium salt. The infrared spectrum was similar to that of the potassium salt, except that the absorption due to CS₂ appeared as a wide doublet centered at 880 cm.⁻¹. A cupric complex was also obtained as the hemihydrate, extremely insoluble in water, but a ferrous complex was too rapidly oxidized to be characterized.

The dimethylthioether and diethylthioether are known compounds (7) and were prepared for testing, but the monomethyl- or monoethyl-thioether could not be isolated. The dibutylthioether could not be crystallized or purified as well. Condensations of I with 2,3-dichloropyrazine and 2,3-dichloroquinoxaline were successful, however, giving pyrazino-[2,3-*d*]-1,3-dithiole-Δ^{2,α}-malononitrile (III) and quinoxalino[2,3-*d*]-1,3-dithiole-Δ^{2,α}-malononitrile.

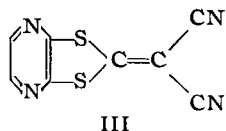
Carbon disulfide condensation with cyanoacetamide to give IVa has been reported (4), using the hydroxide-ethanol method. An attempt to repeat

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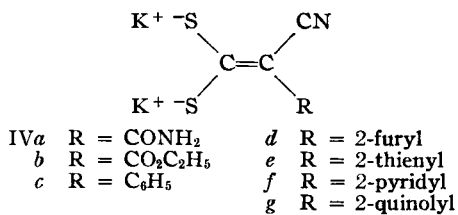
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this gave only potassium ethyl xanthate. Condensation with ethyl cyanoacetate (4, 8, 9) took place readily using hydroxide-ethanol, and the product (IVb) was obtained unsolvated, unlike the other members of this series. The carbon analyses were low and erratic, as was the case with nearly all the compounds described below. This was probably due to retention of carbon as cyanide in the inorganic residue formed on the combustion catalyst. The weight of the residue was found to correspond to the amount the carbon analysis was low, calculated as cyanide, in one case investigated. Infrared absorption, however, showed the presence of $C\equiv N$, $C=C$, and $C-S$ in this and the following compounds, which with generally satisfactory analyses for H, N, and S leaves no question as to the structures.

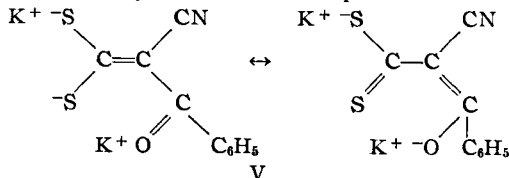


Condensation of carbon disulfide with phenylacetone nitrile has been reported to occur in ether with sodamide but the product was not isolated (8). It has also been claimed to take place in methanol with potassium hydroxide, but no physical constants were reported for this compound (9). Repetition of this synthesis using potassium *n*-propoxide gave only xanthate. Use of *t*-butoxide, however, which is 100 times more basic than *n*-propoxide (10), in *t*-butanol-ether gave a good yield of condensation product (IVc), isolated as the hemi-*t*-butanolate. The reaction of carbanions with carbon disulfide appears to be instantaneous, but difficulties occur when too weak a base is used. A low concentration of carbanion apparently allows the competing reaction of alkoxide with carbon disulfide to predominate, leading to xanthates as major products.

This was illustrated in the case of condensation with furan-2-acetonitrile. Hydroxide in 95% ethanol gave xanthate, *n*-propoxide gave a mixture of xanthate and dithio acid (IVd), and *t*-butoxide gave dithio acid in good yield as the hemi-*t*-butanolate. The corresponding thiophene, pyridine, and quinoline compounds were also isolated as the hemi-alcoholates. Acetonitriles bearing electron-deficient rings such as pyridine and quinoline were sufficiently acidic to allow proton removal by *n*-propoxide. All of these aromatic-substituted compounds were extremely hygroscopic, liquefying after exposure to moist air for a few seconds to a few minutes. Handling in a glove bag under dry nitrogen was necessary. However, aqueous solutions of the compounds appeared to be stable at room temperature. None of these compounds could be recrystallized without decomposition.

A condensation product (V) from benzoylacet-

nitrile and carbon disulfide was obtained unsolvated and in poor yield. Infrared absorption was similar to that observed for the other compounds in the series, but no absorption attributable to a carbonyl group was evident. Instead, bands were observed at 1580, 1530, 1440, and 1270 cm^{-1} which are expected for metal chelates or salts of enols of 1,3-diketones (5), so the resonating structure V appears to be the most logical structure. Soderback (6) has pointed out the existence of similar resonating forms of dicyanodimercaptoethylene. The higher degree of resonance in this compound accounts for its greater stability and ease of handling, in comparison to the heterocyclic-substituted compounds.



Antiradiation Properties—Antiradiation tests were carried out in mice as previously described (11). Data received show that the dimethylthioether and diethylthioether of I were inactive versus 825 r (X-rays), whereas the zinc complex of I showed slight activity versus 1000 r (γ -rays) at a dose level of 25 mg./kg. The condensation product of carbon disulfide with ethyl cyanoacetate (IVb), however, gave 50% protection to mice versus 600 r (γ -rays) at a dose of 100 mg./kg. The phenyl, furyl, and thienyl dimercaptoacrylonitriles, (IVc,d,e) gave no protection versus 825 r (X-rays), but the benzoyl derivative (V) gave slight protection (17% survival) with a dose of 120 mg./kg.

EXPERIMENTAL

Methods—Melting points were determined in capillaries with a Mel-Temp block and are corrected. Infrared spectra were obtained with a Perkin-Elmer Infracord 137B spectrometer in KBr pellets. Carbon-hydrogen analyses were done by Weiler and Strauss, Oxford, England, or by Carol K. Fitz, Needham, Mass. Nitrogen analyses were done by the Kjeldahl method and sulfur analyses by peroxide fusion.

2-Cyano-3,3-dimercaptoacrylonitrile, Dipotassium Salt, Monohydrate—The procedure of Brown (4) gave an 83% yield of yellow crystals, m.p. 313–316° (dec); ν_{min}^{KBr} 3400 (doublet) (OH) 2190 ($C\equiv N$), 1610 ($C=C$), 1310 ($C-C$), 1235 ($C-C$), 960 ($C-S$), 872 ($C-S$) cm^{-1} .

Anal.—Calcd. for $C_4H_2K_2N_2OS_2$: C, 20.3; H, 0.9; K, 33.0; N, 11.9; S, 27.2. Found: C, 20.3; H, 1.1; K, 32.8; N, 11.8; S, 27.0.

2-Cyano-3,3-dimercaptoacrylonitrile, Zinc Complex—A clear solution of the potassium salt of 2-cyano-3,3-dimercaptoacrylonitrile (2.36 g., 0.01 mole) in 5 ml. of water was treated dropwise at 25° with a solution of zinc nitrate hexahydrate (2.97 g., 0.01 mole) in 2 ml. of water. The resulting mixture was cooled at 5°, filtered, and the light yellow solid was washed with a few ml. of ice water and dried, giving 1.8 g. (84% yield) of product which was unmelted at 360°: ν_{min}^{KBr} 3550 (doublet), 2200, 1610, 1400, 1380, 1335, 945, 885, 875 cm^{-1} .

Anal.—Calcd. for $C_4N_2S_2Zn \cdot \frac{1}{2} H_2O$: C, 22.4; H, 0.47; N, 13.1. Found: C, 22.6; H, 0.43; N, 13.4.

2-Cyano-3,3-dimercaptoacrylonitrile, Cupric Com-

plex—The potassium salt of 2-cyano-3,3-dimercaptoacrylonitrile (2.36 g., 0.01 mole) in 14 ml. of water was treated with a solution of cupric nitrate trihydrate (2.41 g., 0.01 mole) in 2 ml. of water. Bulky, red-brown solid appeared at once, and heat was evolved. The product was filtered, washed with water and propanol, and dried to give 2.2 g. (100%) of material unmelted at 360° (darkens above 250°).

Anal.—Calcd. for $C_4CuN_2S_2 \cdot \frac{1}{2}H_2O$: C, 22.6; H, 0.47; N, 13.2. Found: C, 23.6; H, 0.42; N, 13.0.

Pyrazino[2,3-d]-1,3-dithiole- $\Delta^{2,\alpha}$ -malononitrile—The potassium salt of 2-cyano-3,3-dimercaptoacrylonitrile (7.08 g., 0.03 mole) was dissolved in 50 ml. of dimethylformamide, and 2,3-dichloropyrazine (4.44 g., 0.03 mole) (gift of American Cyanamid Co.) was added. The solution was heated at 85° for 16 hr. during which time it became black. It was diluted with 100 ml. of water, cooled to 5°, and filtered. The dried, brown powder (2.0 g.) was sublimed at 0.5 mm. using a free flame to give 1.1 g. (17%) of yellow powder, m.p. 175–205° and 0.25 g. (4%) of yellow needles, m.p. 212–213° (analytical sample); ν_{min}^{KBr} 2210, 1480, 1340, 1155, 1075, 850 cm^{-1} .

Anal.—Calcd. for $C_8H_2N_4S_2$: C, 44.0; H, 0.93; N, 25.7; S, 29.3. Found: C, 43.9; H, 1.16; N, 25.4; S, 29.0.

Quinoxalino [2,3-d]-1,3-dithiole- $\Delta^{2,\alpha}$ -malononitrile—The potassium salt of 2-cyano-3,3-dimercaptoacrylonitrile (7.08 g., 0.03 mole), 2,3-dichloroquinoxaline (6.0 g., 0.03 mole) (Eastman Organic Chemicals), methanol (200 ml.), and water (20 ml.) were refluxed 2 hr., diluted with 150 ml. of water, and filtered. Recrystallization of the solid from 250 ml. of dimethylformamide and drying at 140°/0.2 mm. for 2 hr. gave bright yellow crystals, 3.2 g. (25%), m.p. 298–320° (dec.); ν_{min}^{KBr} 2210, 1505, 1250, 1180, 1120, 780, 770 cm^{-1} .

Anal.—Calcd. for $C_{12}H_4N_4S_2$: N, 20.8; S, 23.9. Found: N, 20.5; S, 23.6.

All manipulations in this and the following procedures were carried out under nitrogen.

2-Phenyl-3,3-dimercaptoacrylonitrile, Dipotassium Salt—Trimmed potassium metal (3.9 g., 0.1 mole) was allowed to dissolve in 100 ml. of *t*-butanol under nitrogen with stirring. Phenylacetonitrile (5.8 ml., 0.05 mole) in 25 ml. of dry ether was added in one portion at 30°, and carbon disulfide (3.8 g., 0.05 mole) in 25 ml. of dry ether was added dropwise at 10° during 10 min. The yellow product was filtered at 5°, washed with ether, and dried to give 10.2 g. (67%) of extremely deliquescent material, m.p. 45–60°; ν_{min}^{KBr} 3400, 2180, 1625, 1570, 1500, 1460, 1350, 1290, 1390, 910, 760, 700 cm^{-1} .

Anal.—Calcd. for $C_9H_8K_2NS_2 \cdot \frac{1}{2}C_4H_9OH$: N, 4.6; S, 20.9. Found: N, 4.7; S, 21.2.

2-(2-Furyl)-3,3-dimercaptoacrylonitrile, Dipotassium Salt—The previous procedure was applied to furan-2-acetonitrile (Aldrich Chemical Co.) to give an 87% yield of deliquescent tan powder, m.p. 110° (dec.); ν_{min}^{KBr} 3400, 2180, 1625, 1570, 1500, 1460, 1350, 920, 765, 730 cm^{-1} .

Anal.—Calcd. for $C_7H_4K_2NOS_2 \cdot \frac{1}{2}C_4H_9OH$: N, 4.7; S, 21.6. Found: N, 4.5; S, 20.9.

2-(2-Thienyl)-3,3-dimercaptoacrylonitrile, Dipotassium Salt—The previous procedure was applied to thiophene-2-acetonitrile (12) to give a 76% yield of deliquescent yellow powder, m.p. 160–170° (dec.);

ν_{min}^{KBr} 3400, 2180, 1625, 1610, 1500, 1480, 1440, 1380, 1325, 1240, 920, 775, 690 cm^{-1} .

Anal.—Calcd. for $C_7H_4K_2NS_2 \cdot \frac{1}{2}C_4H_9OH$: N, 4.5; S, 30.8. Found: N, 3.9; S, 30.9.

2-(2-Pyridyl)-3,3-dimercaptoacrylonitrile, Dipotassium Salt—The previous procedure was employed with pyridine-2-acetonitrile (13) except that propanol was used in place of *t*-butanol. Bright yellow solid was obtained in 59% yield, after washing with propanol, m.p. 290–310° (dec.), and was extremely hygroscopic. ν_{min}^{KBr} 3300, 2180, 1630, 1590, 1460, 1425, 1380, 1295, 1260, 920, 825, 775, 670 cm^{-1} .

Anal.—Calcd. for $C_8H_4K_2N_2S_2 \cdot \frac{1}{2}C_3H_7OH$: N, 9.3; S, 21.3. Found: N, 9.3; S, 21.1.

2-(2-Quinoly)-3,3-dimercaptoacrylonitrile, Dipotassium Salt—The previous procedure was employed with quinoline-2-acetonitrile (14) to give an 81% yield of bright orange, granular solid, m.p. 225–235° (dec.) (loses liquid at 200°) which was very hygroscopic. ν_{min}^{KBr} 3300, 2180, 1640, 1610, 1600, 1550, 1500, 1450, 1420, 1350, 1310, 1270, 1240, 1050, 920, 895, 825, 780, 760, 750 cm^{-1} .

Anal.—Calcd. for $C_{12}H_8K_2N_2S_2 \cdot \frac{1}{2}C_3H_7OH$: N, 8.0; S, 18.3. Found: N, 8.0; S, 18.0.

2-Benzoyl-3,3-dimercaptoacrylonitrile, Dipotassium Salt—Potassium hydroxide (4.8 g., 0.072 mole) dissolved in 50 ml. of methanol was treated with a solution of carbon disulfide (2.2 ml., 0.036 mole) and benzoylacetonitrile (5.24 g., 0.036 mole) in 100 ml. of 50% ether-methanol. The solid that separated after 4 days at 20° was washed with 100 ml. of 50% ether-methanol and dried to give 0.8 g. (7.5%) of light-colored solid, m.p. 247–248° (dec.); ν_{min}^{KBr} 2200, 1580, 1530, 1440, 1350, 1270, 910, 795, 775, 720, 690 cm^{-1} .

Anal.—Calcd. for $C_{10}H_8K_2NOS_2$: C, 40.3; H, 1.7; N, 4.7. Found: C, 40.2; H, 2.1; N, 4.9.

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Keyphrases

Antiradiation compounds

3,3-Dimercaptoacrylonitrile derivatives—synthesis

IR spectrophotometry—identity

Radioprotective activity—3,3-dimercaptoacrylonitrile derivatives