at 204–205° when immersed in the bath at 200°; λ_{max}^{alc} 296 mμ (ε 16,000), 228 (16,000).

Anal. Calcd. for $C_7H_7N_4ClS$: C, 39.2; H, 3.26; N, 26.2; Cl, 16.5. Found: C, 40.6; H, 3.3; N, 26.3; Cl, 16.1.

Reaction Product of 3-Chloro-5-hydrazino-4-isothiazolecarbonitrile (18b) and β-Naphthol.—A mixture of 1.45 g. (0.011 mole) of β-naphthol and 1.74 g. (0.01 mole) of the hydrazinoisothiazole **8b** in 100 ml. of methanol was stirred at room temperature as 10 g. of 10% sodium hydroxide solution was added dropwise. The solution became light violet. The addition of a solution of 10 g. of potassium ferricyanide in 50 ml. of water and 40 ml. of methanol caused the formation of a slurry which was largely dissolved by the addition of another 100 ml. of water. After being stirred 15 min., the solution was filtered to give 0.98 g. of maroon solid, m.p. 265–270° (31% yield). An analytical sample, crystallized from benzene–chloroform mixture, melted at 281–283°; $\lambda_{max}^{CH_2Cl_2}$ 290 mμ (ε 10,300), 300 (9800), 320 (4750), 430 (13,000), 465 (14,600), 550 (3900).

Anal. Calcd. for $C_{14}H_8ON_4ClS$: C, 53.4; H, 2.6; N, 17.7. Found: C, 53.4, 53.7; H, 2.3, 2.4; N, 17.9.

Preparation of 3,5-Disubstituted 4-Isothiazolecarboxamides (Table IV). **Amides unsubstituted on nitrogen** were prepared by dissolving the corresponding nitrile in 6–8 times its weight of concentrated sulfuric acid, warming the solution on a steam bath for 20 min., and allowing the mixture to stand 18 hr. at room temperature. The products were precipitated by dilution in ice–water and were recrystallized from aqueous alcohol.

4-N-Substituted amides of 3,5-dichloroisothiazole were prepared by reaction of the acid chloride with an excess of the amine in ether or tetrahydrofuran by usual procedures.[15]

***o*-(3-Chloro-5-methylamino-4-isothiazolecarboxy)toluidide and 3-chloro-5-dimethylamino-4-isothiazolecarbanilide** were made by the reaction of the corresponding N-substituted 3,5-dichloroisothiazolecarboxamides in ethereal solution with an excess of gaseous methylamine and dimethylamine, respectively.

4-Isothiazolecarboxylic Acids.—The two acids described in Table IV were prepared by a modification of the method of Sudborough[12] as given below.

3,5-Dichloro-4-isothiazolecarboxylic Acid.—A solution of 3.1 g. (0.045 mole) of sodium nitrite in 10 ml. of water was added over 15 min. to a cold (5–10°) stirred solution of 5.91 g. (0.03 mole) of 3,5-dichloroisothiazolecarboxamide in a mixture of 40 ml. of sulfuric acid and 10 ml. of water. The addition was made through a tube dipping below the surface of the reaction mixture at such a rate that the temperature was maintained at 10–15° and the formation of red fumes was minimized. After addition was complete, the reaction mixture was stirred for 30 min. at room temperature, 20 min. at 50–60° when much foaming occurred, and then poured into an ice–water mixture. The precipitated solid was collected on a filter, dissolved in aqueous sodium carbonate solution, and the solution was treated with decolorizing charcoal and filtered. Acidification of the filtrate gave 3.65 g. of white solid that melted at 155–155.5°. An additional 0.94 g. of acid was obtained by ether extraction of the aqueous, acidic filtrate (total yield 77%). Recrystallization from benzene and sublimation gave an analytical sample that melted at 155–156°.

The acid chloride, prepared by refluxing the acid with an excess of thionyl chloride for 6 hr., boiled at 102° (8 mm.), $n^{25}D$ 1.5945.

Desulfurization of 5-Anilino-3-chloro-4-isothiazolecarbonitrile.—A mixture of 5.0 g. of **8e** 150 ml. of ethanol, and about 25 g. of Raney nickel was heated under reflux overnight, filtered to remove the catalyst, and evaporated under reduced pressure. The residue was washed with water to remove soluble salts and then extracted with hot benzene. Crystallization from the extracts yielded 0.23 g. of light tan crystals that melted at 230–235°. Recrystallization from methanol gave 0.20 g. of crystals, m.p. 244–247°. The infrared spectrum of the product was identical with that of anilinomethylenemalonitrile.[8]

(15) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p. 356.

The Synthesis of Isothiazoles. II. 3,5-Dimercapto-4-isothiazolecarbonitrile and Its Derivatives

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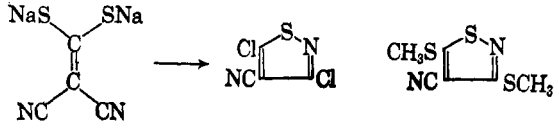
Received August 26, 1963

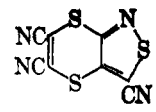
Salts of 3,5-dimercapto-4-isothiazolecarbonitrile were formed by the reaction of salts of dimercaptomethylenemalononitrile with sulfur in boiling methanol. These novel dimercaptoisothiazole salts have been converted to a variety of alkylthio-, acylthio-, and alkylsulfonylisothiazolecarbonitrile derivatives. Hydrolysis gave a series of 3,5-bis(methylthio)-4-isothiazolecarboxylic acid, ester, and amide derivatives.

Earlier we described the preparation of 3,5-dichloro-4-isothiazolecarbonitrile (**2**) by the ring closure of di(sodiomercapto)methylenemalononitrile (**1**) with excess chlorine.[1,2] The dichlorocyanoisothiazole (**2**) provides a route to a number of isothiazole derivatives by replacement and hydrolysis reactions.



1 **2** **3**

One of the products of the earlier described replacement reactions of **2** was 3,5-bis(methylthio)isothiazolecarbonitrile (**3**). With the exception of **3** and similar compounds mentioned in our first paper, no mononuclear isothiazoles having a sulfur atom bonded directly to the heterocyclic ring have been described. However, complex isothiazoles **4** and **5** having sulfur atoms bonded to positions 3 and 4 recently have been reported from this laboratory.[3,4]



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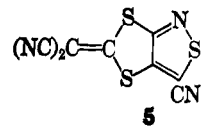


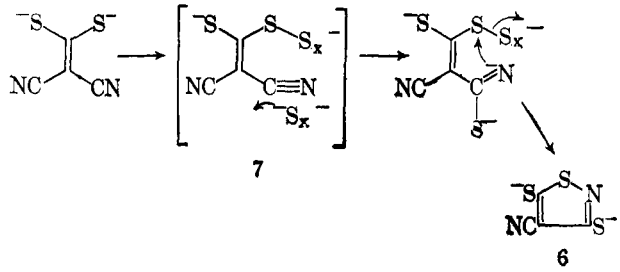
5

The present paper reports the synthesis of salts of 3,5-dimercapto-4-isothiazolecarbonitrile (**6**) and their conversion to a number of isothiazole derivatives substituted with sulfur. The new 3,5-dimercaptoisothiazole salts (**6**) were prepared by reaction of a dibasic salt of dimercaptomethylenemalononitrile with sulfur. For example, a boiling methanol solution of the di-

(1) Part I, W. R. Hatchard, *J. Org. Chem.*, **29**, 660 (1964).
(2) W. R. Hatchard, *ibid.*, **28**, 2163 (1963).
(3) H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.*, **84**, 4746 (1962).
(4) W. R. Hatchard, U. S. Patent 3,048,596 (1962).

sodium salt (**1**) absorbed an atomic equivalent of sulfur quickly to give, in only a few minutes, a new salt identified as 3,5-di(sodiomercapto)isothiazolecarbonitrile (**6**). This salt can be crystallized from aqueous acetone as a tetrahydrate or vacuum dried to give **6** as a powdery, anhydrous salt. It was characterized as an isothiazole by its ultraviolet spectrum and by the nature of its alkylation products. The salt (**6**) shows absorption maxima in 0.1% solution in water (maxima changing with dilution) at 330 mμ (ε 7070), 303 (12,900), 260 (10,500), 240 (9520), and 218 (14,300), a markedly different absorption spectrum from that of **1** which shows maxima at 342 mμ (ε 18,600) and 272 (5400, alcohol). Methylation of the new salt gave **3**, previously obtained by reaction of **2** with sodium sulfide and methyl iodide.[1]

The ring closure reaction probably proceeds by a mechanism similar to that pictured below involving attack by the mercaptide ion on sulfur to give species **7**. Addition of anionic sulfur to the nitrile group and elimination of anionic sulfur effects the formation of the isothiazole ring. There appears to be little tendency for a second similar type of ring closure to occur to form an isothiazole[4,5-*d*]isothiazole, since only one atom of sulfur is absorbed, even when an excess is used.

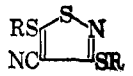


7

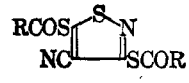
6

Sodium, potassium, barium, and triethylammonium salts of dimercaptomethylenemalononitrile have been used successfully in this reaction to prepare 3,5-dimercaptoisothiazole derivatives. The dimercapto metal salts were conveniently prepared in alcohol by reaction of malononitrile, carbon disulfide, and the metal hydroxide by previously described procedures.[1] Triethylamine as the base gave the new bis(triethylammoniummercapto)methylenemalononitrile as a low-melting crystalline solid, m.p. 95.5–96.5°.

The 3,5-dimercaptoisothiazolecarbonitrile salts are readily alkylated to give bis(alkylthio)isothiazolecarbonitrile derivatives. Two equivalents of benzyl bromide, chloroacetic acid, or allyl bromide gave the corresponding derivatives **8**, **9**, and **10** in good yields.



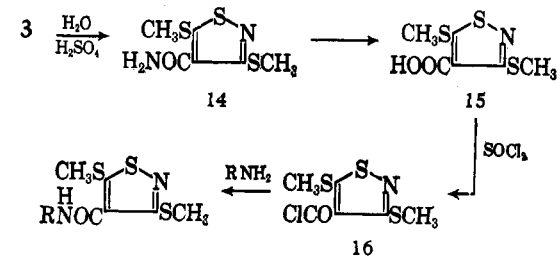
8, R = $C_6H_5CH_2$
9, R = CH_2COOH
10, R = $CH_2 = CHCH_2$



11, R = CH_3
12, R = C_6H_5
13, R = $(CH_3)_2N$

Similarly, acetyl chloride, benzoyl chloride, and N,N-dimethylcarbamoyl chloride gave the corresponding acylthio derivatives **11**, **12**, and **13**.

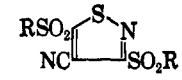
A series of derivatives based on hydrolysis of the nitrile group was prepared from 3,5-dimethylthio-4-isothiazolecarbonitrile (**3**). The nitrile was converted to the amide (**14**) by sulfuric acid hydrolysis. Further hydrolysis of the amide with nitrous acid in sulfuric acid gave the acid (**15**) which was converted to the acid chloride (**16**) with thionyl chloride. The methyl ester (**17**) and substituted amides (**18**, **19**, and **20**) were prepared from the acid chloride.



14 **15** **16**

18, R = CH_3
19, R = C_6H_5
20, R = $C_6H_4NH_2$-*o*

Oxidation of 3,5-bis(methylthio)isothiazolecarbonitrile and 3,5-bis(benzylthio)isothiazolecarbonitrile with 4 equiv. of hydrogen peroxide in acetic acid gave the corresponding bissulfones (**21** and **22**) in high yield.



21, R = CH_3
22, R = $C_6H_5CH_2$

Experimental[5]

Salts of Dimercaptomethylenemalononitrile.—The disodium and dipotassium salts were prepared from malononitrile, carbon disulfide, and the hydroxide in alcohol as earlier described.[1] Use of triethylamine as the base gave a low-melting product whose purity could be determined easily by melting point.

Bis(triethylammoniothio)methylenemalononitrile.—To a solution of 66 g. (1 mole) of malononitrile and 76 g. (1 mole) of carbon disulfide in 200 ml. of acetonitrile was added 202 g. (2 moles) of triethylamine over 15 min., and the solution was stirred for 30 min. and then diluted with ethyl ether. The yellow needles separated quickly and were collected by filtration, washed with ethyl ether, and dried in air, 334 g. (100%), m.p. 91–93°. An analytical sample recrystallized twice from acetone melted at 95.5–96.5°; $\lambda_{max}^{H_2O}$ 340–350 sh 315 mμ, changing with dilution.

Anal. Calcd. for $C_{16}H_{32}N_4S_2$: C, 55.7; H, 9.3; S, 18.6. Found: C, 56.4; H, 9.4; S, 18.5.

3,5-Di(sodiomercapto)-4-isothiazolecarbonitrile (**6**).—A solution of 18.6 g. (0.10 mole) of **1** in 500 ml. of methanol was heated under reflux with 3.2 g. (0.10 g.-atom) of sulfur for 15 min., filtered, and evaporated to dryness under reduced pressure. The residual yellow powder after drying in a vacuum oven at 80° over phosphoric anhydride weighed 20 g. This product was of sufficient purity for use in preparing derivatives. It could be dissolved in acetone but resisted crystallization. The addition of a little water to an acetone solution caused formation of an acetone-insoluble, white crystalline tetrahydrate. The pure anhydrous salt was obtained by drying the tetrahydrate at 80° over phosphoric anhydride at oil pump pressure.

Anal. Calcd. for $C_4N_2S_3Na_2 \cdot 4H_2O$ (air-dried): C, 16.5; H, 2.8; N, 9.7; S, 33.2. Found: C, 16.6; H, 3.1; N, 9.9; S, 32.5.

Anal. Calcd. for $C_4N_2S_3Na_2$ (oven-dried): C, 22.0; N, 12.8; S, 44.08. Found: C, 22.3; N, 12.7; S, 42.8.

The ultraviolet absorption spectrum of the anhydrous salt in water varied with concentration. Approximate values obtained in 0.1% solution in water were sh 330 mμ (ε 7070), 303 (12,900), sh 260 (10,500), sh 240 (9250), 218 (14,300).

The di(sodiomercapto)isothiazole (**6**) could be prepared from malononitrile without isolation of **1** by carrying out the reaction of malononitrile (1 mole), carbon disulfide (1 mole), and sodium

(5) All melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 double-beam infrared spectrometer equipped with sodium chloride optics (2–15 μ). The ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer.

hydroxide (2 moles) in methanol below 20° and boiling the reaction mixture with 1 g.-atom of sulfur for 15 min.

3,5-Bis(benzylthio)-4-isothiazolecarbonitrile (8).—A solution of 9.3 g. (0.05 mole) of **1** in 150 ml. of methanol was heated under reflux with 1.6 g. (0.05 mole) of sulfur for 15 min. To the boiling solution was added a solution of 17.1 g. (0.10 mole) of benzyl bromide in 100 ml. of methanol over 30 min., and the mixture was heated under reflux for 1 hr. Cooling and filtration gave 17.0 g. (97% yield) of white needles. An analytical sample purified by recrystallization from alcohol melted at 96–97.5°; λ_{max}^{alc} 287 mμ (ε 13,600).

Anal. Calcd. for $C_{18}H_{14}N_2S_3$: C, 61.0; H, 4.0; S, 27.1. Found: C, 60.7; H, 4.2; S, 27.6.

3,5-Bis(methylthio)-4-isothiazolecarbonitrile (3).—Sulfur (0.32 g., 0.01 g.-atom) was added to a solution of 3.44 g. (0.01 mole) of bis(triethylammoniothio)methylenemalononitrile in 50 ml. of methanol, and the mixture was boiled 15 min. to effect solution and then cooled to room temperature. Methyl iodide (3.5 ml.) was added, and the mixture was allowed to stand 1 hr. and then was diluted with an equal volume of water to give 1.63 g. (80% yield) of white needles, m.p. 127–129°. The product had an infrared spectrum identical with that of **3**.[1]

3,5-Bis(carboxymethylthio)isothiazolecarbonitrile (9).—A solution of sodium chloroacetate prepared by mixing 9.45 g. (0.10 mole) of chloroacetic acid, 5.3 g. (0.05 mole) of sodium carbonate, and 100 ml. of water was mixed with a solution prepared by boiling 9.3 g. (0.05 mole) of **1** in 200 ml. of ethanol with 1.6 g. (0.05 g.-atom) of sulfur for 15 min. The reaction mixture was heated under reflux for 1 hr., filtered, acidified with hydrochloric acid, and evaporated under reduced pressure. The residue was extracted with hot acetone; the solvent was then evaporated, and the residue was recrystallized from water to give 9.3 g. (64% yield) of slightly yellow solid, m.p. 140–150°. An analytical sample recrystallized from water melted at 156.5–157.5° after oven drying; λ_{max}^{alc} 227 mμ (ε 13,200), 285 (11,900).

Anal. Calcd. for $C_8H_6O_4N_2S_3$: C, 33.1; H, 2.1; S, 33.1. Found: C, 33.1; H, 2.2; S, 32.8.

3,5-Bis(allylthio)isothiazolecarbonitrile (10).—A solution of 24.1 g. (0.20 mole) of allyl bromide in 25 ml. of methanol was added over 30 min. to a stirred solution of 21.8 g. (0.10 mole) of **6** in 200 ml. of methanol. The mixture was stirred 30 min., concentrated to 150 ml. by evaporation on a steam bath, diluted with an equal volume of water, and cooled to give 19.5 g. of brownish crystals. Recrystallization from aqueous methanol and then from a cyclohexane–hexane mixture gave 15.7 g. (67% yield) of white platelets, m.p. 41.6–42.4°; λ_{max}^{alc} 286 mμ (ε 11,600), 229 (13,000).

Anal. Calcd. for $C_{10}H_{10}N_2S_3$: C, 47.1; H, 3.9; N, 11.0. Found: C, 47.4; H, 3.9; N, 11.0.

3,5-Bis(acetylthio)isothiazolecarbonitrile (11).—A slurry of 10.9 g. (0.05 mole) of anhydrous **6** in 100 ml. of acetonitrile was added portionwise to a mixture of 70 ml. of acetyl chloride and 100 ml. of acetonitrile at room temperature. The mixture was stirred for 30 min., filtered, and concentrated by evaporation. The concentrate was diluted with benzene, washed with water, and evaporated. The oily, crystalline residue was recrystallized from a benzene–hexane mixture to give 7.6 g. (43% yield) of light yellow crystals, m.p. 111–112°; $\lambda_{max}^{CH_2Cl_2}$ 277 mμ (ε 12,080).

Anal. Calcd. for $C_8H_6O_2N_2S_3$: C, 37.2; H, 2.3. Found: C, 37.9; H. 2.7.

3,5-Bis(benzoylthio)isothiazolecarbonitrile (12).—A solution of 10.9 g. (0.05 mole) of **6** in 150 ml. of water and 25 ml. of alcohol was shaken vigorously as 11.6 ml. (14.0 g., 0.10 mole) of benzoyl chloride was added portionwise over 15 min. The mixture was shaken for 30 min. and filtered to collect 16 g. of solid product. Recrystallization from benzene gave 10.6 g. (53% yield) of solid that melted at 149–153°. Three recrystallizations from benzene gave white crystals, m.p. 157.5–158.5°; λ_{max}^{alc} 249 mμ (ε 20,600), 28 (14,600), 288 (14,500).

Anal. Calcd. for $C_{18}H_{10}N_2O_2S_2$: C, 56.8; H, 2.6. Found: C, 56.8; H, 2.9.

3,5-Bis(dimethylcarbamoylthio)isothiazolecarbonitrile (13).—A mixture of 10.9 g. (0.05 mole) of anhydrous **6**, 300 ml. of acetone, and 10.6 g. (0.1 mole) of N,N-dimethylcarbamoyl chloride was heated under reflux 90 min., cooled, and diluted with ice. The precipitated solid after collection and air-drying weighed 27 g. (46%) and melted at 190–192.5°. An analytical sample melted at 191.5–193.5°; λ_{max}^{alc} 275 mμ (ε 12,500).

Anal. Calcd. for $C_{10}H_{12}O_2N_4S_3$: C, 37.9; H, 3.8. Found: C, 37.5; H, 3.7.

3,5-Bis(methylsulfonyl)isothiazolecarbonitrile (21).—To a slurry of 2.02 g. (0.01 mole) of **3** in 10 ml. of acetic anhydride and 10 ml. of glacial acetic acid was added over 1 hr. with stirring 4.8 g. (0.044 mole) of 30% hydrogen peroxide. The temperature of the reaction mixture rose slowly at first and then quickly to 90°. An ice bath was applied to moderate the reaction, and addition was continued while the reaction mixture was cooled. After standing for 2 days at room temperature, the reaction mixture had solidified. It was diluted with 200 ml. of water and filtered. The air-dried solid weighed 2.2 g. (83% yield), m.p. 190–198°. Recrystallization from an acetone–methanol mixture gave white needles, m.p. 212–214°; λ_{max}^{alc} 270 mμ (ε 6150).

Anal. Calcd. for $C_6H_6O_4N_2S_3$: C, 27.1; H, 2.3. Found: C, 27.3; H, 2.3.

3,5-Bis(benzylsulfonyl)isothiazolecarbonitrile (22).—To a stirred slurry of 3.5 g. (0.01 mole) of **8** in 20 ml. of glacial acetic acid and 20 ml. of acetic anhydride was added, over 1 hr., 5.4 ml. of 30% hydrogen peroxide. The reaction mixture warmed spontaneously to 45° and became clear. After the reaction mixture had stood overnight at room temperature, the white needles that formed were collected on a filter and washed liberally with water. The airdried product weighed 3.9 g. (95%) and melted at 179–181°. Solution of a sample in a boiling mixture of methylene chloride and chloroform followed by evaporation gave a residue that melted at 198–199°. An analytical sample melted at 203.5–204°; λ_{max}^{alc} 268 mμ (ε 6340).

Anal. Calcd. for $C_{18}H_{14}O_4N_2S_3$: C, 51.7; H, 3.4. Found: C, 51.8; H, 3.3.

3,5-Bis(methylthio)isothiazolecarboxamide (14).—A solution of 0.78 g. of **3** in 2 ml. of concentrated sulfuric acid was warmed 4 hr. at 60–70° and poured into a mixture of ice and water. The precipitated solid was collected on a filter and dried in air to give 0.79 g. (92%) of white product, m.p. 205–207.5°. An analytical sample prepared by crystallization from benzene melted at 210–210.5°; λ_{max}^{alc} 283 mμ (ε 11,400), 235 (11,100), 212 (10,400).

Anal. Calcd. for $C_6H_8ON_2S_3$: C, 32.7; H, 3.7; N, 12.7. Found: C, 33.0; H, 3.9; N, 13.0.

3,5-Bis(methylthio)isothiazolecarboxylic Acid (15).—To a solution of 2.2 g. (0.01 mole) of **14**, in 40 ml. of concentrated sulfuric acid and 10 ml. of water cooled to 5–10° was added slowly a solution of 1.03 g. (0.015 mole) of sodium nitrite in 4 ml. of water. The reaction mixture was maintained at 5–10° during the addition which required about 15 min. and was then warmed on a steam bath for 30 min. and poured into ice–water. The white solid that formed was collected on a filter, washed with water, and redissolved in aqueous sodium carbonate solution. The alkaline solution was filtered, and the filtrate was acidified with dilute hydrochloric acid. Extraction of the mixture with methylene chloride followed by drying of the organic phase and evaporation gave 1.39 g. (63% yield) of white crystals, m.p. 239–241°. An analytical sample recrystallized from a mixture of benzene and petroleum ether (b.p. 60–80°) melted at 241.5–242.5°; λ_{max}^{alc} 282 mμ (ε 29,200), 237 (28,000), 214 (21,900).

Anal. Calcd. for $C_6H_7O_2NS_3$: C, 32.6; H, 3.2; neut. equiv., 221. Found: C, 32.9; H, 3.2; neut. equiv., 220.

3,5-Bis(methylthio)isothiazolecarbonyl Chloride (16).—A mixture of 3.3 g. of **15** and 25 ml. of thionyl chloride was heated under reflux for 6 hr. and allowed to stand 18 hr. at room temperature. Evaporation of the thionyl chloride gave a white solid, m.p. 136–138°. A portion of the product was heated in aqueous ammonium hydroxide to give **14** identified by comparison of its infrared spectrum with that of an authentic sample.

Methyl 3,5-Bis(methylthio)isothiazolecarboxylate (17).—Solution of 0.35 g. of **16** in hot methanol and evaporation gave 0.31 g. of **17**. The white needles melted at 132–133°. An analytical sample purified by sublimation at 110° (1 mm.) melted at 132–133°; λ_{max}^{alc} 284 mμ (ε 14,900), 238 (15,100), 215 (11,350).

Anal. Calcd. for $C_7H_9O_2NS_3$: C, 35.7; H, 3.8. Found: C, 35.9; H, 3.9.

N-Methyl-3,5-bis(methylthio)isothiazolecarboxamide (18).—Gaseous methylamine passed into a solution of the acid chloride (**16**) in ethyl ether gave a product that melted at 162–163° after recrystallization from methanol; λ_{max}^{alc} 283 mμ (ε 11,500), 233 (11,500).

Anal. Calcd. for $C_7H_{10}ON_2S_3$: C, 35.9; H, 4.3. Found: C, 35.9; H, 4.4.

N-Phenyl-3,5-bis(methylthio)isothiazolecarboxamide (19).—A mixture of 0.75 g. (0.003 mole) of **16**, 1.75 g. (0.019 mole) of aniline, and 100 ml. of ethyl ether was heated under reflux for 15 min., then was diluted with water and methylene chloride. The organic phase was washed with dilute hydrochloric acid and water. Evaporation and recrystallization from methanol gave 0.69 g. (82% yield) of the anilide, m.p. 162–163°; λ_{max}^{alc} 287 mμ (ε 13,300), 255 (16,500).

Anal. Calcd. for $C_{12}H_{12}ON_2S_3$: C, 48.6; H, 4.1. Found: C, 48.7; H, 4.3.

N-(*o*-Aminophenyl)-3,5-dimethylthio-4-isothiazolecarboxamide (20).—To a solution of 2.7 g. (0.025 mole) of *o*-phenylenediamine and 2.5 g. (0.025 mole) of triethylamine in 75 ml. of tetrahydrofuran was added 6.24 g. (0.025 mole) of **16** in 130 ml. of tetrahydrofuran over 15 min. at room temperature. The mixture was stirred 1 hr., filtered, evaporated to dryness, and triturated with a little methanol to give 6.8 g. (87%) of a solid that melted at 179–180°. A sample recrystallized from a benzene–methanol mixture melted at 182.5–183°; λ_{max}^{alc} 287 mμ (ε 12,300), 233 (10,100).

Anal. Calcd. for $C_{12}H_{13}ON_3S_3$: C, 46.3; H, 4.2. Found: C, 45.6; H, 4.2.

5,6-Dihydro-4*H*-1,3,4-oxadiazines. I. Synthesis and Structure Proof[1]

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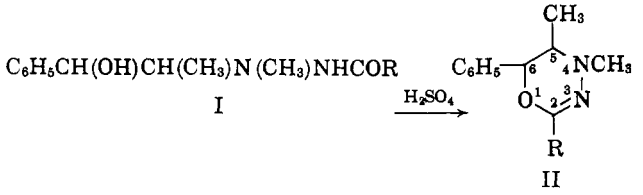
Received September 27, 1963

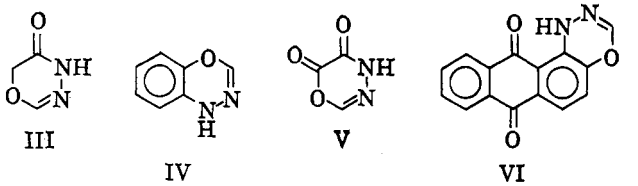
Sulfuric acid dehydration of certain 2-(β-hydroxyalkyl)acid hydrazides has been found to proceed *via* neighboring group participation with concomitant formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine. The structure proof of this novel heterocycle was accomplished by elemental, infrared, and ultraviolet analyses, nuclear magnetic resonance measurements, and chemical degradation.

We have observed that the sulfuric acid dehydration of certain 2-(β-hydroxyalkyl) acid hydrazides (I) proceeds *via* neighboring group participation with concomitant formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine (II). Although much has been reported[3]

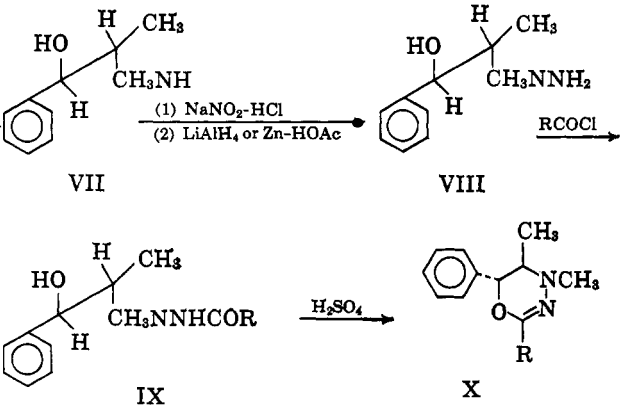


on neighboring group participation between the amido group and the hydroxyl group in the acid-catalyzed cyclodehydration of N-(β-hydroxyalkyl) amides to yield 2-oxazolines, the interaction between the hydrazido group and the hydroxyl group to form 5,6-dihydro-4*H*-1,3,4-oxadiazines has not been explored. Only one example of this novel heterocyclic system has heretofore been reported. Ishidate, *et al.*,[4] reportedly obtained 4-(β-chloroethyl)-2-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine as a by-product (15% yield) from the synthesis of 2,2-bis(β-chloroethyl)benzoic acid hydrazide by the treatment of 2,2-bis(β-hydroxyethyl)-benzoic acid hydrazide with thionyl chloride.

Related heterocycles, such as 5,6-dihydro-4*H*-1,3,4-oxadiazin-5-one (III),[5] 5,6-benzo-4*H*-1,3,4-oxadiazine (IV),[6] 5,6-dihydro-4*H*-1,3,4-oxadiazin-5,6-dione (V),[7] and 1,2-anthraquino-4*H*-1,3,4-oxadiazine (VI),[8] have been reported. Type III has been prepared by base-catalyzed dehydrohalogenation of 2-(β-chloroacetyl) acid hydrazides, type IV by the reaction of substituted 1,2-benzoquinone-2-diazides with ethyl diazoacetate, type V by the reaction of carboxylic acid hydrazides with oxalyl chloride, and type VI by base-catalyzed cyclization of 1-(2-benzhydrazido)-2-nitroanthraquinone.



The 5,6-dihydro-4*H*-1,3,4-oxadiazines listed in Table I of this paper were prepared *via* a four-step synthesis starting with commercially available *l*-ephedrine (VII). It was converted to N-amino-*l*-ephedrine (VIII) by nitrosation and reduction. Acylation of VIII produced the N-acyl derivative (IX) which was cyclized by sulfuric acid to the 5,6-dihydro-4*H*-1,3,4-oxadiazine (X).



Examination of the products of the Zn–HOAc reduction of N-nitroso-*l*-ephedrine by gas–liquid chromatography[9] indicated that VIII was a mixture composed,

(1) Presented in part before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) U. S. Industrial Chemicals Co., Tuscola, Ill.

(3) (a) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 377; (b) R. H Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 447 (1949).

(4) M. Ishidate, Y. Sukurai, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **8**, 543 (1960).

(5) J. van Alphen, *Rec. trav. chim.*, **47**, 909 (1928); **48**, 163 (1929); **48**, 417 (1929); **53**, 325 (1934).

(6) R. Huisgen and R. Fleischmann, *Ann.*, **623**, 47 (1959).

(7) J. van Alphen, *Rec. trav. chim.*, **47**, 673 (1928); **53**, 325 (1934).

(8) W. L. Mosby and W. L. Berry, *Tetrahedron*, **8**, 107 (1960).

(9) The column was 5 ft. × 3/8 in., 15% SE-30, 60/80 AW/Chromosorb W with He flow of 200 ml./min., and temperature programmed at 5°/min. from 100 to 255°. The retention times were VII = 11 min., VIII = 15 min., N-nitroso-*l*-ephedrine = 29 min.