Cyclizations of Thiocarbohydrazide and its Mono-hyrazones

Part II *. Reactions with Dialkyl Thithiocarbonates

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Thiocarbohydrazide and mono-thiocarbohydrazones react with thithiocarbonates in strongly alkaline solution to form dithiocarbalkoxy-thiocarbohydrazides and their hyrazones, respectively. When heated in the solid state, these compounds are cyclized, with elimination of hydrogen sulphide, to alkylthio-thiadiazolehydrazines and hyrazones, respectively. In acid medium, the products of decomposition are mercapto-alkylthio-thiadiazoles.

The present investigation was undertaken to test the possibilities of preparing 5-alkylthio-1,3,4-thiadiazol-2-yl-hyrazines (I) by reactions of thiocarbohydrazide or derivatives thereof with dialkyl thithiocarbonates. Thiocarbohydrazide was found to react with dimethyl thithiocarbonate only in strongly alkaline solution, with liberation of methanethiol and formation of 1-dithiocarbomethoxy-thiocarbohydrazide (II, R = CH₃) as alkali salt. The dithiocarbomethoxy-thiocarbohydrazide (II, R = CH₃) could be cyclized by two different methods. When heated above its melting point it eliminated hydrogen sulphide, methanethiol, and hydrazine, and from the reaction mixture could be isolated 5-methylthio-1,3,4-thiadiazol-2-yl-hydrazone (I, R = CH₃, isolated in 55 % yield as acetone hydrazone), 2-mercapto-5-methylthio-1,3,4-thiadiazole¹ (III, R = CH₃, 23 % yield), and 3-mercapto-4-amino-5-hyrazino-4,1,2-triazole² (IV, 10 % yield). The triazole (IV) may be formed in a side reaction between dithiocarbomethoxy-thiocarbohydrazide (II) and hydrazine.

The cyclization of (II) in acid medium followed a different course, with exclusive formation of 2-mercapto-5-methylthio-1,3,4-thiadiazole (III, R=CH₃) and hydrazine.

Mono-thiocarbohydrazones were found to react with dialkyl thithiocarbonates under the same conditions as thiocarbohydrazide, and the products were 5-dithiocarbalkoxy-thiocarbohydrazones (V). When heated above their melting points they eliminated hydrogen sulphide and gave alkylthio-thiadiazolylhydrazones (VI). The acetone 5-dithiocarbalkoxy-thiocarbohydrazones


(V, $R_1 = R_2 = CH_3$) gave some acetone 5-mercapto-1,3,4-thiadiazol-2-yl-hydrazone (VI, $R = H$, $R_1 = R_2 = CH_3$) as by-product. The structure of the benzaldehyde 5-methylthio-1,3,4-thiadiazol-2-yl-hydrazone was demonstrated by its formation from benzaldehyde 5-mercapto-1,3,4-thiadiazol-2-yl-hydrazone (prepared according to Stollé and Fehrenbach) and methyl iodide in alkaline solution.

When the dithiocarbalkoxy-thiocarbohydrazones (V) were heated in hydrochloric acid solution, mercapto-alkylthio-thiadiazoles (III) were formed with elimination of the corresponding hydrazone, which could then be disproportionated to azine and hydrazine.
Like the analogues described in part I, the alkylthio-thiadiazolylhydrazones (VI) are weak acids. The alkylthio-thiadiazolylhydrazines (I) are quite stable in acid solution, and are conveniently prepared by acid hydrolysis of the corresponding acetone hydrazones.

**EXPERIMENTAL**

**Preparation and decomposition of 1-dithiocarbomethoxy-thiocarbohydrazide (II, \( R = \text{CH}_3 \))**

Thiocarbohydrazide (10.6 g, 0.1 mole) was dissolved in 2 N KOH in 75 % aqueous ethanol (50 ml), and dimethyl trithiocarbonate (7.0 g, 0.05 mole) in ethanol (50 ml) was added. After a few hours, the excess thiocarbohydrazide began to separate, and on the following day the filtrate was acidified with acetic acid, and the ethanol was taken off in vacuo at 20°C. Then, colourless plates had separated (9.2 g, 93 % yield), m.p. 134—135°C (decomp.) after recrystallization from 50 % aqueous ethanol. (Found: C 18.0; H 4.07; N 28.6; S 48.5. \( \text{C}_2\text{H}_5\text{N}_2\text{S}_4 \) (196.30) requires C 18.4; H 4.11; N 28.5; S 49.0).

**Thermal decomposition.**

Dithiocarbomethoxy-thiocarbohydrazide (II, \( R = \text{CH}_3 \), 98 g) was heated at 160°C until the evolution of gas had ceased. After cooling, the residue was extracted at 50°C with N HCl (600 ml). The mixture was cooled to 0°C, and the undissolved material was separated (18.5 g). It crystallized from toluene as colourless rods, m.p. 136—137°C, consisting of 2-mercapto-5-methylthio-1,3,4-thiadiazole (III, \( R = \text{CH}_3 \)). (Found: C 22.0; H 2.60; N 16.8; S 58.5. \( \text{C}_6\text{H}_4\text{N}_2\text{S}_4 \) (164.25) requires C 21.9; H 2.45; N 17.1; S 58.6).

The acid filtrate was evaporated in vacuo to about one fourth of the original volume. A further quantity (0.8 g) of less pure mercapto-methylthio-thiadiazole was separated, and then a solution of crystalline sodium acetate (140 g) in water (100 ml) was added. A pale brown crystalline deposit (68.5 g) was obtained, which was extracted with three portions of boiling ethanol (together 400 ml). The undissolved material was a white, microcrystalline powder (7.2 g), m.p. 226—227°C (decomp.), consisting according to analysis of 3-mercapto-4-amino-5-hydrazino-4,1,2-triazole (IV). For this compound Hoggarth\(^2\) reports m.p. 232°C. (Found: C 16.5; H 4.23; N 57.9; S 22.3. \( \text{C}_4\text{H}_4\text{N}_2\text{S}_4 \) (146.18) requires C 16.4; H 4.14; N 57.5; S 21.9).

A dibenzylidene derivative was prepared according to Hoggarth as pale yellow plates, m.p. 242—244°C (245—246°C according to Ref.\(^2\)) (Found: C 60.2; H 4.62. \( \text{C}_{14}\text{H}_{14}\text{N}_2\text{S}_4 \) (522.93) requires C 59.6; H 4.38).

To the ethanolic filtrate from the triazole (IV) was added acetone (40 ml) in water (400 ml). Pale yellow rods separated (56.0 g), which crystallized from ethanol as colourless rods, m.p. 162—163°C, consisting of acetone 5-methylthio-1,3,4-thiadiazol-2-ylhydrazone (VI, \( R = R_1 = R_2 = \text{CH}_3 \)). (Found: C 35.4; H 4.92. \( \text{C}_6\text{H}_4\text{N}_2\text{S}_4 \) (202.29) requires C 35.6; H 4.98). \( \lambda_{\max } \) 2980 Å with \( \varepsilon : 14 \, 900 \). From the filtrate of the acetone thiaidiazolylhydrazone no further definable products could be isolated.

**Decomposition in acid solution.**

Dithiocarbomethoxythiocarbohydrazide (II, 2.0 g) was refluxed for 10 min. in ethanol (10 ml) and 5 N HCl (6 ml). The ethanol was removed in vacuo, and the solution was cooled. Colourless rods separated (1.5 g, 90 % yield), m.p. 136—137°C after recrystallization from toluene, consisting of 2-mercapto-5-methylthio-1,3,4-thiadiazole (III). (Found: N 16.9; S 58.4. \( \text{C}_6\text{H}_4\text{N}_2\text{S}_4 \) (164.25) requires N 17.1; S 58.6). For this compound Busch\(^1\) reports m.p. 136°C.

Benzaldehyde (2.2 g) in ethanol (10 ml) was added to the acid filtrate, and benzaldehyde (1.9 g, 90 % yield) crystallized at once, m.p. and mixed m.p. 92—93°C.

5-Dithiocarbalkoxy-thiocarbonyldrazones (V)

The general procedure for the preparation of these compounds was to dissolve the appropriate mono-thiocarbonyldrazones (Part I) in 2 equivalents of N-sodium ethoxide in absolute ethanol, add the calculated quantity of the dialkyl thithiocarbonate, and leave the solution at room temperature for 24 h. Addition of the calculated volume of N acetic acid was generally sufficient to precipitate most of the product, but often a further quantity could be obtained by evaporating the mother liquor. On recrystallization, prolonged heating must be avoided. As the compounds melt with decomposition, the melting points are not sharp and are of little use for characterization.

Acetone dithiocarbalkoxy-thiocarbonyldrazones (V, $R_1 = R_2 = CH_3$) was obtained in 65% yield and crystallized from ethanol as colourless rods, m.p. 134 -- 139 (decomp.). (Found: C 30.1; H 5.13; N 23.4; S 41.0. $C_{12}H_{22}N_2S_2$ (236.37) requires C 30.5; H 5.12; N 23.7; S 40.7). $\lambda_{max}$: 3 200 Å with $\epsilon$: 13 300, $\lambda_{max}$: 2 690 Å with $\epsilon$: 22 800.

Acetone dithiocarbalkoxy-thiocarbonyldrazones (V, $R_1 = CH_3$, $R_2 = CH_4$) was obtained from acetone mono-thiocarbonyldrazones and dibenzyl thithiocarbonate in 55% yield, and crystallized from absolute ethanol as colourless rods, m.p. 132 -- 138 (decomp.). (Found: C 46.3; H 5.28; N 17.9; S 31.0. $C_{12}H_{18}N_2S_2$ (312.46) requires C 46.1; H 5.16; N 17.9; S 30.8).

Benzyldihyde dithiocarbalkoxy-thiocarbonyldrazones (V, $R_1 = CH_2$, $R_2 = H$, $R_3 = Ph$) was obtained in quantitative yield, and crystallized from a mixture of absolute ethanol and toluene as colourless hair, m.p. 185 -- 195. (Found: C 42.2; H 4.23; N 19.9; S 33.6. $C_{12}H_{12}N_2S_2$ (284.41) requires C 42.2; H 4.25; N 19.7; S 33.8).

Acetophenone dithiocarbalkoxy-thiocarbonyldrazones (V, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = Ph$) was obtained in 85% yield when monoacetophenone thiocarbonyldrazones reacted with diethyl thithiocarbonate under the conditions described above. It crystallized from ethanol as colourless plates, m.p. 178 -- 179 after considerable sintering between 130 and 140. (Found: C 46.4; H 5.16; N 18.0; S 30.8. $C_{12}H_{14}N_2S_2$ (312.46) requires C 46.1; H 5.16; N 17.9; S 30.8).

Monoacetophenone thiocarbonyldrazones has not been described before. It was prepared like the mono-thiocarbonyldrazones described in Part I, in 45% yield, and it crystallized from glacial acetic acid as long, pale yellow plates, m.p. 213 -- 214 (decomp.). (Found: C 62.5; H 5.20; N 20.5; S 11.7. $C_{12}H_{12}N_2S$ (270.34) requires C 62.2; H 5.22; N 20.7; S 11.9).

Benzyldihyde dithiocarbalkoxy-thiocarbonyldrazones (V, $R_1 = CH_2$, $R_2 = H$, $R_3 = Ph$) was obtained in quantitative yield and crystallized from a mixture of absolute ethanol and toluene as colourless rods, m.p. 155 -- 158. (Found: C 53.7; H 4.60; N 15.6; S 26.8. $C_{12}H_{14}N_2S_2$ (300.50) requires C 53.3; H 4.47; N 15.6; S 26.7).

Alkyldithiadiazolylhydrazones (VI)

These were prepared by heating the dithiocarbalkoxy-thiocarbonyldrazones above their melting points until the evolution of gas had ceased. The molten residues crystallized on cooling and could in most cases be recrystallized directly, if the comparatively small amounts of by-products did not interfere.

Acetone 5-methylthio- and 5-mercapto-1,3,4-thiadiazol-2-yl-hydrazones (VI, $R_1 = R_2 = CH_3$, and VI, $R_1 = H$, $R_2 = CH_3$). The residue after melting acetone dithiocarbalkoxythiocarbonyldrazones consisted of a mixture of acetone methylthiodiazolylhydrazones and its 5-mercapto analogue. Boiling toluene extracted the former, and when the toluene was taken off in vacuo the product was obtained in 80% yield. It crystallized from ethanol as colourless rods, m.p. 162 -- 163, not depressed on admixture with the hydrazones described on p. 000. (Found: C 35.2; H 4.95; N 27.4; S 32.0. $C_{12}H_{18}N_2S_2$ (202.29) requires C 35.6; H 4.95; N 27.7; S 31.7). The soluble-insoluble material (VI, $R_1 = H$, $R_2 = CH_3$, 15% yield) crystallized from ethanol as colourless rods, m.p. 216 -- 217 (decomp.). (Found: C 31.9; H 4.14; N 29.8; S 34.2; equiv. wt.: 189.6. $C_{12}H_{12}N_2S_2$ (188.26) requires C 31.9; H 4.28; N 29.8; S 34.1). $\lambda_{max}$: 3 270 Å with $\epsilon$: 17 500.

When this compound was methylated with methyl iodide in alkaline solution, the methylthio derivative described above was formed.

Acetone benzylthio-thiadiazolylhydrazones (VI, $R_1 = PHC_6H_5$, $R_2 = CH_3$) was obtained in 70% yield after separation from 15% of the thiol (VI, $R_1 = H$, $R_2 = CH_3$).

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It crystallized from absolute ethanol as colourless rods, m.p. 139—140°. (Found: C 51.5; H 5.07; N 20.3; S 23.3. \( \text{C}_{12}\text{H}_{16}\text{N}_{4}\text{S}_{4} \) (278.38) requires C 51.8; H 5.07; N 20.1; S 23.0).

Benzaldehyde methylthio-thiadiazolylhydrazone (VI, \( R = \text{CH}_3, R_1 = \text{H}, R_2 = \text{Ph} \)) was obtained in 70 % yield after recrystallization from n-butanol, colourless rods, m.p. 208—209°. (Found: C 48.3; H 4.08; N 22.4; S 25.6. \( \text{C}_{12}\text{H}_{19}\text{N}_{4}\text{S}_{4} \) (250.33) requires C 48.0; H 4.03; N 22.4; S 25.6). \( \lambda_{\text{max}}: 3250 \text{ Å with e: } 25000; \lambda_{\text{max}}: 2540 \text{ Å with e: } 8300; \lambda_{\text{max}}: 2260 \text{ Å with e: } 13700.

Benzaldehyde 6-mercapto-1,3,4-thiadiazol-2-yl-hydrazone (V, \( R = R_1 = \text{H}, R_2 = \text{Ph} \), 0.20 g), prepared according to Stollé and Fehrenbach, was dispersed in ethanol (3 ml). Methyl iodide (0.2 g) and \( \text{N NaOH} \) (1 ml) were added, and the hydrazone rapidly dissolved. Within a few minutes a pale yellow precipitate began to form (0.22 g), which crystallized from n-butanol as colourless rods, m.p. and mixed m.p. 208—209°. The UV spectrum of this specimen was found to be identical with that of the benzaldehyde methylthio-thiadiazolylhydrazone described above.

Acetophenone ethylthio-thiadiazolylhydrazone (VI, \( R = \text{C}_6\text{H}_5, R_1 = \text{CH}_3, R_2 = \text{Ph} \)) was obtained in 80 % yield after recrystallization from ethanol. Colourless rods, m.p. 170—171°. (Found: C 58.9; H 4.41; N 17.2; S 19.6. \( \text{C}_{12}\text{H}_{16}\text{N}_{4}\text{S}_{4} \) (326.42) requires C 58.9; H 4.42; N 17.2; S 19.6).

Decomposition of dithiocarbalkoxy-thiocarbohydrazones in acid solution

Acetone dithiocarbamethoxy-thiocarbohydrazone was decomposed exactly as dithiocarbamethoxy-thiocarbohydrazide (II, p. 1841). The same products were obtained in much the same yields.

Benzaldehyde dithiocarbamethoxy-thiocarbohydrazone (2.8 g) was refluxed in ethanol (50 ml) and concentrated hydrochloric acid (1 ml) for 5 min. The mixture was evaporated to dryness on a boiling water bath, and the residue was extracted with water (10 ml), and the extract added to benzaldehyde (1.2 g) in ethanol (10 ml). Benzalazine (0.95 g, 90 % yield) separated, m.p. and mixed m.p. 92—93°. The water-insoluble residue was ground with \( \text{N NaOH} \) (20 ml), and benzalazine (1.0 g, 96 % yield) remained undissolved. The alkaline solution was acidified with \( \text{N HCl} \), and colourless rods were deposited (1.4 g, 87 % yield), m.p. 135—136°, not depressed by addition of mercapto-methylthio-thiadiazole (III, \( R = \text{CH}_3 \)). Obviously the initially formed benzaldehyde hydrazone had proportionated to benzalazine and hydrazine.

Alkylthio-thiadiazolylhydrazines (I)

Methylthio-thiadiazolylhydrazine (I, \( R = \text{CH}_3 \)). Acetone methylthio-thiadiazolylhydrazone (20.3 g) was refluxed for one hour with ethanol (100 ml) and 5 % \( \text{HCL} \) (100 ml). The solvents were removed by distillation under reduced pressure, and the flask was immersed in a boiling water bath to prevent the separation of unchanged starting material. The dry residue was dissolved in ethanol (200 ml) and ether (800 ml) was added. A hydrochloride of not very well defined composition separated as colourless prisms (18.3 g). It was dissolved in water (300 ml), and the free thiadiazolylhydrazine was precipitated by the addition of crystalline sodium acetate (30 g). Colourless rods separated at once (13.5 g, 83 % yield), m.p. 117—118° after recrystallization from toluene. (Found: C 22.4; H 3.69; N 34.6; S 39.4. \( \text{C}_{12}\text{H}_{16}\text{N}_{4}\text{S}_{4} \) (162.23) requires C 22.2; H 3.73; N 34.5; S 39.5). \( \lambda_{\text{max}}: 2820 \text{ Å with e: } 8200 \).

Benzylothio-thiadiazolylhydrazine (I, \( R = \text{PhCH}_3 \)). Acetone benzylothio-thiadiazolylhydrazone was hydrolyzed as above, but the isolation of a crystalline hydrochloride was not attempted. Instead, the residue after evaporation was directly dissolved in water, and the hydrazine was precipitated by the addition of crystalline sodium acetate. The

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yield was 76 %, colourless rods with m.p. 111—112° after recrystallization from absolute ethanol. (Found: C 45.4; H 4.3; N 23.5; S 26.7. \( \text{C}_9\text{H}_{13}\text{N}_6\text{S}_3 \) (238.32) requires C 45.4; H 4.3; N 23.5; S 26.9).

The UV-spectra were recorded with a Beckman DU spectrophotometer in absolute ethanol solution.

The technical assistance of Miss Monica Linders is acknowledged. The investigation has been supported by grants from the Swedish Natural Science Research Council, from Stiftelsen Lars Hiertas Minne, and from Hierta- Retzius Stipendiefond.

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Received May 18, 1960.