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Cyclizations of Thiocarbohydrazide and its Mono-hydrazones Part II *. Reactions with Dialkyl Trithiocarbonates

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Thiocarbohydrazide and mono-thiocarbohydrazones react with trithiocarbonates in strongly alkaline solution to form dithiocarbalkoxy-thiocarbohydrazides and their hydrazones, respectively. When heated in the solid state, these compounds are cyclized, with elimination of hydrogen sulphide, to alkylthio-thiadiazolhydrazines and hydrazones, 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-hydrazines (I) by reactions of thiocarbohydrazide or derivatives thereof with dialkyl trithiocarbonates. Thiocarbohydrazide was found to react with dimethyl trithiocarbonate only in strongly alkaline solution, with liberation of methanethiol and formation of 1-dithiocarbomethoxy-thiocarbohydrazide (II, R = CH_3) as alkali salt. The dithiocarbomethoxy-thiocarbohydrazide (II, R = CH_3) 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-hydrazine (I, R = CH_3, isolated in 55 % yield as acetone hydrazone), 2-mercapto-5-methylthio-1,3,4-thiadiazole [1] (III, R = CH_3, 23 % yield), and 3-mercapto-4-amino-5-hydrazino-4,1,2-triazole [2] (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=CH_3) and hydrazine.

Mono-thiocarbohydrazones were found to react with dialkyl trithiocarbonates 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

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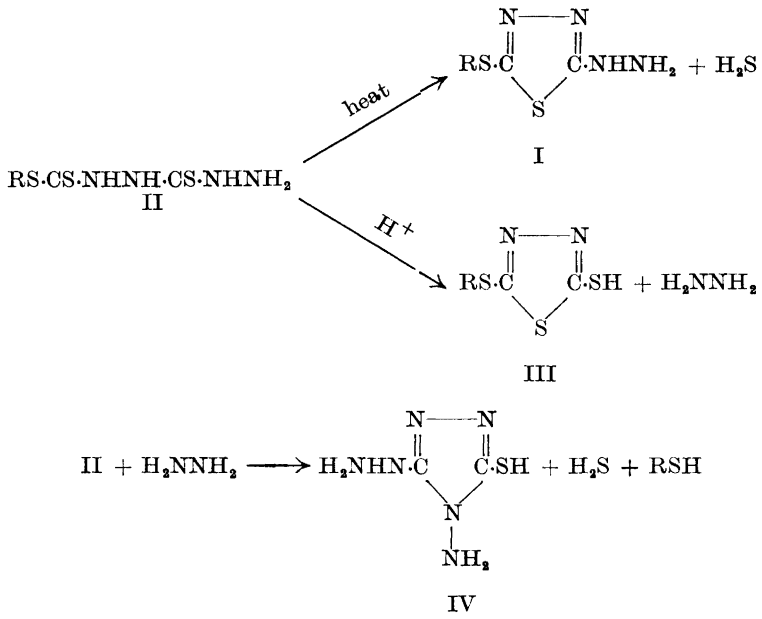
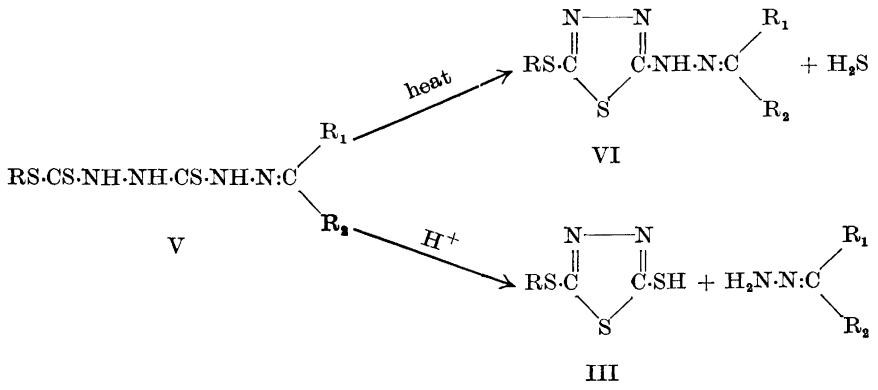


I III IV

(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 [3]) and methyl iodide in alkaline solution.



V VI III

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 = 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°. Then, colourless plates had separated (9.2 g, 93 % yield), m.p. 134—135° (decomp.) after recrystallization from 50 % aqueous ethanol. (Found: C 18.6; H 4.07; N 28.6; S 48.5. $C_3H_8N_4S_3$ (196.30) requires C 18.4; H 4.11; N 28.5; S 49.0).

Thermal decomposition.

Dithiocarbomethoxy-thiocarbohydrazide (II, R = CH_3, 98 g) was heated at 160° until the evolution of gas had ceased. After cooling, the residue was extracted at 50° with N HCl (600 ml). The mixture was cooled to 0°, and the undissolved material was separated (18.5 g). It crystallized from toluene as colourless rods, m.p. 136—137°, consisting of 2-mercapto-5-methylthio-1,3,4-thiadiazole (III, R = CH_3). (Found: C 22.0; H 2.60; N 16.8; S 58.5. $C_3H_4N_2S_3$ (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° (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°. (Found: C 16.5; H 4.23; N 57.9; S 22.3. $C_2H_6N_6S$ (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° (245—246° according to Ref.[2]) (Found: C 60.2; H 4.62. $C_{16}H_{14}N_6S$ (322.38) 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°, consisting of acetone 5-methylthio-1,3,4-thiadiazol-2-yl-hydrazone (VI, R = R_1 = R_2 = CH_3). (Found: C 35.4; H 4.92. $C_6H_{10}N_4S_2$ (202.29) requires C 35.6; H 4.98). λ_{max}: 2 980 Å with ε : 14 900. From the filtrate of the acetone thiadiazolylhydrazone 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 (5 ml). The ethanol was removed *in vacuo*, and the solution was cooled. Colourless rods separated (1.5 g, 90 % yield), m.p. 136—137° after recrystallization from toluene, consisting of 2-mercapto-5-methylthio-1,3,4-thiadiazole (III). (Found: N 16.9; S 58.4. $C_3H_4N_2S_3$ (164.25) requires N 17.1; S 58.6). For this compound Busch [1] reports m.p. 136°.

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

5-Dithiocarbalkoxy-thiocarbohydrazones (V)

The general procedure for the preparation of these compounds was to dissolve the appropriate mono-thiocarbohydrazone (Part I) in 2 equivalents of N sodium ethoxide in absolute ethanol, add the calculated quantity of the dialkyl trithiocarbonate, 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 dithiocarbomethoxy-thiocarbohydrazone (V, R = 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. $C_6H_{12}N_4S_3$ (236.37) requires C 30.5; H 5.12; N 23.7; S 40.7). λ_{max}: 3 200 Å with ε: 13 300, λ_{max}: 2 690 Å with ε: 22 800.

Acetone dithiocarbobenzoxy-thiocarbohydrazone (V, R = $PhCH_2$, R_1 = R_2 = CH_3) was obtained from acetone mono-thiocarbohydrazone and dibenzyl trithiocarbonate 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. $C_{12}H_{16}N_4S_3$ (312.46) requires C 46.1; H 5.16; N 17.9; S 30.8).

Benzaldehyde dithiocarbomethoxy-thiocarbohydrazone (V, R = CH_3, R_1 = H, R_2 = Ph) was obtained in quantitative yield, and crystallized from a mixture of absolute ethanol and toluene as colourless hairs, m.p. 185–195°. (Found: C 42.2; H 4.23; N 19.9; S 33.6. $C_{10}H_{12}N_4S_3$ (284.41) requires C 42.2; H 4.25; N 19.7; S 33.8).

Acetophenone dithiocarbethoxy-thiocarbohydrazone (V, R = C_2H_5, R_1 = CH_3, R_2 = Ph) was obtained in 85 % yield when monoacetophenone thiocarbohydrazone reacted with diethyl trithiocarbonate 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. $C_{12}H_{16}N_4S_3$ (312.46) requires C 46.1; H 5.16; N 17.9; S 30.8).

Monobenzophenone thiocarbohydrazone has not been described before. It was prepared like the mono-thiocarbohydrazones 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. $C_{14}H_{14}N_4S$ (270.34) requires C 62.2; H 5.22; N 20.7; S 11.9).

Benzophenone dithiocarbomethoxy-thiocarbohydrazone (V, R = CH_3, R_1 = R_2 = 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. $C_{16}H_{16}N_4S_3$ (360.50) requires C 53.3; H 4.47; N 15.6; S 26.7).

Alkylthio-thiadiazolylhydrazones (VI)

These were prepared by heating the dithiocarbalkoxy-thiocarbohydrazones 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-hydrazone (VI, R = R_1 = R_2 = CH_3, and VI, R = H, R_1 = R_2 = CH_3). The residue after melting acetone dithiocarbomethoxythiocarbohydrazone consisted of a mixture of acetone methylthiothiadiazolylhydrazone 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 hydrazone described on p. 000. (Found: C 35.2; H 4.95; N 27.4; S 32.0. $C_6H_{10}N_4S_2$ (202.29) requires C 35.6; H 4.98; N 27.7; S 31.7). The toluene-insoluble material (VI, R = H, R_1 = 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. $C_5H_8N_4S_2$ (188.26) requires C 31.9; H 4.28; N 29.8; S 34.1). λ_{max}: 3 270 Å with ε: 17 500. When this compound was methylated with methyl iodide in alkaline solution, the methylthio derivative described above was formed.

Acetone benzylthio-thiadiazolylhydrazone (VI, R = $PhCH_2$, R_1 = R_2 = CH_3) was obtained in 70 % yield after separation from 15 % of the thiol (VI, R = H, R_1 = R_2 = CH_3).

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. $C_{12}H_{14}N_4S_2$ (278.38) requires C 51.8; H 5.07; N 20.1; S 23.0).

Benzaldehyde methylthio-thiadiazolylhydrazone (VI, R = CH_3, R_1 = H, R_2 = 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. $C_{10}H_{10}N_4S_2$ (250.33) requires C 48.0; H 4.03; N 22.4; S 25.6). λ_{max}: 3 350 Å with ε: 25 000; λ_{max}: 2 540 Å with ε: 8 300; λ_{max}: 2 260 Å with ε: 13 700.

Benzaldehyde 5-mercapto-1,3,4-thiadiazol-2-yl-hydrazone (V, R = R_1 = H, R_2 = Ph, 0.20 g), prepared according to Stollé and Fehrenbach [3], was dispersed in ethanol (3 ml). Methyl iodide (0.2 g) and 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 = C_2H_5, R_1 = CH_3, R_2 = Ph) was obtained in 80 % yield after recrystallization from ethanol. Colourless rods, m.p. 182—183°. (Found: C 51.9; H 5.04; N 20.2; S 22.9. $C_{12}H_{14}N_4S_2$ (278.38) requires C 51.8; H 5.04; N 20.1; S 23.0). λ_{max}: 3 250 Å with ε: 20 500; λ_{max}: 2 260 Å with ε: 11 700.

Benzophenone methylthio-thiadiazolylhydrazone (VI, R = CH_3, R_1 = R_2 = Ph) was obtained in 87 % yield. It crystallized from toluene as pale yellow, irregular prisms, m.p. 170—171°. (Found: C 58.9; H 4.41; N 17.2; S 19.6. $C_{16}H_{14}N_4S_2$ (326.42) requires C 58.9; H 4.32; N 17.2; S 19.6).

Decomposition of dithiocarbalkoxy-thiocarbohydrazones in acid solution

Acetone dithiocarbomethoxy-thiocarbohydrazone was decomposed exactly as dithiocarbomethoxy-thiocarbohydrazide (II, p. 1941). The same products were obtained in much the same yields.

Benzaldehyde dithiocarbomethoxy-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 N NaOH (20 ml), and benzalazine (1.0 g, 96 % yield) remained undissolved. The alkaline solution was acidified with 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 = CH_3). Obviously the initially formed benzaldehyde hydrazone had disproportionated to benzalazine and hydrazine.

Alkylthio-thiadiazolylhydrazines (I)

Methylthio-thiadiazolylhydrazine (I, R = CH_3). Acetone methylthio-thiadiazolylhydrazone (20.3 g) was refluxed for one hour with ethanol (100 ml) and 5 N 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 (200 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. $C_3H_6N_4S_2$ (162.23) requires C 22.2; H 3.73; N 34.5; S 39.5). λ_{max}: 2 820 Å with ε: 8 200.

Benzylthio-thiadiazolylhydrazine (I, R = $PhCH_2$). Acetone benzylthio-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

yield was 76 %, colourless rods with m.p. 111—112° after recrystallization from absolute ethanol. (Found: C 45.4; H 4.30; N 23.5; S 26.7. $C_9H_{10}N_4S_2$ (238.32) requires C 45.4; H 4.32; N 23.5; S 26.9).

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

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