

Cyclizations of Thiocarbohydrazide and its Mono-hydrazones

Part IV *. Reactions with Carboxymethyl Dithiobenzoate

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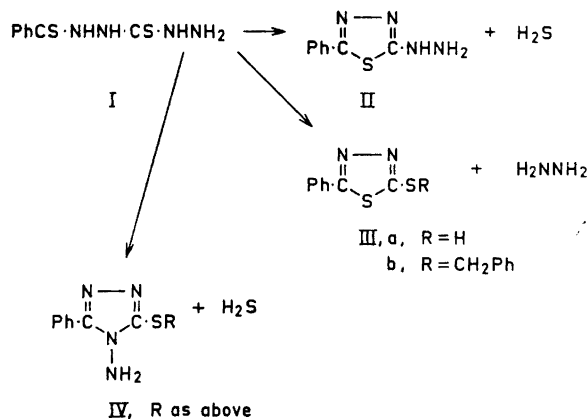
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Thiocarbohydrazide and carboxymethyl dithiobenzoate react to give 1-thiobenzoylthiocarbohydrazide. This is cyclized by heat to a mixture of 5-phenyl-1,3,4-thiadiazol-2-yl-hydrazine, 2-mercapto-5-phenyl-1,3,4-thiadiazole, and 3-mercapto-4-amino-5-phenyl-4,1,2-triazole. In acid medium only the two former compounds are formed. Mono-thiocarbohydrazones and carboxymethyl dithiobenzoate react in boiling pyridine to form phenylthiadiazolyhydrazones.

In the previous parts of this series,¹⁻³ the reactions of thiocarbohydrazide and its monohydrazones with different cyclizing agents have been investigated with the aim of preparing differently substituted 1,3,4-thiadiazolyhydrazines. It was found that whereas the reactions with mono-thiocarbohydrazones gave thiadiazolyhydrazones, the reactions with free thiocarbohydrazide gave either 4-aminotriazole derivatives^{1,3} or a mixture of thiadiazolyhydrazine and 2-mercapto-1,3,4-thiadiazole². The investigation has now been extended to the phenyl analogues, and carboxymethyl dithiobenzoate⁴ has been found to be a suitable cyclizing agent. Hoggarth⁵ has shown that hydrazinolysis of methyl 3-benzoyldithiocarbamate gives 3-mercapto-4-amino-5-phenyl-4,1,2-triazole (IVa) in 80 % yield, probably with 1-benzoylthiocarbohydrazide as an intermediate. The thermal cyclization of the labile 1-thiobenzoylthiocarbohydrazide (I), which is formed in the reaction between thiocarbohydrazide and carboxymethyldithiobenzoate sodium salt in water, gives the same product, but only in 5 % yield. The main products are 5-phenyl-1,3,4-thiadiazol-2-yl-hydrazine (II, 45-50 % yield) and 2-mercapto-5-phenyl-1,3,4-thiadiazole⁶ (IIIa, 38-40 % yield).

In alkaline medium thiobenzoylthiocarbohydrazide (I) is stable even at elevated temperatures, but in acid solution it is rapidly decomposed to a mixture of (II, 31 % yield) and (IIIa, 65 % yield). This result is different from that obtained with the rather similar 1-dithiocarbomethoxy-thiocarbo-

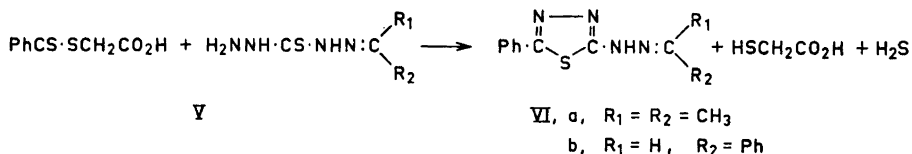
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hydrazide,² which gives the corresponding mercaptothiadiazole as the sole product.

When attempts were made to react (I) with carbonyl compounds, non-crystalline materials were formed, from which no definable products could be isolated. Similar results were obtained, when mono-thiocarbohydrazones (V) reacted with carboxymethyl dithiobenzoate in aqueous medium. When the reaction was performed in boiling pyridine, reasonable yields of 5-phenyl-1,3,4-thiadiazol-2-yl-hydrazones (VI) were obtained.

From the acetone thiadiazolyldiazone (VIa) the free thiadiazolyldiazone (II) could readily be obtained by acid hydrolysis. (II) has previously been



prepared by Fujii *et al.*⁷ by hydrazinolysis of 2-methanesulphonyl-5-phenyl-1,3,4-thiadiazole, and by the present author⁸ by oxidation of dibenzaldehyde thiocarbohydrazone with iron(III) chloride and subsequent hydrolysis of the benzaldehyde phenylthiadiazolyldiazone (VIb) formed.

The phenylthiadiazolyldiazones are weak acids, but because of their low solubility in water they are only slightly soluble in N aqueous sodium hydroxide.

EXPERIMENTAL

1-Thiobenzoylthiocarbohydrazide (I). Thiocarbohydrazide (21 g, 0.2 mole) was dissolved in N HCl (200 ml), the solution was cooled to + 5°, and carboxymethyl dithiobenzoate (21.2 g, 0.1 mole) in 3 N NaOH (100 ml) was added. The excess of thiocarbohydrazide was employed in order to prevent bis-thiobenzoylation. A pale yellow precipitate was formed, which was purified by dissolution in an equivalent amount of N NaOH, filtration from

a small amount of unreacted thiocarbohydrazide, and precipitation with acetic acid. The precipitate was extracted twice with boiling chloroform, and the residue (20.2 g, 90% yield) was fairly pure 1-thiobenzoylthiocarbohydrazide (I). On heating, hydrogen sulphide could be detected above 80°, and at 148–150° the material melted with effervescence. (Found: C 42.2, H 4.38; N 24.5; S 28.0. $C_8H_{10}N_4S_2$ (226.33) requires C 42.5; H 4.45; N 24.8; S 28.3).

Thermal decomposition. Solid (I), (2.3 g) was heated up in a flask in a metal bath to 150° and kept there until the evolution of gas had ceased. The residue was dissolved in hot ethanol (20 ml), and benzaldehyde (1 ml) was added. A pale yellow precipitate was obtained (1.35 g), which crystallized from butanol as pale yellow rods, m.p. 256–257°, undepressed on admixture with authentic benzaldehyde phenylthiadiazolylylhydrazone⁸ (VIb). (Found: C 64.4; H 4.27. $C_{15}H_{12}N_4S$ (280.34) requires C 64.3; H 4.31).

To facilitate their separation by chromatography on alumina, the thiols in the remaining material were transformed to benzylthioethers. N NaOH (15 ml) and benzyl chloride (1.3 g) were added to the filtrate from (VIb). The mixture soon turned cloudy and deposited an oil, and on the following day the ethanol was evaporated in a stream of air. The undissolved material was taken up in benzene and, after drying, the benzene solution was subjected to chromatography on alumina. A 1:1 mixture of benzene-light petroleum (b.p. 80–100°) eluted colourless prisms (1.15 g), m.p. 111.5–112.5°, undepressed on admixture with an authentic specimen of 2-benzylthio-5-phenyl-1,3,4-thiadiazole (IIIb) prepared according to Young and Wood⁹. (Found: C 63.5; H 4.28; N 9.79; S 22.5. $C_{15}H_{12}N_2S_2$ (284.39) requires C 63.3; H 4.26; N 9.84; S 22.6).

The elution was continued with benzene, which gave a small amount (0.08 g) of unidentified, noncrystalline material, and with a 1:1 mixture of benzene and ether, which eluted colourless prisms (0.21 g), m.p. 127–127.5°, consisting of the benzaldehyde Schiff base of (IVb). (Found: C 71.3; H 4.92; N 15.1; S 8.37. $C_{22}H_{18}N_4S$ (370.45) requires C 71.3; H 4.90; N 15.1; S 8.65).

The same compound was prepared from 3-mercapto-4-amino-5-phenyl-4,1,2-triazole (IVa). This triazole (1.9 g) was dissolved in N NaOH (10 ml), and benzyl chloride (1.3 ml) in ethanol (20 ml) was added. The mixture soon set to a solid mass of colourless prisms (2.7 g), which crystallized from toluene as colourless plates, m.p. 199–200°, consisting of 3-benzylthio-4-amino-5-phenyl-4,1,2-triazole (IVb). (Found: C 63.9; H 5.04; N 19.8; S 11.3. $C_{15}H_{14}N_4S$ (282.35) requires C 63.8; H 5.00; N 18.8; S 11.4). The triazole (IVb, 0.29 g) was dissolved in ethanol (5 ml) and benzaldehyde (0.5 ml) and one drop of conc. HCl were added. A solid deposit was formed (0.27 g), which crystallized from benzene-heptane as colourless, rhombic prisms, m.p. 127–127.5°, undepressed on admixture with the 3-benzylthio-4-benzylideneamino-5-phenyl-4,1,2-triazole described above. (Found: C 71.4; H 5.01, required C 71.3; H 4.90).

Decomposition in acid medium. (I), (2.3 g) was refluxed in ethanol (30 ml) and conc. HCl (2 ml) for 15 min. Hydrogen sulphide was formed, and when water (40 ml) was added, a precipitate was formed (1.30 g), which crystallized from butanol as pale yellow prisms, m.p. 216–217°, undepressed on admixture with authentic 2-mercapto-5-phenyl-1,3,4-thiadiazole⁶ (IIIa). (Found: Equiv.wt. 195 (NaOH) and 192 (iodine). $C_8H_8N_2S_2$ (194.27) requires equiv.wt. 194). Benzaldehyde (3.3 ml) in ethanol (10 ml) was added, and a yellow, crystalline precipitate was formed (2.14 g). This was extracted with benzene (20 + 20 ml) and gave a residue (0.84 g) which crystallized from butanol as pale yellow rods, m.p. 256–257°, undepressed on admixture with the benzaldehyde phenylthiadiazolylylhydrazone (VIb) described above. The benzene extract on evaporation gave benzalazine (1.25 g, calc. 1.35 g), m.p. and mixed m.p. 92–93°.

Acetone phenylthiadiazolylylhydrazone (VIa). Acetone mono-thiocarbohydrazone¹ (Va), (6.0 g) and carboxymethyl dithiobenzoate (8.5 g) were refluxed for 1 h in 50 ml of pyridine. On cooling, pale yellow rods separated (5.0 g), which crystallized from glacial acetic acid as colourless rods, m.p. 242–243°. (Found: C 56.7; H 5.21; N 23.9; S 14.0. $C_{11}H_{12}N_2S$ (232.30) requires C 56.8; H 5.20; N 24.1; S 13.8). On the addition of water (200 ml) to the pyridine mother liquor, a further quantity (1.7 g) of slightly less pure product was obtained, making a total yield of 72%.

Benzaldehyde phenylthiadiazolylylhydrazone (VIb). Benzaldehyde monothiocarbohydrazone (Vb), (4.0 g) and carboxymethyl dithiobenzoate (4.3 g) were refluxed for 1 h in pyridine (50 ml). Precipitation with water (200 ml) gave a yellow product (4.1 g, 73% yield), which crystallized from butanol as pale yellow rods, m.p. 256–257°, undepressed on

admixture with the hydrazone (VIb) described above. (Found: C 64.4; H 4.38; required C 64.3; H 4.31).

Phenylthiadiazolyldiazine (II). Acetone phenylthiadiazolyldiazone (VIa), (4.6 g) was refluxed with ethanol (20 ml) and 5 N HCl (20 ml) for 2 h, and then the solvents were removed in a slight vacuum with continued heating in order to prevent the precipitation of starting material. The dry residue was dissolved in hot water (20 ml) and filtered from a small amount of unreacted (VIa). Crystalline sodium acetate (4.0 g) was added, and pale yellow rods separated (3.7 g, 96 % yield), which crystallized from absolute ethanol as colourless rods, m.p. 190–191°, undepressed on admixture with an authentic specimen⁸. (Found: N 29.0; S 16.7. $C_8H_8N_4S$ (192.23) requires N 29.1; S 16.7).

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