Studies of Thioacids and Their Derivatives

VI. Formation of Thiadiazoles and Tetrazines in the Preparation of Thiohydrazides

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Some by-products and transformation products obtained in the preparation of thiohydrazides have been shown to be thiadiazoles and tetrazines. The formation of these compounds in some cases proceeds at such a rate that no thiohydrazides can be isolated. 2,5-Disubstituted thiadiazoles are generally obtained in good yields from thiohydrazides and carboxymethyl dithioates.

Thiohydrazides are easily transformed into heterocyclic compounds. Such reactions are well known in the case of thiosemicarbazides and thiosemicarbazones, and similar reactions with phenylhydrazides of thioacids and thio-benzhydrazide have been extensively investigated by Wuyts and Holmberg, respectively.

The main purpose of the present paper is to prove the identity of some by-products obtained in the preparation of thiohydrazides, but at the same time it demonstrates the general character of the reactions studied by Wuyts and Holmberg. Besides, some new thiadiazoles have been prepared, among these the basic 1,3,4-thiadiazole, which in the meantime has been prepared by Goerdeler et al. in a different way.

In the preparation of thiohydrazides, the formation of tetrazines and thiadiazoles sometimes proceeds at such a rate that no thiohydrazides can be isolated. It has already been mentioned (No. III of this series) that no thiohydrazides could be obtained from the reaction of aliphatic thioacids or thio-esters with at least one hydrogen atom at the α-carbon atom. When for instance dithiopropionic acid reacts with hydrazine, a white sulfur-free compound with 34—38 % nitrogen is formed. This compound turns red in air, and this property together with its high nitrogen content shows that it mainly consists of diethylidihydrotetrazine (calc. 40.0 % N), although this was not obtained in a pure state. Also dithioformic acid gives a product which turns red in air, but from which no definite compound could be isolated. On the other hand, from the reaction of potassium dithioformate or carboxymethyl dithiopro-

pionate with hydrazine, 1,3,4-thiadiazole and 2,5-diethyl-1,3,4-thiadiazole could be isolated in good yields.

Phenylthioacethydrazide often decomposes on standing with evolution of hydrogen sulfide, and from this product 2,5-dibenzyl-1,3,4-thiadiazole could be isolated. This decomposition is catalysed by impurities and proceeds only slowly in pure samples of the thiohydrazide. It was shown that the much more stable furanthiocarboxyhydrazide on heating is similarly transformed into 2,5-di-(2'-furyl)-1,3,4-thiadiazole.

Jensen and Miquel noticed that thiobenzoylthiosemicarbazide on heating is transformed into another substance. This has now been shown to be the expected 2-phenyl-5-amino-1,3,4-thiadiazole.

Thiadiazoles are also formed by oxidation of thiohydrazides and by the reaction of thiohydrazides with carboxymethyl dithioates (see below). In the preparation of phenylthioacethydrazide, the corresponding dihydrotetrazine is a frequent contaminant of the crude product, which often assumes a red colour when exposed to air. In one case when we tried the preparation of phenylthioacethydrazide on a larger scale (100 g) we obtained no thiohydrazide at all. Instead, a colourless substance with a higher melting point was formed, and when this product was exposed to air it rapidly assumed the characteristic red-violet colour of a tetrazine. From this product we succeeded in obtaining pure 3,6-dibenzyl-1,2,4,5-tetrazine (m.p. 74°C). The formation of the tetrazine was probably caused by a local excess of hydrazine, since Wuyts has shown that tetrazines are formed in the reaction of N-phenylthiohydrazides with hydrazine.

When phenylthioacethydrazide reacts with methyl iodide, 3,6-dibenzyl-dihydro-1,2,4,5-tetrazine is formed:

\[ 2C_6H_5CH_2CSNHNH_2 + 2CH_3I \rightarrow C_6H_5CH_2N = N \longrightarrow C_6H_5CH_2N \longleftrightarrow C_6H_5CH_2C_S + 2CH_3SH + 2HI \]

Similarly 3,6-(2'-furyl)-dihydro-1,2,4,5-tetrazine was obtained from 2-furanthiocarboxyhydrazide. Holmberg has obtained 3,6-diphenylidihydro-1,2,4,5-tetrazine in a similar reaction. All three compounds were already prepared by Pinner from the corresponding imidoesters.

The thiohydrazides in most cases react easily with carboxymethyl dithioates with formation of thiadiazoles. This reaction undoubtedly proceeds via dithioacetylated hydrazine, which spontaneously splits off hydrogen sulfide:

\[ RCSNH_2 + RCSC_{(4)}COOH \rightarrow HSC_{(4)}COOH + R-C-C-R \rightarrow R-C-S + R \rightarrow HC_S \]

This reaction was observed by Holmberg in the case of thiobenzhydrazide \((R = C_6H_5)\), and we have observed similar reactions with phenylthioacethydrazide, phenylthiopropionic hydrazide, 2-furanthiocarboxyhydrazide, 2-thio-

phenethiocarboxhydrazide, salicylic thiohydrazide and \( p \)-hydroxythiobenzhydrazide. It is generally not possible to isolate the intermediate dithiocaclylated hydrazines. However, as mentioned in our paper No. III, such compounds were formed from carboxymethyl \( o \)-isobutoxydithiobenzoate or carboxymethyl \( o \)-pentyloxidithiobenzoate and hydrazine. They are transformed into the corresponding thiadiazoles on heating.

When carboxymethyl dithiobenzoate is added to a solution of \( N^1 \)-methylthiobenzhydrazide, \( C_5 H_5 CSN(CH_3)NH_2 \), hydrogen sulfide is similarly formed, but the reaction product is of course not a thiadiazole. There are two possible formulae for the reaction product, of which II has been shown to be the correct one by comparison with the authentic compounds I and II prepared by benzylation of \( N^1 \)-methylthiobenzhydrazide and by thiobenzylation of \( N^1 \)-methylthiobenzhydrazide, respectively.

\[
\begin{align*}
C_5 H_5 CSN(CH_3)NHCOCH_3 & \quad \text{or} \quad \quad C_5 H_5 CON(CH_3)NHCSCH_3 \\
& \quad \text{I} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quarters
Table 1. 2,5-Disubstituted-1,3,4-thiadiazoles:

<table>
<thead>
<tr>
<th>R</th>
<th>Yield %</th>
<th>M.p., °C</th>
<th>Formula</th>
<th>Analyses</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbon</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
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<tr>
<td>H</td>
<td>52</td>
<td>41 - 42</td>
<td>C₆H₄N₄S</td>
<td>28.00</td>
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<tr>
<td>Methyl</td>
<td>44</td>
<td>65 - 67</td>
<td>C₆H₄N₄S</td>
<td>42.00</td>
</tr>
<tr>
<td>Benzyl</td>
<td>85</td>
<td>100 - 102</td>
<td>C₆H₄N₄S</td>
<td>10.28</td>
</tr>
<tr>
<td>β-Phenyethyl</td>
<td>75</td>
<td>72 - 74</td>
<td>C₆H₄N₄S</td>
<td>73.20</td>
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<tr>
<td>o-Hydroxyphenyl</td>
<td>88</td>
<td>231 - 232</td>
<td>C₈H₈N₂O₃S</td>
<td>62.20</td>
</tr>
<tr>
<td>o-Isoalloxyphenyl</td>
<td>90</td>
<td>85 - 86</td>
<td>C₈H₈N₂O₃S</td>
<td>69.20</td>
</tr>
<tr>
<td>o-Pentylalloxyphenyl</td>
<td>90</td>
<td>&gt;300</td>
<td>C₁₀H₁₀N₂O₃S</td>
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<tr>
<td>p-Hydroxyphenyl</td>
<td>75</td>
<td>115 - 116</td>
<td>C₁₀H₈N₂O₃S</td>
<td>55.25</td>
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<tr>
<td>2-Furyl</td>
<td>72</td>
<td>118 - 119</td>
<td>C₁₀H₈N₂O₃S</td>
<td>48.05</td>
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<tr>
<td>2-Thienyl</td>
<td>69</td>
<td>157 - 158</td>
<td>C₁₀H₈N₂S</td>
<td>28.00</td>
</tr>
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</table>

immediately. After 24 h at room temperature 20 ml of water was added; an oily product separated, but it soon crystallised. It was filtered off and washed with water. The substance was recrystallised from light petroleum (b.p. 60 - 100°C). It forms colourless crystals of m.p. 72 - 74°C (Table 1).

Most of the other 2,5-disubstituted 1,3,4-thiadiazoles with aromatic or heterocyclic substituents were prepared in the same way. The reaction between 2-hydroxythiobenzhydrazide and carboxymethyl dithioacetylated ester is completed in a few minutes; for this reason it is difficult to prepare the thiodyrazide by the usual method, the thiazolediazole being obtained instead (see No. III of this series). The corresponding p-hydroxythiobenzhydrazide reacted rather slowly, 72 h being necessary to complete the formation of thiadiazole. In the other cases the reaction time was less than 24 h.

The 2,5-(dialkoxyphenyl)-1,3,4-thiadiazoles were prepared by melting the corresponding dithioacetylated hydrazines (cf. our paper No. III) and keeping them in a molten state for half an hour. The yellow substances then turned colourless with evolution of hydrogen sulfide. The reaction products were recrystallised from hexane. Further data are given in Table 1.

The formation of the thiadiazoles by heating the thiodyrazides was demonstrated in the case of 2-furanthioacarboxyhydrazide: 0.5 g of the thiodyrazide was melted and kept at 140 - 150°C for a quarter of an hour. Hydrogen sulfide and ammonia were evolved, and a black mass was formed; it was extracted with ether. The ether was evaporated and the residue dissolved in benzene; the solution was treated with decolourising carbon and filtered. On addition of light petroleum a yellowish substance crystallised. The substance was crystallised once more from ethanol-water. M.p. 119 - 120°C, no depression on mixing with an authentic sample of 2,5-di(2'-furyl)-1,3,4-thiadiazole.

The rather unstable phenylthioacetyldiazide is transformed into a thiazolediazole already at room temperature: An old preparation of phenylthioacetyldiazide, which had m.p. 83 - 90°C (originally 68 - 69°C), was recrystallised from ethanol + water, and the product was extracted with ether; from the ether solution a yellow crystalline substance separated on addition of light petroleum. After one crystallisation from ethanol + water this product had m.p. 98 - 100°C and showed no depression on mixing with an authentic sample of 2,5-dibenzyli-1,3,4-thiadiazole.

2-Phenyl-1,3,4-thiazole. To a solution of thiobenzhydrazide (0.5 g) in water (5 ml) + ethanol (5 ml) was added a solution of potassium dithioformate (0.38 g) in water (5 ml).
The mixture was kept over night at room temperature. The ethanol was then removed in vacuo, dilute hydrochloric acid was added to bring the solution to pH 7, and the solution was extracted with ether (3 × 10 ml). The ether solution was dried (Na₂SO₄), and the ether was removed in vacuo leaving an oil which crystallised on cooling. The crystals were washed with light petroleum and recrystallised from benzene-light petroleum. M.p. 40–41°C, in accord with Holmberg (Found: C 59.50; H 3.84; N 17.07. Calc. for C₅H₅N₂S: C 59.23; H 3.73; N 17.27).

2-Benzyl-1,3,4-thiadiazole was prepared by the same procedure from phenylthioacetamide. The product was recrystallised from light petroleum (b.p. 40–60°C). Yield 56 %. Colourless crystals of m.p. 28–29°C. (Found: C 61.45; H 4.28; N 16.00. Calc. for C₅H₅N₂S: C 61.30; H 4.58; N 15.91).

2-Phenyl-5-mercapto-1,3,4-thiadiazole. To a solution of thiobenzhydrazide (0.5 g) in 1 N alcoholic KOH (6.6 ml; 2 equiv.) was added 0.5 g of carbon disulfide in 5 ml of ethanol. The mixture was kept overnight at room temperature. Ethanol and excess carbon disulfide were removed in vacuo and enough water was added to dissolve the potassium salt which had separated. Acidification with dilute hydrochloric acid precipitated the thiadiazole as colourless crystals, which were filtered off and washed with water. Yield 0.8 g (94 %). After recrystallisation from 70 % ethanol the m.p. was 215–216°C in accord with Sandström (Found: N 14.54. Calc. for C₅H₅N₂S: N 14.40).

2-Benzyl-5-mercapto-1,3,4-thiadiazole was prepared in the same way from phenylthioacetamide in 75 % yield. The product was recrystallised from benzene-light petroleum. (b.p. 60–100°C). Colourless crystals with m.p. 115–116°C. (Found: C 52.05; H 3.90; N 13.58. Calc. for C₅H₅N₂S: C 51.90; H 3.87; N 13.46).

2-Phenyl-5-amino-1,3,4-thiadiazole. Thiobenzoylthiosemicarbazide (1.5 g) was heated to 140°C for half an hour and then dissolved in hot 1 N hydrochloric acid. The filtered solution was neutralised with NaOH and the white solid which separated was filtered, washed with water and recrystallised twice from ethanol. M.p. 222–223°C, in accord with the literature (N₂H₄). (Found: N 23.72. Calc. for C₅H₅N₂S: N 23.71).

N₂-Methyl-N₂-thiobenzoylbenzhydrazide. N₂-Methyl-benzhydrazide (0.5 g) was added to a neutralised aqueous solution of carboxymethyl dithiobenzoate (0.7 g). In the course of two days a yellow substance separated. The solution was brought to pH 7 and filtered. Yield 0.75 g (83 %) with m.p. ca. 160°C. The compound was purified by dissolving in 1 N NaOH, filtering, precipitation with hydrochloric acid and recrystallisation, first from benzene + light petroleum and then from ethanol. M.p. 166–168°C. (Found: C 66.80; H 5.23; N 10.24. Calc. for C₅H₅N₄OS: C 66.60; H 5.22; N 10.36).

This compound was also prepared from N₁-methylthiobenzhydrazide (0.5 g), which was dissolved in ethanol (2 ml) and added to a neutral solution of carboxymethyl dithiobenzoate (0.64 g) in 1 N NaOH. A precipitate separated; it was filtered, dried, extracted with light petroleum, which removed some unchanged methylthiobenzhydrazide, and recrystallised from benzene. Yield 0.20 g (25 %) with m.p. 165–166°C, unchanged on mixing with the above mentioned preparation, but strongly depressed on mixing with the isomer. (Found: C 67.00; H 5.22; N 10.60; S 11.85. Calc. for C₅H₅N₄OS: C 66.60; H 5.22; N 10.36; S 11.85).

N₂-Methyl-N₂-thiobenzoylbenzhydrazide. N₁-Methylthiobenzhydrazide (0.5 g) was dissolved in dry pyridine (5 ml), and with cooling in ice benzoyl chloride (0.35 ml) was added. After 24 h the solution was diluted with water, hydrochloric acid was added, and the precipitate was filtered and washed with water. The substance was purified by solution in 1 N NaOH, filtering, precipitation with acid, and recrystallisation from benzene + light petroleum and then from ethanol + water. M.p. 166–167°C. (Found: C 66.80; H 5.18; N 10.36. Calc. for C₅H₅N₄OS: C 66.60; H 5.22; N 10.36).

3,6-Dibenzyl-dihydro-1,2,4,5-tetrazine. Phenylthioacetamide (0.5 g) was dissolved in 3 ml 1 N NaOH + 3 ml ethanol, and 0.5 ml of methyl iodide was added. The solution soon became turbid and smelled of methanethiol. After ca. 12 h the mixture was diluted with water, the precipitate filtered and recrystallised from ethanol. M.p. 162–164°C (Finner *: 158 – 160°C). (Found: C 72.75; H 6.04. Calc. for C₅H₅N₂: C 72.70, H 6.10).

The same procedure was used for the preparation of 3,6-di-(2-furyl)-dihydro-1,2,4,5-tetrazine. M.p. 214–216° (Finner *: 208°). (Found: C 55.65; H 4.07; N 25.02. Calc. for C₅H₅N₄O₂: C 56.55; H 3.75; N 25.92).

REFERENCES

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5. Holmberg, B. Arkiv Kemi 9 (1955) 47.

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