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Cyclizations of Thiocarbohydrazide and its Mono-hydrazones

Part I. Reactions with Orthoesters

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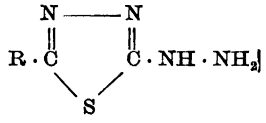
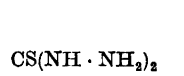
Free thiocarbohydrazide is cyclized by orthoesters to 3-mercapto-4-amino-4,1,2-triazoles, whereas mono-thiocarbohydrazones with the same reagents give the weakly acidic 1,3,4-thiadiazolylhydrazones.

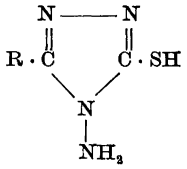
The present investigation was undertaken to find the possibilities of preparing 1,3,4-thiadiazolylhydrazines (I) by cyclization of thiocarbohydrazide (II) with derivatives of carboxylic acids.



I



II



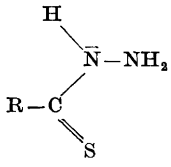
III

However, a direct cyclization of the unsubstituted thiocarbohydrazide was not expected to lead to success, since Stollé and Bowles [1] have shown that this compound reacts with triethyl orthoformate in a closed tube to give 3-mercapto-4-amino-4,1,2-triazole (III, R = H). In the present work, the same compound was obtained when thiocarbohydrazide reacted with formic acid and with formamide. A series of reactions was performed to establish the structure of the triazole, but when the investigation was finished, the author was informed about a more extensive investigation on the same subject by Beyer and Kröger, the results of which were already published [2]. Therefore, the results of the cyclization of the free thiocarbohydrazide are omitted in the present publication.

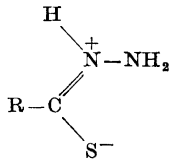
Thiadiazolylhydrazines (I) have previously been prepared by Stollé and Fehrenbach [3], by Fujii *et al.*[4], and by Kanaoka [5,6] by reduction of 2-nitrosamino-thiadiazoles. Fujii has also used hydrazinolysis of 2-alkylsulphonyl-

thiadiazoles, and Kanaoka has used hydrazinolysis of 2-bromo-thiadiazoles. Goerdeler and Galinke [7] have prepared 1,3,4-thiadiazolylhydrazine (isolated as benzaldehyde hydrazone) by reduction of 2-nitramino-thiadiazole.

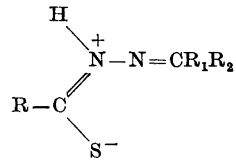
In a previous communication [8], attention has been directed to the property of a benzylidene group of inhibiting cyclization of carboxymethyl 3-benzylidene-dithiocarbazate to benzylidenamino-rhodanine. It was now expected that a similar effect might prevent the 2-nitrogen atom of mono-thiocarbohydrazones from taking part in the cyclization with orthoesters, and thus lead the cyclization to hydrazones of (I), rather than to Schiff bases of the carbonyl compounds and 3-mercapto-4-amino-4,1,2-triazole (III). This expectation has been partly fulfilled, not only with monobenzaldehyde thiocarbohydrazone, but also with monoacetone, mono*cyclo*hexanone, and monoacetophenone thiocarbohydrazone. However, the mechanism proposed in Ref.[8] cannot be responsible for the course of the cyclization of the acetone and *cyclo*hexanone derivatives. Possibly a steric effect is also at work to make the 2-nitrogen atom less available for cyclization than the sulphur atom. However, Hünig [9] has recently found a directing effect, which probably has a bearing on the present problem. He found, that 4-phenylthiosemicarbazide condenses with chloroacetone to give 3-amino-4-methyl-thiazol-2(3)-one phenylimine, whereas acetone 4-phenylthiosemicarbazone with chloroacetone gives acetone 3-phenyl-4-methylthiazol-2(3)-one azine. In the first case the 2-nitrogen atom of the thiosemicarbazide is preferred in the cyclization, whereas in the second case the 4-nitrogen atom seems to be the more available one. Obviously the 1-*iso*-propylidene group has some influence on the availability of the 2-nitrogen atom, and in this case a steric effect seems less likely. Instead, the following proposal is made. Thiohydrazides are resonance hybrids with, among others, the limiting structures (IV a) and (IV b).



IV a



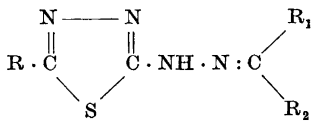
IV b



V

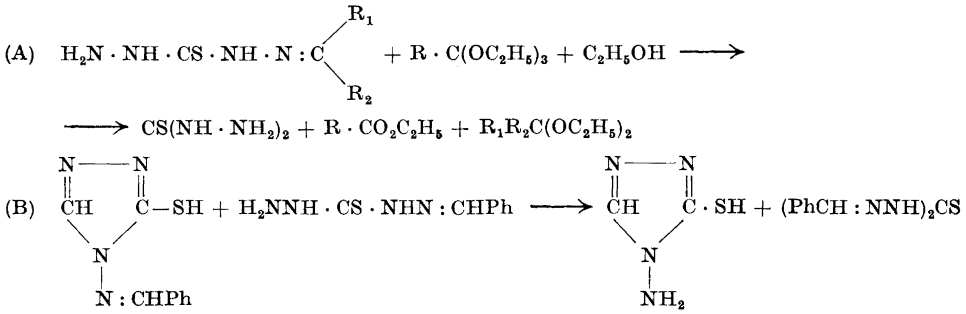
In a thiohydrazone the polar structure, (V), becomes relatively more important, because of the conjugation. Therefore, the 2-nitrogen atom is less basic in thiohydrazones than in thiohydrazides. A similar argumentation can be performed for the amidine structures in Hünig's example. Evidence for the existence of such a conjugation is given by the UV-spectra of the thiohydrazides and thiohydrazones. As an example, methyl dithiocarbazate has its maximum at 2 690 Å, with $\varepsilon = 10\,100$, in absolute ethanol, whereas methyl 3-ethylidene-dithiocarbazate has its maximum at 2 970 Å, with $\varepsilon = 21\,200$ in the same solvent. This bathochromic shift obviously calls for some kind of conjugation between the azomethine group and the thioamide group. The yields have been far from quantitative, and as dibenzaldehyde thiocarbohydrazone and 3-

mercapto-4-benzylidenamino-4,1,2-triazole were found among the products of the reaction between monobenzaldehyde thiocarbohydrazone and triethyl orthoformate, the side reaction (A) may be at least partly responsible.



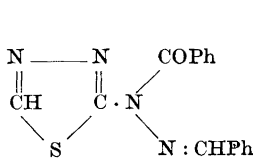
VI

However, a direct formation of 3-mercapto-4-benzylidenamino-4,1,2-triazole cannot be excluded, and the occurrence of dibenzaldehyde thiocarbohydrazone can be explained by the reaction (B), which has been found to occur in boiling toluene.

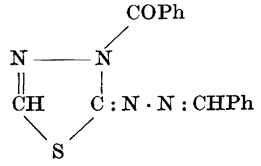


For starting materials, a series of mono-thiocarbohydrazones were prepared by reaction between thiocarbohydrazide and the appropriate carbonyl compound in weakly acidic medium. There is a striking difference between the ease with which the first and the second hydrazine group in thiocarbohydrazide reacts with ketones [10]. The mono-thiocarbohydrazones were refluxed with triethyl orthoformate and triethyl orthoacetate in toluene and without solvent, and the corresponding thiadiazolylhydrazones (VI, R = H and CH_3) were formed in varying yields. Attempts to prepare the free thiadiazolylhydrazines (I) by acid hydrolysis of the acetone hydrazones have failed because the simple thiadiazolylhydrazines are rearranged in acid medium to derivatives of aminotriazole, as will be described in a later publication.

The thiadiazolylhydrazones (VI) are weak acids, and they dissolve readily in aqueous N NaOH but not in N potassium carbonate solution. With benzoyl chloride in pyridine, benzaldehyde thiadiazolylhydrazone (VI, R = R_1 = H, R_2 = Ph) gives two benzoyl derivatives, (VII), and (VIII).



VII



VIII

EXPERIMENTAL

Mono-thiocarbohydrazones

The preparation of monobenzaldehyde thiocarbohydrazone has been described by Stollé and Gaertner [11]. Three new mono-ketone thiocarbohydrazones have been prepared by adding a 50 % excess of the ketone in ethanol to a hot solution of thiocarbohydrazide in N acetic acid. The *monoacetone thiocarbohydrazone* separated as colourless, pointed prisms, m. p. 194—195° (decomp.), in 93 % yield. The product is very slightly soluble in the common organic solvents and in water, and it dissolves with partial decomposition in acidic and alkaline solvents. According to analysis, the crude product is sufficiently pure for all practical purposes. (Found: C 32.9; H 6.99; N 38.2; S 21.9. $C_4H_{10}N_4S$ (146.21) requires C 32.9; H 6.89; N 38.3; S 21.9.)

Monocyclohexanone thiocarbohydrazone was obtained in 83 % yield and crystallized as colourless flakes, m. p. 166—167° (decomp.), from a mixture of absolute ethanol and glacial acetic acid. (Found: C 45.1; H 7.43; N 29.9; S 17.3. $C_7H_{14}N_4S$ (186.27) requires C 45.1; H 7.58; N 30.1; S 17.2.) λ_{max}: 2 500 Å with ε = 12 600.

Monoacetophenone thiocarbohydrazone was obtained in 98 % yield and crystallized from 80 % aqueous ethanol as colourless flakes, m. p. 170—171°. (Found: C 52.1; H 5.95; N 26.9; S 15.3. $C_9H_{12}N_4S$ (208.28) requires C 51.9; H 5.81; N 26.9; S 15.4.) λ_{max}: 3 020 Å with ε = 13 400, λ_{max}: 2 350 Å with ε = 12 000.

1,3,4-Thiadiazolylhydrazones

Acetone thiadiazolylhydrazone (VI, R = H, $R_1 = R_2 = CH_3$). Monoacetone thiocarbohydrazone (9.0 g) and triethyl orthoformate (15 ml) were refluxed for 45 min, and then the volatile material was removed *in vacuo*. The sticky residue was shaken for two days with water (100 ml), and the undissolved material (6.1 g, 63 % yield) crystallized from *n*-butanol as colourless, pointed prisms, m. p. 173—174°. (Found: C 38.6; H 5.26; N 35.8; S 20.6, mol. wt. 160 (Rast). $C_5H_8N_4S$ (156.20) requires C 38.4; H 5.16; N 35.9; S 20.5.) λ_{max}: 2 790 Å with ε = 13 500.

Cyclohexanone thiadiazolylhydrazone (VI, R = H, $R_1R_2 = (CH_2)_5$). Monocyclohexanone thiocarbohydrazone (7.2 g) and triethyl orthoformate (15 ml) were refluxed for 30 min, and then the volatile material was removed *in vacuo*. The sticky residue was dissolved in hot toluene (10 ml), and on cooling, colourless needles separated (1.5 g, 20 % yield), m. p. 168—169° after a further recrystallization from toluene. (Found: C 49.3; H 6.26; N 27.5; S 16.3. $C_8H_{12}N_4S$ (196.27) requires C 49.0; H 6.16; N 28.5; S 16.3.) λ_{max}: 2 790 Å with ε = 14 000.

Benzaldehyde thiadiazolylhydrazone (VI, $R = R_1 = H$, R_2 = Ph). Monobenzaldehyde thiocarbohydrazone (10.0 g) and triethyl orthoformate (10 ml) were refluxed in toluene (100 ml) for one hour. The solution was filtered hot, and on cooling, a colourless crystalline product separated (8.2 g), melting between 165° and 190°. The product was rubbed with a solution of potassium carbonate (10 g) in water (50 ml). The undissolved material was removed by filtration, and the filtrate was acidified with glacial acetic acid. A colourless precipitate was formed (0.9 g, 9 % yield), m. p. 171—172°, identified by mixed m. p. and formation of benzyl derivative [2], as 3-mercapto-4-benzylidenamino-4,1,2-triazole.

The material which did not dissolve in the potassium carbonate solution (6.9 g) was shaken with N NaOH (50 ml) and methanol (50 ml) for 12 h. The undissolved material (1.4 g, 10 % yield) was filtered, and crystallized from glacial acetic acid as colourless needles, m. p. 194—195°, not depressed on admixture with authentic dibenzaldehyde thiocarbohydrazone [1]. (Found: C 63.6; H 4.94. $C_{15}H_{14}N_4S$ (282.37) requires C 63.8; H 5.00.)

Glacial acetic acid (6 ml) was added to the alkaline filtrate, and a pale brown crystalline powder separated (4.8 g, 47 % yield), which crystallized from *n*-butanol as colourless needles of benzaldehyde thiadiazolylhydrazone, m. p. 226—227°. (Found: C 52.9; H 3.94; N 27.5; S 15.7. $C_9H_8N_4S$ (204.24) requires C 52.9; H 3.95; N 27.4; S 15.7.) λ_{max}: 3 210 Å with ε = 24 500, λ_{max}: 2 280 Å with ε = 12 900.

Reaction B: Monobenzaldehyde thiocarbohydrazone (0.5 g) and 3-mercapto-4-benzylidenamino-4,1,2-triazole (0.5 g) were refluxed in toluene for one hour. After cooling, the undissolved material was isolated and extracted with hot water (20 ml). The aqueous

extract was found to be acidic and was neutralized against phenolphthalein with 3.9 ml of 0.1 N NaOH, which corresponds to about 15 % conversion. The aqueous solution was acidified with N HCl (0.5 ml) and a solution of benzaldehyde (0.2 g) in ethanol (10 ml) was added. On the following day the solution had deposited long, colourless needles of 3-mercapto-4-benzylidenamino-4,1,2-triazole (0.09 g), m. p. and mixed m. p. 172—173°.

Benzaldehyde thiadiazolylhydrazone (2.1 g) was dissolved in pyridine (15 ml), and benzoyl chloride (2 ml) was added. On the following day, the brown solution was poured into water (100 ml), and a brownish yellow crystalline product (3.1 g) was precipitated. It was dissolved in 250 ml of boiling ethanol, and on cooling, colourless plates separated (0.5 g, 16 % yield), m. p. 184—186° after recrystallization from toluene. The product was a benzoyl derivative of benzaldehyde thiadiazolylhydrazone. (Found: C 62.5; H 4.00; N 18.0; S 10.3. $C_{16}H_{12}N_4OS$ (308.35) requires C 62.3; H 3.92; N 18.2; S 10.4). λ_{max}: 3 350 Å with ε = 22 000.

An isomer of this compound was obtained by evaporating the mother liquor to one tenth of the original volume. First, unchanged starting material was deposited (0.6 g) and in the filtrate a further amount of crystalline material (0.5 g, 16 % yield) was deposited, m. p. 95—96° after recrystallization from 70 % aqueous ethanol. (Found: C 62.5; H 4.00; N 18.0; S 10.3.) λ_{max}: 2 780 Å with ε = 19 500.

Acetophenone thiadiazolylhydrazone (VI, R = H, R_1 = CH_3, R_2 = Ph). Monoacetophenone thiocarbohydrazone (4.2 g) and triethyl orthoformate (5 ml) were refluxed for 30 min, and then the ethanol and ester were taken off *in vacuo*. The slightly sticky residue was stirred with ethanol (10 ml), and the undissolved material (2.6 g, 60 % yield) crystallized from absolute ethanol as colourless needles, m. p. 198—199°. (Found: C 54.8; H 4.61; N 25.7; S 14.7. $C_{10}H_{10}N_4S$ (218.27) requires C 55.0; H 4.62; N 25.7; S 14.7.) λ_{max}: 3 110 Å with ε = 20 000, λ_{max}: 2 260 Å with ε = 13 000.

5-Methyl-1,3,4-thiadiazol-2-yl-hydrazones (VI, R = CH_3)

By refluxing monoacetone and monobenzaldehyde thiocarbhydrazones with triethyl orthoacetate and working up the solutions as above, low yields of the methyl analogues of the compounds just described were obtained.

Acetone 5-methyl-1,3,4-thiadiazol-2-yl-hydrazone (VI, R = R_1 = R_2 = CH_3) was obtained in 27 % yield and crystallized from absolute ethanol as colourless prisms, m. p. 176—177°. (Found: C 42.4; H 5.92; N 32.9; S 18.8. $C_6H_{10}N_4S$ (170.23) requires C 42.3; H 5.92; N 32.9; S 18.8.) λ_{max}: 2 800 Å with ε = 15 000.

When the mother liquor was made alkaline, and benzyl chloride was added, a 19 % yield of 3-benzylthio-4-amino-5-methyl-4,1,2-triazole [2] was obtained.

Benzaldehyde 5 methyl-1,3,4-thiadiazol-2-yl-hydrazone (VI, R = CH_3, R_1 = H, R_2 = Ph) was obtained in 8 % yield and crystallized from absolute ethanol as colourless needles, m. p. 212—213°. (Found: C 55.2; H 4.71; N 25.6; S 14.6. $C_{10}H_{10}N_4S$ (218.27) requires C 55.0; H 4.62; N 25.7; S 14.7.) λ_{max}: 3 240 Å with ε = 23 800, λ_{max}: 2 300 Å with ε = 12 700.

In the extraction with potassium carbonate solution, a 55 % yield of 3-mercapto-4-benzylidenamino-5-methyl-4,1,2-triazole [12] was obtained.

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