Five-membered Heterocyclic Thiones. Part III.[1] 1,2,5-Thiadiazole-3-thiones

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Stable salts of 3-mercapto-1,2,5-thiadiazoles were prepared by the alkaline hydrolysis of the corresponding *N,N*-dimethylthionocarbamates.

Les sels stables de mercapto-3 thiadiazoles-1,2,5 ont été préparés par l'hydrolyse alcaline des *N,N*-diméthylthionocarbamates correspondants. [Traduit par le journal]

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During the past decade, the chemistry of 1,2,5-thiadiazoles has been investigated in considerable detail (2). These studies have encompassed, among other compounds, the remarkably stable, completely enolic, 3-hydroxy derivatives. The corresponding 3-mercapto compounds have not heretofore been described, although at least one unsuccessful attempt to prepare such substances has been reported (3). This publication describes the synthesis of stable salts of two 3-mercapto-1,2,5-thiadiazoles, one of which is the parent member of the series.

The preparation of the title compounds (see Scheme 1) was based on the rearrangement of thionocarbamates to thiolcarbamates which has been successfully utilized by Newman and Karnes for the conversion of phenols to thiophenols (4). The method was first applied to 4-cyano-3-hydroxy-1,2,5-thiadiazole because it was considered that an electron-withdrawing group at C-4 would impart added stability to the product **5**, irrespective of whether it existed in the thione or the thiol form. Oxygen acylation of **1** (R = CN) was easily accomplished with dimethylthiocarbamyl chloride, and the thionocarbamate thus produced (**2**, R = CN; $\nu_{C=S}$ = 1562 cm^{-1}; see Table 1) rearranged to the thiolcarbamate (**3**, R = CN; $\nu_{C=O}$ = 1693 cm^{-1}) at 130°. Hydrolysis of the thiolcarbamate occurred in refluxing ethanolic potassium hydroxide solution and was accompanied by the expected hydration of the nitrile function. The crude, stable, potassium salt (**4**, M = K) was characterized as the 4-methoxycarbonylmethyl derivative (**6**, R = $CONH_2$, R′ = CH_3)[3] and as the readily purifiable dicyclohexylammonium salt (**4**, M = $(C_6H_{11})_2NH_2$).

In a manner similar to that described above, the parent hydroxy thiadiazole (**1**, R = H) gave a thionocarbamate (**2**, R = H), the rearrangement of which required more vigorous conditions (170°, 3 h) than did the aforementioned cyano analog (**2**, R = CN). Hydrolysis of the thiolcarbamate (**3**, R = H) was effected in the usual manner to give a mixture of salts from which a crystalline mercuric salt (M = Hg/2) could be obtained with ease. The presence of the thiolate in the salt mixture was further substantiated by the preparation of the 4-carboxymethyl derivative (**6**, R = R′ = H; obtained by saponification of the crude, oily, methyl ester).[3]

The thiols derived from the above salts were much less stable than the corresponding hydroxy compounds. Indeed, extraction of the acidified aqueous solution of the crude potassium salt of the parent thiol failed to yield any alkali soluble

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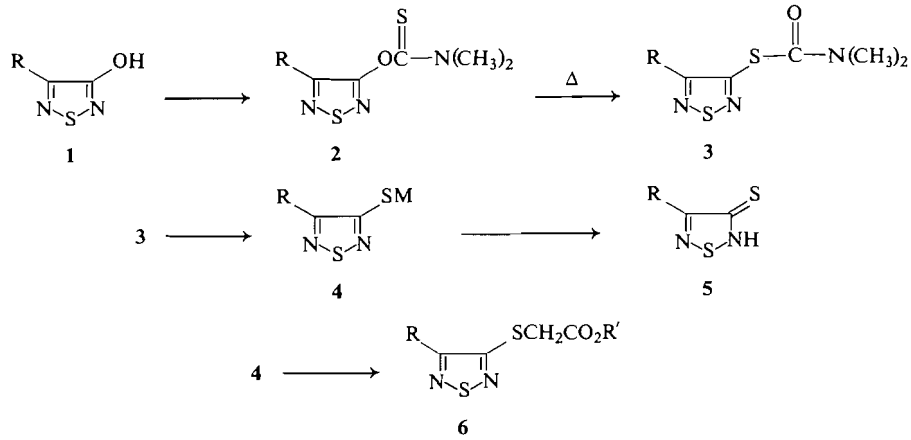
[3]A referee has expressed some reservations concerning the assigned site of alkylation of the ambident anionic system in the salts **4** (R = H, $CONH_2$). In our opinion there can be little doubt that *S*- and not *N*-alkylation occurred in view of the well-known fact that a wide variety of compounds containing the —N—C=S system alkylate, either as the neutral or the anionic species, essentially exclusively on sulfur (6). Indeed, we are unaware of deviations from this pattern irrespective of whether the —N—C=S group is incorporated in an heterocyclic or an acyclic system.

Finally, the n.m.r. spectra (see Table 1) of compounds **6** (R = H, R′ = CH_3 and R = $CONH_2$, R′ = CH_3) are consistent with the assigned structure (*e.g.* the —SCH_2— group in 2-allylthiobenzothiazole appears at δ 3.95 (7)).



SCHEME 1

TABLE 1. Spectral properties of some 1,2,5-thiadiazoles

Compound	I.r. (cm^{-1})[a]	U.v. spectra[b] λ_{max}(mμ)(log ε)	N.m.r. δ (p.p.m.)[c]
2 (R = H)	3090, 1561[d]	206(3.68), 253(4.24)	3.40(3H), 3.45(3H), 8.50(1H)
2 (R = CN)	2240, 1562[e]	206(3.71), 256(4.30)	
3 (R = H)	3095, 1681[d]	210(3.87), 278(3.94)	3.12(6H), 8.92(1H)
3 (R = CN)	2243, 1693[e]	209(4.00), 274(3.81)	
4 (R = H)[f]	3070[g]		
4 (R = $CONH_2$)[h]	3460, 3290, 3175[g] 2820–2470 (br) 1662, 1597, 1586	209(sh.)(3.76), 233(4.11), 268(4.15), 359(3.53)	
6 (R = R′ = H)	3078, 2705–2390 (br)[g] 1716	208(3.71), 297(3.93)	3.75(3H), 4.05(2H), 8.38(1H)[i]
6 (R = $CONH_2$ R′ = CH_3	3515, 3400, 1747[e] 1698, 1584	208(sh)(3.48), 231(4.05), 242(sh)(3.97), 315(3.75)	3.75(3H), 4.05(2H), 7.58(2H, w_H = 9 Hz)[j]

[a]Recorded with a Unicam SP-200G i.r. spectrophotometer.
[b]Measured in 95% ethanol on a Unicam SP 800 u.v. spectrophotometer.
[c]Recorded in $CDCl_3$ (unless otherwise indicated) with a Varian A-60A spectrometer; all resonances were of singlet multiplicity.
[d]Liquid film.
[e]Measured in chloroform.
[f]Mercuric salt.
[g]Nujol mull.
[h]Dicyclohexylammonium salt.
[i]Spectrum of methyl ester; recorded in CCl_4.
[j]Recorded in DMSO-d_6 – $CDCl_3$ (1:2).

material. The 4-carboxamido derivative was, however, sufficiently stable to be isolable, but a specimen left at room temperature for 1 day was only 50% soluble in dilute sodium hydroxide solution.

The solution i.r. spectrum ($CHCl_3$) of 3-mercapto-4-carboxamido-1,2,5-thiadiazole (**5**, R = $CONH_2$) was devoid of absorptions in the 2600–2500 cm^{-1} region[4] showing that the thione tautomer was the major if not exclusive species present under these conditions.

[4]The SH stretching absorption of thiophene 2- and 3-thiols is reported (5) to occur in the 2540–2510 cm^{-1} region, and 2-methyl-1,2,3-triazole-4-thiol has a strong band at 2540 cm^{-1} (8).

Experimental

The melting points were determined in a Gallenkamp m.p. apparatus and are not corrected.

*3-Cyano-4-hydroxy-1,2,5-thiadiazole (**1**, R = CN)*

This compound was prepared from isonitrosocyanoacetamide and sulfur dichloride according to Ross and Smith (3) but with the following modification: The solid residue obtained after evaporation of the reaction mixture was dissolved in sodium carbonate solution (100 g/l) and the solution was washed with ether. The aqueous phase was made acidic with 10% hydrochloric acid, the product was extracted into ether, the extract was dried over sodium sulfate, treated with activated charcoal and then evaporated *in vacuo*. The residual solid (61–63% yield) had m.p. 157–160° (lit. (3) m.p. 157–160°).

*3-Hydroxy-1,2,5-thiadiazole (**1**, R = H)*

This compound was prepared from glycinamide (9) and

sulfur monochloride as described by Weinstock *et al.* (10) except that the crude product was first freed of impurities by solution in sodium carbonate, etc., as described above for the 4-cyano derivative.

4-Cyano-1,2,5-thiadiazol-3-yl-N,N-dimethylthionocarbamate (2, R = CN)

The general procedure of Newman and Karnes (4) was modified as follows: A 55% dispersion of sodium hydride in mineral oil (6.25 g) was washed with hexane, layered with dry DMF (125 ml), and cooled with stirring, in an atmosphere of dry nitrogen, to 0°. The hydroxy nitrile (16.5 g, 130 mmol) was added portionwise, and when gas evolution was complete, dimethylthiocarbamyl chloride (17.6 g, 143 mmol) was added all at once. The cooling bath was removed, and after 20 h at room temperature the solution was poured into ice-water. The mixture was extracted with benzene, the extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was crystallized from benzene – petroleum ether (b.p. 30–60°) to give a yellow solid (21.22 g, 76%), m.p. 84–87°. Recrystallization of this material (charcoal) gave an analytical specimen, m.p. 85–87°.

Anal. Calcd. for $C_6H_6N_4OS_2$: C, 33.63; H, 2.82; N, 26.15. Found: C, 33.68; H, 2.80; N, 26.20.

1,2,5-Thiadiazol-3-yl-N,N-dimethylthionocarbamate (2, R = H)

This compound was prepared in the same way as the above cyano derivative except that the crude oily thionocarbamate was purified by dry column chromatography (11) on silica gel (Brinkman, Activity II–III, 10 g/g substrate) using 2% methanol in chloroform (v/v) as the eluant. The first 200 ml of the eluate (reaction scale, 200 mmol) was discarded, and the next 600 ml contained the pure thionocarbamate (26.83 g). An additional small amount of the product (1.39 g), which was slightly contaminated with more polar substances, was contained in the next 100 ml of the eluate. The main fraction was sufficiently pure to be used in the next step. A portion of this fraction was analyzed.

Anal. Calcd. for $C_5H_7N_3OS_2$: C, 31.73; H, 3.73; N, 22.20. Found: C, 31.79; H, 3.78; N, 22.22.

4-Cyano-1,2,5-thiadiazol-3-yl-N,N-dimethylthiolcarbamate (3, R = CN)

The thionocarbamate (20.5 g, 96 mmol) was heated in an oil bath at 130° under an atmosphere of nitrogen for 40 min. The deeply-colored material was slurried with ether (800 ml), the mixture was filtered, the filtrate was treated with activated charcoal, and finally evaporated *in vacuo*. The residual yellow solid (16.03 g, 78.5%) had m.p. 74–78° and was sufficiently pure to be used in the next step. Recrystallization of this material from benzene–cyclohexane gave a white solid m.p. 79–81°.

Anal. Calcd. for $C_6H_6N_4OS_2$: C, 33.63; H, 2.82; N, 26.15. Found: C, 33.75.; H, 2.80; N, 26.20.

1,2,5-Thiadiazol-3-yl-N,N-dimethylthiolcarbamate (3, R = H)

The chromatographically pure thionocarbamate (18.6 g) was stirred in a nitrogen atmosphere at 170° for 3 h. The deeply-colored oil was dissolved in a small amount of 2% methanol in chloroform, absorbed onto silica gel (20 g, Brinkman, Act II–III) and dried *in vacuo*. This material was placed on top of a dry packed column of silica gel (200 g) and the column was developed with 2% methanol-in-chloroform (100 ml fractions). Fractions 2–3 contained the starting material (5.76 g), and fractions 4–6 contained the product (12.46 g). The recovered starting material was subjected to the above rearrangement conditions (170°, 2.5 h) and after chromatography there was obtained 1.47 g of starting material, and 4.10 g of the thiolcarbamate. The combined product was distilled to give the pure thiolcarbamate (14.12 g, 76%), b.p. 107–108°/0.05 mm. A portion of this material was redistilled for analysis.

Anal. Calcd. for $C_5H_7N_3OS_2$: C, 31.73; H, 3.73; N, 22.20. Found: C, 31.73; H, 3.76; N, 22.46.

4-Carboxamido-1,2,5-thiadiazole-3-thiol dicyclohexylammonium salt (4, R = $CONH_2$)

A solution of 4-cyano-1,2,5-thiadiazol-3-yl-*N,N*-dimethylthiolcarbamate (14.0 g, 65.5 mol) in absolute ethanol (400 ml) containing potassium hydroxide (20.4 g of a 45 wt. % solution, 164 mmol) was heated under reflux for 1 h. The yellow solid (10.0 g, 76.5%; m.p. 265–267° dec.) which separated on cooling was collected by filtration and dried *in vacuo*. This salt was not readily recrystallized, and could not be obtained analytically pure. It was, however, sufficiently pure to be used for alkylation purposes. The thiol was characterized as its dicyclohexylammonium salt which was prepared in the following manner: The crude potassium salt (1.0 g) was dissolved in water, the solution was acidified with 10% hydrochloric acid, and the product was immediately extracted into ethyl acetate. The extract was dried over sodium sulfate and evaporated *in vacuo*. The white solid which remained (594 mg, m.p. 117–121°) was immediately dissolved in ethanol and added to an equimolar amount of ethanolic dicyclohexylamine. Dilution of the solution to turbidity with ether caused the crystallization of the salt (1.01 g), m.p. 166–169°. Recrystallization gave material with m.p. 168–170°.

Anal. Calcd. for $C_3H_3N_3OS_2$:$C_{12}H_{23}N$: C, 52.60; H, 7.65; N, 16.36. Found: C, 52.38; H, 7.67; N, 16.61.

1,2,5-Thiadiazole-3-thiol mercuric salt (4, R = H)

1,2,5-Thiadiazol-3-yl-*N,N*-dimethylthiolcarbamate was hydrolyzed in the manner described for the 4-cyano derivative. The ethanolic solution of the product was evaporated *in vacuo* to give a yellow solid (17.0 g from a 74.6 mmol reaction) which was not easily freed from inorganic materials. It could be shown by alkylation with methyl bromoacetate or by conversion to the mercuric salt, that the above mixture contained *ca.* 62% by weight of the potassium salt. This therefore corresponded to a 90% yield of the thiolate. The mercuric salt was prepared as follows: A solution of the crude salt (1.26 g, 5 mmol) was dissolved in water and the p*H* of the solution (p*H* meter) was adjusted to p*H* 7 by the addition of a few drops of glacial acetic acid. A solution of mercuric acetate (0.8 g, 2.5 mmol) in water (10 ml) was added and the precipitated solid (1.0 g), m.p. 177–180°, was collected by filtration and dried *in vacuo*. Crystallization of this solid from acetone gave material with m.p. 177–179°.

Anal. Calcd. for $C_2HN_2S_2$:0.5 Hg: C, 11.05; H, 0.46; N, 12.88. Found: C, 11.10; H, 0.58; N, 12.98.

4-Carboxamido-3-methoxycarbonylmethylthio-1,2,5-thiadiazole (6, R = H, R′ = CH_3)

The crude potassium salt described above (1.99 g, 10 mmol) and methylbromoacetate (1.8 g, 11.8 mmol) in

methanol (10 ml) was heated under reflux for 1 h. The solution was evaporated *in vacuo*, the residue was treated with hot benzene and filtered. The filtrate on cooling deposited a crystalline solid (1.12 g, 48%) m.p. 144.5–146°. Recrystallization gave material with m.p. 145–146°.

Anal. Calcd. for $C_6H_7N_3O_3S_2$: C, 30.89, H, 3.03; N, 18.01. Found: C, 30.84; H, 3.05; N, 17.88.

3-Carboxymethylthio-1,2,5-thiadiazole (6, R = R′ = H)

(a) From Crude Potassium-1,2,5-thiadiazole-3-thiolate

A solution of the crude salt (1.06 g) in methanol (50 ml) containing an excess of ethyl bromoacetate (1.9 g, 12.4 mmol) was heated at reflux temperature for 1 h. The cooled mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with water, and the product was extracted into dichloromethane. The extract was dried over sodium sulfate, the solvent was removed *in vacuo*, and the residue was evaporatively distilled at 95–105°/0.05 mm to give the ester (803 mg, 4.23 mmol). On the basis of the yield of the ester obtained, the crude salt described above contained a minimum of 62% by weight of the potassium thiolate. Redistillation of the ester (b.p. 72–74°/0.005 mm) did not remove a small amount of an impurity (< 10%). The ester was therefore saponified as follows. A solution of the ester (380 mg, 2 mmol) in 50% aqueous methanol (20 ml) containing 45 wt. % aqueous potassium hydroxide (250 mg, 2 mmol) was boiled under reflux for 1.25 h. Most of the methanol was removed *in vacuo*, the residue was extracted with benzene, and the aqueous phase was then made acidic with 10% hydrochloric acid. The product crystallized (326 mg, 92%) and had m.p. 127–129°. Two recrystallizations of this material from water gave a solid with m.p. 128–129°.

Anal. Calcd. for $C_4H_4N_2O_2S_2$: C, 27.26; H, 2.29; N, 15.90. Found: C, 27.05; H, 2.31; N, 15.97.

(b) From the Mercuric Salt

Following the method of Soderback (12) for the conversion of mercuric thiolates to sodium thiolates, the mercuric salt (784 mg, 1.8 mmol) was added portionwise to a stirred solution of sodium sulfide nonahydrate (385 mg, 1.6 mmol) in water at 0°. After 30 min at 0°, the test for soluble sulfide ion (sodium plumbite solution) was negative. The mixture was filtered through Celite, the filtrate was diluted with methanol (50 ml), and methyl bromoacetate (400 mg, 2.63 mmol) was added. The solution was heated at reflux temperature for 1 h and then processed in the manner described above to give the crude ester which was saponified without purification. There was obtained a solid (145 mg, 31% based on methyl bromoacetate), m.p. 126–127° identical to the carboxylic acid prepared by method *a*.

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