Five-membered Heterocyclic Thiones. Part IV.[1] 1,2,4-Thiadiazole-3-thiolates and 1,2,4-Thiadiazole-5-thione

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1,2,4-Thiadiazole-5-thione (**2***a*) was synthesized from the corresponding 5-bromo compound. An alternative synthesis of the known 3-methyl-1,2,4-thiadiazole-5-thione is described. It was shown by i.r. spectroscopy that the parent compound and its 3-methyl derivative existed in the thione form in the solid state.

Mercuric-1,2,4-thiadiazole-3-thiolate (**5**) was prepared by cleavage of the corresponding disulfide with mercury. The mercuric salt was converted to a stable (in solution) sodium salt, but the free thio compound was not isolable.

Le thiadiazole-1,2,4 thione-5 (**2***a*) a été synthétisé à partir du composé correspondant bromo-5. On décrit une nouvelle synthèse du composé connu suivant, le méthyl-3 thiadiazole-1,2,4 thione-5. Il a été montré à l'aide de la spectroscopie i.r. que le composé parent et son dérivé méthyl-3 existe à l'état solide sous la forme thione.

Le thiolate-3 mercurique de thiadiazole-1,2,4 (**5**) a été préparé par clivage à l'aide du mercure du disulfure correspondant. Le sel mercurique a été converti en un sel de sodium stable (en solution) mais le composé thio libre n'a pu être isolé. [Traduit par le journal]

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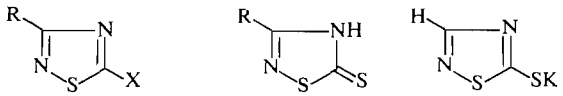
There are two possible 1,2,4-thiadiazole thiols, and ring-substituted representatives of each isomer are known (2,3), but the parent members have not, to our knowledge, been previously described.

3-Substituted-1,2,4-thiadiazole-5-thiones (**2**, Scheme 1) are easily prepared (4) by the base-promoted fragmentation of the corresponding isothiouronium salts (*e.g.*, **1***b*, **1***e*) which in turn are obtained from the readily available (4–7) 5-chloro compounds (1, X = Cl) and thiourea. When the conditions are suitably modified, this method is also applicable to the synthesis of the parent thione (**2***a*).



1 **2** **3**

a R = H; X = Br

b R = H; X = $S-\overset{+}{C}(NH_2)-NH_2\ Br^-$

c R = H; X = SCH_3

d R = CH_3; X = Cl

e R = CH_3; X = $S-\overset{+}{C}(NH_2)-NH_2\ Cl^-$

f R = CH_3; X = $S-P(=O)(ONa)_2$

a R = H
b R = CH_3

SCHEME 1

The isothiouronium bromide **1***b* (prepared in the usual way from the bromo compound **1***a*), when treated with slightly less than 2 equiv of alkali at room temperature, followed by careful acidification to p*H* 3, gave the crystalline thione **2***a* in 52% overall yield. The structure of this compound was fully substantiated by its elemental analysis and spectral properties (see Table 1), and by conversion to a very stable potassium salt **3** and an oily *S*-methyl ether **1***c*.

The known 3-methyl analog **2***b* of **2***a* was prepared (for comparative purposes) from **1***d* via the isothiouronium salt **1***e* according to the published procedure (4). This thione could also be obtained by the acid-catalyzed decomposition of the salt **1***f* which was prepared from the chloro compound **1***d* and trisodium thiophosphate. This latter substance has often been used to prepare aliphatic thiols from the corresponding halo alkanes (see ref. 8 for example),[3] but to our knowledge it has not heretofore been utilized for the synthesis of heterocyclic thiones.

[1]For Part III, see ref. 1.

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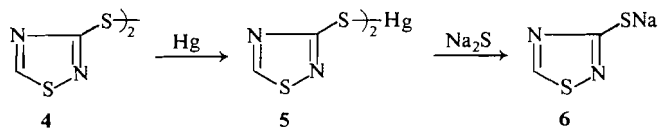
[3]We thank Dr. T. Conway of these laboratories for suggesting the use of this reagent.

TABLE 1. Spectral properties of some 1,2,4-thiadiazole-5-thiones and related compounds

Compound	N.m.r. δ (p.p.m.)[a]	Solvent	I.r. (cm^{-1})[b]
3	8.28 (1H)	DMSO-d_6	1380, 1260, 1180, 1036, 862[c]
2*a*	8.82(1H), 11.98(1H, w_H = 44 Hz)	D_2O	3460, 2660, 1535, 1440, 1298, 1222, 1070, 900, 838, 790[d]
1*c*	2.80(3H), 8.58(1H)	$CDCl_3$	3075, 1463, 1434, 1345, 1321, 1275, 1174, 1063, 1048, 971, 911, 866, 755[e]
2*b*	2.27(3H), 12.85(1H, w_H = 58 Hz)	DMSO-d_6	3450, 3050, 2665, 1592, 1562, 1476, 1421, 1320, 1233, 1095, 1083, 980, 749[d]

[a]Measured with a Varian A-60A spectrometer; all resonances were of singlet multiplicity.
[b]Recorded with a Unicam SP-200G i.r. spectrophotometer.
[c]Nujol mull.
[d]Recorded in KBr.
[e]Liquid film.



4 5 6 7

SCHEME 2

3-Mercapto-5-substituted-1,2,4,-thiadiazoles are prepared in several ways (ref. 2, pp. 567–573 and ref. 3, pp. 147–150) none of which is general. The parent member of this series was obtained from the known (9) disulfide **4** (Scheme 2) in a manner identical to that described by Soderback (10) for the preparation of the 5-chloro analog. Thus, cleavage of the above disulfide with mercury gave the stable mercuric salt **5** of 1,2,4-thiadiazole-3-thiol, which was transformed to the corresponding sodium salt **6** with sodium sulfide. The stability of the free thio compound was minimal since extraction of an acidified aqueous solution of the sodium salt did not result in the isolation of any alkali soluble material. Furthermore, it was not possible to isolate the sodium salt **6**, but its presence in solution was confirmed by transformation to the known (11) crystalline *S*-methyl ether **7**.

The solid state i.r. spectrum of 1,2,4-thiadiazole-5-thione (**2***a*) and its 3-methyl analog **2***b* were devoid of absorptions in the 2600–2500 cm^{-1} region,[4] showing that the thione tautomer predominated under these conditions. This contention is supported by the presence of a strong band, tentatively assigned to the C=S stretching

[4]A referee has suggested that the absorption at 2660 cm^{-1} for **2***a* cannot be ignored. In fact, it is exceedingly unlikely that this band is due to the mercapto form of **2***a*, since it is well-known that the SH stretching absorption of a wide variety of mercaptans occurs within the specified region (12). For example, for thiophene-2- and 3-thiols this absorption occurred at 2540–2510 cm^{-1} (13), while isoxazole-5-thiols absorbed at 2550 cm^{-1} (14), and 2-methyl-1,2,3-triazole-4-thiol had a strong band at 2540 cm^{-1} (15). The absence of an absorption in this region for compounds in which thione–thiol tautomerism is possible is now generally considered to be diagnostic of the thione form (16).

U.v. spectroscopy is also often utilized for the study of thione–thiol tautomerism. To be useful, however, the u.v. of an *N*-alkyl and an *S*-alkyl derivative must be compared to that of the thione (thiol), and even then a definite conclusion is often not possible (16).

vibration, at 1222 cm^{-1} in **2***a* and 1233 cm^{-1} in **2***b*.[5]

Experimental

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

*1,2,4-Thiadiazole-5-thione (**2***a*) *and potassium-1,2,4-thiadiazole-5-thiolate (**3**)*

A solution of 5-bromo-1,2,4-thiadiazole (9.10 g, 59.5 mmol (19)), in absolute ethanol (250 ml) containing thiourea (4.50 g, 59.1 mmol) was boiled under reflux in a nitrogen atmosphere for 2 h. The solution was evaporated to 50 ml *in vacuo*, 1 *N* sodium hydroxide (118 ml) was added, and the resultant was stirred at room temperature in an atmosphere of nitrogen for 20 min. The solution was extracted with ether (discarded) and the aqueous phase was made acidic to p*H* 3 (p*H* meter) with 4 *N* sulfuric acid. The product was extracted into ether, the extract was dried over sodium sulfate, and evaporated *in vacuo* ($T \leq 20°$) to give the crude crystalline thiol. This material could not be recrystallized; for analysis a small portion of this substance was sublimed at 65°/0.005 mm to give a solid m.p. 93°.

Anal. Calcd. for $C_2H_2N_2S_2$: C, 20.33; H, 1.71; N, 23.71. Found: C, 20.06; H, 1.62; N, 23.90.

The crude thiol from above was dissolved in absolute ethanol (25 ml), an equimolar amount of 1 *N* alcoholic potassium hydroxide was added, and the solution was diluted with dry ether (400 ml). The solid (4.27–5.11 g, 46–55% based on the bromo compound), m.p. 220° dec. was collected by filtration. Crystallization of this material from ethanol–ether (2:3) did not raise the melting point.

Anal. Calcd. for $C_2HN_2S_2K$: C, 15.37; H, 0.65; N, 17.93. Found: C, 15.53; H, 0.74; N, 17.92.

*5-Methylthio-1,2,4-thiadiazole (**1***c*)

A mixture of methyl iodide (3.42 g, 24 mmol) and water (45 ml) containing potassium-1,2,4-thiadiazole-5-thiolate (2.50 g, 16 mmol) was stirred at room temperature for 18 h. The product was extracted into dichloromethane, the extract was dried over sodium sulfate, and evaporated *in vacuo*. The residual oil was distilled at reduced pressure, and a fraction (1.62 g, 77%), b.p. 30–32°/0.1 mm was collected.

Anal. Calcd. for $C_3H_4N_2S_2$: C, 27.25; H, 3.05; N, 21.19. Found: C, 27.36; H, 3.05; N, 21.28.

*1,2,4-Thiadiazol-3-yl Disulfide (**4**)*

The 3-*t*-butylthio-1,2,4-thiadiazole which was required, was prepared by the method of Goerdeler and Budnowski (11) from *t*-butylisothiouronium chloride (20) and dichloromethanesulfenyl chloride (11). It contained an impurity which lacked an aromatic proton absorption in the n.m.r. spectrum. Although this material could be removed at this stage by column chromatography on silica gel, in general it was more conveniently separated at the disulfide stage. The disulfide, was prepared by the partial chlorination (9) of the above sulfide, but the quantity of chlorine was adjusted to the true sulfide content as determined from the n.m.r. spectrum. The crude product was purified by dry column chromatography (21) on silica gel (Brinkman, *ca.* Act. II, 20 g/g of substrate) using chloroform as the eluant. A portion (13 g) of the disulfide when purified in this way (100 ml fractions) gave a crystalline solid (8.4 g, from fractions 16–25), m.p. 116–119° (reported (9) m.p. 119°). The n.m.r. spectrum (1:1 DMSO-d_6 – $CDCl_3$) consisted of a singlet at δ 10.38.

*Mercuric-1,2,4-thiadiazole-3-thiolate (**5**)*

The cleavage of the disulfide was effected by the method of Soderback (10). A mixture of the disulfide (3.4 g, 14.5 mmol), mercury (10 ml), and dry ether (100 ml) was shaken mechanically for 18 h. The ether was decanted and the residual mixture was suspended in ether and decanted from the mercury. The product was collected by filtration, and dried *in vacuo*. It had m.p. 195° dec. (6.2 g, 98%) and could be recrystallized from a large amount of benzene, but the melting point was not improved.

Anal. Calcd. for $C_4H_2N_4S_4Hg$: C, 11.05; H, 0.46; N, 12.88. Found: C, 11.15; H, 0.53; N, 12.97.

*Generation of Sodium-1,2,4-thiadiazole-3-thiolate in situ and Preparation of 3-Methylthio-1,2,4-thiadiazole (**7**)*

The method described by Soderback (10) was used. The above mercuric salt (1.01 g, 2.32 mmol) was added at 0° to a stirred solution of sodium sulfide nonahydrate (504 mg, 2.1 mmol) in water (50 ml). The mixture was stirred in a nitrogen atmosphere at 0° for ½ h, methyl iodide (640 mg, 4.5 mmol) was added, and stirring at room temperature was then maintained for 18 h. Ether was added to the mixture, and after thorough agitation the mixture was filtered through Celite. The ether phase was separated, dried over sodium sulfate, and evaporated *in vacuo*. The residual oil was distilled to give a fraction b.p. 38–40°/0.05 mm (500 mg, 90%). On crystallization from petroleum ether (b.p. 30–60°) at −70°, a solid, m.p. 32° (reported (11), m.p. 32.5°), with physical properties different from 5-methylthio-1,2,4-thiadiazole, was obtained. The n.m.r. spectrum (CCl_4) showed two singlets at δ 2.73 (3H) and 9.88 (1H).

*3-Methyl-1,2,4-thiadiazole-5-thione **2**b*

A mixture of the chloro thiadiazole (**1***d*; 1.34 g, 10 mmol) and an aqueous solution of trisodium thiophosphate (3.40 g, 20 mmol) was stirred at room temperature until solution of the chloro compound had occurred (66 h). The solution was extracted with benzene, and the aqueous phase was made acidic with concentrated hydrochloric acid at 0°. The solid which precipitated (1.27 g, 96%) had m.p. 147–149° (reported (4), m.p. 151°) and was spectroscopically (i.r., n.m.r.) indistinguishable from the thiol prepared by the isothiouronium salt method (4).

[5]The position of this absorption varies considerably (17, 18) and its diagnostic value is thus limited.

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