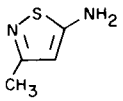
4-Acyl-1,2,3-thiadiazoles from 4-Aminoisothiazoles

F. T. Lee and G. P. Volpp

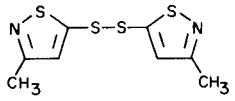
FMC Corporation, Central Research Department

When preparing heterocyclic disulfides, we encountered an interesting rearrangement involving the 4-isothiazolediazonium salt and thiourea. Aromatic diazonium salts have long been known to react with aqueous thiourea to give the corresponding thiophenols (1). Recently, Kealy and Freiser (2) reported the preparation of 8-mercaptoquinoline from 8-aminoquinoline and thiourea. The method was described as rapid and simple with much improvement in yield as compared to other methods.

When diazotized 5-amino-3-methylisothiazole (I) and aqueous thiourea were reacted, followed by oxidation of the intermediate thiol, the expected bis(3-methylisothiazol-5-yl) disulfide (II) was isolated in 60% yield.



I



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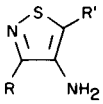
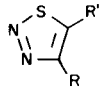


III R = CH_3, R' = H
IV R = H, R' = H
V R = H, R' = CH_3



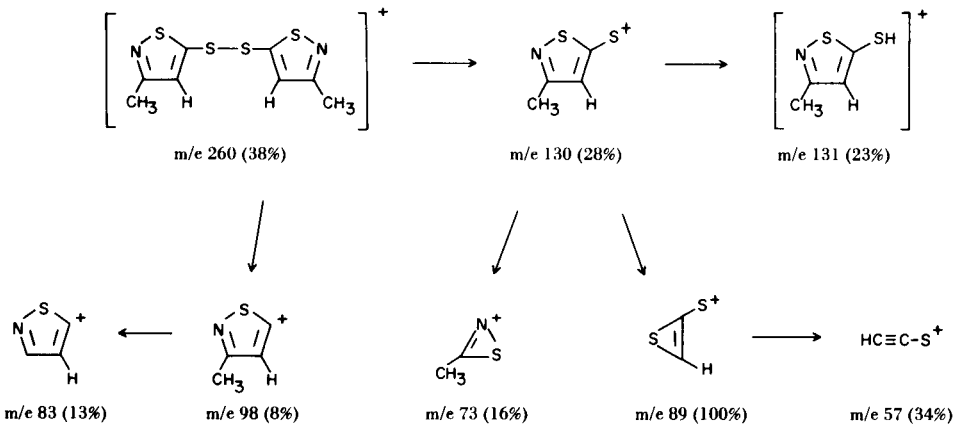
VI R = $COCH_3$, R' = H
VII R = CHO, R' = H
VIII R = CHO, R' = CH_3
IX R = COOH, R' = H

The mass spectrum of the disulfide II showed a base peak at 89 resulting from homolysis and fragmentation of the molecular ion with loss of acetonitrile. The main fragmentation pattern is shown in Scheme I and is compatible with the mass spectra of diphenyl disulfide (3) and of other isothiazoles (4,5).

When 4-amino-3-methylisothiazole (III) was diazotized and reacted with thiourea under identical conditions a new product (VI) was obtained instead of bis(3-methylisothiazol-4-yl)disulfide. Compound VI had a strong ir absorption band at 5.85 μm indicative of a carbonyl group. The nmr spectrum (in deuteriochloroform) showed two singlets at 2.95 (3H) and 9.32 ppm (1H) downfield from internal TMS. The proton signal at 2.95 ppm would be in accord with the methyl proton signal of an alkyl aryl ketone or heterocyclic alkyl ketone. The proton signal at 9.32 ppm was too far downfield to be caused by the 5-hydrogen on the isothiazole ring unless there was a strong electron withdrawing group in the 4-position. The chemical shifts for the 5-hydrogen in 4-cyano-3-methylisothiazole and 3-methylisothiazole are 9.17 and 8.55 ppm, respectively. The neighboring disulfide grouping would have a minimal impact on the 5-hydrogen in bis(3-methylisothiazol-4-yl) disulfide. The disulfide group in II shifts the 4-hydrogen only 0.03 ppm downfield as compared with 3-methylisothiazole.

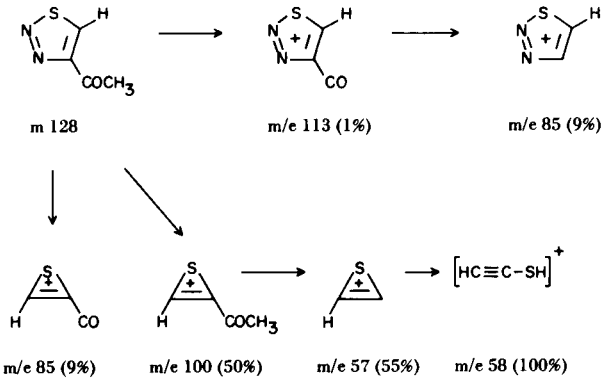
The mass spectrum of ketone VI had no molecular ion

SCHEME I



at m/e 128 which would have confirmed the elemental composition $C_4H_4N_2OS$. The structure of 4-acetyl-1,2,3-thiadiazole (VI) is, however, in good agreement with the observed fragmentation of VI with loss of N_2, CH_3, CO. A possible fragmentation pattern is depicted in Scheme II.

SCHEME II



When the ionization voltage was lowered from 70 to 15 V the relative intensity of the signal m/e 100 increased from 50% to 95%, whereas at both voltages the relative intensity of m/e 85 remained the same. Fragment m/e 85 must be predominantly formed from a precursor other than m/e 100.

The presence of the 3-methyl substituent in III is not essential for the observed conversion. When 4-amino-isothiazole (IV) and 4-amino-5-methylisothiazole (V) were subjected to diazotization and reaction with thiourea 4-formyl-1,2,3-thiadiazole (VII) and 4-formyl-5-methyl-1,2,3-thiadiazole (VIII) were formed as the major products.

The structural assignment of these new thiadiazoles is based on elemental analysis, and the following spectral data. The ir spectra of VII and VIII had carbonyl absorptions at 5.82 and 5.88 μm and were generally similar to the ir of 4-acetyl-1,2,3-thiadiazole (VI). The nmr spectrum of VII in δ-DMSO showed only two singlets of equal intensities at 9.4 and 10.56 ppm downfield from internal TMS. These signals could be ascribed to the 5-hydrogen and the formyl-hydrogen of VII. The spectrum of VIII had two singlets whose intensity ratio was 3:1 at 2.92 and 9.26 ppm assignable to the 5-methyl- and the 4-formyl-hydrogen in VIII. The fragmentation observed in the mass spectrum of VII and VIII was very similar to the one of VI as evident from Table I.

That the rearrangement products VI-VIII were indeed derivatives of 1,2,3-thiadiazole was shown by mild oxidation of the aldehyde VII with acidic potassium permanganate. The carboxylic acid IX isolated as sole product was identified with an authentic sample of 1,2,3-thiadiazole-4-carboxylic acid (6) by melting point, mixed melting point, ir and nmr spectra.

TABLE I

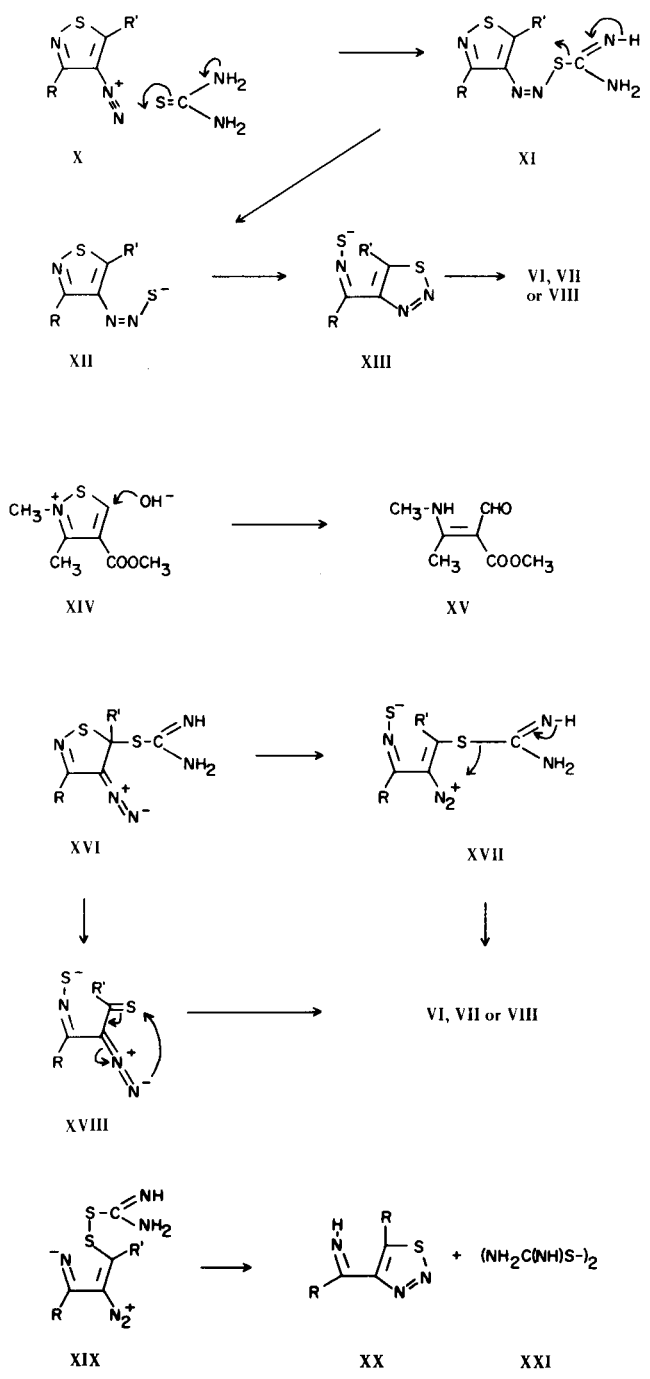
Mass Spectral Fragments (70V)

VI (128)	m/e			113	100		85		58	57
	%			1	50		9		100	55
VII (114)	m/e					86	85	70	58	57
	%					37	5	10	100	88
VIII (128)	m/e	128	113	100		85	72		58	57
	%	0.14	0.42	23		7	1		100	57

While a study of the reaction mechanism was beyond the scope of our work, we wish to present three mechanisms of which the third one can be eliminated by the experimental observations. In analogy to the known (1) formation of *S*-diazo compounds from diazonium salts and thiolo compounds, like thiolsulfuric acid, thioformic acid, xanthates, etc., one may assume that thiourea is added to the 4-diazonium group in X to give a *S*-diazo-isothiazole XI. The latter can fragment to cyanamide and the diazothiolate XII which could rearrange to the thiadiazole XIII. This imine XIII would lose sulfur and ammonia with formation of the observed 4-keto substituted 1,2,3-thiadiazoles VI-VIII. While the first step in this sequence is close to available analogies no precedent could be found for the addition-elimination required from XII to XIII.

The second mechanism assumes the addition of thiourea to the 5-position of X rather than to the diazo group. The 4,5-double bond in X is in conjugation with a positive charge and the 5-position should be subject to nucleophilic attack similar to the known attack of hydroxyl ion on the 5-position of quarternary isothiazoles. In the latter case fragmentation with elimination of sulfur and formation of an enaminoaldehyde follow as illustrated by structures XIV and XV. After the addition of thiourea to the 5-position has taken place two paths are open for the anion XVI. The diazonium group and the 4,5-double bond may be restored with concomitant opening of the isothiazole ring to give XVII, or cyanamide may be lost and a species XVIII formed which would be expected to close to the 1,2,3-thiadiazole system. In each case loss of sulfur and hydrolysis would complete the conversion to the acetylthiadiazole VI and the formylthiadiazoles VII and VIII.

A third mechanism can be postulated when one considers the known attack of strong nucleophiles like the butyl or phenyl anion on isothiazole (7). In this case



iminothio ethers are formed. The attack of thiourea on the isothiazolediazonium salt X would be expected to lead to structure XIX which could be protonated and then react with a second molecule of thiourea with formation of the iminothiadiazole XX and the formamidine disulfide XXI.

The isolation of sulfur from each of the reactions of an isothiazole-4-diazonium salt with thiourea and the absence of the known (8) XXI in the reaction mixture speaks against the third mechanism. Each of the first two mechanisms is compatible with the available evidence.

EXPERIMENTAL (9)

Bis(3-methylisothiazol-5-yl) Disulfide (II).

With slight modification, disulfide II was prepared according to the procedure of Kealy and Freiser as given in their preparation of 8-mercaptoquinoline (2).

5-Amino-3-methylisothiazole (12.5 g., 0.11 mole) was dissolved in 12 *N* sulfuric acid (23.5 g. of concentrated sulfuric acid in 16.5 ml. of water). The acid solution was cooled to 0-5° and an aqueous solution of sodium nitrite (7.7 g., 0.11 mole in 20 ml. of water) was added. After dilution with 50 ml. of water, the diazonium salt was added in small portions to an aqueous solution of thiourea (9 g., 0.11 mole in 100 ml. of water) kept at 50-55°. The decomposition occurred smoothly as evidenced by the evolution of nitrogen. Heating was maintained until no nitrogen was given off. The mixture was then cooled to room temperature and made alkaline (*p*H 8~9) with sodium carbonate powder. A small amount of a black oily residue was extracted into chloroform and discarded as an impurity. The basic solution was then oxidized with a slight excess of 6% aqueous hydrogen peroxide (20 ml. of 30% hydrogen peroxide in 80 ml. of water). The disulfide separated out as a dark oil and was taken up in chloroform. The combined extracts were washed with dilute hydrochloric acid, water and then dried. After the chloroform was removed *in vacuo*, the oily residue solidified upon cooling with Dry Ice to give 6.6 g. of crude disulfide II, m.p. 37-39°. The crude product was best purified by passing a benzene solution through neutral alumina. Pure bis(3-methylisothiazol-5-yl) disulfide melted at 44-47°; ir (chloroform), 6.72, 6.94, 7.25, 7.38 μm; nmr (deuteriochloroform), 2.49 (s, 3), 7.08 (s, 1) ppm.

Anal. Calcd. for $C_8H_8N_2S_4$: C, 36.96; H, 3.10. Found: C, 37.18; H, 3.23.

4-Acetyl-1,2,3-thiadiazole (VI).

4-Amino-3-methylisothiazole (III, 5.0 g., 0.044 mole) was diazotized in 12 *N* sulfuric acid by adding sodium nitrite solution (3.0 g. in 8 ml. of water) at 0-5°. The diazonium salt solution was then slowly added to an aqueous solution of thiourea (3.6 g. in 40 ml. of water) kept at 50-55°. A red-brown precipitate formed which was separated by filtration and triturated with boiling benzene. The remaining solid melted at 210-212° with decomposition. The benzene extracts were combined and the solvent removed *in vacuo*. The remaining solid (1.0 g.) was purified by vacuum sublimation. Additional VI was obtained from the above aqueous solution. When the solution was made basic and treated with 6% hydrogen peroxide an oil separated which partitioned into chloroform. After washing and removal of the solvent another 0.6 g. of VI was isolated. Pure 4-acetyl-1,2,3-thiadiazole melted at 95-97°; ir (chloroform), 3.18, 5.85, 6.80, 7.05, 7.35, 7.69, 10.72 and 11.90 μm; nmr (δ-DMSO), δ 2.82 (s, 3), 9.9 ppm (s, 1); (deuteriochloroform), δ 2.95 (s, 3), 9.32 ppm (s, 1).

Anal. Calcd. for $C_4H_4N_2OS$: C, 37.51; H, 3.15; N, 21.87; S, 25.00. Found: C, 37.39; H, 3.00; N, 21.57; S, 24.80.

4-Formyl-1,2,3-thiadiazole (VII).

4-Aminoisothiazole (IV, 5.0 g., 0.046 mole) was diazotized in 12 *N* sulfuric acid with sodium nitrite (3.1 g. in 8 ml. of water) and reacted with thiourea (3.8 g. in 42 ml. of water) at 45° as described above. A brown solid separated which analyzed for 96.3% sulfur. The aqueous filtrate was extracted with dichloromethane.

On removal of the solvent a white crystalline solid resulted which gave 3.0 g. of pure VII on vacuum sublimation, m.p. 86-87°; ir (chloroform), 3.17, 3.27, 5.82, 6.80, 8.98, 10.10, 11.20 μm; nmr. (δ-DMSO), δ 9.4 (s, 1), 10.56 ppm (s, 1).

Anal. Calcd. for $C_3H_2N_2OS$: C, 31.57; H, 1.76; N, 24.55. Found: C, 31.33; H, 1.77; N, 24.43.

4-Formyl-5-methyl-1,2,3-thiadiazole (VIII).

4-Amino-5-methylisothiazole (V, 4.0 g., 0.035 mole) was diazotized in 7.3 *N* sulfuric acid with sodium nitrite (2.4 g. in 6.4 ml. of water) and reacted with thiourea (2.9 g. in 32 ml. of water) as described above. Some oily material separated which was taken up in chloroform. The chloroform was removed and the residue extracted with ether. The ether insoluble part of the residue proved to be sulfur. The ether soluble material afforded on sublimation pure VIII, m.p. 94-96°; ir (chloroform), 3.4, 5.88, 6.85, 7.38, 7.70, 7.79 and 11.20 μm; nmr (deuteriochloroform), δ 2.92 (s, 3), 9.26 ppm (s, 1).

Anal. Calcd. for $C_4H_4N_2OS$: C, 37.51; H, 3.15; N, 21.87. Found: C, 37.61; H, 3.00; N, 21.89.

12,3,-Thiadiazole-4-carboxylic Acid (IX) from VII.

To a stirred solution of 50 mg. 4-formyl-1,2,3-thiadiazole (VII) in 10 ml. of 25% sulfuric acid a 10% aqueous potassium permanganate solution was added dropwise until no further manganese dioxide was formed. The mixture was filtered and the filtrate extracted with chloroform. After drying the solvent was removed. The white solid residue melted at 210-213° with effervescence; ir (potassium bromide), 3.22, 5.98, 6.73, 7.11, 8.08, 10.15 and 12.25 μm. The ir spectrum was superimposable on the one of authentic 1,2,3-thiadiazole-4-carboxylic acid.

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(6) A sample of 1,2,3-thiadiazole-4-carboxylic acid was kindly provided to us by Prof. R. A. Olofson of Pennsylvania State University.

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(9) Melting points were determined on a Hoover melting point apparatus and are not corrected. Infrared spectra were obtained on a Perkin-Elmer 421 grating spectrophotometer. The nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer.

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