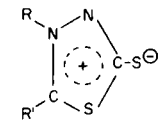
The Synthesis of Dialkyl *Mesoionic* 1,3,4-Thiadiazoles

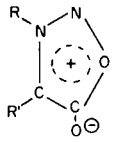
Lemont B. Kier and Malcolm K. Scott

Battelle Memorial Institute, Columbus Laboratories

The first mesoionic 1,3,4-ψ-thiadiazoles (I) were synthesized by Busch before 1900, from phenylhydrazine (1). Because the molecule could not be represented with a reasonable covalent structure, Schonberg proposed a hybrid structure derived from several charged forms (2). Baker later regarded this molecule as a member of a class of heterocycles, which he designated as mesoionic (3). The best known of the mesoionic compounds are the sydnones (II) (4). Stewart and Kier synthesized a number of new aryl-substituted mesoionic 1,3,4-ψ-thiadiazoles (III) from potassium phenyldithiocarbazinate and the appropriate acyl chloride and reported on their antibacterial activity (5).



I



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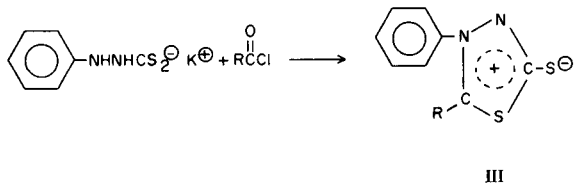

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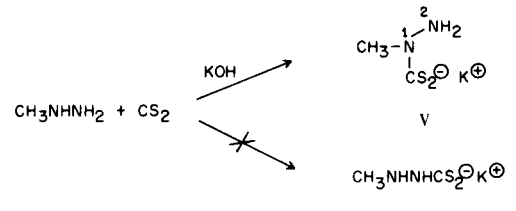
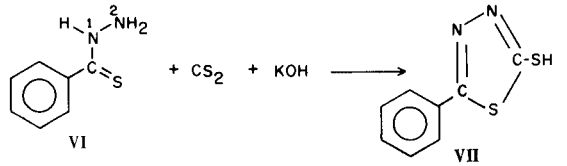


IV

V



VI

VII

To date, all of the compounds synthesized have been derived from phenylhydrazine; hence, they have an aryl group on the 3-position. In an effort to advance our studies on the biological and chemical properties of these molecules, we synthesized and tested several alkyl-substituted compounds.

The 2,3-dialkyl-substituted mesoionic 1,3,4-ψ-thiazdiazoles could not be synthesized by the procedure used for the 2-alkyl-3-aryl compounds (5). Potassium 1-methyldithiocarbazinate (IV) could not be prepared from methylhydrazine because the greater nucleophilicity of the 1-nitrogen of methylhydrazine favored the formation of potassium 1-methyldithiocarbazinate (V) (6). However, Jensen and Pedersen were able to prepare 2-phenyl-5-mercapto-1,3,4-thiadiazole (VII) from thiobenzyhydrazide (VI) and carbon disulfide by utilizing the ability of thiobenzhydrazide to attack carbon disulfide via the 2-nitrogen (7). Using N^1-methylthioacethydrazide (VIIIa) (8) in place of thiobenzhydrazide, and conducting the reaction in ethanol/ether with no base present, we obtained 2,3-dimethyl-1,3,4-ψ-thiadiazoles (IXa) in 78% yield. The 2-ethyl-3-methyl and 2-isopropyl-3-methyl-1,3,4-ψ-thiadiazoles (IXb and IXc) were prepared in the same way. Compounds IXa, IVb, and IXc, as well as compounds of Type III display two very strong absorptions in their infrared spectra at 1050 cm^{-1} (ν C=S) and 1350 cm^{-1} (5). The position of the thiocarbonyl stretching frequency (1050 cm^{-1}), which is shifted to lower frequency compared to the unperturbed thiocarbonyl band (1140 ± 80 cm^{-1}), supports the mesoionic structure of IXa, IXb, IXc, and III where there is extensive charge separation in the thiocarbonyl group (9). The band at 1350 cm^{-1} may arise from resonance of the various vibrational modes of the electron deficient heterocyclic ring. The most abundant fragment ion in the mass spectra of IXa, IXb, IXc, and related compounds of Type III, which seems to be characteristic of mesoionic 1,3,4-thiadiazoles, was that arising from the cleavage depicted in Figure 1. The 2,3-dimethyl-1,3,4-ψ-thiadiazole (IXa) was found inactive against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus faecalis*, *Bacillus cereus*, *Candida albicans*, and *Tricophyton mentagrophytes*.

A non-mesoionic, 1,3,4-thiadiazole, 2,4-dimethyl-1,3,4-thiadiazole (XI), was prepared by reacting potassium

1-methyl dithiocarbazinate (V) with the sodium salt of dithioacetic acid (X) (10). The 1350 cm^{-1} band seen in the infrared spectra of IXa, IXb, IXc, and III is also present in the infrared spectrum of XI but is much weaker whereas the thiocarbonyl stretching frequency, also weakened, appears at a higher frequency (1100 cm^{-1}). A structure such as XI where there is much less charge delocalization in the ring and less charge separation in the thiocarbonyl group compared with a mesoionic compound is consistent with the spectral data. Also the ultraviolet and mass spectral (Figure 1B) properties of this molecule are quite different from those of IXa, its mesoionic positional isomer.

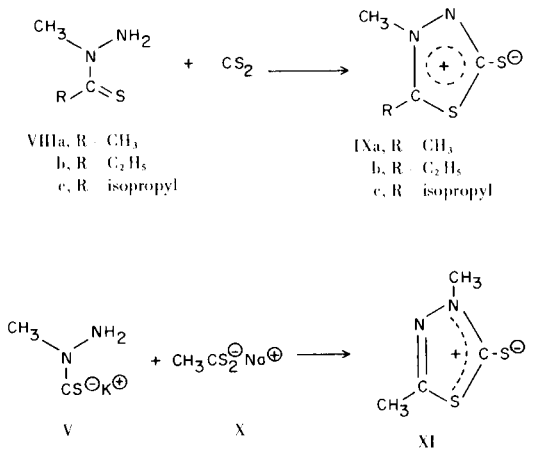
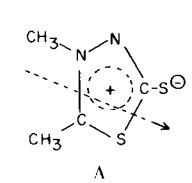
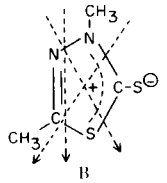


Figure 1



A

Fragments were recognized as coming from the cleavage (dotted line) depicted (11).



B

Fragments were recognized as arising from the cleavages (dotted lines) depicted. Details of the mass spectra are being published elsewhere (11).

EXPERIMENTAL

2,4-Dimethyl-1,3,4-thiadiazole (XI).

The potassium salt of 1-methyldithiocarbazinic acid (7.6 g., 0.047 mole) in 13 ml. of water was added to a solution of 5.4 g. (0.047 mole) of sodium dithioacetate in 25 ml. of water, and the resulting solution was stirred for 15 minutes at room temperature. After standing 24 hours, large white prismatic crystals had formed, which were filtered off and recrystallized from ethanol to give 1.3 g. (19%) of 2,4-dimethyl-1,3,4-thiadiazole, m.p. 52-54° (lit. (10) m.p. 52-53°); λ max. (ethanol) 307 mμ (ε = 12,190) and 254 mμ (ε = 3,030); ν (potassium bromide) 1100 cm^{-1} (C=S). The mass spectrum of this compound supports the nonmesoionic 2,4-dimethyl-1,3,4-thiadiazole structure.

N^1-Methylthioacethydrazide (VIIIa).

N^1-Methylthioacethydrazide was prepared from acetylpiperidine via the carboxymethyl dithioacetate according to the method of Jensen, *et al* (8). Thioacetylpiperidine, synthesized from acetylpiperidine and phosphorus pentasulfide, gave the corresponding *S*-carboxymethylthiopiperidinium bromide when treated with bromoacetic acid in benzene. Thiohydrolysis of the bromide in methanol yielded carboxymethyldithioacetate which reacted with methyl hydrazine in aqueous sodium hydroxide to give N^1-methylthioacethydrazide (10% based on acetylpiperidine) m.p. 77-78°. The same procedure was used for the synthesis of VIIIb and VIIIc.

2,3-Dimethyl-1,3,4-ψ-thiadiazole (IXa).

A solution of 6.0 g. (0.058 mole) of N^1-methylthiohydrazide in 80 ml. of ether and 40 ml. of ethanol was treated with 5.0 g. (0.065 mole) of carbon disulfide, and the solution was allowed to stand for 24 hours at room temperature. The white needles which formed were collected and the filtrate was treated with 5.0 g. of carbon disulfide. More crystals were formed, which were collected and added to the first batch, giving a total of 6.6 g. (78%) of crystalline solid, m.p. 107-110°. Recrystallization from methanol raised the melting point to 111-112°; λ max. (ethanol) 344 mμ (ε = 4,050) and 264 mμ (ε = 7,250); ν (potassium bromide) 1050 cm^{-1} (C=S) and 1350 cm^{-1}.

The mass spectrum of the compound showed it to be the mesoionic compound 2,3-dimethyl-1,3,4-ψ-thiadiazole.

Anal. Calcd. for $C_6H_4N_2S_2$: C, 32.86; H, 4.10; N, 19.17; S, 43.87. Found: C, 32.66; H, 3.94; N, 18.94 S, 44.58.

2-Ethyl-3-methyl-1,3,4-ψ-thiadiazole (IXb).

2-Ethyl-3-methyl-1,3,4-thiadiazole, prepared from VIIIb in the same manner as 2,3-dimethyl-1,3,4-ψ-thiadiazole, was a crystalline solid, m.p. 110-111°; λ max. (ethanol) 349 mμ (ε = 2,930) and 264 mμ (ε = 5,334); ν (potassium bromide) 1050 cm^{-1} (C=S) and 1350 cm^{-1}.

Anal. Calcd. for $C_5H_8N_2S_2$: C, 37.42; H, 4.99; N, 17.49; S, 40.02. Found: C, 37.89; H, 5.13; N, 17.44; S, 39.50.

2-Isopropyl-3-methyl-1,3,4-ψ-thiadiazole (IXc).

2-Isopropyl-3-methyl-1,3,4-ψ-thiadiazole, prepared from VIIIc in the same manner as 2,3-dimethyl-1,3,4-ψ-thiadiazole, melted at 167-169°; λ max. (ethanol) 348 mμ (ε = 3,840) and 265 mμ (ε = 6,350); ν (potassium bromide) 1030 cm^{-1} (C=S) and 1340 cm^{-1}.

Anal. Calcd. for $C_6H_{10}N_2S_2$: C, 41.36; H, 5.74; N, 16.09; S, 36.81. Found: C, 41.46; H, 5.65; N, 15.89; S, 36.40.

Acknowledgment.

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