Some Novel *S*-Mono- and *S,S'*-Unsymmetrical Di-substituted Derivatives of 1,3,4-Thiadiazoledithione

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Preparations of *S*-mono- and unsymmetrical *S,S*-di-substituted derivatives of 1,3,4-thiadiazole-2,5-dithione are described.

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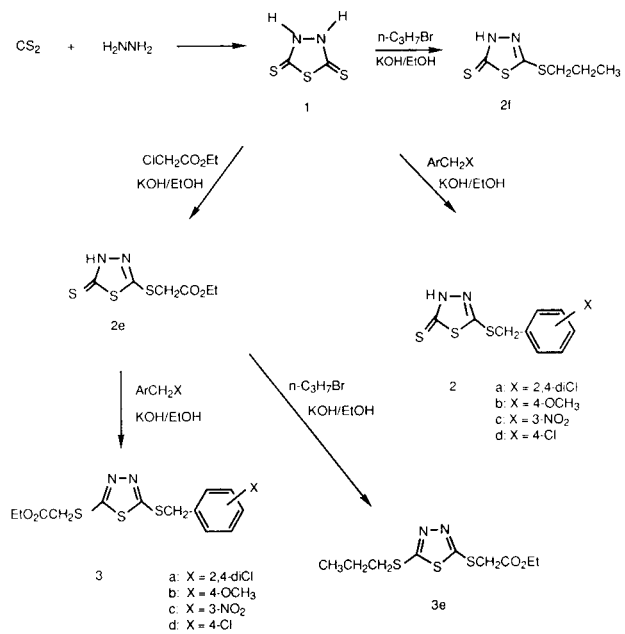
Sulfur containing substituted derivatives of 1,3,4-thiadiazole are of considerable biological [1] and analytical [2] interest. Thiadiazole-2,5-dithione (**1**), easily available from hydrazine and carbon disulfide [3], has been used in metals analysis [4], and together with its *S*-substituted derivatives, as a herbicide [5]. Thiadiazole-2,5-dithione exists as the dithione [6], but alkylation with alkyl halides in alkali gives the *S*-alkylated derivatives [7] as expected, due to the high kinetic nucleophilicity of sulfur. A variety of 2-alkylthio-1,3,4-thiadiazole-5-thiones have been reported [8-10], however, unsymmetrical *S,S'*-dissubstituted 1,3,4-thiadiazoles have received less attention [11]. Recently, we have reported a facile synthesis of unsymmetrical 2,5-dialkylthio-1,3,4-thiadiazoles containing a dodecyl group [12]. We now report further compounds of type **2** and **3**.

The alkylation of thiadiazoledithione **1** in ethanol gave the monoalkyl thioethers **2a-2f** in good yields (85-97%) using one equivalent of the substituted benzyl bromide or chloride for **2a-2d**, or the alkyl halide for **2e-2f**, in the presence of potassium hydroxide (Scheme 1 and Table 1). The unsymmetrical bis-substituted compounds **3a-3e** were made in good yields (71%-83%) by further alkylation of ethoxycarbonylmethylthio-1,3-4-thiadiazole-5(4*H*)-thione (**2e**) with the appropriate alkyl halide in basic ethanol.

Scheme 1



Of the eleven thiadiazoledithione derivatives now described only 2-*n*-propylthio-1,3,4-thiadiazole-5(4*H*)-thione (**2f**) had previously been reported [13]. Compounds are characterized by ^{1}H and ^{13}C nmr spectra and by their elemental analyses. The ^{1}H nmr spectra for the monoalkyl thioeters (**2**) show peaks integrating for one proton at 12.10-14.18 ppm for the NH of the monothione structure. Two proton signals in the 3.14-4.48 ppm region are seen for the SCH_2 groups. Other signals are as expected and are assigned in the experimental section.

The ^{13}C nmr spectra for the monoalkylated thiadiazolethiones show resonances for C=S at 188.1-189.1 ppm, and for the ring carbons at 155.8 to 160.2 ppm. The unsymmetrical bis-*S*-substituted derivatives each exhibted two peaks at 159.3 to 167.7 ppm for the ring carbons. Both monoalkylated and dialkylated compounds displayed SCH_2 carbon signals at 34.4 to 38.1 ppm. The remaining resonances in the ^{13}C nmr spectra are recorded in the experimental.

EXPERIMENTAL

The melting points were recorded on a Thomas-Hoover melting point apparatus equipped with a microscope and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75 MHz) nmr spectra were taken on a QE-300 or a VXR-300 spectrometer in deuteriochloroform. Mass spectra were obtained on an AEI MS 30 mass spectrometer. Microanalyses were performed at the University of Florida. 3*H*,4*H*-1,3,4-thiadiazole-2,5-dithione (**1**) was prepared by a literature method [3]. Commercially available reagent grade solvents and regents were used without further purification.

General Method for the Preparation of Monoalkylated Thiadiazoles.

A mixture of 3*H*,4*H*-1,3,4-thiadiazole-2,5-dithione (1.5 g, 0.01 mole) and potassium hydroxide (0.56 g, 0.01 mole) in 75 ml of ab-

solute ethanol was heated under reflux for 15 minutes and the substituted benzyl bromide (or chloride) was added. The reflux was continued for 8 hours and the mixture diluted with water. The precipitate was filtered off and recrystallized from ethanol to give the product as needles.

2-(2,4-Dichlorobenzylthio)-1,3,4-thiadiazole-5(4*H*)-thione (**2a**).

This compound was obtained as colorless needles (91%), mp 112-114°; ^{1}H nmr: δ 4.42 (s, 2H, CH_2), 7.28 (d, J = 8.1 Hz, 1H), 7.43-7.55 (m, 2H), 14.15 (s, 1H, NH); ^{13}C nmr: δ 34.4 (CH_2), 126.9, 128.9, 131.7, 131.9, 133.8, 134.3, 155.7,. 188.1 (C=S).

Anal. Calcd. for $C_9H_6Cl_2N_2S_3$: C, 34.96; H, 1.96; N, 9.06. Found: C, 34.56; H, 1.71; N, 9.06.

2-(4-Methoxybenzylthio)-1,3,4-thiadiazole-5(4*H*)-thione (**2b**).

This compound was obtained in 86% yield as colorless needles, mp 119-120°; ^{1}H nmr: δ 3.76 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 6.83 (d, J = 7 Hz, 2H), 7.27 (d, J = 7 Hz, 2H), 14.10 (s, 1H, NH); ^{13}C nmr: δ 36.9 (CH_2), 54.8 (OCH_3), 113.7, 126.9, 130.0, 156.8, 159.2, 188.2 (C=S).

Anal. Calcd. for $C_{10}H_{10}N_2OS_3$: C, 44.42; H, 3.73; N, 10.36. Found: 44.83; H, 3.59; N, 10.07.

2-(3-Nitrobenzylthio)-1,3,4-thiadiazole-5(4*H*)-thione (**2c**).

The compound **2c** was prepared in 88% yield as light yellow needles, mp 174-175°; ^{1}H nmr: δ 4.56 (s, 2H, CH_2), 7.63 (t, J = 7.2 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 8.31 (s, 1H), 14.18 (s, 1H, NH); ^{13}C nmr: δ 35.8 (CH_2), 122.4, 123.6, 129.7, 135.5, 138.7, 147.6, 155.6, 188.1 (C=S).

Anal. Calcd. for $C_9H_7N_3O_2S_3$: C, 37.88; H, 2.47; N, 14.73. Found: 37.65; H, 2.35; N, 14.68.

2-(4-Chlorobenzylthio)-1,3,4-thiadiazole-5(4*H*)-thione (**2d**).

This compound was obtained as colorless needles (88%), mp 115-117°; ^{1}H nmr: δ 4.48 (s, 2H, CH_2), 7.27-7.36 (AB system, 4H), 13.85 (s, 1H, NH); ^{13}C nmr: δ 36.3 (CH_2), 128.3, 129.3, 130.0, 133.6, 156.3, 188.4 (C=S).

Anal. Calcd. for $C_9H_7ClN_2S_3$: C, 39.34; H, 2.57; N, 10.19. Found; C, 39.57; H, 2.71; N, 10.02.

2-Ethoxycarbonylmethylthio-1,3,4-thiadiazole-5(4*H*)-thione (**2e**).

This compound was prepared in 97% yield as colorless needles, mp 63-65°; ^{1}H nmr: δ 1.25 (t, 3H, CH_3), 3.90 (s, 2H, SCH_2), 4.20 (q, 2H, OCH_2), 12.10 (s, 1H, NH); ^{13}C nmr: δ 14.1 (CH_3), 35.0 (SCH_2), 62.6 (OCH_2), 157.5, 167.8 (C=O), 189.1 (C=S).

Anal. Calcd. for $C_6H_8N_2O_2S_3$: C, 30.50; H, 3.41; N, 11.85. Found: C, 30.28; H, 3.62; N, 11.56.

n-Propylthio-1,3,4-thiadiazole-5(4*H*)-thione (**2f**).

This compound was obtained as colorless needles (85%), mp 98-99° (lit [13] mp 102-103°); ^{1}H nmr: δ 1.04 (t, J = 7.2 Hz, 3H, CH_3), 1.78-1.85 (m, 2H, CH_2), 3.14 (t, J = 7.2 Hz, 2H, SCH_2), 12.41 (s, 1H, NH); ^{13}C nmr: δ 13.1 (CH_3), 22.4 (CH_2), 35.5 (SCH_2), 159.7, 188.7 (C=S).

General Method for the Preparation of Unsymmetrical Bisalkylated Thiadiazole.

A mixture of 2-ethoxycarbonylmethylthio-1,3,4-thiadiazole-5-(4*H*)-thione (2.36 g, 0.01 mole) and potassium hydroxide (0.56 g, 0.01 mole) in 75 ml of absolute ethanol was heated under reflux for 15 minutes. The substituted benzyl chloride (0.01 mole) was added and the mixture was refluxed for 8 hours. After cooling, the solution was diluted with water, extracted with chloroform, washed with 10% sodium hydroxide (3 x 50 ml), dried (magnesium sulfate) and the solvent evaporated. Recrystallization from ethanol gave the pure product as needles, **3a-3d**. Compound **3e** was prepared in the same way from 1-bromopropane and isolated as an oil.

2-Ethoxycarbonylmethylthio-5-(2,4-dichlorobenzylthio)-1,3,4-thiadiazole (**3a**).

This compound was obtained in 83% yield, mp 45-46°; ^{1}H nmr: δ 1.27 (t, J = 7.0 Hz, 3H, CH_3), 4.09 (s, 2H, $ArCH_2S$), 4.14 (q, J = 7.0 Hz, 2H, OCH_2), 4.58 (s, 2H, SCH_2CO_2), 7.17 (d, J = 8.7 Hz, 1H), 7.40 (s, 1H), 7.49 (d, J = 8.7 Hz, 1H); ^{13}C nmr: δ 14.1, 35.1, 35.6, 62.2, 127.3, 129.5, 132.2, 132.5, 134.5, 135.0, 163.8, 164.6, 167.7.

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_2S_3$: C, 39.50; H, 3.06; N, 7.09. Found: C, 39.31; H, 2.97; N, 7.09.

2-Ethoxycarbonylmethylthio-5-(4-methoxybenzylthio)-1,3,4-thiadiazole (**3b**).

This compound was prepared in 78% yield, mp 65-67°; ^{1}H nmr: δ 1.27 (t, J = 7.2 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3); 4.08 (s, 2H, $ArCH_2S$), 4.21 (q, J = 7.2 Hz, 2H, OCH_2), 4.45 (s, 2H, SCH_2CO_2), 6.85 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH); ^{13}C nmr: δ 13.9, 35.4, 38.0, 55.1, 62.0, 114.0, 127.3, 130.3, 159.1, 163.3, 165.5, 167.7.

Anal. Calcd. for $C_{14}H_{16}N_2O_3S_3$: C, 47.17; H, 4.52; N, 7.86. Found: C, 47.48; H, 4.27; N, 7.74.

2-Ethoxycarbonylmethylthio-5-(3-nitrobenzylthio)-1,3,4-thiadiazole (**3c**).

This compound was obtained in 71% yield, mp 66-67°; ^{1}H nmr: δ 1.27 (t, 3H, CH_3), 4.10 (s, 2H, CH_2), 4.23 (q, 2H, CH_2), 4.60 (s, 2H, CH_2), 7.55 (m, 1H), 7.80 (dd, 1H), 8.12 (dd, 1H), 8.30 (d, 1H); ^{13}C nmr: δ 14.1, 35.6, 37.0, 62.3, 122.9, 124.0, 129.6, 129.7, 135.3, 148.3, 163.9, 164.0, 167.7.

Anal. Calcd. for $C_{13}H_{13}N_3O_4S_3$: C, 42.04; H, 3.53; N, 11.31. Found: C, 41.93; H, 3.36; N, 11.45.

2-Ethoxycarbonylmethylthio-5-(4-chlorobenzylthio)-1,3,4-thiadiazole (**3d**).

This compound was prepared in 72% yield, mp 100-102°; ^{1}H nmr δ 1.28 (t, J = 7 Hz, 3H, CH_3), 4.10 (s, 2H, SCH_2Ar), 4.24 (q, J = 7 Hz, 2H, OCH_2), 4.46 (s, 2H, SCH_2CO_2), 7.27-7.35 (A_2B_2 system, 4H, ArH); ^{13}C nmr: δ 13.9 (CH_3), 35.4, 37.4, 62.1, 128.7, 130.4, 133.6, 134.3, 163.5, 164.6, 167.6.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2S_3$: C, 43.27; H, 3.63; N, 7.76. Found: C, 42.95; H, 3.54; N, 7.75.

2-Ethoxycarbonylmethylthio-5-*n*-propylthio-1,3,4-thiadiazole (**3e**).

This compound was obtained as an oil in 72% yield, ^{1}H nmr: δ 0.95 (t, J = 7 Hz, 3H, CH_3), 1.20 (t, 3H, CH_3), 1.68-1.82 (m, 2H, CH_2), 3.12-3.22 (t, 2H, SCH_2), 4.00 (s, 2H, SCH_2CO_2), 4.10-4.20 (m, 2H, OCH_2); ^{13}C nmr: δ 13.2, 14.0, 22.6, 35.5, 36.2, 62.1, 162.7, 166.2, 167.7; hrms. Calcd. for $C_9H_{14}N_2O_2S_3$: 278.0217. Found: 278.0194.

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