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SOME DERIVATIVES OF 2,5-DIMERCAPTO-1,3,4-THIADIAZOLE

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Reaction of 2,5-dimercapto-1,3,4-thiadiazole with diethylamine, morpholine, and piperidine under the conditions of the Mannich reaction gives N,S-aminomethylated thiadiazoles, but urea, thiourea, semicarbazide, and thiosemicarbazide form N,N-aminomethylated thiadiazoles. Condensation of 2,5-dimercapto-1,3,4-thiadiazole with formaldehyde leads, depending on the pH, to an N,N-, N,S-, or S,S-derivative, but reaction with 1,3-propanesultone or with the sodium salt of bromoethanesulfonic acid in alkaline medium leads to an S,S-derivative of thiadiazole.

Certain derivatives of 2,5-dimercapto-1,3,4-thiadiazole are used as potential antimicrobial agents [1], herbicides [2], or corrosion inhibitors for steel [3], and may also be used as bifunctional compounds for the synthesis of polyethers, polyamides, polyurethanes, and polyhydrazides [4].

On continuing the investigations started by us in [5] on the synthesis of new heterocycles based on 2,5-dimercapto-1,3,4-thiadiazole we have now synthesized new derivatives of 2,5-dimercapto-1,3,4-thiadiazole containing aliphatic, aromatic, and heterocyclic fragments in the molecule.

2,5-Dimercapto-1,3,4-thiadiazole contains the tautomeric system N=C–SH HN–C=S in its molecule. Depending on the conditions and reactant structure it may react either at nitrogen or at sulfur forming N,N-, N,S-, or S,S-derivatives.

Compounds containing at least one active hydrogen atom react with formaldehyde and amines forming Mannich bases. The range of compounds undergoing the Mannich reaction is extended significantly by substances with an acidic hydrogen atom at nitrogen or sulfur, such as benzotriazole [6], 2-mercaptobenzothiazole, 2-mercaptobenzimidazole, 2-mercaptobenzoxazole [7], etc.

The Mannich reaction with 2,5-dimercapto-1,3,4-thiadiazole has been little studied from the point of view of the structure of the bases obtained [8]. The synthesis of Mannich compounds from 2,5-dimercapto-1,3,4-thiadiazole (I), the study of their properties, and the clarification of their structure are the problems of the present investigation. Diethylamine, morpholine, piperidine, urea, thiourea, semicarbazide, and thiosemicarbazide were used as second components in the reaction. It was established with the aid of IR spectra and PMR spectra that N,S-aminomethylated thiadiazoles (IIa-c) were formed with diethylamine, morpholine, and piperidine under Mannich conditions, but N,N-aminomethylated thiadiazoles (IIIa-d) were formed with urea, thiourea, semicarbazide, and thiosemicarbazide.

Condensation of thiadiazole (I) with formaldehyde was carried out at various pH values. At neutral pH 3,4-bis(hydroxymethyl)-1,3,4-thiadiazole-2,5-dithione (IVa) was formed in 87% yield. On carrying out the reaction in neutral medium with subsequent basification to pH 8.0 a mixture of N,N- and S,S-thiadiazole derivatives (IVa) and (Va) was formed consisting of 76% (IVa) and 24% (Va), according to PMR spectral data. In alkaline medium with subsequent acidification to pH 3 a mixture of N,N-, S,S-, and N,S-thiadiazole derivatives (IVa), (Va), and (VIa) (60, 24, and 16% respectively) was formed.

Since only the N,N-disubstituted thiadiazole (IVa) was formed on carrying out the condensation in neutral medium, other aldehydes such as benzaldehyde, 2,4-dihydroxybenzaldehyde, and 2-hydroxy-3-methoxybenzaldehyde were condensed under analogous conditions to give the N,N-thiadiazole derivatives (IVb-d).

Thiadiazole (I) reacts with 1,3-propanesultone or with sodium bromoethanesulfonate in alkaline medium at an S atom forming 83% dipotassium or 85% disodium salt of the disulfonic acids (VII) or (VIII). The latter gives the corresponding salt (IX) in 57% yield with S-benzylisothiouronium chloride under mild conditions. Hydroxymethylated thiadiazole (IVa) also reacts with 1,3-propanesultone in alkaline medium forming the dipotassium salt of the disul-

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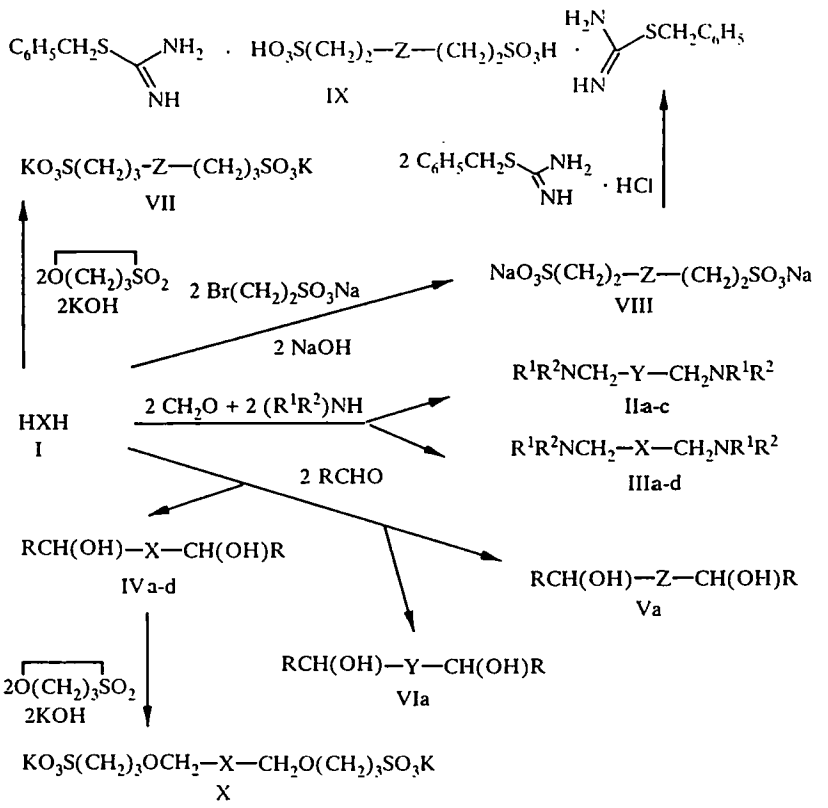
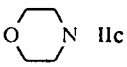
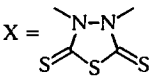
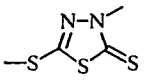
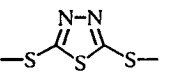


IIa $R^1 = R^2 = C_2H_5$, IIб $(R^1R^2)N =$  IIc $(R^1R^2)N =$ 

IIIa $(R^1R^2)N = NHCONH_2$, IIIb $(R^1R^2)N = NHCSNH_2$;
IIIc $(R^1R^2)N = NHNHCONH_2$, IIId $(R^1R^2)N = NHNHCSNH_2$;
IVa – VIa R = H, IVb R = C_6H_5, IVc R = 2,4-$(HO)_2C_6H_3$,
IVd R = 2-HO-3-$CH_3OC_6H_3$

X =  Y =  Z = 

fonic acid (X), but in low (37.5%) yield. The structures of compounds synthesized were confirmed by data of IR and PMR spectra.

EXPERIMENTAL

The IR spectra were obtained on a UR 10 spectrometer in KBr disks, and the PMR spectra on a Hitachi R 22 (90 MHz) spectrometer, internal standard was HMDS. Quantitative determinations were carried out based on fivefold integration of PMR signals for SCH_2 and NCH_2 groups. A check on the progress of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV 254 plates, visualizing with UV light or iodine.

3-Diethylaminomethyl-5-diethylaminomethylthio-1,3,4-thiadiazole-2-thione (IIa). Diethylamine (3.7 g: 50 mmole) was placed in a flask cooled with ice, then 28% formalin (10 ml) and a solution of thiadiazole (I) (3.7 g: 25 mmole) in dioxan (50 ml) were added gradually. The reaction mixture was stirred at room temperature for 3 h, filtered, the dioxan was distilled from the filtrate, and the crystals of compound (IIa) were filtered off and washed with ether. PMR spectrum (DMSO-D_6): 0.96 (6H, t, CH_2CH_3); 2.58 (4H, q, CH_2); 5.04 (2H, s, NCH_2N); 4.36 ppm (2H, s, SCH_2N).

TABLE 1. Characteristics of Thiadiazoles (II)-(X)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
IIa	$C_{12}H_{24}N_4S_3$	44,78 44,96	7,63 7,55	17,36 17,48	65 (decomp.)	70
IIb	$C_{12}H_{20}N_4O_2S_3$	41,24 41,36	5,68 5,78	15,88 16,08	112 (decomp.)	65
IIc	$C_{14}H_{24}N_4S_3$	48,62 48,80	6,86 7,02	16,02 16,26	108 (decomp.)	69
IIIa	$C_6H_{10}N_6O_2S_3$	24,70 24,48	3,26 3,42	28,55 28,28	215 (decomp.)	91
IIIb	$C_6H_{10}N_6S_5$	22,33 22,07	2,87 3,09	25,56 25,74	207 (decomp.)	93
IIIc	$C_6H_{12}N_8O_2S_3$	22,39 22,21	3,55 3,73	34,22 34,54	190 (decomp.)	88,5
IIId	$C_6H_{12}N_8S_5$	20,42 20,21	3,17 3,39	31,18 31,43	160 (decomp.)	97,5
IVa	$C_4H_6N_2O_2S_3$	23,05 22,85	2,67 2,87	13,24 13,32	111...112	87,5
IVb	$C_{16}H_{14}N_2O_2S_3$	53,23 53,01	3,71 3,89	7,57 7,73	193 (decomp.)	66
IVc	$C_{16}H_{14}N_2O_6S_3$	44,84 45,06	3,13 3,31	6,35 6,57	242 (decomp.)	70
IVd	$C_{18}H_{18}N_2O_6S_3$	47,28 47,56	3,89 3,99	6,02 6,16	210 (decomp.)	88
Va	$C_4H_6N_2O_2S_3$	22,75 22,85	2,78 2,87	13,16 13,32	121...122	77
VIa	$C_{18}H_{18}N_2O_2S_3$	22,68 22,85	2,62 2,87	13,36 13,32	141...142	94
VII	$C_8H_{12}K_2N_2O_6S_5$	20,31 20,41	2,43 2,57	5,85 5,95	212 (decomp.)	83
VIII	$C_6H_8Na_2N_2O_6S_5$	17,39 17,55	1,87 1,96	6,78 6,82	265 (decomp.)	85
IX	$C_{22}H_{30}N_6O_6S_7$	37,94 37,80	4,21 4,33	11,96 12,02	150...151	57
X	$C_{10}H_{16}K_2N_2O_8S_5$	22,45 22,63	2,98 3,04	5,17 5,27	240 (decomp.)	47,5

3-Morpholinomethyl-5-morpholinomethylthio-1,3,4-thiadiazole-2-thione (IIb) was obtained analogously to compound (IIa) from morpholine (4.4 g: 50 mmole), 28% formalin (10 ml), and thiadiazole (I) (3.7 g: 25 mmole) dissolved in dioxan (50 ml). PMR spectrum (CD_3COCD_3): 2.64 (4H, t, CH_2OCH_2); 3.42 (4H, t, $CH_2CH_2NCH_2CH_2$); 4.96 (2H, s, NCH_2N); 4.28 ppm (2H, s, SCH_2N).

3-Piperidinomethyl-5-piperidinomethylthio-1,3,4-thiadiazole-2-thione (IIc) was obtained analogously to compound (IIa) from piperidine (4.3 g: 50 mmole), 28% formalin (10 ml), and thiadiazole (I) (3.7 g: 25 mmole) dissolved in dioxan (50 ml). PMR spectrum (CD_3COCD_3): 1.36 (6H, m, $CH_2CH_2CH_2CH_2CH_2$); 2.62 (4H, m, $CH_2CH_2CH_2CH_2CH_2$); 4.98 (2H, s, NCH_2N); 4.28 ppm (2H, s, SCH_2N).

3,4-Bis(ureidomethyl)-1,3,4-thiadiazole-2,5-dithione (IIIa). A mixture of compound (I) (3.7 g: 25 mmole), 28% formalin (10 ml), urea (3.0 g: 50 mmole), cuprous chloride (0.3 g), and dioxan (100 ml) was stirred and boiled for 5 h. After cooling to room temperature the mixture was filtered, the dioxan evaporated from the filtrate, the crystals of compound (IIa) were filtered off, and recrystallized from ethanol. PMR spectrum ($CDCl_3$): 5.02 (2H, s, NCH_2N); 7.40 (2H, s, NH_2); 8.19 ppm (1H, s, NH). IR spectrum: 1210 (ν C=S), 1620 (νNH), 1640 (ν CO amide), 3180-3200, 3340-3360 cm^{-1} (ν NH2).

3,4-Bis(thioureidomethyl)-1,3,4-thiadiazole-2,5-dithione (IIIb) was obtained from thiadiazole (I) (3.7 g: 25 mmole), 28% formalin (10 ml), thiourea (3.8 g: 50 mmole), cuprous chloride (0.3 g), and dioxan (100 ml) on stirring and heating the reaction mixture at 80°C for 5 h. After cooling, the mixture was filtered, the dioxan evaporated

from the filtrate, the crystals of compound (IIIb) were filtered off, and recrystallized from ethanol. PMR spectrum ($CDCl_3$): 4.96 (2H, s, NCH_2N); 7.42 (2H, s, NH_2), 8.35 ppm (1H, s, NH). IR spectrum: 1200 (ν C=S), 1515 (ν NHC=S), 1610 (δ NH), 3160-3200, 3340-3380 cm^{-1} (ν NH_2).

3,4-Bis(semicarbazidomethyl)-1,3,4-thiadiazole-2,5-thione (IIIc) was obtained from thiadiazole (I) (3.7 g: 25 mmole), 28% formalin (10 ml), semicarbazide (3.8 g: 50 mmole), cuprous chloride (0.3 g), and dioxan (100 ml) by the procedure for preparing compound (IIIa). IR spectrum: 1210 (ν C=S), 1650 (δ NH), 1675 (νCO amide), 3140-3180, 3320-3360 cm^{-1} (ν NH_2).

3,4-Bis(thiosemicarbazidomethyl)-1,3,4-thiadiazole-2,5-dithione (IIId) was obtained from thiadiazole (I) (3.7 g: 25 mmole), 28% formalin (10 ml), thiosemicarbazide (4.6 g: 50 mmole), cuprous chloride (0.3 g), and dioxan (100 ml) by the procedure for synthesizing compound (IIIb). IR spectrum: 1210 (ν C=S), 1500 (ν NHC=S), 1610 (δ NH), 3180-3200, 3360-3380 cm^{-1} (ν NH).

3,4-Bis(hydroxymethyl)-1,3,4-thiadiazole-2,5-dithione (IVa). Thiadiazole (I) (15 g: 10 mmole) was dissolved in hot 2-propanol (500 ml), and 28% formalin (40 ml) was added. The mixture was stirred for 1 h at room temperature, filtered, and water (100 ml) added to the filtrate. The precipitated crystals of compound (IVa) were filtered off and washed with acetone. PMR spectrum (DMSO-D_6): 5.35 ppm (2H, s, NCH_2O). IR spectrum: 1207 (ν C=S), 1047, 1285 (δ OH), 3200-3600 cm^{-1} (ν OH).

2,5-Bis(hydroxymethylthio)-1,3,4-thiadiazole (Va). Formalin (28%: 10 ml) was added to a solution of thiadiazole (I) (3.7 g: 25 mmole) in ethanol (150 ml). The mixture was boiled for 15 min, cooled, adjusted to pH 9 with aqueous ammonia solution, and set aside for a day. The crystals of a mixture of compounds (IVa) and (Va) in a percentage ratio 76:24 (from PMR spectral data) were filtered off, washed with acetone, and passed through a column packed with aluminum oxide (eluent isopropanol), which separated (Va) from (IVa). PMR spectrum (DMSO-D_6): 4.53 ppm (2H, s, SCH_2O).

3-Hydroxymethyl-5-hydroxymethylthio-1,3,4-thiadiazole-2-thione (VIa). Formalin (28%: 10 ml) was added to a solution of thiadiazole (I) (3.7 g: 25 mmole) in 10% NaOH solution (16 ml). The mixture was heated for 2 h at 50°C, cooled, and acidified to pH 3 with conc. hydrochloric acid. The precipitate of a mixture of compounds (IVa), (Va), and (VIa) in a percentage ratio 60:24:16 (from PMR spectral data) was filtered off, washed with acetone, and passed through a column of aluminum oxide (eluent isopropanol), which separated (VIa) from (IVa) and (Va). PMR spectrum (DMSO-D_6): 4.53 and 4.64 ppm (2H, d, SCH_2O), 5.33 and 5.44 ppm (2H, d, NCH_2O).

3,4-Bis(phenylhydroxymethyl)-1,3,4-thiadiazole-2,5-dithione (IVb). Benzaldehyde (5.3 g: 50 mmole) was added to a solution of thiadiazole (I) (3.7 g: 25 mmole) in 2-propanol (150 ml), the mixture was boiled for 1 h, filtered, and the 2-propanol distilled off. The crystals of compound (IVb) formed were filtered off and washed with ethanol. PMR spectrum (DMSO-D_6): 7.04 (10H, s, Ph); 7.31 ppm (2H, s, PhC<u>H</u>). IR spectrum: 1210 (ν C=S), 1100, 1285 (δ OH), 3200-3600 cm^{-1} (ν OH).

3,4-Bis(2,4-dihydroxyphenylhydroxymethyl)-1,3,4-thiadiazole-2,5-dithione (IVc). 2,4-Dihydroxybenzaldehyde (2.8 g: 20 mmole) was added to a solution of thiadiazole (I) (1.5 g: 10 mmole) in ethanol (50 ml), the mixture was boiled for 2 h, and filtered. The precipitated crystals of compound (IVc) were filtered off and washed with ether. PMR spectrum (DMSO-D_6): 7.03 (10H, s, Ph); 7.3 (2H, s, PhC<u>H</u>); 9.60 (1H, d, OH); 11.44 ppm (1H, s, OH). IR spectrum: 1210 (ν C=S), 1100, 1285 (δ OH), 3200-3600 cm^{-1} (ν OH).

3,4-Bis(2-hydroxy-3-methoxyphenylhydroxymethyl)-1,3,4-thiadiazole-2,5-thione (IVd) was obtained from thiadiazole (I) (1.5 g: 10 mmole) and 2-hydroxy-3-methoxybenzaldehyde (3.0 g: 20 mmole) by the procedure described for compound (IVc). PMR spectrum (DMSO-D_6): 3.71 (3H, s, CH_3); 7.01 (6H, s, Ar); 7.28 (2H, s, PhC<u>H</u>); 8.93 ppm (1H, s, OH). IR spectrum: 1210 (ν C=S), 1100, 1285 (δ OH), 3200-3600 cm^{-1} (ν OH).

Dipotassium Salt of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(3-mercaptopropanesulfonic Acid) (VII). Potassium hydroxide (2.8 g: 50 mmole) in water (20 ml) was added to thiadiazole (I) (3.7 g: 25 mmole). The reaction mixture was boiled for 1 h, the water was then distilled off, and the residue dissolved in dioxan (100 ml). Propanesultone (6.1 g: 50 mmole) was added to the solution, the mixture boiled for 3 h further, after which the dioxan was distilled off. The residue of compound (VII) was filtered off and recrystallized from ethanol. PMR spectrum (D_2O): 3.05 (4H, t, $CH_2CH_2\underline{CH_2}SO_3K$); 2.10 (4H, m, $CH_2\underline{CH_2}CH_2SO_3K$); 3.31 ppm (4H, t, $S\underline{CH_2}CH_2CH_2SO_3K$).

Disodium Salt of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptoethanesulfonic Acid) (VIII). A solution of NaOH (4 g: 0.1 mole) in water (10 ml), thiadiazole (I) (7.5 g: 0.05 mole), and sodium β-bromoethanesulfonate (21.1 g: 0.1 mole) were added to a mixture of 2-propanol (100 ml) and methanol (20 ml). The reaction mixture was stirred and heated at 80°C for 3 h, the amorphous precipitate of salt (VIII) was filtered off, and recrystallized from methanol. PMR spectrum (D_2O): 3.64 (4H, m, $CH_2\underline{CH_2}SO_3Na$); 3.80 ppm (4H, m, $S\underline{CH_2}CH_2SO_3Na$).

S-Benzylisothiouronium Salt of S,S′-(1,3,4-thiadiazole-2,5-diyl)bis(2-mercaptoethanesulfonic Acid) (IX). Salt (VIII) (4.1 g: 10 mmole) was dissolved in water (30 ml) at 40°C and was mixed with a solution of S-benzylisothiouronium chloride (4.1 g: 20 mmole) in water (20 ml). The oil which precipitated crystallized straight away. The crystals of salt (IX) were filtered off and recrystallized from water. PMR spectrum (DMSO-D_6): 3.02 (4H, m, $CH_2C\underline{H}_2SO_3H$); 3.49 (4H, m, $S\underline{CH}_2CH_2SO_3H$); 4.51 (4H, s, $PhCH_2$); 7.27 ppm (10H, m, Ph).

Dipotassium 5,5′-(2,5-Dithioxo-3,4-dihydro-1,3,4-thiadiazole-3,4-diyl)bis(4-oxapentanesulfonate) (X). A solution of KOH (1.1 g: 20 mmole) in water (2 ml) was added to a solution of compound (IVa) (2.1 g: 10 mmole) dissolved in dioxan (50 ml) and the mixture was heated for 1 h at 50°C. After cooling, 1,3-propanesultone (2.4 g: 20 mmole) was added, the mixture was stirred a further 5 h at room temperature, and the dioxan distilled off. The precipitate of salt (X) which separated was filtered off and recrystallized from ethanol. PMR spectrum (D_2O): 3.2 (4H, t, $CH_2CH_2\underline{CH}_2SO_3K$); 2.24 (4H, m, $CH_2\underline{CH}_2CH_2SO_3K$); 3.45 (4H, t, $\underline{CH}_2CH_2CH_2SO_3K$); 5.35 ppm (2H, s, NCH_2O).

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