SYNTHESIS AND PROPERTIES OF 5-AMINO-1,2,3-THIADIAZOLE-4-CARBOTHIOAMIDES

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5-Amino-1,2,3-thiadiazole-4NR-carboxamides were reacted with P_4S_{10}, and 5-NR-amino-1,2,3-thiadiazole-4-carbonitriles with H_2S. The reversible rearrangement of 5-amino-1,2,3-thiadiazole-4-NR-carbothioamides to 5-NR-amino-1,2,3-thiadiazole-4-carbothioamides was discovered.

The thioamides of 1,2,3-thiadiazole-4-carboxylic acid have been studied very little, and are represented only by isolated examples in the literature [1]. Furthermore, due to the high lability of the ring and the nucleophilicity of the carbothioamide group of these compounds new chemical conversions and interesting biological properties could be expected.

We have already found the rearrangement of 5-amino-1,2,3-thiadiazole-4-NR-carbothioamides to 5-mercapto-1-NR-1,2,3-triazole-4-carbothioamides [2]. For the purpose of synthesizing new derivatives of 5-amino-1,2,3-thiadiazole-4-carbothioamide with substituents at the amino and carbothioamide nitrogens, and studying their spectral and chemical properties, we have reacted 5-amino-1,2,3-thiadiazole-4-NR-carboxamides, Ia-i, with phosphorus decasulfide (P_4S_{10}), and 5-NR-amino-1,2,3-thiadiazole-4-carbonitriles IIa,b,e,f,j with hydrogen sulfide (Table 1). The starting compounds I, II were synthesized from thioamides III by reaction with benzenesulfonyl azide (Table 2).

In the reaction of 5-amino-1,2,3-thiadiazole-4-carboxamides Ia,b with P_4S_{10} 5-amino-1,2,3-thiadiazole-4-carbothioamides IVa,b [3] are formed. The replacement of carbothioamide hydrogen by butyl or cyclohexyl gives mixtures of N-butyl-(IVc) or N-cyclohexylcarbothioamide (IVd) with a small amount of their isomerization products, 5-N-butylamino- (Vc) or 5-N-cyclohexylamino-1,2,3-thiadiazole-4-carbothioamide (Vd) respectively. In the case of N-arylamides Ie-1 the content of 5-aminosubstituted 1,2,3-thiadiazoles Ve-h becomes predominant. An exception is 5-amino-1,2,3-thiadiazole-4-N-(2,4,6-trichlorophenyl)carboxamide (Ii), which by thionation gives a mixture containing more than 90% of thiadiazole IVi.

All the isomeric vapors have the same chromatographic mobility in all the systems used. Their mass spectra contain intense molecular ion signals that are stronger than in the spectra of the 5-mercapto-1,2,3-triazoles, viz., the signals of $[M-N_2]^+$, which are typical of 5-amino-1,2,3-thiadiazoles [4]. The ^1H NMR spectra of solutions of the mixture contain the dual

TABLE 1. Conditions and Yields of Sulfohydrogenation of 5-Aminosubstituted 1,2,3-Thiadiazole-4-Carbonitriles IIa, b, e, f, j

Compound	Solvent	Catalyst	Duration of reaction, h (T, °C)	Yield, %
IIa	Chloroform	Triethylamine	0,5 (0...5)	98
IIb	Chloroform	Triethylamine	0,5 (0...5)	98
IIe	Chloroform	Triethylamine	0,5 (60)	96
IIf	Ethanol	Sodium ethylate	4,0 (80)	80
IIj	Ethanol	Triethylamine	0,5 (80)	77

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TABLE 2. Properties of Synthesized Compounds

Compound	mp, °C	IR spectrum, ν, cm⁻¹	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
Ic	63...64	3390, 3293, 3160 (NH), 2978, 2948, 2885 (CH), 1645 (C=O)	42,3	6,1	27,3	15,6	$C_7H_{12}N_4OS$	42,0	6,0	28,0	16,0	15
Ih	173	3450, 3390, 3350 (NH), 1650 (C=O)	36,7	2,3	18,8	10,5	$C_9H_7BrN_4OS$	36,2	2,3	18,7	10,7	44
Ii	138...139	3450, 3320 (NH), 3090 (CH), 1650 (C=O)	34,0	1,8	17,4	10,0	$C_9H_5Cl_3N_4OS$	33,4	1,6	17,3	9,9	42
IIj	125	3283 (NH), 2252 (C≡N), 1720 (C=O)	36,1	2,4	32,8	19,3	$C_5H_4N_4OS$	35,7	2,4	33,3	19,1	77
IIIe	95...96	3300, 3165 (NH), 2935 (CH), 2280 (C≡N)	62,0	4,5	16,0	17,6	$C_9H_8N_2S$	61,4	4,6	15,9	18,1	43
IIIf	135	3290, 3138 (NH), 3070, 2908 (CH), 2270 (C≡N)	63,8	5,3	14,5	17,3	$C_{10}H_{10}N_2S$	63,2	5,3	14,7	16,8	22
IVc Vc	116...117	3320, 3270, 3150 (NH), 3050, 2920, 2840 (CH)	39,1	5,3	26,0	29,2	$C_7H_{12}N_4S_2$	38,9	5,5	26,0	29,6	55
IVd Vd	96	3330, 3270, 3156 (NH), 3050, 2920, 2840 (CH)	45,0	5,8	22,7	26,7	$C_9H_{14}N_4S_2$	44,6	5,8	23,1	26,5	88
IVg Vg	169	3420, 3310, 3200 (NH), 2920 (CH)	45,1	3,8	21,0	23,9	$C_{10}H_{10}N_4OS$	45,1	3,8	21,0	24,0	90
IVh Vh	167	3450, 3310, 3200 (NH), 2920 (CH)	34,3	2,2	17,5	20,3	$C_9H_7BrN_4S_2$	34,3	2,2	17,8	20,3	88
IVi Vi	115	3450, 3320, 3190 (NH), 3090 (CH)	31,6	1,1	16,5	19,2	$C_9H_5Cl_3N_4S_2$	31,8	1,4	16,5	18,9	45
Vj	156	3340, 3305, 3212 (NH), 1695 (C=O)	30,1	3,1	27,9	32,1	$C_5H_6N_4OS_2$	29,7	3,0	27,7	31,7	76

TABLE 3. Spectral Properties of 5-Amino,2,3-thiadiazole-4-carboxamides and 4-carbonitriles

Compound	Mass spectrum, m/z (%)*	¹H NMR spectrum, δ, ppm (TMS internal standard)
Ic	M+ 200 (100), 172 (66), 139 (93), 166 (97), 89 (17)	0,9...1,5 (6H, m, $(CH_2)_3$); 3,1...3,5 (3H, m, CH_3); 8,4 (2H, s, NH_2)
Ih	M+ 298 (53)**, 253 (14), 225 (16), 171 (14), 73 (100)	7,3...7,9 (4H, m, C_6H_4); 8,1 (2H, s, NH_2); 10,4 (H, s, NH)
Ii	M+ 322 (100)**, 294 (1), 287 (35)	7,2...7,8 (2H, m, $C_6H_2Cl_3$); 8,1 (2H, s, NH_2); 10,4 (H, s, NH)
IIj	M+ 168 (100); 140 (84), 98 (59), 71 (60), 70 (66)	2,4 (3H, s, CH_3)

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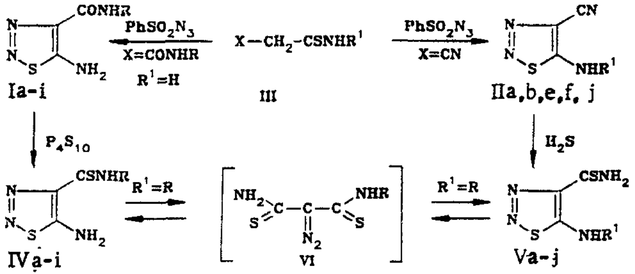
*The five most intense peaks in the mass spectrum are given.

**Peaks of ions containing ^{79}Br and ^{35}Cl isotopes are given.

signals of the amino and thioamide protons, while the ^{13}C NMR spectra contain the dual signals of the ring and carbothioamide carbons. The weak field signals in the 182-187 ppm region have been assigned to the carbothioamide carbons, while the signals at 160-170 ppm have been assigned to the ring $C_{(5)}$ atoms in accordance with [3, 5]. It is known that replacement of amino hydrogen by alkyl or aryl displaces the chemical shift of the α-carbon to the strong field [5]. The spectra of compounds IVa, b and IIa, g confirm these data as regards the derived 5-amino-1,2,3-thiadiazole-4-carbothioamides. Therefore the signals at 183-185 and 168-170 ppm in the ^{13}C NMR spectra of the mixtures were assigned to the 5-amino-1,2,3-thiadiazole-4-NR-carbothioamides IV, and the signals in the 164-166 and 186-187 ppm regions to the 5-R-amino-1,2,3-thiadiazoles V. The proportions of isomers in the mixture were determined from the integral curves in the ^1H and ^{13}C NMR spectra (see Table 4).

The rearrangement of thiadiazoles IV to thiadiazoles V apparently proceeds via the intermediate 2-diazomalonodithioamide VI, and belongs to type 3 of the L'Abbe classification (with participation of the two side-chain atoms) [6]. Since thioamides IV rearrange only partially, it might be expected that this rearrangement is reversible. Actually in the reaction of 5-methylamino-1,2,3-thiadiazole-4-carbonitrile (IIb) with hydrogen sulfide we obtained not thioamide Vb, but thioamide IVb, the product of its rearrangement [7].

In the case of the 5-N-arylamino-1,2,3-thiadiazoles IIe, f a mixture of isomeric thiadiazoles IVe, f and V, e, f is formed with the same proportion of isomers as in the reaction of N-arylamides Ie, f with P_4S_{10}. In contrast to thiadiazoles IVe, f and Ve, f 5-acetamino-1,2,3-thiadiazole-4-carbothioamide (Vj) does not rearrange.



I—VI a R=H; b, R=CH_3; c R=C_4H_9; d R=C_6H_{11}; e R=C_6H_5; f R=$C_6H_4CH_3$-*p*; g R=$C_6H_4OCH_3$-*p*; h R=C_6H_4Br-*p*; i R=$C_6H_2Cl_3$-2,4,6; j R=$COCH_3$

Since the same products are formed in different reactions (thionation, sulfohydrogenation), it might be concluded that the isomer ratio is determined not by the experimental conditions, but by the electron properties of the substituents at amino or carbothioamide nitrogen. Introduction of electron-donor substituents gives predominantly the N-alkyl carbothioamides IVa-d, and introduction of the electron-acceptor acetyl group to the 5-acetamido-1,2,3-thiadiazole Vj, while introduction of aryl radicals (an intermediate case) forms a mixture of thiadiazoles IV and V.

EXPERIMENTAL

IR spectra were recorded with a UR-20 spectrometer with KBr tablets. ^1H NMR spectra were obtained with Perkin-Elmer 12B (60 MHz) and Bruker WP-80 (80 MHz) instruments in DMSO-D_6, with TMS internal standard. ^{13}C NMR spectra were obtained with a Bruker WP-80 (20 MHz) spectrometer, in DMSO-D_6, with TMS internal standard. Mass spectra were recorded with a MAT-311A instrument. Reactions were monitored and compound individuality was confirmed with TLC on Silufol UV-254 plates in the following solvent systems: 3:1 propanol—3% ammonia; 1:1:30 chloroform—methanol—acetic acid; 6:1 chloroform—hexane; and ethanol—chloroform in various proportions.

The synthesis and physicochemical and spectral properties of the following compounds are given in the literature: Ia, b [8]; Id-g [9]; IIb, e, f [7]; Va, b [2].

5-R-Aminosubstituted 1,2,3-thiadiazole-4-carboxamides (Ic, h, i). 2-Thiocarbamoyl-NR-acetamide, 1 mole, was suspended in a sodium ethylate solution (0.1 mole of sodium in 1 liter of absolute ethanol), and 1 mole of benzenesulfonyl azide was added at 0-5°C with stirring. The precipitate that formed after 5 min was filtered off and crystallized from alcohol.

TABLE 4. Spectral Properties and Isomer Proportions in Mixtures of Substituted 5-Amino-1,2,3-Thiadiazole-4-carbothioamides IV and V

Compound	Mass spectrum, m/z* (%)	^{1}H NMR spectrum, δ, ppm (TMS internal standard)	^{13}C NMR spectrum, δ, ppm (TMS internal standard)	Concentration in mixture, %	
				IV	V
Vc (IVc)	M+ 216 (100), 188 (1), 132 (23), 105 (22), 72 (24)	0,9 (3H, q, CH_3); 1,3 (2H, t, CH_2CH_3); 1,6 (2H, t, CH_2CH_2); 3,3 (2H, t, CH_2NH); 3,7 (2H, t, $NHCH_2$); 8,9 (2H, s, NH_2); 9,5 (2H, d, $CSNH_2$); 10,1 (H, s, NH); 10,4 (H, s, CSNH)	135,2 (136,7)** ($C_{(4)}$); 166,7 (167,1) ($C_{(5)}$); 186,1 (183,3) (C=S)	80	20
Vd (IVd)	M+ 242 (64), 214 (10), 181 (28), 122 (100), 98 (33)	1,0...2,1 (11H, m, C_6H_{11}); 8,9 (2H, s, NH_2); 9,5 (2H, d, $CSNH_2$); 10,0 (H, s, CSNH); 10,3 (H, s, NH)	134,1 (136,6) ($C_{(4)}$); 167,0 (167,2) ($C_{(5)}$); 186,9 (182,1) (C=S)	70	30
Vg (IVg)	M+ 266 (100), 238 (5), 221 (62), 173 (35), 134 (34)	3,8 (3,7) (3H, s, OCH_3); 9,1 (2H, s, NH_2); 9,9 (2H, d, $CSNH_2$); 11,7 (H, s, CSNH); 12,4 (H, s, NH)	55,4 (OCH_3); 133,5 (137,2) ($C_{(4)}$); 164,9 (168,1) ($C_{(5)}$); 186,4 (183,8) (C=S)	35	65
Vh (IVh)	M+ 314 (90)***, 286 (13), 105 (100), 88 (82), 60 (68)	7,2...7,8 (4H, m, C_6H_4); 9,1 (2H, s, NH_2); 9,9 (2H, d, $CSNH_2$); 11,9 (H, s, CSNH); 12,8 (H, s, NH)	—	33	67
Vi (IVi)	M+ 338 (17)***, 303 (100), 175 (78), 105 (57), 88 (50)	7,6...7,9 (2H, m, $C_6H_2Cl_3$); 9,1 (2H, s, NH_2); 9,9 (2H, d, $CSNH_2$); 11,5 (H, s, NH); 11,8 (H, s, CSNH)	134,5 (136,5) ($C_{(4)}$); 166,7 (167,1) ($C_{(5)}$); 186,1 (183,3) (C=S)	91	9
Vj	M+ 202 (84), 174 (63), 141 (74), 132 (100), 105 (79)	2,4 (3H, s, CH_3); 10,2 (2H, s, $CSNH_2$); 13,1 (H, s, NH)	22,7 (3H, q, CH_3); 141,0 ($C_{(4)}$); 153,9 ($C_{(5)}$); 168,9 (C=O); 186,9 (C=S)	0	100

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*The five most intense peaks in the mass spectrum are given.

**In the ^{13}C NMR spectrum signals of V are given first, signals of isomer IV are in parentheses.

***Peaks of ions containing ^{79}Br and ^{35}Cl isotopes are given.

N-Substituted α-cyanothioacetamides (IIIe, f). N-substituted α-cyanoacetamide, 1 mole, was suspended in 1 liter of xylene, 2 moles of P_4S_{10} was added, and the mixture was boiled for 1 h. The hot solution was filtered and cooled to 0°C. The precipitated crystals were filtered off and crystallized from water.

5-Acetamino-1,2,3-thiadiazole-4-carbonitrile (IIj). To a suspension of 1 g (8.0 mmoles of 5-amino-1,2,3-thiadiazole-4-carbonitrile (IIa) in 20 ml of chloroform was added 1.24 ml (1.75 mmole) of acetyl chloride and 1.1 ml (1.75 mmole) of triethylamine, and the mixture was held for 5 h at 50°C. Then it was evaporated to dryness and the residue was crystallized from water.

General Procedure for Sulfohydrogenation of 5-NR-amino-1,2,3-thiadiazole-4-carbonitriles (IIa, b, e, f, j). Carbonitrile II, 1 mole, was dissolved in 1 liter of organic solvent, 0.1 mole of catalyst was added, and the mixture was saturated with hydrogen sulfide at 0°C. Reaction conditions for sulfohydrogenation of compounds IIa, d, e, f, j are given in Table 1.

General Procedure for Thionation of 5-amino-1,2,3-thiadiazole-4-NR-carboxamides (IVc-i). Compound IV, 1 mole, was suspended in 1.5 liter of absolute dioxane, and 2 moles of P_4S_{10} were added at 50°C with intense stirring. The mixture was held for 1 h at 101°C; then the hot solution was filtered and the solvent was distilled off. The residue was ground in water and crystallized from alcohol.

Physicochemical constants, yields, melting points, and spectral properties of the synthesized substances are given in Tables 2-4.

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