STUDY OF DIRECTION OF CYCLIZATION OF MALONODITHIOAMIDES AS A METHOD OF INVESTIGATION OF REACTIVITY OF α-DIAZOTHIOACETAMIDES

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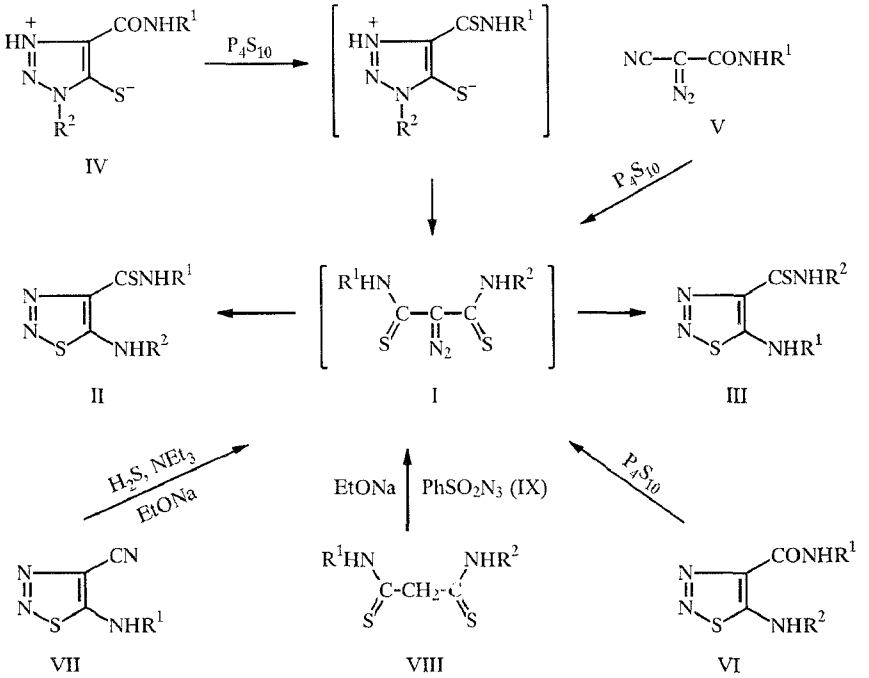
The reaction of malonothioamides with benzene-sulfonyl azide and 2-azido-3-ethylbenzthiazolium tetrafluoroborate gave amides of 2-diazothiomalonic acid, which underwent cyclization to a mixture of 5-N-R-amino-1,2,3-thiadiazole-4-carbothioamides and 5-amino-1,2,3-thiadiazole-4-N-R-carbothioamides. The ratio of the isomeric thiadiazoles formed in this reaction is the same as in the reactions of 2-diazo-2-cyanoacetamides, 5-amino-1,2,3-thiadiazole- and 5-mercapto-1,2,3-triazole-4-carboxamides with P_4S_{10} and of 5-amino-1,2,3-thiadiazole-4-carbonitriles with H_2S; it is characteristic of the influence of substituents on the reactivity of α-diazothioacetamides. It was found that the cyclization of the diazo compounds is accelerated when electron-acceptor substituents are attached to the nitrogen atom of the carbothioamide group.

α-Diazothiocarbonyl compounds are intermediates in the synthesis of 1,2,3-thiadiazole and -triazole derivatives which have a wide spectrum of biological activity [1, 2]. Their existence was confirmed by the isolation of a complex with iron nonacarbonyl [3]. Since α-diazathiones are highly active and slightly stable compounds, which cyclize into the isomeric heterocyclic compounds even under conditions of their preparation, it is impossible to study their reactivity by the usual kinetic methods. However, knowledge of the reactivity characteristics makes it possible to predict the path of the synthesis of the heterocyclic compounds and to control its selectivity.



IV V II I III VII VIII VI

I—VIII a R^2=H, R^1=H; b R^2=H, R^1=Me; c R^2=H, R^1=Bu; d R^2=H, R^1=c-C_6H_{11}; R^2=H, R^1=C_6H_4Me-*p*, e R^2=H, R^1=C_6H_4OMe-*p*; f R^2=H, R^1=C_6H_4Br-*p*; h R^2=H, R^1=COMe, i R^2=H, R^1=Py-2; j R^2=H, R^1=Bz; k R^2=H, R^1=Et; m R^1=R^2=Me; n R^1=R^2=Ph; o R^1=Me, R^2=Ph

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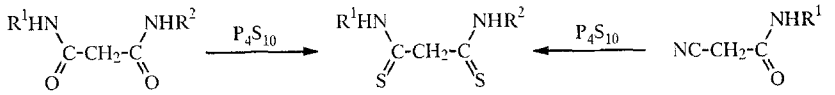
In the present work it is proposed to determine the reactivity of α-diazothioacetamides by studying the direction of the cyclization of diazomalonodithioamides I. The method consists essentially in the determination of the ratio of the isomeric 5-amino-1,2,3-thiadiazole-4-carbothioamides II and III (see scheme), formed during the cyclization of the generated α-diazothioacetamides I having two carbothioamide groups in the molecule with different substituents at the nitrogen atoms.

We have previously shown that compounds I are intermediates in the reactions of compounds IV-VI with phosphorus decasulfide (P_4S_{10}) and nitriles VII with hydrogen sulfide [4-6]. In all these reactions a mixture of isomeric thiadiazoles II and III is formed, such that the direction of the cyclization is independent of the conditions of the generation of the diazo compounds I, but is determined by the properties of substituents R^1 and R^2. Since thiadiazoles II and III in alkaline solutions and on heating in acidic media may rearrange into one another, their ratio may characterize both the reactivity of diazo compounds I and the relative stability of these heterocyclic compounds.

In order to study the reactivity of diazo compounds I, we have carried out their synthesis by the reaction of malonodithioamides VIII with benzenesulfonyl azide (BSA) in the presence of a catalytic amount of sodium ethylate, and also with the azidinium salt IX at 0-20°C, i.e., under conditions excluding the rearrangement processes.

Compounds VIII were obtained by exhaustive thionation with P_4S_{10} of the corresponding malonodiamides X or cyanoacetamides XI:



Xa,b, m-o VIII a, b, e, g, k, m-o XI e, g, k

Since no examples of the "diazo transfer" are known in the literature, we studied the possibility in principle of the realization of this reaction on symmetric malonodithioamines VIIIa, m, n. In this case, as a result of the "diazo transfer" reaction, individual 5-amino-1,2,3-thiadiazoles IIa, m, n were formed, the structure of which was confirmed by the IR, UV, ^1H, and ^{13}C NMR spectroscopy and mass-spectrometry data. The asymmetrically substituted malonodithioamides VIIIb, e, g, k, o in the reaction with BSA in the presence of sodium ethylate, as well as thioamides VIIIb, e in the reaction with the azidinium salt IX, give a mixture of isomeric thiodiazoles II and III in the same ratio as in the preparation of other methods from compounds IV-VI (see scheme). It should be noted that pairs of thiadiazoles IIk, o and IIIk, o were synthesized in the present work for the first time by the "diazo transfer" reaction to dithioamides VIIIk, o, and also by the thionation with P_4S_{10} of the corresponding carboxamides VIk, o. The isomers II*l* and III*l* were obtained by the thionation of compound VI*l* by a method described in [4]. Thus, during the generation of diazamalonodithioamides Ib, e, g, k, o under conditions excluding the rearrangement processes, the same compounds are formed as during their generation from compounds IV-VI by reaction with P_4S_{10} and from nitriles VII by reaction with hydrogen sulfide.

TABLE 1. Content of Isomeric Pairs of 5-N-R^2-Amino-1,2,3-thiadiazole-4-N-R^1-carbothioamides (II) and 5-N-R^1-Amino-1,2,3-thiadiazole-4-N-R^2-carbothioamides (III) and the Competition Constant of the Cyclization of Diazomalonodithioamides I

R^1	R^2	Content, %		K
		II	III	
Me	H	95	5	19
Et	H	90	10	9
Bu	H	86	14	6,1
Bz	H	90	10	9,0
C_6H_{11}-c	H	73	27	2,7
Ph	H	25	75	0,33
C_6H_4Me-*p*	H	27	73	0,37
C_6H_4Br-*p*	H	32	68	0,47
C_6H_4OMe-*p*	H	35	65	0,54
$C_6H_2Cl_3$-2,4,6	H	91	9	10
Py-2	H	0	100	0
COMe	H	0	100	0
Me	Ph	90	10	9,0

TABLE 2. Physicochemical Properties of 5-Amino-1,2,3-thiadiazole-4-carbothioamides IIk-o and IIIk, *l*, o

Compound	mp, °C	IR spectrum (KBr) cm^{-1}	NMR spectrum, δ, ppm		Mass spectra, m/z (%)*
			^1H	^{13}C	
IIk + IIIk	119...121	3340, 3270 (NH), 3130 (CH)	4,6 (2H, d, *J* = 5,6 Hz, CH_2 (III)), 4,9 (2H, d, *J* = 5,6Hz, CH_2 (II)), 7,2...7,4 (5H, m, Ph), 9,0 (2H, s, NH_2 (II)), 9,5; 9,6 (2H, ss, NH_2 (III)), 10,5 (H, t, *J* = 6,4 Hz, NH (III)), 10,9 (H, t, *J* = 6,4Hz, NH (II))	46,21 (CH_2 (II)), 53,55 (CH_2 (III)), 135,52 (4-C (III)), 136,92 (4-C (III)), 167,51 (5-C (II)), 169,08 (5-C (III)), 184,38 (C=S (II)), 186,57 (C=S (III))	
IIo + IIIo	124...125	3315, 3265 (NH), 3140, 2960 (CH)	1,2 (3H, t, *J* = 7,2 Hz, CH_3 (II)), 1,3 (3H, t, *J* = 7,2 Hz, CH_3 (III)), 3,6 (2H, s, CH_2 (III)), 3,7 (2H, m, CH_2 (II)), 8,9 (2H, s, NH_2 (II)), 9,4; 9,5 (2H, s.s NH_2 (III)), 10,1 (H, t, NH (III)), 10,4 (H, t, NH (II))	13,03 (CH_3 (II)), 13,40 (CH_3 (III)), 38,49 (CH_2 (II)), 45,90 (CH_2 (III)), 167,38 (5-C (II)), 169,95 (5-C (III)), 135,22 (4-C (III)), 136,82 (4-C (II)), 183,48 (C=S (II)), 186,51 (C=S (III))	
IIm	125	3160 (NH), 2940 (CH)	2,9...3,2 (6H, t, CH_3, CH_3), 9,6 (H, s, CSNH), 10,2 (H, s, NH)		M^+ 188 (100), 160 (18), 119 (19), 86 (24), 74 (34)
IIn	289	3295 (NH), 2890 (CH)	7,2...7,8 (10H, m, Ph, Ph), 12,1 (H, s, CSNH), 12,5 (H, s, NH)	139,62 (4-C), 162,87 (5-C), 183,09 (C=S)	M^+ 312 (100), 284 (13), 219 (31), 191 (42), 148 (52)
IIo + IIIo	153...155	3335 (NH), 2800 (CH)	1,8 (3H, d, *J* = 3,6 Hz, CH_3 (III)), 3,2 (3H, d, *J* = 3,6Hz, CH_3 (II)), 7,2...7,5 (5H, m, Ph), 9,1 (H, s, $NHCH_3$ (III)), 10,8 (H, d, *J* = 4,4Hz, $NHCH_3$ (II)), 11,0 (H, s, NHPh (III)), 12,5 (H, s, NHPh (II))		

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

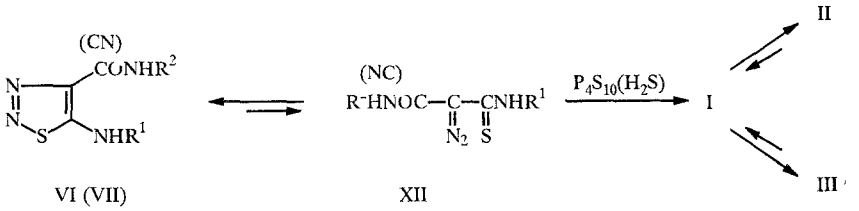
TABLE 3. Yields and Physicochemical Characteristics of 5-Amino-1,2,3-thiadiazole-4-carboxamides VIk, *l*, o and Malonodithioamides VIIIb, e, g, k, m, o

Compound	mp, °C	IR spectrum (KBr) cm^{-1}	PMR spectrum (in DMSO-ℓ_6), δ, ppm	Yield, %
VIk	124	3300, 3196 (NH), 3090, 3060, 2920 (CH), 1625 (C=O)	4,5 (2H, d, J = 4,4 Hz, CH_2), 7,2...7,4 (5H, m, Ph), 8,0 (2H, s, NH_2), 9,1 (H, t, J = = 5,6 Hz, NH)	83
VI ℓ	117	3390, 3350, 3230, 3190, 3120 (NH), 3060, 2966, 2920, 2860 (CH), 1610 (C=O)	1,1 (3H, t, J = 6,8 Hz,, Me), 3,3 (2H, q.d, ^3J = 7,2 Hz, ^5J = 2,8 Hz,, CH_2), 8,0 (2H, s, NH_2), 8,5 (H, t, J = 5,6 Hz, NH)	85
VIo	163	3370 (NH), 3060 (CH), 1625 (C=O)	2,8 (3H, d,, J = 10,4 Hz, Me), 7,2...7,5 (5H, m, Ph), 8,9 (H, s, NH), 11,0 (H, s, NH)	88
VIIIb	128...130	3335, 3300, 3230, 3165 (NH), 2940 (CH)	3,0 (3H, d, J = 5,5 Hz, Me), 3,9 (2H, s, CH_2), 9,5 (2H, d, $CSNH_2$), 10,2 (H, s, CSNH)	17
VIIIe	121	3335, 3300, 3240, 3160 (NH), 3065 (CH)	4,0 (2H, s, CH_2), 7,1...7,8 (5H, m, Ph), 9,4 (2H, d, $CSNH_2$), 11,5 (H, s, CSNH)	13
VIIIg	136...138	3335, 3300, 3235, 3160 (NH), 2960 (CH)	3,8 (3H, s, Me), 4,0 (2H, s, CH_2), 7,0...7,9 (4H, m, C_6H_4), 9,6 (2H, d, $CSNH_2$), 11,1 (H, s, CSNH)	16
VIIIk	96	3200 (NH), 2970 (CH)		15
VIII ℓ	164...166	3235, 3095 (NH), 3005 (CH)	2,9 (3H, s, Me), 3,0 (3H, s, Me), 3,9 (2H, s, CH_2), 10,0 (2H, s, NH, NH)	25
VIIIo	170...171	3390, 3220 (NH), 3005 (CH)	2,9 (3H, d, J = 5,5 Hz, Me), 3,9 (2H, s, CH_2), 7,1...7,7 (5H, m, Ph), 10,3 (H, s, NHMe), 11,6 (H, s, NHPh)	24

This leads to the conclusion that in all the reactions studied the ratio of thiadiazoles II and III is determined by the reactivity of diazo compounds I.

The problem of the transformation mechanism of compounds VI and VII into diazo compound I still remains unsolved. If it is assumed that these reactions proceed via the thiadiazoles II and III, it must be concluded that substituents R^1 and R^2 equally influence both the reactivity of the diazo compounds I and the thermodynamic stability of heterocyclic compounds II and III, which for a series made up from 13 compounds appears not to be very probable.

For these reactions one further mechanism can be proposed:



VI (VII) XII

This is in conformity with the possibility of transformation of analogs of compounds XII — diazo compounds Va-c, into thiadiazoles II and III and with the reactivity of nitriles VII in the reaction with hydrogen sulfide. It is known that deprotonation of 5-amino-1,2,3-thiadiazoles leads to ring opening, while 5-N,N^1-dimethylamino-1,2,3-thiadiazole-4-carbonitrile, unlike 5-amino- and 5-methylamino-1,2,3-thiadiazole-4-carbonitriles, react with hydrogen sulfide under more rigorous conditions [7].

To establish a relationship between the properties of the substituents and the reactivity, the competition constants of the cyclization of diazo compounds I into the isomeric thiadiazoles II and III were determined.

$$K = \frac{k_H}{k_R} = \frac{[II]}{[III]},$$

where K is the competition constant; $k_{H,R}$ is the rate constant of the formation of thiadiazoles II and III, respectively; [II] and [III] are the concentrations of thiadiazoles II and III in mixtures. The calculated competition constants are listed in Table 1.

Analyzing the data of Table 1, the following reactivity series can be composed:

Alk < H < Ar < Py;
Me < Et < Bz < C_6H_{11}-cyclo;
C_6H_4OMe-*p* < C_6H_4Me-*p* ~ C_6H_4Br-*p* < Ph.

In turn, in the examination of these series the tendency is distinctly seen for the cyclization of the diazo compounds I to be accelerated when electron-accepting substituents are attached to the nitrogen atom of the carbothioamide group.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord IR-75 spectrophotometers in KBr tablets. The ^1H and ^{13}C NMR spectra were run in DMSO-d_6 on a Varian VXR-400 spectrometer at frequencies of 399.9 and 100.6 MHz, respectively. Tetramethylsilane was used as internal standard. The mass spectra were recorded on an MAT-311A spectrometer (accelerating voltage 70 eV). The course of the reactions was monitored and the purity of the compounds was verified by means of TLC on Silufol UV-254 plates in an ethanol—chloroform (1:15) system of solvents or in chloroform.

The data of the elemental analysis corresponded to the calculated values. The physicochemical and spectral characteristics of the compounds are given in Tables 2 and 3.

The synthesis and the characteristics of thiadiazoles IIa-h and IIIb-i were published in [4-6]. Carboxamides VIk, *l* were obtained in analogy to [5].

5-Phenylamino-1,2,3-thiadiazole-4-N-methylcarboxamide (VIo). A 1-g portion (7 mmoles) of 5-chloro-1,2,3-thiadiazole-4-N-methyl carboxamide [8] was dissolved in 100 ml of ethanol and 1 ml (11 mmoles) of aniline was added at room temperature. The mixture was stirred for 2 h, the solvent was distilled off at reduced pressure, and the residue was suspended in water and filtered off. The product was crystallized from a chloroform—hexane (1:5) mixture.

Thionation of 5-N-R^2-Amino-1,2,3-thiadiazole-4-N-R^1-carboxamides VIk, *l*, o. A 1-mole portion of compound VIk, *l*, o was suspended in 1.5 liters of dry dioxane. A 0.5-mole portion of P_4S_{10} was added at 50°C with vigorous stirring, and the mixture was boiled for 1 h. The hot solution was filtered off and the solvent was distilled off at reduced pressure. The residue was rubbed in water to an oil. In the case of compound VIk, the product was boiled in water with carbon and filtered. The resinous precipitate was dissolved in hot ethanol, filtered, and the solvent was distilled off. The residue was rubbed in chloroform,

filtered off, washed with chloroform, and a mixture of isomers IIk and IIIk was obtained and crystallized from ethanol. Yield 43%. Thiadiazoles II*l* and III*l* were isolated from the oil by extraction with hot water with carbon and recrystallized twice from water. Yield 30%. Isomers IIo and IIIo were obtained by rubbing the oil in cold water to a crystalline residue, which was filtered off and recrystallized from ethanol. Yield 60%.

β-N-R^1,β-N-R^2-Malonodithioamides VIIIa, b, e, g, k, m-o. A 1-mole portion of the corresponding malonodiamide Xa, b, m-o or cyanoacetamide XIe, g, k was suspended in 1 liter of dry dioxane, and 1 mole of P_4S_{10} was added at 50°C with vigorous stirring. The mixture was boiled for 2 h. The hot suspension was filtered off, and the filtrate was evaporated at reduced pressure. Malonodithioamides VIII were extracted from the residue by hot water with carbon. The precipitate that separated out after cooling was crystallized from water or ethanol. The yield of compound VIIIa was 21%, mp 110°C; the literature [9] gives 112°C. The yield of dithioamide VIIIm was 15%, mp 150°C (from ethanol); the literature [10] gives 152°C.

"Diazo Transfer" to Malonodithioamides VIIIa, b, e, g, k, m-o. A. A 1-mole portion of the corresponding malonodithioamide VIIIa, b, e, g, k, m-o was suspended in a solution of 0.1 mole of sodium ethylate in 1 liter of ethanol, and 1 mole of benzenesulfonyl azide was added with stirring at 0-20°C. The precipitate that separated out after 10 min was filtered off and crystallized from ethanol of water. The yields of thiadiazoles II and III varied from 30-80%.

B. A 1-mole portion of dithioamide VIIIb or VIIIe was dissolved in 500 ml of methanol. The solution was cooled to 0°C and 1 mole of diazonium salt IX was added with stirring. The reaction mixture was held for 2 h at 0-10°C. The precipitate was filtered off and recrystallized from ethanol. The yield of isomers IIb and IIIb was 47%, IIe and IIIe — 27%.

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