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STUDY OF THE CHARACTERISTICS OF REARRANGEMENTS OF 5-AMINO-1,2,3-THIADIAZOLE-4-CARBOTHIOAMIDES

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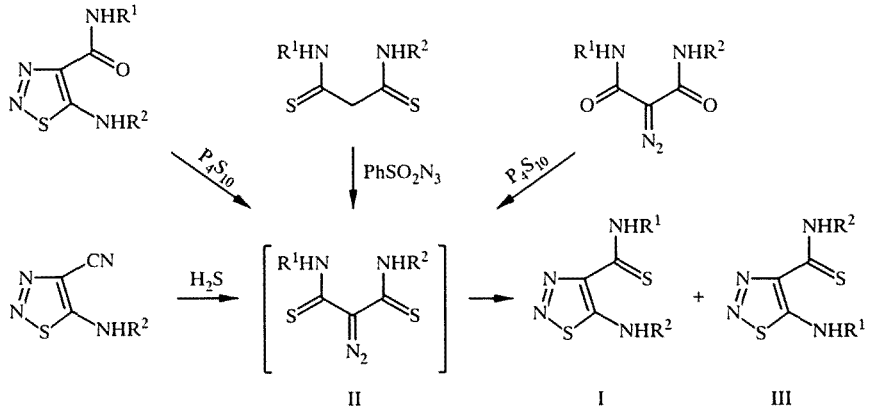
Using NMR spectroscopy, we have determined the relative stability and the effect of the solvent on the ratio of isomeric N,N-disubstituted 5-amino-1,2,3-thiadiazole-4-carbothioamides in a mixture. We carried out chromatographic separation of a mixture of 5-benzylamino-1,2,3-thiadiazole-4-N-methylcarbothioamide and 5-methylamino-1,2,3-thiadiazole-4-N-benzylcarbothioamide and we show that when each compound dissolves, it rapidly isomerizes with formation of the initial composition. We conclude that the orientation of the rearrangement process is thermodynamically controlled.

Earlier we described novel rearrangements of amides and thioamides of 5-hydroxy-1,2,3-triazole- and 5-amino-1,2,3-thiadiazole-4-carboxylic acid [1-3], occurring with participation of two atoms in the side chain [4]. We also showed that these rearrangements occur through highly reactive diazo compounds having two diazophilic groups in the molecule [1]. Methods for generation of such diazo compounds are described in [1-3]. We showed in [5] that rearrangements of 5-hydroxy-1,2,3-triazolyl-4-carboxamides are reversible, and the orientation of the process is determined by the relative stability of isomeric heterocycles (thermodynamic control). In contrast to 5-hydroxy-1,2,3-triazoles, rearrangements of 5-amino-1,2,3-thiadiazoles to 5-mercapto-1,2,3-triazoles occurring in basic media are irreversible, and the orientation of the reaction is determined by the reactivity of the intermediate diazo compound [6] (kinetic control).



The thioamides of 2-diazomalonic acid II formed in the reaction of thionation of diazomalonodiamides, 5-amino-1,2,3-thiadiazole-, and 5-mercapto-1,2,3-triazole-4-carboxamides, and also in the reaction of diazo transfer to malonodithioamides [2], are converted to a mixture of isomeric 5-R-amino-1,2,3-thiadiazole-4-N-R^1-carbothioamides. Before our investigation, the factors determining the orientation of cyclization of diazomalonodithioamides II were not understood and it was not clear what determines the orientation of the rearrangement of 5-amino-1,2,3-thiadiazoles I and II occurring in neutral and acid media.

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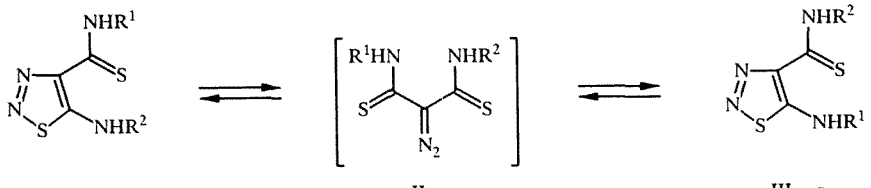
TABLE 1. Equilibrium Constant and Composition of a Mixture of I and III in Different Solvents

Radicals R^1-R^2 in compounds I and III	Equilibrium constant K = [III]/[I] and composition of the mixture of I and III (I-III), % in the solvents					
	C_6D_6	$CDCl_3$	$(CD_3)_2CO$	CD_3OD	ДМСО-D_6	CDCN
Me-Bu (b)	2,23	1,63	4,55	2,03	1,94	5,67
	(31...69)	(38...60)	(18...82)	(33...67)	(34...66)	(15...85)
Me-CH_2Ph (d)	1,27	1,08	3,35	1,94	1,70	2,45
	(44...56)	(48...52)	(23...77)	(34...66)	(37...63)	(29...71)
Me-Ph (e)	0,754	1,33	7,33	11,5	15,7	19,0
	(57...43)	(43...57)	(12...88)	(8...92)	(6...94)	(5...95)
Me-H (f)	2,57	1,13	4,88	11,5	19,0	7,33
	(28...72)	(47...53)	(17...83)	(8...92)	(5...95)	(12...88)
H-C_6H_4OMe (m)	7,24	1,00	2,33	1,86	1,63	2,70
	(58...42)	(50...50)	(30...70)	(35...65)	(38...62)	(27...73)

TABLE 2. Compositions of the Mixture and Equilibrium Constants in DMSO-d_6 for Compounds Ia-q and IIIa-q

Compounds I, III	Comp. of isomer mixture in DMSO-d_6, %		Equilib. const. K = [III]/[I]	Compounds I, III	Comp. of isomer mixture in DMSO-d_6		Equilib. const. K = [III]/[I]
	I	III			I	III	
a	31	69	2,23	j	92	8	0,087
b	34	66	1,94	k	25	75	3,0
c	17	83	4,88	l	30	70	2,33
d	37	63	1,70	m	38	62	1,63
e	6	94	15,7	n	33	67	2,03
f	5	95	19,0	o	91	9	0,099
g	80	20	0,25	p	< 0,1	> 99,9	> 10000
h	70	30	0,43	q	< 0,1	> 99,9	> 10000
i	90	10	0,11				

In order to clarify the question of the reversibility of cyclization of compounds II, we investigated the composition of mixtures of compounds Ib,d-f,k,m and IIIb,d-f,k,m in different solvents by proton magnetic resonance spectroscopy. The PMR spectrum of the mixture of isomers was recorded immediately after dissolution and after drying. The isomer ratio wa determined from the ratio of the integrated intensities of the signals from the protons of the methyl and methylene groups on the nitrogen atoms of the 5-amino- and 4-thiocarbamoyl functional groups, and also (if possible) from the ratio of the integrated intensities of the signals from the NH protons; the measurement error was not more than 4%. From the data obtained we see that the composition of the mixture strongly depends on the nature of the solvent (see Table 1) and does not change over time. The latter suggests that this reaction is an equilibrium. Furthermore, we separated the two isomers Id and IIId using preparative thin-layer chromatography and we observed that upon dissolution of each isomer, formation of the initial mixture occurs; the equilibrium isomer ratio is attained in at least 3 min.



I a-q II a-q III a-q

I, II, III a R^1 = Me, R^2 = *i*-Pr, b Bu, c *cyclo*-C_6H_{11}, d CH_2Ph, e Ph, f H; g R^1 = H, R^2 = Bu, h *cyclo*-C_6H_{11}, i CH_2, j Et, k Ph, l C_6H_4Me-*p*, mC_6H_4OMe-*p*, n C_6H_4Br-*p*, o $C_6H_2Cl_3$-2,4,6, p Ac, q Py-2

In Table 2, we present the compositions of the mixture and the equilibrium constants in DMSO-d_6 for compounds Ia-c and IIIa-c. The substituents on the nitrogen atom of the 5-amino group can be arranged in the following series according to the degree of increase in the thermodynamic stability of the thiadiazole ring: Me < CH_2Ph < Bu < *i*-Pr < *c*-C_6H_{11} < Ph

TABLE 3. PMR Spectra of Compounds I and III

Compound	Chemical shifts (DMSO - d_6), δ, ppm				Compound	Chemical shifts (DMSO - d_6), δ, ppm			
	4-CSNHR	5-NHR	4-CSNHR	5-NHR		4-CSNHR	5-NHR	4-CSNHR	5-NHR
Ia	10,7	9,8	1,30 (Me), 4,5...4,9 (CH)	3,1 (Me)	Ii	10,55	9,61, 9,53	4,95 (CH_2)	—
IIIa	10,0	10,4	3,0 (Me)	1,27 (Me), 3,15...3,65 (CH)	IIIi	8,99	10,91	—	4,58 (CH_2)
Ib	10,8	9,7	3,5...3,8 (CH_2)	3,11 (Me)	Ij	10,41	9,44, 9.54	3,66...3,75 (CH_2)	—
IIIb	9,98	10,2	3,1 (Me)	3,15...3,45 (CH_2)	IIIj	8,94	10,60	—	3,26...3,38(CH_2)
Ic	10,0	9,7	4,2...4,6 (CH)	3,09 (Me)	Ik	11,8	9,1	7,13...7,9 (Ph)	—
IIIc	9,6	10,46	3,12 (Me)	3,1...3,4 (CH)	IIIk	9,9	12,8	—	7,12...7,9 (Ph)
Id	10,3	9,70	4,93 (CH_2), 7,35 (Ph)	3,03 (Me)	Il	11,8	9,1	2,2 (Me), 7,1...7,5 (C_6H_4)	—
IIId	10,5	10,88	3,09 (Me)	4,59 (CH_2), 7,35 (Ph)	IIIl	9,9	12,6	—	2,3 (Me), 7,1...7,5 (C_6H_4)
Ie	12,5	8,9	7,1...7,5 (Ph)	2,87 (Me)	Im	11,7	9,1	3,8 (OMe), 7,1...7,5 (C_6H_4)	—
IIIe	10,8	11,0	3,18 (Me)	7,1...7,5 (Ph)	IIIm	9,7	12,4	—	3,7 (OMe), 7,1...7,5(C_6H_4)
If	10,4	9,0	—	3,0 (Me)	In	11,9	9,1	7,2...7,8 (C_6H_4)	—
IIIf	9,2	10,2	3,1 (Me)	—	IIIn	9,9	12,8	—	7,2...7,8 (C_6H_4)
Ig	10,4	8,9	3,7 (CH_2)	—	Io	11,8	9,1	7,6...7,9 (C_6H_2)	—
IIIg	9,5	10,1	—	3,3 (CH_2)	IIIo	9,9	11,5	—	7,6...7,9 (C_6H_2)
Ih	10,0	8,9	4,1...4,5 (CH)	—	IIIp	10,2	13,1	—	2,4 (Me)
IIIh	9,5	10,4	—	3,1...3,4 (CH)	IIIq	10,0	13,2	—	7,0...8,6 (C_5H_4N)

As we see from this series, the bulkier substituents stabilize the thiadiazole ring. Evidence for this comes from the correlation we found between the logarithms of the equilibrium constants in DMSO-d_6 and the induction and steric substituent constants using the Taft equation [7]:

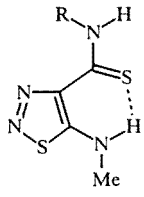
$$\lg([III]/[I]) = 0 \times \sigma^* + (1.1 \pm .2) \times E_s,\ r = 0.996$$

We should note that from this series we get the values for the monosubstituted thiadiazoles I and III, although for them we also observe an increase in the fraction of the isomer with the bulkier substituent on the nitrogen atom of the 5-amino group:

$$Me < Et < CH_2Ph < Bu < c\text{-}C_6H_{11} < Ph < H$$

$$\lg([III]/[I]) = 0 \times \sigma^* + (1.2 \pm .2) \times E_s,\ r = 0.990$$

As we see from the equations obtained, the equilibrium constants depend only on the steric constants and do not depend at all on the induction effect of the substituents. The higher stability of the structure with the bulkier substituent on the nitrogen atom of the amino group can be explained by comparing the tautomeric forms A and B. These structures are more stable than the other isomers (B and D) as a result of formation of a hydrogen bond between the sulfur atoms of the thioamide group and the hydrogen atom of the amino functional group. In turn, as a result of repulsion between the substituent R (larger in volume than the methyl group) and the thiadiazole ring, the sulfur and hydrogen atoms prove to be closer in structure B than in structure A and form a stronger hydrogen bond, which leads to greater stabilization of structure B compared with structure A. The predominance in the mixture of the isomer with the unsubstituted amino group can be explained with similar reasoning.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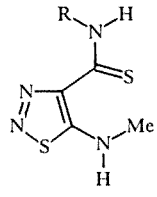
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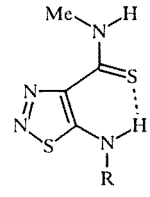
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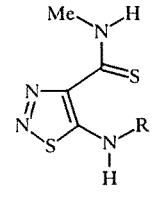
D

Thus, as a result of our investigations, we have shown that cyclization of the diazomalonodithioamides II is reversible, while the orientation of the rearrangement of thiadiazoles I and III is thermodynamically controlled and is determined by the relative stability of the isomeric heterocycles: the bulkier substituent on the nitrogen atom of the 5-amino group stabilizes the ring as a result of formation of a hydrogen bond with the sulfur atom of the thioamide group.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on the Bruker WR-80 and VXR-400, internal standard HMDS. The IR spectra were recorded on the IR-75 in KBr disks. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in the systems: chloroform, 15:1 chloroform–hexane, 15:1 chloroform–ethanol. The melting points were uncorrected. Preliminary chromatographing was done on glass plates; the sorbent was a 1:1 mixture of silica gel 40/100μ and 100/250μ, the eluent was chloroform.

The elemental analysis data for C, H, N, and S for all the synthesized compounds correspond to the calculated values.

5-Methylamino-4-N-isopropylthiocarbamoyl-1,2,3-thiadiazole (Ia, $C_7H_{12}N_4S_2$) and 5-isopropylamino-4-N-methylthiocarbamoyl-1,2,3-thiadiazole (IIIa, $C_7H_{12}N_4S_2$) (mixture). 2.2 g (0.01 moles) P_4S_{10} was added to a solution of 1.86 g (0.01 moles) 5-isopropylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole in 100 ml absolute dioxane at 80°C. The mixture was boiled for 2 h; the solvent was driven off at reduced pressure and the residue was poured into 100 ml water. The tarry material obtained was triturated and crystallized from water, then from alcohol. Yield 0.76 g (38%), mp 96°C, IR spectrum: 3360, 3110, 3050 (NH), 2965, 2920 cm^{-1} (CH).

The following compounds were obtained analogously.

5-Methylamino-4-N-butylthiocarbamoyl-1,2,3-thiadiazole (Ib, $C_8H_{14}N_4S_2$) and 5-butylamino-4-N-methylthiocarbamoyl-1,2,3-thiadiazole (IIIb, $C_8H_{14}N_4S_2$) from 5-butylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole, yield 42%, mp 73°C, IR spectrum: 3370, 3330 (NH), 2930, 2855 cm^{-1} (CH).

5-Methylamino-4-N-cyclohexylthiocarbamoyl-1,2,3-thiadiazole (Ic, $C_{10}H_{16}N_4S_2$) and 5-cyclohexylamino-4-N-methylthiocarbamoyl-1,2,3-thiadiazole (IIIc, $C_{10}H_{16}N_4S_2$) from 5-cyclohexylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole, yield 44%, mp 89°C, IR spectrum: 3310, 3100, 3040 (NH), 2920, 2850 cm^{-1} (CH).

5-Methylamino-4-N-benzylthiocarbamoyl-1,2,3-thiadiazole (Id, $C_{11}H_{12}N_4S_2$) and 5-benzylamino-4-N-methylthiocarbamoyl-1,2,3-thiadiazole(IIId, $C_{11}H_{12}N_4S_2$) from5-benzylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole,yield 41%, mp 70°C, IR spectrum: 3335, 3260 cm^{-1} (NH).

5-Methylamino-4-N-phenylthiocarbamoyl-1,2,3-thiadiazole (Ie, $C_{10}H_{10}N_4S_2$) and 5-phenylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole (IIIe, $C_{10}H_{10}N_4S_2$) from 5-phenylamino-4-N-methylcarbamoyl-1,2,3-thiadiazole, yield 88%, mp 158°C, IR spectrum: 3330, 2980 cm^{-1} (NH).

5-Amino-4-N-methylthiocarbamoyl-1,2,3-thiadiazole (IIIf, $C_4H_6N_4S_2$) and 5-methylamino-4-thiocarbamoyl-1,2,3-thiadiazole (If, $C_4H_6N_4S_2$) from 5-amino-4-N-methylcarbamoyl-1,2,3-thiadiazole, yield 74%, mp 138-140°C, IR spectrum: 3300, 3260 cm^{-1} (NH).

5-Amino-4-N-butylthiocarbamoyl-1,2,3-thiadiazole (Ig, $C_7H_{12-4}S_2$) and 5-butylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIg, $C_7H_{12}N_4S_2$) from 5-butylamino-4-carbamoyl-1,2,3-thiadiazole, yield 34%, mp 116-117°C, IR spectrum: 3320, 3270, 3150 (NH), 2920, 2840 cm^{-1} (CH).

5-Amino-4-N-cyclohexylcarbamoyl-1,2,3-thiadiazole (Ih, $C_9H_{14}N_4S_2$) and 5-cyclohexylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIh, $C_9H_{114}N_4S_2$) from 5-cyclohexylamino-4-carbamoyl-1,2,3-thiadiazole, yield 57%, mp 96°C, IR spectrum: 3330, 3270 (NH), 2920, 2840 cm^{-1} (CH).

5-Amino-4-N-benzylthiocarbamoyl-1,2,3-thiadiazole (Ii, $C_{10}H_{10}N_4S_2$) and 5-benzylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIi, $C_{10}H_{10}N_4S_2$) from 5-benzylamino-4-carbamoyl-1,2,3-thiadiazole, yield 44%, mp 108°C, IR spectrum: 3330, 3190 (NH), 2920, 2840 cm^{-1} (CH).

5-Amino-4-N-ethylthiocarbamoyl-1,2,3-thiadiazole (Ij, $C_5H_8N_4S_2$) and 5-ethylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIj, $C_5H_8N_4S_2$) from 5-ethylamino-4-carbamoyl-1,2,3-thiadiazole, yield 38%, mp 115°C, IR spectrum: 3320, 3180 (NH), 2940 cm^{-1} (CH).

5-Amino-4-N-phenylthiocarbamoyl-1,2,3-thiadiazole (Ik, $C_9H_8N_4S_2$) and 5-phenylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIk, $C_9H_8N_4S_2$) from 5-amino-4-N-phenylcarbamoyl-1,2,3-thiadiazole, yield 36%, mp 120-121°C, IR spectrum: 3318, 3170 (NH), 2940 cm^{-1} (CH).

5-Amino-4N-p-methoxyphenylthiocarbamoyl-1,2,3-thiadiazole (Il, $C_{10}H_{10}N_4S_2$) and 5-p-methylphenylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIℓ, $C_{10}H_{10}N_4S_2$) from 5-amino-4-N-p-methylphenylcarbamoyl-1,2,3-thiadiazole, yield 42%, mp 130°C, IR spectrum: 3290, 3200 (NH), 2930 cm^{-1} (CH).

5-Amino-4-N-p-methoxyphenylthiocarbamoyl-1,2,3-thiadiazole (Im, $C_{10}H_{10}N_4OS_2$) 5-p-methoxyphenylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIm, $C_{10}H_{10}N_4OS_2$) from5-amino-4-N-p-methoxyphenylcarbamoyl-1,2,3-thiadiazole,yield 66%, mp 169°C, IR spectrum: 3310, 3200 (NH), 2920 cm^{-1} (CH).

5-Amino-4-N-p-bromophenylthiocarbamoyl-1,2,3-thiadiazole (In, $C_9H_7BrN_4S_2$) and 5-p-bromophenylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIn, $C_9H_7BrN_4S_2$) from 5-amino-4-N-p-bromophenylcarbamoyl-1,2,3-thiadiazole, yield 30%, mp 167°C, IR spectrum: 3310, 3190 (NH), 2920 cm^{-1} (CH).

5-Amino-4-N-(1,2,3-trichlorophenyl)thiocarbamoyl-1,2,3-thiadiazole (Io, $C_9H_5Cl_3N_4S_2$) and 5-(1,2,3-trichlorophenyl)amino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIo, $C_9H_5Cl_3N_4S_2$) from 5-amino-4-N-(1,2,3-trichlorophenyl)carbamoyl-1,2,3-thiadiazole, yield 42%, mp 115°C, IR spectrum: 3320, 3190 (NH), 3090 cm^{-1} (CH).

5-Acetylamino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIp, $C_5H_6N_4OS_2$) from 5-acetylamino-4-carbamoyl-1,2,3-thiadiazole, yield 66%, mp 156°C, IR spectrum: 3340, 3305 (NH), 1695 cm^{-1} (C=O).

5-(2-Pyridyl)amino-4-thiocarbamoyl-1,2,3-thiadiazole (IIIq, $C_8H_7N_5S_2$) from 5-amino-4-N-(2-pyridyl)carbamoyl-1,2,3-thiadiazole, yield 32%, mp 235°C, IR spectrum: 3280, 3170 (NH), 3000 cm^{-1} (CH).

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