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SULFUR-CONTAINING DERIVATIVES OF FIVE-MEMBERED CYCLIC SULFONES.

2.[*] INTRAMOLECULAR CYCLIZATION OF ISOTHIOUREIDOTHIOLENE 1,1-DIOXIDE SALTS

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cis-2-Imino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-dioxides were obtained by intramolecular cyclization of 4-isothioureido-2-thiolene 1,1-dioxide salts. The reaction of N-substituted thioureas with 4-bromo-2-thiolene 1,1-dioxide leads to 3-substituted cis-2-imino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-dioxides.

Compounds that contain a thiazolidine ring are of interest as diuretics, CNS stimulators [2], and substances that have anti-inflammatory activity [3]. We have previously reported [1, 4] the synthesis of isothioureidothiolene 1,1-dioxide salts. In a continuation of our research we studied the possibility of the use of these salts to obtain condensed two-ring systems that contain thiazolidine and thiolane 1,1-dioxide rings.

We established that 4-isothioureido-2-thiolene 1,1-dioxide hydrobromides Ia, b in aqueous solutions in the presence of sodium bicarbonate form products of intramolecular cyclization – cis-2-imino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-dioxides IIa, b.

Other isothioureidothiolene 1,1-dioxide salts [1] do not undergo this sort of transformation under these conditions. Considering the fact of the formation of salts Ia, b from thiourea and 4-bromo-2-thiolene 1,1-dioxides [1, 4], as well as the ability of these salts to undergo intramolecular cyclization, we investigated the reaction of 4-bromo-2-thiolene

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[*] See [1] for Communication 1.

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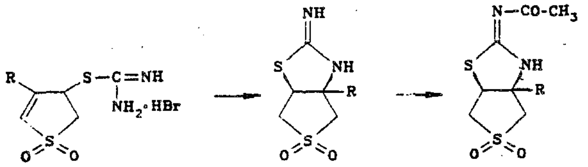
TABLE 1. Conditions for Obtaining the Synthesized Compounds and Their Characteristics

Compound	mp,* °C	Reaction conditions		Found, %			Empirical formula	Calc., %			Yield, %
		solvent vol., ml	time, h	Cl(Br)	N	S		Cl(Br)	N	S	
IIb	202—204	30	1	—	13,4	31,1	$C_6H_{10}N_2O_2S_2$	—	13,6	31,1	14
IIa	196—197	30	2	—	15,0	33,2	$C_5H_8N_2O_2S_2$	—	14,6	33,3	56
Va	289—290	20	2	(27,6)	9,4	21,9	$C_6H_{10}N_2O_2S_2 \cdot HBr$	(27,9)	9,8	22,3	74
Vb	218—219	30	2	(25,8)	9,3	20,5	$C_8H_{12}N_2O_2S_2 \cdot HBr$	(25,5)	8,9	20,4	81
Vc	257—258	50	4	(22,3)	—	18,1	$C_{12}H_{14}N_2O_2S_2 \cdot HBr$	(22,0)	—	17,7	66
Vd	301—302	40	3	(37,7)	—	14,9	$C_{11}H_{11}BrN_2O_2S_2 \cdot HBr$	(37,3)	—	15,0	81
Ve	257—258	40	10	16,9 (19,1)	6,6	15,0	$C_{11}H_{10}Cl_2N_2O_2S_2 \cdot HBr$	17,0 (19,1)	6.7	15,3	55
Vf	229—231	40	12	23,1 (17,4)	6,2	14,3	$C_{11}H_9Cl_3N_2O_2S_2 \cdot HBr$	23,5 (17,7)	6,2	14,1	73
VIa	210—212	50	2	—	11,7	25,9	$C_8H_{12}N_2O_3S_2$	—	11,3	25,8	80
VIb	180—183	50	2	—	10,6	23,5	$C_{10}H_{14}N_2O_3S_2$	10,2	23,4	—	36
VIc	201—204	50	2	—	8,8	20,2	$C_{14}H_{16}N_2O_3S_2$	8,6	19,8	—	69
VId	266—267	50	2	(20,7)	—	16,1	$C_{13}H_{13}BrN_2O_3S_2$	—	16,5	(20,5)	53
VIe	195—196	50	2	19,0	7,5	17,1	$C_{13}H_{12}Cl_2N_2O_3S_2$	7,4	16,9	18,7	65
VIf	210—212	50	2	25,5	6.5	15,6	$C_{13}H_{11}Cl_3N_2O_3S_2$	6,8	15,5	25,7	79
IIIa	187—189	60	2	—	11,8	27,8	$C_7H_{10}N_2O_3S_2$	12,0	27,4	—	73

*The compounds were crystallized: IIb and VIa, c, e, f from ethanol, IIa and Va from ethanol—water (1:1), Vb-f and VIb from water, VId from CH_3COOH, and IIIa from DMF.

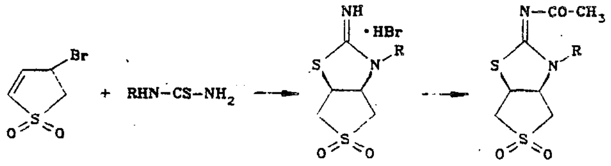
1,1-dioxide (IV) with N-substituted thioureas in order to obtain two-ring thiazolidines in one step. We established that the reaction of such thioureas with sulfone IV in isopropyl alcohol at 80°C for 2-12 h leads to cis-2-imino-3-alkyl(aryl)-4,6,7,8-tetrahydrothieno[3,4-d]-thiazole 5,5-dioxide hydrobromides Va-f. We assumed cis fusion of the thiolane 1,1-dioxide and thiazolidine rings in IIa, b and Va-f on the basis of data on the intramolecular cyclization reactions of derivatives of thiolene 1,1-dioxides [5, 6].



Ia,b IIa,b IIIa

I—III a R=H; b $R=CH_3$

Compounds Va-f are readily acylated by acetic anhydride in water in the presence of sodium acetate to give 3-substituted cis-2-acylimino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-dioxides VIa-f, while base IIa reacts with acetic anhydride in the absence of sodium acetate to give the corresponding mono-2-acylimino derivative IIIa.



IV Va-f VIa-f

V, VI a $R=CH_3$; b $R=CH_2CH=CH_2$; c $R=CH_2C_6H_5$; d $R=p\text{-}BrC_6H_4$; e $R=2,6\text{-}Cl_2C_6H_3$; f $R=2,4,6\text{-}Cl_3C_6H_2$

The characteristics of the synthesized compounds are presented in Tables 1 and 2. To establish the structures of IIa, b, Va-f, and VIa-f we investigated their IR and ^{13}C NMR spectra (Table 2). In the IR spectra of Va-f a band of the stretching vibrations of the C=N bond is observed at 1640-1650 cm^{-1}; this is characteristic for thiazolidines that have an exocyclic azomethine bond [7]. The absorption frequencies of the stretching vibrations of the C=O bond observed in the spectra of acyl derivatives VIa-f at 1610-1650 cm^{-1} are characteristic for acylimines [8], and the location of the band of the stretching vibrations of

TABLE 2. Spectral Characteristics of the Synthesized Compounds*

Compound	IR spectrum, cm^{-1}					^{13}C NMR spectrum, δ, ppm		
	$\nu_{C=N}$	$\nu_{C=O}$	ν_{SO_2}	$\nu_{=N-H}$ (ν_{N-H})	$\delta_{=N-H}$	$C_{(8)}$, d	$C_{(7)}$, d	Δδ
IIb	1640	—	1110, 1290	3440 (3300)	1590	80,4**	54,5	25,9
IIa	1650	—	1140, 1280	3430 (3310)	1600	72,4	49,0	23,4
Va	1640	—	1115, 1310	3280	1590	66,2	39,5	26,7
Vb	1640	—	1100, 1310	3380	1590	68,6	42,7	25,9
Vc	1650	—	1115, 1315	3370	1600	68,2	42,8	25,4
Vd	1650	—	1135, 1305	3320	1575	69,8	42,0	27,8
Ve	1640	—	1130, 1310	3320	1565	69,1	44,4	24,7
Vf	1650	—	1130, 1300	3420	1555	71,1	46,8	24,3
VIa	1540	1610	1125, 1300	—	—	62,0	39,4	22,6
VIb	1520	1620	1110, 1305	—	—	66,2	42,3	23,9
VIc	1535	1615	1120, 1310	—	—	67,3	42,2	25,1
VId	1500	1630	1110, 1300	—	—	68,3	41,9	26,4
VIe	1520	1650	1130, 1290	—	—	67,2	43,7	23,5
VIf	1540	1640	1120, 1290	—	—	68,7	43,8	24,9
IIIa	1520	1660	1130, 1330	—	—	69.6	42,2	27,4

*Solvents: CH_3OD for IIa, b, D_2O for Va and VIa, and CF_3COOH with the addition of 5% (by volume) d_6-acetone for Vb-f, VIb-f, and IIIa.

**Singlet.

the C=N bond at 1500-1540 cm^{-1} constitutes evidence for the existence of conjugation between the C=O and C=N groups [9]. These data make it possible to conclude that 2-imino(acylimino)-thiazolidine rings are present in V and VIa-f; this is possible only when substituent R is attached to the endocyclic nitrogen atom. In contrast to thiazolidines Va-f and VIa-f, the imino structure of which is fixed by radical R, two tautomeric forms – aminothiazoline and iminothiazolidine – may be realized for two-ring systems IIa, b and IIIa. To establish the structures of these compounds we compared their ^{13}C NMR spectra with the spectra of two-ring systems V and VIa-f, which have an imino structure. We found that the differences in the chemical shifts of the signals of the carbon atoms that belong simultaneously to the thiolane 1,1-dioxide and thiazolidine rings are found in the same range for IIa, b and IIIa (23.4-27.4 ppm) and Va-f and VIa-f (22.6-27.8 ppm). This indicates the identical character of the structures of the two-ring systems described; this constitutes evidence for the realization of a 2-iminothiazolidine structure in products IIa, b and IIIa. The IR spectral data (Table 2) also confirm this assumption.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The ^{13}C NMR spectra were obtained with a Bruker CXP-200 spectrometer (50 MHz) under pulse conditions with subsequent Fourier transformation; the external standard was tetramethylsilane, and the resonance conditions were stabilized with respect to the ^2H nuclei of the solvent of d_6-acetone, which was added to solutions of the samples in trifluoroacetic acid.

cis-2-Imino-4,6,7-trihydrothieno-8-methyl[3,4-d]thiazole 5,5-Dioxide (IIb). A mixture of 2.87 g (0.01 mole) of salt Ib, 0.84 g (0.01 mole) of sodium bicarbonate, and 30 ml of water was stirred for 1 h at 70°C, after which the solution was evaporated to dryness in the vacuum created by a water aspirator, and the residue was recrystallized with hot filtration. The yield was 0.3 g.

cis-2-Imino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxide (IIa). A mixture of 2.73 g (0.01 mole) of salt Ia, 0.84 g (0.01 mole) of sodium bicarbonate, and 30 ml of water was stirred for 2 h at 20°C. The precipitated IIa was removed by filtration and recrystallized. The yield was 1.03 g.

cis-2-Imino-3-methyl-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxide Hydrobromide (Va). A mixture of 1.97 g (0.01 mole) of sulfone IV, 0.9 g (0.01 mole) of N-methylthiourea, and 20 ml of isopropyl alcohol was heated at 80°C for 2 h, after which it was cooled to 20°C, and the resulting precipitate was removed by filtration and crystallized to give 2.14 g of hydrobromide Va.

3-Substituted cis-2-Imino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxide Hydrobromides Vb-f (Table 1). These compounds were similarly obtained from sulfone IV and the corresponding substituted thioureas.

cis-2-Acylimino-3-methyl-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxide (VIa). A 1.24-g (0.01 mole) sample of crystalline sodium acetate and 0.94 ml (0.01 mole) of acetic anhydride were added with vigorous stirring at 60-70°C to a solution of 2.87 g (0.01 mole) of hydrobromide Va in 50 ml of water, and the mixture was stirred at this temperature for 2 h. It was then cooled to 5°C, and the resulting precipitate was removed by filtration and recrystallized. The yield was 2.00 g.

3-Substituted cis-2-Acylimino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxides (VIb-f). These compounds were similarly obtained by acylation of the corresponding hydrobromides Vb-f.

cis-2-Acylimino-4,6,7,8-tetrahydrothieno[3,4-d]thiazole 5,5-Dioxide (IIIa). A 0.94-ml (0.01 mole) sample of acetic anhydride was added with vigorous stirring at 60-70°C to a solution of 1.92 g (0.02 mole) of two-ring system IIa in 60 ml of water, after which the mixture was stirred at this temperature for 2 h and then cooled to 5°C. The precipitate was removed by filtration and crystallized. The yield was 1.71 g.

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