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SYNTHESIS AND SPECTROMETRIC INVESTIGATION OF THE THIOAMIDES OF THIAZOLE- AND BENZOTHIAZOLE-2-CARBOXYLIC ACIDS

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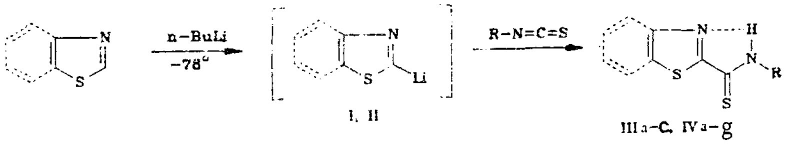
The reaction of 2-lithiumthiazole and benzothiazole with isothiocyanates gave the corresponding thioamides. Based on the IR, UV, and PMR spectra it was established that an intramolecular hydrogen bond is formed in these thioamides between the NH fragment of the thioamide grouping and the nitrogen atom of the thiazole ring. The main routes of the mass-spectrometric decomposition of the obtained thioamides have been determined.

As reported earlier [1], the reaction of thiophene with isocyanates and isothiocyanates in a nitromethane solution of $AlCl_3$ leads to the formation of amides and thioamides of the thiophene-2-carboxylic acid. The IR and UV spectra, and quantum-mechanical calculations by the CNDO/2 method showed that the thioamides of the thiophene-2-carboxylic acid exist mainly in the trans-s-trans form [2]. The present work is devoted to the synthesis and spectrometric investigation of the thioamides of thiazole- and benzothiazole-2-carboxylic acids. The corresponding thioamides (IIIa-c, IVa-g) were obtained in the reactions of 2-lithiumthiazole (I) and 2-lithiumbenzothiazole (II) with isothiocyanates [3-7].



III a $R=CH_3$, b $R=C_6H_5$, c $R=\alpha$-naphthyl; IV a $R=CH_3$, b $R=$-cyclo-C_6H_{11}, c $R=C_6H_5$, d $R=4\text{-}ClC_6H_4$, e $R=4\text{-}BrC_6H_4$, f $R=4\text{-}CH_3C_6H_4$, g $R=4\text{-}CH_3OC_6H_4$

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TABLE 1. Characteristics of Compounds IIIa-c and IVa-g

Compound	mp*, °C	Found, %			Empirical formula	Calculated, %			Yield†, %
		C	H	S		C	H	S	
IIIa	82,5—83	38,1	3,9	40,8	$C_5H_6N_2S_2$	37,9	3,8	40,5	96,0
IIIb	73—74 (75.5—77 [6])	54,8	3,9	29,2	$C_{10}H_8N_2S_2$	54,5	3,7	29,1	45,5
IIIc	104—105	62,6	4,0	23,9	$C_{14}H_{10}N_2S_2$	62,2	3,7	23,7	23,7
IVa	120—121	51,8	4,3	30,9	$C_9H_8N_2S_2$	51,9	3,9	30,8	76,8
IVb	112—113	61,0	6,0	23,3	$C_{14}H_{16}N_2S_2$	60,8	5,8	23,2	63,7
IVc	154—155	64,6	3,9	23,9	$C_{14}H_{10}N_2S_2$	62,2	3.7	23,7	57,7
IVd	159—160	55.5	3,5	21,2	$C_{14}H_9ClN_2S_2$	55,2	3,0	21,0	90,8
IVe	159—159,5	48,3	2,9	18,8	$C_{14}H_9BrN_2S_2$	48,1	2,6	18,4	95,0
IVf	160—161	63,7	4,6	22,8	$C_{15}H_{12}N_2S_2$	63,3	4,3	22,5	57,7
IVg	130—131	60,4	4,4	21,5	$C_{15}H_{12}N_2OS_2$	60,0	4,0	21,3	69,0

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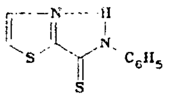
*The compounds IIIa-c and IVa, b, f, g, were crystallized from a 1:2 mixture of CCl_4 and petroleum ether, the compounds IVc-e from CCl_4.

†Of raw product.

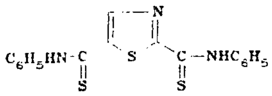
TABLE 2. IR Spectra of Thioamides IIIa-c and IVa-g in Vaseline Oil, cm^{-1}

Compound	ν_{NH}	Thioamide bands			$\nu_{C=S}$	ν_{NH}	Ring absorption bands
		I	II	III			
IIIa	3235	1553	1359	1057, 930	660		592, 624, 666, 680, 764, 883, 1160, 1160, 1329, 1487
IIIb	3279	1520	1364	1140, 986	701		602, 624, 686, 761, 882, 1070, 1161, 1180
IIIc	3300	1521	1356	1143, 975	610		609, 623, 676, 770, 888, 1064, 1148, 1174, 1481
IVa	3300	1540	1363	1055, 940	650	694	634, 649, 734, 762, 870, 1162, 1319, 1483
IVb	3290	1519	1408	1109, 940	621	730	666, 729, 750, 854, 1015, 1154, 1321, 1408, 1460, 1482
IVc	3289	1543	1382	1194, 990	686	740	657, 732, 760, 875, 1013, 1161, 1321, 1460, 1492
IVd	3275	1526	1380	1188, 999	700	709	645, 726, 761, 865, 1015, 1072, 1160, 1320, 1400, 1460, 1493
IVe	3275	1523	1380	1191, 996	701	701	651, 723, 761, 864, 1013, 1073, 1161, 1318, 1460, 1489
IVf	3279	1532	1381	1190, 996	695	740	656, 731, 758, 873, 1012, 1071, 1162, 1319, 1400, 1460
IVg	3290	1542	1390	1191, 1000	720	720	650, 730, 758, 873, 1015, 1071, 1160, 1321, 1460

In the reaction of 2-lithiumthiazole I with phenylisothiocyanate the disubstituted product V is formed besides the expected thioamide of thiazole-2-carboxylic acid (ratio IIIb:V = 8:1).



IIIb



V

In the other cases, only the monoadducts are formed. Generally, the reactions give good yields with the aliphatic as well as with the aromatic isothiocyanates. The reaction does not take place only in the case of tert-butyl isothiocyanate, due to steric effects and also due to the weak electrophilic character of the initial isothiocyanate.

Except in the case of the N-methylthioamide of the thiazole-2-carboxylic acid (IIIa), the IR spectra of the thioamides IIIa-c and IVa-g (Tables 1-3) shows narrow absorption bands of the NH groups appearing in the interval 3300-3270 cm^{-1}. This leads to the conclusion that the hydrogen atom of the thioamide grouping is involved in intra- and intermolecular bonds. In carbon tetrachloride the band ν_{NH} appearing in the interval 3300-3373 cm^{-1} is narrow and

TABLE 3. IR Spectra of Thioamides IIIa-c and IVa-g in CCl_4 and THF Solution, cm^{-1}

Compound	In CCl_4 solution					In THF solution				
	ν_{NH}	thioamide bands			$\nu_{C=S}$	ν_{NH}	thioamide bands			$\nu_{C=S}$
		I	II	III			I	II	III	
IIIa	3373		1365	1057, 930		3375, 3270	1540	1362		672
IIIb	3320		1371	1151, 996	689	3300, 3235	1541	1380	1152, 996	706
IIIc	3300		1356	1152, 980	660	3315, 3190	1510	1371	980	
IVa	3367		1369	1061, 938	610	3300, 3250	1542	1376		695
IVb	3345	1520	1401	1110, 940	625	3350, 3260	1530	1410	1000	
IVc	3316		1383	1198, 1010		3300, 3235	1543	1389	1010	706
IVd	3300		1375	1194, 1004		3210	1529	1381	998	695
IVe	3310		1374	1194, 1003		3220	1531	1381	1000	700
IVf	3314		1381	1196, 1005		3300, 3235	1533	1389	1003	700
IVg	3316		1387	1197, 996		3290, 3220	1521	1386	996	695

TABLE 4. UV and PMR Spectra of Thioamides IIIa-c and IVa-g

Compound*	UV spectrum, λ_{max}, nm (log ε)		PMR spectrum†, ppm		
	in methanol	in cyclohexane	Ar	CH_3 [CH_3O]	NH (c)
IIIa	206 (4,06), 328 (3,78), 4,08 (2,15) sh	284 (3,92), 286 (3,93), 290 (3,92), 298 (3,83) sh., 303 (3,77) sh., 333 (3,70), 435 (1,90)	7,35—7,80 (м)	3,3 (d)	9,12
IIIb	315 (4,15), 353 (3,88) sh., 441 (2,32) sh.	318 (4,17), 358 (3,91), 377 (3,83) sh, 400 (3,60) sh., 465 (2,13)	7,10—8,00 (м)	—	10,67
IIIc	289 (4,20), 317 (4,02) sh.	279 (3,97) sh., 300 (4,02) sh., 314 (4,04) sh., 328 (4,04), 373 (3,86) sh., 471 (2,43), 500 (2,24) sh	7,20—8,20 (м)	—	11,0
IVa	245 (3,90) sn 250 (3,94), 254 (4,00), 299 (4,26), 347 (3,70) sh, 417 (2,30) sh	247 (3,74) sh., 250 (3,72), 256 (3,74), 305 (4,23), 312 (4,20) sh, 346 (3,72) sh., 446 (2,11), 476 (1,84)	7,12—8,00 (м)	3,24 (d)	9,22
IVb	246 (3,81) sh, 250 (3,83), 355 (3,86), 308 (4,26), 322 (4,14) sh, 350 (3,66) sh., 420 (2,30) sh.	2,47 (3,79) sh., 250 (3,76) sh., 256 (3,75), 305 (4,24) sh., 311 (4,25), 325 (4,09) sh., 351 (3,68) sh., 447 (2,13), 481 (1,90) sh.	6,85—7,75 (м)	—	8,52
IVc	250 (3,98) sh, 323 (4,29), 454 (2,42) sh.	253 (3,87) sh, 325 (4,30), 333 (4,28) sh, 383 (3,79) sh. 404 (3,48) sh, 472 (2,20)	6,90—7,80 (м) 7,00—7,95	—	10,6 10,65
IVd	230 (4,39) sh, 326 (4,33), 455 (2,48) sh	239 (4,36), 329 (4,33), 337 (4,32) sh., 385 (3,88) sh., 408 (3,56) sh., 473 (2,26), 500 (2,15) sh.	7,10—8,00 (м)	—	10,8
IVe	230 (4,40) sh, 328 (4,35), 457 (2,51) sh	239 (4,36), 329 (4,34), 337 (4,34) sh, 385 (3,91), 410 (3,60) sh., 476 (2,28), 505 (2,15)	7,12—8,05 (м)	—	10,85
IVf	253 (3,95) sh., 325 (4,31), 385 (3,81) sh, 459 (2,59) sh	258 (3,75) sh., 312 (4,21) sh, 325 (4,29), 334 (4,28) sh, 355 (4,15) sh, 388 (3,84) sh, 416 (3,48) sh., 467 (2,30) sh	7,00—8,00 (м)	2,27 (d)	10,78
IVg	253 (3,90) sh, 329 (4,24), 383 (3,85) sh	298 (4,08) sh., 310 (4,15) sh, 326 (4,23), 334 (4,22) sh, 356 (4,11) sh, 388 (3,89) sh, 500 (2,30) sh.	6,63—8,00 (м)	[3,7 (d)]	10,73

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*Due to the poor solubility of compounds IVd-g, the spectra were obtained on their saturated solutions.

†For compound IVb cyclo-C_6H_{11} 1.7 m, N-CH 4.1 s.

its position is independent of the concentration. This indicates that in solution the hydrogen atom of the thioamide grouping is linked within the molecule to the nitrogen atom of the thiazole ring (Table 3). In a more polar solvent (tetrahydrofuran) the intramolecular hydro-

TABLE 5. Peak Intensities of Characteristic Ions in the Mass Spectra of Thioamides IIIa-c and IVa-g [% Σ_{38}]

Compound	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	W_M
				70 eV				
IIIa	0,45	1,77	—	3,22	1,94	—	—	17,57
IIIb	1,44	9,47	—	3,16	3,10	14,0	—	17,0
IIIc	0,97	5,73	—	2,6	1,6	5,3	—	10,8
IVa	4,71	1,49	4,0	—	1,66	—	—	12,43
IVb	2,74	—	2,68	2,7	1,0	—	—	7,02
IVc	1,5	3,77	1,5	0,43	1,94	7,03	—	8,94
IVd	1,95	4,0	1,63	1,12	2,37	3,18	1,27	8,1
IVe	2,58	3,4	2,97	1,53	3,37	4,0	3,22	16,52
IVf	1,26	8,6	1,31	1,1	2,84	6,60	7,5	12,00
IVg	1,16	9,24	0,8	1,54	2,61	3,70	2,16	13,51
				15 eV				
IIIa	0,04	2,4	—	—	2,04	—	—	41,37
IIIb	1,16	14,46	—	1,21	1,68	25,85	—	39,38
IIIc	1,30	10,1	—	0,4	1,0	15,7	—	32,48
IVa	0,06	1,4	2,35	—	1,7	—	—	40,22
IVb	—	—	0,8	1,11	—	—	—	20,25
IVc	—	0,75	—	—	—	26,17	—	36,8
IVd	4,2	11,53	2,22	1,58	5,63	—	4,44	30,57
IVe	3,35	5,87	1,55	0,96	4,56	15,0	7,3	46,11
IVf	1,04	11,77	0,6	0,3	3.0	12,26	18,9	31,8
IVg	1,24	11,00	0,42	0,57	2,88	5,64	3,4	29,92

gen bond is weakened and a broad absorption band can be seen in the region of ν_{NH} absorption, due to the hydrogen bond formed with the solvent molecule; a shoulder can be observed at higher frequencies, corresponding to the intramolecular bond (Table 3). There is no reason to doubt the assignment of the absorption band of the thioamide group for compounds I and II, although its position is not always exactly determined, due to superposition of absorption bands of the heteroaromatic ring. It depends on the substituent R as well as on the aromatic fragment of the molecule (thiazole, benzothiazole). It indicates a contribution of the vibrations of the C—N and C—C bonds, as well as their noticeable conjugation. The assignment of the band $\nu_{C=S}$ band is very difficult, due to superposition of signals of the conjugation of the atomic groupings and to the appearance of a signal in this region of the spectrum (650-800 cm^{-1}) caused by plane-deformation vibrations. In compound IV the deformation vibrations of the thioamide group are observed in the interval 550-570 cm^{-1}.

The UV spectra of the thioamides in the interval 230-505 nm are given in Table 4. In the electron spectra of compounds IIIa-c and IVa-g the bands of three chromophores appear in the investigated absorption range: the CSNH group and thiazole and phenyl rings. In the UV spectra of the thioamides IIIa, b three absorption bands appear in methanol in the range 286-441 nm (Table 4). The long-wavelength low-intensity absorption band which shows a strong shift in the transition from the nonpolar to the polar solvent, is assigned to the n-π* transition of the thioamide grouping.

Substitution of the alkyl radical, linked to the nitrogen atom of the thioamide group, by the phenyl radical leads to a bathochromic shift of the band (~30 nm). No absorption bands of the type n-π* are present in the UV spectrum of the α-naphthylamide IIIc in methanol. The absorption curves of the thioamides IIIa-c in cyclohexane are characterized by several shoulders and the n-π* transition bands are present in all spectra.

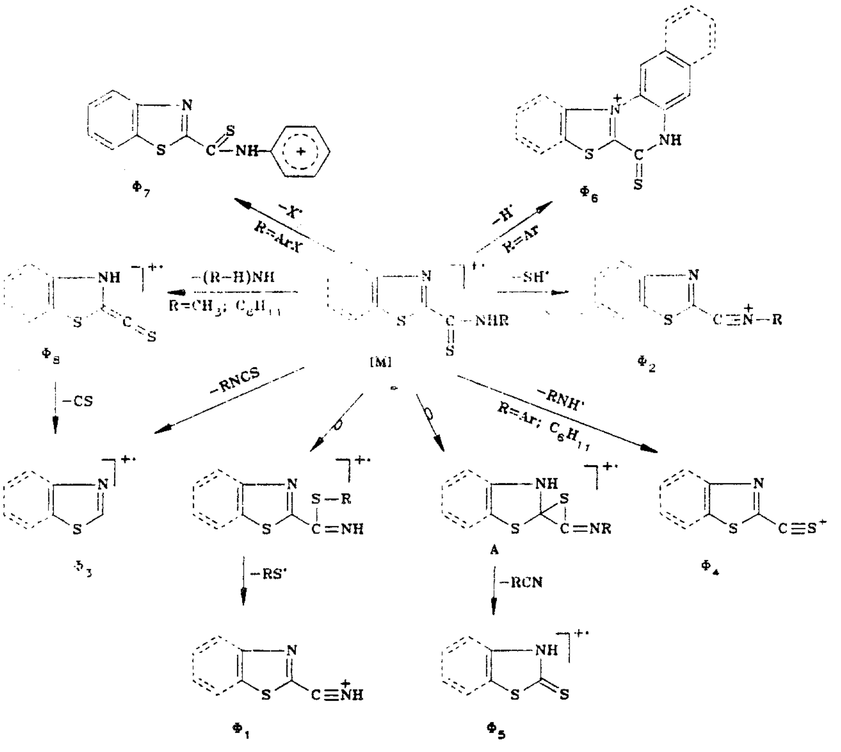
The spectra of compounds IVa-g in a polar and a nonpolar solvent differ significantly. In cyclohexane the absorption bands can be found in the longer wavelength region of the spectrum and their intensity decreases only negligibly in comparison with the analogous spectra in methanol. The transition bands of the thioamides IVa-g, as the other absorption bands, are shifted to the short-wavelength region of the spectrum as the dielectric constant of the solvent increases. Thus, it is very difficult to establish the type of transition for all absorption bands present in the spectra of the thioamides IVa-g. Substitution of the alkyl radical by the phenyl group shifts the entire spectrum to the long-wavelength region. In the case of the para-substituted thioanilides IVd-g the UV spectra also show shifting of the absorption maxima to the long-wavelength region, which indicates conjugation of the phenyl group with the remaining fragment of the molecule. Thus, effect is more strongly pronounced than in the earlier investigated thioamides of the thiophene-2-carboxylic acid [2]; it indicates that in the presence of an intramolecular hydrogen bond between the NH group and the nitrogen atom of the thiazole ring the molecules of the investigated thioamides IVa-g are coplanar.

The PMR spectra of compounds IIIa-c and IVa-g are presented in Table 4. They show that the substituent, linked to the nitrogen atom of the thioamide group affects the position of the signal of the amide proton. Substitution of the alkyl radical by a phenyl radical strongly shifts the position of this signal towards the weaker fields. In the case of compounds IIIa and IVa, where R = CH_3, the signal of the methyl group appears as a doublet, due to interaction with the proton of the amino group, and the signal broadens [9].

In order to determine the character of the hydrogen bond appearing in the spectra of the thioamides, we have obtained PMR spectra of saturated and diluted solutions of compound IVc. The data in Table 4 show that the shift of the proton signals of the amide group is negligible (0.05 ppm); this indicates the presence of an intramolecular hydrogen bond in the molecule. These data are confirmed by the IR spectra.

The mass spectra of the thioamides IVa-g indicate that the molecular ion (M^+) is relatively stable. One of the decomposition routes of M^+ is the elimination of the fragment RS with the formation of the cation Φ_1. This is related to the migration of the substituent R to the sulfur atom of the thioamide group [10-13]. Simple rupture of the thioamide bond and ejection of the radical leads to the ion Φ_4. Such a destruction of the molecule can occur with the rearrangement of the hydrogen atom and formation of ions Φ_8.

Another interesting decomposition route of the molecular ions of the thioamides IVa-g is the elimination of nitrile molecules RCN with the formation of ions Φ_5. This is apparently also related to another rearrangement with the formation of the spyrocyclic structure A:



The mass spectra of N-deuterated thioamides IVa-g confirm the rearrangement, because in these spectra the peaks of the ions Φ_1 and Φ_5 are shifted by one a.m.u. towards higher m/z values. Except in the case of the N-cyclohexylthioamide IVb, the mass spectra of the other thioamides show relatively strong peaks of the ions Φ_2, created by the elimination of the fragment $SH^{\bullet}$ (in the deuterated thioamides $SD^{\bullet}$) by the molecular ions. This indicates that in the gaseous phase the ions of thioamides IVa-g exist in the thiolo- as well as in the thiono-form. We have described these phenomena in [2, 10]. A decrease in the ionizing potential leads to a significant increase in the stability of M^+ as well as to a simpler spectrum (Table 5).

The character of the mass-spectrometric decomposition of thioamides IIIa-c is the same as that of thioamides IVa-g (see scheme and Table 5). The decomposition route have been confirmed by the analysis of the mass spectra of the N-deuterated analogs. The summary intensity of the ions represents 35-50% of the total ion current (at an ionization energy of 70 eV) and 60-85% (at 15 eV).

EXPERIMENTAL

The electron spectra were recorded on a UV-Vis spectrophotometer in methanol and cyclohexane ($c = 5 \cdot 10^{-5}$ M) and the IR spectra on a Pye-Unicam IR 1100 instrument, as suspensions in Vaseline oil or in CCl_4 ($c = 0.03$ M) and tetrahydrofuran ($c = 0.18$ M). The PMR spectra were taken on an NMR-BS Tesla 487C spectrometer (80 MHz) in $CDCl_3$ ($c = 0.5$ M), with HMDS as internal standard. The mass spectra were obtained on an LKB-2901 spectrometer with direct sample introduction, at ionizing potentials 70 and 15 eV.

Thioamides of Thiazole- and Benzothiazole-2-carboxylic Acids (IIIa-c, IVa-g) (general procedure). 0.025 mole thiazole (or benzothiazole) in 50 ml absolute tetrahydrofuran was placed in a four-neck flask. The mixture was cooled to −78° (with dry ice + acetone) and treated dropwise in a stream of argon with 0.025 mole (2 M) of a solution of n-butyllithium in hexane during 30 min. The reaction mixture was stirred at the same temperature for a further 30 min, 0.025 mole of the corresponding isothiocyanate in 20 ml tetrahydrofuran was added dropwise, and the stirring continued at −50° for another hour. The reaction mixture was decomposed with an aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. The solvent was stripped off on a rotary evaporator and the raw reaction product purified on a column packed with silica gel, using benzene as the eluent, and crystallized. The yields, the results of elemental analysis, and the melting points of the obtained thioamides are given in Table 1.

Dithioanilide of Thiazole-2,5-dicarboxylic Acid (V). The compound was obtained by the above procedure from thiazole and phenylisothiocyanate. The raw reaction product was dissolved in benzene, the precipitate formed filtered off and recrystallized from methanol (at −15°). Yield 6.0%, mp 214°. Found, %: C 57.4; H 3.9; S 27.2; M^+ 356. Calculated, %: C 57.3; H 3.6; S 27.0. The benzene solution containing the thioanilide IIIb was purified on a column packed with silica gel with benzene as the eluent.

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