SYNTHESIS AND PROPERTIES OF 2-AMINO-5-(5-NITRO-2-FURYL) THIAZOLE DERIVATIVES

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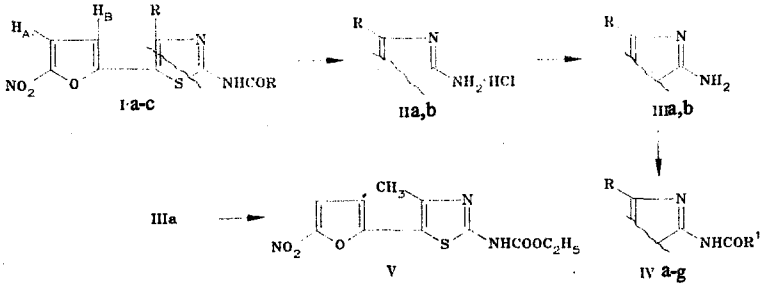
The hydrochlorides of the corresponding 2-aminothiazoles, which were converted to the free bases, were obtained by hydrolysis of 2-acylamino-5-(5-nitro-2-furyl) thiazoles. Reactions that take place at the amino group of 2-amino-5-(5-nitro-2-furyl)thiazoles are described.

The chemical and biological properties of 2- and 4-furyl-thiazoles have been previously described [1-5]; however, only one publication [6] has been devoted to 5-(2-furyl)thiazole derivatives. In a previous communication [7] we described a new method of synthesis that makes it possible to obtain 2-acylamino-4-R-5-(5-nitro-5-furyl)thiazoles I in high yields. The aim of the present research was to study the chemical properties of a new series of bisheterocyclic compounds, viz., 2-amino-5-(5-nitro-2-furyl)thiazoles, and, in particular, to investigate reactions that take place at the amino group.

Depending on the nature of the acyl fragment, acylamino-thiazoles Ia-c behave differently with respect to hydrolysis. Thus alkylamides Ia, b are hydrolyzed in both acidic and alkaline aqueous alcoholic media (refluxing for 8-10 h). The corresponding hydrochlorides IIa, b are formed in high yields in an acidic medium (hydrochloric acid). Aminothiazoles IIIa, b are obtained directly in the case of alkaline hydrolysis, but their yields are considerably lower, apparently as a consequence of partial destruction of the nitrofuran ring under the influence of hydroxide anions. Benzamide Ic is more resistant to any hydrolyzing agents — refluxing for 120 h in a 5% aqueous alcohol solution of hydrochloric acid gives trace amounts of the corresponding hydrochloride.



I—III a $R=CH_3$, b $R=C_2H_5$, c $R=C_6H_5$; IV a–d, f, g $R=CH_3$, e $R=C_2H_5$; a $R^1=C_2H_5$; b $R^1=C_3H_7$; c $R^1=C_4H_9$-*i*; d $R^1=C_9H_{19}$; e $R^1=CH_3$; f $R^1=C_6H_5$; g $R^1=2\text{-}NO_2C_6H_4$

Hydrochlorides IIa, b are stable only in acidic solutions; they undergo quantitative conversion to 2-aminothiazoles IIIa, b in neutral and alkaline aqueous media.

It is known that 2-aminothiazoles react with electrophilic agents in a different way: either at the endocyclic nitrogen atom or at the exocyclic amino group [8-10]. The direction of the reaction is determined by both the "hardness" of the electrophile and the experimental conditions.

Carboxylic acid anhydrides and chlorides, which are "hard" electrophiles, react with aminothiazoles IIIa, b only at the exocyclic amino group to give the corresponding acylaminothiazoles IV. Similarly, ethyl chlorocarbonate reacts with IIIa to give carbamate V.

The electronic spectra of all amides Ia, b and IVa-g and carbamate V contain three absorption maxima at 225, 285-315, and 403-410 nm. Diphenyl derivative Ic, the electronic spectrum of which contains four absorption bands (Table 1), constitutes an exception. At

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TABLE 1. Spectral Characteristics of 5-(5-Nitro-2-furyl) thiazoles

Compound	Electronic spectrum, λ_{max} nm (log ϵ) in ethanol)	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)			
			H_A	H_B	R^1	R^2
Ia	225 (3,95), 292 (3,85), 406 (4,19)	1668 (C=O)	7,1 d (4,0)	6,50 d (4,0)	2,32 s	2,12 s
Ib	225 (3,97), 292 (3,88), 406 (4,18)	1673 (C=O)	7,25 d (4,0)	6,65 d (4,0)	0,9 t (7,8); 2,4 q (7,8)	1,1t (8,0); 2,7 q (8,0)
Ic	237 (4,80), 275 (4,12), 314 (3,99), 412 (4,14)	1670 (C=O)	6,96 d (4,0)	6,05 d (4,0)	7,22 s	7,2—7,7 m
IIa	225 (3,78), 290 (3,93), 440 (4,19)	2685 (NH), 2750 (NH), 3260 (NH)	7,12 d (4,0)	6,37 d (4,0)	2,17 s	
IIb	225 (3,85), 290 (3,98), 440 (4,23)	2710 (NH), 2760 (NH), 3290 (NH)	7,13 d (4,0)	6,35 d (4,0)	1,03 t (7,5); 2,58 q (7,5)	
IIIa	225 (3,83), 290 (3,99), 440 (4,25)	3310 (NH), 3410 (NH), 1660 (NH)	7,35 d (4,0)	6,63 d (4,0)	2,48 s	
IIIb	225 (3,84), 290 (3,98), 440 (4,23)	3310 (NH), 3400 (NH), 1656 (NH)	7,14 d (4,0)	6,40 d (4,0)	1,0 t (7,8); 2,53 q (7,8)	
IVa	225 (3,97), 292 (3,88), 406 (4,21)	1673 (C=O)	7,12 d (4,0)	6,53 d (4,0)	2,32 s	0,9 t (8,0); 2,35 q (8,0)
IVb	225 (3,94), 292 (3,85), 406 (4,18)	1670 (C=O)	7,12 d (4,0)	6,55 d (4,0)	2,35 s	0,93t . 1,41 hr. m ; 2,35
IVc	225 (3,95), 292 (3,88), 406 (4,19)	1705 (C=O)	7,11 d (4,0)	6,55 d (4,0)	2,31 s	0,91—1,13 m (7H); 2,25 d (2H)
IVd	225 (3,90), 292 (3,81), 406 (4,18)	1670 (C=O)	7,12 d (4,0)	6,55 d (4,0)	2,32 s	0,9—1,4 m (17H); 2,35 t (2H)
IVe	225 (4,05), 292 (3,93), 406 (4,24)	1658 (C=O)	7,12 d (4,0)	6,51 d (4,0)	1,0 t (7,0); 2,7 q (7,0)	2,12 s
IVf	236 (4,26), 315 (3,99), 406 (4,31)	1670 (C=O)	7,13 d	6,55 d	2,35 s	7,5—7,7 m (5H)
IVg	300 (3,88), 403 (4,16)	1695 (C=O)	7,15 d (4,0)	6,58 d (4,0)	2,35 s	7,33—7,91 m (4H)
V	225 (3,89), 285 (3,93), 410 (4,20)	1731 (C=O)	7,12 d (4,0)	6,52 d (4,0)	2,27 s	1,0 t (7,5); 4,08 q (7,5)
VII	228 (3,96), 287 (3,85), 385 (4,17)	2120 ($N_{(3)}$)	7,45 d (4,0)	6,80 d (4,0)	2,45 s	
IX	225 (4,15), 420 (4,37)		7,18 d	6,68 d	2,48 s	3,63 s (OCH_3); 6,75 d (10,0; H_A); 7,76 d (10,0; H_B)

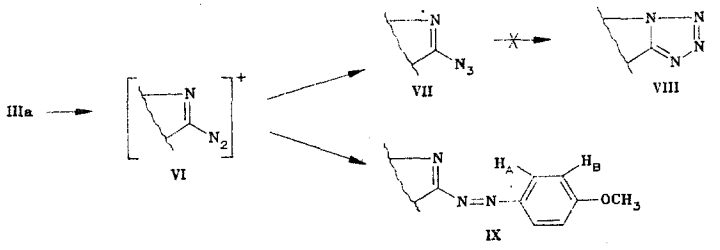
the same time, replacement of the alkyl radical by a phenyl group in the 4 position of the thiazole ring leads to a bathochromic shift of the long-wave absorption maximum of only 6 nm (IVf and Ic); this constitutes evidence for insignificant conjugation between the benzene and thiazole rings. Anomalous positions of the signals of the furan protons as compared with Ia, b and IV are also observed in the PMR spectrum of 4-phenyl-thiazole Ic. It is apparent from Table 1 that the doublets of the protons of the furan ring in the spectrum of phenyl derivative Ic are shifted to strong field. The signal of the H_B proton undergoes the most significant shift; this is the result of the anisotropic effect of the phenyl substituent in the 4 position of the thiazole ring on the β protons of the furan ring. On the basis of the electronic and PMR spectra it may be assumed that Ic has an O, S-cis form of the orientation of the furan and thiazole rings and that the phenyl substituent is, as it were, "twisted away" from the plane of the furan and thiazole rings.

Aminothiazole IIIa reacts with nitrous acid under severe conditions to give diazonium salt VI, which undergoes several characteristic reactions.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, * deg C (from acetic acid)	Found, %			Empirical formula	Calculated, %			M^+	Yield, %
		C	H	S		C	H	S		
IIa	195	36,29	3,17	12,12	$C_8H_8ClN_3O_3S$	36,70	3,63	12,63		92
IIb	190	39,67	3,14	11,53	$C_9H_{10}ClN_3O_3S$	39,21	3,62	11,97		95
IIIa	250	42,87	3,45	13,81	$C_8H_7N_3O_3S$	42,41	3,13	14,23	225	100
IIIb	211—212	45,49	3,23	12,92	$C_9H_9N_3O_3S$	45,49	3,28	12,95	239	100
IVa	240—242	46,45	3,59	11,82	$C_{11}H_{11}O_4SN_3$	46,80	3,95	11,38	281	71
IVb	173—174	40,42	4,03	11,07	$C_{12}H_{13}N_3O_4S$	40,70	4,40	10,75	295	85
IVc	169—170	50,87	4,62	10,81	$C_{13}H_{15}N_3O_4S$	50,45	4,89	10,37	309	86
IVd	115—116	50,52	6,89	8,87	$C_{18}H_{25}N_3O_4S$	50,95	6,64	8,45	379	90
IVe	224—225	47,15	3,59	11,82	$C_{11}H_{11}N_3O_4S$	47,15	3,95	11,37	281	95
IVf	214—215	54,23	3,80	10,03	$C_{15}H_{11}N_3O_4S$	54,68	3,37	9,74	329	90
IVg	215—217	48,44	2,29	8,21	$C_{15}H_{10}N_4O_6S$	48,11	2,69	8,57	374	90
V	280—282	44,75	3,28	11,13	$C_{11}H_{11}N_3O_5S$	44,42	3,73	10,79	297	90
VII	128—130	38,55	1,71	11,85	$C_8H_5N_5O_3S$	38,38	1,99	12,12	251	61
IX	243—244	52,23	3,28	16,07	$C_{15}H_{12}N_4O_4S$	52,35	3,49	16,28	344	44

*Compounds IIa, b and IIIa melt with decomposition.



Thus the addition of sodium azide to a solution of salt VI gives 2-azidothiazole VII, which apparently exists exclusively in azido form VII, since we were unable to detect tautomeric tetrazolothiazole form VIII by either spectral or chromatographic methods. Diazo coupling of diazonium salt VI with anisole gives the expected azo product IX.

The mass spectra of III-V and VII contain peaks of the corresponding molecular ions (Table 2), the fragmentation of which corresponds to the proposed structures. The analysis of the mass spectra of 5-(5-nitro-2-furyl)thiazoles will be the subject of future publications.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CF_3COOH were recorded with a Tesla-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The electronic spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Varian CH-8 spectrometer with direct introduction of the samples into the ion source; the temperature of the ionizing chamber was 100-150°C, and the ionizing-electron energy was 70 eV.

The course of the reactions and the individuality of the substances were monitored by thin-layer chromatography (TLC) on Silufol plates in a toluene—ethanol system (10:3).

The characteristics of II-V, VII, and IX are presented in Table 2.

2-Amino-4-methyl-5-(5-nitro-2-furyl)thiazole Hydrochloride (IIa). A 50-ml sample of concentrated HCl and 50 ml of water were added to 19 g (72 mmole) of Ia in 500 ml of ethanol, and the mixture was refluxed for 8-10 h. It was then cooled, and the precipitated hydrochloride IIa was removed by filtration, washed with dry ether, and air dried.

2-Amino-5-(5-nitro-2-furyl)-4-ethylthiazole Hydrochloride (IIb). This compound was similarly obtained.

2-Amino-4-methyl-5-(5-nitro-2-furyl)thiazole (IIIa). A mixture of 18 g (69 mmole) of IIa hydrochloride and 2.0 g (69 mmole) of NaOH in 200 ml of water was stirred vigorously at room temperature for 10-20 min, after which the red precipitate of thiazole IIIa was removed by filtration, washed with water, and air dried.

2-Amino-5-(5-nitro-2-furyl)-4-ethylthiazole (IIIb). This compound was similarly obtained from hydrochloride IIb.

4-Methyl-5-(5-nitro-2-furyl)-2-propionylaminothiazole (IVa). A solution of 2.25 g (10 mmole) of amine IIIa in 50 ml of propionic anhydride was heated on a boiling-water bath for 1 h, after which it was cooled, and the precipitated yellow crystals of IVa were removed by filtration, washed with water, and air dried.

2-Acetamido-5-(5-nitro-2-furyl)-4-ethylthiazole (IVe). This compound was similarly obtained.

2-Isovalerylamino-4-methyl-5-(5-nitro-2-furyl)thiazole (IVc). A 0.97-g (7.5 mmole) sample of isovaleryl chloride was added to a solution of 1.12 g (5 mmole) of amine IIIa in 30 ml of pyridine, after which the mixture was heated on a boiling-water bath for 0.5 h, cooled, and poured into a mixture of 70 ml of water, 70 g of ice, and 30 ml of concentrated HCl. The yellow precipitate of IVc was removed by filtration, washed with 20 ml of 5% Na_2CO_3 solution and 20 ml of water, and air dried.

Compounds IVb, d, f, g and V. These substances were similarly obtained.

2-Azido-4-methyl-5-(5-nitro-2-furyl)thiazole (VII). A 0.88-g (3.9 mmole) sample of amine IIIa was dissolved in 20 ml of boiling acetic acid, and the solution was cooled rapidly to 10-20°C. The resulting paste was added to a solution of 0.4 g (5.8 mmole) of $NaNO_2$ in 2.8 ml of concentrated H_2SO_4 and 2 ml of acetic acid in the course of 0.5 h while maintaining the temperature at 10-20°C, after which a solution of 0.42 g (7.8 mmole) of NaN_3 in 2 ml of water was added, and the mixture was stirred for 30-40 min until nitrogen evolution ceased. It was then treated with 50 ml of ice water, and the red precipitate of VII was removed by filtration, washed thoroughly with water, and recrystallized from acetic acid.

4-Methyl-2-(4-methoxyphenylazo)-5-(5-nitro-2-furyl)thiazole (IX). A solution of the diazonium salt obtained from 0.88 g (3.9 mmole) of amine IIIa by the method described for VII was added to a solution of 0.63 g (5.8 mmole) of anisole in 40 ml of acetic acid, and the mixture was stirred at room temperature for 2 h. It was then made weakly alkaline (pH ~ 8-9) with sodium carbonate solution, and the precipitated IX was removed by filtration, washed with 50-80 ml of water, and recrystallized from acetic acid.

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