SYNTHESIS AND STUDY OF TAUTOMERIC PROPERTIES OF 2-(5-R-2-FURYL)THIAZOLIN-4-ONES

G. D. Krapivin, P. A. Pavlov, and V. G. Kul'nevich

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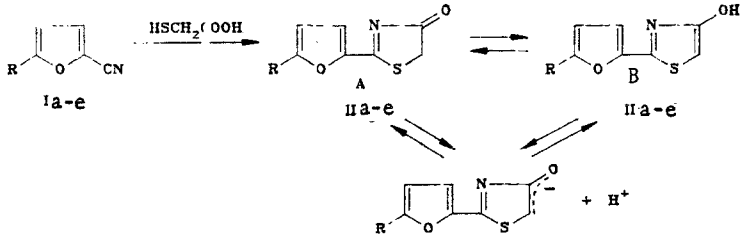
Compounds were synthesized by reaction of 5-R-2-cyanofurans with thioglycolic acid, which, according to IR, PMR, and mass spectrometric data, exist in the form of two tautomers, 4-hydroxythiazole and thiazolin-4-one.

In review [1], it was noted that the least studied thiazolin-4-one ⇌ hydroxythiazole system is the thiazolin-4-one ⇌ 4-hydroxythiazole system. According to [2, 3], one of the reasons for this is the instability of most of the 5-unsubstituted thiazolin-4-ones, the high activity of the methylene group of which leads to the formation of various dimerization products, especially characteristic of 2-phenyl derivatives.

In continuation of our study of furylthiazoles [4-6], we endeavored to prepare 2-furylthiazoles, expecting that the most suitable method for their synthesis would be the reaction of nitriles with thioglycolic acid, which was successfully used for the synthesis of 2-alkyl and 2-aryl derivatives [1, 7, 8].

We studied the reaction of 2-cyanofurans Ia-e with thioglycolic acid and found that the solvent used substantially influenced the course of the reaction and the make-up of the products. Thus, in acetic acid, a complex mixture of compounds is formed, from which only insignificant amounts of the desired end products could be isolated. In pyridine, the reaction proceeds more selectively, and compounds IIa-e were obtained in a fairly high yield. Cyanofurans Ia, b, e react with thioglycolic acid on heating (80°C, 6 h). Bromo- and nitro-substituted Ic, d react at a lower temperature; in this case heating of the reaction mixture above 10°C leads to resin formation and a decrease in the yield of the corresponding desired end product.

According to the data of elemental analysis (Table 1), compounds II are condensation products of cyanofurans and thioglycolic acid, being formed with the elimination of one molecule of water, and both structure IIA and IIB can be ascribed to it.



I, II a R=H; b R=CH_3; c R=Br; d R=NO_2; e R=2,4,6-$C_6H_2Cl_3$

In the IR spectra of crystals of II there are absorption bands of stretching vibrations of the carbonyl groups in the 1715-1770 region and of the hydroxyl group in the vicinity of 2700 cm^{-1}, which indicates the simultaneous presence of both ketonic and enolic forms in the crystalline state.

In most of the solvents studied (Table 2), compounds IIa-c, e have one set of signals in the PMR spectrum, corresponding to the thiazoline form A: a characteristic signal — a singlet of the methylene group protons (2H) in the 3.78-3.90 ppm region. Only in separate instances (compound IIa in acetone, IIb, c, e in DMSO) were two sets of signals observed in

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TABLE 1. Physicochemical Characteristics of Synthesized Compounds

Compound	mp,* °C	λ_{max},† nm (log ε) in ethanol [in acetic acid]	λ_{max},† nm (log ε) in water NI	λ_{max},† nm (log ε) in water I	pK_a	IR spectrum, cm^{-1} ν_{CO}	IR spectrum, cm^{-1} ν_{OH}	Found, % C	Found, % H	Found, % N	Found, % S	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % S	Yield, %
IIa	165	217 (2,40), 238 (2,39), 305 (4,14), 438 (3,02)	319	367	9,07±0,02	1715	2700	50,3	2,9	8,4	19,1	$C_7H_5NO_2S$	50,3	3,0	8,4	19,2	70
IIb	178	208 (2,63), 238 (2,54), 331 (4,37), 449 (2,58)	347	364	9,70±0,07	1720	2750	53,0	3,8	7,7	17,6	$C_8H_7NO_2S$	53,1	3,7	7,7	17,7	79
IIc	173	224 (3,33), 330 (3,75), 438 (3,21)	336	373	8,97±0,04	1770	2680	34,1	1,8	5,6	12,8	$C_7H_4BrNO_2S$	34,1	1,6	5,7	13,1	86
IId	175	211 (3,87), 298 (3,88), 399 (4,03)	402	478	7,14±0,02	1710	2705	39,6	1,8	13,8	15,0	$C_7H_4N_2O_4S$	39,6	1,0	13,3	15,1	71
IIe	185	[334 (4,26), 458 (2,38)]	336	377	8,87±0,02	1755	2680	44,8	1,7	4,0	9,2	$C_{13}H_6Cl_3NO_2S$	45,0	1,7	4,0	9,2	89

*Temperature at beginning of decomposition is given.

†Values of λ_{max} of the long-wave bands of the molecular nonionized (NI) and ionized (I) forms are given.

TABLE 2. PMR Spectra of Synthesized Compounds*

Compound	Solvent	Tautomer	PMR spectra, ppm (J, Hz)					
			β-protons of furan ring			thiazolinone 5-CH_2	thiazole 5-CH	other proton signals
			3-H	4-H	$J_{3,4}$			
IIa	$CDCl_3$	A	7,47	6,62	3,3	3,78	—	7,71 (5-H); $J_{3,5}$=1,2; $J_{4,5}$=1,9
	$(CD_3)_2CO$	A:B=3:7	7,67	6,56	4,0	3,03	—	7,96 (5-H); $J_{3,5}$=1,1; $J_{4,5}$=2,1
			7,53	6,76	4,0	—	6,1	8,0 (5-H); $J_{3,5}$=1,1; $J_{4,5}$=2,0
	$(CD_3)_2SO$	A	7,56	5,82	4,0	3,06	—	7,20 (5-H); $J_{3,5}$=1,0; $J_{4,5}$=1,95
	CF_3COOH	A	7,91	6,75	4,0	4,16	—	7,90 (5-H); $J_{3,5}$=1,8; $J_{4,4}$=2,0
IIb	$CDCl_3$	A	7,40	6,29	4,0	3,88	—	2,43 ($-CH_3$)
	$(CD_3)_2CO$	A	7,01	5,98	4,0	3,55	—	2,11 ($-CH_3$)
	$(CD_3)_2SO$	A:B=3:2	6,41	5,41	3,8	3,0	—	1,33 ($-CH_3$)
			5,70	5,13	3,2	—	5,0	1,41 (OH); 1,20 ($-CH_3$)
	CF_3COOH	A	7,68	6,30	4,0	3,98	—	2,15 ($-CH_3$)
IIc	$CDCl_3$	A	7,46	6,55	4,0	3,90		
	$(CD)_3SO$	A:B=1:1	5,93	5,35	4,0	3,0	—	
			5,73	5,47	3,5	—	5,2	1,45 (OH)
IId	$(CD_3)_2SO$	B	5,98	6,50	4,0	—	5,24	1,45 (OH)
	CF_3COOH	B	7,16	7,16	0	—	6,61	
IIe	$(CD_3)_2SO$	B	6,01	5,76	4,0	—	5,08	6,61 (2H, $C_6H_2Cl_3$)
	CF_3COOH	A	7,83	6,75	4,0	4,1	—	6,97 (2H, $C_6H_2Cl_3$)

*The choice of solvents is limited by the solubility of the compounds studied.

the PMR spectra, corresponding to the A and B forms: for the hydroxythiazole form, a singlet of the CH proton of the thiazole ring (1H) and a singlet of the hydroxyl proton are characteristic. The presence of a hydroxyl proton signal in the strong fields region (in DMSO, relative to tert-butanol as internal standard) can be attributed to the formation of hydrogen bonds in the solution, in which the hydroxylic hydrogen atom is associated with the endocyclic nitrogen atom, which, according to [9], should lead to a strong-field shift of the hydroxyl group signal. For the hydroxythiazole form B of compound IIa in acetone, the hydroxyl proton signal was not observed: this may be the result of either a masking of the hydroxyl group proton signal by the solvent signal, or by strong broadening of the signal as the result of exchange processes proceeding at an "intermediate" rate [10].

The nitro derivative IId in DMSO-D_6 and CF_3COOH (Table 2) has one set of signals, corresponding to the hydroxythiazole form B.

In trifluoroacetic acid, compounds II are possibly protonated at the endocyclic nitrogen atom, as indicated by a shift of the furan 3-H proton signal to a weak field. The protonated thiazole ring becomes an electron acceptor, comparable in strength with the nitro group, and therefore the β-proton signals of the furan ring of the nitro-derivative IId merge, similarly as observed in the PMR spectra of 2,5-dinitrofuran and 5-nitrofurfural [11].

Addition of a few drops of D_2O or CF_3COOD to all the solutions of compounds II leads to the rapid (2-3 min, 25°C) disappearance of the methylene group proton signals of the thiazoline ring, and also of the aromatic and hydroxylic protons of the thiazole ring. This indicates, on the one hand, a higher rate of exchange of a proton for deuterium, and shows, on the other hand, that in solutions, where the signals of the second tautomer are spectrally not observed, this tautomer is present at low concentrations.

We attempted to study the tautomeric equilibrium A $\rightleftarrows$ B in aqueous solutions by the method of applied correlations of log k/k_0 vs. σ, proposed by Kabachnik, et al. [12, 13]. The values of the acidity constants of compounds IIa-e were determined (Table 1) and a correlational analysis of the pK_a values with different σ-constants of the substituents was carried out by using the method of spectrophotometric titration in aqueous buffer solutions (universal buffer with a ionic strength of 0.11). Thus, a good linear dependence for the pK_a values was found only with respect to the Brown σ^+-constants

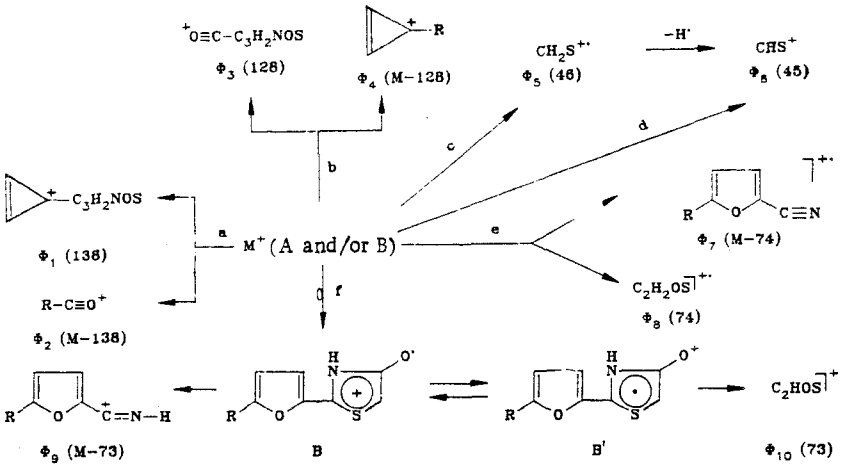
$$pK_a = (9.07 \pm 0.02) - (2.45 \pm 0.01)\sigma^+_{para} \quad (r = 0.989;\ S = 0.02). \qquad (1)$$

The existence of a linear dependence of pK_a on σ^+_{para} indicates a strong shift of the equilibrium in the direction of one of the tautomeric forms [14]. The extent of the influence of substituents R on the reaction center (ρ = 2.45), and in particular, on the pK_a

TABLE 3. Peak Intensity of Characteristic Fragmentary Ions in Mass Spectra of Compounds II in Total Ionic Current

Compound	M^+	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	Φ_{10}
IIa	17,2	2,5	—	—	4,8	7,9	4,1	7,5	4,7	15,0	0,04
IIb	12,4	6,3	4,6	0,1	3,9	3,9	2,9	10,2	1,7	12,4	0,08
IIc	13,2	5,8	0,3	0,02	1,6	5,5	4,5	6,4	3,9	5,7	0,1
IId*	14,6			1,8	0,2	8,3	8,1			1,6	0,2
IIe	15,7	5,1	2,4	0,3	5,9	2,3	1,8	6,3	2,2	9,1	0,7

*The m/z of ions Φ_1 and Φ_7 (I = 6.5) and ions Φ_2 and Φ_8 (I = 8.7) coincide.



The m/z values are shown in brackets.

value of compounds II shows that in aqueous solutions the hydroxythiazole form B is predominant.

The study of the mass spectra of compounds II was of interest for the determination of the tautomeric forms in the gaseous phase.

The main paths of the fragmentation of the molecular ions (M^+) are shown in the scheme above and are related to the competing dissociation of the furan (paths a and b) and thiazole (paths c-f) fragments of the molecules.

The substituent R, which influences the charge distribution in M^+, determines the competitiveness of one or another path of dissociation (Tables 3, 4). Thus, paths a and b, known for 2,5-disubstituted furans, with the formation of ions Φ_1 and Φ_2 are due to the ability of the substituent to undergo a charge delocalization: in the mass spectra of compounds II, the peaks of ions Φ_2 and Φ_3 have low intensity. An exception is provided by by the RCO^+ cations arising during the dissociation of M^+ of compounds IIb, e. The formation of ions Φ_1 in the case of compound II occurs as the result of splitting the entire $CH_3CO^\cdot$ radical; for compounds IIc-e, a successive splitting of radical $R^\cdot$ and the CO group also takes place. At the same time, ion Φ_4 forms only as a result of the elimination of the $^\cdot OC-C_3H_2NOS$ radical. As shown in [15, 16] ions Φ_1 and Φ_4 contain a cyclopropane grouping. We should note that in none of the above cases was the rupture of the furan–thiazole bond observed.

Analysis of the paths of fragmentation of M^+ with splitting of the thiazole part of the molecule leads to certain conclusions about their tautomeric state. On the one hand, in analogy with the 3-oxo-2,3-dihydrofuran derivatives, for which the 3-hydroxy furan form predominates in the gaseous phase [17, 18], it can be assumed that most of M^+ should have a hydroxythiazole structure, which is stabilized by the formation of an aromatic thiazole system. On the other hand, the presence of intense peaks of ions Φ_5 in the mass spectra confirms the presence of the thiazoline form of M^+ in the gaseous phase also. Depending on the localization of the charge, both oxo- and hydroxy forms of M^+ can dissociate with the formation of odd-electronic fragments Φ_7 and Φ_8 (path e). There is also a dissociation

TABLE 4. Mass Spectra of Compounds IIa-e

Compound	The m/z values* (relative peak intensity in % of maximal value is given)
IIa	167 (100), 138 (14), 94 (87), 93 (44), 74 (27), 64 (16), 46 (46), 45 (24), 39 (28), 38 (16)
IIb	181 (100), 138 (51), 108 (100), 107 (82), 106 (28), 53 (31), 52 (30), 46 (31), 45 (23), 43 (37)
IIc	245 (88)**, 172 (38)**, 171 (41)**, 138 (77), 120 (44)**, 74 (52), 64 (100), 46 (73), 45 (61), 38 (36)
IId	21 (100), 182 (13), 138 (42), 128 (12), 74 (59), 64 (36), 46 (60), 45 (56), 38 (17), 37 (13)
IIe	345 (98)**, 272 (59)**, 217 (39)**, 207 (12)**, 181 (11), 147 (18), 138 (76), 74 (33), 46 (35), 45 (27)

*Ten most intense peaks are shown.
**The m/z values of ions are shown containing a light halogen isotope.

path (f) with the formation of even-electronic fragments Φ_9 and Φ_{10}. Cation Φ_{10} can, in principle, be formed also in another way: as the result of elimination of the hydrogen atom from cation-radical Φ_8, while the formation of cation Φ_9 may occur only as the result of a preliminary regrouping of M^+, i.e., of a transfer of a hydrogen atom to an endocyclic nitrogen atom from the hydroxy group of the thiazole form or from the methylene group of the thiazoline form of M^+. The substituent R in the furan ring sharply alters the amount of M^+ dissociating by path f (Table 4), which is probably due to the influence of the substituent on the basicity of the endocyclic nitrogen atom and the ability of the substituent to undergo a charge delocalization; this is well evident from the change in the intensity of ion Φ_9 in the mass spectra.

Thus, compounds II, obtained as a result of the reaction of cyanofurans with thioglycolic acid, represent a typical thiazolin-4-one — 4-hydroxythiazole tautomeric system, which, in contrast to the 2-phenyl-substituted analogs [3], are stable towards dimerization processes. The possibility of the formation of structure B in the gaseous phase of M^+ gives the expectation of discovery in the future of still another tautomeric form with a mesoionic structure.

EXPERIMENTAL

The electronic spectra were recorded and spectrophotometric titration was carried out on a Specord UV-vis spectrophotometer, using universal buffer solutions with an ionic strength of 0.11. The pK_a values were corrected for the salt effect of the solvent [19]. The IR spectra were recorded on a UR-20 spectrophotometer, using the compounds in the form of a suspension in mineral oil, the PMR spectra on a Tesla 467 spectrometer (60 MHz), using HMDS as internal standard. The mass spectra were measured on an LKB-2091 apparatus with energy of ionizing electrons 70 eV and with direct introduction of the compound into the ionization chamber at 170°C. The course of the reactions and the purity of the products were monitored by TLC (Silufol) in a 20:3 toluene—ethanol system.

2-(2-Furyl)thiazolin-4-one (IIa). A mixture of 9.2 g (0.1 mole) of thioglycolic acid and 9.3 g (0.1 mole) of 2-cyanofuran in 50 ml of pyridine was heated for 6 h at 80°C. Pyridine was evaporated in vacuo, and the residual oil crystallized on grinding. The reaction product was purified by recrystallization from ethanol. Compounds IIb, e were obtained in a similar way.

2-(5-Bromo-2-furyl)thiazolin-4-one (IIc). A mixture of 9.2 g (0.1 mole) of thioglycolic acid and 17.2 g (0.1 mole) of 5-bromo-2-cyanofuran in 50 ml of pyridine was stirred at 10°C until a homogeneous mixture was formed. The solution was allowed to stand overnight in a refrigerator and poured into 100 ml of cold water. The crystals that precipitated were washed with water and recrystallized from chloroform. Compound IId was obtained in a similar way.

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SYNTHESIS OF SUBSTITUTED THIENO[2,3-d]THIAZOLES AND INDOLO[3,2-d]THIAZOLES

L. D. Pinkin, V. G. Dzyubenko,
P. I. Abramenko, and I. S. Shpileva

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Alkylene-, halo-, and aryl-substituted 2-methylthieno[2,3-d]thiazoles were obtained by the action of phosphorus pentasulfide on the corresponding 2-acetylamino-3-bromo- or 2-acetylamino-3-hydroxythiophenes in an organic solvent with heating. 2-Oximes of halo- and methyl-substituted isatins were converted by reduction and acylation into 2-hydroxy-3-acetylaminoindoles, from which 2-methylindolo[3,2-d]-thiazoles were obtained by the action of phosphorous pentasulfide with heating in xylene.

The spectral and photographic properties of polymethine dyes, derivatives of thieno- and indolothiazoles which do not contain substituents in the heterocyclic rings have already been studied in [1-3]. It is also known that the photographic effectiveness of sensitizing dyes, derivatives of benzothiazoles [4], is much higher than that of the corresponding unsubstituted compounds. In order to study the influence of substituents on the spectral and photographic properties of thieno- and indolothiazolocyanines, we carried out the synthesis of new thieno[2,3-d]- and indolo[3,2-d]-thiazoles, substituted in the annelated thiophene or benzene ring.

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