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Physicochemical Properties of 4,5-(Aryl,alkyl)-3-substituted 2-Aminothiophenes Sulfonyl Derivatives

L. G. Chekanova[a]*, K. O. Manylova[a], P. T. Pavlov[b], A. N. Vasyanin[b], S. N. Shurov[b], and O. A. Maiorova[a]

[a] *Institute of Technical Chemistry, Ural Branch, Russian Academy of Sciences,*
ul. Akademika Koroleva 3, Perm, 614013 Russia
**e-mail: larchek.07@mail.ru*

[b] *Perm State National Research University, Perm, Russia*

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Abstract—Physicochemical properties of 4,5-(aryl, alkyl)-3-substituted 2-sulfonylaminothiophenes have been studied. The effect of the nature of the substituents in the thiophene ring on acid-base properties, solubility, and chemical stability was investigated.

Keywords: sulfonyl derivatives of aminothiophenes, acid-base properties, solubility, chemical stability

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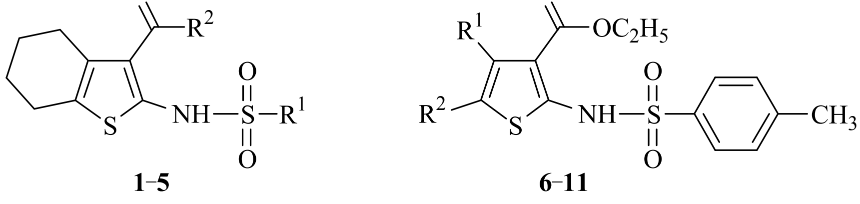
Earlier, we have studied a series of ethyl 2-aryl(methyl)sulfonylamino-4,5,6,7-tetrahydro[*b*]-thiophene-3-carboxylates as reagents for ionic flotation of nonferrous metals [1, 2]. Considering all properties, for further investigation we have chosen ethyl-{2-mesyl(tosyl)amino-4,5,6,7-tetrahydro-benzo[*b*]thiophene}-3-carboxylates. We planned to investigate the variations in the physicochemical properties of these compounds depending on the nature of the functional group in the position *3*, as well as on substituents in the positions *4* and *5* of the thiophene ring. For this purpose we have synthesized 2-(aryl, methyl)-sulfonylamino-4,5,6,7-tetrahydrobenzo[*b*]-3-substituted thiophenes **1–5** and ethyl-2-tosylamino-4,5-(aryl, alkyl)-thiophene-3-carboxylates **6–11** (Scheme 1).

Compounds **1, 3, 4** were obtained by the reaction of the corresponding thiophenes with tosyl chloride. Compounds **2** and **5** were obtained by the hydrolysis of the corresponding esters with aqueous-alcohol-dioxane solution of NaOH. We failed to isolate the products with the amide or substituted amide group from the synthesis of 2-mesylamino-4,5,6,7-tetrahydrobenzo[*b*]-3-substituted thiophenes because of the formation of a large amount of side products. Compounds **6–11** were obtained by the reaction of the corresponding thiophenes with tosyl chloride, as we described earlier [1]. The obtained compounds are crystalline products (Table 1).

The structure of the synthesized compounds was proved by IR and NMR spectra. The IR spectra of

Scheme 1.



R^1 = Tol, R^2 = OEt (**1**), OH (**2**), NH_2 (**3**), NHPh (**4**); R^1 = Me; R^2 = OH (**5**); R^1 = Ph, R^2 = Ph (**6**); R^1 = Bn, R^2 = Ph (**7**); R^1 = Me, R^2 = Ph (**8**); R^1 = Me, R^2 = Me (**9**); R^1 = Ph, R^2 = Me (**10**); R^1 = Ph, R^2 = Et (**11**).

compounds **1–5** contain absorption bands of stretching vibrations of the secondary amino group at 3117–3312 cm^{-1}; ester **1** (1657 cm^{-1}), carboxyl **2** (1627 cm^{-1}), **5** (1650 cm^{-1}); primary **3** (1660 cm^{-1}) and secondary amide groups **4** (1640 cm^{-1}). The absorption bands of symmetric and asymmetric stretching vibrations of the SO_2 group appear in the range 1153–1169 and 1323–1340 cm^{-1}. Besides, the IR spectrum of **2** contains a separate band of the carboxyl hydroxy group at 3300 cm^{-1}. The absorption band of the NH_2 group in the spectrum of compound **3** appears at 3300 cm^{-1}. In the spectrum of compound **4** the band of the anilide group appears at 3363 cm^{-1}. In the IR spectra of compounds **6–11** the absorption bands are observed of the stretching vibrations of secondary amino group (3147–3312 cm^{-1}) and of ester group (1656–1677 cm^{-1}); the absorption bands of symmetric and asymmetric stretching vibrations of SO_2 group appear in the range 1156–1165 and 1327–1340 cm^{-1}.

^{1}H NMR spectra of solutions of compounds **1–11** in DMSO-d_6 contain singlet signals of the NH group protons (10.22–10.82 ppm) and the protons of the aromatic ring at the SO_2 group (7.09–7.82 ppm). In the spectra of compounds **1–5** the multiplets of the methylene group protons 5,6-$(CH_2)_2$ (1.65–1.70 ppm) and 4,7-$(CH_2)_2$ group (2.51–2.63 ppm) are observed, and for compound **5** also a singlet of the methyl group appears (3.14 ppm). The OEt group in **1** is observed as a quartet at 4.24 ppm (CH_2O) and a triplet at 1.27 ppm (CH_3). In the spectra of **2** and **5** the carboxyl and sulfamide protons give a wide combined signal at 10.79 and 10.32 ppm, respectively. The primary amide protons in the spectrum of compound **3** resonate as a wide singlet at 7.14 ppm. The anilide proton in the spectrum of compound **4** resonates at 9.70 ppm. In the spectra of compounds **6–11** the signals of aromatic protons appear in the range 6.87–7.52 ppm, the OEt group is seen as a quartet at 3.80–4.23 ppm (CH_2O) and a triplet at 0.78–1.31 ppm (CH_3).

All compounds, except **5**, are poorly soluble in isoamyl alcohol, hexane, and water (Table 2). Compounds **2–5** are readily soluble in diluted solutions of KOH and in ethanol, so, the use of these solutions is possible in flotation processes. For extraction the solutions are suitable of compounds **1**, **6–11** with the ester group in position *3* of the thiophene ring due to their moderate solubility in *p*-xylene and chloroform.

Table 1. Physicochemical characteristics of compounds **1–11**

Comp. no.	mp, °C	R_f[a]	pK_a	
			pK_{a1}	pK_{a2}
1	125–127	0.53	7.77±0.05	
2	189–191	0.49	4.74±0.07	–
3	201–203	0.64	6.86±0.04	
4	187–189	0.53	4.19±0.08	–
5	172–174	0.30	4.68±0.06	8.18±0.07
6	141–144	0.80	6.48±0.07	
7	108–110	0.73	7.02±0.05	
8	120–123	0.81	7.28±0.05	
9	91–92	0.73	7.85±0.08	
10	110–112	0.74	7.16±0.06	
11	117–119	0.87/0.41[b]	7.07±0.05	

[a] Eluent – benzene : ether = 10 : 1 (**1**, **6–11**); benzene : ether = 5 : 1 (**2**); ethyl acetate : benzene = 2 : 1 (**3–5**).

[b] Eluent – benzene.

Compounds **1–11** are NH-acids. Ionization in alkaline media can be represented by Scheme 2. For compounds **2, 4, 5** both elimination of the NH proton (Scheme 2) and the formation of the salt on the carboxyl group in the position *3* of the thiophene ring is possible (Scheme 3).

For compounds **6–11**, as well as for **1** and **3**, the constants of acid dissociation were measured by the method of potentiometric titration (Table 1). On the curve of conductometric titration of compounds **2, 4, 5** with alkali, two inflection points are observed (Fig. 1), apparently corresponding to two dissociation steps.

Scheme 2.

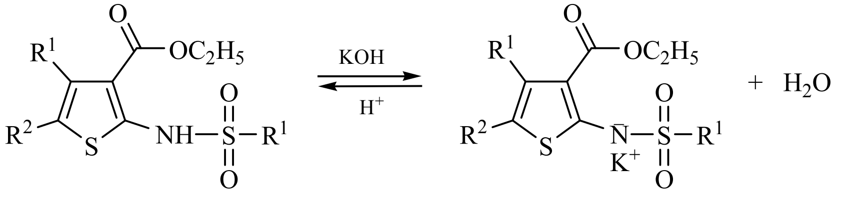


Table 2. Solubility of compounds **1–11**

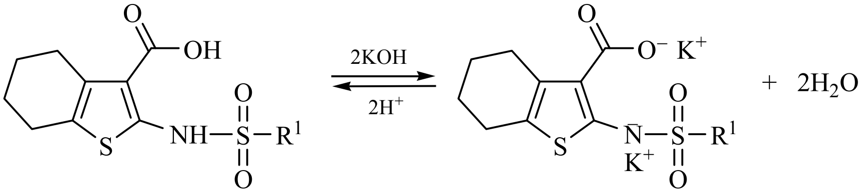
Comp. no.	Solubility, mol/L (g/L)						
	EtOH, $\times 10^3$	0.1 M KOH, $\times 10^4$	H_2O, $\times 10^4$	hexane, $\times 10^3$	*p*-xylene, $\times 10^2$	*i*-AmOH, $\times 10^2$	chloroform, $\times 10^2$
1	25.0 (9.60)	9.0 (0.33)	4.0 (0.16)	7.0 (2.64)	68.0 (258.60)	2.1 (7.83)	195.0 (741.5)
2	22.8 (8.0)	312.5 (10.97)	8.5 (0.30)	1.7 (0.60)	0.43 (1.50)	1.5 (5.30)	5.3 (18.70)
3	7.3 (2.55)	720.0 (25.23)	5.7 (0.22)	0.01 (0.01)	0.4 (1.30)	0.2 (0.70)	5.3 (18.60)
4	9.9 (4.2)	162.5 (6.92)	Insoluble	Insoluble	0.5 (2.20)	0.8 (3.30)	37.4 (159.30)
5	100.0 (27.6)	625.0 (17.19)	29.0 (0.80)	4.4 (1.20)	0.4 (1.20)	2.8 (7.80)	10.2 (28.00)
6	7.0 (3.20)	0.2 (0.01)	8.0 (0.40)	1.7 (0.80)	15.9 (76.00)	0.5 (2.60)	83.9 (400.00)
7	0.8 (0.40)	0.5 (0.03)	Insoluble	0.8 (0.40)	22.7 (111.40)	Insoluble	99.6 (489.00)
8	11.0 (4.60)	0.4 (0.02)	9.6 (0.40)	4.0 (1.80)	38.6 (160.20)	0.9 (3.80)	118.5 (492.00)
9	25.0 (8.99)	45.0 (1.59)	Insoluble	5.0 (1.80)	70.9 (250.20)	2.7 (9.67)	140.0 (494.70)
10	20.7 (8.60)	13.0 (0.54)	4.8 (0.20)	6.7 (2.80)	54.9 (228.00)	1.3 (5.33)	147.5 (613.00)
11	13.0 (5.60)	2.0 (0.09)	Insoluble	8.6 (3.70)	68.9 (296.00)	1.4 (6.00)	107.8 (463.00)

In the electron absorption spectra with the increase of pH of solutions of **2** and **5** an increase in the intensity of the band with the maximum at 225–230 nm is observed and a band appears at 280–290 nm, which can be tentatively assigned to the superposition of the two ionized forms. The presence of two isosbestic points in the spectrum of compound **2** (Fig. 2) proves the equilibrium of three forms in the solution. In the case of compound **4** with the increase in pH three absorption bands are observed in the spectrum with the maxima at 235, 335, and 220 nm (pH > 11).

By potentiometric titration two acid dissociation constants were determined for compound **5** (Table 1). For compound **2** and **4** we failed to calculate the value of the second constant from the experiment.

To determine the site of primary deprotonation we have calculated the total energies (E_{tot}) of compounds **1–5** and the corresponding anions in gas phase using the B3LYP/6-311G(d) method (Table 3). The comparison of the energies of the anions shows that for compound **2** the O-anion **2b** is by 53.8 kJ/mol more stable than the *N*-anion **2a**. The Δ*E* value for the pair **2**

Scheme 3.



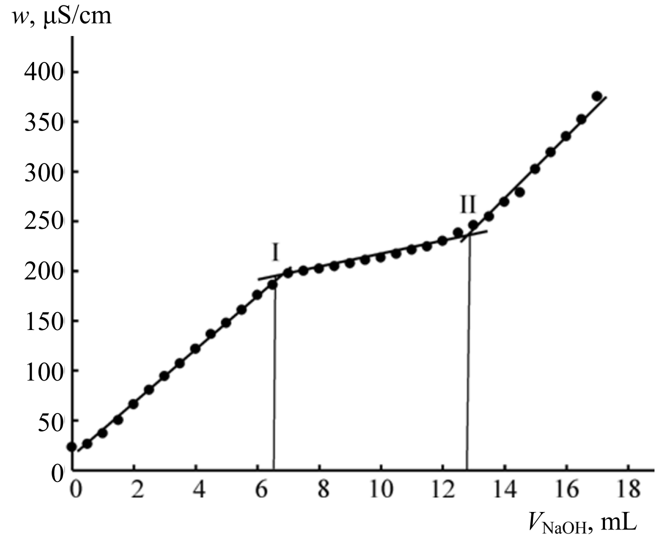


Fig. 1. Conductometric titration of 2-mesylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid **5**. pH ~ 5, V_0 = 76 mL, m_5 = 0,2573 g; c_{KOH} = 0.094 mol/L.

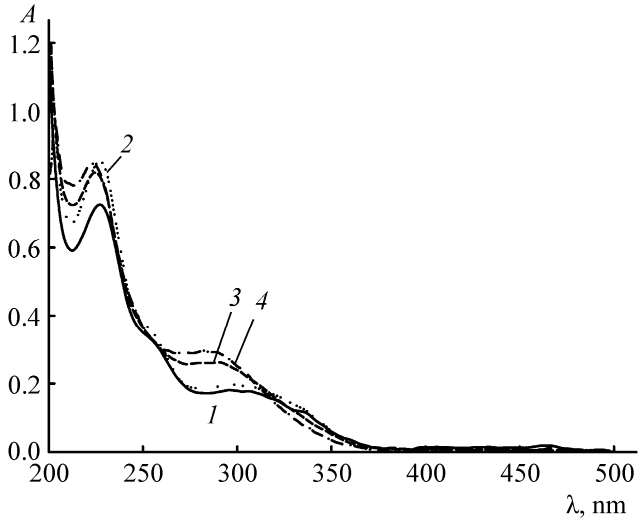
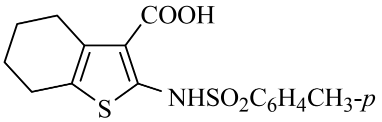
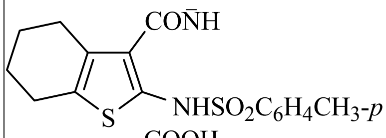
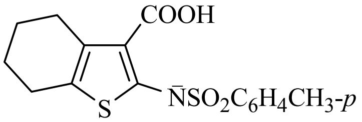
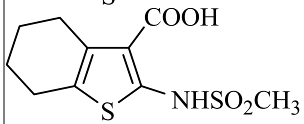
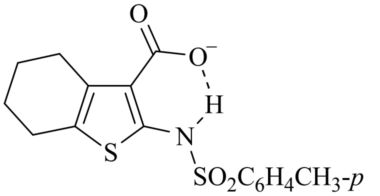
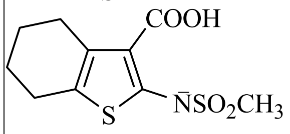
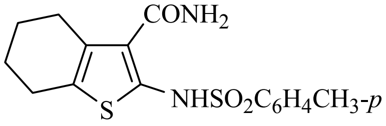
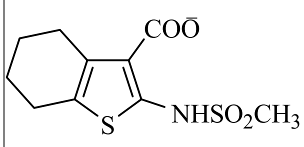
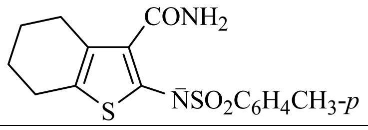


Fig. 2. Electron absorption spectra of aqueous-alcohol solution of 2-tosylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid **2** at pH (*1*) 5.1; (*2*) 6.7; (*3*) 9.2; (*4*) 11.7; $c_2 = 10^{-5}$ mol/L.

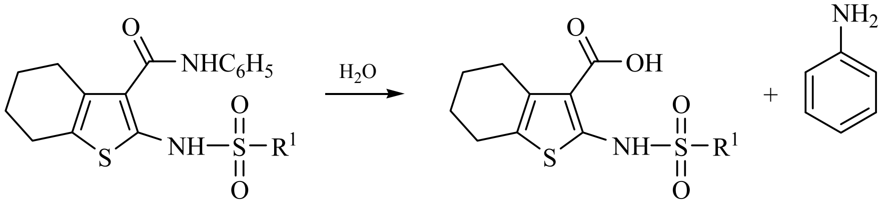
and **2b** is 0.5209 a.u., while for compound **5** and its O-anion **5b** it increases to 0.5303 a.u. suggesting a lower acidity of compound **5** as compared to compound **2** in the gas phase.

To confirm the course of ionization of compounds **2** and **5** we have synthesized a model compound, 4,5,6,7-tetrahydrobenzo[*b*]-3-thiophenecarboxylic acid, lacking the second site of ionization. The pK_a value

Table 3. Electronic characteristics of compounds, B3LYP/6-311G(d)

Comp. no.	Structure	Total energy, Hartrees	Comp. no.	Structure	Total energy, Hartrees
2		–1172.2068	**3b**		–1751.7717
2a		–1171.6654	**5**		–1541.1089
2b		–1171.6859	**5a**		–1540.5672
3		–1752.3279	**5b**		–1540.5786
3a		–1751.8039			

Scheme 4.



determined by potentiometric titration is 5.32. For comparison, pK_a for compounds **2** and **5** are 4.74 and 4.68, respectively, and for **1** (having one center of ionization according to Scheme 2) it is 7.77 (Table 1). These data prove the assumption that ionization of thiophenes **2** and **5** occurs first on the carboxyl and later on the sulfonamide group.

The analysis of the ^{1}H NMR spectra of solutions of compound **4** in DMSO-d_6 revealed that in comparison with the neutral solution, in the alkaline solution the signal of the sulfonamide proton at 10.27 ppm is retained whereas the signal of the anilide proton at 9.70 ppm disappears. Also signals appear at 11.53 and 4.4 ppm, whose intensity increases with the NaOH concentration. It is presumable that in the alkaline medium compound **4** is hydrolyzed (Scheme 4). The signals at 11.53 and 4.4 ppm may be assigned, respectively, to the protons of the carboxyl group and aniline.

The hydrolysis of compound **4** was proved by the method of TLC (R_f = 0.50, benzene:ether = 5 : 1) with 2-tosylamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (R_f= 0.35) and aniline (R_f = 0.42) as authentic samples.

For compound **3** the possibility is presumable of a proton addition due to the presence of a free lone electron pair on nitrogen of the NH_2 group. However, potentiometric titration with HCl solution did not prove the formation of the protonated form.

Spectrophotometrically it was found that compounds **1–3** and **5–11** are stable in 0.1 M KOH solution at 60°C for 4 h, and at 20°C for 1 day. The substituents in the positions *4* and *5* of the thiophene ring do not affect the stability.

The comparison of the properties of the sulfonyl derivatives of aminothiophenes allows a conclusion that the reagents with the ester group in the position *3* of the thiophene ring **1**, **6–11** are of the most interest for further investigations as flotoreagents for non-ferrous metals due to their moderate solubility in aqueous alkali and in alcohol, as well as in a number of organic solvents.

EXPERIMENTAL

IR spectra were recorded on a IFS-66/S Fourier spectrometer (Bruker, Germany). ^{1}H NMR spectra were registered on a MERCURY plus 300 spectrometer (Varian, USA) in DMSO-d_6, internal reference HMDS. Melting points were determined on a PTP instrument in capillaries. Elemental analysis was performed on a CHNS-932 analyzer (LECO Co., USA). Conductometric titration was performed on an Anion 4100 conductometer. UV spectra were registered on a SF-2000 spectrophotometer, refraction indices were measured on an IRF-22 refractometer. The solubility of the products was determined by known procedures using the methods of gravimetry [5, 6], spectrophotometry [5] and refractometry [7]. The reactions were monitored by TLC on Silufol UV-254 plates in appropriate systems of mobile phases, and developed by iodine vapor.

The content of metal ions in solutions was determined on an atomic absorption spectrometer iCE 3500 with flame atomization (Thermo Fisher Scientific, USA).

Acid dissociation constants were determined by the methods of spectrophotometry [8] and potentiometry [9]. pH values and EMF of solutions were measured on a I-160M ionomer with glass and silver chloride electrodes. pH values were corrected for the presence of ethanol; the correction was required to calculate the true concentration of hydrogen ions as described in [10, 11].

The content of the main compound was determined by potentiometric [3] and conductometric titration [4]; it was no less than 97%. For conductometric titration, the specimen of 0.2–0.3 g was dissolved in the mixture of water and EtOH (1 : 3) and titrated with 0.1 M KOH solution. The assay was determined from the plot of electroconductivity of the solution versus the titrant volume by the formula

$$c, \% = (VME)/(m \times 10), \qquad (1)$$

where V is the titrant volume at the point of first inflection, mL; M is concentration of KOH titrant solution, mol/l; *m* is the mass of specimen, g; *E* is equivalent equal to molecular mass of the compound. The hydrolytic stability was investigated spectrophotometrically by the procedure described in [5].

Quantum-chemical calculations with full geometry optimization were performed on a supercomputer PSU-Tesla of the Center of parallel and distributed calculations of the Perm State National Research University using Firefly program package [12].

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