Preparation and cyclization of 3-substituted 1-(2-cyanophenyl)-thioureas

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The reactions of 2-isothiocyanatobenzonitrile with ethyl-, *tert*-butyl-, cyclohexyl-, and benzylamine as well as with aniline, 4-toluidine, 4-anisidine, 4-bromoaniline, phenylhydrazine, and hydrazine were studied. In dependence on the structure of the starting amine and on the reaction conditions either 3-substituted 1-(2-cyanophenyl)thioureas, 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones or a mixture of both compounds were formed. 4-Amino-1,2-dihydroquinazoline-2-thione was formed in the reaction of 2-isothiocyanatobenzonitrile with ammonia. The structure of the latter was proved by an independent synthesis.

3-Substituted 1-(2-cyanophenyl)thioureas with the exception of the last were cyclized in boiling ethanol to corresponding 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones.

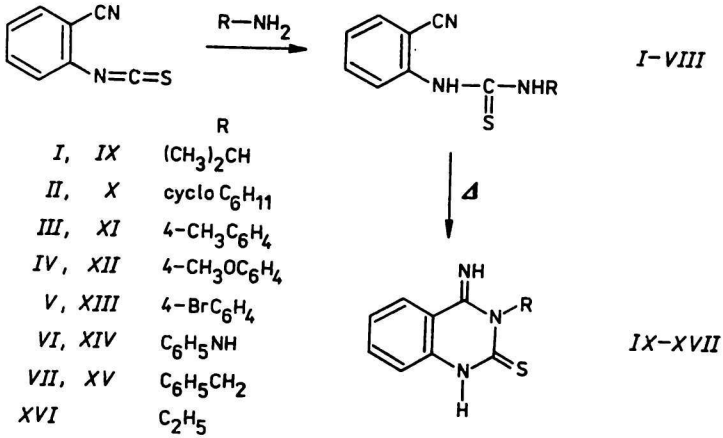
Исследована реакция 2-изотиоцианатобензонитрила с этил-, *трет*-бутил-, циклогексил- и бензиламином, анилином, 4-толуидином, 4-анизидином, 4-броманилином, фенилгидразином и гидразином. В зависимости от структуры исходного амина и от реакционных условий, образовывались 3-замещенные 1-(2-цианофенил)тиомочевины, 3-замещенные 4-имино-1,2,3,4-тетрагидрохиназолин-2-тионы, или же смесь веществ обоих типов. 4-Амино-1,2-дигидрохиназолин-2-тион образовался реакцией 2-изотиоцианатобензонитрила с аммиаком и его структура была подтверждена встречным синтезом.

3-Замещенные 1-(2-цианофенил)тиомочевины кроме последней были подвержены циклизации путем кипячения в этиловом спирте с образованием соответствующих 3-замещенных 4-имино-1,2,3,4-тетрагидрохиназолин-2-тионов.

Syntheses leading to 3-substituted 1-(2-cyanophenyl)thioureas utilizing the interaction of isothiocyanato group with amino group may start with two different substrates. Either it is 2-aminobenzonitrile reacting with substituted isothiocyanates or it may be 2-isothiocyanatobenzonitrile that reacts with primary amines. Both ways were applied to the synthesis of 3-phenyl-1-(2-cyanophenyl)thiourea [1, 2]. This compound is thermally unstable and can immediately enter into pyrimidine ring closure by the interaction of cyano group with thioureido group.

The reaction of 2-aminobenzonitrile with phenyl isothiocyanate without any solvent for 20 h at the temperature of 50 °C [1] was unsuccessfully reproduced [2]. In all cases under varied conditions the only product of cyclization of 3-phenyl-1-(2-cyanophenyl)thiourea, *i.e.* 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione was obtained. The synthesis of 3-phenyl-1-(2-cyanophenyl)thiourea by the reaction of 2-isothiocyanatobenzonitrile with aniline at room temperature in the medium of dichloromethane—petroleum ether in the yield of 98 % is reported in literature [2]. The structure of the product was proved by IR and ^{1}H NMR spectroscopies.

The aim of our work was the synthesis of 3-substituted 1-(2-cyanophenyl)-thioureas *I—VIII* by the reaction of 2-isothiocyanatobenzonitrile with primary amines (Scheme 1). These were the intermediates for the synthesis of 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones.



Scheme 1

Experimental

Melting points were measured on a Kofler hot-stage, Wägetechnik Rapido 79-2106.

The composition of the prepared compounds was checked by the elemental analysis with C. Erba 1102 instrument.

IR spectra were measured with Unicam SP 1000 in KBr pellets, ^{1}H and ^{13}C NMR spectra were recorded with Tesla BS 567 (100 or 25 MHz) in hexadeuteroacetone (internal standard TMS) or in hexadeuterodimethyl sulfoxide (internal standard HMDSO) in 1 M solution.

TLC was carried out on Silufol UV 254 plates (Kavalier, Votice); detection with the instrument Fluotest Universal (Quarzlampen, Hanau). As eluents were used benzene, chloroform, diisopropyl ether, diethyl ether, and acetonitrile in a container saturated by the vapours of the used solvent. The compounds were deposited on the plates dissolved in acetonitrile [3].

Characteristics of the synthesized compounds are presented in Tables 1—6.

3-Substituted 1-(2-cyanophenyl)thioureas I—VIII

Solution of amine (0.05 mol) in dichloromethane (75 cm^3) was dropwise added during 10 min into solution of 2-isothiocyanatobenzonitrile (8 g; 0.05 mol) [2] in the mixture dichloromethane—petroleum ether ($\varphi_r = 1:1$) (100 cm^3). After 2-isothiocyanatobenzonitrile disappeared (checked by TLC) petroleum ether (50—75 cm^3) was added and thus white crystals formed were filtered off, washed with dichloromethane and petroleum ether, dried in vacuum at room temperature.

3-Substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones IX—XV

Compounds *I—VII* (1 mmol) were cyclized refluxing in ethanol (50 cm^3). When the reaction finished (checked by TLC in 1 min intervals) the solution was cooled down to the temperature of 0—5 °C and the crystals formed were filtered off and dried in vacuum.

3-Ethyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione (XVI)

The compound was prepared by the reaction of 2-isothiocyanatobenzonitrile (4 g; 0.025 mol) in the mixture dichloromethane—petroleum ether ($\varphi_r = 1:1$, 75 cm^3) with ethylamine (1.5 g; 0.033 mol) dissolved in dichloromethane (20 cm^3) at room temperature. White crystalline compound was obtained, m. p. = 210—211 °C, yield = 4.9 g (95 %). For $C_{10}H_{11}N_3S$ ($M_r = 205.31$) w_i(calc.): 58.53 % C, 5.37 % H, 20.48 % N; w_i(found): 58.45 % C, 5.28 % H, 20.40 % N. ^{13}C NMR spectrum (DMSO-d_6, TMS), δ/ppm: 174.06 (s, C=S), 152.82 (s, C=N), 135.73 (s), 132.89 (d), 125.80 (d), 123.78 (d), 115.90 (d), 114.79 (s), 42.07 (t, CH_2), 11.27 (q, CH_3).

3-Amino-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione (XVII)

The compound was prepared by the reaction of 2-isothiocyanatobenzonitrile (4 g; 0.025 mol) with hydrazine hydrate (100 %, 1.25 g; 0.025 mol) in the mixture dichloromethane—petroleum ether ($\varphi_r = 1:1$) at room temperature. White crystalline compound was formed, m. p. = 223—225 °C, yield = 4.4 g (92 %). For $C_8H_8N_4S$ ($M_r = 192.32$) w_i(calc.): 49.99 % C, 4.17 % H, 29.16 % N; w_i(found): 49.89 % C, 4.09 % H, 28.99 % N.

Table 1

Characteristics of synthesized 3-substituted 1-(2-cyanophenyl)thioureas *I*—*VIII*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M. p.	R_f		Temperature of the reaction °C
			C	H	N	%	°C	$(C_2H_5)_2O$	$CHCl_3$	
I	$C_{11}H_{13}N_3S$	219.30	60.25	5.98	19.16	90	156—158	0.66	0.30	20—25
			60.31	5.87	19.16					
II	$C_{14}H_{17}N_3S$	259.37	64.83	6.61	16.19	92	171—173	0.72	0.29	20—25
			64.71	6.50	16.24					
III	$C_{15}H_{13}N_3S$	267.33	67.39	4.90	15.71	94	181—183	0.65	0.31	0
			67.40	4.80	15.60					
IV	$C_{15}H_{13}N_3OS$	283.33	63.59	4.63	14.82	96	204—206	0.42	0.27	0
			63.65	4.54	14.78					
V	$C_{14}H_{10}N_3BrS$	332.20	50.61	3.03	12.64	95	239—241	0.37	0.28	20—25
			50.55	2.98	12.55					
VI	$C_{14}H_{12}N_4S$	268.32	62.67	4.51	20.88	90	191—193	0.61	0.28	0
			62.60	4.41	20.79					
VII	$C_{15}H_{13}N_3S$	267.33	67.39	4.90	15.71	92	196—198	0.62	0.24	−15 to −10
			67.58	4.80	15.65					
VIII	$C_{12}H_{15}N_3S$	233.31	61.79	6.44	18.02	76	163—164	0.71	0.35	20—25
			61.75	6.40	17.93					

Table 2

IR spectral characteristics ($\tilde{\nu}$/cm^{-1}) of the synthesized compounds

Compound	ν(C≡N)	ν(NHCS)	ν(NH)	ν(C_{sp^3}—N)	ν(Ar—N)	ν(C=C)	ν_s(COC)
I	2240	1550, 1210	3190, 3280	1195	1300	1600, 1590	—
II	2240	1560, 1220	3200, 3280	1185	1300	1600, 1590	—
III	2230	1555, 1230	3190, 3280	—	1290, 1310	1595, 1450	—
IV	2240	1550, 1220	3180, 3260	—	1305	1600, 1460	1040
V	2230	1550, 1230	3190, 3270	—	1280, 1315	1590, 1490	—
VI	2230	1540, 1210	3150, 3240	3300	1300, 1335	1600, 1450	—
VII	2240	1555, 1210	3180, 3300	1195	1310	1600, 1590	—
VIII	2220	1540, 1205	3190, 3230	1200	1300	1585, 1450	—

Table 3

^{1}H NMR characteristics of the synthesized compounds

Compound	δ/ppm
I[b]	7.14—8.50 (m, 4H, Ar—H), 8.80 (s, 1H, N—H), 8.59 (s, 1H, N—H), 6.48 (m, 1H, CH, J = 7.0 Hz), 1.63 (d, 6H, CH_3, J = 7.0 Hz)
II[b]	7.25—7.90 (m, 4H, Ar—H), 8.75 (s, 2H, N—H), 1.00—2.40 (m, 11H, cyclo C_6H_{11})
III[b]	7.18—8.20 (m, 8H, Ar—H), 9.22 (s, 1H, N—H), 8.84 (s, 1H, N—H), 2.42 (s, 3H, CH_3)
IV[b]	7.10—8.23 (m, 8H, Ar—H), 8.58 (s, 1H, N—H), 8.33 (s, 1H, N—H), 3.90 (s, 3H, OCH_3)
V[b]	7.24—8.25 (m, 8H, Ar—H), 10.33 (s, 1H, N—H), 10.02 (s, 1H, N—H)
VI[a]	6.82—8.70 (m, 9H, Ar—H), 9.15 (s, 1H, N—H), 10.02 (s, 1H, N—H), 10.60 (s, 1H, N—H)
VII[a]	7.24—7.98 (m, 9H, Ar—H), 8.13 (s, 1H, N—H), 9.13 (s, 1H, N—H), 5.00 (s, 2H, CH_2)
VIII[a]	7.25—7.93 (m, 4H, Ar—H), 8.52 (s, 1H, N—H), 8.78 (s, 1H, N—H), 1.58 (s, 9H, CH_3)

The spectra were measured in hexadeuteroacetone[a] (internal standard TMS) or in hexadeuterodimethyl sulfoxide[b] (internal standard HMDSO).

Table 4

Characteristics of 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones prepared by the cyclization of compounds *I—VII*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M. p.	τ
			C	H	N	%	°C	min
IX	$C_{11}H_{13}N_3S$	219.30	60.25	5.98	19.16	91	259—260	40
			60.20	5.85	19.12			
X	$C_{14}H_{17}N_3S$	259.37	64.83	6.61	16.19	92	318—320	20
			64.74	6.49	16.20			
XI	$C_{15}H_{13}N_3S$	267.33	67.39	4.90	15.71	97	298—300	10
			67.35	4.78	15.61			
XII	$C_{15}H_{13}N_3OS$	283.33	63.59	4.63	14.82	93	284—285	8
			63.54	4.50	14.75			
XIII	$C_{14}H_{10}N_3BrS$	332.20	50.61	3.03	12.64	84	276—278	15
			50.51	2.95	12.60			
XIV	$C_{14}H_{12}N_4S$	268.32	62.67	4.51	20.88	90	210—212	5
			62.61	4.40	20.76			
XV	$C_{15}H_{13}N_3S$	267.33	67.39	4.90	15.71	98	209—211	4
			67.40	4.81	15.67			

τ is the time of cyclization.

Table 5

IR spectral characteristics ($\tilde{\nu}$/cm^{-1}) of the synthesized compounds

Compound	ν(C=N)	ν(NHCS)	ν(C=C)	ν(NH)	ν(C_{sp^3}—H)
IX	1620	1540	1580, 1460	3200, 3290	2980, 2880
X	1630	1550	1595, 1500, 1455	3160, 3250	2950, 2880
XI	1640	1550	1600, 1490	3180, 3280	2960, 2280
XII	1640	1550	1595, 1490	3190, 3270	2950, 2890
XIII	1640	1540	1585, 1495	3170, 3280	—
XIV	1640	1550	1600, 1500, 1450	3190, 3260, 3300	—
XV	1630	1540	1590, 1500, 1445	3190, 3250	2950
XVI	1625	1550	1590, 1470	3250, 3390	2980, 2880
XVII	1640	1560	1600, 1455	3200, 3280, 3400	—

4-Amino-1,2-dihydroquinazoline-2-thione (XVIII)

Procedure A

Gaseous ammonia was introduced into solution of 2-isothiocyanatobenzonitrile (4 g; 0.025 mol) in chloroform (50 cm^3) as long as a white precipitate was formed and TLC

Table 6

^{1}H NMR spectral characteristics of the synthesized compounds

Compound	δ/ppm
IX[a]	7.25—8.48 (m, 4H, Ar—H), 9.10 (s, 1H, N—H), 10.52 (s, 1H, N—H), 4.75 (m, 1H, CH, J = 6.5 Hz), 1.30 (d, 6H, CH_3, J = 6.5 Hz)
X[b]	7.19—8.11 (m, 4H, Ar—H), 1.00—2.03 (m, 11H, cyclo C_6H_{11})
XI[a]	7.15—8.30 (m, 8H, Ar—H), 8.93 (s, 1H, N—H), 10.48 (s, 1H, N—H), 2.42 (s, 3H, CH_3)
XII[b]	7.15—8.25 (m, 8H, Ar—H), 3.90 (s, 3H, OCH_3)
XIII[b]	7.25—8.30 (m, 8H, Ar—H), 9.38 (s, 2H, N—H)
XIV[a]	6.70—8.36 (m, 9H, Ar—H), 8.90 (s, 1H, N—H), 10.40 (s, 2H, N—H)
XV[b]	7.02—8.20 (m, 9H, Ar—H), 5.98 (s, 2H, CH_2)
XVI[a]	7.38—8.20 (m, 4H, Ar—H), 9.18 (s, 1H, N—H), 10.48 (s, 1H, N—H), 5.09 (q, 2H, CH_2, J = 6.5 Hz), 1.35 (t, 3H, CH_3, J = 6.5 Hz)
XVII[b]	7.18—8.20 (m, 4H, Ar—H), 11.49 (s, 4H, N—H)

The spectra were measured in solution[a] (c = 1 mol dm^{-3}), or in saturated solution[b] in hexadeuterodimethyl sulfoxide (internal standard HMDSO).

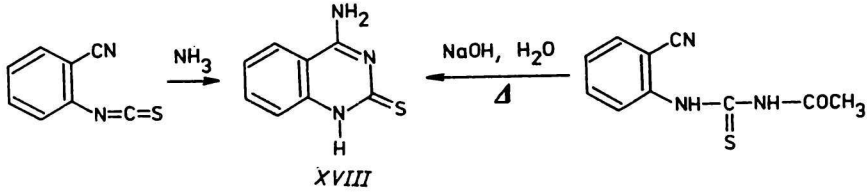
showed unreacted 2-isothiocyanatobenzonitrile (about 3 min). Then the product was filtered off, washed with chloroform and dried in vacuum. White crystalline compound was obtained, m.p. = 306—308 °C, yield = 4.3 g (97 %). For $C_8H_7N_3S$ (M_r = 177.31) w_i(calc.): 54.23 % C, 3.96 % H, 23.73 % N; w_i(found): 54.15 % C, 3.85 % H, 23.70 % N. IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3280, 3370 ν(NH_2), 3400 ν(NH), 1630 ν(C=N), 1550 ν(NHCS), 1660 ν(C=C). ^{1}H NMR spectrum (saturated solution in hexadeuterodimethyl sulfoxide, internal standard TMS), δ/ppm: 7.22—8.15 (m, 4H, Ar—H), 10.50 (s, 2H, NH_2), 12.38 (s, 1H, NH).

Procedure B

1-Acetyl-3-(2-cyanophenyl)thiourea [4, 5] (2.2 g; 0.01 mol) was suspended in water (50 cm^3) and heated to boiling point. During boiling aqueous solution of sodium hydroxide (10 %, 10 cm^3) was dropwise added and then boiling continued for another 3—4 min. Reaction mixture was then filtered with charcoal and acidified with acetic acid to pH = 5—7. The precipitated compound *XVIII* was crystallized from acetic acid. White crystals were formed, m.p. = 305—307 °C, yield = 1.7 g (91 %).

Results and discussion

3-Substituted 1-(2-cyanophenyl)thioureas were tried to be prepared by the addition of amines (isopropyl-, cyclohexyl-, *tert*-butyl-, ethyl-, and benzylamine, aniline, 4-toluidine, 4-anisidine, 4-bromoaniline, ammonia, hydrazine hydrate, and phenylhydrazine) to 2-isothiocyanatobenzonitrile (Scheme 1). Using the knowledge about the synthesis of 3-phenyl-1-(2-cyanophenyl)thiourea [2] we carried out the reaction in the mixture dichloromethane—petroleum ether at room temperature. TLC and IR spectra of the reaction products proved that the reaction proceeded in all cases but only in the case of the addition of isopropyl-, cyclohexyl-, *tert*-butylamine and 4-bromoaniline we were able to isolate the pure 3-substituted 1-(2-cyanophenyl)thioureas. Compounds *I*—*III* and *VIII* showed in the IR spectrum the stretching vibration of the nitrile group in the region of 2220—2240 cm^{-1}. A band of the vibration ν(C=N) in 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thione in the region of 1620—1640 cm^{-1} was not observed, which supports our previous statement. On the other hand, the addition of ethylamine, hydrazine hydrate, and ammonia led only to cyclized compounds — 3-substituted 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones *XVI*, *XVII* and 4-amino-1,2-dihydroquinazoline-2-thione (*XVIII*). The structure of *XVIII* was proved by an independent synthesis, *i.e.* by the cyclization of 1-acetyl-3-(2-cyanophenyl)thiourea in boiling aqueous sodium hydroxide solution (Scheme 2).



XVIII

Scheme 2

The structure of compounds *XVI—XVIII* was proved by IR spectroscopy. There was no band of stretching vibration of the nitrile group in their spectra but the significant vibration ν(C=N) at $\tilde{\nu} = 1630—1640\ cm^{-1}$. The proof that the reaction proceeded by way of interaction of nitrile group with the nitrogen atom of thioureido group (similarly as during the cyclization of 3-phenyl-1-(2--cyanophenyl)thiourea [1, 2]) forming pyrimidine ring and not by way of interaction with the sulfur atom was gained from IR and ^{13}C NMR spectra. In the IR spectrum characteristic vibration bands of NHCS group were found. In the ^{13}C NMR spectrum of 3-ethyl derivative *XVI* the signal of the carbon atom of the C=S group at $\delta = 174.06$ ppm was found.

The reaction of 2-isothiocyanatobenzonitrile with benzylamine, 4-toluidine, 4-anisidine, and phenylhydrazine led to the mixture of 3-substituted 1-(2-cyanophenyl)thiourea and its cyclization product, *i.e.* 3-substituted 4-imino--1,2,3,4-tetrahydroquinazoline-2-thiones *XI*, *XII*, *XIV*, and *XV* as it was proved by TLC and by the presence of the stretching vibration of nitrile group and imino group in their IR spectra.

In order to suppress the cyclization of 3-substituted 1-(2-cyanophenyl)thioureas we reduced the reaction temperature to 0 °C under the same conditions of the reaction. So we succeeded to isolate a pure 3-(4-tolyl)- (*III*), 3-(4-methoxyphenyl)- (*IV*), and 3-phenylamino-1-(2-cyanophenyl)thiourea (*VI*). But the addition of benzylamine led again to the mixture of *VII* and *XV* The pure compound *VII* was succeeded by the addition reaction at the temperature of −15 °C. In all the other cases only the products of cyclization *XVI—XVIII* were isolated. No 3-ethyl-, 3-amino-1-(2-cyanophenyl)thiourea and 2-cyanophenylthiourea were proved either in the reaction mixture or in the product of the reaction.

The reason for it seems to be the high nucleophility of the 3-substituted nitrogen atom which after its attack at the cyano group forms the pyrimidine ring with higher conjugation of π and nonbonding electrons within the six--member plane ring than that of the noncyclic derivative of thiourea.

Our statement may seem to be in contradiction with the fact that the compounds *I*, *II*, and *VIII* under the same conditions during the preparation do not

cyclize although the nucleophility of their nitrogen atom attacking the cyano group is comparable (this statement is at least valid for the basicity of corresponding amines characterized by pK_B^A (Table 7)). This contradiction may be explained by the steric hindrance of the interaction of the nitrogen atom of thioureido group with the carbon atom of cyano group by the substituent bound at the nitrogen atom.

Table 7

Values of the negative decadic logarithms of the basicity constants pK_B^A [6] of the amino derivatives used for the preparation of 3-substituted 1-(2-cyanophenyl)thioureas, the Taft constants E_S [7], and the steric constants φ_f [8] of the substituents

Substitution	pK_B^A	E_S	$\varphi_f/(10^4\,J\,mol^{-1})$
C_2H_5	3.3	−0.07	0.86
$(CH_3)_2CH$	3.3	−0.47	2.29
cyclo C_6H_{11}	3.3	−0.79	2.29
$(CH_3)_3C$	3.6	−1.54	3.82
$C_6H_5CH_2$	4.6	−0.38	–
4-$C_6H_4CH_3$	8.9	–	–
4-$C_6H_4OCH_3$	8.8	–	–
4-C_6H_4Br	10.1	–	–
C_6H_5NH	8.8	–	–
NH_2	5.5	–	–
H	4.8	1.24	–

In order to support our conclusion with experiment we tried to cyclize the synthesized thioureas *I*—*VII* in boiling ethanol following the *Taylor* and *Ravindranathan* method [1] who cyclized 3-phenyl-1-(2-cyanophenyl)thiourea to 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione. If our conclusion about the steric hindrance is right, then the reaction time needed for the cyclization of 3-substituted 1-(2-cyanophenyl)thioureas should increase from isopropyl derivative through cyclohexyl to *tert*-butyl derivative (for the measure of the steric hindrance the Taft constant E_S is taken [7] (Table 7)).

As it was found 3-*tert*-butyl-1-(2-cyanophenyl)thiourea (*VIII*) did not cyclize even after 10 h boiling in ethanol. The reaction time of the other substances *I*—*VII*, given in Table 4, is not in good agreement with the considerations about the nucleophility of the nitrogen atom of thioureido group which attacks the cyano group. However, simultaneously it is not in a good agreement with the Taft constants E_S of substituents, not even with the values of steric constants of substituents φ_f [8].

Thus respecting the values of pK_B^A of isopropylamine and cyclohexylamine compound *I* should cyclize more quickly than *II* in case that the steric effect is

expressed by the constant E_S. In case the steric effect is expressed by the constant φ_f, compound *I* should cyclize at the same rate as *II*. But our data found about the time of cyclization do not correspond to even one of the mentioned cases, but on the other hand, compound *I* needs at the same concentration double time than compound *II*. Therefore the steric effect of the substituent must be expressed by another parameter, so far unconsidered, the determination of which will be the contents of the following work dealing with a kinetic measurement in a number of 3-substituted 1-(2-cyanophenyl)thioureas.

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