2-(3-Acylthioureido)benzonitriles
I. Synthesis and cyclization reactions of 2-(3-acylthioureido)benzonitriles

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2-(3-Acylthioureido)benzonitriles prepared by the addition of 2-aminobenzonitrile to acylisothiocyanates in acetone solution underwent the cyclization reaction either in concentrated sulfuric acid at room temperature forming 2-acylamino-4-imino-4*H*-benzo[*d*]-[1,3]-thiazines or under base catalysis with aqueous solution of sodium hydroxide, ammonia or sodium carbonate at room temperature forming 4-amino-1,2-dihydroquinazoline-2-thione. This was also prepared by the rearrangement of 2-acylamino-4-imino-4*H*-benzo[*d*]-[1,3]-thiazines in aqueous solution of sodium hydroxide. Under the same conditions ethyl 2-(3-acylthioureido)benzoates reacted to 2-acylamino-4*H*-benzo[*d*]-[1,3]-thiazin-4-ones and to known 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one. This compound is also a product of acid-catalyzed rearrangement of 2-acylamino-4-imino-4*H*-benzo[*d*]-[1,3]-thiazin-4-ones and 2-acylamino-4*H*-benzo[*d*]-[1,3]-thiazin-4-ones rearrangement under acid or base catalysis, respectively.

While the synthesis and cyclization reaction of 2-(3-benzoylthioureido)benzoic acid and its amide has already been studied, the synthesis and reactions of 2-(3-acylthioureido)benzonitriles have not been described so far.

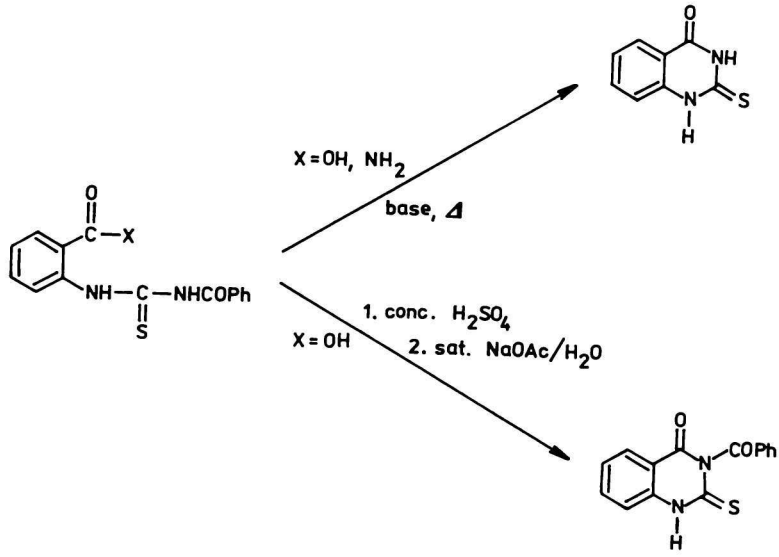
2-(3-Benzoylthioureido)benzoic acid and its amide were prepared by the addition of derivatives of 2-aminobenzoic acid to benzoyl isothiocyanate in an organic solvent. Their cyclization led in basic medium (aqueous or aqueous-ethanolic solution of sodium hydroxide or ammonia) to 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one [1, 2] (Scheme 1).

On the other hand, the cyclization of 2-(3-benzoylthioureido)benzoic acid in concentrated sulfuric acid at room temperature after working up the product of this reaction with saturated solution of sodium acetate led to 3-benzoyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one [1, 3].

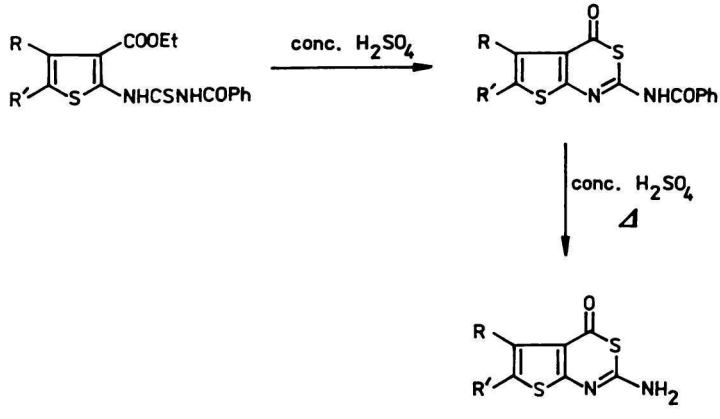
But this knowledge differs from the fact that similar compounds, *i.e.* 4,5-disubstituted ethyl 2-(3-benzoylthioureido)thiophene-3-carboxylates, give under

treatment of concentrated sulfuric or polyphosphoric acid in dependence on the reaction conditions either 4,5-disubstituted 2-amino- or 2-benzoylamino-thieno[2,3-*d*]-[1,3]-thiazin-4-one [4] (Scheme 2).

The aim of our work was the synthesis of 2-(3-acylthioureido)benzonitriles and ethyl 2-(3-acylthioureido)benzoates and their cyclization reactions.



Scheme 1



Scheme 2

Experimental

Melting points were determined on a Kofler hot-stage PHMK 79/2106 (Wägetechnik Rapido). Elemental analyses were performed with an elemental analyzer CHN 1102 (Erba). The found values correspond with the calculated ones. Infrared spectra were taken on a spectrophotometer 580B (Perkin—Elmer) or SP 1000 (Unicam) in KBr pellets, ^{1}H NMR spectra on WH-90/DS (Bruker, 90 MHz) and ^{13}C NMR spectra on BS 567 (Tesla, 25 MHz) in saturated or 1 M solution of DMSO-d_6 with TMS as an internal standard at the temperature of 25 °C. TLC was performed on Silufol UV 254 (Kavalier, Votice), the detection was carried out with Fluotest Universal (Quartzlampen, Hanau). The mobile phase was chloroform, ether or acetonitrile in a chromatographic container saturated by vapours of the used solvent.

Characteristics of the synthesized compounds are given in Tables 1 and 2.

Derivatives of 2-(3-acylthioureido)benzoic acid Ia—Ih

2-Aminobenzonitrile (0.05 mol) or ethyl 2-aminobenzoate, respectively, were added into acetone solution (100 cm^3) of acyl isothiocyanate (0.07 mol). After 45—120 min the formed product was filtered off, washed with ether and dried in vacuum at the temperature of 40—50 °C.

4-Acylamino-1,2-dihydroquinazoline-2-thiones IIIa—IIId

Aqueous solution of sodium carbonate (50 cm^3, 5 %) was added into suspension of *Ia—Id* (0.01 mol) in ethanol (100 cm^3) and the mixture was stirred till the starting compound disappeared (1 h). Then the pH was set up by the addition of acetic acid (10 %) to the value of 6—8, the solid fraction was filtered off and refluxed with acetone (50 cm^3). The acetonic solution was filtered through a column (length 10 cm, diameter 1.5 cm) with silica gel (grain size 100—160 μm). The filtered solvent was evaporated to dryness and the product recrystallized from ethanol.

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

Procedure A. Compounds *Ia—Id* (0.05 mol) were cyclized according to the procedure in [5] or by the reflux (5 min) in aqueous ammonia (250 cm^3, 25 %). Then the solution was concentrated to 2/3 of the original volume and the product was isolated after acidulation with acetic acid to pH 6—8 in the yield of 88—92 %. M.p. = 306—308 °C (acetic acid). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3280, 3370 ν(NH), 3400 ν(NH), 1630 ν(C=N), δ(NH_2), 1550 ν(NHCS), 1560 ν(C=C). ^{1}H NMR spectrum (saturated solution in DMSO-d_6), δ: 7.22—8.05 (m, 4H, H_{arom}), 10.50 (s, 2H, NH), 12.38 (s, 1H, NH). ^{13}C NMR

Table 1

Characterization and IR spectral data of the synthesized compounds *I*, *III*, *V*, *VII*

Compound	Yield %	M.p. °C	$\tilde{\nu}$/cm^{-1}					
			ν(C≡N)	ν(C=N)	ν(C=O)	ν(NHCS)	ν(NHCO)	ν(NH)
Ia	89	190—192	2230			1510, 1230	1705, 1550	3400, 3170
Ib	86	187	2230			1530, 1250	1695, 1565	3360, 3160
Ic	77	129—131	2230			1510, 1240	1725, 1560	3390, 3140
Id	80	172—173	2230			1510, 1240	1660, 1530	3390, 3140
Ie	90	146—147			1700	1540, 1260	1675, 1580	3220, 3150
If	86	129—130			1730	1540, 1250	1685, 1560	3250, 3180
Ig	82	108—109			1725	1520, 1260	1705, 1550	3220, 3150
Ih	85	104—105			1710	1540, 1250	1690, 1580	3380, 3220
IIIa	69	241—242		1645		1540, 1230	1710, 1560	3420, 3140
IIIb	57	163—165		1640		1520, 1240	1695, 1575	3380, 3150
IIIc	48	154—156		1650		1515, 1250	1700, 1575	3380, 3120
IIId	63	258—260		1640		1535, 1235	1686, 1570	3400, 3150
Va	72	249—250		1650			1710, 1560	3420, 3160
Vb	67	168—170		1650			1690, 1585	3410, 3150
Vc	68	159—160		1655			1690, 1575	3380, 3130
Vd	79	261—262		1660			1710, 1560	3400, 3150
VIIa	82	274—276		1640	1660		1690, 1580	3160
VIIb	76	188—190		1645	1650		1740, 1580	3280
VIIc	74	115—118		1640	1660		1725, 1580	3220, 3160
VIId	86	148—150		1630	1670		1685, 1560	3250

Table 2

^{1}H NMR characteristics of the synthesized compounds *I, III, V, VII*

Compound	δ
Ia	12.33 (s, 1H, NH), 10.47 (s, 1H, NH), 7.02—8.03 (m, 4H, H_{arom})
Ib	11.72 (s, 1H, NH), 11.64 (s, 1H, NH), 7.40—8.20 (m, 4H, H_{arom}), 3.84 (s, 3H, CH_3)
Ic	11.60 (s, 2H, NH), 7.36—8.00 (m, 4H, H_{arom}), 4.28 (q, 2H, CH_2, J = 6.5 Hz), 1.28 (t, 3H, CH_3, J = 6.5 Hz)
Id	12.82 (s, 1H, NH), 10.68 (s, 1H, NH), 7.37—8.12 (m, 9H, H_{arom})
Ie	12.94 (s, 1H, NH), 10.40 (s, 1H, NH), 7.32—8.32 (m, 4H, H_{arom}), 4.40 (q, 2H, CH_2, J = 6.0 Hz), 2.30 (s, 3H, CH_3), 1.34 (t, 3H, CH_3, J = 6.0 Hz)
If	12.33 (s, 1H, NH), 10.60 (s, 1H, NH), 7.30—8.40 (m, 4H, H_{arom}), 4.12 (q, 2H, CH_2, J = 6.0 Hz), 3.70 (s, 3H, CH_3), 1.30 (t, 3H, CH_3, J = 6.0 Hz)
Ig	12.36 (s, 1H, NH), 10.00 (s, 1H, NH), 7.28—8.36 (m, 4H, H_{arom}), 4.20—4.56 (m, 4H, CH_2), 1.25—1.40 (m, 6H, CH_3)
Ih	13.32 (s, 1H, NH), 10.40 (s, 1H, NH), 7.36—8.40 (m, 9H, H_{arom}), 4.40 (q, 2H, CH_2, J = 6.0 Hz), 1.35 (t, 3H, CH_3, J = 6.0 Hz)
IIIa	11.92 (s, 1H, NH), 8.15 (s, 1H, NH), 7.35—7.89 (m, 4H, H_{arom}), 2.25 (s, 3H, CH_3)
IIIb	12.11 (s, 1H, NH), 8.06 (s, 1H, NH), 7.45—7.86 (m, 4H, H_{arom}), 3.75 (s, 3H, CH_3)
IIIc	11.89 (s, 1H, NH), 7.43—8.02 (m, 5H, H_{arom}, NH), 4.36 (q, 2H, CH_2, J = 6.5 Hz), 1.34 (t, 3H, CH_3, J = 6.5 Hz)
IIId	12.24 (s, 1H, NH), 8.09 (s, 1H, NH), 7.38—7.82 (m, 9H, H_{arom})
Va	12.50 (s, 0.4H, NH), 12.28 (s, 0.6H, NH), 11.69 (s, 1H, NH), 7.08—8.35 (m, 4H, H_{arom}), 2.08 (s, 3H, CH_3)
Vb	11.72 (s, 1H, NH), 10.37 (s, 1H, NH), 7.40—8.40 (m, 4H, H_{arom}), 3.90 (s, 3H, CH_3)
Vc	11.20 (s, 1H, NH), 10.00 (s, 1H, NH), 7.20—8.40 (m, 4H, H_{arom}), 4.36 (q, 2H, CH_2, J = 6.5 Hz), 1.32 (t, 3H, CH_3, J = 6.5 Hz)
Vd	11.51 (s, 1H, NH), 10.55 (s, 1H, NH), 7.16—8.40 (m, 9H, H_{arom})
VIIa	11.96 (s, 1H, NH), 7.44—8.22 (m, 4H, H_{arom}), 2.18 (s, 3H, CH_3)
VIIb	12.42 (s, 1H, NH), 7.25—8.25 (m, 4H, H_{arom}), 3.67 (s, 3H, CH_3)
VIIc	11.80 (s, 1H, NH), 7.40—8.26 (m, 4H, H_{arom}), 4.24 (q, 2H, CH_2, J = 6.5 Hz), 1.36 (t, 3H, CH_3, J = 6.5 Hz)
VIId	12.48 (s, 0.5H, NH), 11.08 (s, 0.5H, NH), 7.48—8.35 (m, 9H, H_{arom})

spectrum (saturated solution in DMSO-d_6), δ: 180.63 (s, C=S), 159.33 (s, C=N), 141.29 (s), 134.55 (s), 124.39 (d), 123.45 (d), 115.57 (d), 109.37 (d).

Procedure B. Suspension of compound *Va—Vd* (5.0 mmol) in aqueous solution of sodium hydroxide (50 cm^3, 5 %) was refluxed till a solution was formed (4—6 min). Product was isolated following procedure *A*. M.p. = 305—307 °C, yield 87—91 %.

Procedure C. Compound *IIIa—IIId* (1.0 mmol) was refluxed for 2—3 min in aqueous solution of sodium hydroxide (5 %) and the product was isolated by the procedure *A*. M.p. = 306—307 °C, yield 89—94 %.

2-Acylamino-4-imino-4H-benzo[d]-[1,3]-thiazines Va—Vd

Compound *Ia—Id* (0.01 mol) was dissolved at room temperature in concentrated sulfuric acid (25—30 cm^3). After 2—4 h the solution was poured into crashed ice (200 g), the pH of the mixture set to 4—6 and the formed precipitate filtered off, washed with water and recrystallized from ethanol.

2-Thioxo-1,2,3,4-tetrahydroquinazolin-4-one (VI)

Procedure A. Ie—Ih (0.05 mol) was refluxed for 5—10 min in aqueous solution of sodium hydroxide (10 %) or aqueous ammonia (25 %), respectively. The product was precipitated by acetic acid (pH 6—8), recrystallized from acetic acid and dried in a vacuum oven. M.p. = 294—296 °C (Ref. [2] gives m.p. = 295—296 °C, acetonitrile), yield 90—95 %. IR spectrum (KBr pellet), $\tilde{\nu}/cm^{-1}$: 3180 ν(NH), 1690 ν(C=O), 1620 ν(C=N), 1550 ν(NHCS). ^1H NMR spectrum (DMSO-d_6, internal standard HMDSO), δ: 6.92—8.19 (m, 4H, H_{arom}), 12.33, 12.53 (s, 1H, NH). ^{13}C NMR spectrum (saturated solution in DMSO-d_6), δ: 180.10 (s, C=S), 173.67 (s, C=O), 141.01 (s), 133.19 (s), 125.60 (d), 120.14 (d), 114.31 (d), 109.95 (d).

Procedure B. Suspension of compound *IIIa—IIId* or *IV* (0.01 mol) in aqueous solution of sulfuric acid (10 %) was heated for 6 h. Then the suspension was poured into water (50 cm^3), filtered using hot filtration and the product was recrystallized from acetic acid. M.p. = 295—297 °C, yield 85—90 %.

Procedure C. Compound *VIIa—VIId* or *X* (0.01 mol) was refluxed for 1/2—2 h in aqueous solution of sodium hydroxide (75 cm^3, 5 %) till a solution was formed. This was acidulated with hydrochloric acid to pH 4—6. Hot suspension was filtered and the product recrystallized from acetic acid. After drying in vacuum compound *VI* was obtained in the yield of 86—92 %, m.p. = 295—298 °C.

Procedure D. Suspension of compound *Va—Vd* or *VIIa—VIId* (0.01 mol) in aqueous sulfuric acid solution (75 cm^3, 10 %) was refluxed for 12—15 h. Then ethanol (50 cm^3) was added and the hot suspension was filtered. The separated product was recrystallized from acetic acid, yield 82—89 %, m.p. = 295—297 °C.

2-Acylamino-4H-benzo[d]-[1,3]-thiazin-4-one VIIa—VIId

Compound *Ie—Ih* (0.01 mol) was dissolved at room temperature in sulfuric acid (50 cm^3, 96 %) and after 4—5 h the solution was poured into crashed ice (200 g). The formed precipitate was filtered off, washed with water, and recrystallized from ethanol.

4-Amino-2-methylthioquinazoline (VIII)

Compound *IV* (3.5 g; 0.02 mol) was dissolved in aqueous sodium hydroxide solution (15 %) and under vigorous agitation during 5 min at room temperature dimethyl sulfate

(3.8 g; 0.03 mol) was added. The reaction mixture was stirred for another 5 min and then the formed product was filtered off, washed with water and ethanol and recrystallized from acetonitrile. Yield 3.6 g (95 %), m.p. = 234—236 °C (Ref. [6] gives m.p. = = 235—236 °C). IR spectrum (KBr pellet), $\tilde{\nu}/cm^{-1}$: 3350, 3280 ν(NH), 1645 ν(C=N), 1625 ν(C=N), δ(NH_2). ^{1}H NMR spectrum (DMSO-d_6, internal standard HMDSO), δ: 7.24—8.00 (m, 4H, H_{arom}), 7.22 (s, 2H, NH_2), 2.45 (s, 3H, CH_3).

4-Ethoxycarbonylamino-2-methylthioquinazoline (IX)

Procedure A. Compound *IIIc* (2.5 g; 0.01 mol) was refluxed in the mixture of acetonitrile (50 cm^3), methyl iodide (4.2 g; 0.03 mol), and sodium hydrogen carbonate (3 g) for 20 h. Then the mixture was evaporated to dryness and this rest was boiled with ethanol (50 cm^3) for a while. Inorganic salts were filtered off and the remaining solution was concentrated to crystallization. Yield 1.9 g (73 %), m.p. = 144—146 °C. IR spectrum (KBr pellet), $\tilde{\nu}/cm^{-1}$: 3360, 3120 ν(NH), 1640, 1625 ν(C=N), 1705, 1565 ν(NHCO). ^{1}H NMR spectrum (DMSO-d_6, internal standard HMDSO), δ: 7.34—7.98 (m, 5H, H_{arom}, NH), 4.23 (q, 2H, CH_2, J = 7.5 Hz), 1.35 (t, 3H, CH_3, J = 7.5 Hz), 2.47 (s, 3H, CH_3).

Procedure B. Compound *VIII* (3.6 g; 0.02 mol) was refluxed in the mixture of acetonitrile (50 cm^3), ethyl chloroformate (5.4 g; 0.05 mol), and sodium hydrogen carbonate (5 g) for 24 h. Then the reaction mixture was worked up as in procedure *A*. Yield 2.9 g (56 %), m.p. = 145—146 °C.

2-Amino-4H-benzo[d]-[1,3]-thiazin-4-one (X)

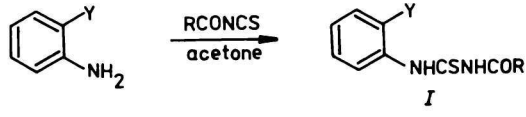
Compound *Ia—Ih* (0.01 mol) was dissolved in sulfuric acid (30 cm^3, 96 %) and heated on a steam bath for 6 h. After cooling down to room temperature the mixture was poured into crashed ice (200 g) and then addition of aqueous ammonia (50 cm^3, 25 %) caused precipitation. Yield 1.6 g (90 %), m.p. = 289—300 °C. IR spectrum (KBr pellet), $\tilde{\nu}/cm^{-1}$: 1695 ν(C=O), 1630 ν(C=N), δ(NH_2), 3100, 3150 ν(NH). ^{1}H NMR spectrum (DMSO-d_6, internal standard HMDSO), δ: 12.76 (s, 1H, NH), 12.56 (s, 1H, NH), 7.20—8.16 (m, 4H, H_{arom}). ^{13}C NMR spectrum (saturated DMSO-d_6, internal standard TMS), δ: 172.81 (s, C=O), 164.10 (s, C=N), 140.25 (s), 130.34 (s), 125.30 (d), 122.14 (d), 116.56 (d), 110.10 (d).

1-Acetyl-2-acetylimino-4-imino-1,2-dihydrobenzo[d]-[1,3]-thiazine (XI)

Compound *Va—Vd* (5 mmol) in acetic anhydride (50 cm^3) was refluxed for 5—8 h. Then the mixture was concentrated to the volume of 5—10 cm^3 The obtained crystals were filtered off, washed with dichloromethane and crystallized from acetic anhydride. M.p. = 263—265 °C, yield 88—92 %. IR spectrum (KBr pellet), $\tilde{\nu}/cm^{-1}$: 3400, 3160 ν(NH), 1655 ν(C=O), 1630 ν(C=N). ^{1}H NMR spectrum (saturated DMSO-d_6, internal standard TMS), δ: 11.90 (s, 1H, NH), 7.40—8.16 (m, 4H, H_{arom}), 2.15 (s, 6H, CH_3).

Results and discussion

Compounds *Ia*—*Ih* were prepared by the addition of nitrile or ethyl 2-aminobenzoate to corresponding acyl isothiocyanate in acetonic solution at room temperature [7] (Scheme 3).



I

	Y	R		Y	R
a:	CN	Me	*e*:	COOEt	Me
b:	CN	OMe	*f*:	COOEt	OMe
c:	CN	OEt	*g*:	COOEt	OEt
d:	CN	Ph	*h*:	COOEt	Ph

Scheme 3

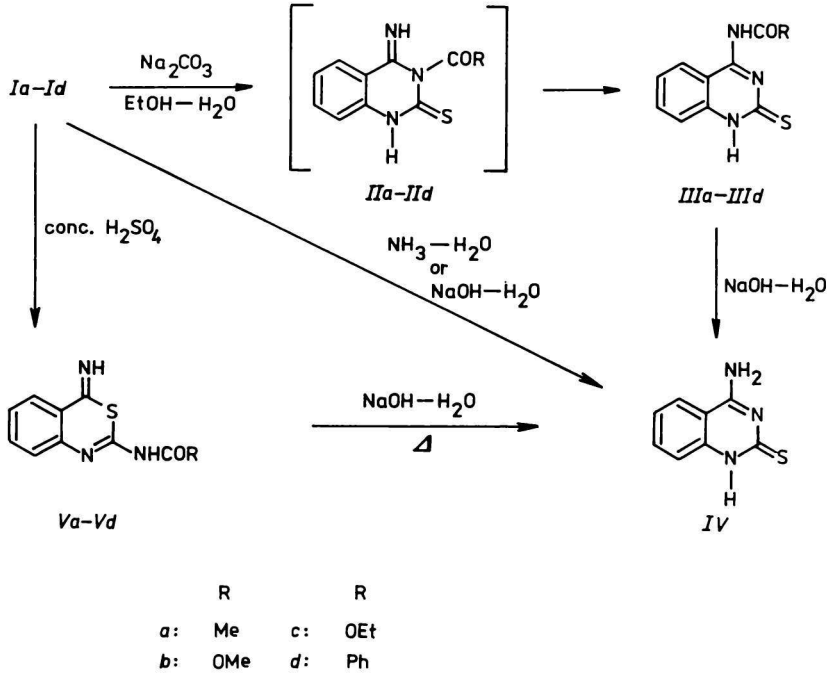
Acyl isothiocyanates were at first prepared *in situ* in acetonic solution by the reaction of acyl chloride with potassium thiocyanate [8]. However, higher yields and better purity of compounds *Ia*—*Ih* were reached by the application of acyl isothiocyanates freshly distilled under vacuum. Using TLC, IR and ^{1}H NMR spectroscopy and elemental analysis only the compounds *Ia*—*Ih* were found.

The cyclization reactions of compounds *Ia*—*Id* were tried to be performed at first thermally, it means boiling their ethanolic solutions, similarly as the cyclization of 2-(3-alkyl- or 2-(3-arylthioureido)benzonitriles [5]. But these attempts were not successful. After the reaction (boiling for 100 h and more) only unreacted compounds *Ia*—*Id* were always isolated. The same results were obtained in 2-methoxyethanol, in DMF or smelting always accompanied with decomposition of the starting compounds.

Therefore we tried to carry out the cyclization of benzonitriles *Ia*—*Id* in basic medium. It was shown that these compounds are soluble in aqueous sodium hydroxide solution (5—10 %) and after a few minutes a reaction proceeds. The course of the reaction was followed by TLC; the sample on the TLC plate was before development left under treatment of hydrochloride vapours. The reaction might proceed more quickly under boiling the reaction mixture for a while. After acidification of the mixture to pH 6—8 in all cases the only one, identical, very polar product was obtained. In its IR spectrum a band corresponding to the cyano group (or bands of amide or carboxylic group as possible products of its hydrolysis) as well as a band of acyl group were missing. Bands of vibrations of NH, C=N, and NHCS groups were present only. ^{1}H NMR

spectrum showed signals of four aromatic protons, one plus two protons on heteroatoms. In ^{13}C NMR spectrum besides other signals the signal of thioxo group at $\delta = 180.63$ appeared.

These data together with the results of elemental analysis led us to the conclusion that the compound *IV*, *i.e.* the product identical with the product of the addition of ammonia to 2-isothiocyanatobenzonitrile described in [5] (Scheme 4) was synthesized. The same results were obtained during cyclization of compounds *Ia—Id* boiling them in 25 % aqueous ammonia.

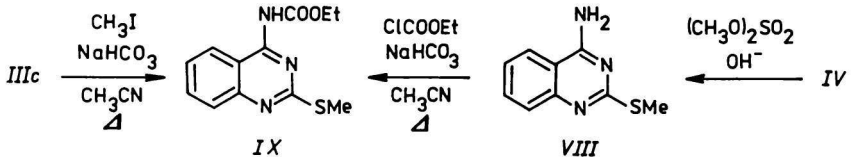


Scheme 4

In order to suppress the hydrolysis of acyl groups during the cyclization of *Ia—Id* we tried to choose an appropriate basic catalyst and condition for this reaction. We found that in suspension of ethanol—aqueous sodium carbonate (5 %; $\varphi_r = 2:1$) at room temperature besides the compound *IV* also a compound with acyl group is formed. We believed that it was the compound *IIa—IId*. But a detailed study of the IR spectrum proved the presence of bands of NHCO group characteristic of *N*-monosubstituted amide. Therefore we concluded it was the compound *IIIa—IIId*. These were probably formed as the thermodynamically more stable product *via* Dimroth rearrangement from for-

merly originated 3-acyl derivatives *IIa—IId* under the presence of base. No presence of compounds *IIa—IId* in the reaction mixture was proved. When the reaction was carried out at higher temperature or in solution the only product isolated was compound *IV*

The structure of compound *IIIc* was proved by an independent synthesis. Because direct acylation of *IV* with ethyl chloroformate in basic medium would lead to an *S*-acyl derivative we prepared at first compound *VIII* by the methylation of compound *IV* with dimethyl sulfate in the presence of sodium hydroxide. The product so formed was treated with ethyl chloroformate in acetonic solution boiling in the presence of sodium hydrogen carbonate (Scheme 5).



Scheme 5

The compound *IX* was shown to be identical with the product of methylation of compound *IIIc* with methyl iodide in acetonitrile in the presence of sodium hydrogen carbonate. The identity was proved by the comparison of melting points, IR and ^{1}H NMR spectra.

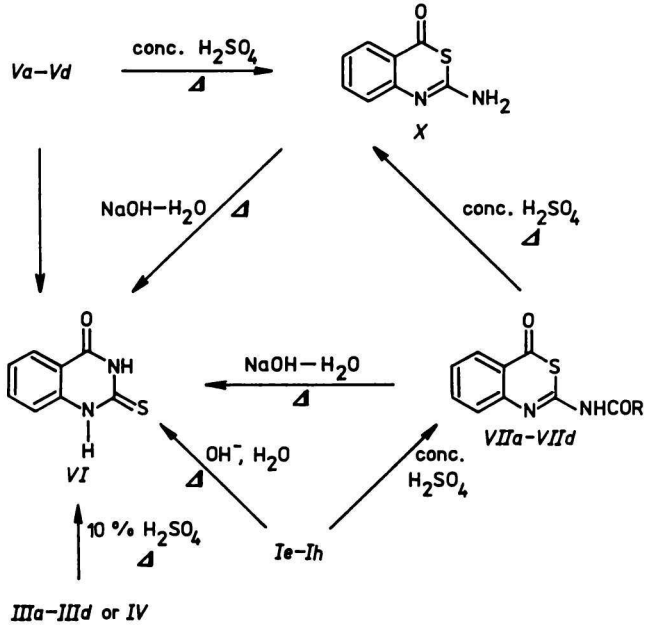
Similarly as nitriles *Ia—Id* we tried to cyclize benzoates *Ie—Ih* under base catalysis. Although these compounds came into alkaline solution (aqueous solution or an aqueous ethanolic solution of sodium hydroxide or carbonate) at room temperature the cyclization reaction was not observed. After acidification of solutions the mixture of the starting compound and 2-(3-acylthioureido)benzoic acid was found (constitution proved by the IR and ^{1}H NMR spectra).

However, cyclization occurred after a few minutes' reflux of the alkaline solutions and after acidification of the reaction mixture the earlier mentioned compound *VI* [1, 2] was isolated. The same product was formed during hydrolysis of compounds *IIIa—IIId* or *IV* under boiling them in suspension of aqueous sulfuric acid (10 %) (Scheme 6).

Our attention was also concentrated on the cyclization of compounds *Ia—Ih* in concentrated sulfuric acid. Analogously to the results in [1, 3] one could expect the formation of 3-acyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4--ones or 4-imino analogues, respectively, after cyclization of *Ia—Ih* derivatives. TLC, IR, and ^{1}H NMR spectra of products isolated after the reaction in sulfuric acid at room temperature showed that these were not the starting compounds and that the product of the reaction of nitrile *Ia—Id* and corresponding ester

Ie—Ih is not identical. An absence of the bands corresponding to cyano or ester group, respectively, and NHCS group was observed. On the other hand, the bands of vibrations of NHCO group were found which are characteristic of a monosubstituted amide. ^{1}H NMR spectra proved the presence of proton signals of acyl groups and the protons bound at nitrogen.

All the summed data of elemental analysis, IR and ^{1}H NMR spectra led us to the conclusion that compounds *Ia—Id* under given conditions cyclize to *Va—Vd* and compounds *Ie—Ih* to *VIIa—VIId*. This is analogous to the cyclization of 4,5-disubstituted ethyl 2-(3-benzoylthioureido)thiophene-3-carboxylates in concentrated sulfuric acid [4].



	R		R
a:	Me	*c*:	OEt
b:	OMe	*d*:	Ph

Scheme 6

Cyclization of *Ia—Ih* in concentrated sulfuric acid on a steam bath always ended at compound *X* the structure of which was approved by elemental analysis, IR and ^{1}H NMR spectra.

From ^{1}H NMR spectra of compounds *Va*, *VIId*, and *X* measured at room temperature in DMSO we can conclude that these compounds exist in two

isomeric forms, either as tautomers or conformers. The hydrogen atom bound at nitrogen atom of acylamino or amino group gives two signals. The sum of their relative integral intensities is equal to one. The other compounds from the series of compounds *V* and *VII* had in ^{1}H NMR spectrum at room temperature as well as at lower temperature (the value was limited by the solubility in acetone and the temperature of solidification of DMSO to 10 °C) the only one signal of hydrogen atom bound at nitrogen of CONH group.

This fact could be explained in two ways. Either one can expect that the acylamino group in *Va* and *VIId* or amino group in *X* is in conjugation with 1,3-thiazine system and at the temperature of measurement (25 °C) is not allowed a free rotation about the bond C-2—N. Their spectra taken at 50 °C give a broad band with the chemical shift in the region between both signals NH found in the spectrum measured at 25 °C. The signal of the hydrogen atom situated in *syn* position with respect to N=C group is due to an anisotropic effect of this double bond shifted to a higher value of chemical shift than that of hydrogen atom in position *anti*.

The other explanation might be in existence of two tautomeric forms of compounds *Va*, *VIId*, and *X* that are in equilibrium, it means 2-acylamino and 2-acylimino form, or 2-amino and 2-imino form, respectively.

We tried to approve the tautomerism in synthesized series of 1,3-thiazines by the methylation of compounds *Va—Vd*, *VIIa—VIId*, and *X* in order to get corresponding 2-imino-1-methyl-1,2-dihydrobenzo[*d*]-[1,3]-thiazines. Direct methylation by methyl iodide or dimethyl sulfate in boiling acetonitrile solution without a base was not successful. In the presence of a base (triethylamine, pyridine or sodium hydrogen carbonate in the presence of cetyltrimethylammonium bromide as phase-transfer catalyst) under the same conditions compound *VIII* from *Va—Vd* and 2-methylthio-3,4-dihydroquinazolin-4-one from compounds *VIIa—VIId* and *X* were formed. Probably by the effect of the present base Dimroth rearrangement of thiazine derivative to the corresponding 2-pyrimidinethione proceeded which was then methylated on sulfur atom.

This explanation is supported by the fact that compounds *Va—Vd* by the action of aqueous sodium hydroxide solution (5 %) as well as sodium carbonate, ammonia and other bases boiling undergo an isomerization with hydrolysis of acyl group to quinazoline derivative *IV* and compounds *VIIa—VIId* and *X* to compound *VI*. A similar Dimroth rearrangement was mentioned earlier at 2-phenylamino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-[1,3]-thiazin-4-one that under treatment of sodium methoxide in methanol boiling gave 2-mercapto-3--phenyl-3,4,5,6,7,8-hexahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-one [9].

Besides this, compounds *Va—Vd*, *VIIa—VIId*, and *X* boiling in aqueous solution of sulfuric acid (10 %) give *via* Dimroth rearrangement quinazoline derivative *VI*.

Therefore in respect to the mentioned facts the formation of 3-benzoyl-2--thioxo-1,2,3,4-tetrahydroquinazolin-4-one by the cyclization of 2-(3-benzoylthioureido)benzoic acid presented in [1, 3] seems not to be very probable.

In order to overcome the complications connected with the methylation of thiazines *Va—Vd*, *VIIa—VIId*, and *X* in the presence of a base we tried acylation with acetic anhydride. Compound *VIIa* after reflux for several hours was not acetylated. In compounds *VIIb—VIId* the exchange of acyl groups for acetyl was observed under formation of *VIIa*. The same compound was formed from compound *X*. The reason for these results is probably a low basicity of nitrogen atoms — atom N-1 and the nitrogen atom bound in position 2 of thiazinones.

Completely different results were obtained under the same conditions during the acetylation of thiazines *Va—Vd*. As shown by TLC at first stage an exchange of acyl group for acetyl occurred (after probably 15—30 min) and compound *Va* was formed. After further reflux (5—8 h) the acetylation took place in all cases under formation of the same product. Elemental analyses, IR and ^{1}H NMR spectra proved that it was the compound *XI*. In its IR spectrum (KBr pellet) a broad band at $\tilde{\nu} = 1655\,\mathrm{cm}^{-1}$ was observed which corresponds to the vibration of C=O group of both acetyl groups characteristic of tertiary amides. The position of the band was independent of the concentration of the compound in acetonitrile. In IR spectrum we could observe bands at wavenumber $1630\,\mathrm{cm}^{-1}$ (ν(C=N)), 3400 and $3160\,\mathrm{cm}^{-1}$ These bands are stretching vibrations (ν(NH)) of free and associated imino group in position 4 of the thiazine ring. The vibrations at $\tilde{\nu} = 3160\,\mathrm{cm}^{-1}$ disappeared when the spectrum of *XI* was measured in acetonitrile solution. It shows that this vibration is a vibration of NH group bound by intramolecular hydrogen bridge with oxygen atom of acetyl group.

In ^{1}H NMR spectrum of compound *XI* there were found signals of six protons of two acetyl groups, signals of four protons of the benzene ring and at $\delta = 11.90$ a signal of NH. In analogy with spectrum of *Va* (Table 2) we expect it to be the signal of the imino group proton.

All these results support the hypothesis about the existence of thiazines *Va—Vd*, *VIIa—VIId*, and *X* in the two tautomeric structures.

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