Reactivity of Esters and Nitriles of 2-(3-Acylthioureido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic Acids I. Acid-Catalyzed Cyclization and Desulfanation Reaction in the Presence of Secondary Amines

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Esters and nitriles of 2-(3-acylthioureido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids were cyclized in a solution of concentrated sulfuric acid at room temperature to substituted thieno[2,3-*d*]-[1,3]-thiazines. Further they were treated with mercuric oxide (desulfanation reaction) in the presence of secondary amines (diethylamine, morpholine, piperidine) forming corresponding 1-acylguanidines in some cases accompanied by the cyclization to thieno[2,3-*d*]-pyrimidines. These were also prepared by the cyclization of 1-acylguanidines in concentrated sulfuric acid at room temperature.

Cyclization reactions of nitriles, amides, and esters of 2-(3-acylthioureido)benzoic acids have been already studied [1—4]. In the presence of a base these compounds cyclize to 4-substituted 2-thioxoquinazolines by the interaction of the acylthioureido group nitrogen atom with alkoxycarbonyl, carboxyl, carbamoyl or cyano group.

In a strongly acid medium (concentrated sulfuric acid) the alkoxycarbonyl or cyano group is attacked by the sulfur atom in the acylthioureido group and a substituted 1,3-benzothiazine ring is formed [2, 3].

Similarly, 4,5-disubstituted ethyl 2-(3-benzoylthioureido)thiophene-3-carboxylate [5] cyclizes under the influence of concentrated sulfuric acid at room temperature to substituted 2-benzoylaminothieno-[2,3-*d*]-[1,3]-thiazin-4-ones. At the temperature of boiling water bath the cyclization is accompanied with the benzoyl group splitting.

On the other hand, 2-(3-benzoylthioureido)thiophene-3-carbonitriles underwent cyclization at the temperature of boiling water bath in concentrated sulfuric acid to 2-amino-4-iminothieno[2,3-*d*]-[1,3]-thiazinium salts [6] (isolated as insoluble perchlorates) stable only in an acid medium. A neutralization led to the thiazine ring opening under formation of 2-thioureidothiophene-3-carbonitriles.

Desulfanation reaction of esters and nitriles of 2-(3-acylthioureido)thiophene-3-carboxylic acids has not been so far studied. Desulfanation reaction of nitriles with mercuric oxide in the presence of primary and secondary amines (ethylamine, diethylamine, aniline) at room temperature is known [7]. The reaction gave the corresponding substituted guanidines and products of their cyclization, *i.e.* 2,4-disubstituted quinazolines.

1-Monosubstituted 2-acyl-3-(2-cyanophenyl)-guanidines cyclized always by the interaction of the nitrogen carrying alkyl or aryl substituent with the cyano group, in case of 1,1-disubstituted guanidine derivatives by the attack of acylamino or acylimino group.

The aim of our work was to find out whether under treatment of concentrated sulfuric acid esters and nitriles of 2-(3-acylthioureido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids undergo the same changes as it has been already found with 2-(3-benzoylthioureido)thiophene derivatives [5, 6]. Further we wanted to study desulfanation reaction of acylthioureido derivatives in the presence of selected secondary amines.

EXPERIMENTAL

For the methods and instruments see Refs. [3, 7]. The found values of elemental analyses of the synthesized compounds corresponded to the calculated ones.

Ethyl ester and nitrile of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid were prepared according to paper [8]. Nitriles *Ia—If* and esters *IIa—IId* of 2-(3-acylthioureido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids were prepared by the method already used in the synthesis of 2-(3-acylthioureido)benzonitriles according to patent [9] and their characteristics are presented in Tables 1—3.

Table 1. Characteristics of the Synthesized Compounds *Ia—If*, *IIa—IId*

Compound	R	Yield/%	M.p./°C	R_f (Et_2O)
Ia	Me	36.5	230—231	0.66
Ib	Ph	88.7	217—218	0.77
Ic	*t*-Bu	86.8	188—189	0.79
Id	4-MeOPh	82.8	219—220	0.70
Ie	Bn	90.6	213—215	0.71
If	OMe	39.7	192—193	0.68
IIa	Me	41.3	219—220	0.63
IIb	Ph	58.3	161—163	0.75
IIc	*t*-Bu	88.0	187—189	0.77
IId	4-MeOPh	92.4	191—193	0.72

Table 2. IR Spectral Characteristics of Compounds *Ia—If*, *IIa—IId*

Compound	$\tilde{\nu}$/cm^{-1}				
	ν(NH)	ν(C≡N)	ν(C=O)	ν(NHCO)	ν(NHCS)
Ia	3170	2220		1695, 1550	1550, 1255
Ib	3380, 3270	2210		1660, 1550	1530, 1245
Ic	3380, 3240	2200		1685, 1555	1550, 1250
Id	3395	2220		1655, 1570	1550, 1255
Ie	3250, 3170	2200		1670, 1550	1550, 1250
If	3380, 3170	2220		1720, 1570	1530, 1255
IIa	3180		1670	1700, 1550	1550, 1250
IIb	3220		1670	1690, 1565	1540, 1260
IIc	3290, 3170		1670	1690, 1560	1540, 1260
IId	3390, 3180		1670	1685, 1570	1550, 1250

2-Acylamino-4-imino-5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]-[1,3]-thiazinium Perchlorates *IIId*, *IIIf*

Compound *Id* or *If* (2.5 mmol) was dissolved at room temperature in sulfuric acid (94—96 %, 40—50 cm^3) and left to react for 2 d. Then the reaction mixture was cooled down to 0—5 °C and the same volume of perchloric acid (40 % aqueous solution) was added into the reaction mixture so as to prevent raising of the temperature over 20 °C.

Suspension so formed was left for 2—3 h at the temperature of 0—5 °C and then the crystals were filtered off, washed with water and acetone. Product was dried *in vacuo* at room temperature.

4-Methoxybenzoyl derivative *IIId*: Yield 87 %, m.p. = 258—260 °C (decomposition). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3280, 3200 ν(NH), 3040, 2950, 2880 ν(CH), 1660, 1560 ν(NHCO), 1645 ν(C=N), 1240, 1060 ν(COC), 1025 ν(ClO_4^-). ^{1}H NMR spectrum ($(CD_3)_2SO$, TMS), δ: 1.60—2.00 (m, 4H, CH_2), 2.60—3.11 (m, 4H, CH_2), 3.90 (s, 3H, CH_3), 7.00—7.25 (m, 2H, H_{arom}), 8.38—8.50 (m, 2H, H_{arom}), 12.05 (br s, 3H, NH).

Methoxycarbonyl derivative *IIIf*: Yield 91 %, m.p. = 190—192 °C (decomposition). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3350, 3200 ν(NH), 2940, 2870, ν(CH), 1720, 1535 ν(NHCO), 1635 ν(C=N), 1230, 1135 ν(COC), 1070 ν(ClO_4^-). ^{1}H NMR spectrum ($(CD_3)_2SO$, TMS), δ: 1.70—2.03 (m, 4H, CH_2), 2.65—3.07 (m, 4H, CH_2), 3.83 (s, 3H, CH_3), 11.65 (br s, 3H, NH).

2-Amino-4-imino-5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]-[1,3]-thiazinium Perchlorate (*IV*)

Compounds *Ia—Ic* and *Ie* (2.5 mmol) were treated in concentrated sulfuric acid similarly as compounds *Id* and *If* for 2—4 d. The isolation was analogous as for compounds *IIId* and *IIIf*. Yield 88—95 %, m.p. = 178—180 °C (decomposition). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3280, 3150 ν(NH), 2960, 2870 ν(CH), 1650 ν(C=N) and ν(NH), 1060 ν(ClO_4^-). ^{1}H NMR spectrum ($(CD_3)_2SO$, TMS), δ: 1.63—2.05 (m, 4H, CH_2), 2.70—3.13 (m, 4H, CH_2), 12.65 (br s, 4H, NH).

Table 3. ^{1}H NMR Spectral Characteristics of Compounds *Ia—If*, *IIa—IId*

Compound	δ
Ia	14.22 (s, 1H, NH), 12.02 (s, 1H, NH), 2.44—2.80 (m, 4H, CH_2), 2.21 (s, 3H, CH_3), 1.64—1.96 (m, 4H, CH_2)
Ib	14.12 (s, 1H, NH), 12.17 (s, 1H, NH), 7.60—8.28 (m, 5H, H_{arom}), 2.56—2.84 (m, 4H, CH_2), 1.76—2.00 (m, 4H, CH_2)
Ic	14.03 (s, 1H, NH), 8.68 (s, 1H, NH), 2.45—2.85 (m, 4H, CH_2), 1.65—2.05 (m, 4H, CH_2), 1.33 (s, 9H, CH_3)
Id	14.64 (s, 1H, NH), 11.03 (s, 1H, NH), 8.00—8.20 (m, 2H, H_{arom}), 7.00—7.24 (m, 2H, H_{arom}), 3.88 (s, 3H, OCH_3), 2.44—2.76 (m, 4H, CH_2), 1.64—1.96 (m, 4H, CH_2)
Ie	14.13 (s, 1H, NH), 12.34 (s, 1H, NH), 7.28—7.56 (m, 5H, H_{arom}), 3.92 (s, 2H, CH_2Ph), 2.40—2.80 (m, 4H, CH_2), 1.60—1.96 (m, 4H, CH_2)
If	12.33 (s, 1H, NH), 11.89 (s, 1H, NH), 3.75 (s, 3H, OCH_3), 2.46—2.73 (m, 4H, CH_2), 1.58—1.93 (m, 4H, CH_2)
IIa	14.45 (s, 1H, NH), 11.63 (s, 1H, NH), 4.40 (q, 2H, CH_2, J = 8.0 Hz), 2.48—2.88 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 1.60—1.92 (m, 4H, CH_2), 1.32 (t, 3H, CH_3, J = 8.0 Hz)
IIb	14.27 (s, 1H, NH), 11.96 (s, 1H, NH), 7.52—8.24 (m, 5H, H_{arom}), 4.46 (q, 2H, CH_2, J = 8.0 Hz), 2.52—2.96 (m, 4H, CH_2), 1.60—1.92 (m, 4H, CH_2), 1.36 (t, 3H, CH_3, J = 8.0 Hz)
IIc	14.12 (s, 1H, NH), 11.62 (s, 1H, NH), 4.40 (q, 2H, CH_2, J = 7.5 Hz), 2.60—2.90 (m, 4H, CH_2), 1.58—1.93 (m, 4H, CH_2), 1.35 (t, 3H, CH_3, J = 7.5 Hz), 1.28 (s, 9H, CH_3)
IId	14.75 (s, 1H, NH), 9.03 (s, 1H, NH), 7.75—8.10 (m, 2H, H_{arom}), 6.80—7.10 (m, 2H, H_{arom}), 4.45 (q, 2H, CH_2, J = 8.0 Hz), 3.85 (s, 3H, OCH_3), 2.50—3.00 (m, 4H, CH_2), 1.40—2.00 (m, 4H, CH_2), 1.40 (t, 3H, CH_3, J = 8.0 Hz)

2-Thioureido-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carbonitrile (*V*)

Procedure A. The compound was prepared according to paper [6] by the reaction of *Ia—If* in concentrated sulfuric acid at the temperature of boiling water bath followed by the neutralization of the reaction mixture diluted with water. The same results were obtained when the reaction was carried out at room temperature for 2—4 d.

Yield 88—96 %, m.p. = 184—186 °C (decomposition), Ref. [6] gives m.p. = 185 °C (decomposition). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3380, 3280, 3180 ν(NH), 2940, 2840 ν(CH), 2210 ν(C≡N), 1540, 1250 ν(NHCS). ^{1}H NMR spectrum ((CD$_3$)$_2$SO, TMS), δ: 10.08 (s, 1H, NH), 7.92 (s, 2H, NH$_2$), 2.37—2.75 (m, 4H, CH$_2$), 1.65—1.92 (m, 4H, CH$_2$).

Procedure B. Perchlorate *IV* (1 mmol) was suspended in saturated aqueous solution of sodium hydrogen carbonate (50 cm^3). After 1 h the product was filtered off, washed with hot water and dried *in vacuo*. Yield 94 %.

Retrocycloaddition Reaction of *III*

Compound *IIId*, *IIIf* (1 mmol) was suspended in aqueous ammonia (10 %, 50 cm^3) and the mixture was stirred for 1 h at room temperature. The isolated products were identical with compound *Id* and *If*, respectively. Yield 90—94 %.

2-Benzoylamino-5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]-[1,3]-thiazin-4-one (*VI*)

The compound was prepared from *IIb* in addition to 2-amino-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]-[1,3]-thiazin-4-one (*VII*) following the procedure described in [5] by 2 d reaction in concentrated sulfuric acid at room temperature in the yield of 92 %. M.p. = 205—207 °C, Ref. [5] gives m.p. = 206—207 °C. IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3350, 3150 ν(NH), 2950, 2880 ν(CH), 1680, 1520 ν(NHCO), 1650 ν(C=O), 1625 ν(C=N). ^{1}H NMR spectrum ((CD$_3$)$_2$CO, TMS), δ: 11.96 (s, 1H, NH), 7.50—8.40 (m, 5H, H$_{arom}$), 2.58—2.98 (m, 4H, CH$_2$), 1.70—1.98 (m, 4H, CH$_2$).

2-Amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-[1,3]-thiazin-4-one (*VII*)

The compound was prepared from *IIa*, *IIc*, and *IId* analogously as *VI* in the yield 92—96 %. Reaction time was 2—4 d. M.p. = 213—216 °C, Ref. [5] gives m.p. = 212—214 °C. IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3380, 3270, 3160 ν(NH), 2940, 2860 ν(CH), 1645 ν(C=O), 1600 ν(C=N). ^{1}H NMR spectrum ((CD$_3$)$_2$CO, TMS), δ: 12.46 (s, 2H, NH$_2$), 2.58—2.93 (m, 4H, CH$_2$), 1.65—2.00 (m, 4H, CH$_2$).

1-Acyl-2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thien-2-yl)-3,3-(diR')guanidines *VIII-1-a—VIII-3-f*

The compound *Ia—If* (15 mmol) was at room temperature suspended in dried acetone (200 cm^3). Then under agitation the equivalent amount of secondary amine (morpholine, piperidine, diethylamine) was dropwise added and finally 3-fold molar excess of finely ground mercuric oxide was added.

After the starting acylthiourea disappeared (reaction was monitored by TLC) the reaction mixture was filtered with charcoal and the filtrate evaporated on a vacuum evaporator at room temperature. In case of an oily product this was left to crystallize at room temperature or in a fridge and then it was recrystallized from ethanol. Compounds *VIII-2-e* and *VIII-3-a* were purified on a column with silica gel (eluent chloroform).

Characteristics of the prepared compounds are presented in Tables 4—6.

Table 4. Characteristics of the Synthesized Compounds *VIII* and *XIII*

Compound	R	NR$'_2$	Yield/%	M.p./°C	R_f (Et$_2$O)
VIII-1-a	Me	morpholino	43	194—195	0.26
VIII-1-b	Ph	morpholino	57	206—207	0.48
VIII-1-c	*t*-Bu	morpholino	70	203—205	0.51
VIII-1-d	4-MeOPh	morpholino	32	215—218	0.47
VIII-1-e	Bn	morpholino	41	189—191	0.46
VIII-1-f	OMe	morpholino	53	169—171	0.49
VIII-2-b	Ph	piperidino	58	185—187	0.75
VIII-2-d	4-MeOPh	piperidino	45	188—190	0.62
VIII-2-e	Bn	piperidino	45	195—197	0.60
VIII-2-f	OMe	piperidino	40	142—144	0.74
VIII-3-a	Me	NEt$_2$	40	155—157	0.62
VIII-3-b	Ph	NEt$_2$	94	212—215	0.52
VIII-3-c	*t*-Bu	NEt$_2$	94	149—153	0.59
VIII-3-d	4-MeOPh	NEt$_2$	38	185—187	0.50
VIII-3-f	OMe	NEt$_2$	56	140—142	0.44
XIII-1-a	Me	morpholino	60	159—161	0.17
XIII-1-b	Ph	morpholino	44	158—160	0.40
XIII-1-c	*t*-Bu	morpholino	36	114—116	0.53
XIII-1-d	4-MeOPh	morpholino	73	90—93	0.33
XIII-2-a	Me	piperidino	40	143—145	0.26
XIII-2-b	Ph	piperidino	27	156—157	0.52
XIII-2-c	*t*-Bu	piperidino	55	98—100	0.63
XIII-2-d	4-MeOPh	piperidino	62	120—122	0.19
XIII-3-a	Me	NEt$_2$	34	116—118	0.12
XIII-3-b	Ph	NEt$_2$	51	104—107	0.15
XIII-3-c	*t*-Bu	NEt$_2$	26	87—89	0.20
XIII-3-d	4-MeOPh	NEt$_2$	21	91—95	0.14

Table 5. IR Spectral Characteristics of Compounds *VIII*

Compound	$\tilde{\nu}$/cm^{-1}			
	ν(NH)	ν(C≡N)	ν(C=N)	ν(NHCO)
VIII-1-a	3170	2210	1610	1670, 1570
VIII-1-b	3160	2205	1600	1650, 1565
VIII-1-c	3260	2210	1610	1670, 1570
VIII-1-d	3160	2205	1600	1650, 1540
VIII-1-e	3180	2205	1605	1675, 1565
VIII-1-f	3160	2200	1600	1730, 1570
VIII-2-b	3240	2200	1600	1650, 1565
VIII-2-d	3150	2200	1600	1640, 1550
VIII-2-e	3150	2210	1600	1650, 1565
VIII-2-f	3200	2200	1610	1715, 1565
VIII-3-a	3200	2200	1600	1680, 1570
VIII-3-b	3220	2210	1615	1655, 1570
VIII-3-c	3250	2210	1605	1660, 1575
VIII-3-d	3170	2200	1600	1635, 1570
VIII-3-f	3240	2200	1600	1645, 1565

3-Acyl-4-imino-2-piperidino-3,4,5,6,7,8-hexahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines *IX*

Acetyl derivative *IX-2-a* was prepared by the reaction of *Ia* (5.0 g; 17.9 mmol), piperidine (1.5 g; 17.9 mmol), and mercuric oxide (11.6 g; 53.7 mmol) in acetone (200 cm^3) during 2 d. The reaction mixture was filtered with charcoal. After removing the solvent the oily product was dissolved in chloroform and filtered through silica gel. Then petroleum ether was added and the solution was left to crystallize in a deep fridge. Yield 2.7 g (45 %), m.p. = 186—188 °C (ethanol), R_f = 0.76 (ether). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3220, 3160 ν(NH), 2940, 2870 ν(CH), 1660 ν(NCO), 1600 ν(C=N), 1580, 1520 ν(C=C). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ: 7.85 (s, 1H, NH), 3.65—3.90 (m, 4H, CH_2), 2.60—2.95 (m, 4H, CH_2), 1.80—2.00 (m, 4H, CH_2), 1.43—1.80 (m, 6H, CH_2), 2.62 (s, 3H, CH_3).

Pivaloyl derivative *IX-2-c* was prepared by the reaction of *Ic* (5.0 g; 15.6 mmol), piperidine (1.3 g; 15.6 mmol), and mercuric oxide (10.1 g; 46.8 mmol) in acetone (200 cm^3) during 2 d. Then the mixture was filtered and the oily product which remained after evaporation of the solvent was left to crystallize in a deep fridge. Yield 2.9 g (45 %), m.p. = 195—197 °C (ethanol), R_f = 0.75 (ether). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3200 ν(NH), 2940, 2860 ν(CH), 1655 ν(NCO), 1590, 1500 ν(C=N) and ν(C=C). ^{1}H NMR spectrum ($CDCl_3$, TMS) , δ: 7.88 (s, 1H, NH), 3.70—3.93 (m, 4H, CH_2), 2.60—2.90 (m, 4H, CH_2), 1.75—1.98 (m, 4H, CH_2), 1.50—1.75 (m, 6H, CH_2), 1.35 (s, 9H, CH_3).

2-Dialkylamino-4-acylamino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines *X*

Procedure A. 2-Diethyl-4-phenylacetyl derivative *X-3-e* was prepared as the product of desulfanation reaction of *Ie* in the presence of diethylamine by the procedure mentioned above. After three days the reaction mixture was filtered with charcoal and acetone evaporated. The remainder was dissolved in chloroform, filtered with silica gel and the product was isolated by evaporation of the solvent. Yield 54 %, m.p. = 151—153 °C, R_f = 0.76 (ether). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3240 ν(NH), 2940, 2860 ν(CH), 1665, 1565 ν(NHCO), 1590, 1520, 1500 ν(C=N) and ν(C=C). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ: 7.85 (s, 1H, NH), 7.30—7.58 (m, 5H, H_{arom}), 4.28 (s, 2H, CH_2Ph), 3.70 (q, 4H, CH_2, *J* = 7.5 Hz), 2.33—2.83 (m, 4H, CH_2), 1.63—1.98 (m, 4H, CH_2), 1.20 (t, 6H, CH_3, *J* = 7.5 Hz).

Procedure B. Morpholino-methoxycarbonyl derivative *X-1-f* was prepared by the cyclization of guanidine *VIII-1-f* (1.00 g; 2.9 mmol) during 3 d reaction in concentrated sulfuric acid (96 %, 20 cm^3) at room temperature. Then the mixture was poured into crashed ice (100 g) and neutralized with aqueous solution of ammonia (10 %) to pH 6—8. Yield 0.86 g (86 %), m.p. = 168—171 °C. IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3350 ν(NH), 2940, 2880 ν(CH), 1735, 1555 ν(NHCO), 1580, 1530, 1040 ν(C=N) and ν(C=C), 1110 ν(COC). ^{1}H NMR spectrum ($(CD_3)_2CO$, TMS), δ: 5.93 (s, 1H, NH), 3.53—3.90 (m, 8H, CH_2), 3.73 (s, 3H, OCH_3), 2.68—3.20 (m, 4H, CH_2), 1.80—2.00 (m, 4H, CH_2).

Piperidino-methoxycarbonyl derivative *X-2-f* was prepared similarly as *X-1-f* by the cyclization of guanidine *VIII-2-f* (1.0 g; 2.9 mmol). Yield 0.85 g (85 %), m.p. = 105—108 °C. IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3340 ν(NH), 2940, 2860 ν(CH), 1740, 1570 ν(NHCO), 1610, 1520, 1020 ν(C=N) and ν(C=C). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ: 4.93 (s, 1H, NH), 3.75 (s, 3H, OCH_3), 3.60—3.93 (m, 4H, CH_2), 2.43—3.03 (m, 4H, CH_2), 1.70—2.05 (m, 4H, CH_2), 1.43—1.70 (m, 6H, CH_2).

4-Amino-2-dialkylamino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines *XI*

1-Acyl-2-(3-cyano-4,5,6,7-tetrahydrobenzo-[*b*]thien-2-yl)-3,3-(diR')guanidines *VIII* (1.0 g) (except *VIII-1-e*, *VIII-1-f*, and *VIII-2-f*) were mixed with sulfuric acid (96 %, 20 cm^3) and the mixture was left to react for 3 d at room temperature. Then the reaction mixture was worked up by the usual way mentioned above. Yields and ^{1}H NMR data are presented in Tables 7 and 8.

1-(3-Oxapentamethylene)-2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)guanidine (*XII-1*)

Compound *VIII-1-e* (1.0 g; 2.5 mmol) reacted for 3 d in concentrated sulfuric acid (96 %, 25 cm^3).

Table 6. ^{1}H NMR Spectral Characteristics of Compounds *VIII* and *XIII*

Compound	δ
VIII-1-a	7.13 (s, 1H, NH), 3.38—3.95 (m, 8H, CH_2), 2.33—2.85 (m, 4H, CH_2), 2.20 (s, 3H, CH_3), 1.53—2.00 (m, 4H, CH_2)
VIII-1-b	7.45—8.25 (m, 5H, H_{arom}), 3.58—3.85 (m, 8H, CH_2), 2.30—2.60 (m, 4H, CH_2), 1.60—1.90 (m, 4H, CH_2)
VIII-1-c	8.70 (s, 1H, NH), 3.48—3.85 (m, 8H, CH_2), 2.38—2.73 (m, 4H, CH_2), 1.68—1.95 (m, 4H, CH_2), 1.30 (s, 9H, CH_3)
VIII-1-d	7.90—8.08 (m, 2H, H_{arom}), 6.93—7.15 (m, 2H, H_{arom}), 3.89 (s, 3H, OCH_3), 3.55—4.03 (m, 8H, CH_2), 2.40—2.73 (m, 4H, CH_2), 1.68—1.98 (m, 4H, CH_2)
VIII-1-e	9.08 (s, 1H, NH), 7.23—7.50 (m, 5H, H_{arom}), 3.78 (s, 2H, CH_2Ph), 3.43—3.73 (m, 8H, CH_2), 2.33—2.65 (m, 4H, CH_2), 1.65—1.93 (m, 4H, CH_2)
VIII-1-f	3.80 (s, 3H, OCH_3), 3.50—3.95 (m, 8H, CH_2), 2.40—2.78 (m, 4H, CH_2), 1.68—2.00 (m, 4H, CH_2)
VIII-2-b	7.38—8.08 (m, 5H, H_{arom}), 3.48—3.75 (m, 4H, CH_2), 2.38—2.70 (m, 4H, CH_2), 1.53—1.95 (m, 10H, CH_2)
VIII-2-d	7.83—8.05 (m, 2H, H_{arom}), 6.90—7.13 (m, 2H, H_{arom}), 3.88 (s, 3H, OCH_3), 3.48—3.75 (m, 4H, CH_2), 2.38—2.68 (m, 4H, CH_2), 1.55—1.93 (m, 10H, CH_2)
VIII-2-e	7.00—7.45 (m, 5H, H_{arom}), 6.79 (s, 1H, NH), 3.65 (s, 2H, CH_2Ph), 3.15—3.55 (m, 4H, CH_2), 2.25—2.80 (m, 4H, CH_2), 1.33—2.00 (m, 10H, CH_2)
VIII-2-f	3.76 (s, 3H, OCH_3), 3.42—3.68 (m, 4H, CH_2), 2.38—2.85 (m, 4H, CH_2), 1.60—1.95 (m, 10H, CH_2)
VIII-3-a	7.38 (s, 1H, NH), 3.53 (q, 4H, CH_2, J = 7.5 Hz), 2.40—2.70 (m, 4H, CH_2), 2.13 (s, 3H, CH_3), 1.65—1.95 (m, 4H, CH_2), 1.25 (t, 6H, CH_3, J = 7.5 Hz)
VIII-3-b	7.45—8.15 (m, 6H, H_{arom} + NH), 3.58 (q, 4H, CH_2, J = 7.5 Hz), 2.33—2.68 (m, 4H, CH_2), 1.60—1.98 (m, 4H, CH_2), 1.30 (t, 6H, CH_3, J = 7.5 Hz)
VIII-3-c	7.18 (s, 1H, NH), 3.48 (q, 4H, CH_2, J = 7.5 Hz), 2.40—2.73 (m, 4H, CH_2), 1.65—1.98 (m, 4H, CH_2), 1.33 (t, 6H, CH_3, J = 7.5 Hz), 1.28 (s, 9H, CH_3)
VIII-3-d	7.84—8.16 (m, 2H, H_{arom}), 6.96—7.20 (m, 2H, H_{arom}), 3.94 (s, 3H, OCH_3), 3.56 (q, 4H, CH_2, J = 7.5 Hz), 2.28—2.72 (m, 4H, CH_2), 1.52—2.08 (m, 4H, CH_2), 1.28 (t, 6H, CH_3, J = 7.5 Hz)
VIII-3-f	7.63 (s, 1H, NH), 3.76 (s, 3H, OCH_3), 3.40 (q, 4H, CH_2, J = 7.5 Hz), 2.43—2.73 (m, 4H, CH_2), 1.58—2.00 (m, 4H, CH_2), 1.18 (t, 6H, CH_3, J = 7.5 Hz)
XIII-1-a	4.30 (q, 2H, CH_2, J = 7.5 Hz), 3.43—3.95 (m, 8H, CH_2), 2.50—2.85 (m, 4H, CH_2), 2.17 (s, 3H, CH_3), 1.63—1.93 (m, 4H, CH_2), 1.36 (t, 3H, CH_3, J = 7.5 Hz)
XIII-1-b	8.23 (s, 1H, NH), 7.33—7.63 (m, 5H, H_{arom}), 4.38 (q, 2H, CH_2, J = 7.5 Hz), 3.43—3.95 (m, 8H, CH_2), 2.40—2.90 (m, 4H, CH_2), 1.60—1.88 (m, 4H, CH_2), 1.38 (t, 3H, CH_3, J = 7.5 Hz)
XIII-1-c	4.30 (q, 2H, CH_2, J = 7.5 Hz), 3.43—3.93 (m, 8H, CH_2), 2.45—2.83 (m, 4H, CH_2), 1.63—1.93 (m, 4H, CH_2), 1.35 (t, 3H, CH_3, J = 7.5 Hz), 1.15 (s, 9H, CH_3)
XIII-1-d	8.18—8.38 (m, 2H, H_{arom}), 6.88—7.10 (m, 2H, H_{arom}), 4.38 (q, 2H, CH_2, J = 7.5 Hz), 3.90 (s, 3H, OCH_3), 3.50—4.00 (m, 8H, CH_2), 2.45—2.88 (m, 4H, CH_2), 1.63—1.93 (m, 4H, CH_2), 1.39 (t, 3H, CH_3, J = 7.5 Hz)
XIII-2-a	4.31 (q, 2H, CH_2, J = 7.5 Hz), 3.38—3.65 (m, 4H, CH_2), 2.48—2.88 (m, 4H, CH_2), 2.15 (s, 3H, CH_3), 1.58—1.93 (m, 10H, CH_2), 1.36 (t, 3H, CH_3, J = 7.5 Hz)
XIII-2-b	8.23—8.40 (m, 2H, H_{arom}), 7.40—7.60 (m, 2H, H_{arom}), 4.38 (q, 2H, CH_2, J = 7.5 Hz), 3.43—3.68 (m, 4H, CH_2), 2.43—2.85 (m, 4H, CH_2), 1.58—1.90 (m, 10H, CH_2), 1.39 (t, 3H, CH_3, J = 7.5 Hz)
XIII-2-c	4.33 (q, 2H, CH_2, J = 7.5 Hz), 3.35—3.63 (m, 4H, CH_2), 2.48—2.88 (m, 4H, CH_2), 1.58—1.98 (m, 10H, CH_2), 1.38 (t, 3H, CH_3, J = 7.5 Hz)
XIII-2-d	11.63 (s, 1H, NH), 8.12—8.40 (m, 2H, H_{arom}), 6.88—7.08 (m, 2H, H_{arom}), 4.36 (q, 2H, CH_2, J = 7.5 Hz), 3.86 (s, 3H, OCH_3), 3.40—3.64 (m, 4H, CH_2), 2.40—2.88 (m, 4H, CH_2), 1.60—1.92 (m, 10H, CH_2), 1.40 (t, 3H, CH_3, J = 7.5 Hz)
XIII-3-a	11.82 (s, 1H, NH), 4.40 (q, 2H, CH_2, J = 8.0 Hz), 3.60 (q, 4H, CH_2, J = 8.0 Hz), 2.48—3.00 (m, 4H, CH_2), 2.23 (s, 3H, CH_3), 1.64—2.00 (m, 4H, CH_2), 1.40 (t, 3H, CH_3, J = 8.0 Hz), 1.36 (t, 6H, CH_3, J = 8.0 Hz)
XIII-3-b	11.92 (s, 1H, NH), 8.20—8.52 (m, 2H, H_{arom}), 7.44—7.72 (m, 3H, H_{arom}), 4.40 (q, 2H, CH_2, J = 7.5 Hz), 3.60 (q, 4H, CH_2, J = 7.5 Hz), 2.32—2.96 (m, 4H, CH_2), 1.56—1.96 (m, 4H, CH_2), 1.44 (t, 3H, CH_3, J = 7.5 Hz), 1.36 (t, 6H, CH_3, J = 7.5 Hz)
XIII-3-c	11.68 (s, 1H, NH), 4.32 (q, 2H, CH_2, J = 7.5 Hz), 3.48 (q, 4H, CH_2, J = 7.5 Hz), 2.36—2.88 (m, 4H, CH_2), 1.60—2.00 (m, 4H, CH_2), 1.36 (t, 3H, CH_3, J = 7.5 Hz), 1.28 (t, 6H, CH_3, J = 7.5 Hz), 1.28 (s, 9H, CH_3)
XIII-3-d	8.23—8.45 (m, 2H, H_{arom}), 6.95—7.15 (m, 2H, H_{arom}), 4.40 (q, 2H, CH_2, J = 7.5 Hz), 3.93 (s, 3H, OCH_3), 3.58 (q, 4H, CH_2, J = 7.5 Hz), 2.38—2.90 (m, 4H, CH_2), 1.63—1.93 (m, 4H, CH_2), 1.40 (t, 3H, CH_3, J = 7.5 Hz), 1.35 (t, 6H, CH_3, J = 7.5 Hz)

Guanidine *XII-1* has been isolated by the procedure already mentioned above. Yield 0.64 g (88 %), m.p. = 173—175 °C (ethanol). IR spectrum (KBr pellet), $\tilde{\nu}$/cm^{-1}: 3400, 3280, 3180 ν(NH_2), 2930, 2860 ν(CH), 2210 ν(C≡N), 1600 ν(C=N), 1110 ν(COC). ^{1}H NMR spectrum ($(CD_3)_2SO$, TMS), δ: 6.52 (s, 2H, NH_2), 3.52—3.80 (m, 8H, CH_2), 2.52—3.00 (m, 4H, CH_2), 1.52—2.00 (m, 4H, CH_2).

1-Acyl-2-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)-3,3-(diR')guanidines *XIII*

Acylthioureas *II* (15 mmol) were treated with mercuric oxide (45 mmol) in the presence of secondary amine (15 mmol) (morpholine, piperidine, diethylamine) in acetone (200 cm^3). After 12—48 h the starting compounds disappeared (monitored

Table 7. Characteristics and IR Data of the Synthesized Compounds *XI* and *XIV*

Compound	NR'_2	Yield/%	M.p./°C	$\tilde{\nu}$/cm^{-1}		
				$\nu(NH_2)$	$\nu(C{=}N)$ and $\nu(NH_2)$	
XI-1	morpholino	68—80	181—183	3450, 3280	1605	
XI-2	piperidino	86—89	162—164	3450, 3350	1605	
XI-3	NEt_2	82—84	148—150	3410, 3250, 3160	1615	
				$\nu(NH)$	$\nu(C{=}O)$	$\nu(C{=}N)$
XIV-1	morpholino	82—90	350	3140	1660	1600
XIV-2	piperidino	87—93	301—303	3120	1650	1605
XIV-3	NEt_2	92—96	250—252	3200, 3100	1650	1635

Table 8. ^{1}H NMR Characteristics of Compounds *XI* and *XIV*

Compound	δ
XI-1	5.15 (s, 2H, NH_2), 3.83 (m, 8H, CH_2), 2.60—3.03 (m, 4H, CH_2), 1.75—2.13 (m, 4H, CH_2)
XI-2	5.03 (s, 2H, NH_2), 3.63—3.95 (m, 4H, CH_2), 2.55—3.00 (m, 4H, CH_2), 1.75—2.05 (m, 4H, CH_2), 1.43—1.75 (m, 6H, CH_2)
XI-3	4.86 (s, 2H, NH_2), 3.60 (q, 4H, CH_2, J = 7.0 Hz), 2.50—2.95 (m, 4H, CH_2), 1.65—2.08 (m, 4H, CH_2), 1.14 (t, 6H, CH_3, J = 7.0 Hz)
XIV-1	3.48—3.76 (m, 8H, CH_2), 2.50—2.92 (m, 4H, CH_2), 1.66—1.90 (m, 4H, CH_2)
XIV-2	11.36 (br s, 1H, NH), 3.43—3.88 (m, 4H, CH_2), 2.43—3.00 (m, 4H, CH_2), 1.60—2.03 (m, 4H, CH_2), 1.38—1.88 (m, 6H, CH_3)
XIV-3	3.60 (q, 4H, CH_2, J = 7.0 Hz), 2.45—3.05 (m, 4H, CH_2), 1.60—2.05 (m, 4H, CH_2), 1.20 (t, 6H, CH_3, J = 7.0 Hz)

by TLC), the reaction mixture was filtered with charcoal, the filtrate got rid of acetone and products recrystallized from ethanol. Their characteristics are presented in Tables 4, 6, and 9.

2-Dialkylamino-3,4,5,6,7,8-hexahydrobenzo-[*b*]thieno[2,3-*d*]pyrimidin-4-ones *XIV*

Compounds were prepared by the cyclization of guanidines *XIII* (1.0 g) in concentrated sulfuric acid (25 cm^3) at room temperature during 2—3 d. Products have been isolated by the procedure already mentioned above. Characteristics are presented in Tables 7 and 8.

Table 9. IR Spectral Characteristics of Compounds *XIII*

Compound	$\tilde{\nu}$/cm^{-1}			
	ν(NH)	$\nu(C{=}N)$	ν(NHCO)	ν(COC)
XIII-1-a	3230	1620	1680, 1570	1200, 1040
XIII-1-b	3190	1615	1650, 1580	1200, 1020
XIII-1-c	3270	1625	1685, 1560	1205, 1030
XIII-1-d	3190	1610	1650, 1585	1180, 1030
XIII-2-a	3240	1615	1690, 1570	1180, 1040
XIII-2-b	3200	1620	1650, 1560	1185, 1030
XIII-2-c	3180	1605	1680, 1565	1200, 1030
XIII-2-d	3390	1610	1650, 1575	1190, 1025
XIII-3-a	3220	1610	1690, 1570	1210, 1040
XIII-3-b	3160	1610	1655, 1570	1230, 1020
XIII-3-c	3140	1600	1650, 1570	1230, 1035
XIII-3-d	3160	1605	1650, 1570	1230, 1020

RESULTS AND DISCUSSION

Starting acylthioureido derivatives *I* and *II* were prepared by the addition of ester or nitrile of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid to corresponding acyl isothiocyanate.

Selection of the acyl was given by the accessibility of the carboxylic acid or its chloride for the synthesis of acyl isothiocyanate with respect to the possible electronic or steric effect of the acyl group at following reactions of *I* and *II*.

The acyl isothiocyanates were prepared by the reaction of acyl chlorides with ammonium or potassium thiocyanate in anhydrous acetone. After the solvent was removed the product was purified by distillation under reduced pressure.

Because the use of acyl isothiocyanate prepared in such a way had no significant influence on the yield and purity of the products, its crude acetonic solutions were mostly applied.

Pure crystalline products *I* and *II* were formed in all the cases after the addition reaction. Their purity was proved by TLC and elemental analysis, the structure was confirmed by IR and ^{1}H NMR spectroscopy.

Compounds *I* were characterized in the IR spectrum by the vibration band of the cyano group, esters *II* by the band of —COOEt group. Both then contained vibration bands of the —NHCO— group (amide I and amide II) and —NHCS— group (thioamide I and thioamide II).

In the IR spectrum of *I* one can observe an influence of the substituent at the acyl group on the position of the amide I band of the —NHCO— group. Increasing electron-withdrawing effect of the substituent leads to the higher order of the C=O bond, which was demonstrated by a shift of the amide I band to a higher wavenumber [10].

In the series of compounds *I* the methoxycarbonyl

group had the band shifted to the highest wavenumber (1720 cm^{-1}). The methoxy group in this case shows the highest electron-withdrawing effect due to prevailing $-I$ effect of the oxygen atom over its $+M$ effect. The wavenumbers of the amide I band of compounds *Id* (1655 cm^{-1}) and *Ib* (1660 cm^{-1}) were the lowest. We suppose the positive mesomeric effect dominating the negative inductive effect of phenyl or 4-methoxyphenyl group. The influence of the substituent upon the position of the ν(C=O) band at compounds *II* was negligible.

^{1}H NMR spectra of acylthioureido derivatives confirmed the presence of the protons located at acyls as well as the protons at nitrogen atoms. Esters in addition contained the protons of ethoxycarbonyl group.

The stretching vibrations of cyano group in the IR spectrum of nitriles *I*, acyl proton signals and the signals of protons of ethoxycarbonyl group of compound *II* in the ^{1}H NMR spectra enabled us to follow further changes in the structure of synthesized compounds (cyclization and deacylation reactions).

Nitriles *I* and esters *II* reacted in 94—96 % sulfuric acid at room temperature. The reaction time of compounds *I* was within 2—4 d, esters *II* needed 5—7 d.

In order to isolate the thiazinium salts, formed during the cyclization of compounds *I*, which were very soluble in the form of hydrogen sulfate in the reaction mixture and in the neutral medium entered retrocyclization reaction leading to the thiazinium ring opening [6], we added 40 % aqueous solution of perchloric acid. After the reaction of compounds *Ia*—*Ic* and *Ie*, the only product isolated was compound *IV*. The product did not contain any acyl group. Its neutralization led to the known 2-thioureido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (*V*) [6] (Scheme 1).

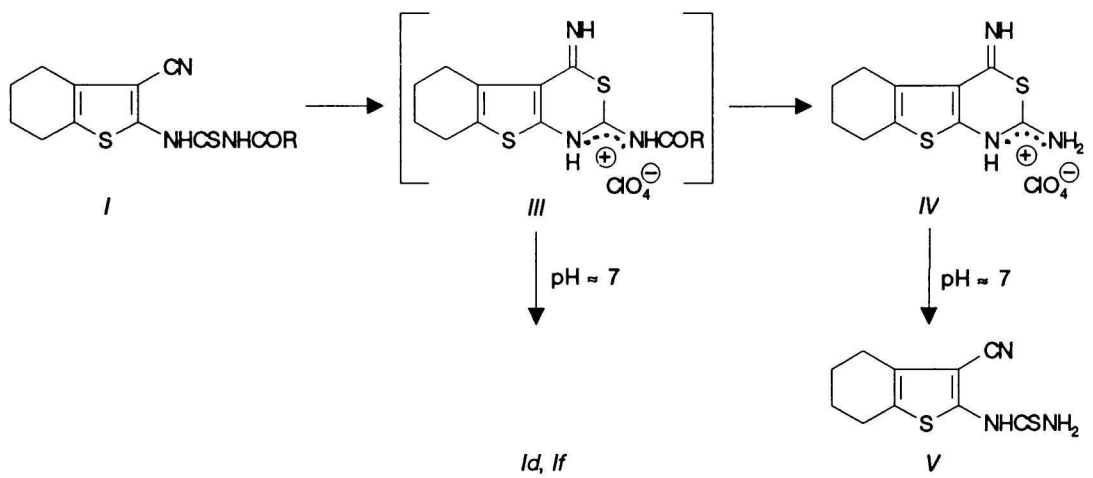
Compound *IV* was identified as 2-amino-4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-[1,3]-thiazinium perchlorate on the basis of IR, ^{1}H NMR spectra and elemental analysis and an analogy with paper [6].

After reaction of *Id* and *If* two different products were isolated that contained in the structure 4-methoxybenzoyl and methoxycarbonyl group, respectively. Their neutralization or neutralization of the reaction mixture after reaction led to nitrile *Id* and *If*, respectively. Studying IR, ^{1}H NMR spectra and elemental analyses we concluded that products of cyclization reaction of *Id* and *If* in sulfuric acid are 2-acylamino-4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-[1,3]-thiazinium perchlorates (4-methoxybenzoyl *IIId* and methoxycarbonyl *IIIf*).

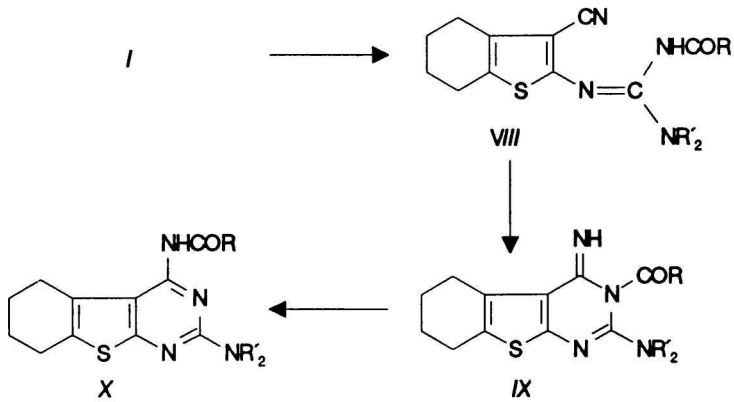
Esters *II* under the same reaction conditions cyclized to 2-amino-5,6,7,8-tetrahydrobenzo[*b*]-thieno[2,3-*d*]-[1,3]-thiazin-4-one (*VII*) which was isolated after neutralization of the reaction mixture. In a good agreement with paper [5] after the cyclization of compound *IIb* in addition to compound *VII* 2-benzoylamino-5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]-[1,3]-thiazin-4-one (*VI*) was isolated.

Desulfanation reactions of compounds *I* and *II* (Scheme 2) were carried out with mercuric oxide in anhydrous acetone at room temperature in the presence of secondary amines (morpholine, piperidine, and diethylamine). Mercuric oxide was used in a three-fold molar excess with respect to starting molar concentration of acylthiourea. Both modifications (red and yellow) were used without any significant influence on the reaction course.

The reaction time in the reaction with morpholine ranged within 3—12 h, with piperidine within 2—3 d and with diethylamine within 2—7 d. The course of the reaction was followed by TLC (chromatograms were eluted by diethyl ether, the presence of starting acylthiourea was monitored with ethanolic solution of silver nitrate). The colour of



Scheme 1



Scheme 2

the reaction mixture during the time turned to dark due to the precipitation of HgS. Without presence of amine the reaction stopped.

In the series of desulfanation reactions with morpholine 1-acyl-2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)-3-(3-oxapentamethylene)-guanidines *VIII-1* were isolated from the reaction mixture in all the cases. Their yields ranged from 32 to 73 % mostly as a consequence of the isolation procedure and due to formation of insoluble complexes of the starting acylthioureido derivatives with mercury.

Similar complexes with a limited solubility in dimethyl sulfoxide were formed also in the mixture of mercuric chloride and acylthiourea in acetone in the presence of triethylamine.

Their decomposition in the presence of secondary amines proceeded under formation of HgS very slowly either at room temperature or boiling in acetone. The fact that the complex contains acylthiourea and mercury in the amount of substance ratio 2 1 was proved by elemental analysis (mercury determination by *Fujita et al.* [11]).

Exchange of mercuric oxide for acetate and carbonate or lead oxide influenced negatively the yield of the substituted derivatives. And because silver derivatives (nitrate, oxide, carbonate) increased the yield only negligibly, we stuck on mercuric oxide.

The fact that compounds *VIII* are present in the tautomeric form shown in Scheme 2 was confirmed by IR and ^{1}H NMR spectra. In the IR spectrum the band of —NHCO— group vibration was found at $\tilde{\nu}$ = 1650—1730 cm^{-1}. In order to distinguish whether the value of the band position corresponds to an associated —NHCO— group or >NCO— group we measured IR spectra of the mentioned compounds in bromoform solution. The position of the band was shifted to higher wavenumbers with dilution of the bromoform solution. This supported our conclusions.

We were not able to isolate or identify guanidines *VIII* formed during desulfanation reactions of *I* in the presence of piperidine and diethylamine by TLC. Compounds *Ia* and *Ic* gave immediately the final cyclic product 3-acyl-4-imino-2-piperidino-3,4,5,-6,7,8-hexahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine only (acetyl *IX-2-a*, pivaloyl *IX-2-c*).

Also acylthiourea *Ie* during desulfanation reaction with diethylamine cyclized to imino derivative *IX* that immediately entered Dimroth rearrangement to 2-diethylamino-4-phenylacetylamino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (*X-3-e*) (Scheme 2).

The spectral characteristics served as the proof of the structure of compounds *IX* which are 3-acyl-4-imino derivatives and not rearranged 4-acylamino derivatives. In the IR spectrum it was the stretching vibration of >NCO— group at $\tilde{\nu}$ = 1655 and 1660 cm^{-1}. The position of these bands has not changed with dilution of the measured bromoform solution. The presence of the imino group is manifested in the ^{1}H NMR spectrum by the signal of NH at δ = 7.85 and 7.88. This is in comparison with the proton signal of derivative *XI-2* without acyl at δ = 5.03 (Scheme 3) shifted downfield due to anisotropic effect of the C=N bond. The proton signals of the —NHCO— group of 4-acylaminopyrimidines *X-1-f* and *X-2-f* are shifted upfield. The same effect of anisotropy of the C=N bond one can observe on the chemical shift of protons in position 5 of compounds *IX* (downfield shift of the multiplet in comparison with *X*).

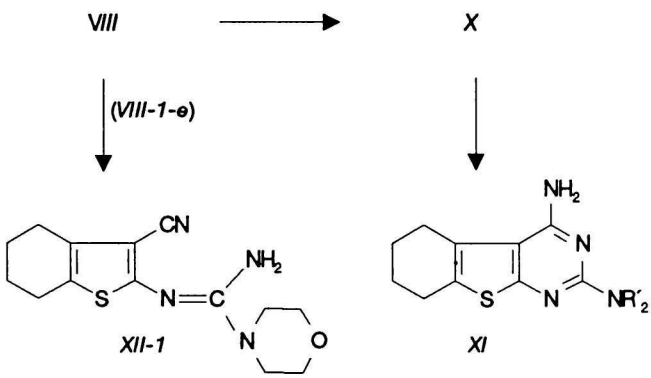
The structure of *X-3-e* is supported by the presence of the amide I and amide II bands in the IR spectrum and the position of the signals of —NH— and —CH$_2$— groups in position 5 in the ^{1}H NMR spectrum.

Guanidines *VIII* were attempted to cyclize boiling for several hours in aqueous-ethanolic solution of sodium hydroxide similarly as analogous acylguanidinobenzonitriles [7]. The cyclization was not

successful and after acidification the starting compound was isolated (proved by TLC, IR and ^{1}H NMR spectra).

We suppose that the difference in the reactivity of 1,1-diethyl-2-acyl-3-(2-cyanophenyl)guanidines [7] and acylguanidines *VIII* is connected with a different geometry and different distribution of electron density on the reaction centres, especially at cyano group (compare conclusions in [12]).

Further the guanidines were treated with concentrated sulfuric acid at room temperature in order to cyclize them (Scheme 3). In the strongly acid



Scheme 3

medium we expected protonation of the nitrogen atom of the cyano group and in this way the electron deficiency at the carbon atom of the cyano group would be increased. That is important for a nucleophilic attack of the nitrogen atom of the acylamino group in the guanidine part of molecule during formation of the pyrimidine skeleton.

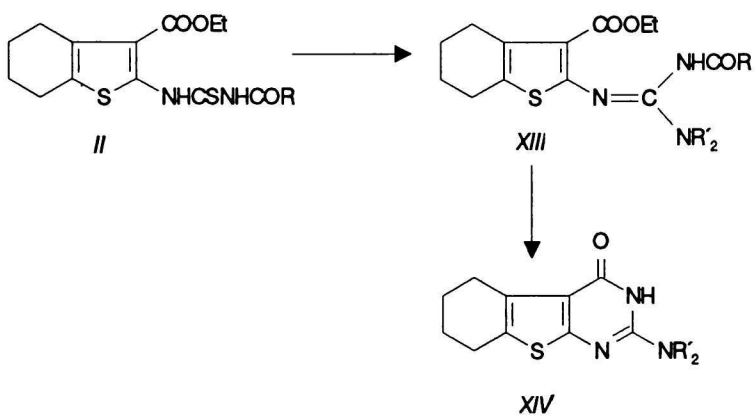
Guanidines *VIII* under the studied conditions gave three types of products. Compounds *VIII-1-f* and *VIII-2-f* cyclized with Dimroth rearrangement forming 4-acylaminopyrimidine derivatives *X*. Their structure has already been discussed above. Guanidine *VIII-1-e* lost its acyl group without cyclization forming 1-(3-oxapentamethylene)-2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)guanidine *XII-1*. Its structure was proved by IR and ^{1}H NMR spectra.

Other compounds *VIII* gave in the cyclization reaction accompanied with the loss of the acyl group 4-amino-2-dialkylamino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines *XI* only. So obtained results do not enable us to conclude whether under the mentioned conditions the cyclization is the first step followed by the deacylation or if the reaction proceeds in an opposite order. As the more probable we suppose the first variant because the attempt to cyclize already deacylated guanidine *XII-1* in concentrated sulfuric acid was not successful either in boiling water bath. The reason for that might be the formation of guanidinium cation with an electron deficiency so needed for a nucleophilic attack of guanidino group nitrogen atom on cyano group.

The structure of compounds *XI* is supported by IR, ^{1}H NMR spectra and elemental analyses.

Acylthioureas *II* were treated similarly as compounds *I* with mercuric oxide in the presence of morpholine, piperidine or diethylamine. The only products of the reaction in this case were acylguanidines *XIII* (Scheme 4). The cyclic products were not formed probably due to lower reactivity of ethoxycarbonyl group in comparison with cyano group. Similar conclusions were already drawn during cyclization of esters and nitriles of 2-(3-acylthioureido)benzoic acids [3].

Cyclization of *XIII* in aqueous-ethanolic solution of sodium hydroxide was not successful. The reaction mixture contained the starting compound and the product of ester hydrolysis only. Compounds *XIII* reacted in concentrated sulfuric acid at room temperature under formation of cyclic products 2-dialkylamino-3,4,5,6,7,8-hexahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-ones *XIV* always with acyl group splitting (Scheme 4). Their structure is in a good agreement with the results of



Scheme 4

elemental analysis and IR and ^{1}H NMR spectral data.

REFERENCES

1. Leistner, S., Gütschow, M., and Stach, J., *Arch. Pharm.* (Weinheim) *323,* 857 (1990).
2. Gütschow, M. and Leistner, S., *Z. Chem. 30,* 440 (1990).
3. Pazdera, P., Potůček, V., Nováček, E., Kalviňš, I., Trapencieris, P., and Pugovics, O., *Chem. Papers 45,* 527 (1991).
4. Chan, Chao-Han and Shish, Fang-Jy, *Heterocycles 26,* 3193 (1987).
5. Leistner, S., Gütschow, M., and Wagner, G., *Pharmazie 43,* 466 (1988).
6. Gütschow, M. and Leistner, S., *Z. Chem. 30,* 23 (1990).
7. Pazdera, P. and Potůček, V., *Chem. Papers 45,* 677 (1991).
8. Gewald, K., Schinke, E., and Böttcher, H., *Chem. Ber. 99,* 94 (1966).
9. Pazdera, P. and Potůček, V., *Czech. Appl.* 262022 (1988).
10. Horák, M. and Papoušek, D., *Infračervená spektra a struktura molekul.* (Infrared Spectra and Structure of Molecules.) P. 611. Academia, Prague, 1976.
11. Fujita, M., Takeda, Y., Terao, T., Hoshino, O., and Whita, T., *Anal. Chem. 40,* 2042 (1968).
12. Pazdera, P., Řezka, M., and Nováček, E., *Chem. Papers 44,* 229 (1990).

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Activative Influence of the Nitro Group in the Cyclization Reactions of the Addition Products of 2-Chloro-5-nitrobenzoyl Isothiocyanate with the Amines and 2-Propanol

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Reaction of 2-chloro-5-nitrobenzoyl isothiocyanate with the primary and secondary alkyl- and arylamines, as well as with 2-propanol yields corresponding thioureas, or *O*-isopropyl monothiocarbamate, respectively. Heating of these thioureas in dimethylformamide with LiH or in the benzene solution of triethylamine leads to formation of the cyclization products, *i.e.* the corresponding 2-alkyl(aryl)amino-6-nitro-4*H*-1,3-benzothiazin-4-ones.

2-Thioxo-6-nitro-2,3-dihydro-4*H*-1,3-benzothiazin-4-one can be obtained by the reaction of 2-chloro-5-nitrobenzoyl isothiocyanate with sodium hydrogen sulfide. The synthesized benzothiazines are stable, their heating or melting does not lead to the rearrangement into the benzopyrimidinic heterocycles.

Studying the cyclization reactions of the products of the addition of 2-chlorobenzoyl isothiocyanate to the amines and alcohols, we came to a conclusion that the cyclization reactions occur only with those thioureas that have been obtained from the primary alkyl- and arylamines [1]. These cyclization reactions result in the derivatives of quinazolinones. Thioureas synthesized from the secondary amines as well as addition products of 2-chlorobenzoyl isothiocyanate with alcohols do not undergo the cyclization reactions. It was interesting to find out what would happen with the nitrogen and oxygen adducts of 2-chlorobenzoyl isothiocyanate that has a nitro group in the position 5. This group has a strong electron-accepting effect on nucleophilicity of the chlorine atom in *para* position of the benzene ring. Such activating influence results in the formation of the benzothiazine derivatives, as well as in the addition-elimination reaction with sodium hydrogen sulfide that produces 2-thioxobenzothiazine *III* (Scheme 1). This effect was utilized by *Deorha et al.* [2, 3] at the preparation of 2,4-dioxobenzothiazines using a reaction of the ester of 2-chloro-5-nitrobenzoic