0.5 h. The resulting colorless precipitate was dissolved by the addition of 10 ml of absolute ethanol, the solvent was removed at reduced pressure, and the precipitate was recrystallized from hexane–ethanol (1:1).

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ACYLATION AND BROMINATION OF SOME 2-MERCAPTOTHIENO[2,3-d]PYRIMIDINONES AND SYNTHESIS OF THEIR 2-AMINO DERIVATIVES

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The acylation of 2-thio-3-R-4-oxo-3,4-dihydrothieno[2,3-d]-pyrimidines by means of benzoyl chloride was studied. Depending on the reaction conditions, it may take place with the formation of S-substituted and N-substituted derivatives. The bromination of the sodium salts of thienopyrimidines and their S- and N-substituted derivatives is accompanied by the formation of disulfides, which do not react with electrophilic reagents but react with amines to give 2-amino derivatives of thienopyrimidines.

It is known [1, 2] that compounds with amido and thioamido groups, having dual reactivities, can undergo reactions with migration of the reaction center. It has been shown [3, 4] that the acylation of triazolo-3-thiones with a thioamido grouping in their compositions by means of acid halides leads to the formation of S- and N-substituted derivatives.

We have studied the acylation of 3-phenyl- (Ia) [5] and 3-allyl-2-thio-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-b]pyrimidine (Ib) [6], as well as sodium salts IIa, b, which were obtained from them by treatment with sodium hydroxide solution. The thioamido grouping in Ia, b and IIa, b is included in the pyrimidine ring. The acylation of Ia, b and IIa, b was carried out by means of benzoyl chloride in benzene.

Compounds Ia, b are not acylated even in the case of prolonged heating. Sodium salts IIa, b are acylated at room temperature to give S-substituted derivatives IIIa, b, and refluxing benzene solutions of the latter for 2 h leads to N-substituted derivatives IVa, b.

The simultaneous formation of S- and N-substituted derivatives IIIa and IVa in approximately equal amounts (38.8 and 41.8%) is observed when IIa is refluxed with benzoyl chloride. The reaction of IIb with benzoyl chloride under similar conditions leads only to N-substituted derivative IVb; this is evidently explained by the effect of different radicals in the 3 position of the pyrimidine ring on the electron density distribution in the thioureide fragment of the starting compounds.

The hydrolysis of S- and N-substituted derivatives IIIa, b and IVa, b by a 2 N aqueous alcohol solution of alkali proceeds at room temperature and gives sodium salts IIa, b, the acidification of which with hydrochloric acid gives starting thienopyrimidines Ia, b.

The bromination of S- and N-substituted derivatives IIIa, b and IVa, b gave benzoyl bromide (identified in the form of benzamide – after separation of the precipitate, the reaction

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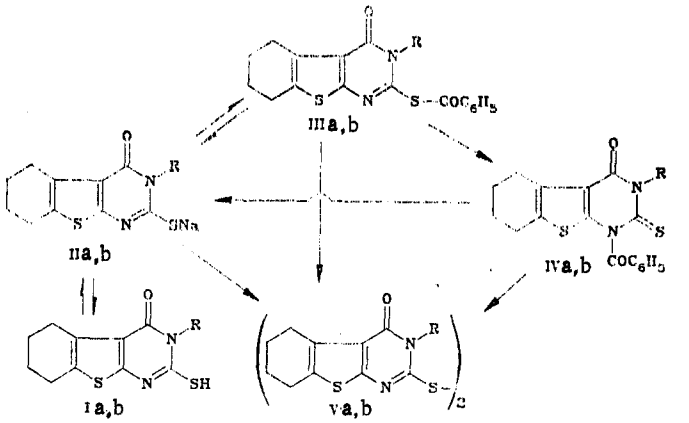


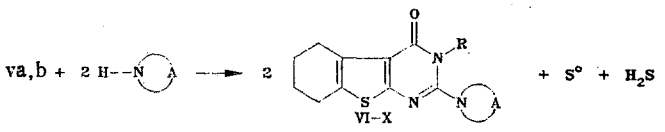
IIa + C_6H_5COCl ⟶ IIIa + IVa

IIb + C_6H_5COCl ⟶ IVb

I–V a R=C_6H_5; b R=$-CH_2CH=CH_2$

solution was treated with ammonia) and disulfides Va, b, which were also formed in the bromination of sodium salts IIa, b.

Cleavage of the disulfide bridge could not be carried out by prolonged (15 h) refluxing of disulfide Va and bromine in benzene solution or by treatment of disulfides Va, b with Lewis acids ($AlBr_3$, $FeBr_3$) under similar conditions; this is probably associated with the decrease in the electron density in the d orbitals of the sulfur atoms of the disulfide bridge under the influence of the positivated carbon atoms in the 2 position of the pyrimidine rings. This assumption is confirmed by the fact that in the action of amines on methanol solutions of disulfides Va, b the latter are cleaved with the liberation of elementary sulfur and hydrogen sulfide and the formation of 2-amino derivatives (VI-X) of thienopyrimidines as a consequence of attack by the nucleophile at the $C_{(2)}$ atom of the pyrimidine ring:



VI, VII A=$(CH_2)_5$; VIII, IX A=$(CH_2)_2O(CH_2)_2$; X A=$(CH_2)_4$

The mechanism of the formation of the 2-amino derivatives of thienopyrimidine in the nucleophilic cleavage of the disulfides is evidently similar to the mechanism of the previously observed nucleophilic cleavage of disulfide derivatives of 1,2,4,5-tetrazine with the formation of amino derivatives [7].

The UV spectra of ethanol solutions of N-acyl derivatives IVa, b, which have a thione group, contain an absorption maximum at 240 nm, as well as maxima at 300 and 350 nm, which are due to the absorption of aromatic systems. Only two absorption maxima at 310 and 340 nm are observed in the spectra of S-acyl derivatives IIIa, b; the spectra do not contain an absorption maximum at 240 nm, since they have a thiol structure. One absorption maximum at 330–340 nm was noted in the spectra of 2-amino derivatives VI-X.

The IR spectra of all of the synthesized I-X contain an intense absorption band of stretching vibrations of a C=O group at 1690-1715 cm^{-1}. Absorption bands at 1548 cm^{-1}, which are characteristic for the $>N-\underset{\underset{S}{\|}}{C}-N<$ group, are present in the spectra of N-acyl derivatives IVa, b, whereas this band is absent in the spectra of IIa, b and S-aryl derivatives IIIa, b.

Thus we have shown that the acylation of the sodium salts of 2-thio-3-R-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidines with benzoyl chloride depends on the nature of the radical in the pyrimidine ring and the acylation conditions. When the S-acyl derivatives of thienopyrimidines are heated, they undergo isomerization to N-acyl derivatives. The bromination of the S- and N-acyl derivatives of thienopyrimidines, like the bromination of the sodium salts, proceeds with the formation of disulfides that do not react with electrophilic reagents but do react with nucleophiles such as amines to give 2-amino derivatives of thienopyrimidines.

TABLE 1. Characteristics of II-X

Compound	mp,* °C	Found, %		Empirical formula	Calc., %		Yield,† %
		N	S		N	S	
IIa	>300	8,4	—	$C_{16}H_{13}NaN_2OS_2$	8,3	—	80
IIb	268—270 (dec.)	9,3	—	$C_{13}H_{13}NaN_2OS_2$	9,3	—	96
IIIa	161—163	6,7	15,2	$C_{23}H_{18}N_2O_2S_2$	6,7	15,3	77,5 (A); 38,8 (B)
IIIb	108—109	7,4	16,9	$C_{20}H_{18}N_2O_2S_2$	7,3	16,8	60,2 (A)
IVa	292—293	6,7	15,5	$C_{23}H_{18}N_2O_2S_2$	6,7	15,3	41,8 (B)
IVb	189—190	7,4	16,6	$C_{20}H_{18}N_2O_2S_2$	7,3	16,8	57,6 (B)
Va	262—264	9,0	20,3	$C_{32}H_{26}N_4O_2S_4$	8,9	20,4	98
Vb	179—181	10,0	23,2	$C_{26}H_{26}N_4O_2S_4$	10,1	23,1	99
VI	203—204	8,9	11,4	$C_{21}H_{23}N_3OS$	8,8	11,5	80
VII	163—164	12,8	9,7	$C_{18}H_{23}N_3OS$	12,8	9,8	82
VIII	216—217	11,4	8,8	$C_{20}H_{21}N_3O_2S$	11,4	8,7	90
IX	165—166	12,5	9,8	$C_{17}H_{21}N_3O_2S$	12,7	9,7	78
X	181—183	12,1	9,0	$C_{20}H_{21}N_3OS$	12,0	9,1	87

*The compounds were crystallized: IIa, b from ethanol—water (5:1), IVa, b and Vb from dioxane, Va from diethylacetamide, and VI-X from methanol.
†Acylation was carried out at room temperature (A) or by heating on a boiling-water bath (B).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra of 10^{-5} M solutions in ethanol were obtained with an SF-26 spectrophotometer. The individuality and purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in CH_3COOH—$CHCl_3$—hexane (2:5:3) (A) and CH_3COOH—$CHCl_3$ (1:9) (B) systems with development by iodine vapors.

The characteristics of the synthesized II-X are presented in Table 1.

2-Mercapto-3-phenyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine Sodium Salt (IIa). A 1.5-g (5 mmole) sample of Ia and 0.4 g (10 mmole) of sodium hydroxide were heated in 10 ml of dioxane on a boiling-water bath for 2 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed successively on the filter with 2 ml of ethanol, 2 ml of ether, and 2 ml of acetone.

2-Mercapto-3-allyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine Sodium Salt (IIb). This compound was obtained from 1.4 g (5 mmole) of Ib and 0.4 g (10 mmole) of sodium hydroxide by the method described for IIa.

2-Mercaptobenzoyl-3-phenyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine (IIIa). A) A 5.4-g (16 mmole) sample of Ib was dissolved in 50 ml of dry benzene at room temperature, 2.24 g (16 mmole) of benzoyl chloride was added, and the mixture was shaken periodically. After 6 h, the precipitated sodium chloride was removed by filtration. The IIIa [R_f 0.65 (A)] that precipitated from the filtrate after 24 h was isolated.

B) A mixture of 2.7 g (8 mmole) of Ib and 1.12 g (8 mmole) of benzoyl chloride was heated on a boiling-water bath for 2.7 h, after which the precipitated IVa was removed from the hot reaction mixture by filtration. Compound IIIa precipitated from the filtrate after 24 h.

2-Mercaptobenzoyl-3-allyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine (IIIb). This compound, with R_f 0.94 (A), was obtained from IIb and benzoyl chloride by a procedure similar to that used to prepare IIIa (method A).

1-Benzoyl-2-thio-3-phenyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine (IVa). This compound, with R_f 0.65 (B), was formed in a mixture with IIIa from Ib and benzoyl chloride by a procedure similar to that used to prepare IIIa (method B).

1-Benzoyl-2-thio-3-allyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine (IVb). A mixture of 0.3 g (1 mmole) of IIb and 0.14 g (1 mmole) of benzoyl chloride in 30 ml of dry benzene was heated on a boiling-water bath for 2 h, and the precipitated IVb was separated by filtration and washed with 2 ml of benzene to give a product with R_f 0.79 (B).

Bis(3-phenyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidin-2-yl) Disulfide (Va). A 4.18-g (10 mmole) sample of IIa was dissolved in 50 ml of CCl_4, and a solution of 0.8 g (5 mmole) of bromine in 20 ml of CCl_4 was added dropwise with constant stirring at room temperature. The resulting precipitate was separated and washed successively with 5 ml of water and 1 ml of alcohol.

Compound Va was also obtained in quantitative yield via a similar method by bromination of Ia, IIIa, and IVa.

Bis(3-allyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyrimidine-2-yl) Disulfide (Vb). This compound was obtained in quantitative yield by bromination of IIb, IIIb, and IVb by the method used to prepare Va.

Compound Vb, with mp 179-181°C, was previously synthesized via an independent method [8].

2-Piperidyl-3-phenyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-d]pyridimine (VI). A mixture of 1.72 g (20 mmole) of piperidine, 0.62 g (1 mmole) of Va, and 2 ml of methanol was heated on a boiling-water bath for 10 min, after which the precipitated sulfur was removed from the hot solution by filtration. The filtrate was cooled to precipitate VI.

The 2-amino derivatives (VII-X) of thieno[2,3-d]pyrimidines were synthesized from disulfides Va, b and the corresponding amines as in the preparation of VI.

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SYNTHESIS AND PROPERTIES OF 5-(5-NITRO-2-FURYL)THIAZOLINES

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The reactions of 2-amino-4-methyl-5-(5-nitro-2-furyl)thiazole with excess methyl iodide leads to 3,4-dimethyl-2-methylamino-5-(5-nitro-2-furyl)thiazolium iodide, which is converted to 2-imino-3,4-dimethyl-5-(5-nitro-2-furyl)thiazoline under the influence of bases. The iminothiazoline structure was proved by comparison of the spectral characteristics of its acetyl derivative and the isomeric 2-(N-acetyl-N-methyl)amino-4-methyl-5-(5-nitro-2-furyl)thiazole. The pK_a values of 2-amino-4-methyl-5-(5-nitro-2-furyl)thiazole and 3,4-dimethyl-2-imino-5-(5-nitro-2-furyl)-thiazoline were determined, and the constant of the aminothiazole–iminothiazoline tautomeric equilibrium was calculated.

In a previous communication [1] we showed that 2-amino-5-(5-nitro-2-furyl)thiazoles react with carboxylic acid anhydrides exclusively at the exocyclic amino group.

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