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RESEARCH ON THIENOPYRIDINES AND PYRIDOTHIENOPYRIMIDINES.

1. SYNTHESIS OF SOME SUBSTITUTED 3-AMINOTHIENO[2,3-b]PYRIDINES

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In recent years the chemistry of thienopyridines and thienopyrimidines has become of more and more interest to researchers. This is explained by the fact that, being isosteres of quinoline and isoquinoline, these compounds may be of interest as biologically active substances. The union in a single heterocyclic system of a pyridine ring, which is inclined to undergo nucleophilic substitution reactions, and a thiophene ring, for which electrophilic substitution reactions are characteristic, makes it possible to obtain various derivatives of thienopyridines and to study the mutual effect of the two heterorings on the reactivity of the system as a whole.

The most widely used method for the preparation of thieno[2,3-b]pyridines up until recently was their synthesis from β-dicarbonyl compounds and substituted aminothiophenes; however, the latter are, as a rule, substances that are difficult to obtain and are unstable [1].

The syntheses of 3-aminothieno[2,3-b]pyridines from 2-mercapto-3-cyanopyridines and halogen-containing compounds with electron-acceptor groups such as carbonyl, cyano, and other groups were recently published [2, 3].

The present paper is devoted to the synthesis of some 3-aminothieno[2,3-b]pyridines that contain various substituents in both the pyridine and thiophene rings (IIa-*l*, Table 2). The starting compounds were various substituted 2-chloro-3-cyanopyridines (Ia-f, Table 1), which were obtained from the corresponding pyridones. Compounds Ia-f were subjected to condensation with thioglycolic acid derivatives in the presence of sodium ethoxide or sodium carbonate.*

In the case of the reaction of 2-chloro-3-cyano-4,6-dimethylpyridine (Ia) with ethyl thioglycolate in the presence of sodium ethoxide, in addition to the corresponding thieno[2,3-b]pyridine (IIa), as a side product we isolated 2-ethoxy-3-cyano-4,6-dimethylpyridine (IIIa),

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*After the start of our research, a communication regarding the use of this method for the preparation of thieno[2,3-b]pyridines that do not contain substituents in the pyridine ring was published [4].

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TABLE 1. 2-Chloro-3-cyanopyridines (I)

Compound	R	R¹	R²	mp, °C (crystallization solvent)	Lit. mp, °C	Yield, %
Ia	CH_3	H	CH_3	98—101 (ethanol)	98—98,5[5] (ethanol)	99
Ib	CH_3	NO_2	CH_3	116—118 (methanol)	114—115[6]	78
Ic	$COOC_2H_5$	H	CH_3	60—61,5 (ethanol)	—[a]	95,6
Id	$COOC_2H_5$	H	C_2H_5	47—49 (petroleum ether)	—[b]	73
Ie	CH_3	H	$COOC_2H_5$	94—96 (hexane)	90—91[7][c]	91,4
If	$COOC_2H_5$	NO_2	CH_3	55—58 (ethanol)	55—57[8] (ethanol)	85,7

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[a] This compound had bp 144-146°C (2.5 mm) [7]. [b] Found: C 54.9; H 4.6; Cl 14.9%. Calculated: C 55.3; H 4.6; Cl 14.9%. [c] This compound had bp 157°C (3 mm).

TABLE 2. 3-Aminothieno[2,3-b]pyridines (II)

Compound	R	R¹	R²	R³	mp, °C[a]	Found, %				Empirical formula	Calc. %				Yield, %
						C	H	N	S		C	H	N	S	
IIa	CH_3	H	CH_3	OC_2H_5	158[b]	57,6	5,6	11,2	12,9	$C_{12}H_{14}N_2O_2S$	57,6	5,6	11,2	12,8	87
IIb	CH_3	H	CH_3	OCH_3	186,5—187,5	56,1	5,2	11,9	13,7	$C_{11}H_{12}N_2O_2S$	55,9	5,1	11,9	13,6	80
IIc	CH_3	NO_2	CH_3	OC_2H_5	205—206	48,7	4,5	14,3	10,6	$C_{12}H_{13}N_3O_4S$	48,8	4,4	14,2	10,9	87
IId	CH_3	H	CH_3	NHC_6H_5	228—229	64,7	5,1	14,2	10,8	$C_{16}H_{15}N_3OS$	64,6	5,1	14,1	10,8	80
IIe	$COOC_2H_5$	H	CH_3	OC_2H_5	100—101,5	54,7	5,4	8,9	10,5	$C_{14}H_{16}N_2O_4S$	54,5	5,2	9,1	10,4	20
IIf	CH_3	H	CH_3	NH_2	246—247	54,5	5,0	18,9	14,5	$C_{10}H_{11}N_3OS$	54,3	5,0	19,0	14,5	90
IIg	$COOC_2H_5$	H	C_2H_5	OC_2H_5	86—88	55,9	5,8	8,8	10,0	$C_{15}H_{18}N_2O_4S$	55,9	5,6	8,7	9,9	42,5
IIh	$COOC_2H_5$	H	CH_3	OH	276 (dec.)	51,4	4,4	10,2	11,4	$C_{12}H_{12}N_2O_4S$	51,4	4,3	10,0	11,4	34,6
IIi	CH_3	H	$COOC_2H_5$	OH	215—218	51,5	4,4	10,0	11,4	$C_{12}H_{12}N_2O_4S$	51,4	4,3	10,0	11,4	17,5
IIj	$COOC_2H_5$	NO_2	CH_3	OC_2H_5	141,5—143,5	47,2	4,2	11,7	9,0	$C_{14}H_{15}N_3O_6S$	47,6	4,3	11,9	9,1	79
IIk	CH_3	NO_2	CH_3	NHC_6H_5	268—270	55,9	4,3	16,1	—	$C_{16}H_{14}N_4O_3S$	56,1	4,1	16,4	9,4	85
IIl	CH_3	NO_2	CH_3	$COOCH_3$	183—184	47,1	3,8	15,2	11,6	$C_{11}H_{11}N_3O_4S$	47,0	3,9	14,9	11,4	81,5

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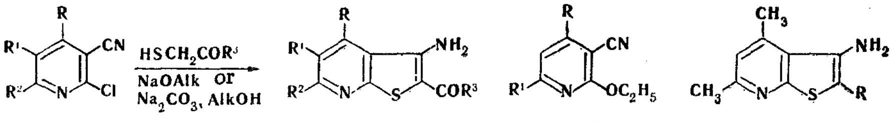
[a] The compounds were crystallized for analysis: IIb-d, f, *l* from alcohol, IIg from hexane, IIa, h, i from 50% alcohol, IIj, from methanol, and IIk from benzene. [b] According to the literature data [3], this compound had mp 156-157 [2] and 154-155°C [3].

i.e., replacement of halogen by an ethoxy group occurred along with replacement of chlorine by a thioglycolic acid residue under the reaction conditions.



I a-f II a-*l* III a,b IV a,b

III a R=R'=CH_3; b R=CH_3, R'=$COOC_2H_5$; IV a R=CN; b R=$CSNH_2$

Attempts to use triethylamine or sodium carbonate, which was successfully used for the preparation of pyridine ring-unsubstituted 3-aminothieno[2,3-b]pyridines [4], in place of sodium ethoxide for the preparation of IIa were unsuccessful: cyclization either did not take place at all or a difficult-to-separate mixture of substances was obtained.

We were able to carry out the condensation with ethyl thioglycolate only when there was a nitro group in the 5 position of the pyridine ring, and the corresponding 5-nitro-thieno[2,3-b]pyridine (IIc) was obtained in high yield: the electron-acceptor nitro group considerably increases the lability of the chlorine atom.

When there is a carbethoxy group in the 4 or 6 position of the 2-chloro-3-cyanopyridine (Ic-e), the reaction with thioglycolic acid derivatives is accompanied by pronounced resinification, and carbethoxythienopyridines are obtained in low yields.

Two compounds, viz., 2,4-dicarbethoxy-6-methylthieno[2,3-b]pyridine (IIe) and the corresponding monocarboxylic acid (IIh), were isolated in the case of treatment of the product of the reaction of 2-chloro-3-cyano-4-carbethoxy-6-methylpyridine (Ic) with ethyl thioglycolate. We were unable to precisely prove the position of the carboxy group in acid IIh; however, since it is known that the hydrolysis of an ester group in the thiophene ring should take place more readily than hydrolysis of an ester group in the pyridine ring, it may be assumed that IIh is 2-carboxy-3-carbethoxy-6-methylthieno[2,3-b]pyridine.

The reaction of 2-chloro-3-cyano-4-methyl-6-carbethoxypyridine (Ie) with ethyl thioglycolate is also accompanied by hydrolysis of one of the carbethoxy group and leads to the formation of 2-carboxy-3-amino-4-methyl-6-carbethoxythieno[2,3-b]pyridine (IIi); 2-ethoxy-3-cyano-4-methyl-6-carbethoxypyridine (IIIb) was isolated as a side product; the latter fact constitutes a confirmation of the fact that the pyridine ring remains unaffected in the reaction of the carbethoxy group.

The presence of a nitro group along with a carbethoxy group in the pyridine ring also facilitates the formation of a two-ring structure in this case: the condensation of If with ethyl thioglycolate takes place even in the presence of sodium carbonate and leads to the formation of IIj in high yield.

Attempts to convert an ester group in the thiophene ring to an amide group by the action of ammonium hydroxide on IIa,b were unsuccessful: the starting esters were recovered unchanged. We were able to obtain amide IIf by reaction of 2-chloro-3-cyano-4,6-dimethylpyridine (Ia) with thioglycolic acid amide, which was synthesized by the method in [10]. Nitrile IVa, the synthesis of which was recently accomplished by another method [3], was obtained by heating amide IIf with phosphorus oxychloride. Thioamide IVb was obtained by prolonged passage of hydrogen sulfide into a hot alcohol solution of IVa in the presence of triethylamine.

Two absorption bands at 3400-3500 and 3200-3300 cm^{-1}, which are characteristic for an unsubstituted amino group, and absorption bands corresponding to substituents in the 2 position are observed in the IR spectra of IIa-*l* and IVa, b.

The presence of three maxima at 220-240, 280-290, and 330-390 nm is characteristic for the UV spectra of the indicated compounds.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra of solutions of the compounds in dimethyl sulfoxide—carbon tetrachloride were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The individuality of the compounds obtained was confirmed by chromatography on Silufol UV-254 plates, the plates were developed in UV light.

2-Carbethoxy-3-amino-4,6-dimethylthieno[2,3-b]pyridine (IIa). A 22.3-ml [24.43 g (0.204 mole)] sample of ethyl thioglycolate [9] and 34 g (0.204 mole) of 2-chloro-3-cyano-4,6-dimethylpyridine (Ia) [5] were added to a solution of sodium ethoxide, prepared from 4.7 g (0.204 g-atom) of sodium metal and 468 ml of absolute alcohol, and the mixture was refluxed for 6 h. It was then cooled, and the precipitate was removed by filtration, triturated with 50 ml of water, and removed by filtration to give 44.48 g of IIa as a light-yellow crystalline substance (see Table 2). IR spectrum: 3440, 3330 (NH_2); 1680 cm^{-1} (CO). UV spectrum, λ_{max}(log ε): 240 (4.10), 283 (4.56), and 360 nm (3.71). PMR spectrum: 1.34 ($COOCH_2CH_3$, t), 2.50, 2.80 (4-CH_3, 6-CH_3, s), 4.27 ($COOCH_2CH_3$, q), 6.70 (3-NH_2, broad s), and 6.91 ppm (5-H, broad s).

A similar method was used to obtain 3-aminothieno[2,3-b]pyridines IIb,d,f (Table 2). The condensation of Ib and If with the corresponding thioglycolic acid derivatives was carried out in the presence of sodium carbonate (Table 2, IIc, j-l).

The alcohol mother liquor after separation of the crude IIa was evaporated to dryness, and the residue was triturated with water and removed by filtration. The precipitate was dried and treated with ethyl acetate, and the insoluble material was separated. The filtrate was evaporated to dryness, and the residue was crystallized several times from hexane to give 1.17 g of IIIa in the form of colorless crystals with mp 81-82°C. IR spectrum: 2220 cm^{-1} (CN). Found: C 68.3; H 6.8; N 16.1%. $C_{10}H_{12}N_2O$. Calculated: C 68.2; H 6.9; N 15.9%.

Reaction of Ic with Ethyl Thioglycolate. A 2.25-g (0.01 mole) sample of Ic [7] and 1.1 ml [1.2 g (0.01 mole)] of ethyl thioglycolate were added to a solution of sodium ethoxide prepared from 0.3 g (0.013 g-atom) of sodium metal and 23 ml of absolute alcohol, and the mixture was refluxed for 5 h. It was then cooled, and the precipitate was removed by filtration and washed with alcohol and water to give 0.6 g of IIe in the form of orange crystals. IR spectrum: 3440, 3320 (NH); 1720, 1680 cm^{-1} (CO).

Compound IIg was similarly obtained (See Table 2).

The alcohol mother liquor from IIe was evaporated in vacuo to dryness, and the residue was triturated with water. The solid material was removed by filtration, and the filtrate was cooled and acidified with glacial acetic acid until precipitation ceased. The precipitate was removed by filtration and washed with cold water to give 0.97 g of IIh in the form of light-yellow crystals that were soluble in aqueous bicarbonate. IR spectrum: 3460, 3350 (NH); 1670, 1605 cm^{-1} (CO). UV spectrum, λ_{max}(log ε): 235 (3.96), 294 (4.32), and 390 nm (3.47).

Reaction of Ie with Ethyl Thioglycolate. A 2.25-g (0.01 mole) sample of Ie [7] and 1.1 ml [1.2 g (0.01 mole)] of ethyl thioglycolate were added to a solution of sodium ethoxide obtained from 0.3 g (0.013 g-atom) of sodium metal and 23 ml of absolute alcohol, and the mixture was refluxed for 9 h. It was then cooled, and the precipitate was removed by filtration, washed with alcohol, dried, and refluxed with hexane. The solid material was removed by filtration.

Cooling of the hexane extracts yielded 0.49 g (21%) of IIIb with mp 103-105°C (hexane). IR spectrum: 2230 (CN), 1740 (CO), and 1240 cm^{-1} (C—O—). Found: C 61.8, H 6.2% $C_{12}H_{14}N_2O_3$. Calculated: C 61.5%; H 6.0%. The hexane-insoluble material was dissolved in 30 ml of hot water, the solution was filtered, and the filtrate was acidified with glacial acetic acid to give 0.49 g (17.5%) of IIi in the form of light-yellow crystals. IR spectrum: 3510, 3340 (NH), 1755, 1680 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 250 (3.97), 287 (4.37), and 387 nm (3.66).

3-Amino-2-cyano-4,6-dimethylthieno[2,3-b]pyridine (IVa). A mixture of 1.1 g (4.98 mmole) of IIf and 10 ml of phosphorus oxychloride was refluxed for 6.5 h, after which it was cooled and poured over ice. The resulting dark-brown solution was treated with charcoal and made alkaline with 20% sodium hydroxide solution, and the precipitate was removed by filtration and washed with water to give 0.49 g (48.5%) of a light-yellow crystalline substance with mp 215-218°C (methanol). IR spectrum: 3450, 3300 (NH); 2180 cm^{-1} (CN). UV spectrum, λ_{max} (log ε): 232 (4.01), 274 (4.38), and 342 nm (3.71). Found: C 59.0; H 4.4; N 20.5%. $C_{10}H_9N_3S$. Calculated: C 59.1; H 4.5; N 20.7%.

3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylic Acid Thioamide (IVb). A stream of dry hydrogen sulfide was passed into a refluxing suspension of 0.34 g (1.67 mmole) of IVa in a mixture of 20 ml of absolute alcohol and 2 ml of triethylamine until the spot of starting IVa on the thin-layer chromatogram disappeared (6 h). The solid material gradually dissolved. The mixture was cooled, and the resulting precipitate was removed by filtration to give 0.39 g (98%) of IVb with mp 212-215°C (alcohol). Found: C 50.7; H 4.7; N 17.6%. $C_{10}H_{11}N_3S_2$. Calculated: C 50.6; H 4.7; N 17.7%.

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RESEARCH ON THIENOPYRIDINES AND PYRIDOTHIENOPYRIMIDINES. 2.* SOME TRANSFORMATIONS OF 2-CARBETHOXY-3-AMINO-4,6-DIMETHYLTHIENO[2,3-b]PYRIDINE

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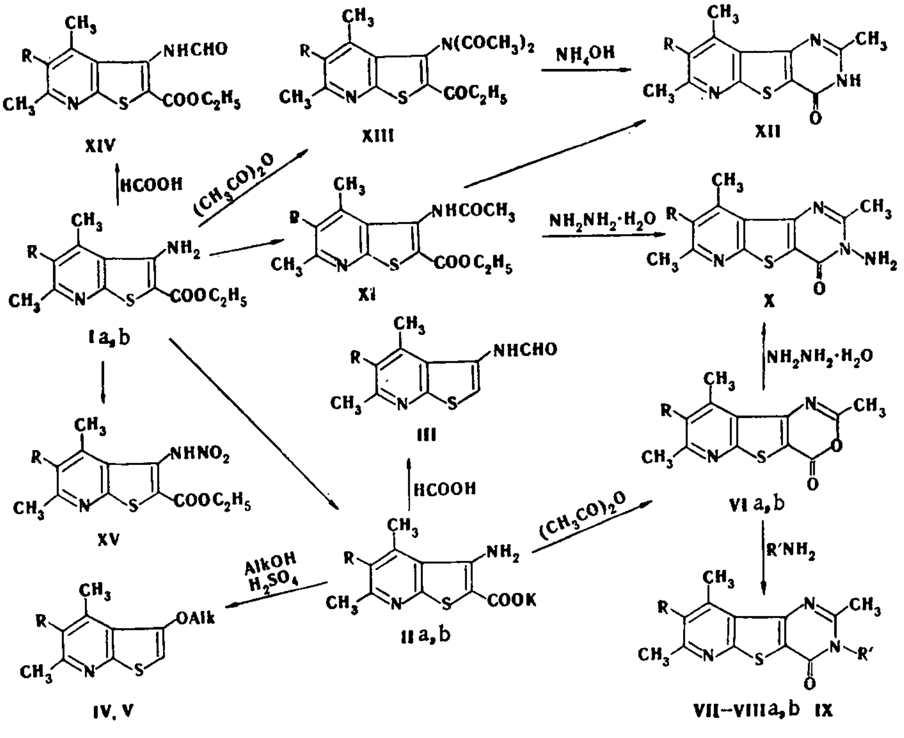
In our previous communication [1] we described the synthesis of a number of 3-aminothieno[2,3-b]pyridines from the corresponding substituted 2-chloro-3-cyanopyridines. The present paper is devoted to a study of the transformations of one of the representatives of these compounds, viz., 2-carbethoxy-3-amino-4,6-dimethylthieno[2,3-b]pyridine (Ia).

Brief heating of Ia in an alcohol solution of potassium hydroxide gives potassium 3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (IIa) [2], refluxing of which with formic acid leads to decarboxylation and the formation of the N-formyl derivative (III). As demonstrated in [2], when IIa is heated with methanol or butanol in the presence of aqueous



I—IIa, VIb R=H; b R=NO_2; III—V, X—XV R=H; IV Alk=CH_3; V Alk=C_4H_9; VIIa R=H; R'=$(CH_2)_3N(CH_3)_2$; VIIb R=NO_2; R'=$(CH_2)_3N(CH_3)_2$; VIIIa R=H; R'=$(CH_2)_2N(C_2H_5)_2$; VIIIb R=NO_2; R'=$(CH_2)_2N(C_2H_5)_2$; IX R=H; R'=C_6H_5

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*See [1] for communication 1.

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