mp 260-261°C. UV spectrum, λ_{max} (log ε): 495 nm (3.69). IR spectrum: 3415, 3295, 1640, and 1620 cm^{-1} (NH_2, C=O). Found, %: N 10.6. $C_{24}H_{21}N_3O_2$. Calculated, %: N 11.0.

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SYNTHESIS OF 3-AMINO-6-METHYL-5-ETHOXYCARBONYL-4,7-DIHYDROTHIENO[2,3-b]PYRIDINE DERIVATIVES

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07:543.422

The alkylation of piperidinium salts of substituted 1,4-dihydropyridine-2-thiols with chloroacetonitrile or iodoacetamide gave 2-cyanomethylthio- and 2-carbamoylmethylthio-substituted 6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridines, which undergo intramolecular cyclization in basic media to give 3-amino-6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-2-cyano(carbamoyl)-4,7-dihydrothieno[2,3-b]pyridines.

3-Aminothieno[2,3-b]pyridines are of theoretical interest, since their molecules simultaneously contain π-surplus thiophene and π-deficient pyridine rings [1]. These compounds have recently become widely used as synthones for the synthesis of complex condensed heterocyclic systems [2-6] and as biologically active compounds [7].

For the first time we have shown that 3-cyano-3,4-dihydropyridine-2(1H)-thiones are readily alkylated by alkyl halides to give 2-alkylthio-3-cyano-1,4-dihydropyridines [8]. 2-Alkylthio-3-cyano-1,4-dihydropyridines that contain an active methylene group in the 2-alkylthio substituent readily form a thiene ring in basic media to give 3-amino-4,7-dihydrothieno[2,3-b]pyridines — a new class of partially hydrogenated nitrogen- and sulfur-containing heterocycles [9, 10].

The goal of the present research was to synthesize 3-amino-6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-2-cyano(carbamoyl)-4,7-dihydrothieno[2,3-b]pyridines and to investigate their properties.

2-Cyanomethylthio- and 2-carbamoylmethylthio-substituted 6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridines II are obtained in high yields by brief heating of piperidine salts of substituted 1,4-dihydropyridine-2-thiols I [11] in absolute ethanol with chloroactonitrile or iodoacetamide.

It is more convenient to obtain 2-carbamoylmethylthio derivatives II without isolation of piperidinium salts I, i.e., it is more convenient to carry out the reaction of benzyli-

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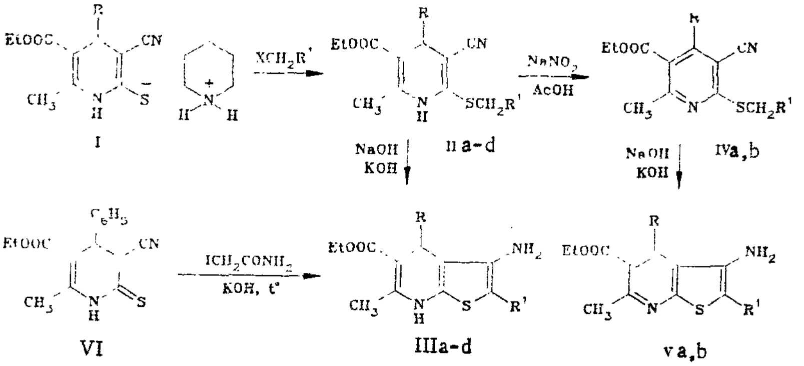
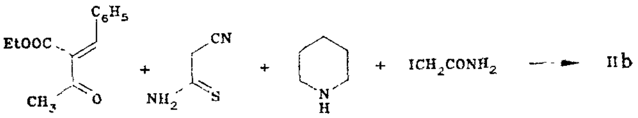


I-V *a*, b R = C_6H_5, c R = m-$NO_2C_6H_5$, d R = 4-pyridyl; *a* R^1 = CN, b-d R^1 = $CONH_2$; X = Cl, I

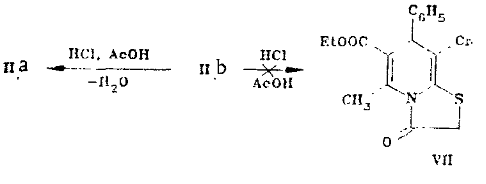
dene-acetoacetic ester, cyanothioacetamide, piperidine, and iodoacetamide in a single flask. In the first case the overall yield of dihydropyridine IIb based on the starting cyanothioacetamide is 63%, as compared with 75% in the second case.



Under the influence of bases (NaOH, KOH) with brief heating, 2-cyanomethylthio- and 2-carbamoylmethylthio-substituted 3-cyano-1,4-dihydropyridines II undergo cyclization to 3-amino-6-methyl-4-aryl(pyridyl)-5-ethoxycarbonyl-2-cyano(carbamoyl)-4,7-dihydrothieno 2,3-b]-pyridines III in high yields. These compounds can also be obtained directly from substituted 3-cyano-3,4-dihydropyridine-2(1H)-thiones VI by alkylation by heating in excess amounts of strong bases [9, 12]. Let us note that 2-ethylthio-3-cyano-1,4-dihydropyridine does not undergo cyclization under these conditions [8].

Attempts to form a thiazole ring and obtain hydrogenated thiazole[1,2-b]pyridine VII by the action of hydrochloric acid in acetic acid on 2-carbamoylmethylthio-1,4-dihydropyridine II did not give positive results; IIb undergoes dehydration to give 2-cyanomethylthio-1,4-dihydropyridine IIa (Table 1).

2-Alkylthio-3-cyano-1,4-dihydropyridines II were oxidized with sodium nitrite in acetic acid to the corresponding 2-cyanomethylthio- and 2-carbamoylmethylthio-substituted 3-cyanopyridines IV. The previously undescribed 3-amino-6-methyl-4-phenyl-5-ethoxycarbonyl-2-cyano(carbamoyl)thieno[2,3-b]pyridines V (Va, b, respectively) were obtained by cyclization of IV under the influence of NaOH.



The structures of II-V were proved by spectroscopy. Two absorption bands of stretching vibrations of a cyano group (ν_{CN}) are observed in the IR spectrum of 2-cyanomethylthio-3-cyano-1,4-dihydropyridine IIa: a band of a conjugated cyano group in the 3 position of the dihydropyridine ring at 2202 cm^{-1} and a band of an unconjugated cyano group of a 2-cyanomethylthio substituent at 2254 cm^{-1}. The IR spectra of 2-carbamoylmethylthio-3-cyano-1,4-dihydropyridines IIb-d contain characteristic ν_{CN} and amide ν_{CO} absorption bands at 2192-2195 cm^{-1} and 1671-1676 cm^{-1}, respectively. In the case of the corresponding oxidized products IV the absorption bands of a conjugated cyano group are shifted to the higher-frequency side to 2218-2223 cm^{-1}.

The characterisitc long-wave absorption of a 1,4-dihydropyridine system at 358 nm is observed in the UV spectra of II.

TABLE 1. Characteristics of the Synthesized II-IV

Compound	mp, °C	R_f	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
IIa	152—154	0,46	63,4	4,9	12,7	9,1	$C_{18}H_{17}N_3O_2S$	63,7	5,0	12,4	9,4	76
IIb	194—196	0.26	60,7	5,5	12,2	8,8	$C_{18}H_{19}N_3O_3S$	60,5	5,4	11,8	9,0	91
IIc	184—186	0,24	52,8	4,6	13,5	7,4	$C_{18}H_{18}N_4O_5S$	53,7	4,5	13,9	8,0	84
IId	196—198	0,12	56,5	5,0	15,2	8,8	$C_{17}H_{18}N_4O_3S$	57,0	5,1	15,6	8,9	78
IIIa	201—203	0,60	63,1	5,0	12,6	9,6	$C_{18}H_{17}N_3O_2S$	63,7	5,0	12,4	9,4	85
IIIb	216—218	0,18	59,8	5,2	11,8	8,6	$C_{18}H_{19}N_3O_3S$	60,5	5,4	11,8	9,0	80
IIIc	222—224	0,16	53,2	4,7	13,5	7,6	$C_{18}H_{18}N_4O_5S$	53,7	4,5	13,9	8,0	84
IIId	218—220	0,10	57,4	5,0	15,3	9,2	$C_{17}H_{18}N_4O_3S$	57,0	5,1	15,6	8,9	72
IVa	108—110	0,74	63,5	4,6	12,8	9,3	$C_{18}H_{15}N_3O_2S$	64,1	4,5	12,5	9,5	70
IVb	156—158	0,27	61,7	4,8	11,5	9,7	$C_{18}H_{17}N_3O_3S$	60.8	4,8	11,8	9,0	82
Va	146—148	0,76	65,1	4,6	12,5	9,7	$C_{18}H_{15}N_3O_2S$	64,1	4,5	12,5	9,5	65
Vb	217—219	0,29	60,5	4,7	11,7	8,9	$C_{18}H_{17}N_3O_3S$	60.8	4,8	11,8	9,0	66

TABLE 2. IR and UV Spectra of II-V

Compound	IR spectrum,* ν, cm^{-1}			UV spectrum, λ_{max}, nm
	C=O	C≡N	NH or NH_2	
IIa	1690	2202, 2254	3315	228, 260 sh., 358
IIb	1676, 1700	2195	3160, 3328	236, 286 sh., 358
IIc	1671, 1686	2192	3140, 3208, 3318, 3342, 3430	230, 270, 358
IId	1677, 1702	2195	3120, 3345, 3420	230, 264, 360
IIIa	1660	2180	3225, 3335, 3330	235, 370
IIIb	1635, 1650	—	3180, 3225, 3290, 3470	242 sh., 288, 373
IIIc	1642, 1672	—	3150, 3328, 3360, 3458	222, 252, 282 sh., 368
IIId	1624, 1658	—	3140, 3310, 3380, 3440	221 sh., 252, 297, 376
IVa	1733	2223, 2258	—	218, 266, 312
IVb	1690, 1723	2218	3175, 3220 sh., 3306	222 sh, 273, 318 sh.
Va	1731	2194	3222, 3338, 3428	235, 283, 360
Vb	1662, 1714	—	3173, 3275, 3332, 3414, 3460	234 sh., 290, 368

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*Suspensions in mineral oil.

In the PMR spectra of II the most characteristic signals are the signals from the 4-H protons in the form of a singlet and from the SCH_2 protons in the form of an AB quartet; this indicates nonequivalence of the CH_2 protons because of the presence of an asymmetric center in the molecule at the $C_{(4)}$ atom.

The absorption band of a conjugated cyano group that is characteristic for II vanishes in the IR spectra of 4,7-dihydrothieno[2,3-b]pyridines III. The ν_{CO} band is shifted 40-50 cm^{-1} to the lower-frequency side, and a number of new bands of stretching vibrations of the 3-amino group appear at 3150-3470 cm^{-1} (Table 2). The amide and ester ν_{CO} shift of III to 1624-1672 cm^{-1} is explained by the formation of specific intermolecular hydrogen bonds. In the IR spectrum of IIIb in dilute solution in dioxane, in which intermolecular hydrogen bonds are not formed, the amide and ester ν_{CO} values are 1650 and 1696 cm^{-1}, respectively. In the UV spectra of III the long-wave maximum is shifted bathochromically to 368-376 nm; this indicates an increase in the conjugation of the molecule. The signals of SCH_2 groups that are characteristic for II are absent in the PMR spectra of 4,7-dihydrothienopyridines III, but signals of 3-NH_2 groups appear. In addition to this, signals of 4-H protons, which, as compared with II, are shifted 0.47-0.52 ppm to the weak-field side, are retained in the spectra; this is explained by an increase in the conjugation of the molecule.

EXPERIMENTAL

The IR spectra of the compounds (in mineral oil and in dioxane) were recorded with a Perkin-Elmer 580 B spectrometer. The UV spectra of solutions of the compounds in ethanol were obtained with a Specord UV-Vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO were recorded with a WH-90/DC spectrometer (90 MHz) with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the individualities of the substances were monitored by means of TLC on Silufol UV-254 plates with chloroform—acetone—hexane (2:1:1) as the eluent.

TABLE 3. PMR Spectra of II-V (in d_6-DMSO)

Compound*	Chemical shifts of the protons, δ, ppm (multiplicity)							
	NH (br.s)	$CONH_2$ (br.s)	NH_2 (br.s)	H_R	CH_2 (d and d)	4-H (s)	6-CH_3 (s)	CH CH_2 (t and q)
IIa	9,62	—	—	7,3—7,1	4,19 and 4,12	4,52	2,27	3,91 and 1,00
IIb	10,40	7,88 and 7,58	—	7,3—7,1	3,68 and 3,55	4,47	2,24	3,91 and 1,00
IIc	10,42	7,87 and 7,56	—	8,1—7,1	3,75 and 3,64	4,70	2,31	3,95 and 1,09
IId	10,44	7,87 and 7,56	—	8,46 and 7,12	3,71 and 3,60	4,48	2,27	3,81 and 1,00
IIIa	9,82	—	6,07	7,3—7,0	—	5,00	2,23	3,91 and 1,08
IIIb	9,70	6,47	6,27	7,3—7,1	—	4,94	2,27	3,91 and 1,07
IIIc	9,89	6,52	6,40	8,2—7,4	—	5,22	2,31	3,97 and 1,16
IIId	9,87	6,56	6,40	8,40 and 7,28	—	5,07	2,31	3,99 and 1,13
IVa	—	—	—	7,6—7,4	4,45	—	2,66	4,02 and 0,87
IVb	—	7,68 and 7,24	—	7,6—7,3	4,04	—	2,60	3,99 and 0,85
Va	—	—	5,46	7,7—7,4	—	—	2,62	3,98 and 0,86
Vb	—	7,57 and 7,24	5,64	7,6—7,3	—	—	2,60	3,96 and 0,86

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*Spin-spin coupling constants (SSCC), $^2J_{SCH_2}$: 16.8 (IIa), 14.4 (IIb, c), and 14.2 Hz (IId).

The principal characteristics of the synthesized substances are given in Tables 1-3.

2-Cyanomethylthio-6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridine (IIa). A) A mixture of 3.85 g (10 mmole) of piperidinium salt Ia of 6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridine-2(1H)-thiol [11] and 1.0 ml (15 mmole) of chloroacetonitrile in 10 ml of absolute ethanol was stirred at 30-40°C for 10 min, after which it was filtered. The filtrate was cooled to 0°C, and the precipitate was removed by filtration and washed with cold ethanol and water to give 2.60 g (76%) of IIa with mp 152-154°C (from ethanol).

B) A mixture of 1.07 g (3 mmole) of 2-carbamoylmethylthio-6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridine (IIb) and 0.5 ml of concentrated HCl in 10 ml of acetic acid was heated on a water bath for 10 min, after which it was cooled to 0°C, and the precipitate was removed by filtration and washed with ethanol to give 0.88 g (86%) of IIa.

2-Carbamoylemethylthio-6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridine (IIb). A) A mixture of 3.85 g (10 mmole) of piperidinium salt Ia of 6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridine-2-thiol and 1.8 g (11 mmole) of iodoacetamide in 20 ml of absolute ethanol was stirred at 30-40°C for 10 min, after which it was cooled to 0°C, and the precipitate was removed by filtration and washed with ethanol and water to give 3.25 g (91%) of IIb with mp 194-196°C (from ethanol).

Compounds IIc, d. These compounds were similarly obtained.

B) A mixture of 4.16 g (20 mmole) of benzylideneacetoacetic ester, 2.0 g (20 mmole) of cyanothioacetamide, 40 ml of absolute ethanol, and 2 ml of piperidine was stirred at room temperature for 5 min, after which 3.6 g (21 mmole) of iodoacetamide was added, and the mixture was stirred at 40-50°C for 15 min. It was then cooled to 0°C, and the precipitate was removed by filtration and washed with cold ethanol to give 5.22 g (73%) of IIb.

3-Amino-6-methyl-4-phenyl-5-ethoxycarbonyl-2-cyano-4,7-dihydrothieno[2,3-b]pyridine (IIIa). A 0.5 ml sample of 3 N NaOH solution was added to a mixture of 1.02 g (3 mmole) of 1,4-dihydropyridine IIa in 20 ml of ethanol, after which the mixture was heated to 50-60°C for 5 min and filtered. The filtrate was cooled to 0°C, and the precipitate was removed by filtration and washed with ethanol. After 5 h, an additional amount of product, which was washed with cold ethanol, was removed from the filtrate by filtration to give a total of 0.85 g (85%) of IIIa with mp 201-203°C (from ethanol).

Compounds IIIb-d. These compounds were similarly obtained.

3-Amino-6-methyl-4-phenyl-5-ethoxycarbonyl-2-carbamoyl-4,7-dihydrothieno[2,3-b]pyridine (IIIb). A mixture of 1.2 g (4 mmole) of 6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2(1H)-thione (V) and 0.7 g (4.1 mmole) of iodoacetamide in 20 ml of ethanol and 3 ml of 2 N KOH solution was refluxed on a water bath for 5 min, after which it was filtered. The filtrate was cooled, and the precipitate was removed by filtration and washed with ethanol and water to give 1.12 g (78%) of IIIb.

2-Cyanomethylthio-6-methyl-4-phenyl-5-ethoxycarbonyl-3-cyanopyridine (IVa). A mixture of 1.0 g (3 mmole) of 1,4-dihydropyridine IIa in 10 ml of glacial acetic acid was heated to 50-60°C, and 1.0 g (15 mmole) of sodium nitrite was added. The reaction mixture was cooled and poured into 20 ml of water, and the precipitate was removed by filtration to give 0.7 g (70%) of IVa with mp 108-110°C (from ethanol).

Compound IVb. This compound was similarly obtained.

3-Amino-6-methyl-4-phenyl-5-ethoxycarbonyl-2-cyanothieno[2,3-b]pyridine (Va). Two drops of 3N NaOH solution were added to a mixture of 0.34 g (1 mmole) of cyanopyridine IVa in 6 ml of ethanol, and the mixture was heated on a water bath for 5 min. It was then cooled, and the precipitate was removed by filtration to give 0.22 g (65%) of Va with mp 146-148°C (from ethanol).

Compound Vb. This compound was similarly obtained.

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