Regioselective synthesis of 5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones and fused heterocycles based on them

L. A. Rodinovskaya, E. V. Belukhina, A. M. Shestopalov, and V. P. Litvinov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

Condensation of 2-hydroxymethylenecyclopentan-1-one or -cyclooctan-1-one sodium salts with cyanothioacetamide afforded 5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones which were regioselectively alkylated at the sulfur atom by alkyl halides. Derivatives of 3-cyanopyridine-2(1*H*)-thione and 2-alkylthio-3-cyanopyridine were used for regioselective synthesis of substituted heterocycles: 3-aminothieno[2,3-*b*]pyridines, pyrido[2,3:2′,3′]thieno[4,5-*d*]pyrimidines, and pyrido[2,3:2′,3′]thieno[4,5-*d*]oxazines.

Key words: fused heterocycles; 5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones; 2-alkylthio-3-cyanopyridines; 3-aminothieno[2,3-*b*]pyridines; pyrido[2,3:2',3']thieno[4,5-*d*]pyridines; pyrido[2,3:2',3']thieno[4,5-*d*]oxazines; regioselective synthesis.

3-Cyanopyridine-2(1*H*)-thiones containing vicinal nitrile and thione (thiol) functional groups are convenient reagents for the synthesis of annelated heterocycles that are difficult to prepare.[1,2] Among compounds of this type, substances with practically valuable properties have been found: cardiotonics, fungicides, antioxidants, and dyes.[1,2] Taking into account that 5,6-trimethylene(or hexamethylene)-3-cyanopyridine-2(1*H*)-thiones have not been described previously, we developed regioselective methods for their synthesis and then used these thiones for preparing fused heterocyclic compounds.

Pyridine-2(1*H*)-thiones were prepared by condensation of the corresponding sodium salts of 2-hydroxymethylenecycloalkan-1-ones (**1a,b**) with cyanothioacetamide (**2**). The highest yield of the products (**3a,b**) was achieved when the starting compounds **1** and **2** were boiled in ethanol in the presence of excess acetic acid for a short period (Scheme 1).

A comparison of the data of the physicochemical analysis of compounds **3a,b** with the results of the physicochemical and X-ray diffraction analyses of previously described 5,6-tetramethylene(or pentamethylene)-3-cyanopyridine-2(1*H*)-thiones and their derivatives[3,4] indicates that the condensation of compound **1** with **2** occurs regioselectively to give 5,6-polymethylenepyridines. Solid compounds **3** are yellow-orange powders stable during storage. On prolonged storage (1—2 days) in ethanolic or DMSO solutions they are oxidized by atmospheric oxygen to afford disulfides (**4a,b**), which have been obtained preparatively by oxidation of pyridine-2(1*H*)-thiones **3** with iodine in ethanol in the presence of KOH.

Compounds **3**, like their numerous analogs substituted in the pyridine ring,[1,2] exist as the tautomeric thione forms. The UV spectra of compounds **3** exhibit a long-wavelength maximum at 408—417 nm typical of pyridine-2(1*H*)-thiones; this maximum is absent from the spectra of compounds **4**. IR spectra of **3** have a C=S band of medium intensity in the range 1224—1228 cm^{-1} characteristic of pyridine-2(1*H*)-thiones[1] and a number of absorption bands due to the NH and C≡N groups (see Experimental). The ^1H NMR spectra of compounds **3** contain, along with the signals for the methylene protons, a low-field broadened singlet at 13.97—14.00 ppm associated with the NH group. The signal for the C(4)H proton occurs at 7.97—8.00 ppm; the signal for the

Scheme 1

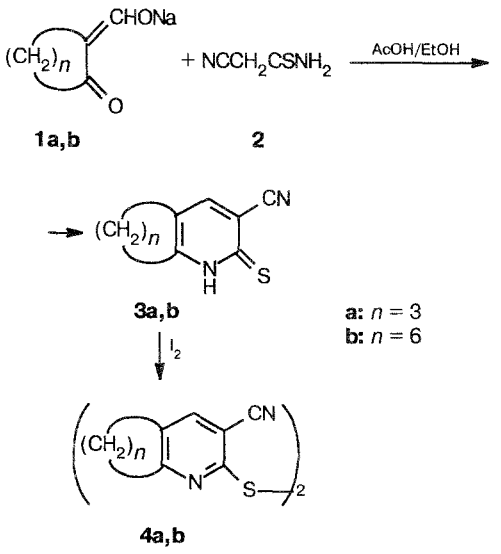

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Table 1. Characteristics of the compounds synthesized

Compound	M.p./°C	Yield* (%)	Found / Calculated (%) C	H	N	S	Molecular Formula
6a	158—160	88	61.0	4.1	19.7	15.2	$C_{11}H_9N_3S$
			61.4	4.2	19.5	14.9	
6b	141—143	81	69.2	4.9	9.5	10.7	$C_{17}H_{14}N_2OS$
			69.4	4.8	9.7	10.9	
6c	113—115	85	55.9	4.4	12.1	14.1	$C_{13}H_{14}N_2O_2S$
			56.4	4.2	12.0	13.7	
6d	213—215	90	60.0	5.1	10.9	11.8	$C_{11}H_{10}N_2O_2S$
			59.5	5.3	10.7	12.2	
6e	207—209	87	56.3	4.5	18.3	13.0	$C_{11}H_{11}N_3OS$
			56.7	4.7	18.0	13.7	
6f	45—47	32	66.5	5.7	13.5	14.3	$C_{12}H_{12}N_2S$
			66.7	5.6	13.0	14.7	
6g	108—109	99	65.3	5.1	16.6	13.0	$C_{14}H_{15}N_3S$
			65.4	5.8	16.6	12.5	
6h	121—122	95	70.9	6.1	8.6	9.8	$C_{20}H_{20}N_2OS$
			71.4	6.0	8.3	9.5	
6i	85—87	95	63.5	6.8	8.8	10.6	$C_{16}H_{20}N_2O_2S$
			63.2	6.6	9.2	10.5	
6j	189—191	93	60.5	5.4	10.6	11.7	$C_{14}H_{16}N_2O_2S$
			60.9	5.8	10.1	11.6	
6k	215—216	99	59.9	6.6	15.7	11.5	$C_{14}H_{17}N_3OS$
			61.1	6.2	15.3	11.6	
6l	122—124	87	67.0	6.9	12.6	13.5	$C_{13}H_{16}N_2S$
			67.2	6.9	12.1	13.8	
6m	67—69	83	67.9	7.8	11.2	13.1	$C_{14}H_{18}N_2S$
			68.3	7.3	11.4	13.0	
6n	79—81	97	71.1	7.1	10.2	12.6	$C_{15}H_{18}N_2S$
			69.8	7.0	10.8	12.4	
6o	57—59	30	72.1	9.2	8.6	10.1	$C_{20}H_{30}N_2S$
			72.7	9.1	8.5	9.7	
8a	> 300 (from dioxane)	95	59.9	4.3	19.6	15.2	$C_{11}H_9N_3S$
			61.4	4.2	19.5	14.9	
8b	223—225	94	69.5	4.4	9.0	11.3	$C_{17}H_{14}N_2OS$
			69.4	4.8	9.5	10.9	
8c	218—220	78	59.3	5.7	11.0	11.8	$C_{13}H_{14}N_2O_2S$
			59.5	5.3	10.7	12.2	
8d	230—232	95	56.3	4.7	12.6	13.4	$C_{11}H_{10}N_2O_2S$
			56.4	4.2	12.0	13.7	
8e	278—280	89	57.1	4.5	18.1	13.7	$C_{11}H_{11}N_3OS$
			56.7	4.7	18.0	13.7	
8f	194—195	83	65.9	5.6	16.6	11.9	$C_{14}H_{15}N_3S$
			65.4	5.8	16.3	12.5	
8g	205—206	99	71.1	6.5	8.8	9.3	$C_{20}H_{20}N_2OS$
			71.4	6.0	8.3	9.5	
8h	224—226	95	63.4	6.0	9.3	10.7	$C_{16}H_{20}N_2O_2S$
			63.2	6.6	9.2	10.5	
8i	240—242	95	60.5	6.0	10.2	12.2	$C_{14}H_{16}N_2O_2S$
			60.9	5.8	10.1	11.6	
8j	254—255	99	61.3	6.8	15.0	11.4	$C_{14}H_{17}N_3OS$
			61.1	6.2	15.3	11.6	

* The yields for compounds **8** prepared according to procedure ***a*** are presented.

C(6)H proton in the unsubstituted 3-cyanopyridine-2(1*H*)-thione is shifted downfield[5] by ~0.4 ppm with respect to the C(4)H signal (δ ~8.1 ppm). This confirms the regioselectivity of condensation of **1** with **2**. The ^{13}C NMR spectra also attest that compounds **3** are in the thione form: the signal for C(2) of the pyridine ring is recorded in the range 175.84—176.05 ppm, which is typical of pyridines containing an exocyclic C(2)=S fragment.

In the presence of an equimolar amount of aqueous KOH pyridine-2(1*H*)thiones **3** are regioselectively alkylated in DMF with alkyl halides or α-halocarbonyl

Table 2. ^{1}H NMR and IR absorption spectra for compounds **6a—o**

Compound	IR, ν/cm^{-1}		^{1}H NMR, δ
	CN	Z	
6a	2224	2248 (CN)	2.11 (m, 2 H, C(6)H$_2$); 2.91 (t, 2 H, C(5)H$_2$); 3.03 (t, 2 H, C(7)H$_2$); 8.12 (s, H, C(4)H); 4.35 (s, 2 H, CH$_2$);
6b	2220	1680 (CO)	1.97 (m, 2 H, C(6)H$_2$); 2.68 (t, 2 H, C(5)H$_2$); 2.82 (t, 2 H, C(7)H$_2$); 4.86 (s, 2 H, CH$_2$); 8.03[a] (s, H, C(4)H); 7.55—8.04[a] (m, 5 H, Ph)
6c	2222	1736 (CO)	2.06 (m, 2 H, C(6)H$_2$); 2.90 (t, 4 H, C(5)H$_2$, C(7)H$_2$); 4.08[a] (s, 2 H, CH$_2$); 8.03 (s, H, C(4)H); 1.19 (t, 3 H, CH$_3$); 4.11[a] (q, 2 H, C<u>H</u>$_2$CH$_3$)
6d	2224	1706 (CO)	2.06 (m, 2 H, C(6)H$_2$); 2.70 (t, 2 H, C(5)H$_2$); 2.89 (t, 2 H, C(7)H$_2$); 4.06 (s, 2 H, CH$_2$); 7.95 (s, H, C(4)H)
6e	2222	3376, 3168 (ν NH$_2$); 1634 (CO); 1613 (δ NH$_2$)	2.07 (m, 2 H, C(6)H$_2$); 2.88 (t, 2 H, C(5)H$_2$); 2.97 (t, 2 H, C(7)H$_2$); 3.95 (s, 2 H, CH$_2$); 8.02 (s, H, C(4)H); 7.16 (H); 7.60 (H)
6f	2222	—	2.07 (m, 2 H, C(6)H$_2$); 2.86 (t, 2 H, C(5)H$_2$); 2.96 (t, 2 H, C(7)H$_2$); 3.91 (d, 2 H, CH$_2$); 7.98 (s, H, C(4)H); 5.11 (q, H, C<u>H</u>$_2$=CH, *cis*); 5.30 (q, H, C<u>H</u>$_2$=CH, *trans*); 5.92 (m, H, C<u>H</u>=CH$_2$)
6g	2226	2238 (CN)	1.30 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.64, 1.75 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.78, 2.99 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 4.34 (s, CH$_2$); 8.08 (s, H, C(4)H)
6h	2220	1696 (CO)	1.21 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.35, 1.56 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.53, 2.65 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 4.81 (s, 2 H, CH$_2$); 7.95 (s, H, C(4)H); 7.55—8.08 (m, 5 H, Ph)
6i	2222	1732 (CO)	1.29 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.65 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.73, 2.87 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 4.08 (s, 2 H, CH$_2$); 7.99 (s, H, C(4)H); 1.18 (t, 3 H, CH$_3$); 4.09 (q, 2 H, C<u>H</u>$_2$CH$_3$)
6j	2237	1591 (CO)	1.37 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.64 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.60, 2.87 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 3.4 (s, 2 H, CH$_2$); 8.00 (s, H, C(4)H)
6k	2220	3376, 3325, 3200 (ν NH$_2$); 1662 (CO); 1628 (δ NH$_2$)	1.30 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.60, 1.69 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.73, 2.92 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 3.93 (s, 2 H, CH$_2$); 7.96 (s, H, C(4)H); 7.14 (H); 7.60 (H)
6l	2220	—	1.30 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.61, 1.68 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.72, 2.91 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 2.57 (s, 3 H, CH$_3$); 7.94 (s, H, C(4)H)
6m	2220	—	1.31[a] (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.62, 1.70 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.73, 2.91 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 3.22 (q, 2 H, CH$_2$); 7.95 (s, H, C(4)H); 1.31[a] (t, 3 H, CH$_3$)
6n	2222	1580 (C=C)	1.30 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.62, 1.70 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.74, 2.94 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 3.93 (d, 2 H, CH$_2$); 7.96 (s, H, C(4)H); 5.10 (q, H, C<u>H</u>$_2$=CH, *cis*); 5.29 (q, H, C<u>H</u>$_2$=CH, *trans*); 5.90 (m, H, C<u>H</u>=CH$_2$)
6o	2222	2852, 2920 (CH$_2$)	1.28 (m, 4 H, C(7)H$_2$, C(8)H$_2$); 1.62 (m, 4 H, C(6)H$_2$, C(9)H$_2$); 2.72, 2.91 (m, 4 H, C(5)H$_2$, C(10)H$_2$); 3.21 (s, 2 H, CH$_2$); 8.13 (s, H, C(4)H); 1.28—1.62 (m, 12 H, (CH$_2$)$_6$); 0.84 (3 H, CH$_3$)

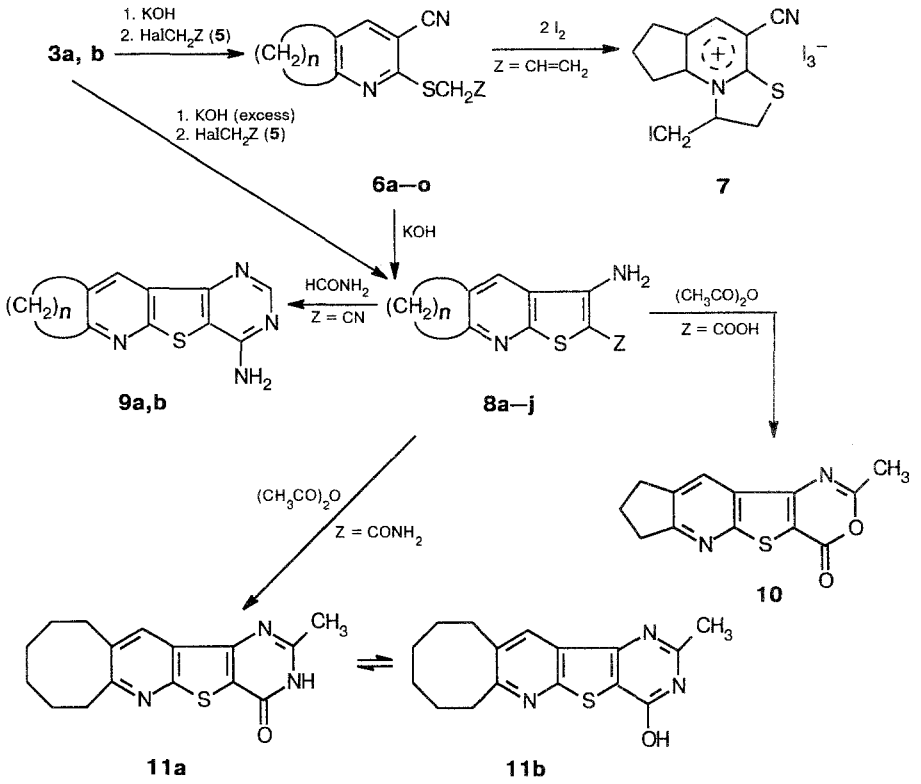
[a] The ^{1}H NMR signals overlap.

compounds (**5**) at the sulfur atom to afford *S*-substituted 3-cyanopyridines (**6a—o**). It should be noted that in the case of 5,6-hexamethylenepyridine-2(1*H*)-thione **3b** the yields of *S*-alkylated pyridine derivatives are higher than those of the derivatives of 5,6-trimethylenepyridine-2(1*H*)-thione **3a** by more than 10 % (Table 1). The structure of pyridines **6** was confirmed by the data of physicochemical analysis (Tables 1—3). The IR spectra of these compounds exhibit an absorption band in the range 2220—2226 cm^{-1} due to the conjugated C≡N group as well as absorption bands of groups Z (CONH$_2$, COOH, COC$_6$H$_5$, CN, COOC$_2$H$_5$). A characteristic

Table 3. ^{13}C NMR spectra for compounds **6a—o**

Compound	^{13}C NMR, δ						
	SCH_2 (t)	CN (s)	C(2) (s)	C(3) (s)	C(4) (d)	Z	The other signals
6a	15.47	115.80	156.06	103.54	137.27	117.67	22.37 (t); 29.36 (t); 34.30 (t); 134.47 (s); 170.62 (s)
6b	37.20	116.3	158.7	102.92	136.84	172.75, 128.20, 128.72, 133.37, 136.28	22.25 (t); 29.21 (t); 33.92 (t); 169.86 (s); 133.13 (s)
6c	32.08	116.12	158.35	102.95	136.85	14.03, 61.02, 170.06	22.29 (t); 29.29 (t); 34.18 (t); 133.30 (s); 168.5 (s)
6d	33.32	115.84	133.12	108.32	126.52	167.93	23.21 (t); 29.62 (t); 33.58 (t); 124.94 (t); 166.27 (s)
6e	33.59	116.28	158.96	103.08	136.78	170.00	22.35 (t); 29.25 (t); 34.23 (t); 133.05 (s); 168.82 (s)
6f	34.21	116.22	158.75	103.47	136.74	118.24, 133.24	22.26 (t); 29.28 (t); 32.17 (t); 132.97 (s); 170.0 (s)
6g	15.51	115.30	154.27	103.87	141.74	117.48	25.17 (t); 29.77 (t); 31.36 (t); 34.15 (t); 133.42 (s); 165.59 (s)
6h	39.60	115.94	157.10	103.38	141.43	128.23, 128.70, 133.39, 138.40, 193.68	25.21 (t); 29.71 (t); 31.39 (t); 33.79 (t); 132.45 (s); 165.12 (s)
6i	32.18	115.80	156.6	103.5	141.52	14.02, 60.97, 168.56	24.92 (t); 25.22 (t); 29.46 (t); 29.64 (t); 30.71 (t); 34.21 (t); 132.50 (s); 165.16 (s)
6j	28.55	117.17	156.65	113.93	145.92	175.77	24.93 (t); 25.29 (t); 29.46 (t); 30.72 (t); 125.59 (s); 172.2 (s)
6k	33.55	115.89	157.26	103.51	141.38	169.00	25.25 (t); 29.71 (t); 29.90 (t); 31.39 (t); 34.14 (t); 132.24 (s); 165.11 (s)
6l	12.53	116.09	158.51	103.61	141.44	—	25.26 (t); 25.34 (t); 29.73 (t); 30.04 (t); 31.42 (t); 34.43 (t); 131.97 (s); 165.33 (s)
6m	23.93	116.02	157.92	104.04	141.47	14.41	25.25 (t); 29.77 (t); 30.03 (t); 31.40 (t); 34.34 (t); 132.01 (s); 165.25 (s)
6n	32.19	115.97	157.08	104.23	141.57	118.22, 133.59	25.26 (t); 29.76 (t); 29.99 (t); 31.40 (t); 34.35 (t); 132.41 (s); 165.24 (s)
6o	22.06	118.07	157.78	103.99	141.52	13.91, 28.45, 28.52, 28.80, 28.92, 31.19, 29.26	25.27 (t); 28.08 (t); 29.78 (t); 30.02 (t); 31.43 (t); 34.34 (t); 132.05 (s); 165.17 (s)

Scheme 2



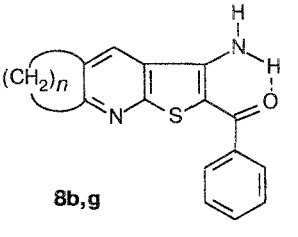
6: Z = CN (**a**, **g**); COC_6H_5 (**b**, **h**); $COOC_2H_5$ (**c**, **i**); COOH (**d**, **j**); $CONH_2$ (**e**, **k**); $CH{=}CH_2$ (**f**, **n**); H (**l**); CH_3 (**m**); n-C_7H_{15} (**o**); n = 3 (**a—f**); n = 6 (**g—o**)
8: Z = CN (**a**, **f**); COC_6H_5 (**b**, **g**); $COOC_2H_5$ (**c**, **h**); COOH (**d**, **i**); $CONH_2$ (**e**, **j**); n = 3 (**a—e**); n = 6 (**f—j**)
9: n = 3 (**a**); n = 6 (**b**)

feature of the ^1H NMR spectra of pyridines **6** is the presence of the singlet for the protons of the SCH_2Z group in the range δ 3.21—4.86. From the ^{13}C NMR spectra of pyridine-2(1*H*)-thiones **3**, disulfides **4**, and compounds **6** it follows that the most shielded atom in the pyridine ring is C(3) bonded with the electron-withdrawing C≡N group, because its signals are in the highest field (δ): 117.18—117.75 (**3**), 105.64—105.82 (**4**) 102.92—113.93 (**6**). The signals for the other carbon atoms of the pyridine ring are exhibited in lower field and their δ are substantially different, which implies that the electron density in the substituted pyridine ring is distributed nonuniformly.

We used compound **6** for the synthesis of difficultly accessible fused pyridines. 2-Allylthiopyridine **6f** reacts with two moles of iodine in chloroform to give the corresponding thiazolo[3,2-*a*]pyridinium triiodide (**7**). The reaction occurs regioselectively similarly to the previously studied transformations of 2-allyl(oxy, thio, or seleno)pyridines.[3,6]

3-Amino[2,3-*b*]pyridines (**8**) were prepared by the Thorpe—Ziegler reaction (Scheme 2). Substituted pyridines **6** undergo cyclization through the action of KOH in a DMF solution at 20 °C to afford 3-aminothieno[2,3-*b*]pyridines (**8**) in good yields (method ***a***). Compounds **8** were prepared in one step, without the preliminary synthesis of substituted pyridines **6**, by the reaction of pyridin-2(1*H*)-thiones **3** with α-halocarbonyl compounds **5** in the presence of excess KOH in DMF (method ***b***). The yields of compounds **8** obtained by methods ***a*** and ***b*** are comparable.

The structure of 3-aminothieno[2,3-*b*]pyridines **8** was confirmed by the data of physicochemical analysis (see Tables 1—3). The IR spectra of compounds **8** display a number of bending and stretching bands of the NH_2 group in the ranges 1590—1655 cm^{-1} and 3136—3490 cm^{-1}.



8b,g

In the IR spectra of substituted 3-amino-2-benzoylthieno[2,3-*b*]pyridines **8b,g** the absorption bands due to the NH_2 and C=O groups are substantially shifted to lower frequencies, compared with those in the spectra of other thieno[2,3-*b*]pyridines, and overlap each other, and the signals for the NH_2-group protons in the ^1H NMR spectra are shifted downfield by 1.17—1.35 ppm (see Table 3). This points to the existence of an N—H · · · O intramolecular hydrogen bond. Similar spectroscopic characteristics were observed for 3-amino-2-benzoyl-5,6-pentamethylenethieno(or selenopheno)[2,3-*b*]pyridines where the formation of the intramolecular hydrogen bond was confirmed[4] by X-ray diffraction analysis.

In the H_2N—C(3)=C(2)—Z moiety of thieno[2,3-*b*]pyridines **8**, electron conjugation occurs, which manifests itself in their spectroscopic characteristics. The chemical shifts of C(2) and C(3) in the ^{13}C NMR spectra of these compounds are in the range 70.4—102.54 and 145.55—150.72 ppm, respectively. The C(2) atoms bonded with the C≡N group are the most electron shielded: their signals are shifted diamagnetically by 30 ppm, compared with the other substituted thieno[2,3-*b*]pyridines **8** (Z = COOH, $CONH_2$, $COOC_2H_5$, $COOC_6H_5$). In general, the distribution of the electron density in the thieno[2,3-*b*]pyridine moiety is nonuniform, which is indicated by the great difference between the chemical shifts of the carbon atoms in the ^{13}C NMR spectra.

The presence of reactive donor-acceptor groups in the vicinal position with respect to the amino group in the molecules of compounds **8a,f,d,j** allowed us to use the latter in the synthesis of pyridothienopyrimidines and pyridothienooxazinones. Brief heating of 3-amino-2-cyanothieno[2,3-*b*]pyridines **8a,f** affords 4-aminopyrido[2,3:2′,3′]thieno[4,5-*d*]pyridines (**9a,b**) in nearly quantitative yields. The IR spectra of these compounds exhibit a number of absorption bands in the 1648—1668 cm^{-1} and 3080—3361 cm^{-1} regions typical of an amino group. The ^1H NMR spectra contain, along with the signals for the methylene protons, the following signals, δ (for **9a** and **9b**, respectively): singlets for the NH_2-group protons at 7.57 and 7.19, singlets for the C(4)H protons of the pyridine ring at 8.51 and 8.00, and for the C(2)H protons of the pyrimidine ring at 8.48 and 7.93.

Boiling 3-amino-2-carboxythieno[2,3-*b*]pyridine **8d** in acetic anhydride gave 2-methylpyrido[2,3:2′,3′]thieno[4,5-*d*]oxazine-4-one (**10**), however, its yield was only 38 %. The IR spectrum of this compound exhibits an absorption band at 1754 cm^{-1} (νCO). The ^1H NMR spectrum of compound **10** contains, along with the signals for the methylene protons, a singlet at 2.53 ppm corresponding to the CH_3 group.

2-Methylpyrido[2′,3′:2,3]thieno[4,5-*d*]pyrimidine-4-one (**11**) was prepared from the carbamoyl derivative **8j** and acetic anhydride in a similar way.

The IR spectra of compound **11** exhibit absorption bands typical of an amino group (1670 and 3268 cm^{-1}) and a CO group (1720 cm^{-1}). Based on the ^1H NMR spectra, one may infer that compound **11** in a DMSO solution exists as two tautomers, **11a** and **11b**, in a ratio of approximately 2:1. This is indicated by two singlets for the protons of the CH_3 group (δ 2.46 and 2.50), two singlets for C(4)H of the pyridine ring (δ 8.28 and 8.05 for tautomers **11a** and **11b**, respectively), and the singlets for the protons of the OH and NH_2 groups (δ 10.62 and 12.76).

Experimental

The IR spectra were recorded on UR-20 and Perkin Elmer-457 spectrophotometers (pellets with KBr), the ^1H NMR spectra were obtained on a Bruker WM-250 spectrometer (250 MHz, solutions in DMSO-d_6, TMS as the internal standard), the ^{13}C NMR spectra were run on a Bruker AM-300 instrument, and UV spectra were recorded on a Specord M-40 instrument. Molecular weights were determined on a Varian MAT CH-6 mass spectrometer. The purity of the compounds obtained was checked by TLC on Silufol-254 plates in an acetone—heptane (3:5) system, chromatograms were vizualized by iodine vapors.

2-Hydroxymethylenecyclopentan-1-one sodium salt (1a). A mixture of cyclopentanone (8.9 mL, 0.1 mol) and ethyl formate (8 mL, 0.1 mol) in 100 mL of ether was added dropwise to finely cut metallic sodium (2.3 g, 0.1 mol) placed under 500 mL of ether, then 0.5 mL of ethanol was added as an initiator, and the mixture was stirred until sodium entirely disappeared. The precipitate was filtered off, washed with ether, and dried with a calcium-chloride tube to give 13.3 g (99 %) of **1a**.

2-Hydroxymethylenecyclooctan-1-one sodium salt (1b). 17.3 g (98 %) of salt **1b** was prepared from 12.6 g (0.1 mol) of cyclooctanone in a similar way as salt **1a**.

5,6-Trimethylene-3-cyanopyridine-2(1*H*)-thione (3a). Glacial AcOH (1.14 mL, 0.01 mol) was added to a solution of cyclopentanone **1a** (2.7 g, 0.02 mol) in 10 mL of ethanol, then cyanothioacetamide (1.15 g, 0.02 mol) was added with stirring. The mixture was heated to boiling, additional AcOH (0.57 mL, 0.01 mol) was added, the mixture was again heated to boiling, and kept for 3 h. The precipitate was filtered off, washed with ethanol and hexane, and recrystallized from AcOH to give 1.8 g (52 %) of **3a**, m.p. 229—231 °C (subl.). Found (%): C, 61.6; H, 4.7; N, 15.5; S, 18.2. $C_9H_8N_2S$. Calculated (%): C, 61.4; H, 4.5; N, 15.9; S, 18.2. IR (KBr), ν/cm^{-1}: 3440 (NH); 2226 (C≡N); 1610, 1576 (δ NH); 1162 (C=S); UV (EtOH), λ_{max}/nm: 213 (ε 11500); 246 (ε 5700); 313 (ε 18100); 417 (ε 5400); ^1H NMR (DMSO-d_6), δ: 2.04 (m, 2 H, C(6)H_2); 2.70 (t, 2 H, C(5)H_2); 2.91 (t, 2 H, C(7)H_2); 8.00 (s, 1 H, C(4)H); 14.35 (br.s, 1 H, NH); ^{13}C NMR (DMSO-d_6), δ: 22.47 (t, C(6)); 29.04 (t, C(5)); 31.30 (t, C(7)); 113.18 (s, C(3)); 117.75 (s, C≡N); 127.68 (s, C(8)); 141.80 (d, C(4)); 160.42 (s, C(9)); 176.05 (s, S=C). MS, *m/z*: 176 [M^+].

5,6-Hexamethylene-3-cyanopyridine-2(1*H*)-thione (3b) was prepared in a similar way as **3a**, yield 61 %, m.p. 251—252 °C (subl.). Found (%): C, 65.9; H, 6.7; N, 13.2; S, 14.2. $C_{12}H_{14}N_2S$. Calculated (%): C, 66.1; H, 6.4; N, 12.8; S, 14.7. IR (KBr), ν/$см^{-1}$: 2920 (NH); 2228 (C≡N); 1588 (δ NH);

Table 4. ^{1}H NMR and IR absorption spectra for compounds **8a—j**

Compound	IR, ν/cm^{-1}		^{1}H NMR, δ
	NH_2	Z	
8a	3232, 3340, 3404; 1642 (δ NH_2)	2188 (CN)	2.10 (m, 2 H, C(6)H_2); 2.96 (m, 4 H, C(5)H_2, C(7)H_2); 8.22 (s, H, C(4)H); 7.16 (s, 2 H, NH_2)
8b	3156, 3236, 3336; 1568[a] (δ NH_2)	1592[a] (CO)	2.21 (m, 2 H, C(6)H_2); 3.00 (m, 4 H, C(5)H_2, C(7)H_2); 8.41 (s, H, C(4)H); 8.35 (s, 2 H, NH_2); 7.55—7.77 (m, 5 H, Ph)
8c	3416, 3296, 3290; 1620 (δ NH_2)	1674 (CO)	2.12 (m, 2 H, C(6)H_2); 3.00 (m, 4 H, C(5)H_2, C(7)H_2); 8.30 (s, H, C(4)H); 7.17 (s, 2 H, NH_2); 1.29 (t, 3 H, CH_3); 4.25 (q, 2 H, C$\underline{H}_2$$CH_3$)
8d	3468, 3440, 3360; 1655 (δ NH_2)	1610 (CO)	2.14 (m, 2 H, C(6)H_2); 3.02 (m, 4 H, C(5)H_2, C(7)H_2); 8.32 (s, H, C(4)H); 7.00 (s, 2 H, NH_2); 7.36 (H, OH)
8e	3490, 3284, 3188; 1594 (δ NH_2)	1650 (CO)	2.11 (m, 2 H, C(6)H_2); 2.99 (m, 4 H, C(5)H_2, C(7)H_2); 8.20 (s, H, C(4)H); 7.06 (s, 2 H, NH_2); 7.10 (s, 2 H, $CONH_2$)
8f	3448, 3336, 3232; 1636 (δ NH_2)	2224 (CN)	1.28 (m, 4 H, C(7)H_2, C(8)H_2); 1.67 (m, 4 H, C(6)H_2, C(9)H_2); 2.83 (m, 2 H, C(5)H_2); 2.96 (m, 2 H, C(10)H_2); 8.17 (s, H, C(4)H); 7.16 (s, 2 H, NH_2)
8g	3356, 3256, 3168; 1618[a] (δ NH_2)	1590[a] (CO)	1.32 (m, 4 H, C(7)H_2, C(8)H_2); 1.70 (m, 4 H, C(6)H_2, C(9)H_2); 2.87 (m, 2 H, C(5)H_2); 3.00 (m, 2 H, C(10)H_2); 8.38 (s, H, C(4)H); 8.35 (s, 2 H, NH_2); 7.53—7.76 (m, 5 H, Ph)
8h	3432, 3304, 3204; 1616 (δ NH_2)	1668 (CO)	1.33[b] (m, 4 H, C(7)H_2, C(8)H_2); 1.70 (m, 4 H, C(6)H_2, C(9)H_2); 2.84 (m, 2 H, C(5)H_2); 2.99 (m, 2 H, C(10)H_2); 8.26 (s, H, C(4)H); 7.17 (s, 2 H, NH_2); 1.27[b] (t, 3 H, CH_3); 4.26 (q, 2 H, C$\underline{H}_2$$CH_3$)
8i	3428, 3316, 3212; 1616 (δ NH_2)	1652 (CO)	1.32 (m, 4 H, C(7)H_2, C(8)H_2); 1.70 (m, 4 H, C(6)H_2, C(9)H_2); 2.85 (m, 2 H, C(5)H_2); 2.99 (m, 2 H, C(10)H_2); 8.25 (s, H, C(4)H)
8j	3448, 3352, 3328, 3136; 1628 (δ NH_2); 1590 (δ NH_2)	1656 (CO)	1.26 (m, 4 H, C(7)H_2, C(8)H_2); 1.65 (m, 4 H, C(6)H_2, C(9)H_2); 2.78 (m, 2 H, C(5)H_2); 2.93 (m, 2 H, C(10)H_2); 8.12 (s, H, C(4)H); 7.00[b] (s, 2 H, NH_2)

[a] The IR absorption bands overlap.
[b] The ^{1}H NMR signals overlap.

1180 (C=S); UV (EtOH), λ_{max}/nm: 213 (ε 13800); 243 (ε 7800); 313 (ε 21900); 408 (ε 6200); ^{1}H NMR (DMSO-d_6), δ: 1.35 (m, 4 H, C(7)H_2, C(8)H_2); 1.56, 1.65 (m, 4 H, C(6)H_2, C(9)H_2); 2.58 and 2.83 (both t, 4 H, C(5)H_2, C(10)H_2); 7.97 (s, 1 H, C(4)H); 13.97 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6), δ: 24.99 (t); 25.35 (t); 28.64 (t); 29.52 (t); 30.76 (t, C(5), C(10)); 113.98 (s, C(3)); 117.175 (d, C≡N); 125.689 (s, C(11)); 145.884 (d, C(4)); 156.718 (s, C(12)); 175.836 (d, S=C). MS, *m/z*: 218 [M^+].

2,2′-bis(5,6-trimethylene-3-cyano-2-pyridyl) disulfide (4a). An equimolar amount of a 10 % aqueous solution of KOH (0.86 mL) was added dropwise to a solution of thione **3a** (0.3 g, 1.7 mmol), and then an ethanolic solution of iodine was added until the iodine decolorized. The precipitate was washed with water and filtered off to afford 0.2 g (73 %) of disulfide **4a**, m.p. 203—204 °C. IR (KBr), ν/cm^{-1}: 2222 (C≡N); ^{1}H NMR (DMSO-d_6), δ: 2.05 (m, 4 H, C(6)H_2, C(6′)H_2); 3.02 (m, 8 H, C(5)H_2, C(5′)H_2, C(7)H_2, C(7′)H_2); 8.13 (s, 2 H, C(4)H_2, C(4′)H_2); ^{13}C NMR (DMSO-d_6), δ: 22.40 (C(6)); 29.44 (C(5)); 34.06 (C(7)); 105.82 (C(3)); 116.10 (C≡N); 134.60 (C(8)); 137.03 (C(4)); 157.20 (C(2)); 174.31 (C(9)).

2,2′-Bis(5,6-trimethylene-3-cyano-2-pyridyl) disulfide (4b) was obtained similarly to **4a** in 82 % yield, m.p. 148—150 °C. IR (KBr), ν/cm^{-1}: 2220 (C≡N); ^{1}H NMR (DMSO-d_6), δ: 1.23 (m, 8 H, C(7)H_2, C(7′)H_2, C(8)H_2, C(8′)H_2); 1.50 (m, 4 H, C(6)H_2, C(6′)H_2); 1.59 (m, 4 H, C(9)H_2, C(9′)H_2); 2.74 (m, 4 H, C(10)H_2, C(10′)H_2); 8.08 (s, 2 H, C(4)H, C(4′)H); ^{13}C NMR (DMSO-d_6), δ: 25.13, 29.03, 29.75, 29.92, 31.38, 34.02 (C(5), C(6), C(7), C(8), C(9), C(10)); 105.64 (C(3)); 115.68 (C≡N); 135.43 (C(11)); 141.74 (C(4)); 154.78 (C(2)); 166.04 (C(12)).

2-*Z*-Methylthio-5,6-trimethylene(hexamethylene)-3-cyanopyridines (6a—o). General procedure. An equimolar amount of a 10 % solution of KOH (1.1 mL, 2 mmol) and 2 mmol of alkyl halide **5** were added successively to a stirred solution or suspension of thione **3a,b** (2 mmol) in 8 mL of DMF. The mixture was stirred for 25—30 min and diluted

Table 5. ^{13}C NMR spectra for compounds **8a—j**

Compound	^{13}C NMR, δ				
	C(2) (s)	C(3) (s)	C(4) (d)	Z	The other signals
8a	70.4	150.33	126.24	115.99	23.13 (t); 29.53 (t); 33.50 (t); 122.30 (s); 133.86 (s); 158.05 (s); 168.59 (s)
8b	102.28	150.60	128.42	169.63, 127.03, 127.24, 130.95, 140.88	23.10 (t); 29.56 (t); 33.73 (t); 123.00 (s); 133.57 (s); 159.99 (s); 163.20 (s)
8c	93.0	147.81	126.31	14.32, 59.71, 168.25	23.02 (t); 29.47 (t); 33.51 (t); 123.55 (s); 133.12 (s); 158.28 (s); 164.51 (s)
8d	101.8	149.7	125.11	164.2	23.44 (t); 29.73 (t); 33.33 (t); 133.0 (s); 156.0 (s)
8e	96.42	145.72	125.89	167.83	23.13 (t); 29.57 (t); 33.49 (t); 124.42 (s); 132.99 (s); 157.00 (s); 167.205 (s)
8f	70.56	150.22	130.97	115.99	25.27 (t); 25.38 (t); 30.35 (t); 31.14 (t); 32.07 (t); 34.18 (t); 122.29 (s); 132.71 (s); 157.08 (s); 163.39 (s)
8g	102.45	150.72	131.10	127.34, 128.51, 131.85, 140.97, 164.77	25.44 (t); 25.51 (t); 30.49 (t); 31.26 (t); 32.21 (t); 34.43 (t); 123.88 (s); 132.77 (s); 158.73 (s); 162.48 (s)
8h	93.25	147.89	131.25	14.49, 59.85, 164.6	25.35 (t); 25.45 (t); 30.41 (t); 31.19 (t); 32.13 (t); 34.27 (t); 124.32 (s); 132.23 (s); 157.36 (s); 163.36 (s)
8i	129.50	147.32	131.19	166.24	25.36 (t); 25.46 (t); 30.46 (t); 31.20 (t); 32.15 (t); 34.25 (t); 124.57 (s); 132.03 (s); 157.18 (s); 162.89 (s)
8j	96.60	145.55	130.51	167.15	25.33 (t); 25.45 (t); 30.44 (t); 31.17 (t); 32.14 (t); 34.20 (t); 125.08 (s); 131.95 (s); 156.12 (s); 162.16 (s)

with 10 mL of water. The precipitate was filtered off, washed with ethanol and hexane, and recrystallized from ethanol. Yields, data of elemental analysis, and physicochemical and spectroscopic characteristics for compounds **6a—o** are summarized in Tables 1—3.

5,6-Trimethylene-3-iodomethyl-8-cyano-2,3-dihydrothiazolo[3,2-*a*]pyridinium triiodide (7). Iodine (1.524 g, 6 mmol) in chloroform was added dropwise to a solution of compound **6f** (0.65 g, 3 mmol) in chloroform, the mixture was stirred for 20 min, and the precipitate was filtered off and washed with ethanol and hexane to give 2.10 g (97 %) of **7** m.p. 192—194 °C (from CH_3CN). Found (%): C, 19.3; H, 1.5; I, 70.7; N, 3.4; S, 5.1. $C_{12}H_{12}I_4N_2S$. Calculated (%): C, 19.9; H, 1.7; I, 70.1; N, 3.9; S, 4.4. IR (KBr), ν/cm^{-1}: 2236 (C≡N); ^1H NMR (DMSO-d_6), δ: 2.26 (m, 2 H, $CH_2\underline{CH_2}CH_2$); 3.07 (m, 4 H, $\underline{CH_2}CH_2\underline{CH_2}$); 3.39 (m, 2 H, CH_2); 4.12 (m, 2 H, C(2)H_2); 5.88 (m, 1 H, C(3)H); 8.77 (s, 1 H, C(7)H).

3-Amino-5,6-trimethylene(hexamethylene)-2-*Z*-thieno[2,3-*b*]pyridines (8a—j). a. A 10 % aqueous solution of KOH (5.6 mL, 0.01 mol) and then alkyl halide **5** (0.01 mol) were added to a vigorously stirred solution or suspension of thione **3a,b** (0.01 mol) in 25 mL of DMF. The mixture was stirred for 20—30 min, an additional 2.8 mL (5 mmol) of the solution of KOH was added, and the mixture was stirred for 15 min and diluted with 10 mL of water. The precipitate of **8** was separated and recrystallized from ethanol.

b. A 10 % solution of KOH (15 mmol) and then alkyl halide **5** (10 mmol) were added to a vigorously stirred solution or suspension of thione **3a,b** (0.01 mol) in 25 mL of DMF. The mixture was stirred for 30 min, and diluted with 10 mL of water; compound **8** was filtered off and recrystallized from ethanol. Yields, data of elemental analysis, physicochemical and spectroscopic characteristics for compounds **8a—j** are summarized in Tables 1, 4, and 5.

4-Amino-7,8-trimethylenepyrido[2′,3′:2,3]thieno[4,5-*d*]pyrimidine (9a). A solution of 0.98 g (4.5 mmol) of thienopyridine **8a** in 10 mL of formamide was refluxed for 1 h, diluted with 5 mL of water, filtered, and washed with ethanol and hexane to give 1 g (93 %) of compound **9a**, m.p. > 300 °C. Found (%): C, 59.0; H, 4.2; N, 23.5; S, 13.3. $C_{12}H_{10}N_4S$. Calculated (%): C, 59.5; H, 4.1; N, 23.1; S, 13.2. IR (KBr), ν/cm^{-1}: 3272 (NH_2); 3080 (NH); 1668 (δ NH); ^1H NMR (DMSO-d_6), δ: 2.16 (m, 2 H, C(6)H_2); 3.08 (m, 4 H, C(5)H_2, C(7)H_2); 7.57 (s, 2 H, NH_2); 8.48 (s, 1 H, C(2)H of pyrimidine); 8.51 (s, 1 H, C(4)H of pyridine).

4-Amino-7,8-hexamethylenepyrido[2′,3′:2,3]thieno-[4,5-*d*]pyrimidine (9b) was prepared from 0.2 g of thienopyridine **8f**, similarly to **9a**. The yield of **9b** was 0.23 g (99 %). m.p. > 300 °C. Found (%): C, 63.6; H, 5.7; N, 19.3; S, 11.4. $C_{15}H_{16}N_4S$. Calculated (%): C, 63.4; H, 5.6; N, 19.7; S, 11.3. IR (KBr), ν/cm^{-1}: 3361, 3316 (NH_2); 3144 (NH); 1654, 1648 (δ NH_2); ^1H NMR (DMSO-d_6), δ: 1.32 (m, 4 H,

$C(7)H_2$, $C(8)H_2$); 1.72 (m, 4 H, $C(6)H_2$, $C(9)H_2$); 2.95 (m, 2 H, $C(5)H_2$); 3.07 (m, 2 H, $C(10)H_2$); 7.19 (s, 2 H, NH_2); 7.93 (s, 1 H, C(2)H of pyrimidine); 8.00 (s, 1 H, C(4)H of pyridine).

2-Methyl-7,8-trimethylenepyrido[2′,3′:2,3]thieno-[4,5-*d*]oxazin-4-one (10). A mixture of acetic anhydride (15 mL) and thienopyridine **8d** (1.17 g, 5 mmol) was refluxed for 1 h, cooled, and diluted with 5 mL of water. The precipitate was filtered off and washed with water, ethanol, and hexane to give 0.5 g (38 %) of compound **10**, m.p. 209—211 °C. Found (%): C, 60.1; H, 3.5; N, 11.5; S, 12.0. $C_{13}H_{10}N_2O_2S$. Calculated (%): C, 60.4; H, 3.9; N, 10.9; S, 12.4. IR (KBr), ν/cm^{-1}: 1754 (C=O); ^1H NMR (DMSO-d_6), δ: 2.17 (m, 2 H, $C(6)H_2$); 2.53 (s, 3 H, CH_3); 3.08 (m, 4 H, $C(5)H_2$, $C(7)H_2$); 8.33 (s, 1 H, C(4)H).

2-Methyl-7,8-trimethylenepyrido[2′,3′:2,3]thieno[4,5-*d*]pyrimidin-4-one (11) was prepared from **8j** (0.14 g, 0.5 mmol) and acetic anhydride similarly to **10**. The yield of **11** was 0.04 g (28 %), m.p. > 300 °C. Found (%): C, 62.9; H, 6.2; N, 14.2; S, 11.3. $C_{15}H_{17}N_3OS$. Calculated (%): C, 62.7; H, 5.9; N, 14.6; S, 11.1. IR (KBr), ν/cm^{-1}: 3268 (NH); 1720 (C=O); 1670 (δ NH); ^1H NMR (DMSO-d_6), δ: 1.33 (m, 4 H, $C(7)H_2$, $C(8)H_2$); 1.74 (m, 4 H, $C(6)H_2$, $C(9)H_2$); 2.46 (s, 3 H, CH_3); 2.50 (s, 3 H, CH_3 of the hydroxy tautomer); 2.96 (m, 2 H, $C(5)H_2$); 3.07 (m, 2 H, $C(10)H_2$); 8.05 (s, 1 H, C(4)H); 8.28 (s, 1 H, C(4)H of the hydroxy tautomer); 10.62 (s, 1 H, OH); 12.76 (s, 1 H, NH).

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