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SYNTHESIS AND REACTIONS OF 3-CYANO-6-METHOXYMETHYL-4-METHYL-2(1H)-PYRIDINETHIONE

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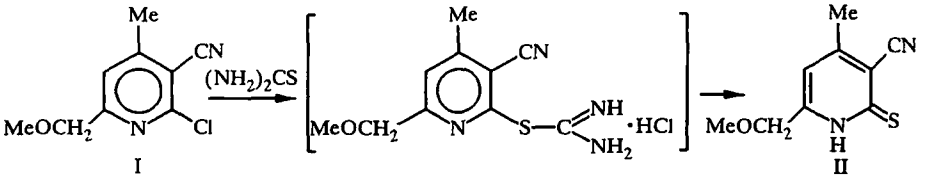
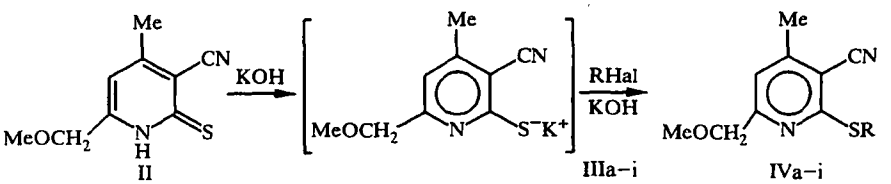
Nucleophilic substitution of the chlorine atom in 2-chloro-3-cyano-6-methoxymethyl-4-methylpyridine by mercapto group produces the corresponding 2(1H)-pyridinethione, alkylation of which by halogenated compounds in the presence of KOH proceeds regioselectively to form S-alkyl derivatives. Thorpe–Ziegler cyclization of S-alkyl derivatives, which contain an active methylene group, yields new 3-aminothieno[2,3-b]-pyridines.

2-Alkylthiopyridines and 3-aminothieno[2,3-*b*]pyridines are interesting as potential biologically active compounds and synthones for constructing of polycondensed heterocyclic systems [1-3]. We previously have demonstrated the advantage of chemically alkylating substituted 3-cyano-2(1H)-pyridinethiones rather than electrochemically thioalkylating 2-halo-3-cyanopyridine [4, 5]. Therefore, on continuing of investigations on the synthesis of substituted 2-thioalkyl- and thieno[2,3-*b*]pyridines we carried out nucleophilic substitution of the chlorine atom in 4-methyl-6-methoxymethyl-3-cyano-2-chloropyridine by mercapto group and prepared pyridinethione II, which was then alkylated using the standard method [4].



Pyridinethione II is formed directly in the reaction mixture upon mixing chloropyridine I and thiourea in boiling butanol. The reaction involves decomposition of the initially formed isothiuronium salt. The properties of II are given in Tables 1-3.



III, IV a R = *n*-C_3H_7; b R = *n*-C_4H_9; c R = CH_2COOH; d R = CH_2COOEt;
e R = CH_2CONH_2; f R = CH_2CH_2COOEt; g R = $CH_2COC_6H_3(OH)_2$-3,4;
h R = CH_2CO-Ad-1; i R = CH_2CO—◁
III, IV a,c,e Hal = I; b,d,f Hal = Br; g,h,i Hal = Cl

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TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
II	$C_9H_{10}N_2OS$	55,61 / 55,65	5,18 / 5,19	14,44 / 14,42	16,52 / 16,51	204...206	63
IVa	$C_{12}H_{16}N_2OS$	60,82 / 60,99	6,77 / 6,82	11,69 / 11,85	13,44 / 13,57	Oil	91
IVb	$C_{13}H_{18}N_2OS$	62,28 / 62,37	7,13 / 7,25	11,06 / 11,19	12,64 / 12,81	Oil	87
IVc	$C_{11}H_{12}N_2O_3S$	52,34 / 52,37	4,70 / 4,79	11,11 / 11,10	12,52 / 12,76	103...105	62
IVd	$C_{13}H_{16}N_2O_3S$	56,69 / 56,70	5,62 / 5,75	9,83 / 9,99	11,29 / 11,44	67...68	87
IVe	$C_{11}H_{13}N_3O_2S$	52,41 / 52,57	5,03 / 5,21	16,60 / 16,72	12,59 / 12,76	129...130	89
IVf	$C_{14}H_{18}N_2O_3S$	57,05 / 57,12	6,10 / 6,16	9,38 / 9,52	10,74 / 10,81	83...84	83
IVg	$C_{17}H_{16}N_2O_4S$	59,15 / 59,29	4,52 / 4,68	8,00 / 8,14	9,17 / 9,31	113...114	85
IVh	$C_{21}H_{26}N_2O_2S$	67,95 / 68,07	6,98 / 7,07	7,42 / 7,56	8,51 / 8,65	71...72	88
IVi	$C_{14}H_{16}N_2O_2S$	60,71 / 60,84	5,73 / 5,84	10,02 / 10,14	11,47 / 11,60	Oil	90
Va	$C_{11}H_{12}N_2O_3S$	52,28 / 52,37	4,79 / 4,79	11,01 / 11,10	12,69 / 12,71	154...155	59
Vb	$C_{13}H_{16}N_2O_3S$	55,62 / 55,70	5,42 / 5,75	9,68 / 9,99	11,35 / 11,44	132...133	83
Vc	$C_{11}H_{13}N_3O_2S$	52,41 / 52,57	5,17 / 5,21	16,60 / 16,72	12,62 / 12,76	232...233	92
Vd	$C_{21}H_{26}N_2O_2S$	68,01 / 68,07	6,99 / 7,07	7,48 / 7,56	8,57 / 8,65	> 200 (dec.)	85
Ve	$C_{17}H_{16}N_2O_4S$	59,18 / 59,29	4,61 / 4,68	8,06 / 8,14	9,24 / 9,31	> 200 (dec.)	82
Vf	$C_{17}H_{15}N_3O_4S$	57,05 / 57,13	4,15 / 4,23	11,69 / 11,76	8,89 / 8,97	> 200 (dec.)	79

TABLE 2. IR Spectral Characteristics of Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}				
	CN	C=C, C=N	C—O—C	CO	N—H
II	2200	1600, 1560	1120, 1090	—	—
IVa	2205	1570	1095	—	—
IVb	2195	1570	1095	—	—
IVc	2210	1580	1095, 1140	1710	—
IVd	2210	1570	1130, 1080	1720	—
IVe	2205	1570, 1610	1090, 1120	1630	—
IVf	2210	1570	1130, 1100 1020	1720	—
IVg*	2210	1575	1130, 1090	1650	—
IVh	2220	1580	1125, 1080 1060	1700	—
Va	—	1580, 1630	1060, 1125	1730	3390, 3275
Vb	—	1550, 1560 1595	1070, 1100	1670	3240, 3350
Vc	—	1590	1070	1625	3130, 3290 3340, 3460
Vd	—	1590, 1550	1115, 1080 1030	1700	3410, 3270
Ve	—	1560	1120, 1095	1650	3250...3450 br. s (N—H, OH)
Vf	—	1555	1120, 1070 1055	1660	3340, 3245

* IVg 3450...3250 cm^{-1}, br. s (ν_{OH}).

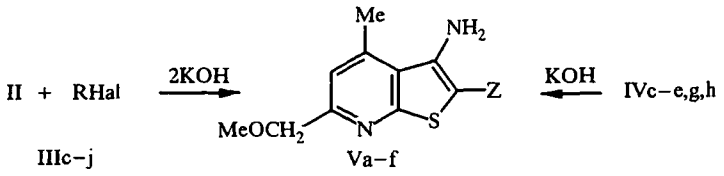
TABLE 3. PMR Spectral Characteristics of Certain Synthesized Compounds

Compound	Chemical shifts, δ, ppm (J, Hz)					
	CH_3–Het, s	OCH_3	SCH_2	OCH_2	H–Het, s	other protons (see R, Z)
II	2,42	3,37 s	—	4,38 s	6,78	12,8 (1H, br. s, NH)
IVb	2,49	3,49 s	3,23 (2H, t, J = 7,5)	4,53 s	7,06	0,95 (3H, t, CH_3, J = 7,5) 1,26...1,72 (4H, m, ΣCH_2)
IVc	2,48	3,48	4,12 s	4,48	7,18	—
IVd	2,51	3,47 s	3,97 s	4,48 s	7,12	1,28 (3H, t, CH_3, J = 7,1) 4,20 (2H, q, OCH_2CH_3, J = 7,1)
IVe	2,47	3,40 s	3,93 s	4,50 s	7,22	7,03 (1H, br. s, NH) 7,48 (1H, br. s, NH)
IVf	2,49	3,48...3,75 (5H, m, ΣOCH_3, SCH_2)		4,52 s	7,10	1,28 (3H, t, CH_3, J = 7,3) 2,76 (2H, t, SCH_2CH_2, J = 7,3) 4,18 (2H, q, OCH_2CH_3, J = 7,3)
IVi	2,28	3,25 s	3,96 s	4,26 s	6,93	0,7...1,0 (5H, m, C_3H_5)
Vb	2,80	3,48 s	—	4,55 s	7,20	1,30 (3H, t, CH_3, J = 7,1) 4,28 (2H, q, OCH_2CH_3, J = 7,1) 6,73 (2H, br. s, NH_2–Het)
Vc	2,78	3,37 s	—	4,53 s	7,18	6,28 (2H, br. s, NH_2) 7,05 (2H, br. s, NH_2)
Vf	2,76	3,28 s	—	4,62 s	7,08	7,68...8,01 (4H, m, C_6H_4)

Alkylation of II by alkyl halides (III) was performed in DMF in presence of KOH in equimolar ratio. The reaction proceeds regioselectively at the sulfur atom regardless of the nature of the halide III and synthesis conditions. The products are S-substituted thiopyridines (IVa-i) in 62-92% yields (Table 1).

Alkylation of 3-cyano-4-methoxymethyl-6-methyl-2(1H)-pyridinethione takes 1-2 h less than alkylation of its structural isomer II by the corresponding alkyl halides [3]. This is apparently due to the mutual steric and electronic influence of the substituents at the pyridine ring. The structure of 2-thioalkylpyridines (IVa-i) was confirmed by spectral data (Table 3).

Thorpe–Ziegler cyclization of the alkylation products of II, which have an active methylene group in the R substituent, leads to formation of the corresponding 3-aminothieno[2,3-*b*]pyridines (Va-f). These can also be prepared directly by alkylation of II in the presence of twofold excess of KOH without isolation of the intermediate.



III j R = $CH_2C_6H_4NO_2$-4; V a Z = COOH; b Z = COOEt; c Z = $CONH_2$;
d Z = COAd-1; e Z = $COC_6H_3(OH)_2$-3,4; f Z = $COC_6H_4NO_2$-4

Absorption band for $\nu_{C=N}$ is absent in the IR spectra of thieno[2,3-*b*]pyridines V whereas it presents in the spectra of the starting pyridinethione II and alkylthiopyridines (IVc-e, g, h). A series of bands at 3460-3130 cm^{-1} assigned to stretching vibrations of the NH_2 group also appears (Table 2). Characteristic singlets of amino groups at 6.73-8.30 ppm appear in the PMR spectra instead of signals of S–CH_2 groups. This is consistent with the literature data [6] (Table 3).

EXPERIMENTAL

PMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ for IVe and in DMSO-d_6 for Vb and Vc. IR spectra were recorded on a Specord IR-75 spectrophotometer for suspensions in vaseline oil. The course of reaction and the purity of the products was measured by TLC on Silufol UV-254 plates with hexane–acetone (1-2):1 eluent with visualization by iodine vapor or $KMnO_4$ solution.

The properties of the synthesized compounds are given in Tables 1-3.

3-Cyano-6-methoxymethyl-4-methyl-2-SR-pyridines (IVa-i). Mixture of pyridinethione II (10 mmol), DMF (20-25 ml), KOH (10% aqueous solution, 10 mmol), and alkylhalide IIIa-i (10 mmol) was maintained for 2-7 h at room temperature, after which water (5-10 ml) was added. The precipitated product (IVa-i) was separated, washed with water, and recrystallized from alcohol.

3-Amino-6-methoxymethylthieno-4-methyl-2-7R-[2,3-*b*]pyridines (Va-f). A. Mixture of pyridinethione IVa-f (10 mmol), DMF (20-25 ml), and KOH (10% aqueous solution, 20 mmol) was maintained for 4-10 h at room temperature. A 2-3-fold excess of water was added. The precipitate was separated, dried and recrystallized from alcohol.

B. Mixture of 2-alkylthiopyridine IVc-e,g,h (10 mmol), DMF (20-25 ml), and KOH (10% aqueous solution, 10 mmol) was maintained at room temperature for 2-10 h. A 2-3-fold excess of water was added. The precipitate was separated. The product Va-e was recrystallized from alcohol.

For preparation of Vb by methods A and B, the reaction mixture must be held for an additional 5 h. Then the product is separated as described above.

3-Amino-2-carboxy-6-methoxymethylthieno-4-methyl-[2,3-*b*]pyridine (Va). Compound IVc (3.4 mmol) was added to solution of sodium ethoxide prepared from metallic Na (7 mmol) and ethanol (20 ml). The mixture was boiled for 2 h. The solvent was evaporated to half the volume. After cooling, the reaction mixture was acidified with 10% aqueous HCl until a precipitate formed. Thienopyridine Va was recrystallized from alcohol.

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