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SYNTHESIS OF 4-ALKYL-3-CYANO-5,6,7,8-TETRAHYDROQUINOLINE-2(1H)-THIONES AND THEIR DERIVATIVES

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*4-Alkyl-3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-thiones, used in synthesis of substituted 2-alkylthioquinolines and thieno[2,3-*b*]pyridines, were obtained by condensation of cyanothioacetamide, aliphatic aldehydes, and morpholinocyclohexene.*

The chemistry of 4-aryl-3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-thiones has recently been developing relatively intensely [1], which could be attributed in particular to the discovery of compounds with antimicrobial activity in this series [2, 3]. The basic methods of their synthesis are: cyclocondensation of 2-arylmethylenecyclohexanones with cyanothioacetamide [2, 4], reaction of cyclohexanone [5] or its enamine [6] with arylmethylenecyanothioacetamides, and recyclization of enamines of the 1,3-dithio-4-cyclohexene series [7].

TABLE 1. Characteristics of Synthesized Compounds IXa-h, XIIIa-c

Compound	Empirical formula	Found, % Calculated, %				mp, °C (solvent for crystallization)	Yield, %
		C	H	N	S(Se)		
IXa	$C_{22}H_{23}ClN_2OS$	66,40 66,23	5,95 5,81	6,88 7,02	7,80 8,04	101...102 (ethanol)	80
IXb	$C_{15}H_{20}N_2S$	69,00 69,19	7,58 7,74	10,85 10,76	12,57 12,31	75...77 (ethanol)	78
IXc	$C_{22}H_{24}BrN_3OS$	57,50 57,64	5,11 5,28	8,98 9,17	7,18 6,99	105...107 (AcOH)	83
IXd	$C_{22}H_{25}N_3OS$	69,51 69,62	6,42 6,64	10,88 11,07	8,59 8,45	160...162 (AcOH)	79
IXe	$C_{16}H_{21}N_3OS$	63,18 63,33	7,13 6,98	13,92 13,85	10,42 10,57	127...128 (AcOH)	69
IXf	$C_{22}H_{23}BrN_2OS$	59,45 59.59	5,14 5,23	6,45 6,32	7,35 7,23	116...118 (AcOH)	74
IXg	$C_{14}H_{16}N_2O_2S$	60,70 60,85	5,75 5,84	10,30 10,14	11,72 11,60	88...90 (ethanol)	80
IXh	$C_{22}H_{18}N_2O_3S$	67,51 67,67	4,49 4,65	7,25 7,17	8,40 8,21	208...210 (AcOH)	85
XIIIa	$C_{12}H_{14}N_2Se$	54,20 54,34	5,45 5,32	10,70 10,56	29,65 29,77	145...147 (ethanol)	77
XIIIb	$C_{18}H_{18}N_2Se$	63,43 63,34	5,15 5,32	8,08 8,21	23,34 23,13	77...79 (ethanol)	72
XIIIc	$C_{13}H_{15}N_3OS$	60,04 59,75	5,88 5,79	15,89 16,08	12,10 12,27	175...177	84

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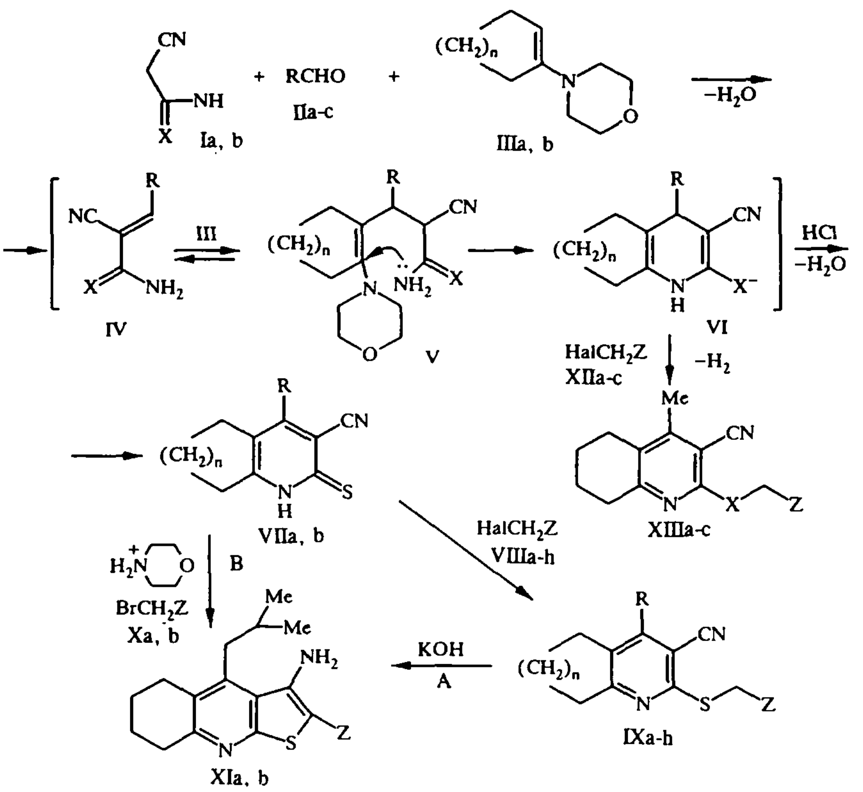
4-Alkyl-substituted analogs of these quinolinethiones were previously unknown, despite the great practical importance of compounds of this series. This induced us to develop methods for synthesizing them and studying some of their properties. We found that as a result of three-component condensation of cyanothioacetamide (Ia), aliphatic aldehydes II, and enamines III, the initially appearing alkylmethylenecyanothioacetamide (IV) adds enamine III with formation of adduct V. Subsequent cyclocondensation of compound V in the conditions of the reaction results in the formation of thiolate VI, whose treatment with hydrochloric acid yields substituted 3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-thiones VIIa, b. Their structure is in agreement with the data from spectral studies (see Experimental section) and chemical transformations. Thiones VIIa, b are alkylated in basic medium by halides VIIIa-e at the sulfur atom with formation of sulfides IXa-h, subsequently undergoing Thorpe–Ziegler transformation into thienoquinolines XIa, b (method A), which corresponds to the general mechanisms of their conversion [1]. Compounds XIa, b can be obtained from thione VIIb in one stage in treatment of the latter with halides Xa, b and a two-fold excess of aqueous solution of KOH (method B) (see Experimental section).

The structure of sulfides IXa-h and thienoquinolines XIa, b is in agreement with the data in the IR and PMR spectra. The IR spectra of compounds IXa-h exhibit absorption bands of stretching vibrations of a conjugated cyano group in the 2205-2224 cm^{-1} region, which disappear in going to thienoquinolines XIa, b. The presence of proton signals of the $S-CH_2$ group in the form of singlets in the region of 2.44-4.75 ppm is characteristic in the PMR spectra of sulfides IXa-h and is not observed in the PMR spectra of compounds XIa, b, in which broadened singlets of proton signals of a conjugated amino group appear at 8.15 ppm instead of the above signals.

Substituted 2-alkylthioquinolines and 2-alkylselenoquinolines similar to compounds IX can be synthesized in one reactor. Chalcogenides XIIIa-c could thus be obtained in the reaction of cyanothio(seleno)acetamides (Ia, b), aliphatic aldehydes II, and enamine IIIb in alcohol under argon at 20°C with subsequent treatment of the reaction mixture with halides XII in the presence of aqueous solution of KOH (see Experimental section). The structure of compounds XIII was confirmed by the IR and PMR spectra (Table 2).



I a X = S; b X = Se. II a R = C_2H_5; b R = $CH_2CH(CH_3)_2$; c R = CH_3. III a n = 1; b n = 2.
VII a R = C_2H_5, n = 1; b R = $CH_2CH(CH_3)_2$, n = 2. VIII, IX a Hal = Br, Z = 4-ClC_6H_4CO; b Z = H;
c Z = 4-BrC_6H_4NHCO; d Z = PhNHCO; e Z = $CONH_2$; f Z = 4-BrC_6H_4CO; g Z = $COOCH_3$;
h Z = coumarin-3-yl carbonyl; VIII, IXa,f,h Hal = Br, b Hal = I, c-e,g Hal = Cl; VIII, IX a-f n = 2,
R = $CH_2CH(CH_3)_2$; g, h n = 1, R = C_2H_5; X, XI a Z = 4-ClC_6H_4CO; b Z = 4-PhC_6H_4CO. XII,
XIII a Hal = I, Z = H, X = Se; b Z = Ph, X = Se; c Z = $CONH_2$, X = S; XII, XIII b, c Hal = Cl

TABLE 2. Spectral Characteristics of Compounds IXa-h, XIIIa-c

Compound	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm			
	C ≡ N	C=O, NH	R	$(CH_2)_n$, m	S—CH_2, Se—CH_2, s	Z
IXa	2222	1712	0,91 (6H, d, $(CH_3)_2$); 1,89 (1H, m, CH); 2,40 (2H, m, CH_2)	2,56 (4H, $(CH_2)_2$); 1,64 (4H, $(CH_2)_2$)	4,75	8,08 d, and 7,62 d, (at 2H, C_6H_4)
IXb	2217	—	0,90 (6H, d, $(CH_3)_2$); 1,89 (1H, m, CH); 2,55 (2H, m, CH_2)	2,64 (2H, CH_2); 2,85 (2H, CH_2); 1,75 (4H, $(CH_2)_2$)	2,53	—
IXc	2219	3314	0,90 (6H, d, $(CH_3)_2$); 1,89 (1H, m, CH); 2,50 (2H, m, CH_2)	2,63 (4H, $(CH_2)_2$); 1,71 (4H, $(CH_2)_2$)	4,10	10,38 (1H, s, CONH); 7,49 (4H, q, C_6H_4)
IXd	2216	3320	0,92 (6H, d, $(CH_3)_2$); 1,93 (1H, m; CH); 2,55 (2H, m, CH_2)	2,70 (4H, $(CH_2)_2$); 1,73 (4H, $(CH_2)_2$)	4,14	10,26 (1H, s, CONH); 7,04...7,57 (5H, m, Ph)
IXe	2218	3300, 3455	0,93 (6H, d, $(CH_3)_2$); 1,90 (1H, m, CH); 2,55 (2H, m, CH_2)	2,68 (2H, CH_2); 2,85 (2H, CH_2); 1,77 (4H, $(CH_2)_2$)	3,90	7,53 br. s and 7,12 br. s, (at 1H, NH_2)
IXf	2216	1700	0,92 (6H, d, $(CH_3)_2$); 1,90 (1H, m, CH); 2,57 (2H, m, CH_2)*	2,57 (4H, $(CH_2)_2$)*; 1,66 (4H, $(CH_2)_2$)	4,74	7,80 (4H, d, C_6H_4)
IXg	2220	1680	1,14 (3H, t, CH_3); 2,05 (2H, q, CH_2)	2,68 (2H, CH_2); 2,90 (4H, $(CH_2)_2$)	4,09	3,64 (3H, s, OCH_3)
IXh	2220	1715	1,15 (3H, t, CH_3); 2,00 (2H, q, CH_2)	2,60...2,92 (6H, $(CH_2)_3$)	4,74	8,65 (1H, s, 4-H); 7,42...7,94 (4H, m, coumarinyl)
XIIIa	2219	—	2,30 (3H, s, CH_3)	2,83 (2H, CH_2); 2,58 (2H, CH_2); 1,76 (4H, $(CH_2)_2$)	2,44	—
XIIIb	2205	—	2,26 (3H, s, CH_3)	2,90 (2H, CH_2); 2,52 (2H, CH_2); 1,73 (4H, $(CH_2)_2$)	4,44	7,24 (5H, m, Ph)
XIIIc	2224	3300, 3400, 3472	2,32 (3H, s, CH_3)	2,81 (2H, CH_2); 2,59 (2H, CH_2); 1,78 (4H, $(CH_2)_2$)	3,88	7,53 br. s and 7,12 br. s (at 1H, NH_2)

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 in liquid petrolatum and the PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) in DMSO-D_6 (TMS internal standard). The evolution of the reaction and individuality of the substances were monitored by TLC on Silufol UV-254 plates in acetone–hexane system, 3:5.

5,6-Trimethylene-3-cyano-4-ethylpyridine-2(1H)-thione (VIIa). A mixture of 10 mmole of cyanoacetamide (Ia), 10 mmole of propionaldehyde IIa, and 10 mmole of enamine IIIa in 15 ml of absolute ethanol at 20°C was stirred for 2 h and diluted with 10% aqueous solution of hydrochloric acid to pH 5, and then left for 24 h. The residue was filtered off and washed with ethanol and hexane, yielding 1.6 g (79%) of thione VIIa, mp = 248-250°C (AcOH). Found, %: C 64.50, H 6.15, N 13.58, S 15.77. $C_{11}H_{12}N_2S$. Calculated, %: C 64.67, H 5.92, N 13.71, S 15.70. IR spectrum: 3300 (NH), 2220 cm^{-1} (C≡N). PMR spectrum: 1.11 (3H, t, CH_3), 2.08 (2H, q, CH_2), 2.45-2.89 ppm (6H, m, $(CH_2)_3$).

4-Isobutyl-3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-thione (VIIb) was obtained similar to thione VIIa, using enamine IIIb. Yield of 1.7 g (70%), mp = 198-200°C (AcOH). Found, %: C 68.18, H 7.21, N 11.42, S 13.19. $C_{14}H_{18}N_2S$. Calculated, %: C 68.25, H 7.36, N 11.37, S 13.01. IR spectrum: 3300 (NH), 2220 cm^{-1} (C≡N). PMR spectrum: 0.92 (6H, d, $(CH_3)_2$), 1.64 (4H, m, $(CH_2)_2$), 1.92 (1H, m, CH), 2.48 (2H, m, CH_2), 2.57 (2H, d, CH_2), 2.70 ppm (2H, m, CH_2).

5,6-Tri(tetra)methylene-4-R-2-Z-methylthio-3-cyanopyridines (IXa-h). Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added to a suspension of 10 mmole of thione VII in 10 ml of ethanol while stirring, and it was filtered into a beaker containing 10 mmole of halide VIII. Then the reaction mixture was stirred for 2 h and diluted with 10 ml of water. The sediment was separated and washed with water, ethanol, and hexane. Sulfides IXa-h were obtained, and the data on them are reported in Tables 1 and 2.

3-Amino-4-isobutyl-2-(4′-chlorobenzoyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (XIa). A. Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added to a suspension of 10 mmole of sulfide IXa in 10 ml of DMF and stirred for 3 h, after which it was diluted with 10 ml of water. The sediment was separated, washed with water, ethanol, and hexane. Yield of 2.7 g (68%), Mp = 170-172°C (ethanol). Found, %: C 66.35, H 5.70, N 7.15, S 7.91. $C_{22}H_{23}ClN_2OS$. Calculated, %: C 66.23, H 5.81, N 7.02, S 8.04. IR spectrum: 3330-3495 (NH_2), 1700 cm^{-1} (C=O). PMR spectrum: 8.15 (2H, br. s, NH_2), 7.77 d and 7.60 d (at 2H, C_6H_4), 2.96 (4H, m, $(CH_2)_2$), 2.75 (2H, m, CH_2), 2.00 (1H, m, CH), 1.80 (4H, m, $(CH_2)_2$), 0.93 ppm (6H, d, $(CH_3)_2$).

B. Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH and 10 mmole of halide VIIIa were added to a solution of 10 mmole of thione VIIb in 12 ml of DMF and stirred for 30 min, then 5.6 ml of 10% aqueous solution of KOH was added and stirred for 4 h. Then it was diluted with 15 ml of water and the sediment was separated. Compound XIa was obtained with a yield of 81%, similar to the compound obtained with method A with respect to melting point and chromatogram.

3-Amino-4-isobutyl-2-(4′-phenylbenzoyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (XIb) was obtained by method B similar to compound XIa (method B) using halide Xb. Yield of 3.2 g (72%), mp = 138-140°C (AcOH). Found, %: C 76.18, H 6.25, N 6.44, S 7.33. $C_{28}H_{28}N_2OS$. Calculated, %: C 76.33, H 6.41, N 6.36, S 7.28. IR spectrum: 3315-3482 (NH_2), 1720 cm^{-1} (C=O). PMR spectrum: 8.15 (2H, br. s, NH_2), 7.47-7.82 (9H, m, H_{arom}), 2.95 (4H, m, $(CH_2)_2$), 2.70 (2H, m, CH_2), 1.97 (1H, m, CH), 1.77 (4H, m, $(CH_2)_2$), 0.93 ppm (6H, d, $(CH_3)_2$).

4-Methyl-2-methylseleno-3-cyano-5,6,7,8-tetrahydroquinoline (XIIIa). A mixture of 10 mmole of cyanoselenoacetamide Ib, 10 mmole of acetaldehyde IIc, and 10 mmole of enamine IIIb in 15 ml of abs. ethanol was stirred for 2 h under argon at 20°C. Then 5.6 ml (10 mmole) of 10% aqueous solution of KOH and 10 mmole of methyl iodide (XIIa) were added to the reaction mixture while stirring, and stirring was continued for 3 h, after which 15 ml of water was added. The sediment was separated and washed with water, ethanol, and hexane. Selenide XIIIa was obtained, and the data on it are reported in Tables 1 and 2.

2-Benzylseleno-4-methyl-3-cyano-5,6,7,8-tetrahydroquinoline (XIIIb) was obtained similar to compound XIIIa using benzyl chloride XII (Tables 1 and 2).

2-Carbamoylmethylthio-4-methyl-3-cyano-5,6,7,8-tetrahydroquinoline (XIIIc) was obtained similar to compound XIIIa using cyanothioacetamide Ia and chloroacetamide XIIc (Tables 1 and 2).

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