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SYNTHESIS AND PROPERTIES OF 6-OXO-3,5-DICYANO-1,4,5,6-TETRAHYDROSPIRO-(4'-R-CYCLOHEXANE-1',4-PYRIDINE)-2-THIOLS AND -SELENOLS

V. D. Dyachenko, A. E. Mitroshin, and V. P. Litvinov

By the interaction of a 4-R-cyclohexylidenecyanoacetic ester with cyanothio(seleno)acetamide, 6-oxo-3,5-dicyano-1,4,5,6-tetrahydrospiro-(4'-R-cyclohexane-1',4-pyridine)-2-thiols and -selenols have been obtained; these have also been synthesized from a cyclohexylidenecyanothioacetamide and cyanoacetic ester. These thiols and selenols have been used to prepare the corresponding disulfides, diselenides, and spiro systems, including the fragments alkylthio(seleno)tetrahydropyridine, thieno[2,3-b]pyridine, and 2,3-dihydrothiazolopyridine.

Various derivatives of spiropyridones have aroused the interest of investigators, as this class of compounds includes substances that are CNS activators [1, 2], antidepressants [3, 4], tranquilizers [5], antiallergic and antiinflammatory substances [6], and stabilizers for various polymers, copolymers, and lacquers [7]. At the same time, methods for synthesizing these compounds are quite limited [8] — a situation that has impelled us to investigate new approaches in pursuit of this promising direction in research.

In this article we will describe methods for the synthesis of previously unknown 6-oxo-3,5-dicyano-1,4,5,6-tetrahydrospiro-(4'-R-cyclohexane-1',4-pyridine)-2-thiols (Ia,b) and -selenols (Ic), consisting of the interaction of a 4-R-cyclohexylidenecyanoacetic ester (IIa,b) with cyanothioacetamide (IIIa) or cyanoselenoacetamide (IIIb) in the presence of a twofold excess of N-methylmorpholine in absolute ethanol at 25°C (Method A). Here, we isolated and characterized the salts Va-c. Compounds IVa,b were also obtained by the reaction of cyclohexylidenecyanothioacetamides (Va,c) with cyanoacetic ester (VI) (Method B). The characteristics and yields of the compounds are listed in Table 1.

The probable mechanism for these reactions is as follows: In the first stage of the interaction, the C–H acid III or VI adds to the α,β-unsaturated nitriles II and V respectively, through a Michael addition reaction that forms the adducts VII, followed by their cyclocondensation to form the salts IV, treatment of which with 10% hydrochloric acid gives the substituted thiols Ia,b and selenol Ic.

The structures of the compounds IV and I are consistent with the data obtained in spectroscopic studies (Table 2). The IR spectra of these compounds contain high-intensity absorption bands of stretching vibrations of the conjugated nitrile group in the 2175 cm^{-1} region, indicating delocalization of negative charge in the fragment $N{\equiv}C-C{=}C-C-X^-$ fragment, which had been observed previously in similar systems; the S or Se atom formally bears a negative charge [9, 10]. This view is also supported by the results of alkylation of the salts IV in DMF by halides (VIIIa-r) (Method A), which proceeds exclusively at the S or Se atom. The structures of the compounds IV and I were also confirmed by the low-intensity bands in their IR spectra from the cyano group in the 2250 cm^{-1} region, characteristic for nonconjugated nitriles [11], and a band of the carbonyl group in the 1700 cm^{-1} region. The PMR spectra of the salts IV contain characteristic signals of protons of the morpholinium cation in the regions 2.76-2.82 (s, N-CH_3), 3.14-3.23 (m, CH_2N), and 3.76-3.79 ppm (m, CH_2O), and also signals of protons of the cyclohexane substituent at 1.44-1.56 (m), the 5-H proton at 4.00-4.04 (s), and the proton of the N-H group at 9.46-9.60 ppm (br.s).

T. G. Shevchenko Lugansk State Pedagogical Institute, Lugansk 348011, Ukraine. N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1235-1242, September, 1996. Original article submitted May 13, 1996.

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TABLE 1. Characteristics of Compounds Ia-c, IVa-c, IXa,b, and XI-XIII

Compound	Found, %				Empirical formula	Calculated, %				mp, °C (and solvent for crystallization)	Yield, %, method A/B
	C	H	N	S (Se)		C	H	N	S (Se)		
Ia	58,13	5,21	17,10	13,09	$C_{12}H_{13}N_3OS$	58,28	5,30	16,99	12,96	213...215 (ethanol)	79
Ib	59,84	5,68	15,91	12,38	$C_{13}H_{15}N_3OS$	59,75	5,79	16,08	12,27	210...212 (ethanol)	73
Ic	49,16	4,60	14,11	26,79	$C_{12}H_{13}N_3OSe$	48,99	4,45	14,28	26,84	203...205 (ethanol)	70
IVa	58,47	7,08	16,20	9,11	$C_{12}H_{24}N_4O_2S$	58,60	6,94	16,08	9,20	165...167*	84/90
IVb	59,55	7,14	15,50	8,94	$C_{18}H_{26}N_4O_2S$	59,64	7,23	15,46	8,85	153...155*	78/81
IVc	51,54	6,01	14,22	20,08	$C_{17}H_{24}N_4O_2Se$	51,65	6,12	14,17	19,97	151...153*	77/69
IXa	58,66	5,05	16,90	12,88	$C_{24}H_{24}N_6O_2S_2$	58,52	4,91	17,06	13,02	216...218 (acetonitrile)	64
IXb	49,29	3,89	14,21	27,02	$C_{24}H_{24}N_6O_2Se_2$	49,16	4,13	14,33	26,93	215...217 (ethanol)	78
XI	53,99	3,95	9,55	7,12	$C_{20}H_{18}BrN_3O_2S$	54,06	4,08	9,46	7,22	165...167 (AcOH)	71
XII	61,70	5,45	15,42	11,60	$C_{14}H_{15}N_3OS$	61,51	5,53	15,37	11,73	156...158 (AcOH)	70
XIII	61,11	5,69	15,41	11,77	$C_{28}H_{32}N_6O_2S_2$	61,29	5,88	15,32	11,69	208...210 (isopropanol)	68

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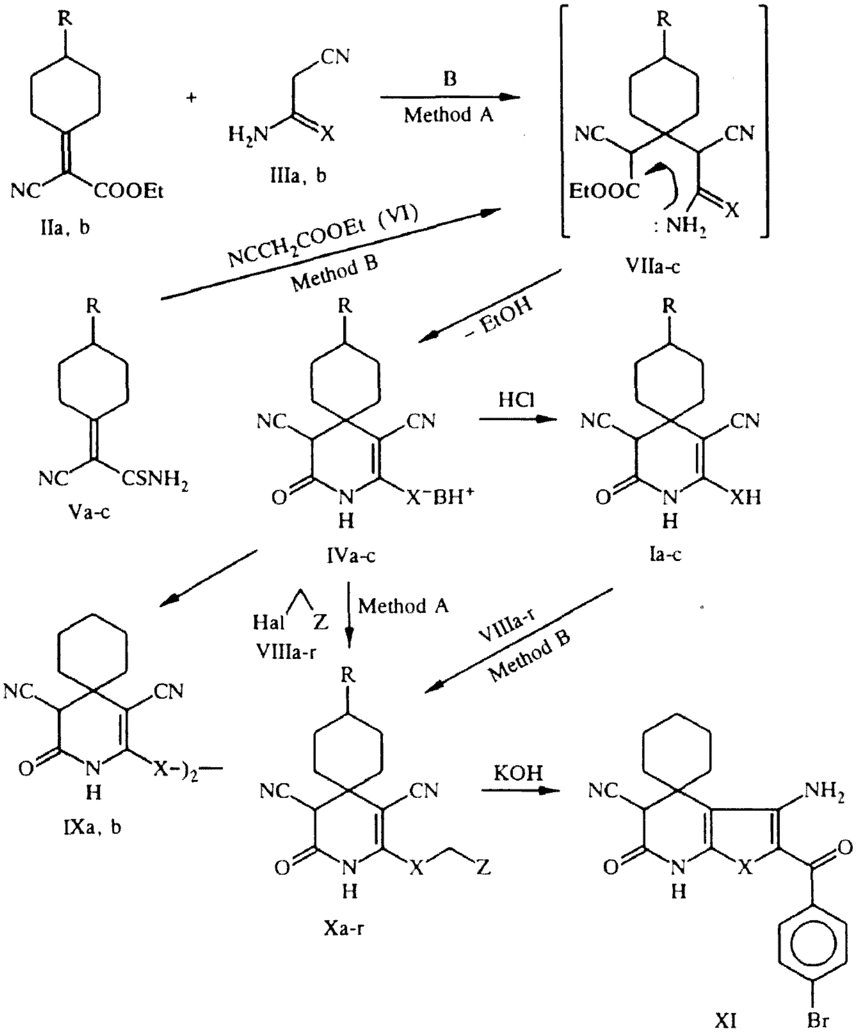
*Compound not recrystallized.

TABLE 2. IR and PMR Spectral Characteristics of Substituted Pyridones Ia-c, IVa-c, IXa,b, and XI-XIII

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm			
	N—H	C=O	$C\equiv N$	NH, s	5-H, s	$(CH_3)_2CHR(CH_2)$, m	other protons
Ia	3283	1724	2204, 2255	11,68	4,42	1,64	3,50 (1H, s, SH)
Ib	3278	1725	2200, 2252	11,69	4,43	1,66	3,52 (1H, s, SH)
Ic	3340	1724	2198, 2250	11,41	4,43	1,66	3,41 (1H, s, SeH)
IVa	3090, 3162	1707	2175, 2249	9,47	4,01	1,44	2,82 (3H, s, CH_3); 3,23 (4H, m, CH_2NCH_2); 3,79 (4H, m, CH_2OCH_2)
IVb	3240, 3303	1700	2178, 2254	9,46	4,00	1,56; 0,86	2,77 (3H, s, CH_3); 3,16 (4H, m, CH_2NCH_2); 3,77 (4H, m, CH_2OCH_2)
IVc	3200, 3395	1702	2198, 2245	9,60	4,04	1,45	2,76 (3H, s, CH_3); 3,14 (4H, m, CH_2NCH_2); 3,76 (4H, m, CH_2OCH_2)
IXa	3300	1739	2220, 2262	11,57	4,38	1,68	
IXd	3270	1725	2198, 2255	11,45	4,46	1,64	
XI	3300, 3485	1680	2250	12,05	4,57	1,55	7,86 (2H, br.s, NH_2); 7,63 (4H, q, Ar)
XII	3300	1712	2222, 2250		4,65	1,63	4,18 (2H, t, SCH_2); 3,43 (2H, t, NCH_2)
XIII	3204, 3308	1718	2218, 2246	11,33	4,58	1,70	3,03 (4H, m, CH_2SCH_2); 1,63 (4H, m, CH_2CH_2)

Scheme 1



B = N-methylmorpholine.
I, IV a R = H, X = S; b R = Me, X = S; c R = H, X = Se. II a R = H; b R = Me. III, IX a X = S; b X = Se.
VIII, X a Hal = Br, Z = 4-BrC_6H_4CO, X = S, R = H; b Hal = Br, Z = Et, X = S, R = H; c Hal = Cl,
Z = 4 -BrC_6H_4NHCO, X = S, R = H; d Hal = I, Z = Me, X = S, R = H; e Hal = Br, Z = 4-ClC_6H_4CO,
X = S, R = H; f Hal = I, Z = n- C_5H_{11}, X = S, R = H; g Hal = Cl, Z = $CONH_2$, X = S, R = H; h Hal = I,
Z = R = H, X = S; i Hal = Cl, Z = Ph, X = S, R = H; j Hal = I, Z = H, X = S, R = Me; k Hal = Br,
Z = CH = CH_2, X = S, R = Me; l Hal = Br, Z = 4-ClC_6H_4CO, X = S, R = Me; m Hal = Br, Z = 3,4-
$Cl_2C_6H_3CO$, X = S, R = H; n Hal = Cl, Z = $CONH_2$, X = Se, R = H; o Hal = I, Z = R = H,
X = Se; p Hal = Br, Z = PhCO, X = Se, R = H; q Hal = Br, Z = CH = CH_2, X = S, R = H;
r Hal = Br, ...; Z = coumarin-3-carbonyl, X = S, R = H.

The salts IVa-c are stable in the crystalline state and in solutions of the substance. However, in the presence of an alcoholic iodine solution, compounds IVa,b are oxidized to the derivatives IXa,b. Treatment of the substituted pyridinechalcogenols I with an aqueous solution of caustic in DMF, followed by the addition of an equimolar quantity of a halide (VIII), leads to the formation of substituted 2-alkylthio(seleno)-1,4,5,6-tetrahydropyridines (X) (Method B); this indicates the presence of an acidic proton, specifically in the XH group. Subsequent treatment of compound Xa with a sodium ethylate solution gives a substituted thieno[2,3-b]tetrahydropyridine (XI). Upon alkylation of the thiol Ia by 1,2-dibromoethane in a basic medium, a new heterocyclic system is obtained: 5-oxo-6,8-dicyano-2,3,6,7-tetrahydro(5H)spiro(cyclohexane-7-thiazolo[3,2-a]pyridine) (XII). In the case of 1,4-dibromobutane, the substituted butane XIII is obtained.

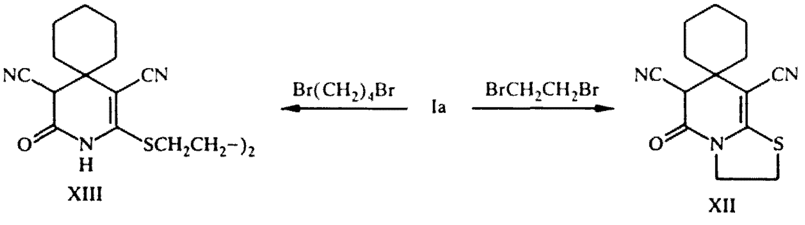


TABLE 3. Chemical Characteristics of Pyridones Xa-r

Compound	Found, %				Empirical formula	Calculated, %				mp, °C (and solvent for crystallization)	Yield, %, method A/B
	C	H	N	S (Se)		C	H	N	S (Se)		
Xa	53,98	4,17	9,33	7,34	$C_{20}H_{18}BrN_3O_2S$	54,06	4,08	9,46	7,22	188...190 (AcOH)	81/78
Xb	62,35	6,54	14,63	10,91	$C_{15}H_{13}N_3OS$	62,25	6,62	14,52	11,08	134...136 (butanol)	85/92
Xc	54,11	4,44	12,51	7,35	$C_{20}H_{19}BrN_4OS$	54,18	4,32	12,64	7,23	209...211 (AcOH)	77/79
Xd	60,94	6,31	12,32	11,55	$C_{14}H_{17}N_3OS$	61,06	6,22	15,26	11,64	155...157 (butanol)	80/85
Xe	60,18	4,62	10,44	7,91	$C_{20}H_{18}ClN_3O_2S$	60,07	4,54	10,51	8,02	173...175 (AcOH)	70/75
Xf	65,13	7,50	12,74	9,75	$C_{18}H_{25}N_3OS$	65,22	7,60	12,68	9,67	78...80 (ethanol)	81/85
Xg	55,17	5,41	18,52	10,48	$C_{14}H_{16}N_4O_2S$	55,25	5,30	18,41	10,53	182...184 (ethanol)	77/79
Xh	59,89	5,65	15,94	12,31	$C_{13}H_{15}N_3OS$	59,75	5,79	16,08	12,27	180...182 (AcOH)	74/82
Xi	67,77	5,51	12,37	9,61	$C_{19}H_{19}N_3OS$	67,63	5,68	12,45	9,50	127...129 (butanol)	75/79
Xj	60,88	6,03	15,31	11,70	$C_{14}H_{17}N_3OS$	61,06	6,22	15,26	11,64	177...179 (methanol)	85/88
Xk	63,65	6,12	14,04	10,75	$C_{16}H_{19}N_3OS$	63,76	6,35	13,94	10,64	119...121 (ethanol)	83/90
X*l*	61,07	4,95	10,02	7,59	$C_{21}H_{20}ClN_3O_2S$	60,94	4,87	10,15	7,75	178...180 (ethanol)	77/79
Xm	55,25	4,09	9,72	7,21	$C_{20}H_{17}Cl_2N_3O_2S$	55,31	3,95	9,67	7,38	185...187 (AcOH)	69/77
Xn	47,92	4,64	15,83	8,92	$C_{14}H_{16}N_4O_2Se$	47,87	4,59	15,95	9,11	181...183 (ethanol)	68/70
Xo	50,49	4,85	13,72	25,71	$C_{13}H_{15}N_3OSe$	50,66	4,91	13,63	25,62	187...189 (ethanol)	85/90
Xp	65,65	5,11	11,70	8,68	$C_{20}H_{19}N_3O_2S$	65,73	5,24	11,50	8,77	136...139 (ethanol)	68/75
Xq	62,80	6,06	14,58	10,98	$C_{15}H_{17}N_3OS$	62,69	5,96	14,62	11,16	144...146 (ethanol)	79/82
Xr	63,83	4,19	9,80	7,31	$C_{23}H_{19}N_3O_4S$	63,73	4,42	9,69	7,40	210...212 (butanol)	63/66

TABLE 4. Spectral Characteristics of Compounds Xa-r

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm; and SSCC (J), Hz				
	N—H	C=O	C≡N	NH, s	5-H, s	$(CH_2)_2CHR(CH_2)_2$, m	XCH_2	Z
Xa	3320	1735	2220, 2250	11,25	4,54	1,57	4,79 d	7,33...8,00 (4H, m, Ar)
Xb	3212	1715	2218, 2254	11,33	4,60	1,61	2,99 m	0,97 (3H, t, CH_3); 1,35 (2H, m, CH_2)
Xc	3300	1712	2210, 2248	11,39	4,55	1,62	3,99 s	10,50 (1H, s, NH); 7,53 (4H, s, Ar)
Xd	3215	1700	2205, 2250	11,30	4,60	1,60	3,02 m	1,21 (3H, t, CH_3)
Xe	3348	1734	2185, 2249	11,25	4,79	1,57	4,54 d	7,47...7,97 (4H, m, Ar)
Xf	3202	1713	2220, 2258	11,40	4,58	1,58	3,00 m	0,85 (3H, t, CH_3); 1,24 (8H, m, $4CH_2$)
Xg	3342, 3435	1711	2206, 2256	11,78	4,54	1,64	3,77 s	7,94 and 7,64 (2H, two-s, NH_2)
Xh	3280, 3435	1720	2195, 2250	11,21	4,59	1,63	2,50 s	—
Xi	3315	1710	2195, 2250	11,43	4,43	1,51	4,31 d, J = 13,4	7,30 (5H, s, Ph)
Xj	3200	1710	2215, 2260	11,18	4,60	1,60 m, 0,86 d	2,50 s	—
Xk	3190, 3275	1728	2230, 2260	11,28	4,48	1,62 m, 0,89 d	3,72 d, J = 7	5,79 (1H, m, CH=); 5,18 d (J = 5) and 5,05 (2H, s, CH_2=)
X*l*	3316	1725	2205, 2264	11,23	4,50	1,71 m, 0,90 m	4,79 s	7,47...8,00 (4H, m, Ar)
Xm	3374	1740	2190, 2250	11,25	4,61	1,61	4,83 s	7,50...8,14 (3H, m, Ar)
Xn	3333, 3435	1688	2205, 2254	11,88	4,53	1,63	3,73 s	7,94 and 7,61 (2H, two-s, NH_2)
Xo	3183	1700	2200, 2253	11,13	4,60	1,63	2,42 s	—
Xp	3300	1733	2188, 2265	11,23	4,50	1,60	4,83 s	7,40...7,98 (5H, m, Ph)
Xq	3174	1700	2215, 2245	11,30	4,51	1,58	3,68 m	5,75 (1H, m, CH=); 5,10 and 5,15 (2H, s and d, CH_2, J = 6)
Xr	3345	1711	2184, 2258		4,76 s, 4,53 s	1,59	3,82 d, 3,28 d	7,41...8,37 (5H, m, coumarinyl)

The spectroscopic and physicochemical data confirm the structure of the synthesized compounds IX-XIII (Tables 1-4).

EXPERIMENTAL

IR spectra of the synthesized compounds were taken on an IKS-29 spectrophotometer in white mineral oil. PMR spectra were registered in a Bruker-WP-100 SU instrument (100 MHz) in solutions in DMSO-d_6, internal standard TMS. The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in a 3:5 acetone-hexane system, developed in iodine vapor.

N-Methylmorpholinium 6-Oxo-3, 5-dicyano-1, 4,5, 6-tetrahydrospiro-(4′-R-cyclohexane-1′,4-pyridine)-2-olates (IVa-c). *A.* To a suspension of 10 mmoles of 4-R-cyclohexylidenecyanoacetic ester II and 10 mmoles of cyanothio(seleno)acetamide III in 15 ml of absolute ethanol, while stirring at 20°C (in the case of IIIb in an argon atmosphere), 20 mmoles of N-methylmorpholine was added. The reaction mixture was held at room temperature for 24 h, and the resulting precipitate of the product IV was filtered off and washed with ethanol and hexane. The characteristics of the salts IVa-c are listed in Tables 1 and 2.

B. To a suspension of 10 mmoles of cyclohexylidenecyanothioacetamide V and 10 mmoles of cyanoacetic ester VI in 15 ml of absolute ethanol, while stirring at 20°C, 20 mmoles of N-methylmorpholine was added, after which stirring was continued for 5 min until the original reactant V had completely disappeared. The reaction mass was held at room temperature for 24 h, and the resulting precipitate was separated and washed with ethanol and hexane. The product IVa obtained in this manner was identical to the sample synthesized by Method A, based on melting point and IR spectra.

6-Oxo-3,5-dicyano-1,4,5,6-tetrahydrospiro-(4′-R-cyclohexane-1′,4-pyridine)-2-thiols (Ia,b) and -selenol (Ic). A suspension of 10 mmoles of the corresponding salt IV in 10 ml of ethanol (in the case of IVc in an argon atmosphere), while stirring, was diluted with 10% hydrochloric acid to pH 5. The original salt thereupon dissolved; the resulting solution was filtered through a folded filter paper, and the filtrate was held for 24 h at room temperature. The resulting precipitate of the product was separated and then washed with ethanol and hexane. The characteristics of the pyridone products Ia-c are listed in Tables 1 and 2.

Bis[6-oxo-3,5-dicyano-1,4,5,6-tetrahydrospiro-(4′-R-cyclohexane-1′,4-pyryl-2-yl)] dilsulfide (IXa) and diselenide (IXb). To a suspension of 10 mmoles of the corresponding salt IV in 10 ml of ethanol, while stirring, 10 mmoles of iodine in 15 ml of ethanol was added at such a rate that the iodine was decolorized. Then the reaction mixture was diluted with 10 ml of water, and the resulting precipitate of the product IX was filtered off. The characteristics of compounds IXa,b are listed in Tables 1 and 2.

2-Alkylthio(seleno)-3,5-dicyano-4,5-dihydrospiro(4′-R-cyclohexane-1′,4-pyridin)-6-(1H)ones (Xa-r). *A.* To a suspension of 10 mmoles of the salt IV in 20 ml of ethanol, while stirring at 20°C, 10 mmoles of the halide VIII was added, and the mixture was stirred another 6 h, after which it was diluted with 10 ml of water and the precipitate of the product X was filtered off. The characteristics of these pyridones Xa-r are listed in Tables 3 and 4.

B. To a solution of 10 mmoles of the pyridone I in 10 ml of DMF, while stirring, 5.6 ml (10 mmoles) of a 10% aqueous KOH solution was added, and then, after 3 min, 10 mmoles of the alkyl halide VIII. The reaction mass was then stirred at room temperature for 4 h, after which it was diluted with 10 ml of water and the precipitated product was filtered off. The pyridones Xa-r that were obtained were identical to samples synthesized by Method A (based on melting point and TLC).

3-Amino-2-(4′-bromobenzoyl)-6-oxo-5-cyano-4,5,6,7-tetrahydrospiro(cyclohexane-4-thieno[2,3-b]pyridine) (XI). To a suspension of 10 mmoles of the pyridone Xa in 15 ml of absolute ethanol, while stirring, a solution prepared from 20 mmoles of metallic sodium and 15 ml of absolute ethanol was added, after which the material was brought to boiling and stirred without healing for 2 h. Then the reaction mass was diluted with 10% hydrochloric acid to pH 5, and the precipitated product was filtered off and washed successively with water, ethanol, and hexane. The characteristics of the thienopyridone XI are listed in Tables 1 and 2.

5-Oxo-6,8-dicyano-2,3,6,7-tetrahydro(5H)spiro(cyclohexane-7-thiazolo[3,2-a]pyridine) (XII). To a solution of 10 mmoles of the pyridone Ia in 10 ml of DMF, while stirring, 5.6 ml (10 mmoles) of a 10% aqueous KOH solution was added, and then 10 mmoles of 1,2-dibromoethane. The reaction mass was stirred for 1 h at 20°C, after which 5.6 ml (10 mmoles) of a 10% aqueous KOH solution was added, and the mixture was stirred for 3 h and then diluted with 10 ml of water. The precipitated product was filtered off and washed with water, ethanol, and hexane. The characteristics of the thiazolopyridone XII that was obtained are listed in Tables 1 and 2.

1,4-Bis[6′-oxo-3′,5′-dicyano-1′,4′,5′,6′-tetrahydrospiro(cyclohexane-4′-pyridin-2′-yl)thio]butane (XIII). To a solution of 10 mmoles of the pyridone Ia in 10 ml of DMF, while stirring, 10 mmoles (5.6 ml) of a 10% aqueous KOH solution was added, and then, after 3 min, 5 mmoles of 1,4-dibromobutane. The reaction mixture was stirred for 4 h at room temperature, then diluted with 10 ml of water. The precipitated product was filtered off and washed successively with water, ethanol, and hexane. The characteristics of this substituted butane XIII are listed in Tables 1 and 2.

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