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SYNTHESIS OF 6-METHYL-3-CYANO-5-ETHYLPYRIDINE-2(1H)-THIONE AND CONDENSED HETEROCYCLES BASED ON THIS COMPOUND

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It has been established that the direction of formylation of methyl propyl ketone depends on the reaction conditions. By condensation of the synthesized salts of 3-hydroxymethylene-2-pentanone with cyanothioacetamide, we have synthesized 6-methyl-3-cyano-5-ethylpyridine-2(1H)-thione and 6-propyl-3-cyanopyridine-2(1H)-thione, respectively, which are alkylated regioselectively by halides $ClCH_2Z$ (Z = Alk, COOAlk, COPh, $CONH_2$, CN) at the sulfur atom. These thiones and the derived 2-SCH_2Z-3-cyanopyridines have been used in the regioselective synthesis of substituted annelated heterocycles: 3-aminothieno[2,3-b]pyridines and 4-aminopyrido[2',3':2,3]thieno[4,5-d]pyrimidines.

Intensive searches for "antispidovye" preparations have led to the discovery of a new group of compounds of the non-nucleoside type that have manifested high activity as inhibitors of HIV-1 specific reverse transferase [1-3]. These are derivatives of 6-methyl-5-ethyl-3-cyano-2(1H)-pyridone (I), synthesized with 2-pentanone (II) as the starting material. On the basis of 2-pentanone, a regioselective method has been developed for the synthesis of a sulfur analog of compound I, namely 6-methyl-3-cyano-5-ethylpyridine-2(1H)-thione (III), also, 6-propyl-3-cyanopyridine-2(1H)-thione (IV) has been obtained. Compounds III and IV had been used previously in constructing certain condensed heterocyclic systems with potential biological activity.

It should be noted that the direction of the first stage in synthesis of the thiones III and IV, i.e., the formylation of the ketone II, is highly dependent on the reaction conditions. For example, if the reaction is carried out by a modified Claisen method (A) that we had used previously [4-8], a mixture of the salts (V) and (VI) is obtained; treatment of this mixture with cyanothioacetamide (VII) affords a mixture of the thiones III and IV in a 1:2 ratio (according to PMR spectroscopic data). The highest yield of these products is obtained by brief refluxing of a mixture of the salts V and VI with cyanothioacetamide VII in ethanol in the presence of acetic acid. By crystallization of the resulting mixture of pyridinethiones III and IV from acetic acid, compound IV is isolated. By varying the formylation conditions, the salt V can be obtained selectively, and from V the desired thione III. For this purpose we used a modified method (B) that was proposed in [1]. Dry ether is added to freshly prepared sodium ethylate; the reaction mass is chilled to 0°C and stirred while adding dropwise a mixture of ethyl formate and the ketone II. By interaction of the salt V with the amide VII in alcohol in the presence of acetic acid, the pyridine-2(1H)-thione III is obtained with a 57% yield.

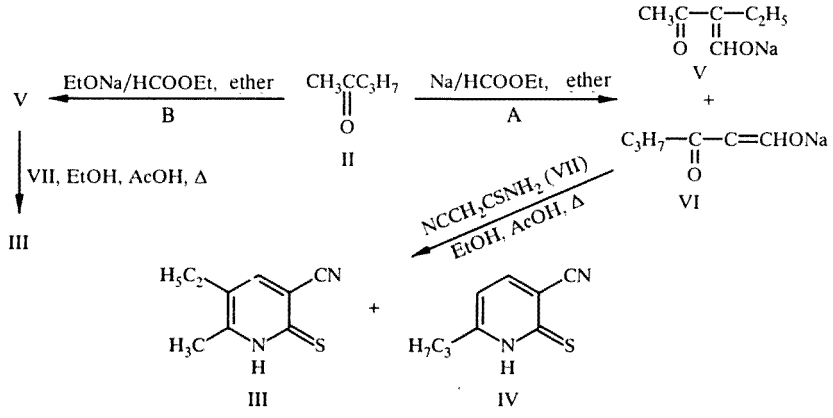

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TABLE 1. Characteristics of Compounds III, IV, and IX-XI

Compound	Empirical formula	mp, °C	Found (%)/ calculated (%)				Yield, %
			C	H	N	S	
III	$C_9H_{10}N_2S$	242...244	60,52 60,64	5,76 5,65	15,32 15,72	18,58 17,99	57
IV	$C_9H_{10}N_2S$	213...215	60,82 60,64	5,33 5,65	15,31 15,72	18,62 17,99	50
IX a	$C_{11}H_{13}N_3OS$	177...178	56,70 56,15	5,13 5,57	18,37 17,86	13,39 13,62	63
IX b	$C_{12}H_{14}N_2O_2S$	77...79	57,34 57,58	5,86 5,64	11,09 11,19	12,34 12,81	71
IX c	$C_{13}H_{16}N_2O_2S$	71...73	58,91 59,07	6,01 6,10	10,95 10,60	11,93 12,13	66
IX d	$C_{17}H_{16}N_2OS$	99...101	68,86 68,89	5,42 5,44	9,13 9,45	10,59 10,82	60
IX e	$C_{25}H_{42}N_2S$	55...56	74,74 74,57	10,24 10,51	6,69 6,96	7,84 7,96	71
IX f	$C_{11}H_{13}N_3OS$	138...139	55,84 56,15	5,63 5,57	16,87 17,86	13,09 13,62	69
X a	$C_{11}H_{13}N_3OS$	256...258	56,11 56,15	5,35 5,57	17,46 17,86	13,72 13,62	65
X b	$C_{12}H_{14}N_2O_2S$	257...259	57,77 57,58	6,00 5,64	10,94 11,19	12,52 12,81	60
X c	$C_{13}H_{16}N_2O_2S$	227...229	59,28 59,07	6,27 6,10	10,00 10,60	11,68 12,13	81
X d	$C_{11}H_{11}N_3S$	224...226	60,57 60,80	4,71 5,10	19,03 19,34	14,46 14,75	81
X e	$C_{17}H_{16}N_2OS$	172...174	68,52 68,89	5,51 5,44	8,75 9,45	10,57 10,82	69
X f	$C_{11}H_{11}N_3S$	139...141	60,95 60,80	4,96 5,10	19,23 19,34	14,58 14,75	59
X g	$C_{17}H_{16}N_2OS$	194...196	68,44 68,89	5,83 5,44	9,19 9,45	10,95 10,82	62
XI a	$C_{12}H_{12}N_4S$	276...277	59,41 58,99	5,14 4,95	22,56 22,93	13,56 13,12	79
XI b	$C_{12}H_{12}N_4S$	251...252	58,43 58,99	5,07 4,95	22,75 22,93	13,44 13,12	95

Compounds III and IV in the solid state are stable, yellowish orange powders. Spectroscopic data (see Experimental section) indicate that these compounds, like their numerous analogs that are substituted in the pyridine ring [4-6], exist in the thione tautomeric form. Thus, in the IR spectra of these compounds, we find a medium-intensity band of the C=S group at 1185 and 1204 cm^{-1} respectively, characteristic for pyridine-2(1H)-thiones [4, 5], and also an absorption band of the C≡N group at 2226 and 2230 cm^{-1}, respectively.

In the PMR spectra of the thiones III and IV, we observe signals in the upfield region from alkyl-group protons, and in the downfield region a broad singlet of the NH group (8.32 and 8.42 ppm, respectively) and a signal from protons bonded to the heterocycle: a 4-H singlet of compound III at 7.83 ppm, or two doublets 4-H and 5-H of compound IV at 7.89 and 6.74 ppm, respectively, with a characteristic SSCC ^3J = 8 Hz. In the ^{13}C NMR spectra, a signal of the $C_{(2)}$ atom of the pyridine ring is manifested at 175.54 and 166.29 ppm for compounds III and IV respectively, which is characteristic for pyridines containing a C=S fragment.

The substituted pyridine-2(1H)-thiones III and IV, in the presence of an equimolar quantity of aqueous KOH, are regioselectively alkylated in DMF solution by halides $ClCH_2Z$ (VIII) at the sulfur atom, forming S-substituted 3-cyanopyridines (IXa-f). The structure of the group IX compounds was proven by data obtained by physicochemical methods of analysis (Tables 1, 2, and 4). Thus, in the IR spectra there is an absorption band of a conjugated nitrile group in the 2220-2228 cm^{-1} region, and also bands of the groups Z (COOAlk, COPh, $CONH_2$, $C_{15}H_{31}$). A characteristic feature of the PMR spectra is the presence of a singlet signal from protons of the SCH_2Z group in the 3.95-4.82 ppm region.

We used the compounds IX in synthesizing annelated heterocycles (X, XI). Under the action of KOH in DMF solution at 20°C, the substituted pyridines IX are cyclized in the Thorpe—Ziegler reaction, forming 3-aminothieno[2,3-b]pyridines X.

It must be noted that when the mixture of thiones III and IV interacts under these conditions with the halides VIII (with Z = CN or COPh), derivatives of 6-propyl-3-cyanopyridine-2(1H)-thione IXf and Xf,g are well segregated in the form of a

TABLE 2. IR and PMR Spectra of Pyridines IX

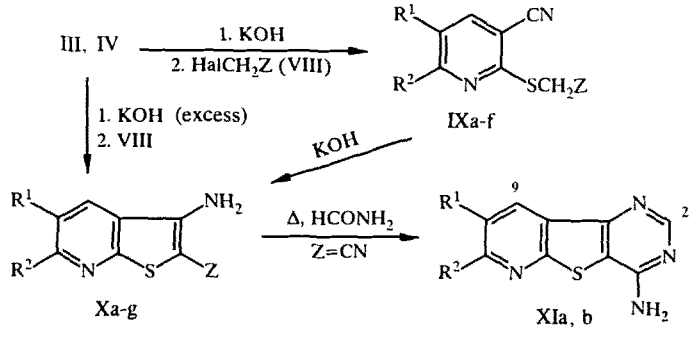
Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, chemical shift, δ, ppm, and SSCC (J), Hz				
		4-H	R^1	R^2	CH_2	Z
IXa	3362, 3190 ($CONH_2$); 2225 (CN); 1664 (δ, NH_2)	7,85 s	1,13 t, 2,51 g	2,39 s	3,97	7,14 s, 7,56 s
IXb	2224 (CN); 1737 (C=O)	7,89 s	1,12 t, 2,54 g	2,43 s	4,05 s	2,63 s
IXc	2224 (CN); 1736 (C=O)	7,84 s	1,12 t, 2,48 g	2,37 s	3,99 s	1,06 t, 4,06 g
IXd	2224 (CN); 1672 (C=O)	7,93 s*	1,08 t, 2,52 g	2,18 s	4,82 s	7,62...8,11 m*
IXe	2228 (CN); 2852, 2918 (alkyl)	7,58 s	* 2,50 s	2,43 s	1,78 t	1,05...1,50 m*
IXf	3364, 3180 ($CONH_2$); 2220 (CN); 1666 (δ, NH_2)	8,09 d, J = 8	7,16 d, J = 8	0,88 t, 1,70 m, 2,73 t	3,95 s	7,59 br. s

*Signal overlapped by signal of other fragment.

TABLE 3. IR and PMR Spectra of Thieno[2,3-b]pyridines X

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, chemical shift, δ, ppm, and SSCC (J), Hz				
		4-H	R^1	R^2	NH_2	Z
Xa	3470, 3420, 3310, 3110 ($CONH_2$); 1664 (δ, NH_2)	8,16 s	1,23 t, 2,65 q	2,54 s	7,08 s	7,13 s
Xb	3420, 3300, 3200 (NH_2); 1676, 1618 (δ, NH_2, C=O)	8,22 s	1,12 t, 2,63 q	2,54 s	7,33	3,75 s
Xc	3307, 3202, 3161 (NH_2); 1674, 1623 (δ, NH_2, C=O)	8,25 s	1,12 t, 2,67 q	2,54 s	7,20 s	1,28 t, 4,24 q
Xd	3400, 3340, 3208 (NH_2); 2188 (CN); 1644 (δ, NH_2)	8,26 s	1,13 t, 2,58 q	2,43 s	7,53 s	
Xe	3372, 3291, 3182 (NH_2); 1624, 1600 (δ, NH_2, C=O)	8,28 s	1,16 t, 2,55 q	2,44 s	8,36 s	7,48...7,72 m
Xf	3388, 3336, 3232 (NH_2); 2169 (CN); 1652 (δ, NH_2)	8,38 d J = 8,5	7,36 d J = 8,5	0,88 t, 1,70 q, 2,79 t	7,23 s	
Xg	3360, 3252, 3124 (NH_2); 1676, 1596 (δ, NH_2, C=O)	8,53 J = 8	7,34 J = 8	0,89 t, 1,71 q, 2,80 t	8,37 s	7,50...7,77 m

precipitate, probably because of their poorer solubility. Therefore, in synthesizing these compounds, it is not necessary to separate the original mixture of pyridinethiones. We had previously observed this sort of behavior of isomers in the alkylation of a mixture of 6-methyl-4-phenyl- and 4-methyl-6-phenyl-3-cyanopyridine-(1H)-thiones that is stably formed on the basis of benzoylacetone [4, 5, 9].



IX a-e, X a-e, XI a $R^1 = C_2H_5$, $R^2 = CH_3$; IXf, Xf, g, XI b $R^1 = H$, $R^2 = C_3H_7$; IX a, f, X a Z = $CONH_2$; IXb, Xb, Z = $COOCH_3$; IX c, X c Z = $COOC_2H_5$; IXd, Xe, g Z = COPh; IXe Z = $C_{15}H_{31}$; Xd, fZ = CN

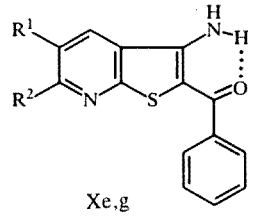
TABLE 4. ^{13}C NMR Spectra of Compounds IX and X

Compound	Chemical shift δ, ppm									
	CN (3-C)*	CH_2 (2-C)*	R^1	R^2	2-C (7a-C)*	3-C (3a-C)*	4-C	5-C	6-C	Z
IX b	115,04 s	32,06 t	13,42 k, 23,93 t	22,30 q	156,04 s	102,42 s	140,39 d	133,73 s	161,12 s	52,42 q, 169,42 s
IXc	115,58 s	32,05 t	13,14 k, 23,71 t	22,00 q	158,80 s	103,38 s	140,07 d	133,43 s	160,75 s	13,89 q, 60,88 t, 168,42 s
IX e	115,80 s	36,95 t	13,29 k, 23,72 t	21,79 q	156,17 s	103,46 s	140,37 d	133,54 s	160,07 s	128,23 d, 128,76 s, 133,38 s, 193,83 s
IX f	115,97 s	33,53 t		13,65 q, 21,57 t, 23,92 t	160,29 s	103,37 s	141,66 d	118,79 d	156,95 s	168,97
X a	145,70 s	96,55 s	13,60 k, 24,81 t	22,21 q	155,35 s	124,87 s	129,10 d	133,02 s	157,89 s	167,22 s
Xc	148,05 s	93,50 s	13,51 k, 24,80 t	22,41 q	156,53 s	124,05 s	129,62 d	133,19 s	159,09 s	14,51 s, 59,84 s
Xd	150,35 s	70,10 s	13,29 k, 24,68 t	22,19 q	156,35 s	122,71 s	129,36 d	133,72 s	159,19 s	115,98 s
Xe	150,79 s	102,16 s	13,22 k, 24,57 t	22,10 q	157,87 s	123,40 s	129,67 d	133,23 s	160,06 s	188,49 s, 126,98 s, 127,33 d, 128,05 d, 128,32 d, 130,56 d, 130,23 s
Xf	150,40 s	70,90 s		13,56 q, 22,15 t	159,9 s	122,12 s	131,28 d	119,49 d	163,94 s	115,84 s

*For compounds X.

The structure of the 3-aminothieno[2,3-d]pyridines X was confirmed by data obtained by physicochemical methods of analysis (see Tables 1, 3, and 4). In the IR spectra of these compounds there is a series of absorption bands of the amino group in the 1596-1664 and 3110-3470 cm^{-1} regions. The PMR spectra, in addition to other characteristic signals, contain signals from protons of the NH_2 group in the 7.08-8.37 ppm region.

It is interesting to note that the compounds Xe,g, in contrast to the other thienopyridines X, have an intramolecular hydrogen bond NH...O. This is evidenced by the shift to lower frequencies and the overlapping of the absorption bands of the NH_2 and CO=O groups in the IR spectra, and also by the shift of the signals from NH_2 group protons in the PMR spectra, 1.14-1.36 ppm downfield (see Table 3). The formation of an analogous intramolecular hydrogen bond in 3-amino-2-benzoyl-5,6-pentamethyleneselenopheno[2,3-b]pyridine, which has similar spectral characteristics, was demonstrated in [7] by means of x-ray structure analysis.



Xe,g

The presence of a reactive cyano group adjacent to the amino group in the molecules of compounds of IXd,f made it possible to use these compounds in the synthesis of pyridothienopyrimidines. Brief heating of the 3-amino-2-cyanothieno[2,3-b]pyridines Xd,f in formamide leads to the formation of the 4-aminopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidines XIa,b respectively, with almost quantitative yields. In the IR spectra of these products there is a series of absorption bands of the NH group in the 1568-1668 and 2956-3245 cm^{-1} regions. In the PMR spectra of compounds XIa,b there are singlet signals from protons of the NH_2 group (at 7.50 and 7.60 ppm, respectively) and from the 2-H proton of the pyrimidine ring (at 8.53 and 8.52 ppm, respectively); the ^{13}C NMR spectra contain a characteristic doublet signal from the $C_{(2)}$ atom (at 155.08 and 155.38 ppm, respectively).

EXPERIMENTAL

The melting points were determined on a Kofler heating stage; IR spectra were taken in Specord M-80 and Perkin-Elmer 457 instruments in KBr tablets; PMR spectra were taken in a Bruker WM-250 instrument in DMSO-d_6 solutions; ^{13}C NMR spectra were taken in a Bruker WM-300 instrument in DMSO-d_6 solutions. Elemental analyses for C, H, and N were performed in a Perkin-Elmer C,H,N-analyzer.

Data from the elemental analyses and other characteristics of the synthesized compounds III, IV, and IX-VI are presented in Table 1.

Mixture of Sodium Salts of 3-Hydroxymethylene-2-pentanone (V) and 1-Hydroxymethylene-2-pentanone (VI). ***Method A.*** To a suspension of 2.3 g (0.1 mole) of finely divided metallic sodium in 150 ml of dry ether, while stirring and cooling with ice, 0.5 ml of ethanol was added, and then over the course of 30 min a solution of 10.6 g (0.1 mole) of the ketone II and 8.0 g (0.1 mole) of ethyl formate in 70 ml of ether. The reaction mixture was stirred for 1 h while cooling, and then another 3 h at room temperature. After one day, the precipitated product was filtered off, washed with ether, and dried, obtaining 11.1 g (yield 82%) of a mixture of the salts V and VI.

Sodium Salt of 3-Hydroxymethylene-2-pentanone (V). ***Method B.*** The reaction was performed under argon. To 1.63 g (71.0 mmoles) of metallic sodium, 15 ml of absolute ethanol was added while cooling, and then, after the reaction had ended, 60 ml of dry ether. To the reaction mass, chilled to 0°C, a mixture of 6.1 g (71.0 mmoles) of the ketone II and 5.7 g (77.0 mmoles) of ethyl formate was added over the course of 2 h. The reaction mixture was left overnight at room temperature, after which the product was filtered off, washed with ether, and vacuum-dried. Yield of salt V 4.0 g (41%). PMR spectrum, ppm: 0.67 (3H, t, CH_3), 1.86 (3H, s, CH_3), 1.97 (2H, q, CH_2, overlapped with CH_3), 8.93 (1H, s, CH).

6-Methyl-5-ethyl-3-cyanopyridine-2(1H)-thione (III). To a solution of 2.72 g (20 mmoles) of the salt V in 10 ml of ethanol, 1.2 ml of glacial acetic acid was added; then, 1.15 g (20 mmoles) of the amide VII was added while stirring. The mixture was heated to boiling, while adding an additional 0.6 ml of acetic acid. The precipitate that formed after cooling was filtered off, washed with alcohol and hexane, and recrystallized from alcohol. IR spectrum, cm^{-1}: 2226 (C≡N), 1185 (C=S).

PMR spectrum, ppm: 1.06 (3H, t, $\underline{CH_3}CH_2$), 2.37 (3H, s, 6-CH_3), 2.43 (2H, q, CH_2), 7.83 (1H, s, 4-H), 8.32 (1H, s, NH). ^{13}C NMR spectrum, ppm: 13.49 ($\underline{CH_3}CH_2$), 16.83 (6-CH_3), 22.72 ($CH_3\underline{CH_2}$), 113.39 ($C_{(3)}$), 117.37 ($\underline{C}\equiv N$), 126.49 ($C_{(5)}$), 144.64 ($C_{(4)}$), 152.99 ($C_{(6)}$), 175.54 (C=S).

6-Propyl-3-cyanopyridine-2(1H)-thione (IV). Analogous to the synthesis of the thione III, from a mixture of the salts V and VI, a 1:2 mixture of the products III and IV was obtained; by recrystallization of this mixture from acetic acid, the pyridinethione IV was obtained. IR spectrum, cm^{-1}: 1204 (C=S), 2230 (C≡N). PMR spectrum, ppm: 0.86 (3H, t, $\underline{CH_3}CH_2CH_2$), 1.52 (2H, m, $CH_3\underline{cH_2}CH_2$), 2.47 (2H, t, $CH_3CH_2\underline{CH_2}$), 6.74 (1H, d, J = 8 Hz, 5-H), 7.89 (1H, d, J = 8.0 Hz, 4-H), 8.42 (1H, s, NH). ^{13}C NMR spectrum, ppm: 13.53 ($\underline{CH_3}CH_2CH_2$), 22.00 ($CH_3\underline{CH_2}CH_2$), 37.37 ($CH_3CH_2\underline{CH_2}$), 103.60 ($C_{(3)}$), 111.40 ($C_{(5)}$), 111.40 ($C_{(5)}$), 119.49 (C≡N), 141.89 ($C_{(4)}$), 160.99 ($C_{(6)}$), 166.29 (C=S).

2-(Z-Methylthio)-3-cyanopyridines (IXa-f). To a solution of 2 mmoles of the thione III or IV in 8 ml of DMF, while stirring, 1.1 ml of a 10% aqueous KOH solution and 2 mmoles of a halide VIII were added. The reaction mixture was stirred for 25-30 min and then diluted with water; the resulting precipitate was filtered off, washed with alcohol and hexane, and recrystallized from alcohol.

3-Amino-2-(Z-thieno)[2,3-b]pyridines (Xa-g). To a solution of 1 mmole of the pyridinethione III or IV in 3 ml of DMF, while stirring vigorously, 0.56 ml of a 10% aqueous KOH solution and 1 mmole of a halide VIII were added. The reaction mixture was stirred for 20 min, after which another 0.5 ml of KOH solution was added and the stirring was continued for 20 min; the product was precipitated by adding water and then filtered off, washed with alcohol and hexane, and recrystallized from alcohol.

4-Aminopyrido[3′2′:4,5]thieno[3,2-d]pyrimidines (XIa,b). A mixture of 0.21 g (1 mmole) of the thienopyridine Xd or Xf and 10 ml of formamide was refluxed for 1 h, 5 ml of water was added, and the resulting precipitate was filtered off and washed with ethanol and hexane.

Compound XIa. IR spectrum, cm^{-1}: 3320, 3244, 3144, 1616 (NH_2). PMR spectrum, ppm: 1.26 (3H, t, $\underline{CH_3}CH_2$), 2.81 (2H, q, CH_2), 2.65 (3H, s, 7-CH_3), 7.50 (2H, s, NH_2), 8.32 (1H, s, 9-H), 8.53 (1H, s, 2-H). ^{13}C NMR spectrum, ppm: 13.54 (q, $\underline{CH_3}CH_2$), 22.33 (q, 6-CH_3), 24.68 (t, CH_2), 112.00 (s, $C_{(4a)}$), 126.30 (s, $C_{(9a)}$), 129.35 (d, $C_{(9)}$), 134.44 (s, $C_{(8)}$), 147.74 (s, $C_{(1a)}$), 155.08 (d, $C_{(2)}$), 158.70 (s, $C_{(5a)}$), 159.71 (s, $C_{(7)}$), 162.94 (s, $C_{(4)}$).

Compound XIb. IR spectrum, cm^{-1}: 3320, 3144, 2956, 1652 (NH_2). PMR spectrum, ppm: 0.9 (3H, t, $\underline{CH_3}CH_2CH_2$), 1.73 (2H, m, $CH_3\underline{CH_2}CH_2$), 2.84 (2H, t, $CH_3CH_2\underline{CH_2}$), 7.41 (1H, d, J = 8.2 Hz, 8-H), 7.61 (2H, s, NH_2), 8.46 (1H, d, J = 8.2 Hz, 9-H), 8.52 (1H, s, 2-H). ^{13}C NMR spectrum, ppm: 13.71 (q, $\underline{CH_3}CH_2CH_2$), 22.45 (t, $CH_3\underline{CH_2}CH_2$), 111.82 (s, $C_{(4a)}$), 120.27 (d, $C_{(8)}$), 125.51 (s, $C_{(9a)}$), 131.39 (d, $C_{(9)}$), 153.50 (s, $C_{(1a)}$), 155.38 (d, $C_{(2)}$), 158.45 (s, $C_{(5a)}$), 161.08 (s, $C_{(7)}$), 164.64 (s, $C_{(4)}$).

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REFERENCES

1. J. M. Hoffman, J. S. Wai, C. M. Thomas, R. B. Levin, J. A. O'Brien, and M. E. Goldman, J. Med. Chem., **35**, 3784 (1992).
2. W. S. Saari, J. M. Hoffman, C. M. Thomas, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, A. M. Stern, and P. S. Anderson, J. Med. Chem., **34**, 2922 (1991).
3. W. S. Saari, J. S. Wai, T. E. Fisher, C. M. Thomas, J. M. Hoffman, C. S. Rooney, A. M. Smith, J. H. Jones, D. L. Bamberger, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero, W. A. Schleif, and P. S. Anderson, J. Med. Chem., **35**, 3792 (1992).
4. L. A. Rodinovskaya, Doctoral Dissertation, Moscow (1994).
5. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, Sulfur Rep., **13**, No. 1, 155 (1992).
6. L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and V. P. Litvinov, Khim. Geterotsikl. Soedin., No. 6, 805 (1988).
7. V. P. Litvinov, Yu. A. Sharanin, L. A. Rodinovskaya, V. N. Nesterov, V. E. Shklover, and Yu. T. Struchkov, Chem. Scripta, **29**, 327 (1989).

8. V. N. Nesterov, L. A. Rodinovskaya, V. P. Litvinov, Yu. A. Sharanin, A. M. Shestopalov, V. Yu. Morshikov, V. I. Shvedov, V. E. Shklover, and Yu. T. Struchkov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 140 (1988).
9. V. P. Litvinov, Yu. A. Sharanin, L. A. Rodinovskaya, A. M. Shestopalov, V. Yu. Morshikov, and V. K. Promonenkov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2760 (1984).