

Synthesis of Ammonium 5-Arylcarbamoyl-4-heteryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates and 4-Heteryl-5-carbamoyl-6-methyl-3-cyano-1,4-dihydropyridine-2-selenolates

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Abstract—The condensation of enamines derived from acetoacetanilides, heterocyclic aldehydes, and cyanothioacetamide yielded ammonium 5-arylcarbamoyl-5-heteryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates, which were subsequently used for the synthesis of substituted 2-alkylthio-1,4-dihydropyridines, 2-alkylthiopyridines, and thieno[2,3-*b*]pyridines. The reaction of acetoacetamide with heteroaromatic aldehydes and cyanoselenoacetamide in the presence of *N*-ethylmorpholine yielded *N*-ethylmorpholinium 4-heteryl-5-carbamoyl-6-methyl-3-cyano-1,4-dihydropyridine-2-selenolates, from which substituted 2-alkylseleno-1,4-dihydropyridines were prepared.

4-Heteryl-substituted pyridine and 1,4-dihydropyridine derivatives exhibit cardiotonic [1], analgetic [2], herbicidal [3, 4], and other kinds of biological activity [5, 6]. Particularly active efforts are made to find among these compounds calcium channel activators [7–12].

Proceeding with the development of new synthetic routes to 4-heteryl-substituted 1,4-dihydropyridine-2-thiols (-selenols) [13, 14], which are potentially bioactive compounds, we studied the condensation of enamines derived from acetoacetanilides (**I**) with heteroaromatic aldehydes **II** and cyanoacetamide **III**. We found that this reaction (ethanol, 20°C) yields ammonium 4-arylcarbamoyl-4-heteryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates **IV**. The reaction apparently involves the Knoevenagel condensation [15] yielding alkenes **V**, which subsequently alkylate enamine **I** following the Stork reaction pattern [15] to give products **VI**. We failed, however, to isolate these products because of their easy subsequent regioselective intramolecular cyclization into compounds **IV**.

The structures of salts **IV** were proved by physicochemical and spectral methods (Tables 1, 2), and also by alkylation with alkyl halides **VII** to obtain sulfides **VIII**. This transformation indicates that compounds **IV** are salts with the negative charge localized on the sulfur atom [16], in line with the general relationships of the chemistry of pyridinechalcogenones [17, 18]. Treatment of substituted 2-carbamoylmethyl-1,4-dihydropyridine **VIIIg** with 10% aqueous KOH in DMF

resulted in aromatization of the dihydropyridine ring and closure of the thiophene ring; the reaction product was 3-amino-2-carbamoyl-6-methyl-4-(5-methylthien-2-yl)-5-(2-methoxyphenylcarbamoyl)thieno[2,3-*b*]pyridine **IX**. Note that the dehydrogenation of 2-alkylthio-1,4-dihydropyridines under the conditions of the Thorpe–Ziegler reaction was found previously in our studies of the chemical properties of compounds related to **VIII** [13].

Treatment of a suspension of salt **IVa** in ethanol with 10% HCl yields substituted pyridine-2(1*H*)-thione **X**. Thus, oxidation of intermediate 1,4-dihydropyridines (apparently, with atmospheric oxygen) occurs under the conditions of both base and acid catalysis. The subsequent reaction of pyridinethione **X** with alkyl halides **VIII** and **VIII***m* in DMF in alkaline solution yields the corresponding 2-alkylthiopyridines **XIa** and **XIb** whose structure was proved by physicochemical and spectral data (Tables 1, 2).

The condensation of enamine **Ib** and cyanothioacetamide **III** with furfural **IIe** yields substituted 3,4-dihydropyridine-2(1*H*)-thione **XII** and not the corresponding ammonium thiolate. Alkylation of **XII** with compounds **VIIb–VIIe** and **VIIg–VIIk** in DMF in the presence of an alkali yields the corresponding organic sulfides **XIIIa–XIIIi**. No products of oxidation of the dihydropyridine core were detected in the reaction mixture. At the same time, in condensation of enamine **Ic** and cyanothioacetamide **III** with 3-furan-carbaldehyde **IIf**, the corresponding salt or dihydro-

Table 1. Constants, yields, melting points, and elemental analyses of salts **IVa–IVd**, **XXa**, and **XXb**, dihydropyridines **VIIIa–VIIIh**, **XII**, **XIIIa–XIIIi**, **XIVa–XIVe**, **XXIIIa**, and **XIIIb**, thieno[2,3-*b*]pyridine **IX**, and pyridines **X**, **XIa**, **XIb**, and **XV**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IVa	77	147–149 ^a	66.92	6.40	15.54	C ₂₅ H ₂₉ N ₅ OS	67.09	6.53	15.65
IVb	72	295–298 ^a	58.59	4.98	14.80	C ₂₃ H ₂₄ ClN ₅ O ₂ S	58.78	5.15	14.90
IVc	70	178–180 ^a	59.39	5.90	11.42	C ₂₄ H ₂₈ N ₄ O ₃ S ₂	59.48	5.82	11.56
IVd	81	151–153 ^a	56.28	4.98	11.37	C ₂₃ H ₂₅ ClN ₄ O ₂ S ₂	56.49	5.15	11.46
VIIIa	62	153–155 (BuOH)	64.78	5.55	11.96	C ₂₅ H ₂₆ N ₄ O ₃ S	64.91	5.67	12.11
VIIIb	61	188–190 (BuOH)	65.94	4.30	11.79	C ₂₆ H ₂₁ ClN ₄ OS	66.02	4.48	11.85
VIIIc	82	241–243 (BuOH)	57.27	3.88	16.03	C ₂₁ H ₁₈ ClN ₅ O ₂ S	57.34	4.12	15.92
VIIId	70	235–237 (BuOH)	54.42	4.13	11.60	C ₂₇ H ₂₁ BrClN ₅ O ₂ S	54.51	3.56	11.77
VIIIe	81	203–204 (BuOH)	55.04	3.97	9.12	C ₂₈ H ₂₅ BrN ₄ O ₃ S ₂	55.17	4.13	9.19
VIII f	74	212–214 (AcOH)	63.20	5.11	10.44	C ₂₈ H ₂₆ N ₄ O ₃ S ₂	63.38	4.94	10.56
VIIIg	63	115–117 (AcOH)	57.96	4.70	12.26	C ₂₂ H ₂₂ N ₄ O ₃ S ₂	58.13	4.88	12.33
VIIIh	69	173–176 (AcOH)	64.11	5.04	10.12	C ₂₉ H ₂₈ N ₄ O ₃ S ₂	63.95	5.18	10.29
IX	76	305–308 ^b (DMF)	58.21	4.19	12.25	C ₂₂ H ₂₀ N ₄ O ₃ S ₂	58.39	4.45	12.38
X	68	288–290 (AcOH)	66.71	4.32	15.40	C ₂₀ H ₁₆ N ₄ OS	66.65	4.48	15.54
XIa	94	68–70 (EtOH)	65.70	4.28	11.12	C ₂₈ H ₂₂ N ₄ O ₄ S	65.87	4.34	10.97
XIb	84	207–209 (AcOH)	65.41	4.07	10.78	C ₂₈ H ₂₁ ClN ₄ O ₂ S	65.56	4.13	10.92
XII	77	275–277 ^b (EtOH)	57.96	3.71	11.27	C ₁₈ H ₁₄ ClN ₃ O ₂ S	58.14	3.80	11.30
XIIIa	65	278–279 (AcOH)	61.72	4.03	10.87	C ₂₆ H ₂₁ ClN ₄ O ₃ S	61.84	4.19	11.09
XIIIb	62	235–238 (AcOH)	65.11	4.25	9.87	C ₃₀ H ₂₃ ClN ₄ O ₃ S	64.92	4.18	10.09
XIIIc	72	178–179 (BuOH)	64.87	4.19	9.02	C ₂₅ H ₂₀ ClN ₃ O ₂ S	65.00	4.36	9.10
XIIId	68	274–275 (BuOH)	53.30	3.29	9.54	C ₂₆ H ₂₀ BrClN ₄ O ₃ S	53.48	3.45	9.60
XIIIe	69	278–280 (AcOH)	55.87	3.92	12.94	C ₂₀ H ₁₇ ClN ₄ O ₃ S	56.01	4.00	13.06
XIII f	91	175–177 (AcOH)	62.28	4.11	7.89	C ₂₇ H ₂₂ ClN ₃ O ₄ S	62.36	4.26	8.08
XIIIg	73	159–160 (BuOH)	59.28	5.14	8.49	C ₂₄ H ₂₄ ClN ₃ O ₄ S	59.32	4.98	8.65
XIIIh	80	193–194 (AcOH)	56.70	3.85	9.31	C ₂₁ H ₁₈ ClN ₃ O ₄ S	56.82	4.09	9.47
XIIIi	69	166–169 (EtOH)	57.62	4.27	9.03	C ₂₂ H ₂₀ ClN ₃ O ₄ S	57.70	4.40	9.18
XIVa	57	220–221 (BuOH)	64.58	4.70	11.05	C ₂₇ H ₂₄ N ₄ O ₄ S	64.79	4.83	11.19
XIVb	64	201–203 (BuOH)	67.58	4.70	10.04	C ₃₁ H ₂₆ N ₄ O ₄ S	67.61	4.76	10.18
XIVc	65	158–160 (EtOH)	68.11	4.89	9.13	C ₂₆ H ₂₃ N ₃ O ₃ S	68.25	5.07	9.18
XIVd	63	233–235 (AcOH)	56.12	3.87	9.54	C ₂₇ H ₂₃ BrN ₄ O ₄ S	55.96	4.00	9.67
XIVe	60	217–219 (BuOH)	59.30	4.69	13.37	C ₂₁ H ₂₀ N ₄ O ₄ S	59.42	4.75	13.20
XV	72	210–212 (AcOH)	63.42	3.85	10.38	C ₂₈ H ₂₁ ClN ₄ O ₃ S	63.57	4.00	10.59
XXa	64	261–263 ^a	50.95	5.64	13.40	C ₁₈ H ₂₄ N ₄ O ₃ Se	51.07	5.71	13.23
XXb	67	183–185 ^a	49.03	5.74	12.80	C ₁₈ H ₂₄ N ₄ O ₂ SSe	49.20	5.51	12.75
XXIIIa	80	191–193 (BuOH)	46.02	3.95	12.28	C ₁₃ H ₁₃ N ₃ OSSe	46.16	3.87	12.42
XXIIIb	71	188–190 (MeOH)	46.12	3.17	15.30	C ₁₄ H ₁₂ N ₄ OSSe	46.29	3.33	15.42

^a Was not recrystallized. ^b Sublimes at 240°C. ^c Sublimes at 200°C.

pyridinethione were not isolated. Chromatographic analysis showed a complex composition of the mixture. Addition of alkyl halides resulted in formation of substituted 2-alkylthio-1,4-dihydropyridines **XIVa–XIVe** in yields not exceeding 65%.

The use of benzyl chloroacetate **VIIj** as alkylating

agent in condensation of enamine **Ib** and cyanothioacetamide **III** with pyridinecarbaldehyde **IIf** results in formation of substituted pyridine **XV**.

Our results show that multicomponent condensation involving enamines derived from acetoacetanilides (**I**), heteroaromatic aldehydes **II**, cyanothioacet-

Table 2. IR and ^1H NMR spectra of salts **IVa–IVd**, **XXa**, and **XXb**, dihydropyridines **VIIIa–VIIIh**, **XII**, **XIIIa–XIIIi**, **XIVa–XIVe**, **XXIIIa**, and **XIIIb**, thieno[2,3-*b*]pyridine **IX**, and pyridines **X**, **XIa**, **XIb**, and **XV**

Comp. no.	IR spectrum, ν , cm^{-1}		^1H NMR spectrum, δ , ppm (<i>J</i> , Hz)		
	$\nu(\text{C}\equiv\text{N})$, $\nu(\text{C}=\text{O})$	$\nu(\text{CH})$, $\delta(\text{CONH})$	CONH (s), N^1H (s)	C^4H (s), C^6Me (s)	other signals
IVa^a	2175	3310, 1684	9.27, 8.65	4.58, 2.12	1.57 m [6H, $(\text{CH}_2)_3$], 1.80 s (3H, Me), 3.00 t (4H, CH_2NCH_2 , <i>J</i> 4.68), 7.06–7.63 m (5H, H arom.), 7.81 s (1H, C^2H), 8.39 m (2H, H arom.)
IVb^a	2188	3324, 3667	9.34, 7.94	4.55, 2.08	3.08 t (4H, CH_2NCH_2 , <i>J</i> 4.65), 3.75 t (4H, CH_2OCH_2 , 7.13 d (2H, C^2H and C^6H of pyridine, <i>J</i> 9.02), 7.24 d and 7.56 d (2H each, C_6H_4 , <i>J</i> 6.01), 8.41 d (2H, C^3H and C^5H of pyridine)
IVc^a	2182	3330, 1672	8.21, 8.01	4.43, 2.20	2.37 s (3H, Me), 3.03 t (4H, CH_2NCH_2 , <i>J</i> 4.65), 3.70 s (3H, MeO), 3.82 t (4H, CH_2OCH_2), 6.64 m (3H, H arom.), 6.92 m (2H, H arom.), 8.15 d (1H, C^3H of thiophene, <i>J</i> 3.32)
IVd^a	2190	3330, 1664	9.22, 7.91	4.95, 2.19	2.06 s (3H, Me), 3.06 t (4H, CH_2NCH_2 , <i>J</i> 4.66), 3.77 t (4H, CH_2OCH_2), 6.63 d (1H, C^4H of thiophene, <i>J</i> 5.04), 7.00 d (1H, C^5H of thiophene), 7.12 d and 7.54 d (2H each, C_6H_4 , <i>J</i> 8.84)
VIIIa	2202, 1730	3295, 1660	9.10, 9.04	4.88, 2.18	0.95 t (3H, $\text{CH}_3\text{CH}_2\text{CH}_2$, <i>J</i> 7.20), 1.62 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.89 s (3H, Me), 3.85 d and 3.94 d (1H each, SCH_2 , 2J 16.0), 4.05 t (2H, OCH_2 , <i>J</i> 7.15), 7.08 m (4H, C_6H_4), 7.33 d.d (1H, C^5H of pyridine, <i>J</i> 2.70), 7.55 d (1H, C^4H of pyridine, <i>J</i> 5.18), 8.96 d (2H, C^6H of pyridine)
VIIIb	2196	3327, 1655	9.60, 9.21	4.75, 2.13	4.23 d and 4.26 d (1H each, SCH_2 , 2J 5.72), 6.96 d (2H, C^3H and C^5H of pyridine, <i>J</i> 4.64), 7.16 d and 7.55 d (2H each, C_6H_4 , <i>J</i> 8.84), 7.28 br.s (5H, Ph), 8.39 d (2H, C^2H and C^6H , <i>J</i> 4.30)
VIIIc	2210	3339, 1660	10.35, 9.66	4.80, 2.16	3.16 s (2H, SCH_2), 7.17 m (4H, H arom.), 7.56 m (3H, H arom. and NH_2), 7.93 br.s (1H, NH_2), 8.45 d (2H, C^2H and C^6H of pyridine, <i>J</i> 1.62)
VIIId	2207	3346, 1677	10.50, 9.68	4.82, 2.17	3.86 s (2H, SCH_2), 7.19 m (4H, H arom.), 7.40 d (2H, H arom., <i>J</i> 8.78), 7.56 m (4H, H arom.), 8.43 d (2H, C^2H and C^6H of pyridine, <i>J</i> 3.82), 9.66 s (1H, NHCO)
VIIIe	2188	3296, 1665	10.49, 8.31	4.71, 2.79	2.43 s (3H, Me), 3.73 s (3H, MeO), 3.84 d and 3.87 d (1H each, SCH_2 , 2J 12.52), 6.63 d (1H, C^3H of thiophene, <i>J</i> 3.50), 6.76 d (1H, H arom., <i>J</i> 3.42), 6.87 t (1H, H arom., <i>J</i> 5.14), 6.92 d (1H, H arom., <i>J</i> 5.14), 7.05 t (1H, H arom., <i>J</i> 5.03), 7.48 d and 7.55 d (2H each, 4- BrC_6H_4 , <i>J</i> 8.86), 7.94 d (1H, C^4H of thiophene, <i>J</i> 3.50), 9.63 s (1H, NHCO)
VIII f	2195	3308, 1654	10.38, 8.10	4.37, 2.30	2.43 s (3H, Me), 3.73 s (3H, MeO), 3.84 d and 3.87 d (1H each, SCH_2 , 2J 12.32), 6.62 d (1H, C^3H of thiophene, <i>J</i> 3.32), 6.78–6.93 m (4H, H arom.), 7.06 t (1H, H arom., <i>J</i> 7.60), 7.24 t (2H, H arom., <i>J</i> 7.48), 7.60 d (2H, H arom., <i>J</i> 7.56), 8.13 d (1H, C^4H of thiophene, <i>J</i> 3.32)
VIIIg	2200	3345, 1674	10.57, 8.19	4.70, 2.25	2.44 s (3H, Me), 3.55 d and 3.64 d (1H each, SCH_2 , 2J 14.94), 3.72 s (3H, MeO), 6.64 d (1H, C^3H of thiophene, <i>J</i> 3.18), 6.77–6.98 m (4H, C_6H_4), 7.60 br.s and 7.93 br.s (1H each, NH_2), 8.07 d (1H, C^4H of thiophene)
VIIIh	2204	3296, 1666	10.14, 8.05	4.71, 2.27	2.29 s (3H, Me), 2.45 s (3H, Me), 3.73 s (3H, MeO), 3.88 s (2H, SCH_2), 6.23 d (1H, C^3H of thiophene, <i>J</i> 3.34), 6.79–7.20 m (H, H arom.), 7.46 d (1H, H arom., <i>J</i> 7.58), 8.15 d (1H, C^4H of thiophene), 9.77 s (1H, CONH)
IX	–	3204, 3345, 3412, 1676	9.35	2.50	2.64 s (3H, Me), 3.79 (3H, MeO), 5.97 br.s (2H, C^3NH_2), 6.78–7.02 m (7H, H arom. and CONH_2), 7.66 d (1H, H arom., <i>J</i> 7.02)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν , cm^{-1}		^1H NMR spectrum, δ , ppm (J , Hz)		
	$\nu(\text{C}\equiv\text{N})$, $\nu(\text{C}=\text{O})$	$\nu(\text{CH})$, $\delta(\text{CONH})$	CONH (s), N^1H (s)	C^4H (s), C^6Me (s)	other signals
X^b	2224	3397, 1658	9.76	2.54	1.87 s (3H, Me), 7.06 m (4H, C_6H_4), 7.54 d.d (1H, C^4H of pyridine, J 4.55), 7.89 t and 7.91 t (1H, C^5H of pyridine, J 1.92), 8.68 s (1H, C^2H of pyridine), 8.73 d (1H, C^6H of pyridine, J 1.90)
XIa	2218, 1703	1675	9.20	2.44	1.85 s (3H, Me), 4.82 s (2H, SCH_2), 6.89 d (1H, H arom., J 4.13), 6.98 d (1H, H arom., J 2.43), 7.09 m (3H, H arom.), 7.44 s (1H, H arom.), 7.52 m (2H, H arom.), 7.90 m (1H, H arom.), 8.68 d (2H, H arom., J 8.25), 9.76 br.s (2H, 2OH)
XIb	2226, 1714	1673	9.75	2.38	1.89 s (3H, Me), 4.90 s (2H, SCH_2), 7.02 m (4H, H arom.), 7.53 m (1H, H arom.), 7.62 d and 8.14 d (2H each, 4- ClC_6H_4 , J 8.29), 7.90 d (1H, H arom., J 5.01), 8.69 m (2H, H arom.)
XII	2254	1662	11.98, 9.96 2.13	4.97 d (J 10.02),	4.54 d (1H, C^3H of pyridine, J 10.02), 6.33 d (1H, C^3H of furan, J 1.94), 7.36–7.60 m (6H, H arom.)
XIIIa	2188	3334, 1675	10.35, 9.59	4.94, 2.16	3.83 s (2H, SCH_2), 6.09 d (1H, C^3H of furan, J 3.10), 6.23 d.d (1H, C^4H of furan, J 1.84), 7.01–7.37 (7H, H arom.), 7.58 m (3H, H arom.), 9.80 br.s (1H, CONH)
XIIIb	2197	3302, 1677	10.43, 9.64	4.99, 2.16	3.96 d and 4.09 d (1H each, SCH_2 , 2J 14.66), 6.12 d (1H, C^3H of furan, J 3.12), 6.27 e. d (1H, C^4H of furan, J 1.78), 7.19 d and 7.63 d (2H each, C_6H_4 , J 8.80), 7.53 m (4H, H arom.), 7.75 d (2H, H arom., J 7.22), 7.86 d (1H, C^5H of furan, J 2.30), 8.12 d (1H, H arom., J 8.24), 9.82 br.s (1H, CONH)
XIIIc	2202	3295, 1590	9.58, 9.19	4.82, 2.11	4.14 d and 4.32 d (1H each, SCH_2 , 2J 13.08), 5.95 d (1H, C^3H of furan, J 2.82), 6.25 d.d (1H, C^4H of furan, J 1.76), 7.18 d and 7.60 d (2H each, C_6H_4 , J 8.80), 7.28 m (5H, Ph), 7.41 d (1H, C^5H of furan, J 1.14)
XIIId	2200	3334, 1645	10.47, 9.62	4.97, 2.14	3.06 s (2H, SCH_2), 6.09 d (1H, C^3H of furan, J 3.08), 6.25 d.d (1H, C^4H of furan, J 1.84), 7.19 d and 7.61 d (2H each, 4- ClC_6H_4 , J 8.84), 7.39 d (1H, C^5H of furan, J 1.96), 7.42 d and 7.54 d (2H each, 4- BrC_6H_4 , J 9.00), 9.63 s (1H, CONH)
XIIIe	2189	3302, 3415, 1587	10.32, 9.60	4.93, 2.14	3.58 s (2H, SCH_2), 6.08 d (1H, C^3H of furan, J 2.96), 6.27 d.d (1H, C^4H of furan, J 1.12), 7.18 d and 7.60 d (2H each, C_6H_4 , J 8.80), 7.40 d (1H, C^5H of furan, J 1.74), 7.55 br.s and 7.90 br.s (1H each, NH_2)
XIIIf	2203, 1711	3332, 1618	9.63, 9.18	4.97, 2.06	3.80 d and 4.04 d (1H each, SCH_2 , 2J 15.40), 5.13 s (2H, OCH_2), 6.08 d (1H, C^3H of furan, J 2.70), 6.26 d.d (1H, C^4H of furan, J 2.02), 7.20 d and 7.63 d (2H each, C_6H_4 , J 8.78), 7.33 m (5H, Ph), 7.35 d (1H, C^5H of furan, J 1.69)
XIIIg	2208, 1714	3315, 1672	9.61, 9.17	4.98, 2.11	0.93 t (3H, Me, J 6.14), 1.38 m (2H, CH_2), 1.60 m (2H, CH_2), 3.74 d and 3.95 d (1H each, SCH_2 , 2J 15.46), 4.08 t (2H, OCH_2 , J 6.56), 6.09 d (1H, C^3H of furan, J 3.06), 6.27 d.d (1H, C^4H of furan, J 1.84), 7.19 d and 7.62 d (2H each, C_6H_4 , J 8.84), 7.42 d (1H, C^5H of furan, J 1.70)
XIIIh	2202, 1719	3307, 1645	9.65, 9.20	4.93, 2.11	3.69 s (3H, MeO), 3.78 d and 3.94 d (1H each, SCH_2 , 2J 15.46), 6.09 d (1H, C^3H of furan, J 3.04), 6.26 d.d (1H, C^4H of furan, J 1.64), 7.19 d and 7.62 d (2H each, C_6H_4 , J 7.90), 7.42 d (1H, C^5H of furan, J 0.80)
XIIIi	2198, 1714	3295, 1668	9.59, 9.17	4.92, 2.12	1.27 t (3H, Me, J 6.24), 3.72 d and 3.91 d (1H each, SCH_2 , 2J 15.08), 4.14 q (2H, OCH_2 , J 6.24), 6.09 d (1H, C^3H of furan, J 3.34), 6.27 d.d (1H, C^4H of furan, J 2.18), 7.18 d and 7.69 d (2H each, C_6H_4 , J 8.58), 7.40 d (1H, C^5H of furan, J 1.90)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν , cm^{-1}		^1H NMR spectrum, δ , ppm (J , Hz)		
	$\nu(\text{C}\equiv\text{N})$, $\nu(\text{C}=\text{O})$	$\nu(\text{CH})$, $\delta(\text{CONH})$	CONH (s), N^1H (s)	C^4H (s), C^6Me (s)	other signals
XIVa	2196	3300, 1663	10.40, 8.16	4.41, 2.28	3.78 s (3H, MeO), 6.43 s (1H, C^2H of furan), 6.87 m (3H, H arom.), 7.03 t (1H, H arom., J 7.52), 7.29 t (2H, H arom.), 7.50 d (2H, H arom., J 9.04), 7.60 d (2H, H arom., J 7.90), 8.09 d (1H, H arom., J 7.72), 9.91 br.s (1H, CONH)
XIVb	2190	3341, 1672	10.41, 8.16	4.51, 2.24	3.75 s (3H, MeO), 4.97 d and 5.06 d (1H each, SCH_2 , 2J 16.15), 6.42 s (1H, C^2H of furan), 6.86 m (3H, H arom.), 7.57 m (5H, H arom.), 7.75 d.d (2H, H arom., J 4.38), 7.86 d (1H, H arom., J 6.44), 8.07 d.d (2H, H arom., J 4.66), 9.90 br.s (1H, CONH)
XIVc	2205	3294, 1666	9.21, 8.16	4.39, 2.21	3.76 s (3H, MeO), 4.14 d and 4.27 d (1H each, SCH_2 , 2J 12.38), 6.28 s (1H, C^2H of furan), 6.87 m (3H, H arom.), 7.28 m (5H, Ph), 7.39 m (1H, H arom.), 7.48 m (1H, H arom.), 8.04 m (1H, H arom.)
XIVd	2198	3337, 1670	10.43, 8.15	4.49, 2.25	3.78 s (3H, MeO), 3.70 d and 3.96 d (1H each, SCH_2 , 2J 14.19), 6.41 s (1H, C^5H of furan), 6.90 m (4H, H arom.), 7.38–7.58 m (5H, H arom.), 8.05 d (1H, H arom., J 7.66), 9.77 br.s (1H, CONH)
XIVe	2191	3345, 1662	10.34, 8.23	4.49, 2.23	3.50 d and 3.71 d (1H each, SCH_2 , 2J 17.11), 3.77 s (3H, MeO), 6.41 s (1H, C^2H of furan), 6.91 m (4H, H arom.), 7.49 m (1H, H arom.), 7.58 br.s and 7.92 br.s (1H each, NH_2), 8.02 d (1H, H arom., J 7.78)
XV	2222, 1718	1668	10.44	2.47	4.20 s (2H, SCH_2), 5.19 s (2H, OCH_2), 7.20 d (2H, C_6H_4 , J 8.82), 7.36 m (9H, H arom.), 8.64 d (2H, C^2H and C^6H of pyridine, J 4.66)
XXa^a	2180	3330, 3456, 1674	7.95	4.48, 2.08	1.15 t (3H, Me, J 6.25), 2.96 m (6H, CH_2NCH_2 and CH_3CH_2), 3.74 t (4H, CH_2OCH_2 , J 4.38), 5.93 d (1H, C^3H of furan, J 2.96), 6.28 d.d (1H, C^4H of furan, J 2.40), 6.65 br.s (2H, NH_2), 7.45 d (1H, C^5H of furan, J 1.20)
XXb^a	2175	3300, 3474, 1682	8.03	4.67, 2.09	1.17 t (3H, Me, J 6.25), 3.05 m (6H, CH_2NCH_2 and CH_3CH_2), 6.65 br.s (2H, NH_2), 6.88 m (2H, C^3H and C^4H of thiophene), 7.24 d (1H, C^5H of thiophene, J 4.6)
XXIIIa	2188	3420, 1684	9.09	4.88, 2.10	2.39 s (3H, Me), 6.90 m (2H, C^3H and C^4H of thiophene), 8.11 br.s (2H, NH_2), 7.36 d (1H, C^5H of thiophene, J 4.01)
XXIIIb	2200, 2252	3338, 1660	9.30	4.99, 2.12	3.98 s (2H, CH_2), 6.84 m (4H, C^3H and C^4H of thiophene and NH_2), 3.42 d (1H, C^5H of thiophene, J 3.98)

^a The N^+H proton signal is not observed, probably because of deuterium exchange. ^b The N^1H proton signal is not observed, probably because of deuterium exchange.

amide **III**, and alkyl halides **VII** is a convenient route to ammonium 5-arylcarbamoyl-4-heteryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates **IV**, 2-alkylthio-1,4-dihydropyridines **VIII**, **XIII**, and **XIV**, and the corresponding dehydrogenated analogs **XI** and **XIV** (Scheme 1).

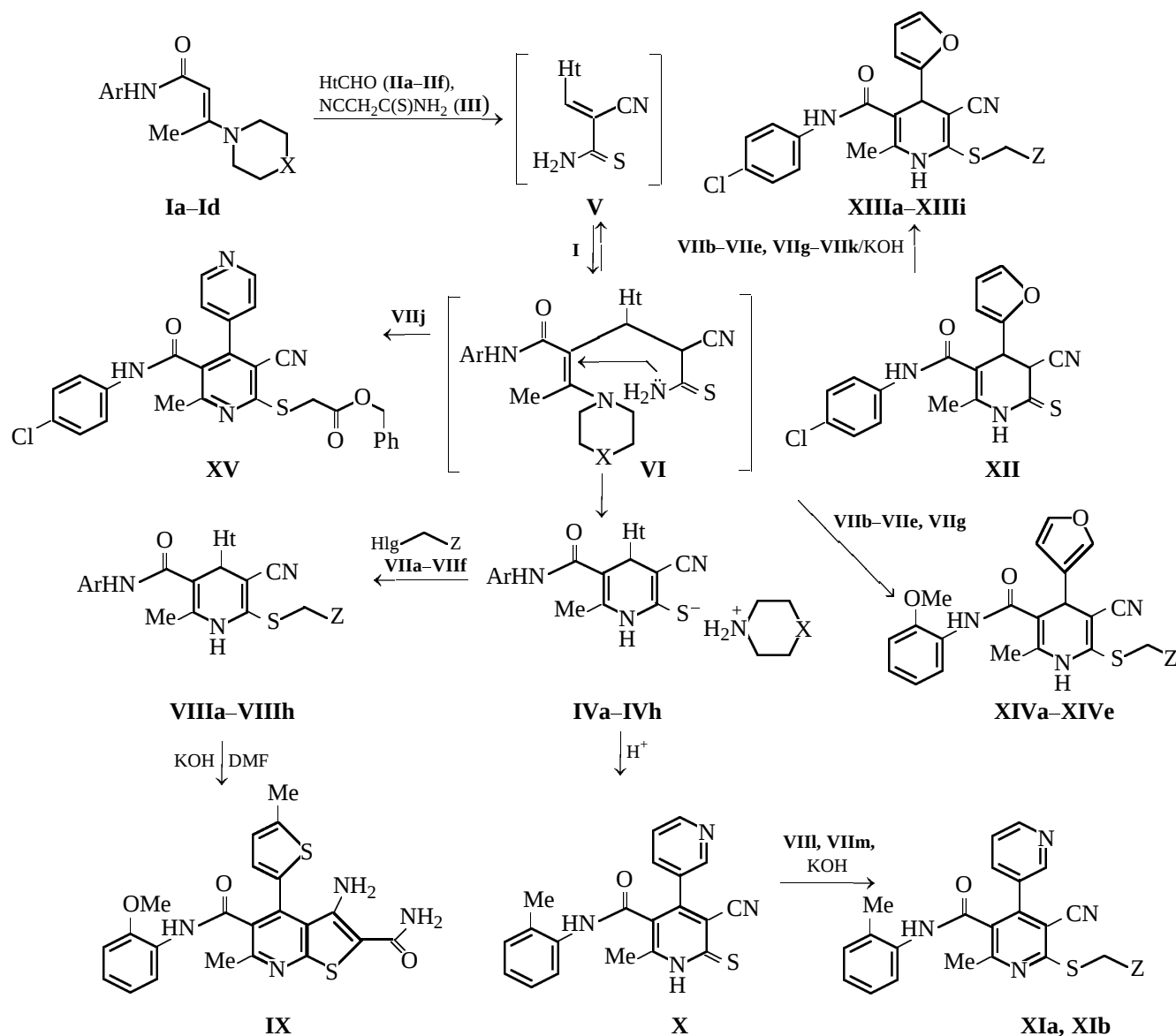
It appeared impossible to prepare by Scheme 1 selenium analogs of compounds **IV** by using cyano-selenoacetamide **XVI** instead of cyanothioacetamide **III** because of the predominance of the competing condensation of enamine **I** with CH acid **XVI**. The reaction yielded morpholinium 4-methyl-6-oxo-3-cy-

ano-1,6-dihydropyridine-2-selenolate **XVII**, which was prepared previously by the reaction of the acetoacetanilide enamine with cyano selenoacetamide [19] (Scheme 2).

The replacement of enamine **I** by acetoacetamide **XVIII** and the use of morpholine as catalyst result in cyclodimerization of cyano selenoamide **XVI** to 4,6-diamino-3-cyanopyridine-2(1*H*)-selenone **XIX**, which was prepared previously by treatment of **XVI** with bases [20] (Scheme 3).

With *N*-ethylmorpholine used as catalyst in the reaction of acetoacetamide **XVIII** with cyanoseleno-

Scheme 1.

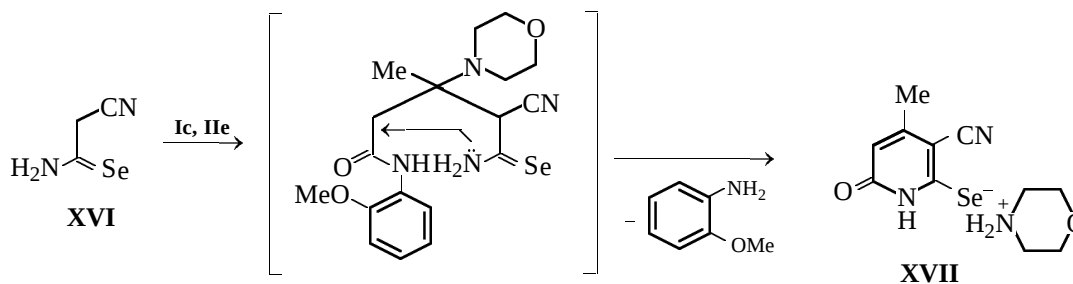


I, Ar = 2-MeC₆H₄, X = CH₂ (**a**); Ar = 4-ClC₆H₄, X = O (**b**); Ar = 2-MeC₆H₄, X = O (**c**); Ar = 4-ClC₆H₄, X = CH₂ (**d**); **II**, Ht = 3-pyridyl (**a**), 4-pyridyl (**b**), 5-methylthien-2-yl (**c**), 3-methylthien-2-yl (**d**), 2-furyl (**e**), 3-furyl (**f**); **IV**, Ar = 2-MeC₆H₄, Ht = 3-pyridyl, X = CH₂ (**a**); Ar = 4-ClC₆H₄, Ht = 3-pyridyl, X = O (**b**); Ar = 2-MeOC₆H₄, Ht = 5-methylthien-2-yl, X = O (**c**); Ar = 4-ClC₆H₄, Ht = 3-methylthien-2-yl, X = O (**d**); **VII**, Hlg = Cl (**a-k**), Br (**l, m**); **VII**, Z = CO₂Pr (**a**), Ph (**b**), CONH₂ (**c**), 4-BrC₆H₄NHCO (**d**), PhNHCO (**e**), 2-MeC₆H₄NHCO (**f**), 1-naphthylcarbamoyl (**g**), CO₂Et (**h**), CO₂Me (**i**), CO₂CH₂Ph (**j**), CO₂Bu (**k**), 3,4-(HO)₂C₆H₃CO (**l**), 4-ClC₆H₄ (**m**); **VIII**, Ar = 2-MeC₆H₄, Ht = 3-pyridyl (**a**); Ar = 4-ClC₆H₄, Ht = 4-pyridyl (**b-d**); Ar = 2-MeOC₆H₄, Ht = 5-methylthien-2-yl (**e-h**); **VIII**, Z = CO₂Pr (**a**), Ph (**b**), CONH₂ (**c, g**), 4-BrC₆H₄NHCO (**d, e**), PhNHCO (**f**), 2-MeC₆H₄NHCO (**h**); **XI**, Z = 3,4-(HO)₂C₆H₃CO (**a**), 4-ClC₆H₄CO (**b**); **XIII**, **XIV**, Z = PhNHCO (**a**), 1-naphthylcarbamoyl (**b**), Ph (**c**), 4-BrC₆H₄NHCO (**d**), CONH₂ (**e**), CO₂CH₂Ph (**f**), CO₂Bu (**g**), CO₂Me (**h**), CO₂Et (**i**).

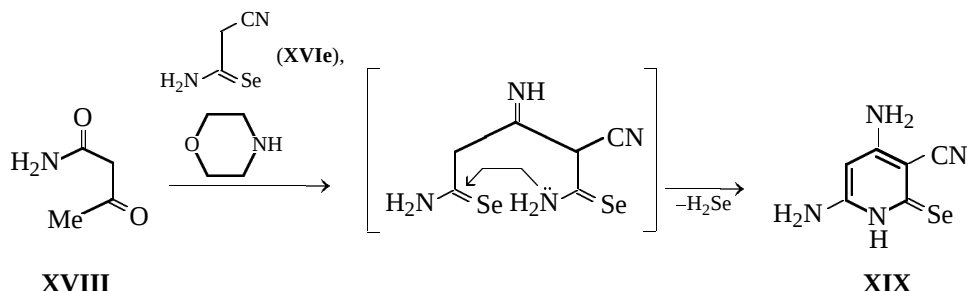
acetamide **XVI** and heteroaromatic aldehydes **II**f and **II**g, the reaction changes pathway toward formation of N-ethylmorpholinium 4-heteraryl-5-carbamoyl-6-methyl-3-cyano-1,4-dihydropyridine-2-selenolates **XX**. The reaction involves the Knoevenagel condensation re-

sulting in formation of hetarylmethylenecyanoselenoacetamides **XXI** *in situ*. They can be obtained and isolated by two-component condensation of aldehydes **II**f and **II**g with cyanoselenoacetamide **XVI** [21]. The subsequent reaction involves formation of the corre-

Scheme 2.

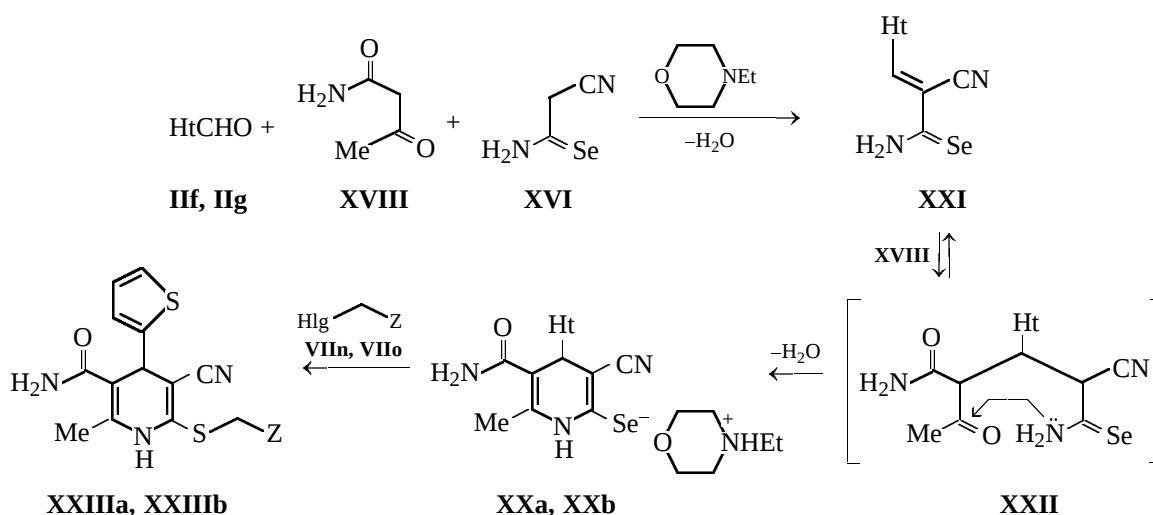


Scheme 3.



II, Ht = 2-thienyl (**g**); **VII**, Hlg = I, Z = H (**n**), Hlg = Cl, Z = CN (**o**); **XX**, Ht = 2-furyl (**a**), 2-thienyl (**b**); **XXIII**, Z = H (**a**), CN (**b**).

Scheme 4.



sponding Michael adducts **XXII** whose regioselective cyclization yields substituted ammonium 1,4-dihydropyridine-2-selenolates **XX** (Scheme 4).

The structures of salts **XX** were confirmed by their transformation into the corresponding organic selenides **XXIII** by alkylation with **VIIIn** and **VIIo**. The IR spectra of substituted 1,4-dihydropyridines **XX** and **XXIII** contain characteristic absorption bands of the stretching vibrations of the conjugated cyano group

at 2175–2200 cm^{-1} . The ^1H NMR spectra of **XX** and **XXIII** contain, along with the signals of protons in substituents (Tables 1, 2), also characteristic signals of the N^1H and C^4H protons of the 1,4-dihydropyridine ring at δ 7.95–9.30 and 4.48–4.99 ppm, respectively, which is consistent with published data [22–25].

EXPERIMENTAL

The IR spectra were taken on an IKS-29 spectrometer (mulls in mineral oil). The ^1H NMR spectra were

taken on Bruker WP-100SY (100 MHz, compounds **IVa**, **IVb**, **X**, **XII**, **XVII**, **XIX**, **XXa**, **XXb**, **XXIIIa**, **XXIIIb**), Gemini-200 (199.975 MHz, compounds **IVd**, **VIIIb–VIIIId**, **VIIIg**, **VIIIh**, **XIIIa–XIIIi**, **XIVa**, **XIVc–XIVe**, **XV**), Bruker AC-200 (200.13 MHz, compound **VIIIa**), Bruker WM-250 (250.13 MHz, compound **XIb**), Bruker AM-300 (300.13 MHz, compound **IVc**), and Bruker DR-500 (500.13 MHz, compounds **VIIIe**, **VIIIf**, **IX**, **XIa**, **XIVb**) spectrometers in DMSO-*d*₆, internal reference Me₄Si. The mass spectra were recorded on a Kratos MS-890 spectrometer (70 eV) (Table 3). The melting points were determined with a Kofler unit. The reaction progress was monitored by TLC (Silufol UV-254, acetone–hexane, 3 : 5, development with iodine vapor).

Ammonium 5-arylcarbamoyl-4-hetaryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates IVa–IVd. A mixture of appropriate enamine derived from acetoacetanilide (**I**), heteroaromatic aldehyde **II**, and cyanothioacetamide **III** (10 mmol each) in 15 ml of ethanol was stirred for 15–20 min at 20°C to obtain a homogeneous phase, after which the mixture was allowed to stand at 20°C for a day. The precipitate was filtered off and washed with ethanol and hexane.

5-Arylcarbamoyl-4-hetaryl-2-Z-methylthio-6-methyl-3-cyano-1,4-dihydropyridines VIIIa–VIIIh. A suspension containing appropriate salt **IV** and alkyl halide **VIII** (10 mmol each) in 12 ml of DMF was stirred for 5 h at 20°C and then diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane.

3-Amino-6-methyl-4-(5-methylthien-2-yl)-5-(2-methoxyphenylcarbamoyl)-2-carbamoylthieno[2,3-*b*]-pyridine IX. A 5.6-ml portion of 10% aqueous KOH was added with stirring to a solution of 4.5 g of **VIIIg** in 15 ml of DMF. The mixture was allowed to stand at room temperature for 48 h, after which it was diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane.

6-Methyl-5-(2-methylphenylcarbamoyl)-4-(3-pyridyl)-3-cyanopyridine-2(1*H*)-thione X. A stirred suspension of 4.5 g of **IVa** in 20 ml of ethanol was slowly acidified with 10% HCl to pH 6. The resulting solution was filtered and kept for 48 h at room temperature. The crystalline precipitate of **X** was filtered off and washed with water, ethanol, and hexane.

6-Methyl-5-(2-methylphenylcarbamoyl)-4-(3-pyridyl)-2-Z-methylthio-3-cyanopyridines XIa and XIb. To a stirred solution of 3.6 g of pyridinethione **X** in 15 ml of DMF, we added in succession 5.6 ml of 10% aqueous KOH and 10 mmol of appropriate

alkyl halide **VII**. The resulting mixture was stirred for 2 h and allowed to stand for a day at room temperature. Then the mixture was diluted with an equal volume of water, and the precipitate was separated and washed with water, ethanol, and hexane.

6-Methyl-4-(2-furyl)-5-(4-chlorophenylcarbamoyl)-3-cyano-3,4-dihydropyridine-2(1*H*)-thione XII was prepared similarly to **IV** starting from enamine **Ib**, furfural **Ile**, and cyanothioacetamide **III**.

6-Methyl-4-(2-furyl)-5-(4-chlorophenylcarbamoyl)-3-cyano-2-Z-methylthio-1,4-dihydropyridines XIIIa–XIIIi were prepared similarly to **XI** starting from 3,4-dihydropyridinethione **XII** and appropriate alkyl halides **VII**.

6-Methyl-5-(2-methoxyphenylcarbamoyl)-4-(3-furyl)-3-cyano-2-Z-methylthio-1,4-dihydropyridines XIVa–XIVe. A mixture of 2.6 g of **Ic**, 0.9 ml of 3-furancarbaldehyde **IIf**, and 1.0 g of cyanothioacetamide **III** in 15 ml of ethanol was stirred for 15 min at 20°C until the starting reactants fully dissolved, after which it was allowed to stand at 20°C for a day. Then 10 mmol of appropriate alkyl halide **VII** was added, and the mixture was stirred for 2 h and then allowed to stand for 48 h, after which it was diluted with an equal volume of water. The precipitate was filtered off.

5-Benzyloxycarbonylmethylthio-6-methyl-4-(4-pyridyl)-5-(4-chlorophenylcarbamoyl)-3-cyanopyridine XV was prepared similarly to **XIV** starting from enamine **Ib**, 4-pyridinecarbaldehyde **IIf**, cyanothioacetamide **III**, and benzyl chloroacetate **VIIj**.

Morpholinium 4-methyl-6-oxo-3-cyano-1,6-dihydropyridine-2-selenolate XVII. A mixture of 1.5 g of cyanoselenoacetamide **XVI**, 2.6 g of enamine **Ic**, and 0.83 ml of furfural **Ile** in 15 ml of absolute ethanol was stirred for 15 min at 20°C under argon and then allowed to stand at 20°C for a day. The precipitate was filtered off and washed with absolute ethanol and hexane; yield 64%. The melting point and ¹H NMR spectrum are in agreement with published data [19].

4,6-Diamino-3-cyanopyridine-2(1*H*)-selenone XIX. A mixture of 1.5 g of cyanoselenoacetamide **XVI**, 0.83 ml of furfural **Ile**, 1 g of acetoacetamide **XVIII**, and 0.9 ml of morpholine in 15 ml of absolute ethanol was stirred for 15 min at 20°C under argon and then allowed to stand at 20°C for a day. The precipitate was filtered off and washed with absolute ethanol and hexane; yield 61%. The melting point and ¹H NMR spectrum are in agreement with published data [20].

Table 3. Mass spectra of compounds **VIIIb–VIIIh**, **IX**, **XIIIa–XIIIi**, **XIVa–XIVe**, and **XV**, m/z (I_{rel} , %)

Comp. no.	$[M]^+$	Other peaks
VIIIb	473 (4)	394 (5), 381 (39), 346 (18), 318 (6), 254 (10), 241 (7), 153 (11), 127 (16), 92 (15), 91 (100), 77 (4), 65 (13), 51 (5), 39 (6)
VIIIc	440 (8)	422 (41), 348 (6), 286 (11), 240 (16), 227 (10), 222 (62), 208 (11), 191 (12), 163 (12), 155 (19), 153 (57), 140 (16), 129 (30), 128 (11), 127 (100), 126 (13), 125 (29), 100 (12), 99 (17), 91 (17), 90 (28), 75 (18), 65 (18), 64 (15), 63 (29), 62 (13), 61 (7)
VIIId	^a	469 (11), 467 (11), 440 (10), 421 (28), 247 (10), 213 (32), 197 (12), 173 (98), 171 (100), 155 (15), 153 (39), 127 (24), 92 (14), 63 (18), 43 (16)
VIIIe	^a	411 (6), 396 (13), 363 (10), 315 (8), 287 (20), 261 (8), 241 (37), 213 (11), 199 (92), 197 (100), 171 (68), 149 (39), 134 (18), 123 (78), 108 (30), 90 (87), 80 (20), 63 (51), 51 (24), 39 (36)
VIII f	^a	396 (12), 288 (11), 262 (25), 261 (36), 260 (15), 241 (20), 149 (45), 135 (34), 123 (50), 120 (32), 119 (100), 108 (49), 106 (36), 98 (13), 97 (25), 93 (90), 92 (26), 91 (62), 80 (43), 78 (18), 77 (19), 66 (17), 65 (35), 64 (34), 63 (29), 62 (11)
VIIIg	454 (8)	455 (2) $[M + 1]^+$, 437 (6), 409 (7), 398 (11), 397 (20), 396 (85), 315 (29), 304 (30), 288 (17), 287 (100), 285 (10), 274 (15), 273 (99), 259 (20), 258 (13), 241 (29), 155 (15), 123 (66), 108 (24), 92 (13), 78 (6), 77 (8), 65 (10)
VIIIh	544 (3)	436 (9), 411 (7), 396 (100), 364 (10), 315 (19), 287 (56), 273 (42), 259 (21), 241 (20), 215 (8), 149 (23), 133 (28), 123 (39), 106 (47), 91 (22), 77 (29), 65 (14), 43 (15)
IX	452 (48)	454 (13) $[M + 2]^+$, 330 (100), 313 (69), 285 (24), 258 (16), 241 (13), 198 (8), 123 (9), 108 (10), 92 (14), 73 (35), 65 (19), 52 (10), 44 (41), 40 (15)
XIIIa	^a	378 (9), 370 (26), 351 (14), 285 (16), 271 (9), 257 (81), 243 (32), 217 (19), 211 (36), 185 (24), 167 (18), 153 (62), 135 (54), 127 (70), 119 (42), 99 (18), 93 (100), 77 (34), 65 (38), 51 (16), 39 (38)
XIIIb	^a	370 (4), 337 (25), 257 (11), 231 (10), 217 (34), 211 (98), 185 (24), 169 (72), 153 (57), 143 (100), 127 (42), 115 (69), 99 (20), 90 (25), 75 (17), 63 (24), 39 (17)
XIIIc	462 (3)	461 (5) $[M - 1]^+$, 370 (49), 335 (21), 307 (28), 243 (29), 217 (10), 127 (9), 99 (4), 91 (100), 77 (3), 65 (14), 39 (5)
XIIId	^a	458 (4), 430 (6), 385 (5), 370 (69), 338 (17), 232 (19), 211 (39), 199 (80), 197 (80), 185 (16), 171 (90), 153 (100), 145 (11), 127 (72), 99 (18), 90 (74), 75 (16), 63 (49), 50 (17), 39 (28)
XIIIe	428 (4)	411 (6), 382 (5), 370 (91), 342 (10), 302 (33), 274 (21), 257 (100), 229 (18), 153 (26), 127 (56), 99 (12), 90 (10), 67 (14), 44 (15)
XIII f	519 (3)	370 (9), 275 (8), 257 (19), 229 (5), 127 (13), 108 (19), 91 (100), 79 (12), 65 (6), 51 (5), 39 (4)
XIIIg	486 (3)	487 (4) $[M + 1]^+$, 485 (11) $[M - 1]^+$, 359 (54), 342 (21), 331 (62), 316 (8), 303 (5), 275 (4), 257 (10), 243 (49), 229 (28), 216 (20), 185 (27), 127 (53), 107 (14), 91 (15), 77 (5), 67 (20), 57 (22), 41 (33)
XIIIh	444 (4)	445 (5) $[M + 1]^+$, 443 (10) $[M - 1]^+$, 370 (38), 342 (11), 317 (62), 289 (42), 257 (100), 229 (18), 216 (14), 185 (13), 162 (10), 127 (31), 91 (15), 67 (18), 42 (9)
XIIIi	457 (10)	370 (42), 342 (18), 331 (65), 303 (64), 285 (12), 257 (100), 243 (39), 229 (23), 216 (15), 185 (14), 127 (28), 91 (12), 77 (5), 67 (16), 42 (9)
XIVa	500 (4)	378 (11), 366 (37), 350 (10), 333 (32), 304 (20), 285 (21), 257 (54), 243 (29), 229 (21), 211 (56), 185 (12), 167 (35), 149 (32), 135 (27), 123 (100), 106 (48), 93 (70), 77 (34), 65 (31), 51 (16), 39 (15)
XIVb	550 (3)	428 (6), 381 (7), 366 (20), 243 (12), 185 (24), 169 (100), 141 (38), 115 (27), 80 (9), 67 (7), 51 (8), 39 (7)
XIVc	457 (8)	366 (39), 335 (10), 307 (11), 243 (56), 126 (59), 108 (12), 91 (100), 77 (4), 65 (14), 51 (3), 39 (4)
XIVd	^a	458 (4), 420 (9), 366 (84), 293 (22), 265 (16), 243 (42), 229 (24), 199 (20), 171 (33), 155 (89), 135 (10), 123 (100), 108 (41), 91 (22), 77 (16), 67 (19), 44 (26)
XIVe	424 (23)	366 (47), 333 (10), 302 (29), 274 (18), 257 (56), 229 (21), 217 (10), 185 (14), 149 (18), 123 (100), 108 (26), 91 (22), 77 (11), 59 (6), 44 (17)
XV	528 (12)	402 (26), 327 (6), 254 (3), 127 (5), 99 (6), 91 (100), 77 (8), 41 (4)

^a The peak is lacking.

N-Ethylmorpholinium 4-heteryl-5-carbamoyl-6-methyl-3-cyano-1,4-dihydropyridine-2-selenolates XXa and XXb. A mixture of 1 g of acetoacetamide XVIII, 10 mmol of appropriate aldehyde II, 1.5 g of cyanoselenoacetamide XVI, and 10 mmol of N-ethylmorpholine in 15 ml of absolute ethanol was stirred for 6 h at 20°C under Ar. The precipitate was filtered off and washed with absolute ethanol and hexane.

6-Methyl-5-carbamoyl-4-(2-thienyl)-3-cyano-2-Z-methylseleno-1,4-dihydropyridines XXIIIa and XXIIIb were prepared similarly to compounds VIII starting from salts XX and alkyl halides VIIa and VIIc.

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