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THIENYLMETHYLENECYANOTHIOACETAMIDE AND 2-ACETOACETOTOLUIDIDE IN THE SYNTHESIS OF SUBSTITUTED DI- AND TETRAHYDRO-3-CYANOPYRIDINE-2-THIOLATES

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Substituted di- and tetrahydro-3-cyanopyridine-2-thiolates, used in the synthesis of the corresponding 2-(thiazol-2-yl)acrylonitriles and partially hydrogenated 2-alkylthiopyridines, were obtained from thienylmethylenecyanothioacetamide and 2-acetoacetotoluidide in the presence of N-methylmorpholine or piperidine.

We have previously developed [1, 2] suitable methods for the preparation of N-methylmorpholinium 5-arylcarbamoyl-3-cyano-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-2-thiolates and have studied their reactions with various substituted methyl halides. The corresponding tetrahydropyridine analogs were not isolated. Taking this into account, we have investigated in this work the influence of organic bases (N-methylmorpholine and piperidine) on the reaction of thienylmethylenecyanothioacetamide (I) with 2-acetoacetotoluidide (II) (Scheme 1).

The reaction of toluidide II with the unsaturated nitrile I in the presence of piperidine gives piperidinium tetrahydropyridinethiolate IIIa. The analogous N-methylmorpholinium salt IIIb is obtained when N-methylmorpholine is used in place of piperidine. Compound IIIb easily loses water in solution and is stabilized as the substituted dihydropyridinium salt IV. A similar process occurs during the recording of the ^{1}H NMR spectrum of salt IIIa in DMSO-d_6.

Substituted 2-acylmethyl-1,4-dihydropyridines VIa-i have been obtained by treatment of DMF solution of compound IV with the halides Va-i. The corresponding tetrahydropyridines VIIa-e have been obtained by the reaction of thiolate IIIa with compounds Va,j-m in ethanol. The ^{1}H NMR spectra of the latter (VIIa-e) contain double set of signals for all protons indicating that a mixture of diastereoisomers is formed. The spin-spin coupling constants of the 4-H and 5-H protons of both the major and minor products are each equal to 12 Hz (Table 1). This value of coupling constant indicates that these protons may have *trans*-diaxial orientation [3].

Tetrahydropyridines VIIa-c,e are quite stable and can be recrystallized from butanol. Heating of compound VIIa in glacial acetic acid causes its dehydration to the corresponding dihydropyridine derivatives VIa. On prolonged contact with DMF compound VIId is converted to substituted thiazole VIIIa, probably via an unstable intermediate of type IX. The same process occurs in ethanol, but addition of aqueous KOH shortens the reaction time and increases the yield of the end product VIIIa. These results permitted the development of a suitable method for the synthesis of thiazoles VIII by the reaction of the salt IIIa with the α-bromo ketones Vb-e,l,n-r in ethanol in the presence of equimolar quantity of 10% aqueous KOH (Scheme 2). The structures of products VIII correspond to spectroscopic results. However they were also independently synthesized from compounds Vb-e,l,n-r and nitrile I in DMF as described elsewhere [4].

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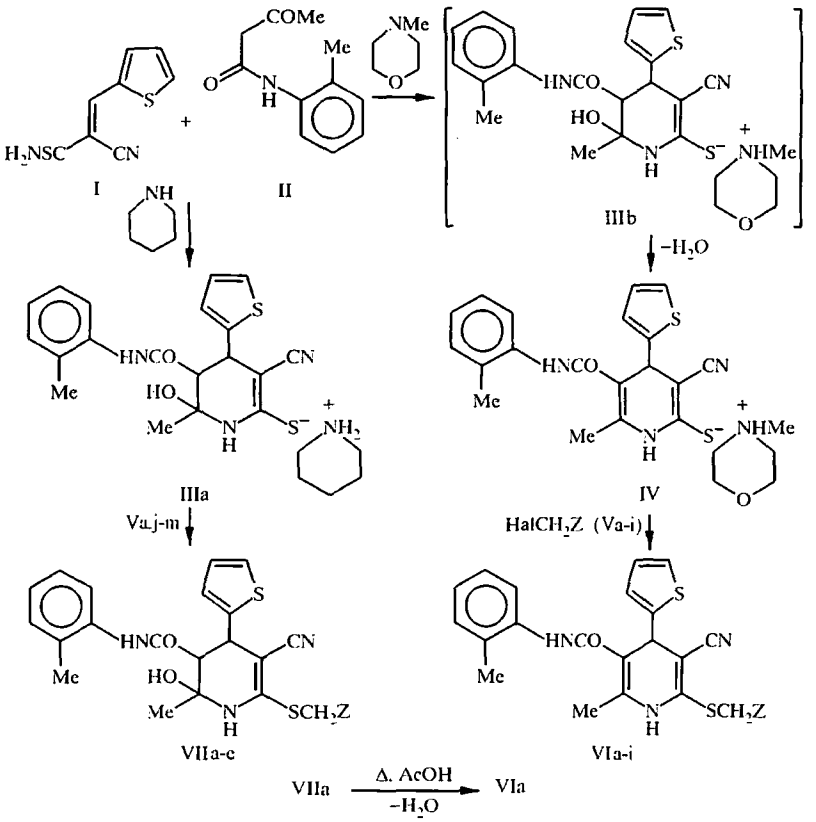
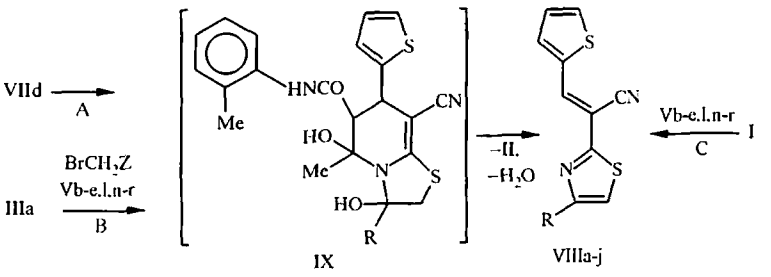
Scheme 1



Va-g,l Hal = Br, h,j,k Hal = Cl, i,o Hal = I; V, VI a Z = NH_2CO, b Z = 4-BrC_6H_4CO, c Z = 4-ClC_6H_4CO, d Z = 4-FC_6H_4CO, e Z = 4-MeC_6H_4CO, f Z = $C_6H_5C_6H_4CO$, g Z = 2,4-$Me_2C_6H_3CO$, h Z = COOMe, i Z = H, j Z = PhNHCO, k Z = 4-BrC_6H_4NHCO, l Z = PhCO, m Z = Me; VII a Z = NH_2CO, b Z = PhNHCO, c Z = 4-BrC_6H_4NHCO, d Z = PhCO, e Z = Me

Scheme 2



V Hal = Br, n Z = 3,4-$Cl_2C_6H_3CO$, o Z = 3-coumarinylcarbonyl, p Z = 4-$MeOC_6H_4CO$, q Z = 4-$C_4H_9C_6H_4CO$, r Z = cyclopropylcarbonyl; VIII a R = Ph, b R = 4-BrC_6H_4, c R = 4-FC_6H_4, d R = 4-ClC_6H_4, e R = 3,4-$Cl_2C_6H_3$, f R = 3-coumarinyl, g R = 4-$MeOC_6H_4$, h R = 4-$C_4H_9C_6H_4$, i R = cyclopropyl, j R = 4-MeC_6H_4

TABLE 1. IR and ^{1}H NMR Spectroscopic Data for the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, SSCC (J), Hz
1	2	3
VIa	3240-3360 (2NH, NH_2), 2205 (CN), 1635, 1660, 1720 (CO)	1.97 (3H, s, 6-CH_3); 2.15 (3H, s, $C\underline{H}_3C_6H_4$); 3.72 (2H, q, SCH_2); 5.10 (1H, s, 4-H); 6.92-7.41 (7H, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.59 and 7.90 (2H, br. s, br. s, $CONH_2$); 9.12 (1H, s, NH); 10.09 (1H, s, CONH)
VIb	3270 (2NH), 2203 (CN), 1659, 1682 (CO)	1.96 (3H, s, 6-CH_3); 2.12 (3H, s, $C\underline{H}_3C_6H_4$); 4.73 (2H, s, SCH_2); 5.07 (1H, s, 4-H); 6.90-7.50 (7H, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.80 and 7.95 (4H, d, d, BrC_6H_4); 9.13 (1H, s, NH); 9.23 (1H, s, CONH)
VIc	3306 (2NH), 2201 (CN), 1644, 1670 (CO)	2.09 (3H, s, 6-CH_3); 2.55 (3H, s, $C\underline{H}_3C_6H_4$); 4.75 (2H, s, SCH_2); 5.10 (1H, s, 4-H); 6.93-7.55 (7H, m, $CH_3C_6\underline{H}_4$ and $H_{thienyl}$); 7.64 and 8.01 (4H, d, d, ClC_6H_4); 9.25 (1H, s, NH); 9.66 (1H, s, CONH)
VId	3285 (2NH), 2200 (CN), 1620, 1650, 1680 (CO)	1.98 (3H, s, 6-CH_3); 2.14 (3H, s, $C\underline{H}_3C_6H_4$); 4.76 (2H, s, SCH_2); 5.07 (1H, s, 4-H); 6.90-7.50 and 8.09 (11H, m, q, $CH_3C_6\underline{H}_4$, $3H_{thienyl}$ and FC_6H_4); 9.12 (1H, s, NH); 9.22 (1H, s, CONH)
VIe	3290 (2NH), 2187 (CN), 1630, 1650, 1680 (CO)	1.98 (3H, s, 6-CH_3); 2.13 (3H, s, $C\underline{H}_3C_6H_4$); 2.38 (3H, s, $C\underline{H}_3C_6H_4$); 4.75 (2H, s, SCH_2); 5.07 (1H, s, 4-H); 6.90-7.12 (7H, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.41 and 7.90 (4H, d, d, $CH_3C_6\underline{H}_4$); 9.14 (1H, s, NH); 9.22 (1H, s, CONH)
VIf	3285 (2NH), 2186 (CN), 1625, 1650, 1680 (CO)	1.98 (3H, s, 6-CH_3); 2.14 (3H, s, $C\underline{H}_3C_6H_4$); 4.82 (2H, s, SCH_2); 5.09 (1H, s, 4-H); 6.90-7.80 (12H, m, $CH_3C_6\underline{H}_4$, $3H_{thienyl}$ and C_6H_5); 7.87 and 8.09 (4H, d, d, $C_6H_5C_6\underline{H}_4$); 9.12 (1H, s, NH); 9.24 (1H, s, CONH)
VIg	3285 (2NH), 2200 (CN), 1640, 1657, 1680 (CO)	1.98 (3H, s, 6-CH_3); 2.14 (3H, s, $C\underline{H}_3C_6H_4$); 2.33 and 2.41 (6H, s, s, $(C\underline{H}_3)_2C_6H_3$); 4.66 (2H, q, SCH_2); 5.06 (1H, s, 4-H); 6.90-7.75 (10H, $CH_3C_6\underline{H}_4$, $3H_{thienyl}$ and $(CH_3)_2C_6\underline{H}_3$); 9.10 (1H, s, NH); 9.19 (1H, s, CONH)
VIh	3240-3315 (2NH), 2190 (CN), 1605, 1635, 1665, 1720 (CO)	1.98 (3H, s, 6-CH_3); 2.15 (3H, s, $C\underline{H}_3C_6H_4$); 3.66 (3H, s, $COOCH_3$); 3.98 (2H, q, SCH_2); 5.11 (1H, s, 4-H); 6.92-7.14 and 7.42 (7H, m, d, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 9.13 (1H, s, NH); 9.27 (1H, s, CONH)
VIi	3150-3390 (2NH), 2180 (CN), 1604, 1650 (CO)	2.01 (3H, s, 6-CH_3); 2.17 (3H, s, $C\underline{H}_3C_6H_4$); 2.53 (3H, s, SCH_3); 5.06 (1H, s, 4-H); 6.91-7.42 (7H, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 9.15 (1H, s, NH); 9.19 (1H, s, CONH)
VIIa	3300, 3525 (2NH, NH_2, OH), 2186 (CN), 1590, 1665 (CO)	1.38*[2] and 1.57 (3H, s, s, 6-CH_3); 1.93 and 1.95*[2] (3H, s, s, $C\underline{H}_3C_6H_4$); 2.73 and 2.98*[2] (1H, d, d, ^3J = 12, ^3J = 12, 5-H); 3.55-3.82 (2H, m, SCH_2); 4.22* and 4.39 (1H, d, d, ^3J = 12, ^3J = 12, 4-H); 5.83 and 6.49*[2] (1H, s, s, OH); 6.90-7.47 (7H, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.55, 7.59*[2], 7.85 and 7.91*[2] (2H, br. s, br. s, br. s, br. s, $CONH_2$); 8.42*[2] and 8.80 (1H, s, s, NH); 8.94*[2] and 9.24 (1H, s, s, CONH) (7 : 1)*[3]
VIIb	3300, 3535 (3NH, OH), 2186 (CN), 1560, 1660 (CO)	1.40*[2] and 1.60 (3H, s, s, 6-CH_3); 1.94 and 1.96*[2] (3H, s, s, $C\underline{H}_3C_6H_4$); 2.77 and 3.00*[2] (1H, d, d, ^3J = 12, ^3J = 12, 5-H); 3.88 (2H, s, SCH_2); 4.24*[2] and 4.40 (1H, d, d, ^3J = 12, ^3J = 12, 4-H); 5.86 and 6.49*[2] (1H, s, s, OH); 6.95-7.43 and 7.59 (12H, m, d, $CH_3C_6\underline{H}_4$, C_6H_5 and $3H_{thienyl}$); 8.05*[2] and 8.37 (1H, s, s, NH); 8.96*[2] and 9.25 (1H, s, s, 5-CONH); 10.4 (1H, s, CONH) (12 : 1)*[3]
VIIc	3300, 3450, 3525 (3NH, OH), 2203 (CN), 1690 (CO)	1.39* and 1.59 (3H, s, s, 6-CH_3); 1.94 and 1.97*[2] (3H, s, s, $C\underline{H}_3C_6H_4$); 2.75 and 2.99*[2] (1H, d, d, ^3J = 12, ^3J = 12, 5-H); 3.90 (2H, s, SCH_2); 4.23*[2] and 4.40 (1H, d, d, ^3J = 12, ^3J = 12, 4-H); 5.83 and 6.45*[2] (1H, s, s, OH); 6.95-7.60 (11H, m, $2CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.95*[2] and 8.29 (1H, s, s, NH); 8.94*[2] and 9.24 (1H, s, s, 5-CONH); 10.50 (1H, s, CONH) (7 : 1)*[3]
VIId	3330, 3410 (2NH, OH), 2166, 2180 sh (CN), 1590, 1680 (CO)	1.35*[2] and 1.59 (3H, s, s, 6-CH_3); 1.95 (3H, br. s, $C\underline{H}_3C_6H_4$); 2.75 and 2.98*[2] (1H, d, d, ^3J = 12, ^3J = 12, 5-H); 4.25*[2] and 4.38 (1H, d, d, ^3J = 12, ^3J = 12, 4-H); 4.73 and 5.10*[2] (2H, br. s, m, SCH_2); 5.73 and 6.20*[2] (1H, br. s and s, OH); 6.95-7.80 and 8.00 (12H, m, d, $CH_3C_6\underline{H}_4$, C_6H_5 and $3H_{thienyl}$); 9.19 (1H, br. s, NH); 9.72 (1H, br. s, CONH) (18 : 1)*[3]
VIIe	3325 (2NH, OH), 2195 (CN), 1670 (CO)	1.27 (3H, t, $C\underline{H}_3CH_2S$); 1.39*[2] and 1.57 (3H, s, 6-CH_3); 1.94 (3H, s, $C\underline{H}_3C_6H_4$); 2.73, 2.90 and 3.12 (3H, d, m, m, ^3J = 12, 5-H and $CH_3C\underline{H}_2S$); 4.26*[2] and 4.40 (1H, d, d, ^3J = 12, ^3J = 12, 4-H); 5.73 and 6.20*[2] (1H, s, s, OH); 6.95-7.18 and 7.42 (7H, m, m, $CH_3C_6\underline{H}_4$ and $3H_{thienyl}$); 7.60*[2] and 7.84 (1H, s, s, NH); 8.89*[2] and 9.23 (1H, s, s, CONH) (14 : 1)*[3]

TABLE 1 (continued)

1	2	3
VIIIa	2215 (CN)	7.43 and 8.01 (8H, m, m, C_6H_5 and $3H_{thienyl}$); 8.25 (1H, s, $H_{thiazolyl}$); 8.60 (1H, s, CH=)
VIIIb	2204 (CN)	7.33, 7.68 and 7.95 (7H, t, d, m, BrC_6H_4 and $3H_{thienyl}$); 8.32 (1H, s, $H_{thiazolyl}$); 8.60 (1H, s, CH=)
VIIIc	2200 (CN)	7.31 and 8.06 (7H, m, m, FC_6H_4 and $H_{thienyl}$); 8.22 (1H, s, $H_{thiazolyl}$); 8.59 (1H, s, CH=)
VIIId	2185 (CN)	7.32, 7.54 and 8.04 (7H, t, d, m, ClC_6H_4 and $3H_{thienyl}$); 8.31 (1H, s, $H_{thiazolyl}$); 8.60 (1H, s, CH=)
VIIIe	2175 (CN)	7.32, 7.68, 7.93-8.10, 8.21 (6H, t, d, m, d, $(CH_3)_2C_6\underline{H}_3$ and $3H_{thienyl}$); 8.37 (1H, s, $H_{thiazolyl}$); 8.55 (1H, s, CH=)
VIIIf	2170 (CN)	7.38-8.04 (7H, m, $4H_{coumarinyl}$ and $3H_{thienyl}$); 8.47 (1H, s, $H_{thiazolyl}$); 8.50 (1H, s, CH=); 8.74 (1H, s, $H_{coumarinyl}$)
VIIIg	2180 (CN)	3.89 (3H, s, OCH_3); 7.17-8.04 and 8.22 (7H, m, d, C_6H_4 and $H_{thienyl}$); 8.19 (1H, s, $H_{thiazolyl}$); 8.57 (1H, s, CH=)
VIIIh	2180 (CN)	0.90, 1.53 and 2.60 (9H, t, m, t, C_3H_6); 7.32 and 7.92 (7H, m, m, C_6H_4 and $3H_{thienyl}$); 8.16 (1H, s, $H_{thiazolyl}$); 8.58 (1H, s, CH=)
VIIIi	2200 (CN)	0.90 and 2.13 (5H, m, m, C_3H_5); 7.29, 7.91 and 8.03 (3H, t, d, d, $3H_{thienyl}$); 7.38 (1H, s, $H_{thiazolyl}$); 8.40 (1H, s, CH=)
VIIIj	2180 (CN)	2.36 (3H, s, CH_3); 7.30 and 8.00 (7H, m, m, C_6H_4 and $3H_{thienyl}$); 8.19 (1H, s, $H_{thiazolyl}$); 8.60 (1H, s, CH=)

* $H_{thienyl}$, $H_{thiazolyl}$, $H_{coumarinyl}$ – thienyl, thiazolyl, and coumarinyl protons respectively.

*[2] Signal of the minor diastereoisomer.

*[3] Ratio of intensities of the signals of the major and minor diastereoisomers.

EXPERIMENTAL

^{1}H NMR spectra of compounds IIIa, V, VI were recorded on a Bruker WP-100 SY, compound VIId on a Bruker WM-250, and compounds VIIa-c,e on a Bruker AM-300 instruments in DMSO-d_6 and with TMS as internal standard (1:2 mixture of DMSO-d_6 and $CDCl_3$ was used for salt IIIa to avoid its dehydration and decomposition). IR spectra of Nujol mulls were recorded on an IKS-29 spectrophotometer. The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates with 3:5 acetone–heptane as eluent. Characteristics of the compounds synthesized are given in Tables 1 and 2.

Piperidinium 3-Cyano-6-hydroxy-6-methyl-5-(2-methylphenyl)carbamoyl-4-(2-thienyl)-1,4,5,6-tetrahydropyridine-2-thiolate (IIIa). Mixture of nitrile I (1.94 g, 10 mmol), anilide II (1.91 g, 10 mmol), and piperidine (1.48 ml, 15 mmol) in ethanol (20 ml) was stirred at 20°C for 3 h. The precipitate of IIIa was filtered off, and washed with ethanol and acetone. Yield 4.41 g (88%), m.p. 150-152°C. IR spectrum: 3165-3300 (2NH, OH), 2190 sh, 2162 (CN), 1670 cm^{-1} (CO). ^{1}H NMR spectrum: 1.65 (6H, m, $3CH_2$); 2.03 (3H, s, 6-CH_3); 2.31 (3H, s, CH_3); 2.80 (1H, d, ^3J = 12 Hz, 5-H); 3.02 (4H, m CH_2NCH_2); 4.40 (1H, d, ^3J = 12 Hz, 4-H); 5.64 (1H, s, OH); 6.90-7.30 and 7.60-7.90 (7H, two m, C_6H_4 and thienyl); 8.74 (1H, s, NH); 8.84 ppm (1H, s, CONH). Found, %: C 60.88; H 6.13; N 11.62; S 13.48. $C_{24}H_{30}N_4O_2S_2$. Calculated, %: C 61.25; H 6.42; N 11.90; S 13.63.

N-Methylmorpholinium 3-Cyano-6-methyl-5-(2-methylphenyl)carbamoyl-4-(2-thienyl)-1,4-dihydropyridine-2-thiolate (IV) was obtained as for IIIa with N-methylmorpholine (1.51 ml, 15 mmol) in place of piperidine. Yield 3.66 g (78%); mp 280°C (decomp.). IR spectrum: 3150-3255 (2NH), 2180 (CN), 1650 cm^{-1} (CO). ^{1}H NMR spectrum: 1.95 (3H, s, 6-CH_3); 2.48 (3H, s, CH_3); 2.50 (3H, s, NCH_3); 2.81 (4H, m, CH_2NCH_2); 3.69 (4H, m, CH_2OCH_2); 4.82 (1H, 4-H); 7.13, 7.44 and 7.87 (7H, two d, C_6H_4 and thienyl); 8.44 (1H, s, NH); 9.72 ppm (1H, s, CONH). Found, %: C 61.28; H 6.44; N 11.62; S 13.46. $C_{24}H_{28}N_4O_2S_2$. Calculated, %: C 61.51; H 6.02; N 11.96; S 13.68.

TABLE 2. Characteristics of Compounds VIa-i, VIIa-e, and VIIIa-j

Compound	Empirical formula	Found, % / Calculated, %				mp °C (recrystallization solvent)	Yield, % (method of preparation)
		C	H	N	S		
VIa	$C_{21}H_{20}N_4O_2S_2$	59.30 / 59.41	4.61 / 4.75	13.27 / 13.20	14.94 / 15.11	254-256 (AcOH)	73 (A) 85 (B)
VIb	$C_{27}H_{22}BrN_3O_2S_2$	57.31 / 57.45	3.84 / 3.93	7.38 / 7.44	11.25 / 11.36	211-213 (butanol)	74
VIc	$C_{27}H_{22}ClN_3O_2S_2$	62.21 / 62.36	4.33 / 4.26	8.16 / 8.08	12.20 / 12.33	208-210 (butanol)	81
VId	$C_{27}H_{22}FN_3O_2O_2$	64.23 / 64.39	4.51 / 4.40	8.25 / 8.34	12.58 / 12.73	197-198 (butanol)	64
VIe	$C_{28}H_{25}N_3O_2S_2$	67.18 / 67.31	5.13 / 5.04	8.29 / 8.41	12.71 / 12.83	221-223 (AcOH)	75
VIf	$C_{33}H_{27}N_3O_2S_2$	70.39 / 70.56	4.72 / 4.84	7.56 / 7.48	11.28 / 11.42	178-180 (butanol)	88
VIg	$C_{29}H_{27}N_3O_2S_2$	67.67 / 67.81	5.18 / 5.30	8.04 / 8.18	12.30 / 12.48	222-224 (butanol)	61
VIh	$C_{22}H_{21}N_3O_3S_2$	59.98 / 60.12	4.73 / 4.82	9.42 / 9.56	14.50 / 14.59	156-158 (ethanol)	83
VIi	$C_{20}H_{19}N_3OS_2$	62.81 / 62.96	4.86 / 5.02	11.12 / 11.01	16.69 / 16.81	185-187 (AcOH)	67
VIIa	$C_{21}H_{22}N_4O_3S_2$	56.82 / 56.99	5.12 / 5.01	12.53 / 12.66	14.34 / 14.49	221-223 (butanol)	78
VIIb	$C_{27}H_{26}N_4O_3S_2$	62.41 / 62.53	5.20 / 5.05	10.68 / 10.80	12.20 / 12.36	255-257 (butanol)	74
VIIc	$C_{27}H_{25}BrN_4O_3S_2$	54.11 / 54.27	4.32 / 4.22	9.24 / 9.38	10.59 / 10.73	264-266 (butanol)	89
VIId	$C_{27}H_{25}N_3O_3S_2$	64.21 / 64.39	5.13 / 5.00	8.46 / 8.34	12.60 / 12.73	216-218	61
VIIe	$C_{21}H_{23}N_3O_2S_2$	60.83 / 60.99	5.43 / 5.61	10.26 / 10.16	15.37 / 15.51	171-173 (butanol)	64
VIIIa	$C_{16}H_{10}N_2S_2$	65.13 / 65.28	3.25 / 3.42	9.64 / 9.52	21.65 / 21.78	156-158 (butanol)	61 (A) 91 (B) 78 (C)
VIIIb	$C_{16}H_9BrN_2S_2$	51.32 / 51.48	2.55 / 2.43	7.36 / 7.50	17.09 / 17.18	175-177 (butanol)	85 (B) 78 (C)
VIIIc	$C_{16}H_9FN_2S_2$	61.42 / 61.52	3.06 / 2.90	8.81 / 8.97	20.47 / 20.53	176-178 (butanol)	77 (B) 66 (C)
VIIId	$C_{16}H_9ClN_2S_2$	58.32 / 58.44	2.83 / 2.76	8.40 / 8.52	19.43 / 19.50	173-175 (butanol)	93 (B) 86 (C)
VIIIe	$C_{16}H_8Cl_2N_2S_2$	52.79 / 52.90	2.32 / 2.22	7.57 / 7.71	17.51 / 17.65	195-197 (butanol)	74 (B) 71 (C)
VIIIf	$C_{19}H_{10}N_2O_2S_2$	62.80 / 62.97	2.89 / 2.78	7.59 / 7.73	17.54 / 17.69	215-217 (butanol)	94 (B) 89 (C)
VIIIg	$C_{17}H_{12}N_2OS_2$	62.81 / 62.94	3.85 / 3.73	8.51 / 8.63	19.61 / 19.77	153-155 (butanol)	67 (B) 63 (C)
VIIIh	$C_{20}H_{18}N_2S_2$	68.39 / 68.54	5.08 / 5.18	7.83 / 7.99	18.16 / 18.30	111-112 (butanol)	77 (B) 74 (C)
VIIIi	$C_{13}H_{10}N_2S_2$	60.31 / 60.44	3.76 / 3.90	10.69 / 10.84	24.71 / 24.82	105-107 (butanol)	60 (B) 57 (C)
VIIIj	$C_{17}H_{12}N_2S_2$	66.01 / 66.20	3.81 / 3.92	9.16 / 9.08	20.63 / 20.79	157-159 (butanol)	78 (B) 77 (C)

3-Cyano-6-methyl-5-(2-methylphenyl)carbamoyl-2-*Z*-methylthio-4-(2-thienyl)-1,4-dihydropyridines (VIa-i). Method A. Halo ketone Va-i (10 mmol) was added to a stirred solution of salt IV (4.69 g, 10 mmol) in DMF (20 ml), the mixture was stirred for 30 min, then water (10 ml) was added. The precipitate was filtered off, washed with water, ethanol, and hexane to give compounds VIa-i.

Method B. Tetrahydropyridine VII (2.22 g, 5 mmol) was heated in glacial acetic acid (30 ml) until it dissolved completely. The precipitate which formed over 12 h was filtered off and washed with ethanol and hexane to give compound VIa (1.8 g, 85%) identical (mp, ^{1}H NMR spectrum) with a sample produced by method A.

3-Cyano-6-hydroxy-6-methyl-5-(2-methylphenyl)carbamoyl-2-*Z*-methylthio-4-(2-thienyl)-1,4,5,6-tetrahydropyridines (VIIa-e) were obtained by method A as described for VI from salt IIIa (4.71 g, 10 mmol) and halo ketone Va,j-m (10 mmol) in 80% ethanol (30 ml).

2-(4-*R*-Thiazol-2-yl)-3-(2-thienyl)- acrylonitriles (VIIIa-j). Method A. Solution of tetrahydropyridine VIIc (2.52 g, 5 mmol) in DMF (20 ml) was kept at room temperature for 12 h. The precipitate of product VIIIa was filtered off and washed with ethanol and hexane.

Method B. 10% Aqueous KOH (2.8 ml, 5 mmol) and α-bromo ketone Vb-e,l,n-r (5 mmol) were added to stirred suspension of salt IV (2.35 g, 5 mmol) in ethanol (30 ml). The precipitate of product VIII which formed after 10 min was filtered off and washed with ethanol and hexane.

Products VIIIa-j were synthesized by a known method [7] from nitrile I (0.97 g, 5 mmol) and the corresponding bromide VIb-e,l,n-r (5 mmol).

Samples of the same structure made by different methods were identical in mp., IR spectra, and ^{1}H NMR spectra.

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