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SYNTHESIS OF 3-CYANO-4-ARYL-5-ETHOXYCARBONYL-6-METHYL-3,4-DIHYDROPYRIDINE-2-THIONES

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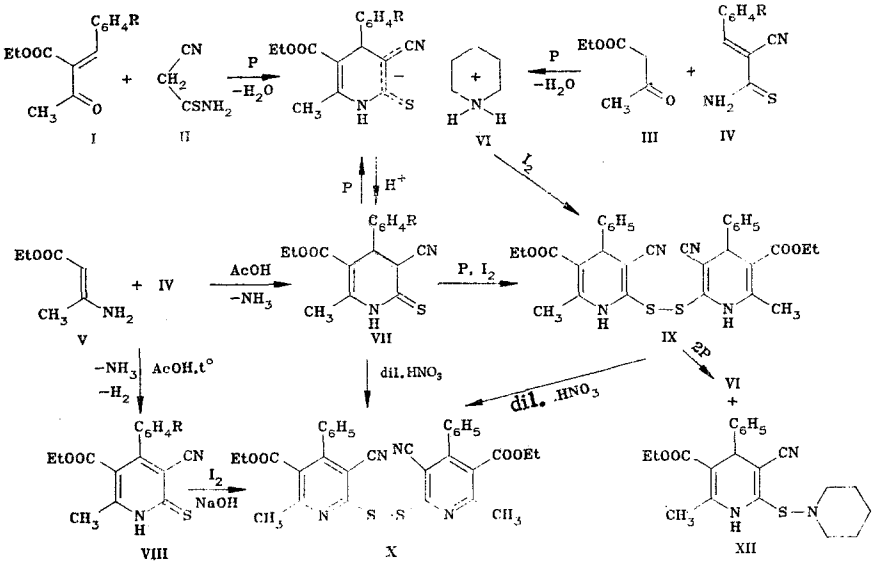
UDC 547.825:543.422.25'4:541.634

The condensation of ethyl arylidenacetoacetate with cyanothioacetamide and of arylidenecyanothioacetamides with ethyl acetoacetate or of arylidenecyanothioacetamides with ethyl β-aminocrotonate gave 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones. PMR spectroscopy showed that the 3-cyano-4-aryl-3,4-dihydropyridine-2-thiones are formed as a mixture of cis and trans isomers.

In a continuation of studies on 3,4-dihydropyridine-2-thiones [1, 2], we synthesized a series of 5-ethoxycarbonyl-3,4-dihydropyridine-2-thiones. The introduction of electron-withdrawing substituents at C-3 and C-5 stabilizes 1,4-dihydropyridines, i.e., reduces their tendency to undergo oxidation to the corresponding pyridines [3]. In the present work, we sought methods of the synthesis of 3,4-dihydropyridine-2-thiones with an electron-withdrawing ethoxycarbonyl group at C-5 and the preparation of compounds more resistant toward oxidation than 3,4-dihydropyridine-2-thiones which are unsubstituted at C-5 [2].

The following methods were developed for the synthesis of 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones: 1) condensation of ethyl arylidenacetoacetate I with cyanothioacetamide II, 2) condensation of ethyl acetoacetate III with arylidenecyanothioacetamide IV, and 3) condensation of ethyl β-aminocrotonate V with arylidencyanothioacetamide IV with subsequent intramolecular cyclization of the δ-keto- and δ-iminothioamides formed in the presence of bases and acids.

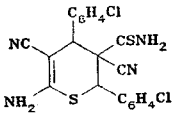


I, IV, VI—VIII a R=H, b R=4-NO_2, c R=4-Cl, d R=4-OCH_3, e R=4-CH_3, f R=4-$N(CH_3)_2$; P = piperidine

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 95-102, January, 1985. Original article submitted February 15, 1984.

0009-3122/85/2101-0077$09.50

The condensation of ethyl arylideneacetoacetate I with cyanothioacetamide II and of ethyl acetoacetate III with arylidenecyanothioacetamide IV proceeds in basic media. The use of piperidine as the condensing agent gave the piperidinium salts of 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones (VI). The acidification of salts VI with an equimolar amount of hydrochloric acid gives good yields of 3-cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones (VII) (Table 1). The condensation of p-chlorobenzylidenecyanothioacetamide IVc with ethyl acetoacetate III in the presence of piperidine gives the dimerization of IVc to 2,4-di(4-chlorophenyl)-3-thiocarbamoyl-3,5-dicyano-6-amino-3,4-dihydro-2H-thiopyran (XI) [4] in addition to the formation of salt VIc.



XI

The condensation of arylidenecyanothioacetamides IV with ethyl β-aminocrotonate V proceeds in acetic acid. Heating over 5 min yields substituted 3,4-dihydropyridine-2-thiones VII, while heating over 1-2 h gives the oxidation products, namely, 3-cyano-4-aryl-5-ethoxycarbonyl-6-methylpyridine-2-thiones (VIII), which were also obtained in low yield upon heating piperidinium salts VI in acetic acid of HCl/ethanol at reflux.

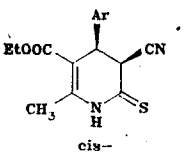
The oxidation of salts VI with an equivalent amount of iodine in ethanol leads to 2,2'-bis(3-cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridyl) disulfide (IX). Heating VIa, VIIa, and IX in nitric acid diluted with seven parts water at reflux gave the corresponding bispyridyl disulfide X which was also obtained by the oxidation of substituted pyridine-2-thione VIIIa by iodine.

The action of piperidine on bis(1,4-dihydropyridyl) disulfide IX leads to cleavage of the molecule at the disulfide bond to form the known salt VI and 2-piperidylmercapto-3-cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine (XII).

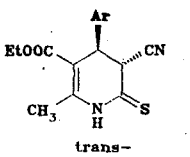
The structures of VI-XII were determined spectroscopically. The IR spectra show characteristic bands for the CO, CN, and NH groups (Tables 2 and 3). The vibrations of the C≡N group of the piperidinium salts of 3,4-dihydropyridine-2-thiones VI as a suspension in vaseline oil are seen at 2166-2182 cm^{-1} while the analogous band is found at 2200-2203 for 2-mercapto-1,4-dihydropyridine derivatives IX and XII, at 2250-2267 cm^{-1} for 3,4-dihydropyridine-2-thiones VII, at 2232-2240 cm^{-1} for pyridine-2-thiones VII and at 2222 cm^{-1} for the corresponding disulfide X. Thus, the vibrational frequency for the C≡N group increases with decreasing nucleophilicity in the series: VI > XII > IX > X > VIII > VII.

The structure and tautomeric equilibrium of 3,4-dihydropyridine-2-thiones VII were studied by NMR and IR spectroscopy (Tables 3, 5, and 6).

The ^1H and ^{13}C NMR spectra of these dihydropyridine-2-thiones show signals corresponding to the cis and trans isomers in 55:45 ratio.



cis-



trans-

The signals with the larger coupling constant between 3-H and 4-H (~7 Hz) in the ^1H NMR spectrum was assigned to the cis isomer while the signals with the smaller coupling constant between these protons (~3 Hz) was assigned to the trans isomer (Table 5). This interpretation is in accord with the data for the oxygen analogs of these compounds [5]. The $^3J_{4-H-4-C-3-C-^{13}C=S}$ and $^3J_{4-H-4-C-3-C-^{13}C\equiv N}$ coupling constants were measured in both isomers of VIIa (8.0 and <0.2 Hz for the cis isomer and 6.6 and 7.8 Hz for the trans isomer). This finding is in accord with the predominantly axial orientation of the 4-Ar ring in both isomers. Thus, the 3-CN group in the cis isomers of VII is equatorial, while this group in the trans isomers is axial. These orientations apparently result from the unfavorable steric interactions between the 5-CO_2Et and 4-Ar groups in the case of equatorial orientation of the 4-Ar group.

TABLE 1. Characteristics of Compounds Synthesized

Compound	R	mp, °C	Prepar. methods	Found, %				Chemical formula	Calculated, %				Yield,* %
				C	H	N	S		C	H	N	S	
VIa	H	140—142	A	64,7	6,9	11,1	8,3	$C_{21}H_{27}N_3O_2S$	65,4	7,1	10,9	8,3	79
VIb	4-NO_2	120—122	A	58,7	6,1	12,9	7,1	$C_{21}H_{26}N_4O_4S$	58,6	6,1	13,0	7,4	84
VIc	4-Cl	128—130	A	60,3	6,4	9,5	7,2	$C_{21}H_{26}ClN_3O_3S$	60,1	6,2	10,0	7,6	59
		127—129	B										46
VId	4-OCH_3	123—125	B	63,0	6,8	10,7	7,4	$C_{22}H_{29}N_3O_3S$	63,6	7,0	10,1	7,7	53
VIe	4-CH_3	133—135	B	66,3	7,4	10,1	7,8	$C_{22}H_{29}N_3O_2S$	66,1	7,3	10,2	8,0	60
VIf	4-$N(CH_3)_2$	135—137	A	64,7	7,3	13,6	7,9	$C_{23}H_{32}N_4O_2S$	64,4	7,5	13,1	7,5	48
VIIa	H	139—141	A	63,4	5,1	9,2	10,3	$C_{16}H_{16}N_2O_2S$	64,0	5,4	9,3	10,7	69
VIIb	4-NO_2	148—150	A	55,0	4,7	11,9	9,6	$C_{16}H_{15}N_3O_4S$	55,6	4,4	12,2	9,3	70
VIIc	4-Cl	145—147	A	56,9	4,4	8,1	9,2	$C_{16}H_{15}ClN_2O_2S$	57,4	4,5	8,4	9,6	57
		145—147	B										54
VIId	4-OCH_3	156—158	A	61,9	5,4	8,1	9,3	$C_{17}H_{18}N_2O_3S$	61,8	5,5	8,5	9,7	42
VIIe	4-CH_3	142—144	A	65,1	5,8	8,9	9,9	$C_{17}H_{18}N_2O_2S$	64,9	5,8	8,9	10,2	41
VIIIa	H	238—240	A	65,0	4,8	9,8	10,5	$C_{16}H_{14}N_2O_2S$	64,4	4,7	9,4	10,7	49
VIIIb	4-NO_2	174—176	B	54,9	3,5	11,6	8,8	$C_{16}H_{13}N_3O_4S$	56,0	3,8	12,2	9,3	24
VIIIc	4-Cl	202—204	A	58,3	4,1	8,2	9,4	$C_{16}H_{13}ClN_2O_2S$	57,7	3,9	8,4	9,6	36
VIIId	4-OCH_3	192—194	A	62,2	4,7	8,5	9,7	$C_{17}H_{16}N_2O_3S$	62,2	4,9	8,5	9,8	35
VIIIe	4-CH_3	186—188	A	64,7	5,2	8,6	10,0	$C_{17}H_{16}N_2O_2S$	65,4	5,2	9,0	10,3	28
VIIIf	4-$N(CH_3)_2$	224—226	B	62,8	5,5	12,7	9,2	$C_{18}H_{19}N_3O_2S$	63,3	5,6	12,3	9,4	39
		223—225	A										18

*The yield of VII was calculated relative to the starting cyanothioacetamide.

TABLE 2. IR and UV Spectra of VI-VIII

Compound	R	IR spectrum, ν, cm^{-1}			UV spectrum λ_{max}, nm(lg ε)
		C=C; C=O	C≡N	NH	
VIa	H	1626, 1692	2181	3306	262 (4,04), 307 (4,31), 366 sh (3,72)
VIb	4-NO_2	1632, 1697	2184	3242	263sh. (4,26), 292 (4,38), 378 sh (3,52)
VIc	4-Cl	1636, 1692	2182	3282	260 sh. (4,00), 307 (4,13), 366 sh. (3,61)
VId	4-OCH_3	1637, 1688	2172	3250	262 (4,19), 307 (4,40), 365 sh. (3,79)
VIe	4-CH_3	1625, 1690	2166	3276	257 sh. (4,02), 306 (4,26), 365sh. (3,64)
VIf	4-$N(CH_3)_2$	1618, 1686	2175	3286	257sh. (4,34), 306 (4,34), 363sh. (3,82)
VIIa	H	1685, 1712	2267	3255. 3295sh.	238 (4,00), 254 sh. (3,90), 336 (4,21)
VIIb	4-NO_2	1640, 1698	2263	3210	264 sh. (4,22), 288 sh. (4,21), 336 (4,19)
VIIc	4-Cl	1648, 1698	2256	3272	222 (4,26), 250 sh. (3,95), 338 (4,23)
VIId	4-OCH_3	1642, 1690	2255	3205	227 (4,16), 252 sh. (3,87), 340 (4,13)
VIIe	4-CH_3	1640, 1694	2250	3270	240 sh. (3,86), 253 sh. (3,80), 336 (4,08)
VIIIa	H	1722	2240	3248	268sh. (4,00), 326 (4,48), 406 (3,70)
VIIIb	4-NO_2	1718	2230	3250	273 (4,15), 326 (4,40), 408 (3,60)
VIIIc	4-Cl	1708	2234	3160	325 (4,35), 406 (3,58)
VIIId	4-OCH_3	1718	2237	3170	242sh. (4,06), 324. (4,53), 406 (3,72)
VIIIe	4-CH_3	1710	2232	3157	264 (3,93), 323 (4,45), 406 (3,65)
VIIIf	4-$N(CH_3)_2$	1720	2236	3148	250 (4,16), 322 (4,37), 403 (4,09)

TABLE 3. IR Spectra of VII and IX in $CHCl_3$

Compound	ν, cm^{-1}				
	C=C	C=O	C≡N thione	C≡N thiol	N—H
VIIa	1640	1704	2250, 2258	2200	3225, 3375
VIIb	1640	1708	2250, 2257	2202	3220, 3375
VIIc	1640	1706	2250, 2258	2201	3235, 3375
VIId	1647	1708	2246, 2258	2203	3225, 3375
VIIe	1646	1707	2248, 2258	2203	3220, 3375
IX	1642	1702		2205	3265, 3415

*For compound IX R = H.

Using the dependence of the coupling constants for 3-H with 4-H, 4-H—4-C—3-C—^{13}C≡N, and 4-H—4-C—3-C—2-^{13}C=S on the dihedral angles [6, 7], we may show that the dihydropyridinethione ring is somewhat flattened and the dihedral angle between the 3-H—4-C—3-C and 4-H—4-C—3-C planes is close to 30° in the cis isomers and close to 110° in the trans isomers.

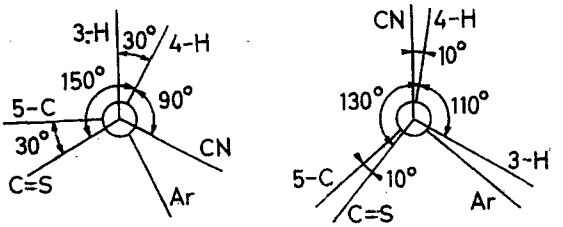
TABLE 4. PMR Spectra of Piperidinium Salts VI in DMSO-d_6

Compound	Chemical shifts, δ, ppm (multiplicity)								
	NH, br.s	Ar, m	4-H, s	CH_2, q	CH_3, t	$N(CH_2)_2$m	$(CH_2)_3$, m	6-CH_3, s	other
VIa	8,15	7,24—6,96	4,17	3,80	1,00	2,9	1,6	2,13	—
VIb	8,32	8,09; 7,27	4,32	3,80	0,99	2,9	1,55	2,18	
VIc	8,19	7,31—7,00	4,18	3,82	1,00	2,93	1,55	2,14	—
VId	8,09	7,07—6,64	4,17	3,86	1,03	2,96	1,57	2,16	3,64,s
VIe	8,08	7,00	4,17	3,85	1,03	2,95	1,58	2,17	2,20,s
VIf	8,03	6,87; 6,53	4,07	3,82	1,02	2,9	1,6	2,11	2,73, s

TABLE 5. ^{1}H NMR Spectra of 3,4-Dihydropyridine-2-thiones VII in $CDCl_3$

Compound*	Isomer	Chemical shifts, δ, ppm (multiplicity)						KCCB, J, Hz		
		NH, br.s	4-C_6H_4R m or d	OCH_2CH_3, q or t	6-CH_3, s	3-H, d	4-H, d	3-H—4-H	CH_3—4-H	NH—3-H
VIIa	cis-	8,94	7,0—7,4	4,13, 1,18	2,47	4,25	4,42	6,9	0,7	0,7
	trans-	8,94	7,0—7,4	4,15, 1,18	2,52	4,19	4,47	2,3	0,9	0,4
VIIb	cis-	8,98	7,40 (H-o); 8,19 (H-м)	4,14, 1,20	2,51	4,30	4,52	6,9	0,6	0,4
	trans-	8,98	7,31 (H-o), 8,18 (H-м)	4,16, 1,20	2,57	4,19	4,56	1,9	0,9	—
VIIc	cis-	8,74	7,13 (H-o); 7,28 (H-м)	4,13, 1,20	2,48	4,22	4,38	6,9	0,7	0,7
	trans-	8,74	7,04 (H-o); 7,26 (H-м)	4,15, 1,20	2,53	4,17	4,43	2,4	1,0	0,6
VIId	cis-	8,87	6,82 (H-м); 7,13 (H-o)	4,13, 1,20	2,47	4,21	4,38	6,8	0,7	0,7
	trans-	8,87	6,80 (H-м); 7,09 (H-o)	4,15, 1,20	2,52	4,18	4,42	2,2	0,9	0,4
VIIe	cis-	8,93	7,08 (H-o, H-м)	4,13, 1,19	2,44	4,22	4,38	6,8	0,7	0,7
	trans-	8,93	7,09 (H-м); 6,98 (H-o)	4,11, 1,19	2,50	4,18	4,44	2,1	0,9	0,6

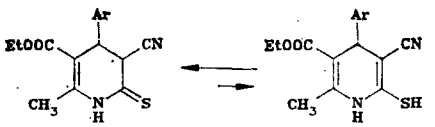
*The OCH_3 signal for VIId is at 3.73 ppm (s) while the CH_3 signal for VIIe is at 2.29 ppm (s).



cis-isomer trans-isomer

Newman projections along the 3-C—4-C bond.

The IR spectra of 3,4-dihydropyridine-2-thiones VII in chloroform show C≡N bands at 2250 and 2258 cm^{-1} which are assigned to stereoisomers of 3,4-dihydropyridine-2-thione and also at 2200 cm^{-1} (see Table 3) which indicate that VII exists in a thione—thiol tautomeric equilibrium in solution.



A study of the PMR spectra of 3-cyano-3,4-dihydropyridine-2-thiones indicates that in low-polarity aprotic solvents such as $CDCl_3$, the thione—thiol equilibrium is shifted toward the thione tautomer. The addition of dimethylsulfoxide or CF_3CO_2H shifts the equilibrium as indicated by marked broadening of the spectral lines both in the ^{1}H and ^{13}C NMR spectra (espec-

ially for the $^{13}C{=}S$ signal). The greater broadening for the spectral lines of the cis isomers relative to the trans isomers indicates that this equilibrium more involves the cis isomers.

EXPERIMENTAL

The IR spectra were taken on UR-20 and Perkin-Elmer 580B spectrometers in vaseline oil and in chloroform solution. The UV spectra were taken on a Specord UV-VIS spectrometer in ethanol. The ^1H NMR spectra were taken on a WH 90/DC spectrometer at 90 MHz with TMS as the internal standard. The ^{13}C NMR spectra were taken on the same spectrometer at 22.63 MHz with cyclohexane (δ = 27.44 ppm) as the internal standard. The $^{13}C{-}^1H$ coupling constants were determined from the ^{13}C NMR spectra taken on a WM-360 spectrometer taken at 90.52 MHz with selective suppression of coupling with individual protons. The precision in the measurement of the ^1H chemical shifts was ±0.03 ppm while that for the ^{13}C chemical shifts was ±0.07 ppm. The major characteristics of the compounds synthesized are given in Tables 1-6.

Piperidinium Salts of 3-Cyano-4-aryl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thione (VI). A. A mixture of 2.18 g (10 mmoles) ethyl benzylideneacetoacetate Ia and 1.0 g (10 mmoles) cyanothioacetamide II was vigorously stirred and dissolved in 8 ml abs. ethanol. Then, 1 ml (12.5 mmoles) piperidine was added and the reaction mixture was filtered. The product crystallizes after 20-30 min and was filtered and washed with cold ethanol to give 3.04 g (79%) VIa, mp 140-142°C (from nitromethane).

Compounds VIb, VIc, and VIf were obtained analogously.

B. A mixture of 2.02 g (10 mmoles) p-tolylmethylenecyanothioacetamide IVe and 1.9 ml (15 mmoles) ethyl acetoacetate was dissolved with vigorous stirring in 20 ml abs. ethanol and then, 1 ml (12.5 mmoles) piperidine was added. The reaction mixture was filtered and cooled to 0°C. The crystals which precipitated after 20-30 min were filtered off and washed with cold ethanol to yield 2.4 g (60%) VIe, mp 133-135°C (from ethanol).

Compounds VIc and VId were prepared analogously.

C. A sample of 0.6 g (2 mmoles) 3,4-dihydropyridine-2-thione VIIa was dissolved in 9 ml abs. ethanol by vigorous stirring and 0.4 ml (5 mmole) piperidine was added. The product which crystallized out after 2-3 min was filtered off and washed with cold ethanol and ether to give 0.68 g (84%) VIa, mp 140-142°C.

Compounds VIb-d were obtained analogously.

3-Cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones (VIIa). A. A sample of 3.86 g (10 mmoles) piperidinium salt VIa in 20 ml 0.5 N hydrochloric acid in ethanol was heated at reflux. The product which crystallized out upon cooling after 5-10 min was filtered off and washed with cold ethanol and water. The residue was dried to give 2.61 g (87%) VIIa, mp 139-141°C (from ethanol).

Compounds VIIb-e were obtained analogously.

B. A mixture of 2.23 g (10 mmoles) p-chlorobenzylidenecyanothioacetamide IVc and 1.9 g (15 mmoles) ethyl β-aminocrotonate V in 5 ml acetic acid and 15 ml ethanol was heated for 5 min on a water bath. The reaction mixture was filtered and cooled. After 15-20 min, the crystalline product was filtered and washed with cold ethanol to give 1.82 g (54%) VIIc, mp 145-147°C (from ethanol).

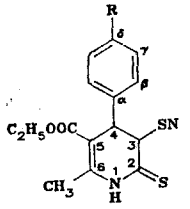
3-Cyano-4-aryl-5-ethoxycarbonyl-6-methylpyridine-2-thiones (VIII). A. A mixture of 1.88 g (10 mmoles) benzylidenecyanothioacetamide IVa and 1.29 g (10 mmoles) ethyl β-aminocrotonate V in 10 ml acetic acid and 20 ml ethanol was heated at reflux for 1 h on a water bath. The reaction mixture was filtered, cooled and left at 0°C for 20 h. The precipitate was filtered off to give 1.45 g (49%) VIIIa, mp 238-240°C (from ethanol).

Compounds VIIIc-f were obtained analogously.

B. A sample of 2.14 g (5 mmoles) piperidinium salt VIf in 10 ml 1.0 N hydrochloric acid in ethanol was dissolved upon heating. The reaction mixture was maintained for 2 h at room temperature, poured into water and 5% aqueous sodium bicarbonate was added to pH ~7. The precipitate was separated and dried to yield 0.68 g (39%) VIIIf, mp 224-226°C (from ethanol).

Compound VIIIb was obtained analogously.

TABLE 6. ^{13}C NMR Spectra of 3-Cyano-4-C_6H_4R-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridine-2-thiones VII and IX and XII in $CDCl_3$



Compound	R	Isomer	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	CN	4-C_6H_4R	COO	OCH_2CH_4	$6CH_3$	RC
VIIa	H	cis-	189,76	49,45	41,99	109,18	145,15	116,33	138,47 (α); 129,31 (β); 128,73 (γ); 127,49 (δ)	166,19	61,33 and 14,59	18,67	—
		trans-	191,25	47,37	42,57	110,94	145,48	116,72	136,91 (α); 129,64 (β); 128,73 (γ); 127,47 (δ)	166,51	61,33 and 14,59	18,67	—
VIIb	4-NO_2	cis-	189,39	48,93	41,79	107,76	144,96	116,33	146,84 (α); 129,33 (β); 124,44 (γ); 148,21 (δ)	166,06	61,30 and 14,59	18,61	—
		trans-	190,67	46,28	42,18	109,25	146,22	116,33	147,10 (α); 128,92 (β); 124,77 (γ); 148,21 (δ)	166,06	61,30 and 14,59	18,94	—
VIIc	4-Cl	cis-	189,27	48,99	41,58	109,39	144,03	115,57	136,82 (α); 128,92 (β); 129,77 (γ); 135,06 (δ)	165,70	61,59 and 14,51	19,19	—
		trans-	190,63	46,76	42,23	111,02	144,26	115,96	135,19 (α); 130,06 (β, γ); 135,06 (δ)	166,00	61,59 and 14,51	19,29	—
VIId	4-OCH_3	cis-	189,88	49,47	41,41	110,24	143,58	116,02	128,40 (α); 129,87 (β); 114,98 (γ); 160,33 (δ)	166,33	61,46 and 14,54	19,09	55,78
		trans-	191,25	47,13	42,06	111,83	143,80	116,35	130,13 (α); 128,66 (β); 115,24 (γ); 160,33 (δ)	166,03	61,46 and 14,54	19,09	55,78
VIIe	4-CH_3	cis-	189,88	49,38	41,74	110,04	143,87	116,09	133,47 (α); 128,60 (β); 130,26 (γ); 138,93 (δ)	166,13	61,50 and 14,54	18,96	21,53
		trans-	191,31	47,10	42,39	111,70	144,13	116,45	135,20 (α); 127,40 (β); 130,52 (γ); 138,70 (δ)	166,39	61,50 and 14,54	18,96	21,53
IX	H	—	140,61	93,47	43,54	103,54	145,25	118,47	144,63 (α); 129,38 (β); 127,95 (γ); 128,14 (δ)	166,96	60,81 and 14,52	19,59	—
XII*	H	—	144,10	79,63	42,65	103,97	146,73	118,40	145,79 (α); 129,12 (β); 127,95 (γ); 127,56 (δ)	167,59	60,46 and 14,54	20,07	—

*Signals for the piperidine carbon atoms: 59.03 (α), 27.63 (β), and 23.44 (γ) ppm.

2,2'-Bis(3-cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridyl) Disulfide (IX). A sample of 8 ml (4 mmoles) 0.5 N ethanolic iodine was added to a solution of 1.93 g (5 mmoles) salt VIa in 5 ml ethanol and stirred for 1 h at room temperature. The reaction mixture was filtered and poured into cold water. The precipitate was separated and dried to give 1.02 g (68%) IX, mp 104-106°C (from ethanol). IR spectrum: 1684, 1705, (CO), 2203 (CN), 3294 cm^{-1} (NH). UV spectrum: 228 (4.59), 313 (4.13), 370 nm (3.90). PMR spectrum (in $CDCl_3$): 7.22 (5H, m, C_6H_5), 6.80 (1H, br. s, NH), 4.62 (1H, s, 4-H), 4.00 (2H, q, J = 7 Hz), 2.29 (3H, s, 6-CH_3), 1.09 ppm (3H, t, J = 7 Hz, CH_3). Found: C 63.4; H 5.3; N 9.2; S 10.4%. Calculated for $C_{32}H_{30}N_4O_4S_2$: C 64.2; H 5.1; N 9.4; S 10.7%.

Reaction of 2,2'-Bis(1,4-dihydropyridyl) Disulfide IX with Piperidine. A sample of 0.3 g (1 mmole) disulfide IX was dissolved with vigorous stirring in 10 ml abs. ethanol and 0.1 ml (1.25 mmole) piperidine. After 5-10 min, 0.15 g (39%) piperidinium salt VIa salt crystallized out. The filtrate was cooled to 0°C and a precipitate was separated after 2 h to yield 0.1 g (28%) XII, mp 130-132°C (from ethanol). IR spectrum: 1692 (CO), 2200 (CN), 3300 cm^{-1} (NH). UV spectrum: 242 (4.38), 276 sh (3.88), 3.60 nm (3.75). PMR spectrum (in $CDCl_3$): 7.40 (1H, br. s, NH), 7.20 (5H, m, CTH_5), 4.64 (1H, s, 4-H), 4.00 (2H, q, J = 7 Hz, OCH_2), 3.00 [4H, m, $N(CH_2)_2$], 2.38 (3H, s, 6-CH_3), 1.58 [6H, m $(CH_2)_3$], 1.08 ppm (3H, J = 7 Hz, CH_3). Found: C 65.2; H 6.6; N 11.0; S 8.1%. Calculated for $C_{21}H_{25}N_3O_2S$: C 65.8; H 6.6; N 11.0; S 8.4%.

2,2'-Bis(3-cyano-4-phenyl-5-ethoxycarbonyl-6-methylpyridyl) Disulfide (X). A. A solution of 1.5 g (5 mmoles) 3,4-dihydropyridine-2-thione VIIa in 10 ml in 1:7 nitric acid—water was heated for 20 min at reflux on a water bath to give 0.76 g (52%) X, mp 152-154°C (from ethanol). IR spectrum: 1710 (CO), 2222 cm^{-1} (CN). UV spectrum: 220 sh (4.66), 268 (4.62), 315 sh nm (3.95). PMR spectrum (in $CDCl_3$): 7.49 (5H, m, C_6H_5), 4.05 (2H, q, J = 7 Hz, OCH_2), 2.62 (3H, s, 6-CH_3), 0.92 ppm (3H, t, J = 7 Hz, CH_3). Found: C 63.8; H 4.2; N 9.5; S 10.8%. Calculated for $C_{32}H_{26}N_4O_4S_2$: C 64.6; H 4.4; N 9.4; S 10.8%.

B. A solution of 0.3 g (0.5 mmole) bis(1,4-dihydropyridyl) disulfide IX in 2 ml 1:7 nitric acid—water was heated at reflux for 20 min on a water bath. The reaction mixture was cooled, diluted with water and the precipitate was filtered off to give 0.16 g (53%) X, mp 152-154°C (from ethanol).

C. A sample of 4 ml 0.5 N iodine in ethanol was added with stirring to a solution of 0.3 g (1 mmole) pyridine-2-thione VIIIa in 10 ml ethanol and 6 ml 0.5 N NaOH. The precipitate was filtered after 15 min to give 0.18 g (60%) X, mp 154-156°C (from ethanol).

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