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SYNTHESIS AND PROPERTIES OF N-METHYLMORPHOLINIUM 4-ARYL-6-METHYL-5-PHENYLCARBAMOYL-3-CYANO-1,4-DIHYDROPYRIDINE-2-THIOLATES. MOLECULAR AND CRYSTALLINE STRUCTURE OF 2-ALLYLTHIO-6-METHYL-5-PHENYLCARBAMOYL-4-(2-CHLOROPHENYL)-3-CYANO-1,4-DIHYDROPYRIDINE

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By the condensation of an aromatic aldehyde, the anilide of acetoacetic acid, cyanothioacetamide, and N-methylmorpholine, substituted N-methylmorpholinium 1,4-dihydropyridine-2-thiolates have been synthesized and subsequently used in the synthesis of the corresponding thiones, 2-alkylthiopyridines, thieno[2,3-b]pyridines, and disulfides. X-ray diffraction has been used to establish the structure of 2-allylthio-6-methyl-5-phenylcarbamoyl-4-(2-chlorophenyl)-3-cyano-1,4-dihydropyridine.

Substituted 2-methylthio-1,4-dihydropyridines containing a carbamoyl group in position 5 of the dihydropyridone ring exhibit hepatoprotector activity [1]. They are obtained by the condensation of cyanothioacetamide, an aromatic aldehyde, and an amide of acetoacetic acid, with subsequent treatment of the reaction mixture with methyl iodide. Another method is known for the synthesis of compounds of this class with a phenylcarbamoyl substituent, the method consisting of the interaction of cyanothioacetamide with the anilide of benzalacetoacetic acid [2]; however, the structure of the products obtained in [2] is subject to some doubt.

In view of the potential usefulness of these pyridines, we have developed a method for the synthesis of N-methylmorpholinium 4-aryl-6-methyl-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolates (I), consisting of the condensation of an aromatic aldehyde (II), cyanothioacetamide (III), the anilide of acetoacetic acid (IV), and N-methylmorpholine. The interaction takes place in the first stage, probably as a Knoevenagel condensation, forming intermediates (V or VI) that add the corresponding thioacetamide III, or correspondingly the anilide IV, to form Michael adducts (VII). Subsequent cyclocondensation of the adducts VII in the presence of a base gives the desired salts I, the structure of which is in agreement with spectroscopic data. Specifically, we find that the IR spectra of these compounds contain absorption bands of stretching vibrations of a conjugated nitrile group in the 2180 cm^{-1} spectrum; the PMR spectra, in addition to the characteristic signals from protons of the aryl substituent, the N-methylmorpholinium cation, and the phenylcarbamoyl group (see Experimental section), contain signals from protons of the dihydropyridine ring in the form of singlets in the regions 4.57-5.05 ppm (4-H) and 9.17-9.28 ppm (NH).

Treatment of the salts I with 10% aqueous solution of HCl in alcohol leads to the formation of thiones (VIII). Interestingly, these thiones are products of dehydrogenation (compare with data of [2]), as confirmed by their spectral characteristics. Thus, in the PMR spectra of the compounds VIII, there is a singlet signal from the proton of the NH group of the pyridine ring in the 14.39-14.54 ppm region, while there is no signal from a 4-H proton.

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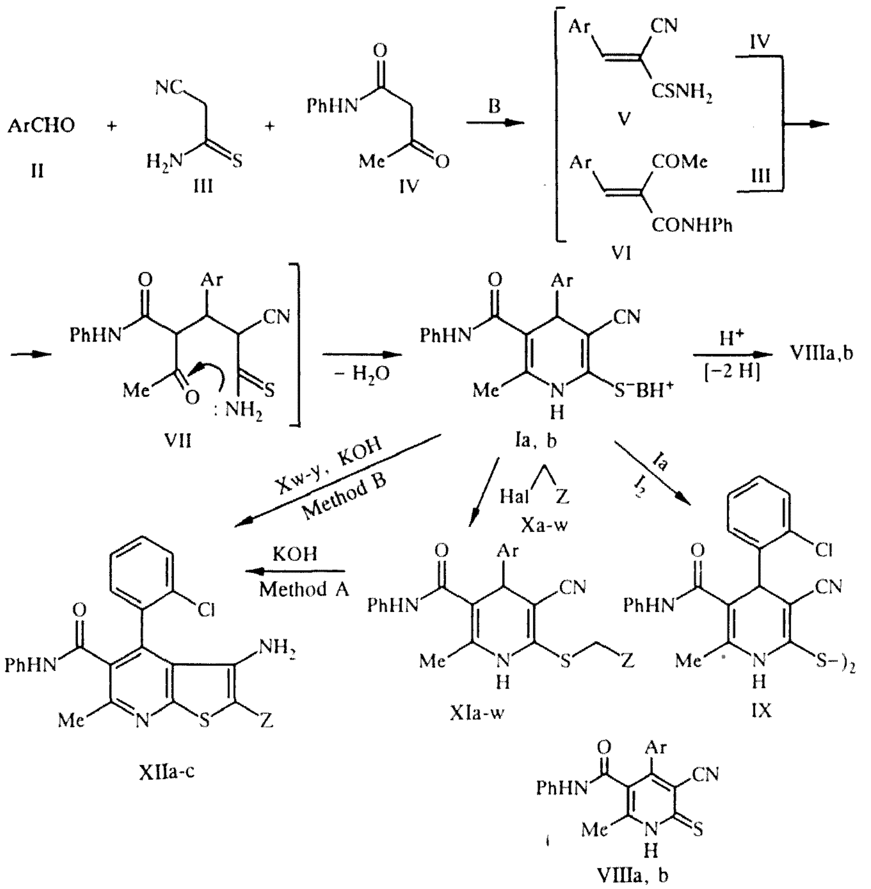

B = N-methylmorpholine. I, VIII a Ar = 2-ClC_6H_4, b Ar = Ph. X, XI a Hal = Br, Z = Et, Ar = Ph; b Hal = Br, Z = 2-MeC_6H_4, Ar = Ph; c Hal = I, Z = Me, Ar = Ph; d Hal = Cl, Z = Ar = Ph; e Hal = Cl, Z = COOMe, Ar = Ph; f Hal = I, Z = H, Ar = Ph; g Hal = I, Z = n-C_5H_{11}, Ar = Ph; h Hal = Br, Z = $CH=CH_2$, Ar = 2-ClC_6H_4; i Hal = Cl, Z = CN, Ar = 2-ClC_6H_4; j Hal = Cl, Z = 4-BrC_6H_4NHCO, Ar = 2-ClC_6H_4; k Hal = I, Z = H, Ar = 2-ClC_6H_4; l Hal = I, Z = Me, Ar = 2-ClC_6H_4; m Hal = Cl, Z = Ph, Ar = 2-ClC_6H_4; n Hal = Br, Z = 4-ClC_6H_4, Ar = 2-ClC_6H_4; o Hal = Cl, Z = COOMe, Ar = 2-ClC_6H_4; p Hal = Br, Z = 2-thenoyl, Ar = ClC_6H_4; q Hal = Br, Z = Et, Ar = 2-ClC_6H_4; r Hal = I, Z = n-C_5H_{11}, Ar = 2-ClC_6H_4; s Hal = Cl, Z = PhNHCO, Ar = 2-ClC_6H_4; t Hal = Br, Z = 4-MeC_6H_4CO, Ar = 2-ClC_6H_4; u Hal = Cl, Z = $CONH_2$, Ar = 2-ClC_6H_4; v Hal = Br, Z = 4-BrC_6H_4CO, Ar = 2-ClC_6H_4; w Hal = Br, Z = PhCO, Ar = 2-ClC_6H_4; x Hal = Br, Z = 3,4-$Cl_2C_6H_3CO$; y Hal = Br, Z = 4-ClC_6H_4CO. XII a Z = PhCO; b Z = 3,4-$Cl_2C_6H_3CO$; c Z = 4-ClC_6H_4CO

The salts I are readily oxidized by iodine to the disulfides IX. In DMF solution, they are alkylated regioselectively at the sulfur atom by alkyl halides X, forming sulfides XI (Tables 1 and 2), thus confirming the localization of negative charge on the sulfur atom. Treatment of the compounds XI with an aqueous solution of KOH in DMF produces thieno[2,3-b]pyridines XII (method A), a reaction that is known in the literature as Thorpe–Ziegler cyclization [3]. It is also possible to synthesize the thienopyridines XII from the salts and halides X in a single stage (method B). Interestingly, upon cyclization to thienopyridines XII, compounds I and XI undergo dehydrogenation, as we had noted previously in a series of 2-alkylthio-1,4-dihydropyridines [4].

In order to establish beyond doubt the position of the substituents in the dihydropyridine Ia and to determine the regioselectivity of its alkylation, we used x-ray diffraction to investigate 2-allylthio-6-methyl-5-phenylcarbamoyl-4-(2-chlorophenyl)-3-cyano-1,4-dihydropyridine (XIh). In Fig. 1 we show a general view of its molecule, and in Tables 3 and 4 we have listed the bond lengths and angles.

In the molecule of XIh, the 1,4-dihydropyridine heterocycle has the boat conformation; the $N_{(1)}$ and $C_{(4)}$ atoms deviate by −0.151 and −0.336 Å, respectively, from the plane of the other atoms of the "bottom of the boat," which are planar within limits of ±0.002 Å. This corresponds to bending of the ring at the lines $C_{(2)}$-$C_{(6)}$ by 13°, $C_{(3)}$-$C_{(5)}$ by 22.4°, and $N_{(1)}$-$C_{(4)}$ by 22.2°. We had established this sort of conformation of the heterocycle previously [5] in the molecule of morpholinium 5-acetyl-1,4-dihydro-6-methyl-4-(2-nitrophenyl)-3-cyanopyridine-2-thiolate (XIII).

TABLE 1. Characteristics of 2-Alkylthio-4-aryl-6-methyl-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridines XIa-w

Compound	Found, %				Empirical formula	Calculated, %				mp, °C (and solvent for crystallization)	Yield, %
	C	H	N	S		C	H	N	S		
XIa	70,99	5,88	10,88	8,02	$C_{23}H_{23}N_3OS$	70,92	5,95	10,79	8,23	163...165 (butanol)	73
XIb	74,55	5,69	9,38	7,28	$C_{28}H_{25}N_3OS$	74,47	5,58	9,31	7,10	174...176 (acetonitrile)	68
XIc	70,25	5,76	11,27	8,43	$C_{22}H_{21}N_3OS$	70,37	5,64	11,19	8,54	164...166 (butanol)	75
XId	74,20	5,21	9,82	7,21	$C_{27}H_{23}N_3OS$	74,12	5,30	9,60	7,33	151...153 (ethanol)	80
XIe	65,93	5,27	10,23	7,51	$C_{23}H_{21}N_3O_3S$	65,85	5,05	10,02	7,64	204...206 (ethanol)	65
XIf	69,84	5,13	11,75	8,72	$C_{21}H_{19}N_3OS$	69,78	5,30	11,62	8,87	168...170 (butanol)	60
XIg	72,49	6,58	9,88	7,31	$C_{26}H_{29}N_3OS$	72,36	6,77	9,74	7,43	109...111 (ethanol)	88
XIh	65,55	4,89	9,87	7,70	$C_{23}H_{20}ClN_3OS$	65,47	4,78	9,96	7,60	155...157 (ethanol)	87
XIi	62,66	4,19	13,43	7,71	$C_{22}H_{17}ClN_4OS$	62,78	4,07	13,31	7,62	192...194 (butanol)	85
XIj	56,72	3,85	9,34	5,28	$C_{28}H_{22}ClBrN_4O_2S$	56,63	3,73	9,43	5,40	219...221 (butanol)	92
XIk	63,59	4,51	10,72	8,19	$C_{21}H_{18}ClN_3OS$	63,71	4,58	10,61	8,10	177...179 (ethanol)	91
XI*l*	64,54	4,85	10,37	7,60	$C_{22}H_{20}ClN_3OS$	64,46	4,92	10,25	7,82	188...200 (ethanol)	89
XIm	68,50	4,63	8,81	6,87	$C_{27}H_{22}ClN_3OS$	68,71	4,70	8,90	6,79	96...98 (ethanol)	85
XIn	64,21	4,11	8,22	6,41	$C_{27}H_{21}Cl_2N_3OS$	64,03	4,18	8,30	6,33	110...112 (methanol)	68
XIo	60,74	4,37	9,37	7,17	$C_{23}H_{20}ClN_3O_3S$	60,86	4,44	9,26	7,06	117...119 (ethanol)	75
XIp	61,59	3,87	8,23	12,75	$C_{26}H_{20}ClN_3O_3S_2$	61,71	3,98	8,30	12,67	178...180 (AcOH)	84
XIq	65,25	5,35	9,83	7,44	$C_{23}H_{22}ClN_3OS$	65,16	5,23	9,91	7,56	176...178 (ethanol)	68
XIr	67,20	6,18	9,24	6,71	$C_{26}H_{28}ClN_3OS$	67,01	6,06	9,02	6,88	121...123 (ethanol)	72
XIs	65,38	4,41	10,94	6,33	$C_{28}H_{23}ClN_4O_2S$	65,30	4,50	10,88	6,23	228...230 (butanol)	81
XIt	67,65	4,63	8,30	6,34	$C_{29}H_{24}ClN_3O_2S$	67,76	4,71	8,17	6,24	145...147 (ethanol)	69
XIu	60,28	4,28	12,57	7,18	$C_{22}H_{19}ClN_4O_2S$	60,20	4,36	12,76	7,31	218...220 (butanol)	85
XIv	58,27	3,59	7,37	5,42	$C_{28}H_{21}ClBrN_3O_2S$	58,09	3,66	7,26	5,54	160...162 (butanol)	87
XIw	67,35	4,36	8,32	6,50	$C_{28}H_{22}ClN_3O_2S$	67,26	4,44	8,40	6,41	170...172 (butanol)	83

TABLE 2. IR and PMR Spectral Data on Dihydropyridines XIa-w

Compound	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm						
	NH	CN	NHCO, s	NH, s	4-H, s	SCH_2	Z	Ar, m	$6\text{-}CH_3$, s
XIa	3210...3364	2205	9,63	9,09	4,75	2,07 m	0,95 m, 1,52 m	7,00...7,82	2,07
XIb	3180, 3300	2190	9,59	9,18	4,76	4,30 s	2,40 s	6,95...7,66	2,12
XIc	3212...3305	2215	9,65	9,11	4,81	3,03 q	1,23 t	7,00...7,65	2,11
XId	3215, 3322	2200	9,57	9,12	4,74	4,24 s		6,90...7,74	2,08
XIe	3270, 3358	2204	9,64	9,11	4,81	3,96 s	3,64 s	7,00...7,66	2,07
XIf	3214...3370	2192	9,65	9,01	4,76	2,50 s		6,94...7,72	2,08
XIg	3211...3294	2190	9,45	8,93	4,80	2,99 m	0,9 m, 1,29 m	6,85...7,70	2,13
XIh	3215...3308	2200	9,64	9,05	5,31	3,68 m	5,13 d, 5,85 m	6,98...7,53	2,06
XIi	3315	2205	9,84	9,32	5,41	4,24 s		7,00...7,66	2,07
XIj	3302, 3347	2220	9,79	9,43	5,31	3,94 s	10,50 s	7,00...7,71	2,06
XIk	3160...3294	2190 sh.	9,77	9,06	5,27	2,51 s		6,92...7,63	2,06
XI*l*	3211...3300	2210 sh.	9,54	8,90	5,30	3,12 q	1,25 t	6,90...7,71	2,07
XIm	3300	2205 sh.	9,74	9,18	5,25	4,29 s		6,94...7,55	2,07
XIn	3150...3291	2212	9,69	9,15	5,24	4,28 s		6,00...7,63	2,05
XIo	3350	2200	9,75	9,20	5,22	3,80 s	3,55 s	6,54...7,70	1,94
XIp	3105, 3312	2188	9,77	9,14	5,31	4,64 s		7,00...7,62 m, 8,08 t	2,02
XIq	3180...3315	2200	9,77	9,16	5,30	2,98 m	0,96 t, 1,57 m	6,90...7,60	2,06
XIr	3270	2213	9,76	9,15	5,30	2,98 q	0,84 t, 1,25 m	6,90...7,60	2,06
XIs	3315, 3360	2218	9,78	9,50	5,33	3,96 s	10,36 s	6,85...7,64	2,07
XIt	3330	2208 sh.	9,75	9,08	5,28	4,74 s	2,38 s	6,96...7,60 m, 7,89 d	2,01
XIu	3300	2207 sh.	9,99	9,78	5,31	3,72 s	7,70 s, 7,89 s	6,90...7,65	2,04
XIv	3320	2216 sh.	9,74	9,08	5,27	4,72	7,74 d, 7,90 d	6,82...7,54	2,01
XIw	3210, 3282	2175	9,50	8,89	5,29	4,72		6,90...7,73, 8,00	2,05

TABLE 3. Bond Lengths (d) in Molecule of XIh

Bond	d, Å	Bond	d, Å
$Cl_{(1)}—C_{(10)}$	1,746(3)	$S_{(1)}—C_{(2)}$	1,758(2)
$S_{(1)}—C_{(21)}$	1,813(3)	$O_{(1)}—C_{(8)}$	1,236(3)
$N_{(1)}—C_{(2)}$	1,367(3)	$N_{(1)}—C_{(6)}$	1,392(3)
$N_{(2)}—C_{(24)}$	1,147(3)	$N_{(3)}—C_{(8)}$	1,350(3)
$N_{(3)}—C_{(15)}$	1,424(3)	$C_{(2)}—C_{(3)}$	1,349(3)
$C_{(3)}—C_{(4)}$	1,522(3)	$C_{(3)}—C_{(24)}$	1,429(3)
$C_{(4)}—C_{(5)}$	1,521(3)	$C_{(4)}—C_{(9)}$	1,526(3)
$C_{(5)}—C_{(6)}$	1,341(3)	$C_{(5)}—C_{(8)}$	1,491(3)
$C_{(6)}—C_{(7)}$	1,505(3)	$C_{(9)}—C_{(10)}$	1,386(3)
$C_{(9)}—C_{(14)}$	1,398(3)	$C_{(10)}—C_{(11)}$	1,385(4)
$C_{(11)}—C_{(12)}$	1,372(4)	$C_{(12)}—C_{(13)}$	1,366(5)
$C_{(13)}—C_{(14)}$	1,379(4)	$C_{(15)}—C_{(16)}$	1,378(4)
$C_{(15)}—C_{(20)}$	1,379(4)	$C_{(16)}—C_{(17)}$	1,390(6)
$C_{(17)}—C_{(18)}$	1,356(7)	$C_{(18)}—C_{(19)}$	1,344(6)
$C_{(19)}—C_{(20)}$	1,387(5)	$C_{(21)}—C_{(22)}$	1,483(7)
$C_{(22)}—C_{(23)}$	1,290(1)		

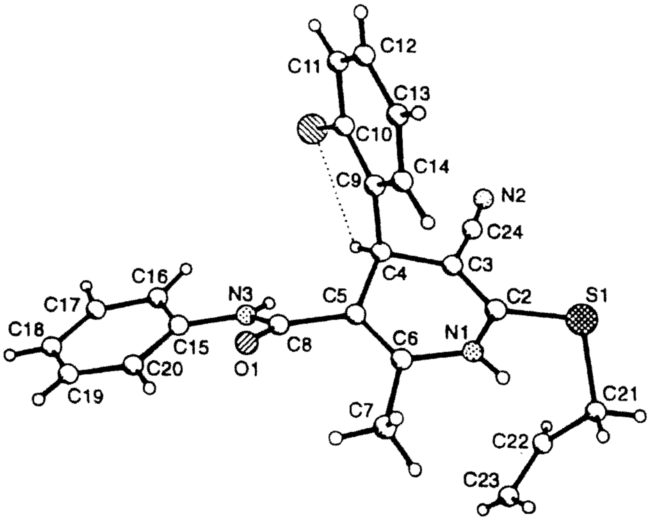

Fig. 1. General view of molecule of XIh.

The pseudoaxial o-chlorophenyl substituent is rotated relative to the "bottom of the boat" of the dihydropyridine ring by 86.4°, and is oriented synperiplanar relative to the $H_{(4)}$ atom (torsion angles $H_{(4)}C_{(4)}C_{(9)}C_{(10)} = -9.7°$, $C_{(4)}C_{(9)}C_{(10)}Cl_{(1)} = 0.7°$). Such a position of the substituent leads to a short nonvalence contact $Cl_{(1)}...H_{(4)}$ 2.60(2) Å (the sum of the van der Waals radii of the atoms is 2.95 Å [6]). The absence of any conjugation between the $C_{(5)}=C_{(6)}$ double bond of the heterocycle and the $C_{(8)}=O_{(1)}$ carbonyl group is due to the substantial rotation of the latter around the $C_{(5)}$-$C_{(8)}$ bond (torsion angle $C_{(6)}C_{(5)}C_{(8)}O_{(1)} = 41.9°$), as evidenced by the length of the $C_{(5)}—C_{(8)}$ bond, which is greater than the standard length of the nonconjugated $C_{sp2}—C_{sp2}$ bond, equal to 1.471 Å [7]. At the same time, slight conjugation of the phenyl substituent with the carbamide fragment $O_{(1)}=C_{(8)}—N_{(3)}$ (torsion angle $C_{(8)}N_{(3)}C_{(15)}C_{(20)} = -17.2°$) favors the appearance of a short nonvalence contact $O_{(1)}$-$C_{(20)}$ 2.882(3) Å, which, according to data from [8], can be regarded as a hydrogen bond of the C—H...O type with the following parameters: $C_{(20)}—H_{(20)}$ 0.88(3), $H_{(20)}...O_{(1)}$ 2.34(3) Å, angle $C_{(20)}—H_{(20)}...O_{(1)}$ 120(3)°. The other geometric parameters of the molecule of XIh have the usual values [7], coinciding with those established in the compound XIII.

In the crystal, intermolecular hydrogen bonds $N_{(1)}-H_{(1)}...O_{(1)}$ (0.5 − x, 0.5 + y, 1.5 − z) ($N_{(1)}...O_{(1)}$ 2.903(3), $N_{(1)}-H_{(1)}$ 0.82(3), $H_{(1)}...O_{(1)}$2.09(3) Å, angle $N_{(1)}-H_{(1)}...O_{(1)}$ 175(2)°), $N_{(3)}-H_{(3)}...N_{(2)}$ (1 − x, −y, 1 − z) ($N_{(3)}...N_{(2)}$ 3.081(3), $N_{(3)} - H_{(3)}$ 0.82(3), $H_{(3)}...N_{(3)}$ 2.27(3) Å, angle $N_{(3)} - H_{(3)}...N_{(2)}$ 170(2)°) connect the molecules in chains along the (101) direction.

TABLE 4. Bond Angles ω (deg) in Structure of XIh

Angle	ω, deg	Angle	ω, deg
$C_{(2)}-S_{(1)}-C_{(21)}$	102,8(1)	$C_{(4)}-C_{(9)}-C_{(10)}$	123,3(2)
$C_{(2)}-N_{(1)}-C_{(6)}$	121,6(2)	$C_{(4)}-C_{(9)}-C_{(14)}$	120,1(2)
$C_{(8)}-N_{(3)}-C_{(15)}$	128,2(2)	$C_{(10)}-C_{(9)}-C_{(14)}$	116,6(2)
$S_{(1)}-C_{(2)}-N_{(1)}$	118,0(2)	$Cl_{(1)}-C_{(10)}-C_{(9)}$	120,1(2)
$S_{(1)}-C_{(2)}-C_{(3)}$	122,1(2)	$Cl_{(1)}-C_{(10)}-C_{(11)}$	117,6(2)
$N_{(1)}-C_{(2)}-C_{(3)}$	119,9(2)	$C_{(9)}-C_{(10)}-C_{(11)}$	122,3(2)
$C_{(2)}-C_{(3)}-C_{(4)}$	121,1(2)	$C_{(10)}-C_{(11)}-C_{(12)}$	119,0(3)
$C_{(2)}-C_{(3)}-C_{(24)}$	121,8(2)	$C_{(11)}-C_{(12)}-C_{(13)}$	120,7(3)
$C_{(4)}-C_{(3)}-C_{(24)}$	117,1(2)	$C_{(12)}-C_{(13)}-C_{(14)}$	119,8(3)
$C_{(3)}-C_{(4)}-C_{(5)}$	109,1(2)	$C_{(9)}-C_{(14)}-C_{(13)}$	121,6(3)
$C_{(3)}-C_{(4)}-C_{(9)}$	111,8(2)	$N_{(3)}-C_{(15)}-C_{(16)}$	117,1(2)
$C_{(5)}-C_{(4)}-C_{(9)}$	111,5(2)	$N_{(3)}-C_{(15)}-C_{(20)}$	123,8(2)
$C_{(4)}-C_{(5)}-C_{(6)}$	120,9(2)	$C_{(16)}-C_{(15)}-C_{(20)}$	119,1(3)
$C_{(4)}-C_{(5)}-C_{(8)}$	118,6(2)	$C_{(15)}-C_{(16)}-C_{(17)}$	119,7(3)
$C_{(6)}-C_{(5)}-C_{(8)}$	120,3(2)	$C_{(16)}-C_{(17)}-C_{(18)}$	120,9(4)
$N_{(1)}-C_{(6)}-C_{(5)}$	119,8(2)	$C_{(17)}-C_{(18)}-C_{(19)}$	119,4(4)
$N_{(1)}-C_{(6)}-C_{(7)}$	112,8(2)	$C_{(18)}-C_{(19)}-C_{(20)}$	121,6(4)
$C_{(5)}-C_{(6)}-C_{(7)}$	127,3(2)	$C_{(15)}-C_{(20)}-C_{(19)}$	119,3(3)
$O_{(1)}-C_{(8)}-N_{(3)}$	122,5(2)	$S_{(1)}-C_{(21)}-C_{(22)}$	113,8(3)
$O_{(1)}-C_{(8)}-C_{(5)}$	121,8(2)	$C_{(21)}-C_{(22)}-C_{(23)}$	122,9(5)
$N_{(3)}-C_{(8)}-C_{(5)}$	115,8(2)	$N_{(2)}-C_{(24)}-C_{(3)}$	175,4(2)

EXPERIMENTAL

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

X-Ray Structure Studies of Compound XIh. Crystals of compound XIh, single-crystal, at 20°C: a = 10.176(2), b = 11.462(3), c = 19.542(5) Å, β = 91.07(2)°, V = 2279(2) Å [7], d_{calc} = 1.235 g/cm^3, Z = 4, space group $P2_1/n$. Cell constants and intensities of 4459 independent reflections were measured in a Siemens P3/PC four-circle automatic diffractometer (λMoKα, graphite monochromator, $\theta/2\theta$ scanning up to θ_{max} = 26°). The structure was deciphered by the direct method after identifying all nonhydrogen atoms, and was refined by full-matrix LSM in the anisotropic approximation for the nonhydrogen atoms on the basis of 3860 reflections with $I > 3\sigma(I)$. All hydrogen atoms were identified objectively by Fourier difference syntheses; however, owing to the large thermal oscillations, they were included in the refinement with fixed thermal parameters U = 0.05 Å [6]. The final values of the divergence factors were R = 0.049, R_w = 0.049 (S = 0.8246). All calculations were performed using the SHELXTL PLUS program [9] (PC version). Coordinates of the atoms are listed in Table 5.

N-Methylmorpholinium 4-Aryl-6-methyl-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolates (Ia,b). A mixture of 10 mmoles of the aromatic aldehyde II, 10 mmoles of cyanothioacetamide III, acetylacetanalide IV, and 20 mmoles of N-methylmorpholine in 20 ml of absolute ethanol was stirred for 6 h at 20°C. The resulting precipitate of the product VII was filtered off and washed with absolute ethanol and hexane.

Salt Ia. Yield 77%, mp 153-155°C. IR spectrum, cm^{-1}: 3225, 3280, 3324 (NH), 2180 (CN). PMR spectrum, ppm: 9.28 (1H, s, NHCO); 7.93 (1H, s, NH); 6.85-7.51 (9H, m, 2Ar); 5.05 (1H, s, 4-H); 3.76 (4H, t, CH_2OCH_2); 3.09 (4H, t, CH_2NCH_2); 2.72 (3H, s, NCH_3); 2.03 (3H, s, CH_3). Found, %: C 62.26; H 5.55; Cl 7.53; N 11.49; S 6.52. $C_{25}H_{27}ClN_4O_2S$. Calculated, %: C 62.17; H 5.63; Cl 7.34; N 11.60; S 6.64.

Salt Ib. Yield 88%, mp 152-154°C. IR spectrum, cm^{-1}: 3240, 3305 (NH), 3185 (CN). PMR spectrum, ppm: 9.17 (1H, s, NHCO); 7.54 (1H, s, NH); 6.93-7.54 (10H, m, 2Ph); 4.57 (1H, s, 4-H); 3.73 (4H, t, CH_2OCH_2); 3.00 (4H, t, CH_2NCH_2); 2.66 (3H, s, NCH_3); 2.08 (3H, s, CH_3). Found, %: C 66.83; H 6.41; N 12.61; S 7.23. $C_{25}H_{28}N_4O_2S$. Calculated, %: C 66.94; H 6.29; N 12.49; S 7.15.

TABLE 5. Coordinates of Atoms ($\times 10^4$, $\times 10^3$ for H) in Molecule of XIh

Atom	x	y	z
$\mathrm{Cl}_{(1)}$	3340(1)	-2293(1)	5261(1)
$\mathrm{S}_{(1)}$	2602(1)	3417(1)	5348(1)
$\mathrm{O}_{(1)}$	3529(2)	-622(1)	7862(1)
$\mathrm{N}_{(1)}$	2639(2)	2300(2)	6557(1)
$\mathrm{N}_{(2)}$	3703(2)	792(2)	4344(1)
$\mathrm{N}_{(3)}$	5036(2)	-1087(2)	7067(1)
$\mathrm{C}_{(2)}$	2832(2)	2181(2)	5870(1)
$\mathrm{C}_{(3)}$	3184(2)	1137(2)	5612(1)
$\mathrm{C}_{(4)}$	3214(2)	49(2)	6058(1)
$\mathrm{C}_{(5)}$	3443(2)	406(2)	6801(1)
$\mathrm{C}_{(6)}$	3081(2)	1463(2)	7023(1)
$\mathrm{C}_{(7)}$	3123(4)	1906(2)	7749(1)
$\mathrm{C}_{(8)}$	3997(2)	-471(2)	7290(1)
$\mathrm{C}_{(9)}$	1963(2)	-674(2)	5969(1)
$\mathrm{C}_{(10)}$	1916(2)	-1725(2)	5619(1)
$\mathrm{C}_{(11)}$	770(3)	-2369(3)	5547(1)
$\mathrm{C}_{(12)}$	-363(3)	-1948(3)	5827(2)
$\mathrm{C}_{(13)}$	-364(3)	-913(3)	6172(2)
$\mathrm{C}_{(14)}$	784(3)	-281(2)	6244(2)
$\mathrm{C}_{(15)}$	5816(2)	-1915(2)	7435(1)
$\mathrm{C}_{(16)}$	6611(4)	-2634(3)	7058(2)
$\mathrm{C}_{(17)}$	7452(4)	-3411(4)	7392(2)
$\mathrm{C}_{(18)}$	7481(4)	-3491(4)	8085(2)
$\mathrm{C}_{(19)}$	6674(4)	-2815(4)	8451(2)
$\mathrm{C}_{(20)}$	5841(3)	-2009(3)	8139(2)
$\mathrm{C}_{(21)}$	3452(4)	4551(2)	5827(2)
$\mathrm{C}_{(22)}$	4823(6)	4245(4)	6026(3)
$\mathrm{C}_{(23)}$	5256(6)	4289(7)	6649(5)
$\mathrm{C}_{(24)}$	3476(2)	990(2)	4905(1)
$\mathrm{H}_{(1)}$	234(2)	291(2)	670(1)
$\mathrm{H}_{(3)}$	529(2)	-97(2)	668(1)
$\mathrm{H}_{(4)}$	393(2)	-38(2)	591(1)
$\mathrm{H}_{(71)}$	358(2)	140(2)	804(1)
$\mathrm{H}_{(72)}$	350(2)	268(2)	777(1)
$\mathrm{H}_{(73)}$	221(2)	195(2)	792(1)
$\mathrm{H}_{(11)}$	84(2)	-309(2)	531(1)
$\mathrm{H}_{(12)}$	-110(2)	-233(2)	580(1)
$\mathrm{H}_{(13)}$	-116(2)	-60(2)	638(1)
$\mathrm{H}_{(14)}$	76(2)	46(2)	646(1)
$\mathrm{H}_{(16)}$	651(2)	-262(2)	656(1)
$\mathrm{H}_{(17)}$	786(2)	-392(2)	711(1)
$\mathrm{H}_{(18)}$	805(2)	-401(2)	832(1)
$\mathrm{H}_{(19)}$	662(2)	-286(2)	890(1)
$\mathrm{H}_{(20)}$	538(2)	-149(2)	837(1)
$\mathrm{H}_{(211)}$	297(2)	481(2)	622(1)
$\mathrm{H}_{(212)}$	342(2)	520(2)	552(1)
$\mathrm{H}_{(22)}$	520(3)	418(2)	566(1)
$\mathrm{H}_{(231)}$	452(3)	460(2)	686(1)
$\mathrm{H}_{(232)}$	595(3)	412(3)	673(1)

4-Aryl-6-methyl-5-phenylcarbamoyl-3-cyanopyridine-2(1H)-thiones (VIIIa,b). A suspension of 10 mmoles of the salt I in 10 ml of ethanol was acidified down to pH 4 by adding a 10% aqueous hydrochloric acid solution while stirring. The resulting solution was filtered, and the filtrate was held for 24 h at 20°C. The precipitate that formed was separated and washed with ethanol and hexane.

Compound VIIIa. Yield 85%, mp 270-272°C (from ethanol). PMR spectrum, ppm: 14.54 (1H, s, NH); 10.34 (1H, s, NHCO); 7.00-7.75 (9H, m, 2Ar); 2.49 (3H, s, CH_3). Found, %: C 63.35; H 3.63; Cl 9.41; N 10.95; S 8.55. $C_{20}H_{14}ClN_3OS$. Calculated, %: C 63.24; H 3.72; Cl 9.33; N 11.06; S 8.44.

Compound VIIIb. Yield 71%, mp 260-262°C (from ethanol). IR spectrum, cm^{-1}: 3150, 3295 (NH), 2224 (CN). PMR spectrum, ppm: 14.39 (1H, s, NH); 10.27 (1H, s, NHCO); 7.00-7.62 (10H, m, 2Ph); 2.48 (3H, s, CH_3). Found, %: C 69.43; H 4.46; N 12.29; S 9.19. $C_{20}H_{15}N_3OS$. Calculated, %: C 69.54; H 4.38; N 12.17; S 9.28.

2-Alkylthio-4-aryl-6-methyl-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridines (XIa-w). To a suspension of 10 mmoles of the salt I in 10 ml of DMF, while stirring at 20°C, 10 mmoles of the halide X was added and stirring was continued for 4 h, after which the mixture was diluted with 10 ml of water and the resulting precipitate was filtered off and washed successively with water and ethanol. Obtained compounds XI, the characteristics of which are listed in Tables 1 and 2.

3-Amino-2-aroyl-6-methyl-5-phenylcarbamoyl-4-(2-chlorophenyl)thieno[2,3-b]pyridines (XIIa-c). *A*. To a solution of 10 mmoles of the pyridine XIw, while stirring, 5.6 ml (10 mmoles) of a 10% aqueous KOH solution was added, and stirring was continued for 6 h. The reaction mixture was diluted with 10 ml of water, and the resulting precipitate of the product XIIa was filtered off. Yield 78%, mp 132-134°C (from AcOH). PMR spectrum, ppm: 10.42 (1H, s, NHCO); 7.00-7.85 (14H, m, 3Ar); 6.61 (2H, br. s, NH_2); 2.69 (3H, s, Me). Found, %: C 67.51; H 4.18; Cl 7.21; N 8.57; S 6.32. $C_{28}H_{20}ClN_3O_2S$. Calculated, %: C 67.53; H 4.05; Cl 7.12; N 8.44; S 6.44.

B. To a suspension of 10 mmoles of the salt I in 10 ml of DMF, while stirring, 10 mmoles of the halide X was added and the stirring was continued for 6 h, after which 5.6 ml (10 mmoles) of 10% aqueous KOH solution was added and stirring was continued for 4 h. The mixture was diluted with 10 ml of water, and the precipitated product XII was filtered off and then washed successively with water and ethanol.

Compound XIIb. Yield 88%, mp 117-119°C. PMR spectrum, ppm: 9.73 (1H, s, NHCO); 6.75-8.11 (12H, m, 3Ar); 5.61 (2H, s, NH_2); 2.06 (3H, s, CH_3). Found, %: C 59.41; H 3.32; Cl 18.56; N 7.33; S 5.55. $C_{28}H_{18}Cl_3N_3O_2S$. Calculated, %: C 59.33; H 3.20; H 3.20; Cl 18.76; N 7.41; S 5.66.

Compound XIIc. Yield 70%, mp 168-170°C. PMR spectrum, ppm: 9.75 (1H, s, NHCO); 6.60-7.82 (13H, m, 3Ar); 5.62 (2H, s, NH_2); 2.07 (3H, s, CH_3). Found, %: C 63.02; H 3.49; Cl 13.45; N 60.14 [sic]; S 5.84. $C_{28}H_{19}Cl_2N_3O_2S$. Calculated, %: C 63.16; H 3.60; Cl 13.32; N 60.01 [sic]; S 6.02.

Bis[6-methyl-5-phenylcarbamoyl-4-(2-chlorophenyl)-3-cyano-1,4-dihydropyridyl] disulfide (IX). To a suspension of 10 mmoles of the salt Ia in 20 ml of ethanol, 13 ml of a 10% solution of iodine in alcohol was added dropwise with stirring over the course of 10 min. After 30 min, the mixture was diluted with 10 ml of water. The precipitated product IX was filtered off and washed with water and ethanol. Yield 70%, mp 153-155°C. IR spectrum, cm^{-1}: 3090, 3275, 3450 (NH); 2170, 2250 (CN). PMR spectrum, ppm: 10.52 and 9.77 (2H, two s, NHCO); 9.58 and 9.48 (2H, two s, NH); 7.00-7.75 (18H, m, 2Ph and 2Ar); 5.40 and 5.35 (2H, two s, $2C_{(4)}H$); 2.07 and 2.10 (3H, two s, $2CH_3$). Found, %: C 63.25; H 3.91; Cl 9.39; N 11.25; S 8.38. $C_{40}H_{30}Cl_2N_6O_2S_2$. Calculated, %: C 63.07; H 3.97; Cl 9.31; N 11.03; S 8.42.

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