SYNTHESIS OF 3-CYANO-4,6-DIARYL-3,4-DIHYDROPYRIDINE-2-THIONES

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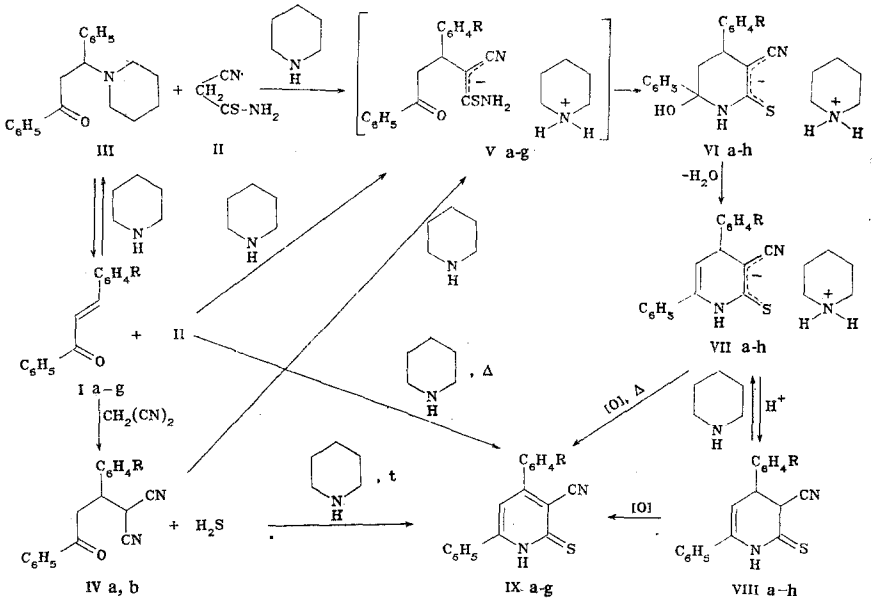
UDC 547.825.07:541.634:543.422

3-Cyano-4,6-diaryl-3,4-dihydropyridine-2-thiones have been synthesized for the first time by the condensation of arylideneacetophenones or 1-piperidino-1-phenyl-2-benzoylethane with cyanothioacetamide and the 1,1-dicyano-2-aryl-3-benzoylpropane with hydrogen sulfide in the presence of bases. It has been established by PMR spectroscopy that 3-cyano-3,4-dihydropyridine-2-thiones exist in solutions in the form of mixture of cis and trans isomers.

In the last few years reports [1-5] on the methods of synthesis and the reactivity of 3,4-dihydro-2-pyridones have appeared with increasing frequency.

In the present work our purpose was to study the possibilities of the synthesis of 3,4-dihydropyridine-2-thiones, i.e., the sulfur analogs of 3,4-dihydro-2-pyridones. We developed the following methods for the synthesis of 3-cyano-4,6-diaryl-3,4-dihydropyridine-2-thiones (VIII): the condensation of arylideneacetophenones (I) or 1-piperidino-1-phenyl-2-benzoylethane (III) with cyanothioacetamide (II) (methods A and B) and the 1,1-dicyano-2-aryl-3-benzoylpropane (IV) with hydrogen sulfide (method C). The essential feature of these methods is the intramolecular cyclization of the δ-ketothioamides formed (V) to 3,4-dihydropyridine-2-thiones in the presence of bases. The Michael addition reaction and the further intramolecular cyclization take place vigorously at room temperature and are completed over the course of several minutes.



I, IV—IX a R=H; b R=4-NO_2; c R=3-NO_2; d R=4-F; e R=4-Cl; f R=4-Br; g R=4-OCH_3; h R=4-$N(CH_3)_2$

Using piperidine as the condensing agent, we isolated the intermediate products, i.e., the piperidinium salts of 3-cyano-4-aryl-6-hydroxy-6-phenylpiperidine-2-thiones (VI) [6]. The salts of thiones VI are unstable. On the 6-hydroxy-piperidine-2-thiones containing elec-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1515-1520, November, 1983. Original article submitted April 11, 1983.

 0009-3122/83/1911-1202$07.50 © 1984 Plenum Publishing Corporation

tron-acceptor substituents in the 4-phenyl ring (VIa, b, d, and e) can be recrystallized from a chloroform–ether mixture. When the 6-hydroxypiperidine-2-thiones of type VI are boiled in nitromethane, the piperidinium salts of 3-cyano-4,6-diaryl-3,4-dihydropyridine-2-thiones (VII) form. In the case of electron-donor substituents in the 4-phenyl ring, a mixture of piperidinium salts of types VI and VII forms already during the synthesis, as indicated by the PMR spectra.

The PMR spectra of the salts of the 6-hydroxypiperidine-2-thiones of type VI show the characteristic signals of the ABX system at 3.76-3.93, 1.74-1.81, and 1.50-1.58 ppm. The value of J_{HH} in the CH_2 fragment (13 Hz) is close to that in the saturated fragments of CH_2 groups which do not contain vicinal double and triple bonds [7]. The values of the vicinal spin–spin coupling constants between 4-H and 5-H (12.0 and 5.3 Hz) in the salts of type VI attest to the pseudoequatorial orientation of the 4-C_6H_4R group. The PMR spectra of the salts of the 3,4-dihydropyridine-2-thiones of type VII show characteristic doublets from the 4-H and 5-H protons at 4.10-4.32 and 4.79-4.90 ppm.

The IR spectra of salts VI and VII do not differ appreciably. Absorption bands of the characteristic groups, viz., CN at 2170-2180 and NH, NH_2, and OH in the 3225-3328-cm^{-1} region, are observed.

The UV spectra of the salts of the 3,4-dihydropyridine-2-thiones of type VII, unlike those of the piperidine-2-thiones of type VI, display a long-wavelength maximum in the form of a hump at 330-350 nm, which attests to a more conjugated system.

The piperidinium salts of the 3,4-dihydropyridine-2-thiones of type VII are stable in the crystalline state; however, they readily undergo further conversions in solutions.

The application of an equimolar quantity of 0.5 N NCl in ethanol to salts of types VI and VII at room temperature results in the formation of 3-cyano-4,6-diaryl-3,4-dihydropyridine-2-thiones (VIII). When the salts of types VI and VII are boiled in acetic acid and ethanol, these compounds undergo protonation and simultaneous dehydrogenation to the known pyridine-2-thiones of type IX [8].

The 3,4-dihydropyridine-2-thiones of type VIII were also obtained with lower yields by the condensation of arylideneacetophenones I with cyanoacetamide II in the presence of ammonia or sodium methoxide at room temperature. The corresponding ammonium and sodium salts of the hydrogenated pyridine-2-thiones could not be isolated under the present reaction conditions due to their high solubility.

Compound VIIIg, which contains a dimethylamino group in the para position of the 4-phenyl ring, is extremely unstable, and it can be recovered under the conditions of the reaction only in the form of a mixture of 3,4-dihydropyridine-2-thione VIIIg and pyridine-2-thione IXg.

The PMR spectra of the 3,4-dihydropyridine-2-thiones of type VIII show characteristic signals of the 3-, 4-, and 5-H protons at 4.72-5.11, 4.05-4.43, and 5.72-6.10 ppm.

The IR spectra show characteristic stretching vibrations of the NH group at 3144-3290 cm^{-1}, but the C≡N vibrations are shifted significantly toward higher frequencies in comparison to the corresponding salts of types VI and VII and are found at 2244-2272 cm^{-1}. This is an indication that in the salts of types VI and VII the negative charge is also partially localized on the CN group. In the UV spectra of the 3,4-dihydropyridine-2-thiones of type VIII, besides the spectra of the salts of type VII, a long-wavelength maximum is observed at 325-332 nm. The absorption at 400-420 nm which is characteristic of the conjugated system in the pyridine-2-thiones of type IX [8] is absent.

In alkaline solutions the 3,4-dihydropyridine-2-thiones of type VIII readily form the corresponding salts, which can be detected spectroscopically, and in the case of piperidine, the salts can be isolated preparatively.

In polar media at room temperature, especially with heating, the compounds of type VIII are readily oxidized by atmospheric oxygen to the pyridine-2-thiones of type IX.

The spatial structure of the 3,4-dihydropyridine-2-thiones of type VIII was studied by PMR spectroscopy (Table 4). Like the spectra of the oxygen analogs [9], the PMR spectra of the 3,4-dihydropyridine-2-thiones contain signals of cis and trans stereoisomers. In the case of the compounds of type VIII, in analogy to 3-cyano-4,6-diphenyl-3,4-dihydro-2-pyridone (X) [9], we may postulate the two idealized conformations A and B, which are capable of fast interconversion.

TABLE 1. Characteristics of Piperidinium Salts of Hydrogenated Pyridine-2-thiones of Types VI and VII

Compound	R	mp, deg C	IR spectrum, cm^{-1}	UV spectrum, λ, nm (log ε)
VIa	H	112—114	2178, 3290, 3317	238 (4,15), 286 (4,13)
VIb	4-NO_2	128—130	2173, 3292	240 (4,11), 290 (4,28)
VId	4-F	120—122	2176, 3303	241 (4,00), 285 (4,00)
VIe	4-Cl	114—117	2174, 3303	240 (4,13), 285 (4,13)
VIIa	H	124—126	2170, 3325	250[a] (4,31), 288 (4,28), 348[a] (3,58)
VIIb	4-NO_2	148—150	2173, 3266	256[a] (4,35), 281 (4,42), 340[a] (3,81)
VIIc	3-NO_2	165—166	2174, 3240	252[a] (4,33), 279 (4,29), 338[a] (3,60)
VIId	4-F	138—140	2173, 3268	252[a] (4,25), 287 (4,24), 346[a] (3,53)
VIIe	4-Cl	141—143	2173, 3268	252[a] (4,30), 286 (4,28), 350[a] (3,58)
VIIf	4-Br	140—142	2172, 3258	250[a] (4,38), 289 (4,31), 350[a] (3,60)
VIIg	4-OCH_3	134—136	2175, 3262	252[a] (4,25), 288 (4,25), 348[a] (3,64)
VIIh	4-$N(CH_3)_2$	128—131	2180, 3277, 3328	256 (4,33), 288[a] (4,17), 348[a] (2,90)

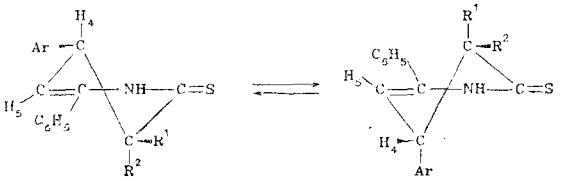
Compound	Found, %				Empirical formula	Calculated, %				Yield, %
	C	H	N	S		C	H	N	S	
VIa	69,9	6,8	10,8	8,3	$C_{23}H_{27}N_3OS$	70,2	6,9	10,7	8,2	84
VIb	63,6	5,7	12,5	7,8	$C_{23}H_{26}N_4O_3S$	63,0	6,0	12,8	7,3	92
VId	67,1	6,7	10,6	7,9	$C_{23}H_{26}FN_3OS$	67,1	6,4	10,2	7,8	83
VIe	65,2	5,9	8,9	7,3	$C_{23}H_{26}ClN_3OS$	64,5	6,1	9,8	7,5	75
VIIa	72,8	6,9	11,0	8,0	$C_{23}H_{25}N_3S$	73,6	6,7	11,2	8,5	60
VIIb	64,8	5,4	13,0	7,5	$C_{23}H_{24}N_4O_2S$	65,7	5,7	13,3	7,6	42
VIIc	64,7	6,1	13,8	7,3	$C_{23}H_{24}N_4O_2S$	65,7	5,7	13,3	7,6	53
VIId	70,6	6,5	10,7	7,9	$C_{23}H_{24}FN_3S$	70,2	6,2	10,7	8,1	61
VIIe	67,8	5,7	10,3	7,6	$C_{23}H_{24}ClN_3S$	67,4	5,9	10,3	7,8	56
VIIf	60,3	5,2	9,7	7,7	$C_{23}H_{24}BrN_3S$	60,8	5,3	9,2	7,1	65
VIIg	70,0	6,5	10,3	8,6	$C_{24}H_{27}N_3OS$	71,1	6,7	10,4	7,9	36
VIIh	71,9	7,4	13,7	8,0	$C_{25}H_{30}N_4S$	71,7	7,2	13,4	7,7	41

[a]Shoulder.

TABLE 2. Parameters of the PMR Spectra of Piperidinium Salts of Piperidine-2-thiones of Type VI and of 3,4-Dihydropyridine-2-thiones of Type VII in DMSO-d_6

Compound	R	Chemical shifts,[a] ppm (multiplicity)				J, Hz	
		4-H	5-H	4-Ar (m)	NH and OH (br s)	4—5	5—5
VIa	H	3,83 (d,d)	1,80(m) & 1,58 (m)	7,4—7,1	5,0	5,0 & 12,0	13,0
VIb	4-NO_2	3,91	1,74 & 1,52	8,0—7,4	5,6	5,2 & 11,8	13,0
VIc	3-NO_2	3,93	1,73 & 1,50	7,9—7,4	5,4	5,2 & 12,0	13,0
VId	4-F	3,83	1,76 & 1,53	7,3—7,0	5,0	5,3 & 11,8	13,0
VIe	4-Cl	3,83	1,81 & 1,56	7,4—7,1	5,0	5,2 & 12,0	13,0
VIf	4-Br	3,78	1,80 & 1,58	7,7—7,1	5,3	5,3 & 12,0	13,0
VIg[b]	4-OCH_3	3,83	1,76 & 1,53	7,4—7,1	5,0	5,4 & 11,8	13,0
VIIa	H	4,16 (d)	4,87 (d)	7,4—7,1	6,76	5,0	
VIIb	4-NO_2	4,32	4,80	8,2—7,3	7,02	5,0	
VIIc	3-NO_2	4,35	4,87	8,0—7,3	7,07	5,0	
VIId	4-F	4,12	4,79	7,3—6,9	6,91	5,0	
VIIe	4-Cl	4,23	4,82	7,4—7,0	6,90	5,0	
VIIf	4-Br	4,10	4,80	7,5—7,0	6,81	5,0	
VIIg[c]	4-OCH_3	4,27	4,90	7,5—7,1	6,70	5,0	
VIIh[d]	4-$N(CH_3)_2$	4,15	4,86	7,4—6,9	6,63	5,0	

[a]The signals of the protons in the $N(CH_2)_2$ and $(CH_2)_3$ groups are at 2.9 (m) and 1.6 (m). [b]The signal of the OCH_3 protons is at 3.67 (s). [c]The signal of the OCH_3 protons is at 3.71 (s). [d]The signal of the $N(CH_3)_2$ protons is at 2.81 (s).



VIII- trans R^1=CN, R^2=H_3; VIII- cis R^1=H_3, R^2=CN

The value $^3J_{H_3H_4}$ = 11 to 12 Hz in one isomer is evidence of the trans-diaxial orientation of 3-H and 4-H. Therefore, the aryl substituent in position 4 and the nitrile group have pseudoequatorial orientations, and this isomer is the trans isomer. A large value of $^3J_{H_3H_4}$ is an indication of the predominance of conformer VIIIA in the solution.

The other isomer, whose signals are observed in the spectra of the compounds of type VIII, clearly has a cis structure. The averaged values $^3J_{H_3H_4}$, which equal ∿6 Hz in this isomer, attest to the rapid A ⇄ B conformational equilibrium.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum, the UV spectra were recorded on a Specord VU-VIS instrument in ethanol, and the PMR spectra were recorded on a WH 90/DC instrument (90 MHz) with HMDS as the internal reference.

Piperidinium Salt of 3-Cyano-4,6-diphenyl-6-hydroxypiperidine-2-thione (VIa). A. A mixture of 2.08 g (10 mmole) of benzylideneacetophenone (Ia) and 1.0 g (10 mmole) of cyanothioacetamide (II) is dissolved with vigorous stirring in 30 ml of absolute ethanol, 2 ml (25 mmole) of piperidine are added, and the reaction mixture is filtered. After 3 min, a white reaction product crystallizes out and is filtered out and washed with cold ethanol and ether. The yield is 3.3 g (84%). Compounds VIb-g are obtained in a similar manner.

B. A mixture of 2.93 g (10 mmole) of 1-piperidine-1-phenylbenzoylethane [10] (III) and 1.0 g (10 mmole) of cyanothioacetamide (II) is dissolved with stirring in 30 ml of absolute ethanol, given an addition of 0.2 ml (2.5 mmole) of piperidine, and filtered. After 5 min, the reaction product crystallizes out and is filtered out and washed with cold ethanol and ether. The yield is 3.1 g (79%).

C. A 2.74 g portion (10 mmole) of 1,1-dicyano-2-phenyl-3-benzoylpropane (IVa) [11] is dissolved in 50 ml of absolute ethanol, 2 ml (25 mmole) of piperidine are added, and hydrogen sulfide is bubbled through the reaction mixture for 1 h. The precipitate is filtered out and washed with cold ethanol and ether. The yield is 2.07 g (53%). Compound VIe is obtained in an analogous manner with a 49% yield (Tables 1 and 2).

Piperidinium Salts of 3-Cyano-4-aryl-6-phenyl-3,4-dihydropyridine-2-thiones (VII) (Tables 1 and 2). A. Salts VII are obtained by the recrystallization of 6-hydroxypiperidine-2-thiones of type VI from nitromethane (VIIa, c-g) or ethanol (VIIb).

B. A 0.29-g portion (1 mmole) of 3,4-dihydropiperidine-2-thione VIIIa is dissolved in 10 ml of a 1:1 ethanol–ether mixture, and 0.2 ml (2.5 mmole) of piperidine is added. After 20 min, product VIIa crystallizes out and is filtered out and washed with cold ethanol and ether. This yields 0.23 g (62%) of compound VIIa. Salts VIIb-f are obtained in a similar manner with 60-72% yields.

3-Cyano-4,6-diphenyl-3,4-dihydropyridine-2-thione (VIIIa). A. A 1.97-g portion (5 mmole) of pyridine-2-thione (VIa) is dissolved with vigorous stirring in 10 ml of 0.5 N HCl in ethanol. After 10 min, a bright yellow reaction product crystallizes out and is filtered out. The yield is 0.95 g (65%), and the mp is 158-160°C (from ethanol). Compounds VIIIb-f are obtained in a similar manner.

B. A mixture of 2.08 g (10 mmole) of benzylideneacetophenone (Ia) and 1.1 g (11 mmole) cyanothioacetamide (II) is dissovled with vigorous stirring in 20 ml of ethanol and 5 ml of aqueous ammonia. The reaction mixture is filtered and poured into acidified ice water (pH ≈ 3 to 4). The precipitate is separated and dried. The yield is 1.41 g (48%), and the mp is 158-160°C (from ether). Compounds VIIIb, d, e, i, and j are obtained in a similar manner.

C. A mixture of 2.08 g (10 mmole) of benzylideneacetophenone (Ia) and 1.1 g (11 mmole) of cyanothioacetamide (II) is dissolved with vigorous stirring in 10 ml of 8.5% sodium methoxide. The reaction mixture is filtered and poured into acidified ice water (pH ≈ 3-4).

TABLE 3. Characteristics of the 3,4-Dihydropyridine-2-thiones of Type VIII and Pyridine-2-thiones of Type IX Synthesized

Compound	R	mp, deg C	IR spectrum, cm^{-1}	UV spectrum λ, nm (log ε)
VIIIa	H	158—160	2244, 3190	260 (4,29), 328 (4,01)
VIIIb	4-NO_2	218—220	2264, 3290	262 (4,22), 325 (3,86)
VIIIc	3-NO_2	140—142	2257, 3200	260 (4,21), 328 (4,00)
VIIId	4-F	150—152	2261, 3180	259 (4,28), 332 (3,98)
VIIIe	4-Cl	152—154	2271, 3210	260 (4,23), 330 (3,93)
VIIIf	4-Br	135—137	2272, 3150, 3205	260 (4,21), 325 (3,96)
VIIIg	4-OCH_3	157—159	2259, 3190	258[b] (4,23), 326 (3,98)
IXc	3-NO_2	200—202	2232, 3155	245[b] (4,38), 270 (4,43), 321 (4,21), 421 (3,58)
IXd	4-F	200—202	2231, 3170, 3325	244 (4,12), 290 (4,32), 312[b] (4,22), 418 (3,51)
IXf	4-Br	216—218	2233, 3150	246 (4,11), 286[b] (4,30), 312 (4,33), 420 (3,59)

Compound	Found, %				Empirical formula	Calculated, %				Yield, % (method)
	C	H	N	S		C	H	N	S	
VIIIa	74,1	5,2	9,7	10,8	$C_{18}H_{14}N_2S$	74,4	4,9	9,6	11,0	55[a] (A), 49 (B), 47 (C)
VIIIb	64,2	4,0	12,4	9,0	$C_{18}H_{13}N_3O_2S$	64,4	3,9	12,5	9,6	55 (A), 54 (B),
VIIIc	64,5	3,9	12,6	9,8	$C_{18}H_{13}N_3O_2S$	64,4	3,9	12,5	9,6	61 (A)
VIIId	69,6	4,1	8,8	9,4	$C_{18}H_{13}FN_2S$	70,1	4,2	9,1	10,4	61 (A), 56 (B)
VIIIe	66,0	4,2	8,4	10,2	$C_{18}H_{13}ClN_2S$	66,6	4,0	8,6	9,8	56 (A), 57 (B), 51 (B)
VIIIf	58,6	3,5	7,2	8,2	$C_{18}H_{13}BrN_2S$	58,5	3,5	7,6	8,7	70 (A)
VIIIg	71,7	4,9	8,7	9,8	$C_{19}H_{16}N_2OS$	71,2	5,0	8,7	10,0	38 (A), 35 (B)
IXc	63,9	3,3	13,0	9,1	$C_{18}H_{11}N_3O_2S$	64,8	3,3	12,6	9,6	42
IXd	69,9	3,8	8,9	10,2	$C_{18}H_{11}FN_2S$	70,6	3,6	9,1	10,4	38
IXf	58,6	2,6	7,9	8,5	$C_{18}H_{11}BrN_2S$	58,9	3,0	7,7	8,7	39

[a]The yield was calculated relative to the original chalcone. [b]Shoulder.

TABLE 4. Parameters of the PMR Spectra of 3-Cyano-4-aryl-6-phenyl-3,4-dihydropyridine-2-thiones of Type VIII in DMSO-d_6

Compound	R	Chemical shifts, ppm (multiplicity)								J, Hz			
		NH (br, s)	4-Ar (m)	3-H (d)		4-H (d)		5-H (d)		3—4		4—5	
				trans	cis	trans	cis	trans	cis	trans	cis	trans	cis
VIIIa	H	12,18 & 12,10	7,6—7,2	4,81	4,98	4,16	4,12	5,81	6,07	11,0	6,8	3,2	6,2
VIIIb	4-NO_2	12,24 & 12,16	8,2—7,4	4,96	5,10	4,42	4,37	5,82	6,10	11,4	6,6	3,2	6,2
VIIIc	3-NO_2	12,24 & 12,20	8,2—7,4	5,00	5,11	4,43	4,38	5,86	6,10	11,4	6,6	3,2	6,2
VIIId	4-F	12,21 & 12,14	7,5—7,1	4,82	4,99	4,21	4,18	5,83	6,07	10,9	6,8	3,0	6,0
VIIIe	4-Cl	12,16 & 12,08	7,5—7,2	4,81	4,98	4,24	4,21	5,77	6,02	11,2	6,8	3,2	6,2
VIIIf	4-Br	12,16 & 12,09	7,6—7,3	4,80	5,00	4,20	4,16	5,77	6,01	11,2	6,6	3,2	6,2
VIIIg[a]	4-OCH_3	12,18 & 12,11	7,6—7,0	4,80	5,00	4,18	4,14	5,87	6,11	11,4	6,8	3,2	6,2
VIIIh[b]	4-$N(CH_3)_2$	12,16 & 12,07	7,6—6,8	4,72	4,94	4,08	4,05	5,81	6,03	10,8	6,6	3,2	6,0

[a]The signal of the OCH_3 protons is at 3.69 (s). [b]The signal of the $N(CH_3)_2$ protons is at 2.97 (m).

The precipitate is separated and dried. The yield is 1.36 g (47%), and the mp is 158-160°C (from ether). Compounds VIIIb-e are obtained in a similar manner. The data on the compounds of type VIII are given in Table 4.

3-Cyano-4,6-diphenylpyridine-2-thione (IXa). A mixture of 5 mmole of piperidine-2-thione VIa or 3,4-dihydropyridine-2-thione VIIa in 20 ml of acetic acid is heated for 30 min in a water bath. After cooling for 2 days, 0.8-0.85 g (54-56%) of compound IXa with mp 227-229°C (from nitromethane) crystallizes out [8]. Compounds IXb-j are obtained in a similar manner with 23-52% yields. The data on the compounds of type IX which have not been described in the literature [8] are presented in Table 4.

LITERATURE CITED

1. H. Meyr, F. Bossert, and H. Horstman, Ann. Chem., No. 9, 1483 (1978).
2. B. Chylinska, Pol. J. Chem., 53, 1913 (1979).
3. Z. A. Bomika, Yu. É. Pelcher, G. Ya. Duber, A. A. Krauze, and É. E. Liepin'sh, Khim. Geterotsikl. Soedin., No. 10, 1377 (1979).
4. R. Balicki and P. Nantka-Namirski, Pol. J. Chem., 53, 2121 (1979).
5. C. Seoane, J. L. Soto, and M. R. Zamorano, Heterocycles, No. 5, 639 (1981).
6. A. A. Krauze, in: Fifth Youth Conference on Synthetic and Natural, Physiologically Active Compounds Dedicated to the Sixtieth Anniversary of Soviet Armenia [in Russian], Izd. Akad. Nauk Arm. SSR, Erevan (1980), p. 23.
7. V. F. Bystrov, Usp. Khim., 41, 512 (1972).
8. A. A. Krauze, Z. A. Bomika, A. M. Shestopalov, L. A. Rodinovskaya, Yu. É. Pelcher, G. Ya. Dubur, Yu. A. Sharanin, and V. K. Promonenkov, Khim. Geterotsikl. Soedin., No. 3, 377 (1981).
9. J. Kuthan, P. Neswadba, Z. Donnerova, and P. Trska, Collect. Czech. Chem. Commun., 42, 2152 (1977).
10. F. M. Menger and J. M. Smith, J. Am. Chem. Soc., 91, 4211 (1969).
11. E. P. Kohler and B. L. Souther, J. Am. Chem. Soc., 44, 2903 (1922).

DERIVATIVES OF 4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID

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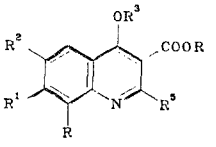
UDC 615.277.3+547.831.9

A new method for the synthesis of ethyl esters of 2-methyl-4-hydroxyquinoline-3-carboxylic acids has been proposed, and their condensation reaction with 5-nitrofurfural has been described. Data on their antiblastic activity has been presented.

Derivatives of 4-hydroxyquinoline-3-carboxylic acid have found application as coccidiostatic agents [1, 2]. Some of them have antibacterial [3, 4] and antiblastic activity [5].

For the purpose of finding new physiologically active substances in this series, we developed a method for the synthesis of ethyl 2-methyl-4-hydroxyquinoline-3-carboxylic acid and its derivatives (I-VIII) and investigated the condensation reaction of these compounds with 5-nitrofurfural (IX-XVIII).



I-XVIII

I $R=R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=CH_3$; II $R=R^1=R^3=H$, $R^2=R^5=CH_3$, $R^4=C_2H_5$; III $R=R^3=H$, $R^1=R^2=R^5=CH_3$, $R^4=C_2H_5$; IV $R=R^1=R^3=H$, $R^2=Br$, $R^4=C_2H_5$, $R^5=CH_3$; V $R=R^1=R^3=H$, $R^2=(CH_3)_2CH$, $R^4=C_2H_5$, $R^5=CH_3$; VI $R=R^2=R^3=H$, $R^1=Cl$, $R^4=C_2H_5$, $R^5=CH_3$; VII $R=OCH_3$, $R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=CH_3$; VIII $R=R^1=R^3=H$, $R^2=OCH_3$, $R^4=C_2H_5$, $R^5=CH_3$; IX $R=R^1=R^2=R^3=R^4=H$, $R^5=$ 5-nitrofurylvinyl; X $R=R^2=R^3=R^4=H$, $R^1=Cl$, $R^5=$ 5-nitrofurylvinyl; XI $R=R^1=R^3=R^4=H$, $R^2=OCH_3$, $R^5=$ 5-nitrofurylvinyl; XII $R=R^3=R^4=H$, $R^1=R^2=CH_3$, $R^5=$ 5-nitrofurylvinyl; XIII $R=R^1=R^2=H$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XIV $R=R^1=H$, $R^2=OCH_3$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XV $R=H$, $R^1=R^2=CH_3$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XVI $R=R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=$ nitrofurylvinyl; XVII $R=R^1=R^3=H$, $R^2=OCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XVIII $R=R^3=H$, $R^1=R^2=CH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl

The method for obtaining ethyl 2-methyl-4-hydroxyquinoline-3-carboxylate not containing substituents in the benzene part of the quinoline nucleus is based on the condensation of

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1521-1523, November, 1983. Original article submitted May 29, 1983.

0009-3122/83/1911-1207$07.50 © 1984 Plenum Publishing Corporation