PREPARATION AND PROPERTIES OF PIPERIDINE SALTS OF 6-HYDROXY-4,6-DIARYL-5-ETHOXYCARBONYL-3-CYANOPIPERIDINE-2-THIONES

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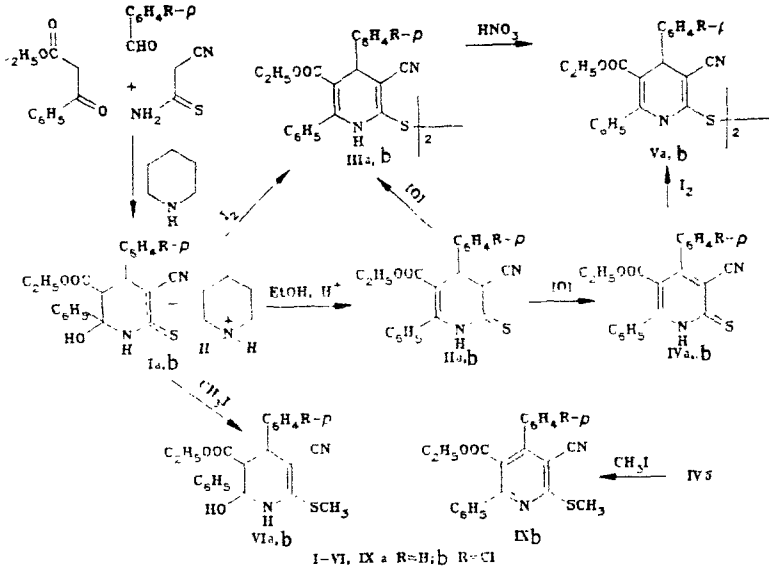
UDC 547.825.07:543.422

Alkylation of piperidine salts of 6-hydroxy-4,6-diaryl-5-ethoxycarbonyl-3-cyanopiperidine-2(1H)-thiones yielded 6-hydroxy-2-alkylthio-4,6-diaryl-5-ethoxycarbonyl-3-cyano-3,4,5,6-tetrahydropyridines which were dehydrogenated with the formation of 2-methylthio-1,4- and 4,5-dihydropyridines. The oxidation of the compounds prepared has been studied.

In our continuing work on the preparation and examination of 3,4-dihydropyridine-2(1H)-thiones [1-5] we have prepared piperidine salts of 6-hydroxy-4,6-diaryl-5-ethoxycarbonyl-3-cyanopiperidine-2-thiones I and we have studied their alkylation and oxidation.

The piperidine salts Ia,b were obtained by an unsymmetrical, three-carbon condensation of the ethyl ester of benzoylacetic acid, an aromatic aldehyde, and cyanothioacetamide in the presence of piperidine. On acidification with hydrochloric acid, the salts Ia,b were converted into the yellow 4,6-diaryl-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2(1H)-thiones (IIa,b).



Although the salts Ia,b possess several nucleophilic centers (3-C, O, N, S), alkylation takes place exclusively at the sulfur atom. Under mild conditions the salts are alkylated by methyl iodide to form the 6-hydroxy-2-methylthio-4,6-diaryl-5-ethoxycarbonyl-3-cyano-3,4,5,6-tetrahydropyridines (VIa,b), which readily lose water.

Depending on the experimental conditions, dehydration can take place in two directions: with the formation of a C=C bond or a C=N bond. On warming the tetrahydropyridine VIa with ethanol, and also on stirring the salt Ia with methyl iodide for 1 h, 2-methylthio-4,6-diphenyl-3-cyano-4,5-dihydropyridine (VII) is formed which, in an acid medium, is rearranged to the 1,4-dihydropyridine VIII in high yield. Compound VIII is also formed on heating compound VIa in acidified ethanol at boiling point, and on alkylating the salt Ia with dimethyl

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 75-80, January, 1987. Original article submitted November 1, 1985.

0009-3122/87/2301-0061$12.50

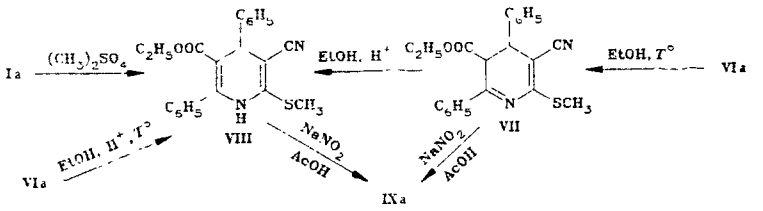
TABLE 1. Characteristics of Compounds I-X

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
Ia	104—106	67.7	6.6	9.1	7.2	$C_{26}H_{31}N_3O_3S$	67.1	6.7	9.7	6.9	76
Ib	112—114	62.3	5.8	8.4	6.2	$C_{26}H_{30}ClN_3O_3S$	62.4	6.0	8.4	6.4	58
IIa	118—120	69.1	4.8	8.0	8.4	$C_{21}H_{18}N_2O_2S$	69.6	5.0	7.7	8.8	43
IIb	130—132	63.1	4.4	6.9	8.2	$C_{21}H_{17}ClN_2O_2S$	63.5	4.3	7.1	8.1	83
IIIa	154—156	70.2	5.0	8.1	8.7	$C_{42}H_{34}N_4O_4S_2$	69.8	4.7	7.8	8.9	72
IIIb	156—158	62.9	4.1	7.4	8.6	$C_{42}H_{32}Cl_2N_4O_4S_2$	63.7	4.1	7.1	8.1	82
IVa	183—185	69.6	4.7	7.4	8.5	$C_{21}H_{16}N_2O_2S$	70.0	4.5	7.8	8.9	14
IVb	222—224	63.7	3.7	7.1	8.0	$C_{21}H_{15}ClN_2O_2S$	63.9	3.8	7.1	8.1	39
Va	182—184	70.8	4.3	8.1	9.4	$C_{42}H_{30}N_4O_4S_2$	70.2	4.2	7.8	8.9	53
Vb	199—201	63.6	3.8	6.9	7.9	$C_{42}H_{28}Cl_2N_4O_4S_2$	64.0	3.6	7.1	8.1	46
VIa	138—140	66.6	6.0	6.9	8.3	$C_{22}H_{22}N_2O_3S$	67.0	5.6	7.1	8.1	91
VIb	173—175	61.8	4.8	6.6	7.2	$C_{22}H_{21}ClN_2O_3S$	61.6	4.9	6.5	7.5	77
VII	126—128	70.6	5.4	7.8	8.3	$C_{22}H_{20}N_2O_2S$	70.2	5.4	7.4	8.5	77*
VIII	157—159	69.8	5.6	7.2	9.0	$C_{22}H_{20}N_2O_2S$	70.2	5.4	7.4	8.5	75*
IXa	97—99	70.9	5.0	7.8	8.8	$C_{22}H_{18}N_2O_2S$	70.6	4.8	7.5	8.6	59
IXb	138—139	64.8	3.9	6.9	7.9	$C_{22}H_{17}ClN_2O_2S$	64.6	4.2	6.9	7.8	73

*From compound Ia.

sulfate. In the latter case, two successive reactions occur: alkylation with the formation of VIa, and dehydration of the latter under the influence of the acidic medium. It is suggested that protonation of the dihydropyridine VII takes place at the ring nitrogen with subsequent removal of the proton at $C_{(5)}$, the mobility of which is determined by the α-ethoxycarbonyl group. Probably, in all cases involving dehydration of compound VI, the sterically favored 2-methyl-thio-4,5-dihydropyridine VII is initially formed and in an acid medium it isomerizes to the thermodynamically more stable 2-methylthio-1,4-dihydro-pyridine (VIII).

On standing, solutions of 3,4-dihydropyridine-2(1H)-thiones IIa,b in ethanol or acetone are readily oxidized by the oxygen of the air to the 2,2'-bis(4,6-diaryl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridyl)disulfides (IIIa,b). These disulfides can be prepared in high yield by the oxidation of the salts Ia,b with iodine in ethanol. On heating the salts Ia,b to boiling in acetic acid, a mixture of compounds IIIa,b with the 4,6-diaryl-5-ethoxycarbonyl-3-cyanopyridine-2(1H)thiones (IVa,b) is obtained, the components of which can be separated by fractional crystallization. Further oxidation of both the bis-products IIIa,b and the pyridine-2(1H)-thiones (IVa,b) leads to the formation of the 2,2'-bis(4,6-diaryl-5-ethoxy-carbonyl-3-cyanopyridyl)disulfides (Va,b). On oxidation of the 4,5-dihydropyridine VII and the 1,4-dihydropyridine VIII with sodium nitrite in glacial acetic acid, the 2-methyl-thio-4,6-diaryl-5-ethoxycarbonyl-3-cyanopyridines (IXa,b) are formed; these can also be prepared by alkylation of the pyridine-2(1H)-thiones IV with methyl iodide.

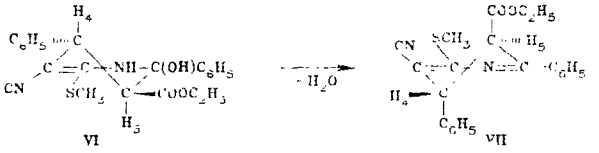


The structure of the compounds prepared was established spectroscopically. In the IR spectra, the most characteristic bands are the stretching vibrations of the cyano-group which for the 3,4-dihydropyridine-2(1H)thiones are observed at 2254-2257 cm^{-1}, and with increased conjugation of the CN group they are shifted hypsochromically to 2225-2234 cm^{-1} for compounds IV and V, to 2198-2208 cm^{-1} for compounds IIIa,b, VIa,b, VII, and VIII, and to 2174-2178 cm^{-1} for the salts Ia,b. Stretching vibrations for the carbonyl groups gave bands at 1708-1737 cm^{-1} for compounds I, IV-VII, and IX; for the dihydroderivatives IIa,b, IIIa,b, and VIII these were shifted to 1652-1685 cm^{-1} which is characteristic for β-aminovinylcarbonyl systems [6]. For compounds I-IV, VI, and VIII bands due to stretching vibrations of the NH group were observed in the 3145-3288 cm^{-1} region and for compounds Ia,b, and VIa,b, a further band in the 3400-3478 cm^{-1} region due to OH.

TABLE 2. IR and UV Spectra of Compounds I-IX

Compound	IR spectrum, ν, cm^{-1}			UV spectrum, λ_{max}, nm
	C=O	C≡N	NH, OH	
Ia	1731	2174	3240, 3420, 3432	236, 298
Ib	1728	2178	3278, 3432	237, 301
IIa	1668	2254	3240	240, 338
IIb	1682	2257	3160, 3288	241, 312, 340 sh
IIIa	1652	2208	3267	256, 314 sh., 372
IIIb	1683	2208		256, 312 sh, 378
IVa	1722	2234	3178	272, 325, 410
IVb	1716	2225	3145	270, 325, 412
Va	1737	2225	—	272, 320
Vb	1725	2227	—	274, 320
VIa	1725	2203	3245, 3454	282
VIb	1708	2204	3240, 3478	219, 284
VII	1728	2198	—	228 sh., 300, 380
VIII	1656	2203	3252	257, 356
IXa	1732	2224	—	277, 338
IXb	1718	2229	—	278, 340

The NMR spectra of compounds Ia, b, and VIa, b had characteristic doublets due to 4-H and 5-H protons at 4.14 and 3.02-2.96 ppm with $^3J_{H_4H_5} \approx 12$ Hz which points to a trans-biaxial arrangement of the 4-H and 5-H protons. The 4-C_6H_4R and 5-$COOC_2H_5$ substituents are therefore orientated trans-equatorially. Rapid deuterium exchange in the OH and NH groups provides further evidence of the structure of compounds I and VI. In the spectrum of the 4,5-dihydropyridine VII, also, there are 4-H and 5-H doublets, at 4.34 and 4.27 ppm with $^3J_{H_4H_5} \approx 1.4$ Hz which supports a biequatorial arrangement of the 4-H and 5-H protons and therefore a trans-axial arrangement of the 4-C_6H_5R and 5-$COOC_2H_5$ substituents. Thus on loss of a molecule of water from compound VIa, the preferred conformation of the ring is changed.



In the NMR spectrum of the 3,4-dihydropyridine-2(1H)-thiones IIa, b signals are observed corresponding to cis- and trans-isomers in 1:1 ratio. By analogy with the results of [1, 2] we assigned the signal with $^3J_{H_3H_4} \approx 7$ Hz to the cis-isomer and that with $^3J_{H_3H_4}$ 2.4 Hz to the trans isomer.

In the UV spectra of compounds I-IX, as conjugation increases the long-wave maximum is shifted bathochromically. Thus, the tetrahydropyridines VIa,b have absorption maxima at 282-284 nm, the dihydropyridine derivatives IIa,b, IIIa,b, VII, and VIII at 338-380 nm, and the pyridine-2(1H)-thiones IVa,b at 410-412 nm.

EXPERIMENTAL

Infrared spectra were run on a Perkin-Elmer 580B instrument in nujol mulls, UV spectra on a Specord UV-Vis in ethanol and NMR spectra on a WN 90/DC (90 MHz) instrument using TMS as internal standard.

The chief characteristics of the compounds prepared are set out in Tables 1-3.

Piperidine Salt of 6-Hydroxy-4,6-diphenyl-5-ethoxycarbonyl-3-cyanopiperidine-2-thione (Ia). A mixture of 1.92 g (10 mmole) ethyl ester of benzoylacetic acid, 1.06 g (10 mmole) freshly distilled benzaldehyde, and 0.5 ml piperidine was stirred 3-5 min at room temperature and a mixture of 1.0 g (10 mmole) cyanothioacetamide in 10 ml absolute alcohol and 0.5 ml piperidine added. The product crystallized out after 5-10 min and was filtered off and washed with ethanol to yield 3.54 g (76%) compound Ia, mp 104-106°C (from ethanol).

Compound Ib was prepared in a similar manner.

4,6-Diphenyl-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2(1H)-thione (IIa). Salt Ia (4.66 g, 10 mmole) was dissolved in 50 ml N hydrochloric acid in ethanol and poured into 50

TABLE 3. Proton NMR Spectra of Compounds I-IV, VI-VIII (in $CDCl_3$)

Compound	Chemical shift, δ, ppm (multiplicity)								Spin-spin coupling constant, Hz J_{4-5} (J_{3-4})
	NH (s)	6-OH	C_6H_5 and C_6H_4R	OC_2H_5 (q and t)	SCH_3 (s)	3-H (d)	4-H (d)	5-H (d)	
Ia*	7,2	5,80	7,6—7,2	3,56 and 0,53	—	—	4,14	3,02	12,0
Ib**	6,76	5,82	7,6—7,2	3,57 and 0,57	—	—	4,14	2,96	12,0
IIa	8,88	—	7,5—7,3	3,90 and 0,86	—	4,42 (cis) 4,27 (trans)	4,53 (cis) 4,60 (trans)	— —	(7,0) (2,4)
IIb	8,80	—	7,5—7,3	3,89 and 0,86	—	4,42 (cis) 4,25 (trans)	4,51 (cis) 4,56 (trans)	— —	(7,0) (2,4)
IIIa	6,58	—	7,5—7,3	3,83 and 0,82	—	—	4,83	—	—
IIIb	6,56	—	7,5—7,3	3,83 and 0,82	—	—	4,80	—	—
IVa***	—	—	7,7—7,4	3,78 and 0,73	—	—	—	—	—
IVb***	—	—	7,6—7,4	3,82 and 0,78	—	—	—	—	—
VIa	5,22	4,90	7,6—7,3	3,63 and 0,57	2,54	—	4,18	3,09	12,0
VIb	5,27	4,79	7,6—7,1	3,62 and 0,60	2,48	—	4,14	3,02	12,0
VII	—	—	7,9—7,1	4,20 and 1,20	2,69	—	4,34	4,27	1,4
VIII	6,27	—	7,5—7,3	3,85 and 0,95	2,50	—	4,80	—	—

*$N(CH_2)_2$ and $(CH_2)_3$ signals at 2.88 (m) and 1.60 (m).
**$N(CH_2)_2$ and $(CH_2)_3$ signals at 2.90 (m) and 1.62 (m).
***Chemical shifts of NH protons not determined on account of great breadth of signal.

ml ice-water. The precipitate was filtered off, dried, and recrystallized from ether. Yield 1.56 g (43%) compound IIa, mp 118-120°C.

4-(p-Chlorophenyl)-6-phenyl-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2(1H)-thione (IIb). The piperidine salt Ib (2.5 g, 5 mmole) was dissolved in 20 ml of N hydrochloric acid in ethanol with heating. On cooling, the product crystallized after 5-10 min and was filtered off and washed with cold ethanol and water. Yield 1.65 g (83%) compound IIb, mp 130-132,C (from ethanol).

2,2'Bis(4,6-diphenyl-5-ethoxycarbonyl-3-cyano-1,4-dihydropyridyl)-disulfide (IIIa). To a solution of 4.66 g (10 mmole) piperidine salt Ia in 25 ml ethanol was added 10 ml 0.5 N iodine in ethanol and the mixture stirred 30 min at room temperature. The reaction mixture was poured into 75 ml ice-water and the precipitate filtered off and washed with ethanol. Yield 2.6 g (72%) compound IIIa, mp 154-156°C.

Compound IIIb was prepared in a similar manner.

Reaction of the Piperidine Salt of 6-Hydroxy-4,6-diphenyl-5-ethoxycarbonyl-3-cyanopiperidine-2-thione Ia with Glacial Acetic Acid. A mixture of 2.3 g (5 mmole) piperidine salt Ia in 10 ml glacial acetic acid and 10 ml absolute alcohol was heated to boiling 1 h on a water bath and kept at room temperature for 20 h. The precipitate was filtered off and washed with cold ethanol. Yield, 1.22 g of a mixture of products which was crystallized from ethanol. The less-soluble compound IIIa (0.4 g, 22%) was separated, the filtrate evaporated and the residue recrystallized from a 1:1 chloroform—ethanol mixture to yield 0.25 g (14%) 4,6-diphenyl-5-ethoxycarbonyl-3-cyanopyridine-2(1H)thione (IVa).

Compounds IIIb (22%) and IVb (39%) were prepared in a similar manner.

2,2'-Bis(4,6-diphenyl-5-ethoxycarbonyl-3-cyanopyridyl)disulfide (Va). A mixture of 0.72 g (1 mmole) disulfide IIIa in 10 ml dilute nitric acid (1:7) was heated for 20 min on a boiling-water bath. The reaction mixture was cooled and diluted with 40 ml water and the precipitate filtered off and washed with ethanol. Yield 0.38 g (53%) compound Va, mp 182-184°C (from 1:1 ethanol—chloroform).

2,2'-Bis(4-p-chlorophenyl-6-phenyl-5-ethoxycarbonyl-3-cyanopyridyl)-disulfide (Vb). To a solution of 0.39 g (1 mmole) pyridine-2(1H)-thione IVb in 10 ml ethanol and 0.3 ml piperidine, 4 ml of a normal solution of iodine in ethanol was added with stirring. After 20 min the precipitate was filtered off. Yield 0.17 g (43%) compound Vb, mp 199-201°C (from 1:1 chloroform—ethanol).

6-Hydroxy-2-methylthio-4,6-diphenyl-5-ethoxycarbonyl-3-cyano-1,4,5,6-tetrahydropyridine (VIa). A mixture of 2.33 g (5 mmole) salt Ia and 1.0 ml methyl iodide in 10 ml absolute

alcohol was stirred 5 min at room temperature and poured into 100 ml ice-water. The precipitate was filtered off to yield 1.8 g (91%) compound VIa.

Compound VIb was prepared in a similar manner.

2-Methylthio-4,6-diphenyl-5-ethoxycarbonyl-4,5-dihydropyridine (VII). A. Tetrahydropyridine VIa (1.97 g, 5mmole) was heated on a water bath with 50 ml ethanol until dissolved, and filtered. The solution was cooled to 0°C and 0.15 g (8%) tetrahydropyridine VIa, mp 138-140°C, filtered off. The filtrate was kept for 1 h at 0°C and 1.2 g (64%) compound VIIa, mp 126-128°C (from ethanol), filtered off.

B. A mixture of 4.66 g (10 mmole) salt Ia and 2.0 ml (32 mmole) methyl iodide in 20 ml absolute alcohol was stirred 1 h at room temperature and poured into 120 ml ice-water. The precipitate was filtered off the yield 2.9 g (77%) compound VIII.

2-Methylthio-4,6-dipehnyl-5-ethoxycarbonyl-1,4-dihydropyridine (VIII). A. A mixture of 0.39 g (1 mmole) 2-methylthiotetrahydropyridine VIa and 10 ml 0.5 N hydrochloric acid in ethanol was heated 15 min and filtered, the filtrate cooled to 0°C and the precipitate filtered off. Yield 0.23 g (61%) compound VIIIa, mp 157-159°C (from ethanol).

B. A mixture of 0.38 g (1 mmole) 2-methylthio-4,5-dihydropyridine VII and 10 ml 0.5 N hydrochloric acid in ethanol was heated for 10 min and filtered. It was then cooled to 0°C and the precipitate filtered off to yield 0.37 g (97%) compound VIII.

C. A mixture of 4.65 (10 mmole) salt Ia and 1.5 ml (16 mmole) freshly distilled dimethyl sulfate in 20 ml absolute alcohol was stirred 15 min at room temperature and then cooled to 0°C. The precipitate was filtered off and washed with cold ethanol and water. Yield 2.0 g (53%) compound VIII.

2-Methylthio-4,6-diphenyl-5-ethoxycarbonyl-3-cyanopyridine (IXa). A. A mixture of 0.38 g (1 mmole) 2-methylthio-1,4-dihydropyridine VIII and 3 ml glacial acetic acid was heated to 50-60°C and 0.35 g (5 mmole) sodium nitrite added. When evolution of nitrogen dioxide had ceased (around 10 min) the reaction mixture was cooled and poured into 40 ml water. Yield 0.22 g (59%) compound IXa, mp 97-99°C (from ethanol).

B. A mixture of 0.33 g (1 mmole) 2-methylthio-4,5-dihydropyridine VIIa and 3 ml glacial acetic acid was heated to 50-60°C on a water bath, 0.7 g (10 mmole) sodium nitrite added and the mixture heated for 15 min. It was then cooled and poured into 50 ml water to yield 0.15 g (40%) compound IXa.

2-Methylthio-4-(p-chlorophenyl)-6-phenyl-5-ethoxycarbonyl-3-cyanopyridine (IXb). A mixture of 0.39 g (1 mmole) pyridine-2(1H)-thione IVb, 0.3 ml piperidine, and 0.5 ml methyl iodide in 10 ml ethanol was heated for 10 min on a water bath. It was then cooled to 0°C and the precipitate filtered off to yield 0.3 g (73%) compound IXb, mp 138-139°C (from ethanol).

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