9. V. A. Petrov, *J. Chem. Soc.*, 888 (1946); *Chem. Abstr.*, **41**, 968 (1947).
10. V. K. Lusis, A. Z. Zandersons, D. Kh. Mutsenietse, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 4, 508 (1984).
11. G. Ya. Dubur, Z. Ya. Ogle, and Ya. R. Uldrikis, *Khim. Geterotsikl. Soedin.*, No. 12, 1642 (1974).

SYNTHESIS AND PROPERTIES OF 6-METHYL-4-(m-NITROPHENYL)-3-CYANOPYRIDIN-2(1H)-ONES, THE CORRESPONDING PYRIDINE-2(1H)-THIONES, AND THEIR HYDROGENATED ANALOGS

A. A. Krauze, H.-I. Ensch, and G. Ya. Dubur

UDC 547.823

The condensation of 4-pyridylacetone, m-nitrobenzaldehyde, and cyanoacetamide (cyanothioacetamide) in the presence of bases was used to obtain 5-pyridyl-substituted 6-methyl-4-(m-nitrophenyl)-3-cyanopyridin-2(1H)-ones, the corresponding pyridine-2(1H)-thiones, and their hydrogenated analogs. 2-Carbamoylmethylthiopyridine was isolated in the alkylation of 5-(4'-pyridyl)pyridine-2(1H)-thione with iodoacetamide under mild conditions, while 2-carbamoylthio-5-(N-carbamoylmethyl-4'-pyridyl)pyridine iodide was isolated under more severe conditions.

3,4'-Dipyridyls are of interest as cardiotonic agents. Among them have been discovered the preparations amirinone and milrinone — 5-(4'-pyridyl)-substituted pyridin-2(1H)-ones, which have a positive inotropic effect on the heart while simultaneously displaying a vasodilating effect [1-6]. 3,4-Dihydropyridin-2(1H)-ones also increase the force of contraction of the papillary muscles [7].

Cardiotonic properties have recently also been discovered for 5-(4'-pyridyl)-substituted pyridine-2(1H)-thiones [8].

In continuing our research on partially hydrogenated pyridin-2(1H)-ones and pyridine-2(1H)-thiones [9, 10] we synthesized 5-(4'-pyridyl)-substituted di- and tetrahydropyridin-2(1H)-ones and dihydropyridine-2(1H)-thiones and accomplished their oxidation and alkylation.

Of the possible methods for the synthesis of these compounds [7, 10-13] we selected the method of unsymmetrical three-carbon condensation [10, 13]. The condensation of 4-pyridylacetone, m-nitrobenzaldehyde, and cyanoacetamide in the presence of strong bases at high temperatures proceeds with the formation of a complex mixture of products. 3-Cyanopyridin-2(1H)-one (IV), 6-hydroxy-3-cyano-3,4,5,6-tetrahydropyridin-2(1H)-one (II), and 3-carbamoyl-3,4-dihydropyridin-2(1H)-one (IIIb) were obtained in low yields when the reaction was carried out at room temperature using an equimolar amount of piperidine as the condensing agent with subsequent treatment of the reaction mixture with excess acetic acid and neutralization with ammonium hydroxide. The corresponding 3-cyano-3,4-dihydropyridin-2(1H)-one (IIIa) was isolated by brief heating of 6-hydroxy derivative II with HCl in ethanol.

The progress of this reaction can be represented in the following way: the initially formed δ-keto amide I undergoes subsequent intramolecular cyclization with the participation of both the amido and cyano groups, which leads to a mixture of hydrogenated 3-cyano- and 3-carbamoyl-substituted pyridin-2-ones II and IIIb. As compared with 3-carbamoyl-substituted IIIb, hydrogenated 3-cyanopyridin-2-ones II and IIIa are distinguished by greater instability; this is explained by their more facile oxidizability in the anionic form [15] and makes it possible to isolate pyridin-2-(1H)-one IV immediately from the reaction

Institute of Organic Synthesis, Latvian Academy of Sciences, Riga 226006. Arzneimittelwerk Dresden GmbH, Radebeul. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1674-1679, December, 1991. Original article submitted March 4, 1991.

0009-3122/91/2712-1347$12.50

TABLE 1. Characteristics of the Synthesized II-IV, VII, and IX-XIII

Compound	mp, °C	Empirical formula	UV spectrum, λ_{max} nm	IR spectrum, ν, cm^{-1}			Yield, %*
				C=O	C≡N	NH, NH_2, OH	
II	140...142	$C_{18}H_{16}N_4O_4$	262	1678, 1712	2256	3080, 3274, 3446	2
IIIa	125...127	$C_{18}H_{14}N_4O_3$	270	1670, 1716	2262	3080, 3232	40
IIIb	126...128	$C_{18}H_{16}N_4O_4$	270	1654, 1681, 1704	—	3142, 3220, 3400	24
IV	340...342	$C_{18}H_{12}N_4O_3$	258, 356	1680	2222	3092, 3196	15
VII	168...170 dec.	$C_{23}H_{25}N_5O_2S$	262, 322, 370 sh	—	2166	3264	75
IX	>320 dec	$C_{18}H_{12}N_4O_2S$	252, 325, 422	—	2224	3182	60
Xb	182...184	$C_{20}H_{17}N_5O_3S$	274, 357	1691	2190	3156, 3324, 3432	83
XIa	203...205	$C_{20}H_{15}N_5O_2S\times$ ×HCl	268, 360, 406 sh	—	2205, 2252	3124, 3160	50
XIb	198...200	$C_{20}H_{15}N_5O_3S\times$ ×HCl	270, 354, 406 sh	1667	2184	3272, 3344 sh	90
XII	112...114	$C_{20}H_{15}N_5O_3S$	272, 322 sh	1684	2226	3170, 3300	
XIII	160...163	$C_{22}H_{19}IN_6O_4S$	263, 327	1662, 1678, 1720	2230	3170, 3272, 3466	54

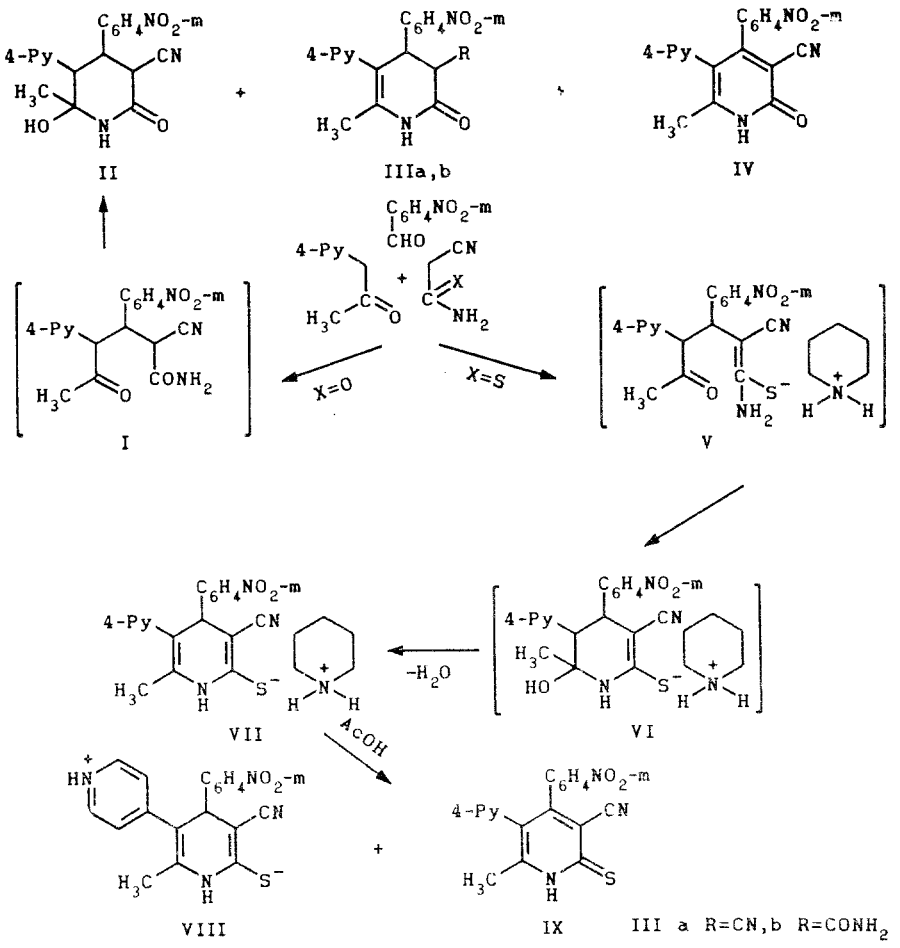
*Yield of compound XII 79% (method A) and 67% (method B).

TABLE 2. PMR Spectra of II-IV and VII-XIII in d_6-DMSO

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)
II	8.92 (1H, s, NH); 8.3...7.1 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 6.28 (1H, s, 6-OH); 4.52 (1H, d, J=12.0, 3-H); 4.30 (1H, dd, 4-H); 3.62 (1H, d, J=11.0, 5-H); 1.16 (3H, s, 6-CH_3)
IIIa	10.28 (1H, s, NH); 8.5...7.0 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 5.08 (0.75 H, d, J=7.0, 3-H cis); 4.78 (0.25 H, d, J=7.6, 3-H trans); 4.54 (0.25 H, d, J=7.6, 4-H trans); 4.52 (0.75 H, d, J=7.0, 4-H cis); 1.90 (3H, s, 6-CH_3)
IIIb	9.76 (1H, s, NH); 8.3...7.0 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 7.46 and 7.16 (2H, s and s 3-$CONH_2$); 4.41 (1H, d J=3.8, 4-H); 3.37 (1H, d, J=3.8, 3-H); 1.87 (3H, s, 6-CH_3)
IV	13.14 (1H, s, NH); 8.4...7.1 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 2.10 (3H, s, 6-CH_3)
VII	7.84 (1H, s, NH); 8.5...7.0 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 4.46 (1H, s, 4-H); 3.00 and 1.60 (10H, m and m, $C_5H_{10}N$); 1.88 (3H, s, 6-CH_3)
VIII	7.94 (1H, s, NH); 8.5...7.0 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 4.52 (1H, s, 4-H); 2.02 (3H, s, 6-CH_3)
IX	14.44 (1H, s, NH); 8.5...7.1 (8H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N); 2.24 (3H, s, 6-CH_3)
X	10.02 (1H, s, NH); 8.4...7.2 (10H, m 4-$NO_2C_6H_4$, 5-C_5H_4N, $CONH_2$); 4.88 (1H, s, 4-H); 3.74 and 3.62 (2H, d and d J=15.0, SCH_2); 1.90 (3H, s, 6-CH_3)
XIa	10.32 (1H, s, 1H); 8.7...7.5 (8H, m 4-$NO_2C_6H_4$, 5-C_5H_4N); 5.22 (1H, s, 4-H); 4.56 and 4.30 (2H, d and d J=17.0, CH_2); 2.18 (3H, s, 6-CH_3)
XIb	10.56 (1H, s, NH); 8.7...7.5 (10H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N, $CONH_2$); 5.12 (1H, s, 4-H); 3.76 and 3.68 (2H, d and d J=15.0, SCH_2); 2.15 (3H, s, CH_3)
XII	8.5...7.1 (10H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N, $CONH_2$); 4.00 (2H, s, SCH_2); 2.32 (3H, s, 6-CH_3)
XIII	8.9...7.1 (10H, m, 4-$NO_2C_6H_4$, 5-C_5H_4N, $CONH_2$); 5.26 (2H, s, $\overset{+}{N}CH_2$); 4.02 (2H, s, SCH_2); 2.38 (3H, s, 6-CH_3)

mixture, in addition to the hydrogenated products, and hinders the isolation of the more soluble 3-cyano-3,4-dihydropyridin-2(1H)-one IIIa.

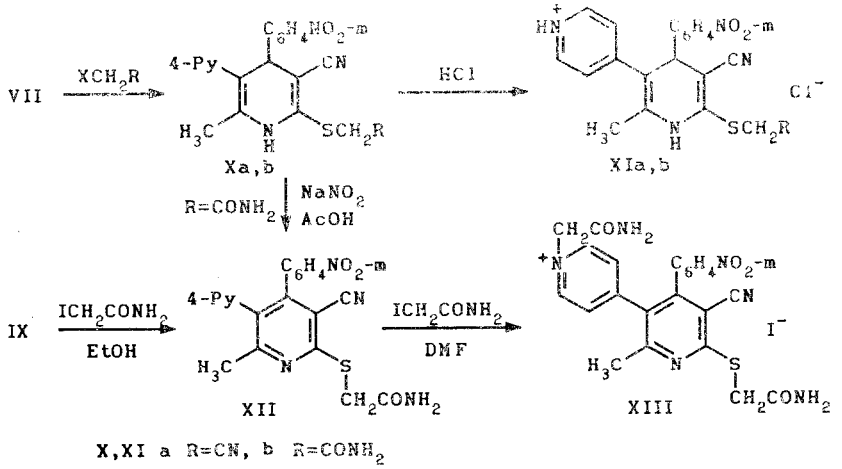
The condensation of 4-pyridylacetone, m-nitrobenzaldehyde, and cyanothioacetamide in the presence of piperidine proceeds vigorously at room temperature to give piperidinium 3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine-2-thiolate VII. As compared with the oxygen analogs, 1,4-dihydropyridine-2-thiolates are even more unstable with respect to oxidation [11]; however, they can be rapidly isolated from the action of the oxidizing agent in the form of insoluble salts VII. Intermediates V and VI cannot be isolated. A mixture of betaine VIII and pyridine-2(1H)-thione IX is obtained in the case of brief heating of thiolate VII in acetic acid. Further treatment of betaine VIII with acetic acid leads to thione IX. In contrast to 4-pyridyl-1,4-dihydropyridine-2-thione betaines [12, 14], 5-pyridyl-1,4-dihydropyridine-2-thione betaines are compounds that are more inclined to undergo oxidation, which hinders their isolation from the reaction mixtures in pure form.



The alkylation of salt VII with iodoacetamide or chloroacetonitrile gave 2-alkylthio-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridines X or the corresponding hydrochlorides XI. The 2-cyanomethylthio derivative can be isolated only in the form of salt XIa.

The corresponding salt XIb is formed in high yield by the action of HCl in ethanol on 1,4-dihydropyridine Xb.

The alkylation of thione IX with an equimolar amount of iodoacetamide by brief heating in ethanol gave 2-carbamoylmethylthiopyridine XII. Compound XII is also formed by oxidation of dihydropyridine X with sodium nitrite. Further alkylation of 5-(4′-pyridyl)pyridine XII with iodoacetamide by brief heating in DMF gave 2-carbamoylmethylthio-6-methyl-4-(m-nitrophenyl)-5-(N-carbamoylmethyl-4′-pyridyl)pyridine iodide (XIII).



Characteristic absorptions of stretching vibrations of cyano groups at 2256-2262 cm^{-1} for tetra- and dihydropyridin-2(1H)-ones II and IIIa and at 2222 cm^{-1} for pyridin-2(1H)-one IV are observed in the IR spectra (Table 1) of variously

hydrogenated pyridin-2-ones. In the case of 3-cyanodihydropyridine-2-thiolate VII ν_{CN} is observed at 2166 cm^{-1}, which indicates clearly expressed conjugation of the cyano group with the anion.

As in the case of pyridin-2-one IV, ν_{CN} for thione IX and 2-alkylthiopyridines XII and XIII is found at 2224-2230 cm^{-1}, while the $\nu_{C\equiv N}$ bands of dihydropyridines X and XI are observed at 2184-2205 cm^{-1}. Compound XIa is also characterized by absorption of the unconjugated cyano group of the 2-alkylthio substituent at 2252 cm^{-1}. The structures of the synthesized compounds are also confirmed by characteristic absorption bands of C=O, NH, and NH_2 groups.

The long-wave maximum in the UV spectra (see Table 1) of variously hydrogenated pyridin-2-ones II, III, and IV and pyridine-2-thiones VII and IX is shifted bathochromically with an increase in the conjugation of the molecule.

Characteristic signals of $C_{(3)}$—H, $C_{(4)}$—H, and $C_{(5)}$—H protons are observed in the PMR spectra (see Table 2) of 3,4,5,6-tetrahydropyridin-2(1H)-one II, and vicinal signals of $C_{(3)}$—H and $C_{(4)}$—H protons are observed in the case of 3,4-dihydropyridin-2(1H)-ones III. According to [9, 15], the $^3J_{H_3H_4}$ spin-spin coupling constant (SSCC) of 3.8 Hz for 3-carbamoyl derivative IIIb indicates a trans form of the compound with pseudoaxially oriented 4-(m-nitrophenyl) and 3-carbamoyl groups. Compound IIIa is produced in the form of a mixture of two isomers in a ratio of 3:1. In accordance with [9, 15], the predominant isomer, with $^3J_{H_3H_4}$ = 7.0 Hz, was identified as the cis stereoisomer, in which the 4-(m-nitrophenyl) substituent is primarily oriented axially, while the 3-cyano substituent is primarily oriented equatorially. The most characteristic signal in the PMR spectra of 1,4-dihydropyridines VII, VIII, X, and XI is the signal of the $C_{(4)}$—H proton in the form of a singlet, while the signals of the protons of the SCH_2 groups in the form of an AB quartet are also characteristic in the case of X and XI, which indicates nonequivalence of the CH_2 protons because of the presence of an asymmetric center at the $C_{(4)}$ atom in the molecule.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin—Elmer 580B spectrometer. The UV spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO were obtained with a WH 90/DC spectrometer (90 MHz) with tetramethylsilane (TMS) as the internal standard. The progress of the reactions and the individuality of the substances were monitored by TLC on Silufol UV-254 plates with chloroform—ethanol—ammonia (15:8:1) as the eluent.

The results of elementary analysis of the synthesized compounds for C, H, N, and S were in agreement with the calculated values.

6-Hydroxy-6-methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-3,4,5,6-tetrahydropyridin-2(1H)-one (II), 6-Methyl-4-(m-nitrophenyl)-3-carbamoyl-5-(4′-pyridyl)-3,4-dihydropyridine-2(1H)-one (IIIb), and 6-Methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)pyridin-2(1H)-one (IV). A mixture of 13.52 g (0.1 mole) of 4-pyridylacetone and 15.11 g (0.1 mole) of m-nitrobenzaldehyde in 20 ml of absolute ethanol and 1 ml of piperidine was stirred for 6 h at room temperature, after which a mixture of 8.41 g (0.1 mole) of cyanoacetamide in 20 ml of absolute ethanol and 9 ml of piperidine was added, and the reaction mixture was stirred for another 1 h and then allowed to stand at room temperature. After 4 days, 15 ml of glacial acetic acid was added, and the mixture was stirred for 4 h and then poured into 500 ml of water. The oily precipitate was washed with 500 ml of water, and the product was refluxed briefly in 100 ml of 80% ethanol and filtered to give 3.03 g (9%) of IV. Water (20 ml) was added to the filtrate, and 0.6 g (2%) of II separated after 4 h. Allowing the latter filtrate to stand at room temperature for 14 days gave another 1.49 g (4%) of IV. The filtrates obtained after separation and washing of the oily precipitate were combined and neutralized with ammonium hydroxide to give 10.3 g of a crude product, which was refluxed in 120 ml of ethanol and then filtered hot to give 0.5 g (1%) of IV, after which 5.4 g (16%) of IIIb crystallized. Concentration of the mother liquor gave an additional 2.82 g (8%) of IIIb.

6-Methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-3,4-dihydropyridin-2(1H)-one (IIIa). A 0.11-g (0.3 mmole) sample of II in 1 ml of 1 N HCl in ethanol was heated briefly on a water bath, after which it was cooled and then neutralized after 5 h with 0.5 ml of 2 N KOH. The next day, 2 ml of water was added and the mixture was allowed to stand for 1 h. The precipitate was removed by filtration and washed with 5 ml of water to give 0.04 g (40%) of IIIa.

Piperidinium 6-Methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine-2-thiolate (VII). A mixture of 2.71 g (20 mmole) of 4-pyridylacetone and 3.02 g (20 mmole) of m-nitrobenzaldehyde in 10 ml of absolute ethanol and 0.5 ml of piperidine was stirred for 10 min at room temperature, after which a mixture of 2.0 g (20 mmole) of cyanothioacetamide in 10 ml of absolute ethanol and 1.5 ml of piperidine was added, and the mixture was stirred for 1 h. The precipitate was removed by filtration and washed with 20 ml of ethanol to give 6.51 g (75%) of VII.

6-Methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine-2(1H)-thione Betaine (VIII) and 6-Methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)pyridine-2(1H)-thione (IX). A 8.71-g (20 mmole) sample of thiolate VII was refluxed in 10 ml of glacial acetic acid for 5 min on a water bath, after which the mixture was filtered hot and treated with 20 ml of absolute ethanol. After 1 h, the first fraction was removed by filtration and washed with 20 ml of ethanol and 20 ml of water to give 6.1 g (84%) of a mixture of VIII and IX. After 24 h, the second fraction was removed by filtration to give 0.45 g (6%) of IX. A 3.5-g (10 mmole) sample of the mixture of VIII and IX was heated in 30 ml of glacial acetic acid for 30 min on a water bath and then allowed to stand for 2 days at room temperature. Ethanol (30 ml) was then added, and the precipitate was removed by filtration after 1 h to give 2.1 g (60%) of IX.

2-Carbamoylmethylthio-6-methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine (Xb). A mixture of 4.36 g (10 mmole) of thiolate VII and 2.04 g (11 mmole) of iodoacetamide in 30 ml of absolute ethanol was heated briefly on a water bath and then filtered. Water (10 ml) was then added, and the mixture was cooled to 0°C. After 24 h, the precipitate was removed by filtration and washed with 20 ml of 50% ethanol to give 3.4 g (83%) of Xb.

2-Carbamoylmethylthio-6-methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine Hydrochloride (XIb). A 0.82-g (2 mmole) sample of 1,4-dihydropyridine Xb was dissolved by heating in 11 ml of 0.2 N HCl in ethanol, and the hot solution was filtered and cooled. The precipitate was separated and washed with 5 ml of ethanol to give 0.80 g (90%) of XIb.

2-Cyanomethylthio-6-methyl-4-(m-nitrophenyl)-3-cyano-5-(4′-pyridyl)-1,4-dihydropyridine Hydrochloride (XIa). A mixture of 4.26 g (10 mmole) of thiolate VII and 1 ml (15.8 mmole) of chloroacetonitrile in 20 ml of absolute ethanol was heated briefly on a water bath, after which it was filtered, cooled to 0°C, and, after 1 h, treated with 10 ml of 1 N HCl in ethanol. After 24 h, the precipitate was removed by filtration and washed with 10 ml of ethanol to give 2.12 g (50%) of XIa.

2-Carbamoylmethylthio-6-methyl-4-(m-nitrophenyl)-5-(4′-pyridyl)pyridine (XII). A. A mixture of 3.48 g (10 mmole) of thione IX and 2.04 g (11 mmole) of iodoacetamide in 20 ml of absolute ethanol and 1.1 ml of piperidine was heated briefly on a water bath, after which it was cooled, and the precipitate was removed by filtration and washed with 20 ml of ethanol and 10 ml of water to give 3.2 g (79%) of XII.

B. A 2.76-g (40 mmole) sample of sodium nitrite was added to a mixture of 4.07 g (10 mmole) of 1,4-dihydropyridine X in 10 ml of glacial acetic acid, and the mixture was heated until nitrogen dioxide evolution ceased. The mixture was then cooled and treated with 10 ml of water, and the precipitate was removed by filtration, washed with 20 ml of 50% ethanol, and recrystallized from ethanol to give 2.7 g (67%) of XII.

2-Carbamoylmethylthio-6-methyl-4-(m-nitrophenyl)-3-cyano-5-(N-carbamoylmethyl-4′-pyridyl)pyridine Iodide (XIII). A mixture of 2.03 g (5 mmole) of pyridine XII and 1.02 g (5.5 mmole) of iodoacetamide in 7 ml of DMF was heated for 3 min on a water bath, after which it was filtered hot and treated with 10 ml of ethanol. The next day, 10 ml of ether was added, and the precipitate was removed by filtration after 1 h to give 1.6 g (54%) of XIII.

LITERATURE CITED

1. G. Y. Lesher and R. E. Philion, US Patent No. 4,313,951; *Chem. Abstr.*, **97**, 216,005 (1982).
2. A. A. Alausi, J. M. Canter, M. J. Monterano, D. J. Fort, and R. A. Ferrasi, *J. Cardiol. Pharmacol.*, No. 5, 792 (1983).
3. A. A. Alausi, G. P. Stankus, J. C. Stuart, and Kl. H. Walton, *J. Cardiovasc. Pharmacol.*, 804 (1983).
4. R. K. Goyal and J. H. Mcneill, *Europ. J. Pharmacol.*, **120**, 267 (1986).
5. H. Landmann and H. Lowe, *Pharmazie*, No. 3, 169 (1986).
6. D. W. Robertson, E. E. Beedle, J. K. Swartzendruber, et al., *J. Med. Chem.*, **29**, 635 (1986).
7. G. Y. Lesher, B. Singh, and P. M. Carabateas, US Patent No. 4,431,651; *Chem. Abstr.* (1982).
8. V. Hagen, A. Rumler, G. Reck, A. Hagen, D. Labes, and S. Heer, *Pharmazie*, No. 12, 809 (1989).
9. A. A. Krauze, É. É. Liepin'sh, Z. A. Kalme, Yu. É. Pelcher, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 11, 1504 (1984).
10. A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 1, 75 (1987).
11. A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, I. V. Dipan, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 1, 95 (1985).

12. A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 5, 630 (1986).
13. A. A. Krauze, Yu. É. Pelcher, Z. A. Kalme, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 12, 1694 (1984).
14. A. A. Krauze, R. O. Vitolinya, M. R. Romanova, and G. Ya. Dubur, *Khim.-farm. Zh.*, No. 5, 548 (1988).
15. J. Kuthan, P. Nesvadba, Z. Donnerova, and P. Trska, *Coll. Czech. Chem. Commun.*, **42**, 2152 (1977).

REDUCTION OF 2,3,4-SUBSTITUTED QUINOLINES WITH SODIUM BOROHYDRIDE

B. A. Vigante, Ya. Ya. Ozols, and G. Ya. Dubur

UDC 547.831.07

1,2-Dihydroquinolines were obtained by the reduction of 3-substituted 2-methyl-4-phenylquinolines with sodium borohydride in aliphatic carboxylic acids; N-alkyl derivatives are also formed. The corresponding 1,4-dihydroquinoline was obtained in the reaction of 2-methyl-3-nitroquinolinium perchlorate with sodium borohydride.

Little study has been devoted to 1,4-dihydroquinolines (1,4-DHQ) [1-3], although they are close analogs of 1,4-dihydropyridines, which are used in practice as coronary dilating agents and antioxidants. 2-Methyl-4-aryl-N-unsubstituted 1,4-DHQ are most interesting from this point of view. However, this group of compounds has not been adequately studied. Only patent data [2] on the possibility of the synthesis of 2-methyl-4-phenyl-1,4-DHQ by the condensation of α-(2-aminophenyl)benzyl alcohol with ethyl acetoacetate are available. A greater amount of study has been devoted to 2- and 4-unsubstituted 1,4-DHQ obtained chiefly by the reduction of 3-substituted quinolines [1, 4, 5] or by the hydrogenation of the corresponding quinolinium salts [4, 6, 7].

It has been shown [1] that the controlling condition for obtaining 1,4-DHQ by the reduction of quinolines with sodium borohydride in ethanol is the presence of electron-acceptor groups in the 3 position and the absence of substituents in the 2 and 4 positions. The reduction of 3-halo-substituted quinolines or quaternary N-methylquinolinium salts leads primarily to 1,2-DHQ [1, 6]. 2-Substituted quinolines are reduced by lithium aluminum hydride or sodium borohydride to 1,2-DHQ [8]. No data on the reduction of 2,4-disubstituted quinolines are available.

We have established that 2-methyl-4-phenyl-3-substituted quinolines Ia-h are not reduced by sodium borohydride even in the case of prolonged refluxing in ethanol; this is in agreement with the proposed [1] mechanism for the reduction of the quinoline ring.

Quinolines Ia-h (Table 1), which are substituted in the 2, 3, and 4 positions, are reduced at 20°C by sodium borohydride in acetic acid to give 1,2-DHQ IIa-h. In addition to reduction of the ring, the hydrogen atom attached to the nitrogen atom is replaced by an ethyl group (see the scheme).

Similarly, N-methyl-1,2-DHQ IIIa-c were obtained in good yields by hydrogenation of quinolines Ia-c with sodium borohydride in formic acid (see the experimental section, method A). It should be noted that formic acid is used in a fivefold molar ratio with respect to Ia-h in ethanol, since reduction does not occur in it without a solvent. Quinolines Ia-c are also satisfactorily reduced by sodium borohydride in propionic acid, but N-propyl-1,2-DHQ were not isolated because of their instability. The structure of the latter is confirmed by the characteristic (for 1,2-DHQ) absorption maxima in the electronic spectra of the reaction mixtures.

Institute of Organic Synthesis, Latvian Academy of Sciences, Riga 226006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1680-1686, December, 1991. Original article submitted December 12, 1990; revision submitted April 1, 1991.

 0009-3122/91/2712-1352$12.50