SYNTHESIS OF N-UNSUBSTITUTED AND N-METHYL DERIVATIVES OF 4-ARYL-2,6-DIMETHYL-1,2-DIHYDROPYRIDINE-3,5-DICARBONITRILES

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In the reduction of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitriles or their N-oxides by sodium borohydride, a mixture of 1,2- and 1,4-dihydropyridine-3,5-dicarbonitriles is formed. 1,2,6-Trimethyl-4-aryl-1,2-dihydropyridine-3,5-dicarbonitriles were obtained by reducing the corresponding pyridinium perchlorates or by alkylating 4-aryl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives by methyl iodide.

In seeking methods for synthesis of 1,2-dihydropyridines, we obtained new derivatives of 2,6-dimethyl- and 1,2,6-trimethyl-4-aryl-1,2-dihydropyridine-3,5-dicarbonitriles.

A convenient method for the synthesis of N-methyl-1,2-dihydropyridines is the reduction of the corresponding pyridinium salts [1, 2]. Methylation of 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles (I) and subsequent oxidation of N-methyl derivatives II leads to pyridinium perchlorates III, which are reduced by sodium borohydride. The reduction proceeds nonselectively and, in addition to 1,2,6-trimethyl-4-aryl-1,2-dihydropyridine-3,5-dicarbonitriles IV, their 1,4-dihydro-isomers are also formed.

It is known [3, 4] that the synthesis of N-unsubstituted 1,2-dihydropyridine-3,5-dicarbonitriles is always accompanied by the formation of other dihydro-isomers. We have observed this in the reduction of 4-aryl-2,6-dimethyl-3,5-dicyanopyridines V by sodium borohydride, despite the fact that the latter is the most selective reducing agent in the preparation of 1,2-dihydro-isomers of pyridine [5, 6]. Thus, in the reduction of 4-(4-methylphenyl)-2,6-dimethyl-3,5-dicyanopyridine (Vb), the yield of the corresponding dihydro-isomers, determined spectrophotometrically at 382 and 344 nm, is 44% (VIb) and 20% (Ib). However, after a preparative separation of the reaction products, the yield of 1,2-dihydropyridine (VIb) reaches 22% only, while the chromatographic mobility of 1,4- and 1,2-dihydro-isomers of 4-aryl-2,6-dimethylpyridine-3,5-dicarbonitriles hardly differs.

With the object of developing a preparative method for synthesis of 1H-1,2-dihydropyridines VI, we studied the possibility of using as the starting material, pyridine N-oxide VII, for which the addition of hydrogen to the $C_{(2)}$ atom is preferred. In the reduction of 4-(4-methylphenyl)-2,6-dimethyl-3,5-dicyanopyridine N-oxide (VIIb) by sodium borohydride in a mixture of acetonitrile and methanol, at the beginning of the reaction (after 15 min) the ratio of the isomers formed is VIb:Ib = 8:1, and the degree of conversion is only 19%. After 24 h, the overall yield of the reduction products reaches 70-74%, while the ratio of the dihydro-isomers VIb and Ib is 3:1, since the N-oxide decomposes and the corresponding pyridine is formed under the reaction conditions.

Taking as an example the compounds synthesized, we carried out the alkylation of 1,2-dihydropyridines for the first time. 4-Aryl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarbonitriles VIa-e, as well as their 1,4-dihydro-analogs I, readily form anions and are alkylated by methyl iodide to form N-methyl derivatives IVa-e.

The structure of the compounds synthesized was confirmed by spectral methods. In the PMR spectra of dihydro-isomers IVa-e, the 2-CH_3 group signal appears in the form of a doublet, while the 2-H signal appears as a quartet. For the N-unsubstituted 1,2-dihydropyridines VI, the 2-H proton signal appears in the form of a multiplet, which indicates a spin–spin coupling both with the protons of the 2-CH_3 group and with the N–H proton, and confirms the

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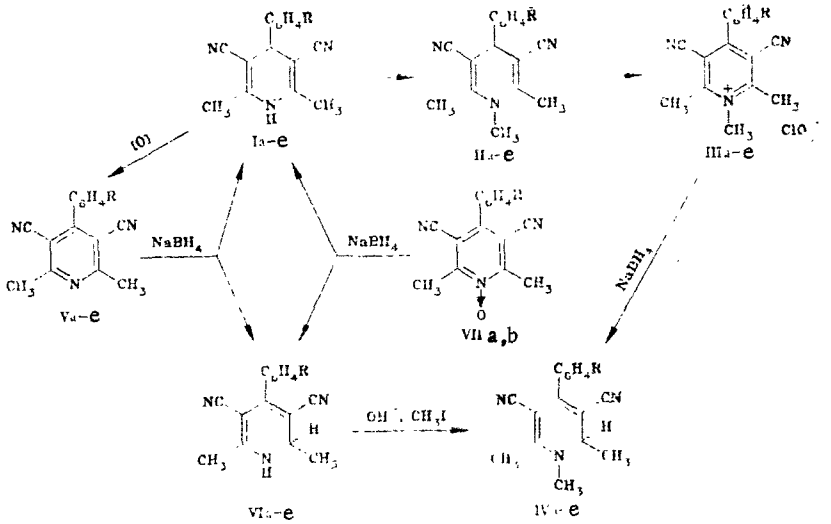
1,2-dihydro-isomeric structure. In the IR spectra of dihydropyridines I and II, the absorption of the CN group is observed at 2200 cm^{-1}, for the 1,2-isomers IV and VI at 2190 cm^{-1}, while the stretching vibrations of the NH group of compounds VI are observed at 3320 cm^{-1}.



I—VII a R=H, b R=4-CH_3; I—VI c R=4-OCH_3, d R=2-NO_2, e R=4-NO_2

The UV spectra conform with general characteristics of the absorption of 1,4- and 1,2-dihydropyridine systems. It should be noted that the absorption of 1,2-dihydropyridines in the 260 nm region is sensitive to changes in the nature of the substituent at the $C_{(4)}$ atom. The absorption maximum of the long-wave band of N-methyl derivatives of 1,2-dihydropyridine IV almost coincides with the maximum of the corresponding band of N-unsubstituted 1,2-dihydropyridines VI, or is bathochromically shifted.

It was found from the PMR spectra that 4-(o-nitrophenyl)-1,2,6-trimethyl-3,5-dicyano-1,2-dihydropyridine (IVd) exists in the form of two isomeric structures. Most probably an

TABLE 1. Characteristics of Compounds I-VII Synthesized

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ib	235—237	76,8	6,2	16,5	$C_{16}H_{15}N_3$	77,1	6,1	16,9	63
Ic	223—225	72,0	5,2	15,6	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	71
Ie	226—228	64,0	4,1	19,7	$C_{15}H_{12}N_4O_2$	64,3	4,3	19,9	48
IIa	193—195	76,8	5,9	16,4	$C_{16}H_{15}N_3$	77,1	6,1	16,9	64
IIb	216—218	77,1	6,4	15,7	$C_{17}H_{17}N_3$	77,5	6,5	16,0	65
IIc	143—145	73,6	6,4	15,2	$C_{17}H_{17}N_3O$	73,1	6,1	15,1	78
IId	223—225	65,2	4,5	18,5	$C_{16}H_{14}N_4O_2$	65,3	4,8	19,0	66
IIe	205—207	65,4	4,6	18,7	$C_{16}H_{14}N_4O_2$	65,3	4,8	19,0	54
IIIa	215—217	55,4	3,8	12,3	$C_{16}H_{14}ClN_3O_4$	55,3	4,1	12,1	57
IIIb	239—241	56,0	4,1	11,5	$C_{17}H_{16}ClN_3O_4$	56,4	4,5	11,6	40
IIIc	217—219	54,3	3,9	11,3	$C_{17}H_{16}ClN_3O_5$	54,1	4,3	11,1	43
IIId	266—268	48,4	3,1	14,0	$C_{16}H_{13}ClN_4O_6$	48,9	3,4	14,3	20
IIIe	260—262	48,2	3,6	14,4	$C_{16}H_{13}ClN_4O_6$	48,9	3,4	14,3	27
IVa*	212—213	76,8	5,9	16,4	$C_{16}H_{15}N_3$	77,1	6,1	16,9	49
IVb	196—198	77,8	6,1	15,3	$C_{17}H_{17}N_3$	77,5	6,5	15,9	60
IVc	179—181	73,3	6,4	15,2	$C_{17}H_{17}N_3O$	73,1	6,1	15,0	41
IVd	198—199	65,5	4,4	19,2	$C_{16}H_{14}N_4O_2$	65,3	4,8	19,0	40
IVe	206—208	65,0	4,3	18,7	$C_{16}H_{14}N_4O_2$	65,3	4,8	19,0	60
Vb	237—238	77,6	5,2	16,6	$C_{16}H_{13}N_3$	77,7	5,3	17,0	87
Vc	181—183	72,4	4,4	15,5	$C_{16}H_{13}N_3O$	72,9	5,0	15,9	86
Ve	195—197	64,3	3,4	20,4	$C_{15}H_{10}N_4O_2$	64,7	3,6	20,1	76
VIa	148—151	76,1	5,0	17,2	$C_{15}H_{13}N_3$	76,6	5,5	17,8	14
VIb	192—194	77,7	6,6	16,4	$C_{16}H_{15}N_3$	77,1	6,1	16,8	22
VIc	182—184	72,0	5,3	16,1	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	19
VId	217—218	64,8	4,5	20,3	$C_{15}H_{12}N_4O_2$	64,3	4,3	20,0	20
VIe	248—250	63,8	4,3	19,6	$C_{15}H_{12}N_4O_2$	64,3	4,3	20,0	24
VIIa	169—171	72,0	4,1	16,4	$C_{15}H_{11}N_3O$	72,3	4,4	16,9	30
VIIb	232—234	73,5	5,3	15,6	$C_{16}H_{13}N_3O$	73,0	5,0	15,9	25

*Compounds IVa-e were obtained by method A.

TABLE 2. Spectral Characteristics of 3,5-Dicyano-1,4-dihydropyridines I, II

Compound	PMR spectrum, δ, ppm					UV spectrum, λ_{max}, nm (log ε)
	1-H (s, 1H)	1-CH_3 (s, 3H)	2,6-CH_3 (s, 6H)	4-H (s, 1H)	4-Ar	
Ia	6,22		2,07	4,31	7,13—7,42 (s, 5H)	343 (3,79)
Ib	9,47		2,04	4,34	2,32 (s, 3H, CH_3), 7,20 (s, 4H)	344 (3,82)
Ic	9,46		2,04	4,33	3,77 (s, 3H, OCH_3), 6,94 (d, 2H), 7,20 (d, 2H)	343 (3,82)
Id	9,04		2,11	5,53	7,36—7,98 (m, 3H)	—*
Ie	9,64		2,07	4,69	7,59 (d, 2H), 8,28 (d, 2H)	357 (3,66)
IIa		3,20	2,29	4,29	7,29 (br. s., 5H)	349 (3,79)
IIb		3,17	2,26	4,23	2,33 (s, 3H, CH_3), 7,13 (s, 4H)	349 (3,82)
IIc		3,18	2,27	4,23	3,78 (s, 3H, OCH_3), 6,88 (d, 2H), 7,17 (d, 2H)	349 (3,81)
IId		3,21	2,29	5,24	7,31—7,98 (m, 4H)	—**
IIe		3,22	2,26	4,67	7,60 (d, 2H), 8,28 (d, 2H)	364 (3,68)

*Has no maximum in the 300-400 nm region.

**Broad, poorly expressed absorption band in the 300-350 nm region (log ε 3.82).

impeded rotation of the 4-(o-nitrophenyl) group takes place here. One of the isomers was isolated in a pure state by the preparative TLC, and the other was characterized by the PMR spectrum taken of the mixture of isomers.

EXPERIMENTAL

The IR spectra were obtained on a PE 580 B spectrophotometer (in mineral oil), UV spectra — on a Specord UV-Vis spectrophotometer (in ethanol), and PMR spectra on a WH-90 spectrometer, relative to TMS as inner standard. The course of the reactions was controlled by TLC on Silufol UV-254 plates in a chloroform—hexane—acetone (9:7:1) system of solvents, with development in UV light. Ethanol was used for crystallization unless otherwise specified.

The principal characteristics of the compounds synthesized are given in Tables 1-3.

4-Aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles were synthesized: Ia according to the method in [7], Id according to [8], and the remaining compounds in analogy with the method in [7].

4-Aryl-2,6-dimethylpyridine-3,5-dicarbonitriles (V). A suspension of 5 mmoles of 1,4-dihydropyridine I in 10 ml of 3 N nitric acid is heated to 60-70°C for 5 min. When cool, the precipitate that separates is washed with water and crystallized.

4-Aryl-1,2,6-trimethyl-1,4-dihydropyridine-3,5-dicarbonitriles (II). A 20 mmole portion of dihydropyridine I is dissolved with gentle (40-50°C) heating in 200-500 ml of acetone, 12.5 mmoles of ground NaOH is added, the mixture is boiled for 10 min, and 9.4 ml (100 mmoles) of dimethyl sulfate is added with stirring. The reaction mixture is cooled, filtered, the solvent is evaporated, the residue is washed with 250 ml of water and crystallized. Light-yellow dihydropyridines IIa-d are obtained. In the preparation of the IId derivative, the reaction is carried out at 5-10°C.

4-Aryl-1,2,6-trimethyl-3,5-dicyanopyridinium Perchlorates (IIIa-e). A 3 ml portion (26 mmoles) of hydrogen peroxide and 6 ml (50 mmoles) of 57% perchloric acid are added to a solution of 20 mmoles of N-methyl derivative II in 60 ml of ethanol, and the mixture is boiled for 6-8 h. When cool, the colorless precipitate that separates is filtered, washed with ether, and recrystallized from isopropanol to yield pyridinium perchlorates IIIa-e.

4-Aryl-1,2,6-trimethyl-1,2-dihydropyridine-3,5-dicarbonitriles (IVa-e). A. A 10 mmole portion of perchlorate III is dissolved in 50-100 ml of acetonitrile, and 0.95 g (25 mmoles) of sodium borohydride is added in the course of 5 min with stirring. The mixture is allowed to stand for 20 min at 20°C. It is then filtered, the filtrate is evaporated, the residue is treated with 20 ml of chloroform, and the insoluble material is filtered. The chloroform extract is concentrated to a volume of 9-10 ml, and the solution is chromatographed three times on a 220 × 260 mm preparative plate with nonstationary L40/100 silica gel layer 2-3 mm thick in a chloroform—hexane—acetone (9:7:1) system of solvents. Yellow-colored

TABLE 3. Spectral Characteristics of 3,5-Dicyano-1,2-dihydropyridines IV, V

Compound	PMR spectrum, δ, ppm						SSCC, Hz		UV spectrum, λ_{max}, nm (log ε)
	1-H (d; 1H)	1-CH_3 (s; 3H)	2-CH_3 (d; 3H)	2-H (1H)	6-CH_3 (s; 3H)	4-Ar	J_{2H-2CH_3}	J_{2H-NH}	
IVa		3,18	1,37	4,27q	2,34	7,42 (s, 5H)	6,5		264 (4,37), 384 (3,92)
IVb		3,18	1,35	4,24q	2,33	2,37 (s, 3H, CH_3), 7,27 (s, 4H)	6,5		269 (4,41), 384 (3,88)
IVc		3,17	1,35	4,23q	2,34	3,81 (s, 3H, OCH_3), 6,93 (d, 2H), 7,38 (d, 2H)	6,5		273 (4,31), 384 (3,81)
IVd*		3,23	1,47	4,31q	2,34	7,37 (d, 1H), 7,64 (t, 1H), 7,74 (s, 1H), 8,27 (d, 1H)	6,5		264 (4,31), 383 (3,89)
IVe		3,23	1,42	4,31q	2,38	7,59 (d, 2H), 8,29 (d, 2H)	7,0		262 (4,41), 342 (3,78), 399 (3,76)
VIa	5,87		1,40	4,36m	2,14	7,41 (s, 5H)	7,0	3,0	262 (4,27), 382 (3,79)
VIb	6,22		1,34	4,29m	2,09	2,37 (s, 3H, CH_3), 7,26 (s, 4H)	6,5	3,0	266 (4,43), 381 (3,85)
VIc	6,02		1,40	4,32m	2,16	3,82 (s, 3H, OCH_3), 6,96 (d, 2H), 7,38 (d, 2H)	6,5	3,0	270 (4,26), 378 (3,70)
VId	5,20		1,51	4,49m	2,24	7,38 (d, 1H), 7,69 (m 2H), 8,23 (d, 1H)	6,5	3,5	261 (4,24), 377 (3,88)
VIe	5,27		1,54	4,54m	2,30	7,60 (d, 2H), 8,31 (d, 2H)	6,5	2,0	261 (4,38), 340 (3,68), 391 (3,64)

*The spectrum was run on a WM-360 spectrometer; the corresponding signals of the second rotamer are: 1.45 (d, 3H, 2-CH_3), 2.35 (s, 3H, 6-CH_3), 3.25 (s, 3H, 1-CH_3), 4.36 (q, 1H, 2-H), 7.44 (d, 1H), 7.66 (t, 1H), 7.77 (t, 1H), and 8.25 (d, 1H) — aromatic protons.

strips are collected from the plates; the 1,2-dihydropyridines IV are eluted from silica gel by ethanol (50 ml for each plate), the solvent is evaporated, and the residue is recrystallized.

B. Dihydropyridine VI (10 mmoles) is dissolved in 50-100 ml of acetone, 0.6 g (15 mmoles) of ground NaOH is added, the mixture is boiled for 10 min, and 3.1 ml (50 mmoles) of methyl iodide is added. The solvent is evaporated and the residue is washed with water (~100 ml) and crystallized to give IVa-e, yield 45-60%.

4-Aryl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarbonitriles (VI). A. A mixture of 10 mmoles of pyridine V in 100-150 ml of acetonitrile and 25 mmoles of $NaBH_4$ is stirred at room temperature for 6 h, followed by treatment as shown for IV. Compound Ve is reduced at the temperature of −5 to −10°C, and the reaction mixture is concentrated at 30°C. To isolate 1,2-dihydropyridines VIa-e, the concentrated chloroform extract is chromatographed twice as shown above in a chloroform–hexane–acetone–ethanol (12:9.3:1.3:1) system of solvents, collecting a yellow colored strip.

B. A 10 mmole portion of N-oxide VII is stirred for 4 h with 0.95 g (25 mmoles) of $NaBH_4$ in a mixture of acetonitrile and methanol (85 + 8.5 ml). The 1,2-dihydropyridines VIa,b are isolated as in the reduction of pyridines V, yield 25-30%.

4-Phenyl- (VIIa) and 4-(4-methylphenyl)-2,6-dimethyl-3,5-dicyanopyridine N-oxide (VIIb) are obtained in similar ways as described in [9].

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REDUCTION AND ALKALINE HYDROLYSIS OF 5-OXOINDENO[1,2-b]PYRIDINIUM SALTS

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5,9b-Dihydro derivatives of indeno[1,2-b]pyridine were obtained by the reduction of the corresponding 1,2-dimethyl-4-aryl-5-oxoindeno[1,2-b]pyridinium perchlorates. 1,2-Dimethyl-3-ethoxycarbonyl-4-phenyl-5-oxoindeno[1,2-b]pyridinium perchlorate forms in alkaline medium with splitting, recyclization and deamination products.

In the monocyclic pyridine series, the transformation of 1,4-dihydro- to 1,2-dihydro-isomers is readily accomplished by the reduction of the corresponding pyridinium salts, but a similar transformation for condensed derivatives is not known. The reduction of pyridinium salts is often carried out in alkaline medium, or agents are used which produce such a medium in the course of the reaction. Therefore, the object of the present work was to study the reduction of indenopyridinium perchlorates and their transformations in alkaline medium.

To reduce the indenopyridinium salts I, we used catalytic hydrogenation and reduction by sodium borohydride and sodium bis(methoxyethoxy)-aluminum hydride. In the catalytic reduction of salts by Raney nickel and Pd/C catalysts, a mixture of 5,9b- and 4,5-dihydro-isomers of the corresponding indenopyridines is formed, as well as products of further reduction of the latter, which will be reported separately.

In the reaction of 5-oxoindeno[1,2-b]pyridinium perchlorates I with sodium borohydride in an acetonitrile solution, a selective reduction of the pyridinium ring takes place, as the result of which the corresponding 1,2-dimethyl-4-aryl-5-oxo-5,9b-dihydroindeno[1,2-b]-pyridines II are formed. The formation of the 5,9b-dihydro-isomer II structure was confirmed by spectral methods of investigation. The appearance in the PMR spectrum of a CH proton signal in the form of a singlet excludes the 2,5-dihydro-isomeric structure, while the 4H-indenopyridine isomers, for which the proton signal at the $C_{(4)}$ atom is also a singlet, are known compounds which we used for the synthesis of the starting indenopyridinium salts I [3]. The frequency of the IR vibrations of the 5-CO groups of compounds II is appreciably decreased (up to 1665 cm^{-1}), which is explained by the increase in the conjugation.

When 1,2-dimethyl-3-ethoxycarbonyl-4-phenyl-5-oxoindeno[1,2-b]pyridinium perchlorate (Ia) is reduced by sodium bis(2-methoxyethoxy)aluminum hydride, whose use is favorably affected by increase in the basicity of the medium [4], not only is 5,9b-dihydro-isomer IIa formed, but 1-methyl-2,5-dioxo-3-acetyl-4-phenylindeno[1,2-b]pyridine (III) is also formed, which indicates splitting of the pyridine ring during the reaction. The subsequently studied reaction of indenopyridinium perchlorate Ia with an aqueous-alcoholic solution of alkali is a special case of nucelophilic recyclization of the pyridine ring [5].

The sole path of formation of 1-methyl-3-acetyl-4-phenyl-2,5-dioxoindeno[1,2-b]pyridine (III) is recyclization of the intermediate formed as the result of cleavage of the $N–C_{(2)}$

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