Amalgam (Na.Hg) Reduction of some 4-Substituted-2-amino-3,5-dicyano-6-methoxypyridines. New Evidence Regarding the Oxidation Step in their Synthesis

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The amalgam (Na.Hg) reduction of some 4-substituted-2-amino-3,5-dicyano-6-methoxypyridines **3** results in the formation, in high yields of 3,4-dihydropyridines **2**. Highfield ^1H and ^{13}C nmr studies provide unambiguous support for the structures proposed. The synthesis of C-4 deuterium labeled dihydropyridine **2c-D**, by this procedure, let us understand the role played by this dihydropyridines as intermediates in the necessary oxidation path into the synthesis of pyridines **3** from malononitrile and benzylidenemalononitriles **1** in methanol/sodium methoxide.

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In recent years the synthesis of dihydropyridines [1-3] has been attempted in several ways, because of their pharmacological effects [4] as well as their herbicidal properties [5,6]. The synthesis of 3,4-dihydropyridines is described in a few number of cases and none of them as part of a reduction process [7-10]. Dihydropyridines obtained by reduction procedures tend to undergo further reductions, so mixtures of several products are obtained in most of the described methods. Separation of 1,2-dihydro- and 1,4-dihydropyridines [11-12] from those mixtures has been achieved.

In the present work, it is the first time 6-amino-4-aryl-3,5-dicyano-2-methoxy-3,4-dihydropyridines **2**, (Scheme 1) have been described. Their synthesis is accomplished in good yields by reduction of pyridines **3** with amalgam (Na.Hg) in tetrahydrofuran/water. Moreover, to explain the results obtained, the reduction potentials of a set of type **3** pyridines was measured (Table 1) and, as it was expected, only those pyridines with a reduction potential more positive than the one corresponding to the amalgam (Na.Hg), -2.15 V (*vs* SCE) [13], were reduced.

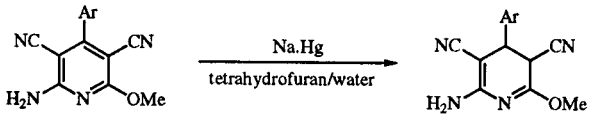
Table 1

Reduction Potentials of Type 3 Pyridines

	Substituent on C-4	E^{red} (V)
a	3-Pyridyl	-1.70
b	*p*-Chlorophenyl	-1.76
c	Phenyl	-1.88
d	*p*-Methylphenyl	-1.94
e	*p*-Methoxyphenyl	-2.23
f	*m*-Aminophenyl	-2.60
g	H	-2.62
h	Methyl	-2.78

Cyclic voltammetry at 25° *vs* Ag/Ag^+ of 2 $10^{-2}M$ solutions in $CH_3CN/-Et_4NClO_4$ recorded at a scan rate of 0.2 Vs^{-1}.

Scheme 1



3 **2**

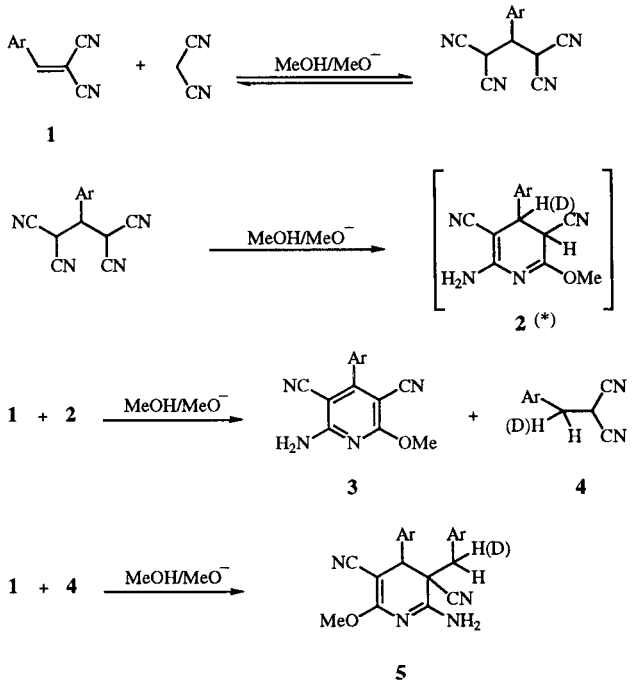
3, 2 Ar

a, 3-Pyridyl
b, *p*-Chlorophenyl
c, Phenyl
d, *p*-Methylphenyl

The 4-arylpyridines **3a-e** were prepared by the reaction of malononitrile with an aldehyde or a benzylidenemalononitrile in methanol/sodium methoxide, as was previously described [14,15]. The oxidation path in this last reaction, see Scheme 2, constituted for us a subject of study in the past [16,17]. Presently we propose that a hydride ion is transfered from the unisolated dihydropyridine **2** to the corresponding benzylidenemalononitrile **1** to yield pyridine **3** and the benzylmalononitrile **4**, which would react, in the same way as malononitrile, with another molecule of **1** to afford the isolated by-products **5**.

Herein, apart of the synthesis of the new 3,4-dihydropyridines **2**, we have studied the oxidation path above. To accomplish this project, we were able to prepare **2c-D**, a labeled product with deuterium on C-4, which reacts with **1** (Ar = Ph) in methanol/sodium methoxide to yield, through a deuterated benzylmalononitrile molecule **4**, the dihydropyridine **5c-D** (Ar = Ph), deuterated at the benzylic methylene, confirming our hypothesis and proving that the hydride ion proceeds from the C-4 position of the dihydropyridine.

Scheme 2



(*) The C4 deuterated dihydropyridine **2** (**2c-D**) is synthesized by reduction of **3c** (see discussion).

The structure of the reduced products was determined from the ^1H and ^{13}C nmr data. The ^1H nmr of **2c** shows a pair of doublets for each C-4 and C-3 protons, which indicate the presence of two main isomers. The *trans* isomer has signals at 3.58 ppm (C3-H) and 4.03 ppm (C4-H), J = 9.03 Hz and the *cis* isomer at 3.94 (C4-H) and 4.00 (C3-H), J = 7.5 Hz. The assignment was supported by selective decoupling in the nmr studies: the signals of the protons on C-4 became sharp when they were decoupled from the *ortho*-Ph protons. On the other hand, the NOE effects observed between *ortho*-Ph protons and H-3, H-4, 5.4% and 4.6% respectively at the 4.03 and 3.58 ppm signals and 0.0% and 3.9% at the 4.00 and 3.94 ppm signals, allowed us to conclude that the former pair of signals belongs to the *trans*-isomer and the later pair to the *cis* isomer with a *trans/cis*: 2/1 ratio.

The positions assigned to methoxy and amino groups are supported by the splitting in a quartet of doublets of the ^{13}C signals at 162.2 ppm and 162.5 ppm, corresponding to carbons linked to a methoxy group.

EXPERIMENTAL

Pyridines **3g,h** were prepared according to the method used in references [14,15] for the corresponding 6-ethoxy derivatives. It should be noted that the physical and chemical properties of **3g,h** are reported in reference [15].

Melting points were determined on a Reichter Thermovar micro hotstage apparatus and are uncorrected. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A. The ir spectra were obtained on potassium bromide discs on a Perkin-Elmer Model 583 spectrometer. The ^1H nmr (300 MHz), ^{13}C nmr (75.4 MHz) and ^1H nmr (500 MHz), ^{13}C nmr (125 MHz) were recorded on a Unity 300 and on a Unity 500 Plus respectively. Elemental analysis was performed on a Perkin-Elmer Model 240-B analyzer.

General Procedure.

A solution of 2-amino-4-aryl-3,5-dicyano-6-methoxypyridine (2 mmoles) in 2 ml of tetrahydrofuran was added to the sodium amalgam (Na.Hg) (0.97% ww, Na = 92 mg = 4 mmoles) amalgam and then water or deuterium oxide for **2c-D** (4 mmoles) was added dropwise. The mixture was stirred at room temperature under argon atmosphere for eight hours. The organic phase was separated and evaporated to dryness. The residue was purified by chromatography on silica gel using dichloromethane as the eluent. White crystals were obtained after recrystallization from ethanol.

6-Amino-3,5-dicyano-2-methoxy-4-phenyl-3,4-dihydropyridine (**2c**).

This compound was obtained in 70% yield, mp 170-172°; ir (potassium bromide): 3439, 3339, 3238, 2190, 1650, 1623, 1563, 1317, 1056, 1018, 975, 765, 697, 635 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): 3.58 (1H, d, C3-H *trans*, J = 9.03 Hz), 3.93 and 3.94 (3H, s, OCH_3), 3.94 (1H, d, C4-H *cis*, J = 7.50 Hz), 4.00 (1H, d, C3-H *cis*, J = 7.50 Hz), 4.03 (1H, d, C4-H *trans*, J = 9.03 Hz), 4.90 and 4.93 (2H, br signals, NH_2), 7.15-7.51 (5H, m, H_{arom}); ^{13}C nmr (125 MHz, deuteriochloroform): 36.9 and 37.1 (C-3), 40.8 and 42.8 (C-4), 56.1 and 56.2 (OCH_3), 60.8 and 61.5 (C-5) 113.6, 114.6, 119.1 and 119.2 (CN), 127.4-137.2 (C_{arom}), 157.6 and 157.7 (C-6), 162.2 and 162.4 (C-2); ms: (EI) m/z (relative intensity) 252 (M^+, 69), 251 (100).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.69; H, 4.80; N, 22.18.

6-Amino-3,5-dicyano-2-methoxy-4-*p*-methylphenyl-3,4-dihydropyridine (**2d**).

This compound was obtained in 85% yield, mp 177-180°; ir (potassium bromide): 3434, 3336, 3238, 1650, 1624, 1562, 1516, 1442, 1402, 1322, 1062, 1022, 974, 802 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform), 2.34 (3H, s, CH_3), 3.58 (1H, d, C3-H, *trans*, J = 9.3 Hz), 3.93 (1H, d, C4-H, *cis*, J = 6.6 Hz), 3.94 and 3.95 (3H, s, OCH_3), 4.00 (1H, d, C3-H, *cis*, J = 6.6 Hz), 4.01 (1H, d, C4-H, *trans*, J = 9.3 Hz), 4.91 and 4.94 (2H, br signals, NH_2), 7.07-7.26 (4H, m, H_{arom}); ^{13}C nmr (75.4 MHz, deuteriochloroform): 21.1 (CH_3), 36.9 and 37.3 (C-3), 40.5 and 42.5 (C-4), 56.1 (OCH_3), 61.1 and 61.7 (C-5), 113.7, 114.7 and 119.3 (CN), 127.3-138.7 (C_{arom}), 157.6 and 157.6 (C-6), 162.2 and 162.5 (C-2); ms: (methane, CI) m/z (relative intensity) 267 (100).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.20; H, 4.56; N, 21.17.

6-Amino-3,5-dicyano-2-methoxy-4-(3-pyridyl)-3,4-dihydropyridine (**2a**).

This compound was obtained in 70% yield, mp 196-200°; ir (potassium bromide): 3477, 3417, 3337, 2188, 1662, 1638,

1575, 1520, 1457, 1393, 1326, 1292, 987 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform), 3.56 (1H, d, C3-H, *trans*, J = 9.0 Hz), 3.95 and 3.96 (3H, s, OCH_3), 3.98 (1H, d, C4-H, *cis*, J = 7.5 Hz), 4.03 (1H, d, C3-H, *cis*, J = 7.5 Hz), 4.07 (1H, d, C4-H, *trans*, J = 9.0 Hz), 4.96 and 4.99 (2H, br signals, NH_2), 7.3-8.9 (4H, H_{arom}); ms: (EI) m/z (relative intensity) 251 (100), 222 (27), 194 (30).

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.63; H, 4.36; N, 27.62.

6-Amino-4-(*p*-chlorophenyl)-3,5-dicyano-2-methoxy-3,4-dihydropyridine (**2b**).

This compound was obtained in 75% yield, mp 160-162°; ir (potassium bromide): 3454, 3340, 3222, 2198, 1666, 1500, 1404, 1320, 1286, 1208, 1144, 1090, 974, 806 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): 3.53 (1H, d, C3-H, *trans*, J = 9.5 Hz), 3.93 and 3.94 (3H, s, OCH_3), 3.94 (1H, d, C4-H, *cis*, J = 7.5 Hz), 3.99 (1H, d, C3-H, *cis*, J = 7.5 Hz), 4.01 (1H, d, C4-H, *trans*, J = 9.5 Hz), 4.92 and 4.96 (2H, br signals, NH_2), 7.12-7.38 (4H, m, H_{arom}); ^{13}C nmr (75.4 MHz, deuteriochloroform): 36.8 and 37.2 (C-3), 40.3 and 42.4 (C-4), 56.1 and 56.2 (OCH_3), 60.3 and 70 (C-5), 113.5, 114.4, 118.9 and 119.2 (CN), 127.5-135.8 (C_{arom}), 157.7 and 157.9 (C-6), 162.1 and 162.4 (C-2); ms: (EI) m/z (relative intensity) 286 (M^+, 40), 252 (60), 251 (100).

Anal. Calcd. for $C_{14}H_{11}N_4OCl$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.67; H, 3.89; N, 19.51.

6-Amino-3,5-dicyano-2-methoxy-4-phenyl-3,4-dihydro-4-*d*-pyridine (**2c-D**).

This compound ws obtained in 70% yield, mp 170-172°; ir (potassium bromide): 3552, 3435, 3238, 2192, 1646, 1620, 1562, 1444, 1399, 1317, 993, 949, 766 and 697 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): 3.58 (1H, C3-H, *trans*) and 4.00 (1H, C3-H, *cis*), 3.93 and 3.94 (3H, s, OCH_3), 4.90 and 4.93 (2H, br signals, NH_2), 7.17-7.34 (5H, m, H_{arom}); ^{13}C nmr (125 MHz, deuteriochloroform): 36.8 and 37 (C-3), 56.1 and 56.2 (OCH_3), 60.7 and 61.5 (C-5), 40.5 and 42.5 two very weak triplets (C-4), 113.6, 114.6 and 119.2 (CN), 127.4-137.3 (C_{arom}), 157.6 and 157.7 (C-6), 162.3 and 162.5 (C-2); ms: (EI) m/z (relative intensity) 253 (M^+, 70), 252 (100).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.40; H, 4.35; N, 22.13. Found: C, 66.61; H, 4.50; N, 22.17

2-Amino-3,5-dicyano-6-methoxy-4-phenyl-3-phenyl(methyl-d_1)-3,4-dihydropyridine (**5c-D**).

A solution of **2c-D** (0.5 g, 2 mmoles) and benzylidenemalononitrile (0.61 g, 4 mmoles) in methanol (15 ml)-sodium methoxide (4 mmoles) was stirred at room temperature for four hours. The mixture was evaporated to dryness and the residue was purified by chromatography on a silica gel column using methylene chloride as the eluent. White crystals (0.48 g) were obtained after recrystallization from ethanol, yield 70%, mp 207-208°; ir (potassium bromide): 3380, 2185, 1642, 1570, 1553, 1448, 1432, 1420, 1310, 1220, 1205, 1132, 690 cm^{-1}; ^1H nmr (300 MHz, deuterioacetone): 3.31 and 3.46 (1H, t, CHD), 3.72 (1H, s, C4-H), 3.89 (3H, s, OCH_3), 7.00 (1H, br signal, NH), 7.10-7.45 (10H, m, H_{arom}), 8.00 (1H, br signal, NH); ^{13}C nmr (75.4 MHz, deuterioacetone): 42.1 (t, J = 20 Hz, CHD), 47.4 (C-4), 49.5 (C-3), 54.6 (OCH_3), 63.3 (C-5), 118.2 and 119.7 (CN), 128.9-138.9 (C_{arom}), 162.4 (C-2), 166.3 (C-6); ms: (EI) m/z (relative intensity) 343 (M^+, 7), 251 (66), 92 (100).

Anal. Calcd. for $C_{21}H_{17}DN_4O$: C, 73.47; H, 4.96; N, 16.33. Found: C, 73.45; H, 4.93; N, 16.35.

2-Amino-4-(*m*-aminophenyl)-3,5-dicyano-6-methoxypyridine (**3f**).

This compound was obtained by the above general procedure, by reduction of 2-amino-3,5-dicyano-4-(*m*-nitrophenyl)-6-methoxypyridine [15] with sodium amalgam in 70% yield, mp 283-285°; ir (potassium bromide): 3465, 3372, 3326, 3211, 2213, 1629, 1568, 1546, 1490, 1467, 1446, 1376, 1288, 1211, 1007, 993, 776 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): 3. 97 (3H, s, OCH_3), 5.40 (2H, s, NH_2), 6.5-7.2 (4H, m, H_{arom}), 7.92 (2H, br signal, NH_2); ms: (methane, CI) m/z (relative intensity) 266 (100).

Anal. Calcd. for $C_{14}H_{11}N_5O$: C, 63.40; H, 4.15; N, 24.61. Found: C, 63.35; H, 4.18; N, 24.57.

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