

# Electrochemical reduction of C-4 nitrosophenyl 1,4-dihydropyridines and their parent C-4 nitrophenyl derivatives in protic media

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## Abstract

A comprehensive study of the electrochemical reduction in protic media of parent C-4 nitrophenyl 1,4-DHPs and their corresponding nitrosophenyl 1,4-DHPs was carried out. The reduction potentials of synthesized aromatic nitro compounds were compared with those of the corresponding nitroso compounds, concluding that the latter were reduced at significant more positive potentials. Arylhydroxylamines formed in the 4-electrons reduction of nitrophenyl 1,4-DHPs at acid pH can be protonated and further reduced. At pH 12, in some compounds the 1-electron reduction to give the nitro radical anion could be distinguished from the cyclic voltammograms. *Ortho*-nitro derivatives were reduced at more negative potentials than other *meta*- and *para*-nitro derivatives. Nitrosophenyl 1,4-DHPs were reduced on Hg in a quasi-reversible process, involving 2- electrons, 2-protons to give the hydroxylamine derivative. Reduction potentials of the nitrosophenyl 1,4-DHPs having methoxycarbonyl- and ethoxycarbonyl-groups in the 3- and 5-positions were not significantly affected. However, a bulky substituent in those positions, such as the isopropoxyloxycarbonyl group, produced an increase in peak potential values, making reduction more difficult than the other derivatives.

*Keywords:* C-4 nitrophenyl; C-4 nitrosophenyl; 1,4-Dihydropyridines; Reduction; Polarography; Cyclic voltammetry

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## 1. Introduction

1,4-dihydropyridines (1,4-DHP) antagonists of L-type calcium channels are widely used as therapeutics in the treatment of hypertension, angina, arrhythmias, congestive heart failure, cardiomyopathy, atherosclerosis, and cerebral and peripheral vascular disorders [1,2]. There exists considerable interest in the synthesis of new 1,4-dihydropyridines derivatives for their activity as calcium antagonists [3,4] and as candidates for the treatment of multidrug resistance (MDR) during cancer chemotherapy [5], as possible thromboxane synthetase

inhibitors [6], PAF-acether antagonists and antithrombotic-antihypertensive agents [7].

The inclusion of a nitrophenyl group in the C4-position of the 1,4-dihydropyridine ring gave rise to several compounds with recognized therapeutic activity that are still used in the treatment of cardiovascular pathologies, i.e. nifedipine, nitrendipine, nicardipine [2,8]. Nevertheless, the presence of this group not only affects the pharmacological properties of this type of compounds, but that also its redox properties. Thus, both the electrochemical reduction of the nitro group and the formation of intermediates, such as the nitro radical anions, have been investigated [9–13]. The electrochemistry of 4-(nitrophenyl) substituted 1,4-dihydropyridines has been also extensively studied in the last few years. The electrochemical reduction of nitrophenyl 1,4-DHP

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derivatives in aqueous media follows the general pattern of nitroaromatic compounds involving a single 4-electron step, producing the hydroxylamine derivative [14,15]. On the other hand, the electrochemical reduction of these derivatives is dramatically affected in mixed media [16–18]. We have recently synthesized a novel series of C-4 nitrosophenyl 1,4-dihydropyridines [19]. Our interest in the synthesis of this type of compounds lies on the (previous knowledge) the fact that some commercial nitrophenyl 1,4-dihydropyridines undergo photolysis when exposed to short-wavelength (below 420 nm), visible or UVC (254 nm) radiation in aqueous solution, oxidizing to their nitroso derivative [20,21].

In general terms, the reduction of nitrosoaromatic compounds has received little attention [22–24] as seen by the low number of reports as compared with the reduction of nitroaromatic compounds. This may be partly due to its chemical instability and the difficulty to be synthesized. Mostly, literature has been devoted to nitrosobenzene [25,26]. A good review about addition, reduction and oxidation reactions of nitrosobenzene was published some years ago by Zuman and Shah [27]. On the other hand, an electrochemical study about the reactivity of the nitroso radical anion electrochemically generated from nitrosobenzene with glutathione was recently reported [28]. The intermediacy of radicals in the chemical and electrochemical reductions of nitrobenzene in aqueous and non-aqueous solvent systems has been well-documented by electron spin resonance studies [29–32]. In another study [33], the electrochemical reduction of two nitrosoderivatives, i.e. *ortho*- and *meta*-nitrosotoluene was reported. In such a study, the UV–Vis and EPR spectroscopic characterization of the one-electron reduction product from these derivatives in aprotic media was also assessed.

Nitroso derivatives constitute both a ubiquitous class of chemicals in nature and a prototype with interesting potential pharmacological and toxicological properties. Therefore, we consider that the knowledge of their redox properties is relevant.

In this paper, we studied systematically the electrochemical reduction of a series of synthesized C-4 nitrosophenyl 1,4-dihydropyridines and their parent nitroaryl 1,4-DHPs in which both the position of the reducible group in the aromatic ring (*ortho*-, *meta*- or *para*-position) and the bulk of the alkyl groups substituting the 3- and 5-positions on the dihydropyridine ring were modified.

## 2. Experimental

### 2.1. Chemicals

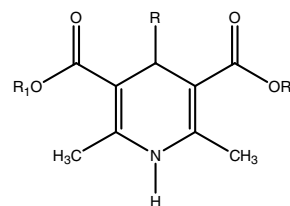
All solvents were of high-pressure liquid chromatography (HPLC) grade and all reagents were of analytical grade.

### 2.2. Compounds

Synthesis of 1,4-dihydropyridine derivatives (Fig. 1) was based on classical Hantzsch synthesis of 1,4-dihydropyridines [34,35].

To obtain the nitrosophenyl 1,4-dihydropyridine derivative, a chemical reduction was carried out of the nitro compound to the corresponding hydroxylamine and later oxidation to the final nitrosophenyl 1,4-dihydropyridine derivative.

All the synthesized compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectroscopy using a 300 MHz spectrometer (Bruker, WM 300), infrared spectroscopy (FT-IR Paragon Spectrometer, 100PC) and Elemental analysis (Fisons).



Compound	R <sub>1</sub>	R
<i>o</i> -NO <sub>2</sub> -iPr	i-Pr	<i>o</i> -nitrophenyl
<i>m</i> -NO <sub>2</sub> -iPr	i-Pr	<i>m</i> -nitrophenyl
<i>p</i> -NO <sub>2</sub> -iPr	i-Pr	<i>p</i> -nitrophenyl
<i>o</i> -NO <sub>2</sub> -Me	methyl	<i>o</i> -nitrophenyl
<i>m</i> -NO <sub>2</sub> -Me	methyl	<i>m</i> -nitrophenyl
<i>p</i> -NO <sub>2</sub> -Me	methyl	<i>p</i> -nitrophenyl
<i>m</i> -NO-iPr	i-Pr	<i>m</i> -nitrosophenyl
<i>p</i> -NO-iPr	i-Pr	<i>p</i> -nitrosophenyl
<i>m</i> -NO-Et	ethyl	<i>m</i> -nitrosophenyl
<i>p</i> -NO-Et	ethyl	<i>p</i> -nitrosophenyl
<i>m</i> -NO-Me	methyl	<i>m</i> -nitrosophenyl
<i>p</i> -NO-Me	methyl	<i>p</i> -nitrosophenyl

Fig. 1. Chemical structures of parent nitrophenyl- and their corresponding nitrosophenyl 1,4-DHPs.

2.2.1. 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (*o*-NO<sub>2</sub>-Me)

m.p.: 169.0 °C. IR (KBr):  $\nu_{\max}$  3331, 2920, 1681, 1530, 1495, 1433, 1350, 1022 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.35 (s, 6H, -CH<sub>3</sub>), 3.60 (s, 6H, -O-CH<sub>3</sub>), 5.73 (s, 1H, Ar-CH<), 5.91 (s, 1H, -NH-), 7.28 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.70 (d, 1H, *J* = 8.1 Hz, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.435 × 2); (34.390 × 2); (50.976 × 2); (103.527 × 2); 123.829; 126.979; 130.965; 132.690; 142.030; 144.887; 147.731; (167.489 × 2) ppm. Calc. C<sub>17</sub>H<sub>18</sub>O<sub>6</sub>N<sub>2</sub>: C = 58.96; H = 5.24; N = 8.09. Found: C = 58.63; H = 5.11; N = 8.52.

2.2.2. 4-(3-Nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (*m*-NO<sub>2</sub>-Me)

m.p.: 208.0 °C. IR (KBr):  $\nu_{\max}$  3350, 2950, 1705, 1646, 1529, 1486, 1431, 1347, 1127, 1100 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.36 (s, 6H, -CH<sub>3</sub>), 3.65 (s, 6H, -O-CH<sub>3</sub>), 5.11 (s, 1H, Ar-CH<), 5.95 (s, 1H, -NH-), 7.40 (m, 1H, Ar-H), 7.65 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.02 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.09 (s, 1H, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.508 × 2); (39.557 × 2); 51.060; 103.026; 121.327; 122.640; 128.646; 129.026; 132.954; 134.115; 144.938; 148.300; 149.488; (167.455 × 2) ppm. Calc. C<sub>17</sub>H<sub>18</sub>O<sub>6</sub>N<sub>2</sub>: C = 58.96; H = 5.24; N = 8.09. Found: C = 58.89; H = 5.22; N = 8.30.

2.2.3. 4-(4-Nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (*p*-NO<sub>2</sub>-Me)

m.p.: 197.0 °C. IR (KBr):  $\nu_{\max}$  3333, 2920, 1682, 1530, 1495, 1434, 1021 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.38 (s, 6H, -CH<sub>3</sub>), 3.66 (s, 6H, -O-CH<sub>3</sub>), 5.12 (s, 1H, Ar-CH<), 5.85 (s, 1H, -NH-), 7.46 (d, 2H, *J* = 8.06 Hz, Ar-H), 8.12 (d, 2H, *J* = 8.06 Hz, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.588 × 2); (39.725 × 2); 51.100; 102.868; 123.377; 123.702; 123.781; 128.520; 129.390; 129.514; 144.859; 146.272; 154.672; (167.386 × 2) ppm. Calc. C<sub>17</sub>H<sub>18</sub>O<sub>6</sub>N<sub>2</sub>: C = 58.96; H = 5.24; N = 8.09. Found: C = 58.76; H = 5.03; N = 8.65.

2.2.4. 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-diisopropylloxycarbonyl-1,4-dihydropyridine (*o*-NO<sub>2</sub>-iPr)

m.p.: 143.3 °C. IR (KBr):  $\nu_{\max}$  3342, 2981, 1694, 1532, 1486, 1367, 1303, 1219, 1103, 1016, 750 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.0 (d, 6H, *J* = 6.279 Hz, >CH-CH<sub>3</sub>), 1.19 (d, 6H, *J* = 6.279 Hz, >CH-CH<sub>3</sub>), 2.3 (s, 6H, -R-CH<sub>3</sub>), 4.9 (m, 2H, -CH(CH<sub>3</sub>)<sub>2</sub>), 5.65 (s, 1H, >NH), 5.94 (s, 1H, -R-CH), 7.2 (t, 1H, *J* = 5.672 Hz, Ar-H), 7.48 (t, 1H, *J* = 7.191 Hz, Ar-H), 7.57 (d, 1H, *J* = 6.441 Hz, Ar-H), 7.8 (d, 1H, *J* = 6.93 Hz, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.753 × 2); (21.336 × 2);

(21.595 × 2); 34.915 (67.300 × 2); (104.184 × 2); (124.004 × 2); 126.735; 131.717; 132.675; 143.074; 143.836; 147.568; (166.842 × 2) ppm. Calc. C<sub>21</sub>H<sub>26</sub>O<sub>6</sub>N<sub>2</sub>: C = 62.67; H = 6.511; N = 6.961. Found: C = 62.377; H = 6.554; N = 7.399.

2.2.5. 4-(3-Nitrophenyl)-2,6-dimethyl-3,5-diisopropylloxycarbonyl-1,4-dihydropyridine (*m*-NO<sub>2</sub>-iPr)

m.p.: 122.0 °C. IR (KBr):  $\nu_{\max}$  3361, 3092, 2978, 1701, 1648, 1530, 1484, 1349, 1219, 1180, 1105, 1016, 804, 750, 700 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.1 (d, 6H, *J* = 6.234 Hz, >CH-CH<sub>3</sub>), 1.2 (d, 6H, *J* = 6.258 Hz, >CH-CH<sub>3</sub>), 2.35 (s, 6H, -R-CH<sub>3</sub>), 4.9 (m, 2H, -CH(CH<sub>3</sub>)<sub>2</sub>), 5.0 (s, 1H, >NH), 5.8 (s, 1H, -R-CH), 7.3 (t, 1H, *J* = 7.923 Hz, Ar-H), 7.6 (d, 1H, *J* = 7.683 Hz, Ar-H), 8 (d, 1H, *J* = 6.753 Hz, Ar-H), 8.1 (s, 1H, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.606 × 2); (21.807 × 2); (22.108 × 2); 40.182; (67.341 × 2); (103.667 × 2); (121.238 × 2); 123.354; 128.487; 134.685; 144.431; 148.030; 150.124; (166.643 × 2) ppm. Calc. C<sub>21</sub>H<sub>26</sub>O<sub>6</sub>N<sub>2</sub>: C = 62.67; H = 6.511; N = 6.961. Found: C = 62.023; H = 6.539; N = 7.052.

2.2.6. 4-(4-Nitrophenyl)-2,6-dimethyl-3,5-diisopropylloxycarbonyl-1,4-dihydropyridine (*p*-NO<sub>2</sub>-iPr)

m.p.: 156.7 °C. IR (KBr):  $\nu_{\max}$  3308, 2982, 1700, 1649, 1523, 1488, 1370, 1344, 1300, 1217, 1103, 1016, 833, 705 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.1 (d, 6H, *J* = 5.888 Hz, >CH-CH<sub>3</sub>), 1.23 (d, 6H, *J* = 6.243 Hz, >CH-CH<sub>3</sub>), 2.34 (s, 6H, -R-CH<sub>3</sub>), 4.9 (m, 2H, -CH(CH<sub>3</sub>)<sub>2</sub>), 5.07 (s, 1H, >NH), 5.9 (s, 1H, -R-CH), 7.4 (d, 1H, *J* = 8.464 Hz, Ar-H), 8.1 (d, 1H, *J* = 8.704 Hz, Ar-H) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): (19.544 × 2); 21.754; 22.002; 40.108; 40.180; (59.901 × 2); 67.288; 102.950; 103.285; 123.072; 123.129; 128.910; 128.983; 144.374; 144.662; 146.129; 155.252; (166.536 × 2) ppm. Calc. C<sub>21</sub>H<sub>26</sub>O<sub>6</sub>N<sub>2</sub>: C = 62.67; H = 6.511; N = 6.961. Found: C = 62.33; H = 6.563; N = 7.361.

2.2.7. 4-(3-Nitrosophenyl)-2,6-dimethyl-3,5-diisopropylloxycarbonyl-1,4-dihydropyridine (*m*-NO-iPr)

m.p.: 130.7 °C. IR (KBr):  $\nu_{\max}$  3347.9, 2979.4, 1699.3, 1648.2, 1489.0, 1369.8, 1295.7, 1216.3, 1104.6, 1016.1, 750.0 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.0 (d, 6H, *J* = 6.24 Hz, >CH-(CH<sub>3</sub>)<sub>2</sub>), 1.18 (d, 6H, *J* = 6.4 Hz, >CH-(CH<sub>3</sub>)<sub>2</sub>), 2.27 (s, 6H, -R-CH<sub>3</sub>), 4.86 (m, 2H, *J* = 6.24 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 5.02 (s, 1H, >CH-), 5.82 (s, 1H, >NH), 7.50 (m, 4H, Ar-H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 18.551; 20.766; 21.085; 39.038; 39.155; 66.229; 66.306; 102.600; 102.804; 118.400; 119.665; 120.208; 122.319; 127.436; 133.663; 134.715; 143.474; 146.997; 148.823; 165.757; 167.849 ppm. Calc. C<sub>21</sub>H<sub>26</sub>O<sub>5</sub>N<sub>2</sub>: C = 65.27; H = 6.78; N = 6.961. Found: C = 63.63; H = 7.03; N = 6.75.

2.2.8. 4-(4-Nitrosophenyl)-2,6-dimethyl-3,5-diisopropiloxycarbonyl-1,4-dihydropyridine (*p*-NO-*i*Pr)

m.p.: 101.2 °C. IR (KBr):  $n_{\max}$  3309.4, 2981.8, 1699.7, 1649.1, 1488.8, 1344.9, 1300.8, 1218.1, 1103.7, 1016.3, 833.1  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.11 (d, 6H,  $J = 6.24$  Hz,  $-\text{CH}-(\text{CH}_3)_2$ ), 1.26 (d, 6H,  $J = 6.24$  Hz,  $-\text{CH}-(\text{CH}_3)_2$ ), 2.35 (s, 6H,  $-\text{R}-\text{CH}_3$ ), 4.96 (m, 2H,  $J = 6.24$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 5.07 (s, 1H,  $>\text{CH}-$ ), 5.85 (s, 1H,  $-\text{R}-\text{NH}$ ), 7.48 (d, 2H,  $J = 8.76$  Hz, Ar-H); 8.11 (d, 2H,  $J = 8.5$  Hz, Ar-H) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 14.274; 19.687; 21.866; 21.116; 40.287; 40.603; 67.402; 103.270; 103.417; 121.063; 123.187; 128.236; 129.098; 144.449; 146.138; 155.345; (2  $\times$  156.057); 165.658; 166.636; 166.695 ppm. Calc.  $\text{C}_{21}\text{H}_{26}\text{O}_5\text{N}_2$ : C = 65.27; H = 6.78; N = 6.961. Found: C = 66.866; H = 6.959; N = 6.986.

2.2.9. 4-(3-Nitrosophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (*m*-NO-*Et*)

m.p.: 118.2–119.1 °C. IR (KBr):  $n_{\max}$  3334.5, 29981.7, 1699.8, 1651.3, 1488.8, 1371, 1300.2, 1213.3, 1102.1, 1020.2  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.2 (t, 6H,  $J = 7.2$  Hz,  $-\text{CH}_2\text{CH}_3$ ), 2.36 (s, 6H,  $\text{R}-\text{CH}_3$ ), 4.1 (m, 4H,  $-\text{CH}_2\text{CH}_3$ ), 5.1 (s, 1H,  $>\text{CH}-$ ), 5.7 (s, 1H,  $>\text{NH}$ ), 7.7 (m, 4H, Ar-H) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): (2  $\times$  13.2302); (2  $\times$  18.5819); 38.852; 58.9277; 102.533; 118.131; 119.819; 127.550; 128.035; 134.542; 143.681; (2  $\times$  148.692); 165.457; 165.796; 166.248; 167.671 ppm. Calc.  $\text{C}_{19}\text{H}_{22}\text{O}_5\text{N}_2$ : C = 63.67; H = 6.286; N = 7.616. Found: C = 63.52; H = 6.48; N = 7.46.

2.2.10. 4-(4-Nitrosophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (*p*-NO-*Et*)

m.p.: 87.2–88.4 °C. IR (KBr):  $V_{\max}$  3342.5, 2997.8, 1671.5, 1486.7, 1369.2, 1303.2, 1217.3, 1120.1, 1020.3, 810.4  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR:  $\delta$  1.21 (t, 6H,  $J = 7.1$  Hz,  $\text{CH}_2\text{CH}_3$ ), 2.36 (s, 6H,  $\text{R}-\text{CH}_3$ ), 4.1 (q, 4H,  $J = 7.1$  Hz,  $-\text{CH}_2-\text{CH}_3$ ), 5.1 (s, 1H,  $\text{R}-\text{CH}$ ), 5.7 (s, 1H,  $>\text{NH}$ ), 7.5 (d, 2H,  $J = 8.26$  Hz, Ar-H), 7.7 (d, 2H,  $J = 8.6$  Hz, Ar-H) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): (2  $\times$  14.242); (2  $\times$  19.657); (2  $\times$  21.436); 40.437; 59.977; 103.095; 121.108; 125.286; 128.214; 128.859; 129.026; 144.588; (2  $\times$  155.740); 165.632; 167.098 ppm. Calc.  $\text{C}_{19}\text{H}_{22}\text{O}_5\text{N}_2$ : C = 63.67; H = 6.286; N = 7.616. Found: C = 66.195; H = 6.549; N = 6.959.

2.2.11. 4-(3-Nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (*m*-NO-*Me*)

m.p.: 208.0 °C. IR (KBr):  $n_{\max}$  3350, 2950, 1705, 1646, 1529, 1486, 1431, 1347, 1127, 1100  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.36 (s, 6H,  $-\text{CH}_3$ ), 3.65 (s, 6H,  $-\text{O}-\text{CH}_3$ ), 5.11 (s, 1H, Ar-CH), 5.95 (s, 1H,  $-\text{NH}-$ ), 7.40 (m, 1H, Ar-H), 7.65 (d, 1H,  $J = 8.1$  Hz, Ar-H), 8.02 (d, 1H,  $J = 8.1$  Hz, Ar-H), 8.09 (s, 1H, Ar-H) ppm.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ): (19.508  $\times$  2); (39.557  $\times$  2); 51.060; 103.026; 121.327; 122.640;

128.646; 129.026; 132.954; 134.115; 144.938; 148.300; 149.488; (167.455  $\times$  2) ppm. Calc.  $\text{C}_{17}\text{H}_{18}\text{O}_6\text{N}_2$ : C = 58.96; H = 5.24; N = 8.09. Found: C = 58.89; H = 5.22; N = 8.30.

2.2.12. 4-(4-Nitrosophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (*p*-NO-*Me*)

m.p.: 147.0 °C. IR (KBr):  $n_{\max}$  3335, 2951, 1704, 1650, 1488, 1435, 1020  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.37 (s, 6H,  $\text{R}-\text{CH}_3$ ), 3.65 (s, 6H,  $-\text{O}-\text{CH}_3$ ), 5.10 (s, 1H,  $>\text{CH}-$ ), 5.86 (s, 1H,  $>\text{NH}$ ), 7.52 (d, 2H,  $J = 8.56$  Hz, Ar-H), 7.79 (d, 2H,  $J = 8.56$  Hz, Ar-H) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): (2  $\times$  18.331); 19.565; 40.011; 51.068; (2  $\times$  58.378); 102.729; (2  $\times$  121.183); (2  $\times$  128.450); 144.869; (2  $\times$  155.315); 165.469; 167.445 ppm. Calc.  $\text{C}_{17}\text{H}_{18}\text{O}_5\text{N}_2$ : C = 61.81; H = 5.49; N = 8.48. Found: C = 62.22; H = 5.63; N = 8.61.

### 2.3. Polarography

Experiments were carried out in a BAS 50 W electrochemical equipment, containing a generator/potentiostat coupled to a PC (Gateway microcomputer, Pentium IV) with suitable software for totally automatic control of the experiments, data acquisition and further data treatment.

Operating conditions: pulse amplitude, 60 mV; potential scan, 5  $\text{mV s}^{-1}$ ; drop time, 1 s, voltage range, 0 to  $-2000$  mV, current range, 1.25–5  $\mu\text{A}$ , temperature, 25 °C. All the solutions were purged with pure nitrogen for 10 min before the polarographic runs.

### 2.4. Cyclic voltammetry

Experiments were carried out in a BAS 100 W assembly similar to that described above. All cyclic voltammograms were recorded at a constant temperature of 25 °C and the solutions were purged with pure nitrogen for 10 min before the voltammetric runs.

### 2.5. Electrodes

A BAS hanging mercury drop electrode (HMDE) with a drop surface of 1.90  $\text{mm}^2$  (VC) and a dropping mercury electrode (DME) (dpp and tast polarography) were used as the working electrodes and a platinum wire as the counter electrode. All potentials were measured against an Ag/Ag/AgCl electrode.

### 2.6. Protic media

All compounds were dissolved in 0.04 M Britton–Robinson buffer + ethanol: 50/50 to obtain the final concentration, which varied between 0.1 and 1 mM.

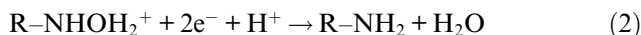
All pH measurements were carried out in aqueous media before the eventual addition of ethanol. Plotted

$E_p/pH$  values (Fig. 6) corresponded to these measurements.

### 3. Results and discussion

#### 3.1. Electrochemical reduction in protic media of parent C-4 nitroaryl 1,4-dihydropyridines Dp and tast polarography

The electroreduction of the parent nitrocompounds was studied in the 1–13 pH range. The waves (ptast mode) or peaks (dp mode) were shifted towards more cathodic potentials with increasing pH. The effect of pH on the electroreduction nitrophenyl 1,4-DHP derivatives is exemplified for *m*-NO<sub>2</sub>-Me in Fig. 2. This figure shows typical dp and tast polarograms. Two signals were found at pH 2, a first signal (I) next to –360 mV (Fig. 2) would correspond to the reduction of the nitro group to give the hydroxylamine derivative involving 4-electrons (Eq. (1)) and a second signal (II) at –980 mV (Fig. 2) would correspond to the reduction of protonated hydroxylamine to the amine derivative according to Eq. (2).



At neutral pH 7, only one signal is observed at approximately –670 mV (Fig. 2), which corresponds to the reduction of nitro group involving 4-electrons to give the hydroxylamine derivative according to Eq. (1). However, from pH 9 the main signal is unfolded into two new signals at –761 and –964 mV (Fig. 2). The first would correspond to the mono-electronic reduction of the group nitro to the nitro radical anion (Eq. (3)) and the second one could correspond to the 3-electrons transfer of the nitro radical anion to give the hydroxylamine derivative (Eq. (4)).



In the case of this compound, a small signal (V) appeared at less negative potentials, –177 mV, which could correspond to the presence of a nitroso derivative (Fig. 2).

*Ortho*-nitro derivatives exhibited some differences in their electro-reduction compared with the remaining compounds; firstly, the reaction summarized in Eq. (2) was not observed for these compounds and secondly, parallel with the increasing of pH, the appearance of signal V at less negative potentials was observed (approximately at –392 mV), which could correspond to a nitroso formation probably due to photodecomposition of the nitro group.

Table 1 summarizes the slopes corresponding to the  $E_p/pH$  plots for each nitrophenyl 1,4-DHP derivative. From the analysis of  $E_p-pH$  plots the following conclusions can be summarized: (a) the main signals corresponding to the *o*-NO<sub>2</sub>-Me and *o*-NO<sub>2</sub>-*i*Pr derivatives exhibited one break at approximately pH 10. Above pH 10,  $E_p$  values behave independent of pH changes

Table 1  
 $\partial E_p/\partial pH$  values for the linear segments for the C4-nitrophenyl 1,4-DHPs in protic media

	Segment 1 (pH 2–5)	Segment 2 (pH 5–9)	Segment 3 (pH 9–12)
<i>m</i> -NO <sub>2</sub> -Me	–73.21 ( $r = 0.9994$ )	–55.0 ( $r = 0.9996$ )	0
<i>p</i> -NO <sub>2</sub> -Me	–73.02 ( $r = 0.998$ )	–52.32 ( $r = 0.994$ )	0
<i>m</i> -NO <sub>2</sub> - <i>i</i> Pr	–65.6 ( $r = 0.9998$ )	–56.6 ( $r = 0.9998$ )	0
<i>p</i> -NO <sub>2</sub> - <i>i</i> Pr	–52.16 ( $r = 0.9992$ )	–65.6 (0.999)	0
	Segment 1 (pH 2–10)	Segment 2 (pH 10–12)	
<i>o</i> -NO <sub>2</sub> -Me	–62.0 ( $r = 0.998$ )	0	
<i>o</i> -NO <sub>2</sub> - <i>i</i> Pr	–56.08 ( $r = 0.997$ )	0	

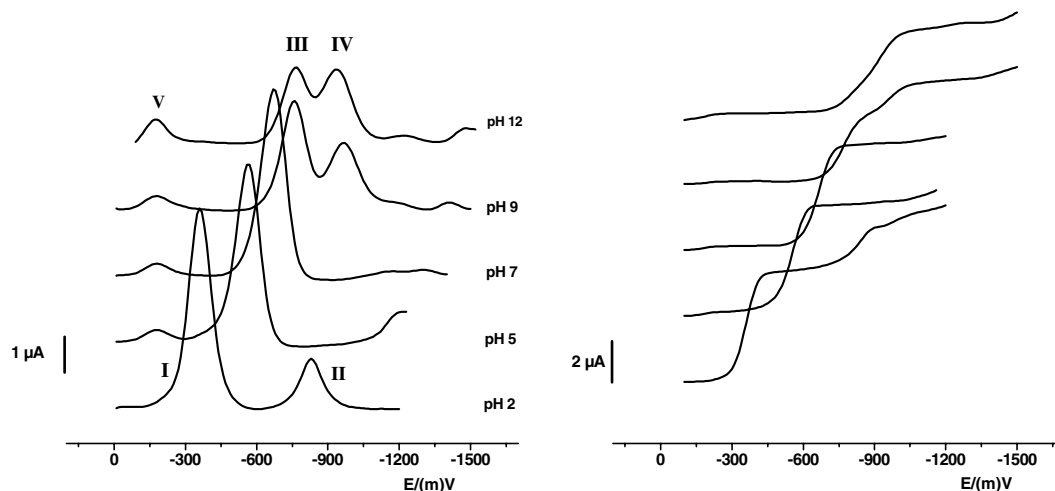


Fig. 2. Dp and tast polarograms at different pH for *m*-NO<sub>2</sub>-Me in protic media.

(b) *meta*- and *para*-nitro derivatives exhibited two breaks approximately at pH 5 and pH 8.5–9.0. The first break at acidic pH would correspond to an apparent pK accounting for the equilibrium between the neutral nitro group and its protonated form, according to the following equation:



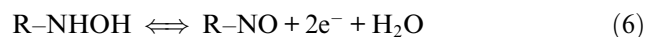
The second break would correspond to a change in the reduction mechanism due to the stabilization of the nitro radical at alkaline pH. Above pH 9.0,  $E_p$  values behave independent from the pH changes.

On the other hand,  $I_{\text{lim}}/\text{pH}$  plots show that at approximately between pH 2 and 10, the current behaves in independent way, indicating that the electrode process is diffusion-controlled. At  $\text{pH} > 10$ , pH exerts a certain kinetic control of the reduction process, probably due a slow protonation, this reaction being the rate limiting step.

### 3.2. Cyclic voltammetric studies of parent nitroaryl 1,4-DHP derivatives in protic media

These studies were conducted at different pH and sweep rates. In general terms, CV of the different nitrophenyl 1,4-DHPs displayed an irreversible signal that moves to more negative potentials with increasing pH, but in some cases, at pH 2–3, a second wave appeared which corresponds to the reduction of the protonated

hydroxylamine to the respective amine derivative (Fig. 3). At neutral pH 7 in all the compounds, the wave was of irreversible character as shown in Fig. 3. However, at pH 12 (Fig. 3), in some compounds it is possible to observe a reversible couple which would correspond to the monoelectronic reduction of the nitro group to the nitro radical anion and then the nitro radical anion is reduced to give the hydroxylamine via 3-electrons and four-protons (Fig. 3). These signals at pH 12 had a current ratio,  $I_{\text{pa}}/I_{\text{pc}}$ , of approximately 1:3, which could confirm the splitting of the original signal corresponding to the transfer of 4-electrons into two new signals. Also, the appearance of an oxidation signal at less negative potentials was observed (Fig. 3). This signal shifts to more cathodic potentials with pH increase, corresponding to the oxidation of hydroxylamine derivative to a nitroso derivative according to the following equation:



Noteworthy, the isolation of the reversible couple corresponding to the nitro radical anion formation was not possible through this technique.

In Fig. 4, a typical cyclic voltammogram of *m*-NO<sub>2</sub>-Me derivative at pH 12 is shown. As can be seen from this figure, this compound exhibits three signals, a reversible couple with a  $E_{\text{pa}} = -748$  mV and  $E_{\text{pc}} = -832$  mV, which would correspond to the 1-electron reduction of the nitro group to give the nitro radical anion, followed by an irreversible signal at

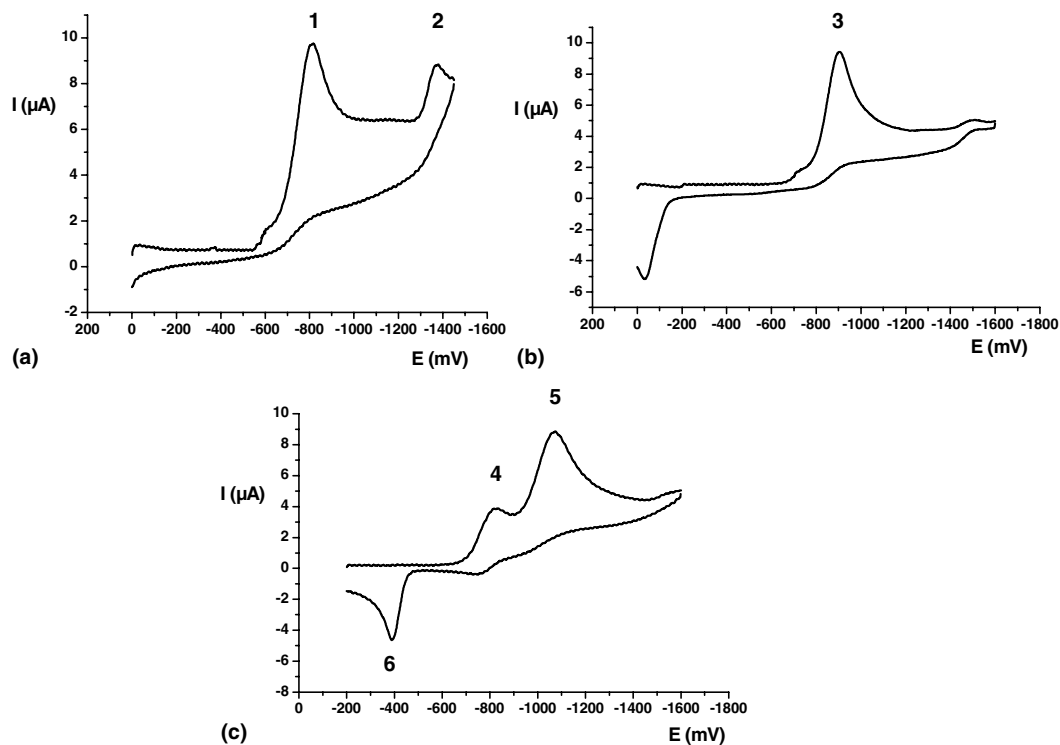


Fig. 3. Cyclic voltammograms corresponding to: (a) *ortho*-NO<sub>2</sub>-Me at pH 2 (b) *ortho*-NO<sub>2</sub>-Me at pH 7 (c) *meta*-NO<sub>2</sub>-Me at pH 12. Concentration: 1 mM and sweep rate 1 V/s.



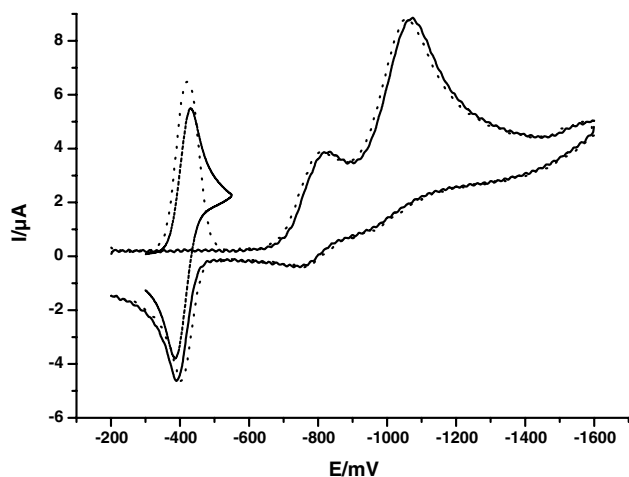


Fig. 4. Cyclic voltammograms of 1 mM solutions of: (—) *m*-NO<sub>2</sub>-Me (---) Second sweep (···) *m*-NO-Me. Sweep rate of 1 V s<sup>-1</sup>.

approximately  $-1075$  mV, which would correspond to the reduction of the nitro radical anion to the hydroxylamine involving 3-electron. At less negative potentials,  $-392$  mV appears as a quasi-reversible wave in the anodic sweep, which corresponds to the oxidation of the formed hydroxylamine. After a second sweep, this signal gave rise to a reversible couple corresponding to the reduction of the nitroso group to the hydroxylamine derivative in the cathodic sweep with an  $E_{pc}$  value of  $-430$  mV, as shown in Fig. 4. The addition of the corresponding *m*-NO-Me derivative to the solution of *m*-NO<sub>2</sub>-Me gives rise to a reversible couple in the same zone of potential with  $E_{pa} = -390$  mV and  $E_{pc} = -431$  mV, thus confirming the nature of the original wave (Fig. 4).

In conclusion, *ortho*-nitrophenyl 1,4-DHPs derivatives were reduced at more negative potentials than the other derivatives. However, no significant differences were established between *meta*- and *para*-nitro derivatives (Table 2). The differences in the reduction poten-

Table 2  
Peak potential values ( $E_{pc}$ ) for parent C-4 nitrophenyl and their corresponding nitrosophenyl 1,4-DHPs in protic media at pH 9

Compound	$-E_{pc} \pm 12$ (mV)
<i>o</i> -NO <sub>2</sub> -Me	853
<i>o</i> -NO <sub>2</sub> - <i>i</i> Pr	850
<i>m</i> -NO <sub>2</sub> - <i>i</i> Pr	712
<i>m</i> -NO <sub>2</sub> -Me	761
<i>p</i> -NO <sub>2</sub> -Me	767
<i>p</i> -NO <sub>2</sub> - <i>i</i> Pr	740
<i>m</i> -NO- <i>i</i> Pr	316
<i>p</i> -NO- <i>i</i> Pr	313
<i>m</i> -NO-Et	266
<i>p</i> -NO-Et	294
<i>m</i> -NO-Me	278
<i>p</i> -NO-Me	282

Concentration: 1 mM.

tials between *ortho*-nitrophenyl DHPs and the resting *meta*- or *para*-nitrophenyl DHPs could be explained by the loss of coplanarity of the nitro group from the plane with respect to the phenyl ring as a consequence of the steric effect due to the substituent in an *ortho*-position on the 1,4-DHP ring in the *ortho*-nitro DHP derivatives. The distortion of the coplanar arrangement decreases the resonance between the nitro group and the aromatic system, and the observed shift towards negative potentials in the *ortho*-nitrophenyl derivatives corresponds to this decrease.

Thus, the lowest delocalization of the charge of the nitro group with the aromatic system would make the reduction more difficult. These results are consistent with a previous study [36] on the electrochemistry of a series of three isomers in which the position of the nitro group in the phenyl group varied from *ortho*- to *para*-position, with a diethoxycarbonyl group substituting the 3- and 5-positions.

In order to support the above assumptions, a HyperChem 6.0 software was used to calculate the torsion angles between the nitro group and the phenyl ring. The compounds were optimized using a theoretical MM2 approximation. The results are shown in Fig. 5. Here, it is possible to observe that the nitro group is nearly coplanar in the case of the *meta*- and *para*-nitro derivatives (Fig. 5(b) and (c)) and, in the case of the *ortho*-nitro derivatives, there are torsion angles ranging from 40 to nearly 50 degrees (Fig. 5(a)). Thus, it is possible to conclude that this sterical hindrance is affecting the electronic delocalization between the aromatic ring and the nitro group. In the case of the *ortho*-nitro derivatives, the nitro group maintains a high electronic density and therefore its reduction is far more difficult than the *meta*- and *para*-nitro derivatives. On the other hand, no significant differences were found in reduction potentials between the different *ortho*-nitro derivatives. A similar conclusion was established in the case of *meta*- and *para*-nitro derivatives. In consequence, alkyl substitutions in 3- and 5-position were not determinants on the easiness of reduction of the derivatives.

### 3.3. Reduction of nitrosoaryl 1,4-DHP in protic media Dp and tast polarography

A protic medium containing 0.04 M Britton-Robinson buffer + ethanol: 50/50 and 0.1 M KNO<sub>3</sub> was used between pH 6 and pH 12. All the compounds were protected from direct light, being stable in this pH range and in the time-scale of the experiments (approximately, 2 h).

At pH < 6, the nitroso derivatives did not produce a polarographic peak or wave since their reduction was masked by the mercury oxidation. However, at pH > 6, the derivatives exhibited a similar polarographic behaviour, showing a well-defined single peak in the

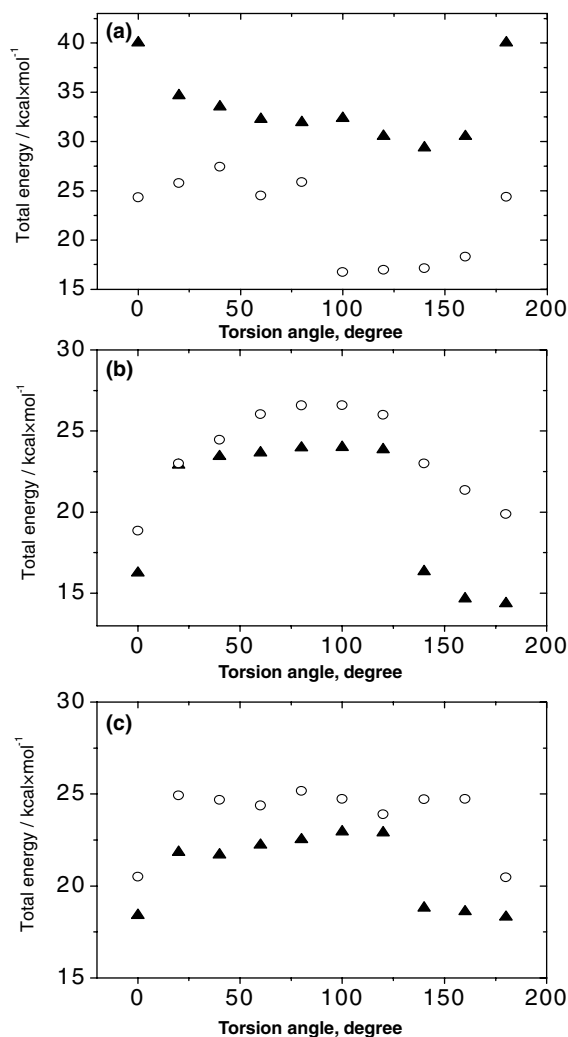


Fig. 5. Energy versus torsion angle between the nitro group and the phenyl ring. (a) *ortho*-nitro derivatives: (○) *o*-NO<sub>2</sub>-*i*Pr, (▲) *o*-NO<sub>2</sub>-Me. (b) *meta*-nitro derivatives: (○) *m*-NO<sub>2</sub>-*i*Pr, (▲) *m*-NO<sub>2</sub>-Me. (c) *para*-nitro derivatives: (○) *p*-NO<sub>2</sub>-*i*Pr, (▲) *p*-NO<sub>2</sub>-Me.

DPP mode. The peaks shift to more negative potentials with increasing pH within the pH 6 and 12. The  $E_p$ /pH plots show two linear segments with a break near to pH 9 for all the studied compounds (Fig. 6). In fast polarography mode, the compounds presented a similar dependence between  $E_{1/2}$  and pH. Table 3 summarizes the slopes of the linear segments and the corresponding breaks for each studied compound.

The limiting currents of the derivatives behave independently of pH variations (Inset Fig. 6). A similar behaviour was observed for the peak current area with pH, indicating the independence of both the kinetic and the reduction mechanism.

Applying Tomes criterion [37], an  $|E_{3/4} - E_{1/4}|$  experimental value was found ranging an average of  $33 \pm 4$  mV at different pHs. This mean value is slightly different from the theoretical value of 28 mV, indicating that the reduction process of the nitrosophenyl 1,4-

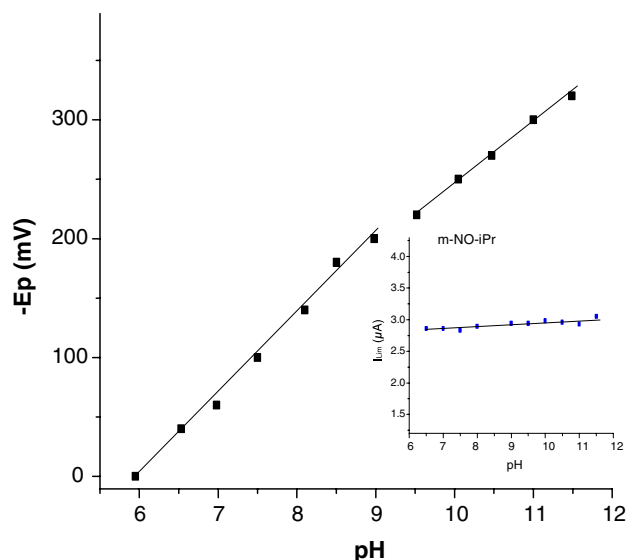


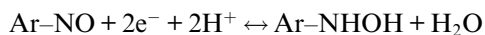
Fig. 6. Dependence of peak potential and limiting current (inset) with pH for a 1 mM solution of *m*-NO-*i*Pr in protic media.

Table 3  
 $\partial E_p/\partial \text{pH}$  values for the linear segments for the C4-nitrosophenyl 1,4-DHPs in protic media

Compound	Segment 1 (pH 6–9)	Segment 2 (pH 9–12)
<i>m</i> -NO- <i>i</i> Pr	-68.0 ( $r = 0.995$ )	-47.0 ( $r = 0.998$ )
<i>p</i> -NO- <i>i</i> Pr	-67.0 ( $r = 0.997$ )	-56.6 ( $r = 0.995$ )
<i>m</i> -NO-Et	-64.6 ( $r = 0.996$ )	-49.3 ( $r = 0.992$ )
<i>p</i> -NO-Et	-65.1 ( $r = 0.996$ )	-50.7 ( $r = 0.995$ )
<i>m</i> -NO-Me	-64.6 ( $r = 0.998$ )	-55.2 ( $r = 0.998$ )
<i>p</i> -NO-Me	-66.9 ( $r = 0.997$ )	-54.4 ( $r = 0.996$ )

DHPs had a non-reversible character, involving two electrons. A comparison of fast polarograms of solutions at the same concentrations and pH of nitroso 1,4-DHP derivatives with the nitrosobenzene solution showed that the ratio of their limiting currents was close to the unity, confirming that the reduction of these nitroso derivatives is due to a 2-electrons, 2-protons overall mechanism as that of nitrosobenzene.

Consequently, according to the polarographic data, the reduction of nitroso derivatives takes place as illustrated by the following equation:



Moreover, a comparison of the electrocapillary curves between buffer solutions with each nitroso derivative in these buffer solutions reveals that there is no adsorption phenomenon, complicating the reduction.

Cyclic voltammetric studies in protic media were conducted at different pH and sweep rates. Under these experimental conditions any signal was registered at  $\text{pH} < 7$ . Fig. 7 displays typical cyclic voltammograms in protic media at different pH corresponding to *p*-NO-Me. As can be seen from the above figure,



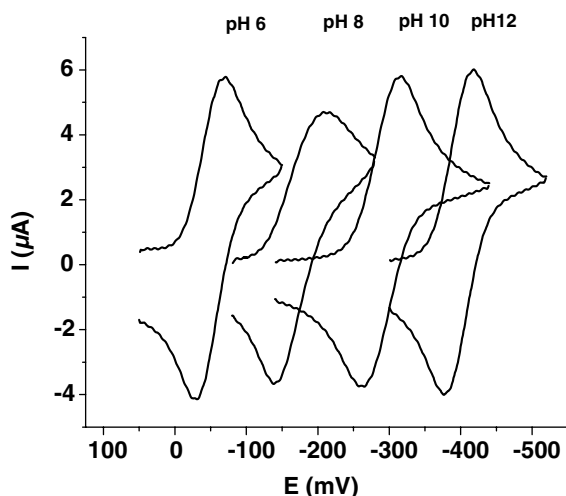
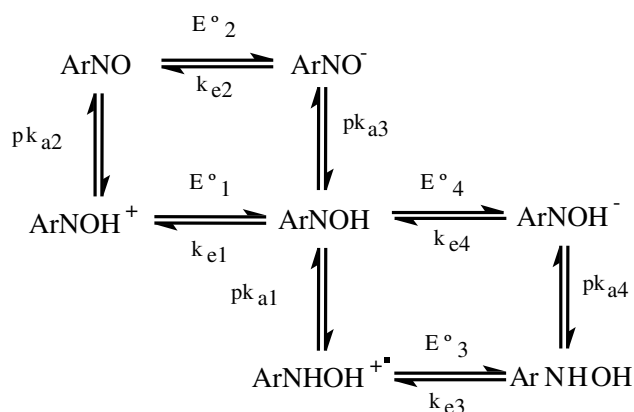


Fig. 7. Cyclic voltammograms in protic media for 1 mM *m*-NO-*i*Pr solutions at different pH.

cyclic voltammograms (CV) appeared as of reversible character. Similar shape and resolution of CV were obtained for the remaining compounds and parallel with pH increase, the potentials of the couples shifted to more negative peak potential values. An average experimental  $\Delta E_p$  value of 40 mV between the anodic and cathodic signals was found.

Since the experimental  $\Delta E_p$  value turned out higher than the theoretical value of 29 mV, it can be concluded that the electron transfer is of quasi-reversible character, involving 2-electrons (EE reaction).

The change of mechanism from pH 7 to pH 9 as supported by the above obtained  $E_p$ /pH voltammetric behavior (Fig. 6, Table 3) turned out to be similar to the previously described for nitrosobenzene [22]. Probably, the different shape of the voltammogram at pH 8 could support this change of mechanism (Fig. 7). Consequently, the existence of a similar mechanism to that of nitrosobenzene in aqueous media can be postulated for these nitroso derivatives. The overall mechanism as proposed by Laviron et al. [22] can be summarized in the following scheme:



Consequently, from the above summarized voltammetric data, the overall reduction process corresponds to the reduction of the nitrosophenyl 1,4-DHP derivatives to give the hydroxylamine derivative, involving 2-electrons and 2-protons, according to the following overall equation:



In conclusion, nitrosophenyl 1,4-DHPs with methyl- and ethyl-groups substituting the 3- and 5-positions did not show significant differences in their reduction potentials. However, the inclusion of a bulky substituent, such as an isopropyl group in those positions on the 1,4-dihydropyridine ring (*m*-NO-*i*Pr and *p*-NO-*i*Pr), caused an increase in the peak potential values, making the reduction more difficult than the other derivatives with  $E_p$  values about 50 mV more negative than *p*-NO-Me (Table 2).

### 3.4. Concluding remarks

A comparison of peak potentials of nitrophenyl 1,4-DHPs with those corresponding nitrosophenyl 1,4-DHPs indicates that reduction of the nitroso derivatives occurs in all instances at more positive potentials than the corresponding nitro derivatives. *Ortho*-nitrophenyl 1,4-DHP derivatives are reduced at more negative potentials (approximately 0.85 V) compared with the remaining derivatives. On the other hand, the differences in the peak potential values for parent either *meta*- or *para*-nitrophenyl 1,4-DHPs compared with the corresponding nitrosophenyl derivatives were greater than 400 mV (Table 2). Also, the effect of the nitro group position in the aromatic ring resulted to be significant in the peak potential values only for *ortho*-nitro position compared with both *meta*- or *para*-nitro position. In the case of nitrosophenyl derivatives no significant differences were found.

The current results could be relevant from the pharmacological and toxicological point of view, since the ease of reduction of nitrosophenyl 1,4-DHPs compared with the parent nitrophenyl derivatives means that the former could generate reactive intermediates such as nitroso radical anion or the hydroxylamine derivative more easily than nitro compounds. In consequence, the highest reactivity of nitroso compounds and their intermediates offers an opportunity to test this type of compounds in pathological conditions in which cytotoxicity is needed to exert therapeutic effects. The findings found here are in line with previous works of in our laboratory [38–40], in which the toxic effects on *Trypanosoma cruzi* epimastigotes cultures were demonstrated for some 1,4-dihydropyridines, which were not dependent on their well-known calcium channel antagonist activity.

Finally, another aspect that should be emphasized is the photodescomposition that some nitrophenyl

1,4-dihydropyridines can suffer, which gives rise to the formation of nitroso derivatives. Such photoproducts could exert toxic effects in humans as previously described for the well-known drug, nifedipine [41]. This drug is photodegraded, producing phototoxic effects which are partly mediated by a nitroso-pyridine derivative (NPD). Furthermore, Hayase et al. [42] isolated various photoproducts of nifedipine from tablets dispensed in pulverized form by hospital prescriptions containing the main photoproduct, 2,6-dimethyl-4-(2-nitrosophenyl)-3,5-pyridine-carboxylic acid dimethyl ester (NPD). More recently [43], we studied the electrochemical and spectroelectrochemical behaviour of NPD, concluding that this photoproduct under certain experimental conditions (mixed and aprotic media) can generate free-radicals. These species reacted significantly with several biological target molecules such as, cysteamine, GSH, N-acetylcysteine, adenine.

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