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Electrochemical Oxidation of 2,3-Dimethylhydroquinone in the Presence of 1,3-Dicarbonyl Compounds

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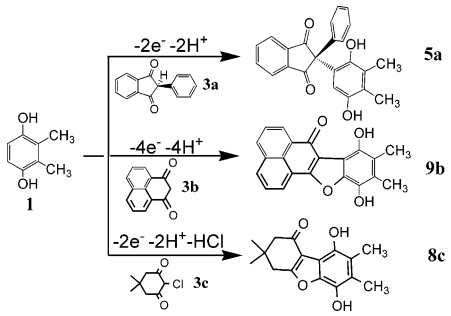
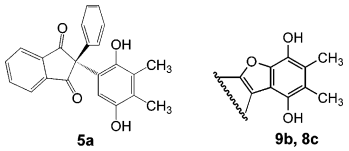


The electrooxidation of 2,3-dimethylhydroquinone (**1**) has been studied in the presence of 2-phenyl-1,3-indandione (**3a**), 3-hydroxy-1*H*-phenalen-1-one (**3b**), and 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3c**) as CH acid nucleophiles in water/acetonitrile (85/15) solution, using cyclic voltammetry and controlled-potential coulometry. The results indicate that *p*-benzoquinone, generated by electrochemically driven oxidation of the 2,3-dimethylhydroquinone (**1**), is scavenged by **3a**−**c**, to give related products (**5a**, **9b**, **8c**) via various electrochemical mechanisms. The electrochemical syntheses of **5a**, **9b**, and **8c** have been successfully performed in one-pot in an undivided cell using an environmentally friendly method with high atomic economy.

In recent years, medicinal properties of benzofuran derivatives have been investigated widely and were shown to be effective as antitumor,[1] anti-depressant,[2] antifungal,[3] anti-hypertensive, and cytotoxic.[4] They are also potent and selective oxytocin antagonists,[5] PDE5 inhibitor for treatment of erectile dysfunction,[6] and H_3 receptor antagonists.[7] On the other hand, it has been reported that some hydroquinone derivatives are active against several types of neoplastic cells[8] or are useful as inhibitors of retrovirus and therapy of aids[9] as well as synthetic intermediates in the manufacturing of food antioxidants[9,10] and antioxidants.[9−11]

With due attention to our experiences on electrochemical synthesis of organic compounds,[12] we thought that synthesis of a new hydroquinone derivative (**5a**) and benzofuran-4,7-diol derivatives (**9b** and **8c**) with both structures of hydroquinone and benzofuran would be useful from the point of view of pharmaceutical properties.



This idea prompted us to investigate the electrochemical oxidation of 2,3-dimethylhydroquinone (**1**) in the presence of some CH acid nucleophiles and represent a facile and one-pot electrochemical method for the synthesis of some new compounds (**5a**, **9b**, and **8c**) in high yield and purity in an undivided cell using an environmentally friendly method.

A cyclic voltammogram of 1.0 mM 2,3-dimethylhydroquinone (**1**) in water/cetonitrile (85/15) solution containing 0.2 M sodium acetate shows one anodic peak (A_1) and the corresponding cathodic peak (C_1) which correspond to the transformation of 2,3-dimethylhydroquinone (**1**) to 2,3-dimethyl-*p*-benzoquinone (**2**) and vice versa within a quasi-reversible two-

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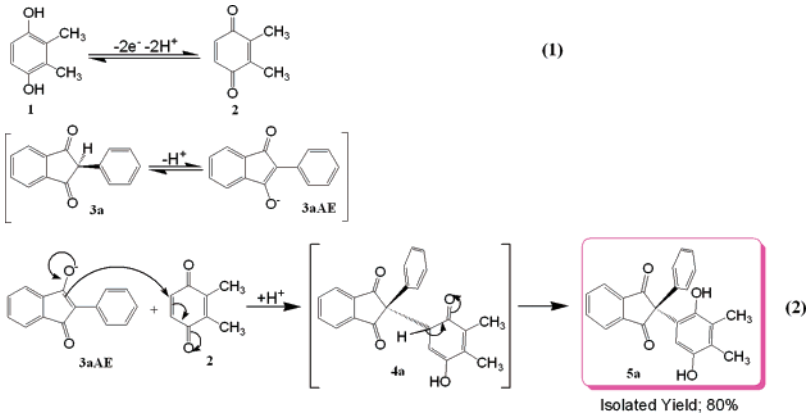
SCHEME 1



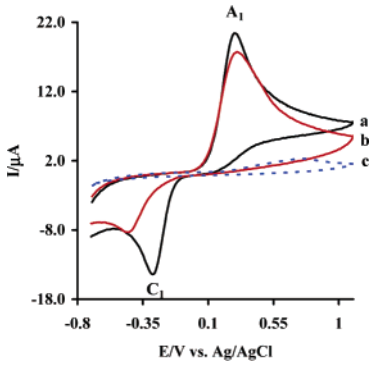


FIGURE 1. Cyclic voltammograms of (a) 1.0 mM 2,3-dimethylhydroquinone (**1**), (b) 1.0 mM 2,3-dimethylhydroquinone (**1**) in the presence of 0.5 mM 2-phenyl-1,3-indandione (**3a**), and (c) 0.5 mM 2-phenyl-1,3-indandione in the absence of **1** at a glassy carbon electrode in water/acetonitrile (85/15) solution containing 0.2 M sodium acetate. Scan rate: 100 mV s^{-1}; $t = 25 \pm 1$ °C.

electron process[13] (Figure 1, curve a). A peak current ratio (I_p^{C1}/I_p^{A1}) of nearly unity, particularly during the recycling of the potential, can be considered as a criterion for the stability of 2,3-dimethyl-*p*-benzoquinone (**2**) produced at the surface of the electrode under the experimental conditions. In other words, any hydroxylation[14] or dimerization[15] reactions are too slow to be observed on the time scale of cyclic voltammetry. The oxidation of 2,3-dimethylhydroquinone (**1**) in the presence of 2-phenyl-1,3-indandione (**3a**) was studied in some detail. Figure 1 (curve b) shows the first cyclic voltammogram obtained for a 1.0 mM solution of **1** in the presence of 0.5 mM 2-phenyl-1,3-indandione (**3a**). The voltammogram exhibits one anodic peak (A_1) and one cathodic peak (C_1) that shows decreasing in comparison to the cathodic peak of 2,3-dimethylhydroquinone (**1**) in the absence of **3a**. In this figure, curve c is the voltammogram of **3a** in the absence of **1**.

Furthermore, we examine the effects of potential scan rate and concentration of 2-phenyl-1,3-indandione (**3a**) on the peak current ratio (I_p^{C1}/I_p^{A1}) in cyclic voltammograms of 2,3-dimethylhydroquinone (**1**) in the presence of 2-phenyl-1,3-indandione (**3a**). It is seen that, proportional to the increasing of the potential scan rate (Figure 2, curves a−f) or decreasing of 2-phenyl-1,3-indandione (**3a**) to the 2,3-dimethylhydroquinone (**1**) concentration ratio, the peak current ratio (I_p^{C1}/I_p^{A1}) increases. A plot of the peak current ratio (I_p^{C1}/I_p^{A1}) versus the scan rate for a mixture of 2,3-dimethylhydroquinone (**1**) and 2-phenyl-1,3-indandione (**3a**) confirms the reactivity of *p*-benzoquinone (**2**) toward 2-phenyl-1,3-indandione (**3a**) (Figure 2, curve g).

Controlled-potential coulometry was performed in a solution containing 0.25 mmol of 2,3-dimethylhydroquinone (**1**) and 0.25 mmol of 2-phenyl-1,3-indandione (**3a**) at 0.30 V versus 3 M Ag/AgCl. Cyclic voltammetric analysis, carried out during electrolysis, shows the disappearance of the A_1 peak. All anodic and cathodic peaks disappear when the charge consumption becomes about $2e^-$ per molecule of 2,3-dimethylhydroquinone (**1**). Using the voltammetric and coulometric data, we propose the pathway in Scheme 1 for the electrooxidation of 2,3-dimethylhydroquinone (**1**) in the presence of 2-phenyl-1,3-indandione (**3a**). According to our results, the final product (**5a**) is obtained via addition reaction of **3a** to *p*-benzoquinone (**2a**) as a Michael acceptor (Scheme 1, eq 2). The overoxidation of **5a** was circumvented during the preparative reaction because of the insolubility of it in water/acetonitrile (85/15) solution.

The electrooxidation of 2,3-dimethylhydroquinone (**1**) in the presence of 3-hydroxy-1*H*-phenalen-1-one (**3b**) as a nucleophile in water/acetonitrile (85/15) solution containing 0.2 M sodium acetate using cyclic voltammetry and controlled-potential coulometry was studied in some detail. The cyclic voltammograms show a decrease in cathodic peak of 2,3-dimethylhydroquinone (**1**) in the presence of **3b** in comparison to **1** in the absence of **3b**. Increasing the concentration of **3b** and/or decreasing the scan rate causes an enhancement in extent of chemical reaction during the time scale of cyclic voltammetry, which appears as increasing in peak current ratio ($I_p^{anodic}/I_p^{cathodic}$). The most important difference between this case and the previous case is the number of transferred electrons during controlled-potential coulometry. The results show that, contrary to the previous case, the consumed charge is about $4e^-$ per molecule of 2,3-dimethylhydroquinone (**1**). This is related to two two-electrons transfer processes (Scheme 2, eqs 2 and 4) giving rise to the presence of two acidic protons in **3b** (Figure 3).

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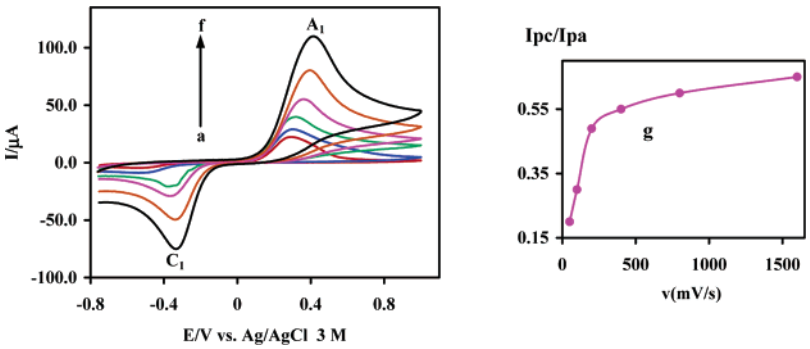
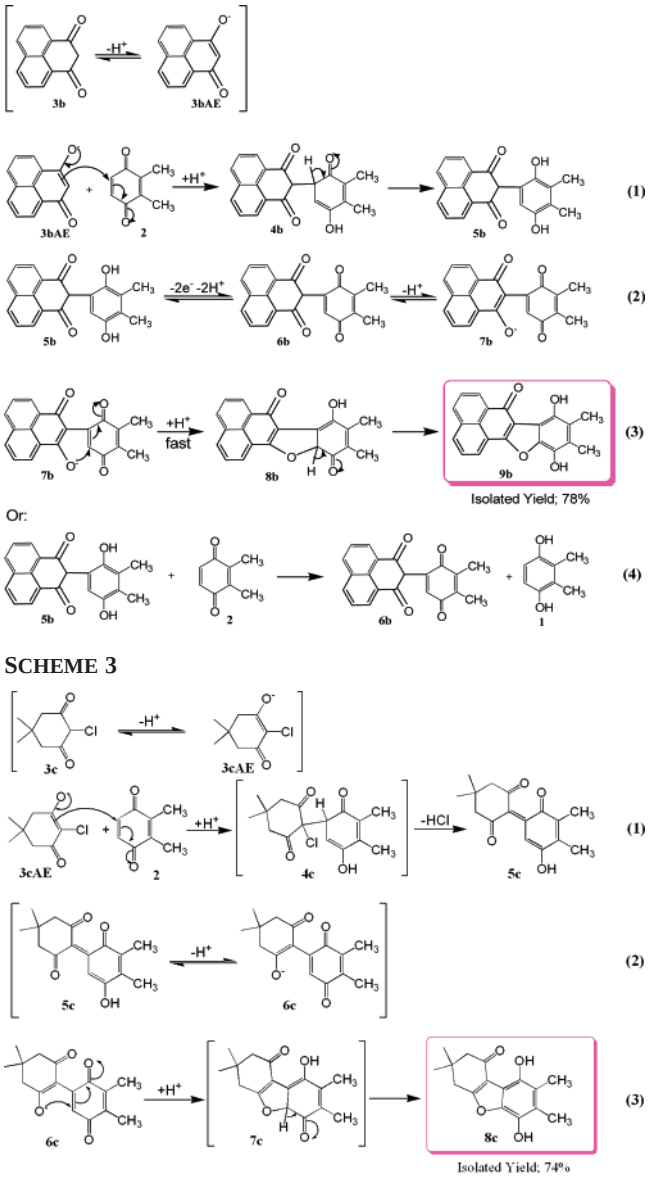


FIGURE 2. Typical cyclic voltammograms of 1.0 mM 2,3-dimethylhydroquinone (**1**) in the presence of 1.0 mM 2-phenyl-1,3-indandione (**3a**) at a glassy carbon electrode in water/acetonitrile (85/15) solution containing 0.2 M sodium acetate. Scan rates for (a)−(f) are: 50, 100, 200, 400, 800, and 1600 mV s^{-1}, respectively. (g) Variation of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate, $t = 25 \pm 1$ °C.

SCHEME 2



SCHEME 3

These coulometry and voltammetry results allow us to propose an ECEC mechanism[12,16] indicated in Scheme 2 for the electrooxidation of **1** in the presence of 3-hydroxy-1*H*-phenalen-1-one (**3b**).

According to the obtained results, the intermolecular (Scheme 2, eq 1) and intramolecular (Scheme 2, eq 3) Michael addition reactions of anion enolate **3bAE** to *p*-benzoquinone (**2**) is faster than the other secondary reactions, leading to the final product **9b**. The oxidation of intermediate **5b** is easier than the oxidation of the parent starting molecule (2,3-dimethylhydroquinone) by virtue of the presence of an electron-donating group. The reaction product (**9b**) can also be oxidized at a lower potential than the starting compound (**1**). However, the overoxidation of product **9b** was circumvented during the preparative reaction because of the insolubility of the product in the water/acetonitrile (85/15) mixture. Alternatively, it is possible that the intermediate **5b** can also be oxidized during reaction with **2** (Scheme 2, eq 4).

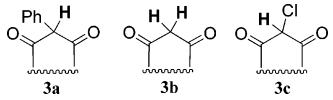


FIGURE 3.

The electrochemical oxidation of 2,3-dimethylhydroquinone (**1**) in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3c**) as a nucleophile in a water/acetonitrile (85/15) solution containing 0.2 M sodium acetate using cyclic voltammetry and controlled-potential coulometry was studied in some detail. This nucleophile (**3c**) has one acidic electron (Figure 3), and the electrooxidation of **1** in the presence of it proceeds in a way similar to that of 2-phenyl-1,3-indandione (**3a**). In this case, the final product is obtained after consumption of $2e^-$ per molecule of 2,3-dimethylhydroquinone (**1**), but contrary to **3a**, the final product (**8c**) is a benzofuran derivative. The coulometry and voltammetry results, along with ^{1}HNMR, ^{13}CNMR, IR, and MS data of the obtained product, allow us to propose the following mechanism for the electrooxidation of **1** in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione.

In conclusion, the results of this work show that 2,3-dimethylhydroquinone (**1**) is oxidized to its respective *p*-benzoquinone (**2**). The formed *p*-benzoquinone is attacked by nucleophiles **3a**−**c** to form final products **5a**, **9b**, and **8c**. We observed an interesting diversity in the electrooxidation mechanisms and products of 2,3-dimethylhydroquinone (**1**) in the presence of **3a**−**c**. In the case of **3a**, the final product (**5a**) is a hydroquinone derivative that was obtained after consumption of $2e^-$ per molecule **1**. In the case of **3b**, the final product (**9b**) is a benzofuran derivative that was obtained after consumption

(16) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods*, 2nd ed.; Wiley: New York, 2001; p 497.

of 4e$^-$ per molecule **1**, via intermolecular and intramolecular Michael addition reactions. And in the case of **3c**, the final product **8b**, which is also a benzofuran derivative, was obtained via an intermolecular Michael addition reaction and followed by elimination of HCl, after consumption of 2e$^-$ per molecule **1**. The overall reactions mechanism for anodic oxidation of 2,3-dimethylhydroquinone (**1**) in the presence of **3a**−**c** are presented in Schemes 1−3. These mechanisms show a good diversity in anodic oxidation of **1** in the presence of **3a**−**c**.

Experimental Section

Apparatus and Reagents. Reaction equipment is described in the Supporting Information. All chemicals (2,3-dimethylhydroquinone, 2-pheny-1,3-indandione, 2-chloro-5,5-dimethyl-1,3-cyclohexanedion, and 3-hydroxy-1*H*-phenalen-1-one) were reagent-grade materials, and sodium acetate was pro-analysis grade. These chemicals were used without further purification.

Electroorganic Synthesis of 5a, 9b, and 8c. In a typical procedure, 80 mL of sodium acetate solution (0.2 M) was pre-electrolyzed at 0.30 V vs Ag/AgCl 3 M in an undivided cell, and then 1 mmol of 2,3-dimethylhydroquinone (**1**) and 1 mmol of **3a**−**c** were added to the cell. The electrolysis (at 0.30 V vs Ag/AgCl 3 M) was terminated when the decay of the current became more than 95%. The process was interrupted during the electrolysis, and the graphite anode was washed in acetone to reactivate it. At the end of electrolysis, a few drops of acetic acid added were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and washed with water. After washing, products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. The isolated yields of **5a**, **9b**, and **8c** after washing are reported in Schemes 1−3.

2-(2,5-Dihydroxy-3,4-dimethylphenyl)-2-phenyl-2*H*-indene-1,3-dione (5a) ($C_{23}H_{18}O_4$): mp 216−218 °C. ^{1}H NMR, δ ppm (300 MHz DMSO d_6): 2.01 (s, 3H, methyl), 2.03 (s, 3H, methyl), 6.56 (s, 1H, aromatic hydroquinone ring), 6.92, 7.29 (dd, J = 6 Hz, 4H, aromatic), 7.64−8.03 (m, 5H, aromatic + 1H −OH), 8.92 (s, 1H, −OH). ^{13}CNMR, δ ppm (300 MHz DMSO-d_6): 12.4, 12.7, 70.9, 109.0, 113.4, 119.3, 122.4, 123.4, 125.4, 127.6, 128.3, 129.9, 131.2, 135.5, 136.9, 137.8, 148.9, 150.3, 152.5, 200.2, 201.7. IR$_{(KBr)}$: 3535, 3460, 2910, 1710, 1599, 1495, 1452, 1376, 1289, 1223, 1198, 1080, 1055, 878, 834, 747, 697 cm^{-1}. MS: *m*/*e* (relative intensity); 358 (M$^+$, 100), 313 (15), 285 (20), 269 (14), 225 (27), 189 (40), 165 (50), 76 (30).

8,11-Dihydroxy-9,10-dimethyl-12-oxaindeno[2,1-a]phenalen-7-one (9b) ($C_{21}H_{14}O_4$): mp 270−273 °C. ^{1}H NMR, δ ppm (300 MHz DMSO d_6): 2.02 (s, 3H, methyl), 2.09 (s, 3H, methyl), 7.61−8.22 (m, 6H, aromatic), 8.36 (br, 2H, −OH). ^{13}C NMR, δ ppm (300 MHz DMSO-d_6): 11.8, 12.4, 112.3, 125.8, 126.0, 126.6, 126.8, 127.9, 131.2, 131.5, 133.1, 136.8, 139.7, 140.2, 141.2, 141.8, 184.7, 187.1. IR$_{(KBr)}$: 3536, 3059, 1648, 1545, 1433, 1385, 1199, 1156, 1105, 846, 798, 776, 666 cm^{-1}. MS: *m*/*e* (relative intensity); 330 (M$^+$, 100), 329 (99), 315 (19), 196 (16), 163 (16).

6,9-Dihydroxy-3,3,7,8-tetramethyl-3,4-dihydro-2*H*-dibenzofuran-1-one (8c) ($C_{16}H_{18}O_4$): mp 180−182 °C. ^{1}H NMR, δ ppm (300 MHz DMSO d_6): 1.09 (s, 6H, methyl), 2.08 (s, 3H, methyl), 2.12 (s, 3H, methyl), 2.34 (s, 2H, methylene), 2.39 (s, 2H, methylene), 7.15 (s, 1H, −OH), 9.31 (s, 1H, −OH). ^{13}C NMR, δ ppm (300 MHz DMSO-d_6): 12.3, 12.5, 28.5, 35.4, 37.2, 51.9, 102.8, 115.0, 120.5, 120.9, 148.2, 153.1, 170.1, 194.3. IR$_{(KBr)}$: 3391, 3290, 2956, 1648, 1452, 1374, 1081, 863 cm^{-1}. MS: *m*/*e* (relative intensity); 274 (M$^+$, 40), 258 (60), 230 (20), 202 (100), 174 (60), 149 (25), 91 (30), 69 (45), 54 (70), 41 (65).

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Supporting Information Available: MS, IR, ^{1}H, and ^{13}C NMR spectra for compounds **5a**, **9b**, and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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