Electrochemical Oxidation of Catechols in the Presence of Ethyl-2-chloroacetoacetate. Synthesis and Mechanistic Study

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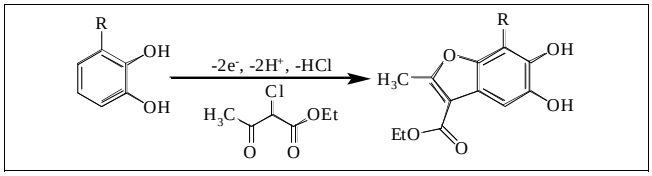

Electrochemical oxidation of catechol and some of 3-substituted catechols (**1a-c**) has been studied in the presence of ethyl-2-chloroacetoacetate (**3**) in water/acetonitrile (90:10) solution using cyclic voltammetry and controlled-potential coulometry. The results indicate that the quinones derived from catechols (**1a-c**) participate in Michael addition reactions with ethyl-2-chloroacetoacetate (**3**), with consumption of only two electrons per molecule of **1**, to form the corresponding benzofurans (**10a-c**). The electrochemical synthesis of benzofurans (**10a-c**) has been successfully performed at a carbon rod electrode and in an undivided cell with good yields and purity. A new two-electron mechanism for the electrode process is proposed.

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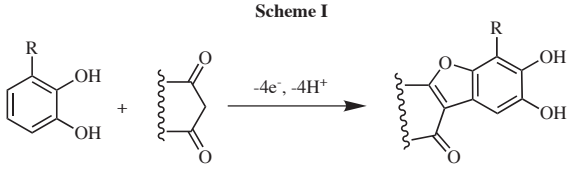
Introduction.

Due to their widespread pharmacological uses, the syntheses and pharmacological properties of benzofuran derivatives have been extensively investigated [1-6]. The anodic oxidation of catechols without [7-9] and with acceptors [10-12] has been a well documented field of research which can be successfully used in the electrosynthesis of many pharmaceutically important compounds. In this direction, we have recently investigated the electrochemical oxidation of catechols in the presence of barbituric acids, acetylacetone and dimedone as nucleophiles. The results indicated the formation of benzofuran derivatives *via* inter and intramolecular Micheal's addition reactions with consumption of four electrons per molecule of catechols (Scheme I) [13-15].

Scheme I



The importance of benzofurans has encouraged us to further synthesize a number of these compounds. In this work, the electrochemical oxidation of catechols (**1a-c**) has been studied in the presence of ethyl-2-chloroacetoacetate (**3**) as a possible nucleophile. The work describes a facile one-pot electrochemical method for the synthesis of some new benzofuran derivatives and proposes a novel mechanism for the electrode process involved.

Results and Discussion.

Cyclic voltammetry of a 2 mM solution of 3-methoxycatechol (**1c**) in water/acetonitrile (90/10 v/v) solution containing 0.2 M sodium acetate as supporting electrolyte shows one anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of **1c** to *o*-benzoquinone (**2c**) and *vice versa* within a quasi-reversible two electron reaction (Figure 1, curve a). A peak current ratio (I_p^{Cl} /I_p^{Al}) of nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-quinones produced at the surface of the electrode under the experimental conditions. Any hydroxylation [14,16-18] or dimerization [8,19] reaction is too slow to be observed on the time scale of cyclic voltammetry. The oxidation of 3-methoxycatechol (**1c**) in the presence of ethyl-2-chloroacetoacetate (**3**) as a nucleophile was studied in detail (Figure 1, curve b). The resulting cyclic voltammogram exhibits two anodic peaks (A_1 and A_2) and a new cathodic peak (C_2) versus 3 *M* Ag/AgCl, while the cathodic counterpart (C_1) of the anodic peak A_1 disappeared. The positive shift of the A_1 peak in the presence of ethyl-2-chloroacetoacetate is probably due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of the electrode process that was enhanced during the repetitive cycling of the potential (Figure 1,

curve c) [8,13-15]. In this figure, curve d is the cyclic voltammogram of ethyl-2-chloroacetoacetate (**3**). The voltammogram shows an irreversible oxidation peak situated at more positive potentials. This behaviour can be attributed to the oxidation of anion derived from the deprotonation of **3**, producing the coupled product [20].

Furthermore, it is seen that, proportionally to augmentation of the potential scan rate, the C_1 peak appeared and its current increased. In other words, the cathodic peak current ratio (I_p^{C1}/I_p^{C2}) increases with increasing potential scan rate. Moreover, proportional to increasing potential scan rate, the anodic peak current ratio (I_p^{A1}/I_p^{A2}) increases (Figure 2, curves a-g). A similar situation is observed when the **3** to **1c** concentration ratio decreased. In addition, a plot of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate for a mixture of 3-methoxycatechol (**1c**) and ethyl-2-chloroacetoacetate (**3**) in water/acetonitrile (90:10) containing 0.2 *M* sodium acetate, confirms the reactivity of **2c** toward **3**, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Figure 3). On the other hand, the peak current function for A_1 peak ($I_p^{A1}/v^{1/2}$), decrease with increasing the scan rate (Figure 3); such behavior is indicative of an EC process [21].

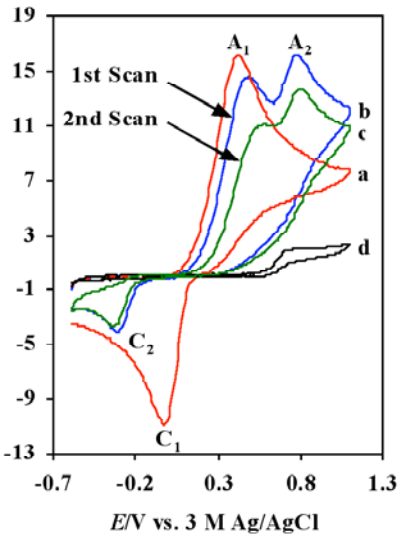


Figure 1. Cyclic voltamogram of 2 mM 3-methoxycatechol: (a), in the absence of ethyl-2-chloroacetoacetate, (b) in the presence of 2 mM ethyl-2-chloroacetoacetate (first cycle), (c) in the presence of 2 mM ethyl-2-chloroacetoacetate (second cycle). (d) Cyclic voltamogram of 2 mM ethyl-2-chloroacetoacetate in the absence of 3-methoxycatechol, at glassy carbon electrode, in water/acetonitrile (90:10) solution containing 0.2 *M* sodium acetate. Scan rate, 100 mVs^{-1}; t, ambient temperature.

Controlled potential coulometry was performed in water/acetonitrile (90:10) containing 0.2 *M* sodium acetate, 0.25 mmol of **1c** and 0.25 mmol of ethyl-2-chloroacetoacetate (**3**) at 0.4 V versus 3 *M* Ag/AgCl. The electrolysis progress was monitored by cyclic voltammetry. It was observed that, proportional to the advancement of coulometry, the anodic peaks $A_1$and A_2 were diminished. When the charge consumption reaches 2 electrons per molecule of **1c**, the final voltammogram does not show any anodic and cathodic peaks. These observations allow us to propose the pathways shown in Scheme II for the electrooxidation of 3-methoxycatechol (**1c**) in the presence of ethyl-2-chloroacetoacetate (**3**).

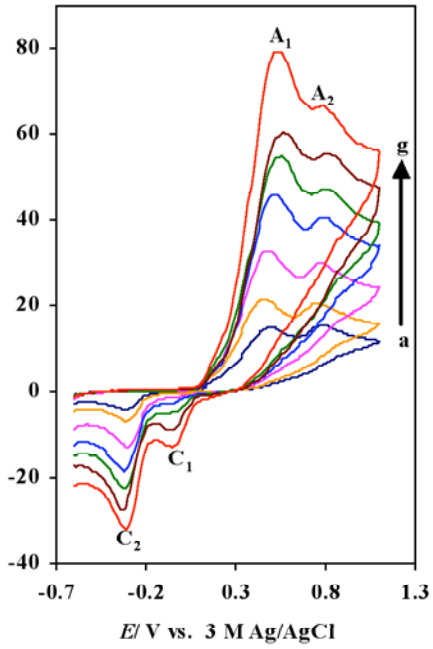


Figure 2. Typical cyclic voltammograms of 2 mM 3-methoxycatechol (**1c**) in the presence of 2 mM ethyl-2-chloroacetoacetate (**3**) in water/acetonitrile (90:10) containing 0.2 *M* sodium acetate at a glassy carbon electrode (1.8 mm diameter) at various scan rates. Scan rates from (a) to (g) are 100, 200, 500, 1000, 1500, 2000 and 3000 mV s^{-1}, respectively.

According to our results, it seems that 1,4-Michael addition reaction of ethyl-2-chloroacetoacetate to *o*-benzoquinones (**2c**) (Eq. (3)) is faster than other secondary reactions, leading to intermediate **4c**, that in the next step is converted to **5c**, during elimination reaction *via* removal of hydrogen chloride. **5c** is in quinone methide form that is in equilibrium with quinone form (**6c**) [22,23], enol (**7c**) and enolate form (**8c**). The intramolecular Michael addition reaction of enolate **8c** causes the formation of a final product **10c**. The over-oxidation of **10c** was circumvented during the preparative reaction because of the more difficult oxidation of dihydroxybenzofurane formed, as well as the insolubility of the product in sodium acetate solution medium.

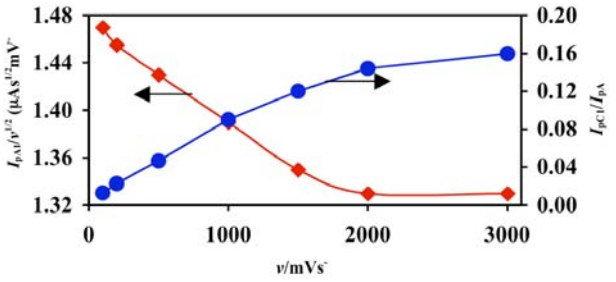
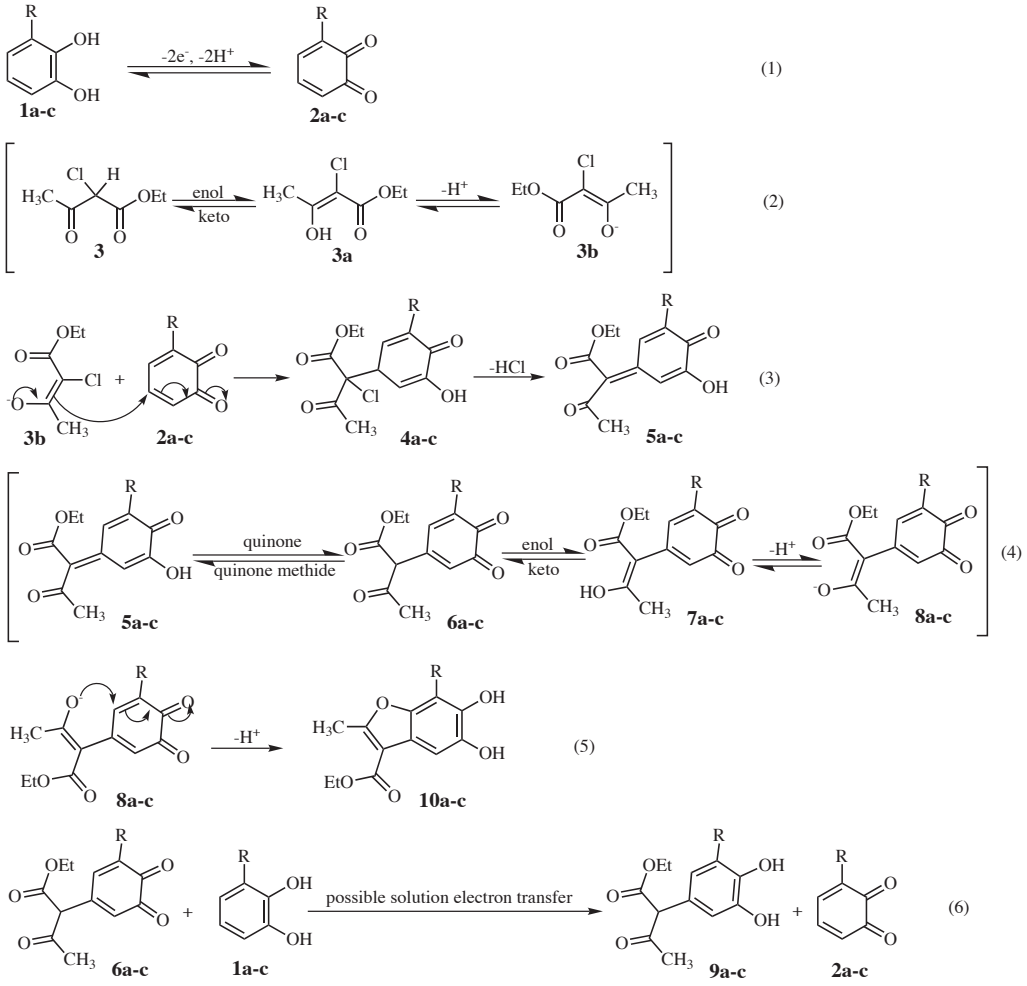


Figure 3. (●) Variation of peak current ratios (I_p^{C1}/I_p^{A1}) versus scan rates, (■) variation of peak current function for A_1 peak ($I_p^{A1}/v^{1/2}$) versus scan rates. t = ambient temperature.

According to the proposed mechanism, the new anodic peak A_2 would be related to electrooxidation of **9c** to **6c** and the new cathodic peak C_2 is the cathodic counterparts of A_2 and is related to electroreduction of **6c** to **9c** (Scheme III).

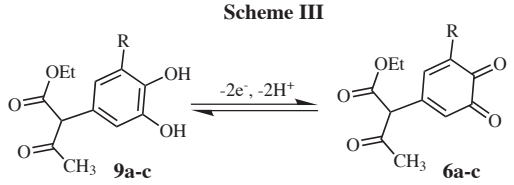
The same results were observed for oxidation of **1a** and **1b** in presence ethyl-2-chloroacetoacetate (**3**). The existence of a methyl or methoxy group at the C-3 position of 3-methoxycatechol (**1c**) or 3-methylcatechol (**1b**) probably causes the Michael acceptors (**2c** and **2b**) to be attacked by the anion enolate ethyl-2-chloroacetoacetate (**3**) at the C-4 and/or C-5 positions to yield two types of product in each case. Furthermore, because of asymmetry in structure of ethyl-2-chloroacetoacetate (**3**), there are two possibilities for enol formation, which yield two types of product in each case (Figure 4). The experimental and empirically calculated [24] ^{13}C NMR results for the methyl carbon in the catechol ring and for the carbonyl carbon of the product, and for the suggested possible structures are shown in Table 1. According to the ^{13}C NMR results, we suggest that *o*-benzoquinones **2b** and **2c** are attacked in all possibilities only in the C-5 position by anion enolate **3b** leading to the formation of the products **10b** and **10c**, respectively.

Scheme II



R = H, 1a, 2a, 4a, 5a, 6a, 7a, 8a, 9a, 10a
R = CH_3, 1b, 2b, 4b, 5b, 6b, 7b, 8b, 9b, 10b
R = OCH_3, 1c, 2c, 4c, 5c, 6c, 7c, 8c, 9c, 10c

Scheme III



The results of this work show that catechols are oxidized in water/acetonitrile (90:10) to their respective *o*-quinones. The quinones are then attacked by the anion of ethyl-2-chloroacetoacetate (**3**) to form benzofuran derivatives. The overall reaction mechanism for anodic oxidation of catechols in the presence of ethyl-2-chloroacetoacetate (**3**) as a nucleophile is presented in Scheme II. The great advantage of present work is development of a one-pot electrolytic method for the synthesis of new benzofuran derivatives (**10a-c**) as final products in high yield and purity, with only $2e^-$ consumption per each molecule of the catechols.

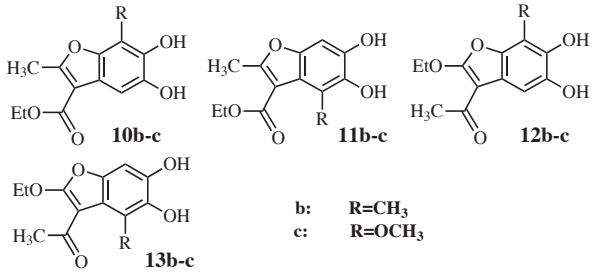


Figure 4

Table 1

Experimental and Calculated ^{13}C NMR Data for Methyl and Carbonyl Carbons

Type	^{13}C NMR data (ppm)	
	Methyl carbon in catechol ring	Carbonyl carbon
Experimental	9.3	164.3
Calculated for **10b**	8.6	159.5
Calculated for **11b**	12.6	159.5
Calculated for **12b**	8.6	194.2
Calculated for **13b**	12.6	194.2

EXPERIMENTAL

Apparatus and Reagents.

The cyclic voltammetric experiments were carried out on a computerized Metrohm voltammetric analyzer model 747-VA. The controlled-potential coulometry and bulk electrolysis were performed using an Autolab model PGSTAT20 potentiostat/ galvanostat. The working electrode used in voltammetric experiments was a glassy carbon disc (1.8 mm diameter, Metrohm) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and bulk electrolysis was an assembly of four carbon rods (38 cm^2, Azar Electrode Company) and a large surface platinum gauze constituted the counter electrode. The working electrode potentials were measured versus a 3 *M* Ag/AgCl reference electrode.

The spectroscopic characterizations of the compounds synthesized were performed on an IFS66 Bruker FT-IR spectrometer, a QP-1100EX Shimadzu Mass spectrometer and an AQS-300 MHz-Avance Bruker NMR spectrometer.

3-Methylcatechol was purchased from Aldrich. All other chemicals including catechol, 3-methoxycatechol, ethyl-2-chloroacetoacetate, sodium acetate, acetonitrile, *etc.* were of reagent and pro-analysis grades from Merck. These chemicals were used without any further purification

General Procedure for Synthesis.

A solution (*ca.* 100 mL) of sodium acetate in water/ acetonitrile (90:10) (0.2 *M*) containing 1 mmol of catechols (**1a**-**c**) and ethyl-2-chloroacetoacetate (**3**) (1 mmol) was electrolyzed in an undivided cell at the selected potential (see Table 2). The electrolysis was terminated when the decay of the current became more than 95%. Because of the formation of a thin film of product at the surface of the electrode, the process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and recrystallized from a mixture of methanol-ethylacetate. After recrystallization, the resulting products were characterized by IR, ^1H NMR, ^{13}C NMR and MS.

Ethyl-5,6-dihydroxy-2-methylbenzofuran-3-carboxylate (**10a**).

Ir (potassium bromide) 3440, 3265, 2980, 1669, 1585, 1486, 1423, 1314, 1258, 1125, 1025, 947, 867, 841, 683 cm^{-1}. ^1H nmr (DMSO-d_6) δ (ppm) 1.35 (t, 3H, methyl); 2.63 (s, 3H, methyl); 4.31 (q, 2H, methylene); 6.92 (s, 1H, aromatic); 7.22 (s, 1H,

Table 2

Electroanalytical, Physical and Analytical Data of Compounds

Compound	Applied Potential V vs 3 *M* Ag/AgCl	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd./Found	
					C	H
10a	0.45	180-182	69	$C_{12}H_{12}O_5$	61.01	5.12
					60.87	5.39
10b	0.40	175-177	80	$C_{13}H_{14}O_5$	62.39	5.64
					62.03	5.41
10c	0.40	170-172	79	$C_{13}H_{14}O_6$	58.64	5.30
					58.95	5.32

aromatic); 8.99 (broad, 1H, hydroxyl) 9.09 (broad, 1H, hydroxyl). ^{13}C nmr (DMSO-d_6) δ (ppm) 14.5, 14.7, 60.3, 98.3, 106.3, 108.6, 117.3, 143.8, 144.7, 147.5, 161.5, 164.2. ms: m/z (relative intensity): 236 (M^+) (100), 207 (95), 191 (70), 162 (40), 135 (30), 43 (12).

Ethyl-5,6-dihydroxy-2,7-dimethylbenzofuran-3-carboxylate (**10b**).

Ir (potassium bromide) 3480, 3254, 2988, 1669, 1582, 1524, 1423, 1315, 1133, 1074, 1011, 854, 786, 673 cm^{-1}. ^{1}H nmr (DMSO-d_6) δ (ppm) 1.36 (t, 3H, methyl); 2.25 (s, 3H, methyl); 2.66 (s, 3H, methyl); 4.31 (q, 2H, methylene); 7.12 (s, 1H, aromatic); 8.37 (broad, 1H, hydroxyl); 9.26 (broad, 1H, hydroxyl). ^{13}C nmr (DMSO-d_6) δ (ppm) 9.3, 14.6, 14.7, 60.2, 103.3, 107.6, 108.8, 116.4, 142.3, 143.5, 147.1, 161.4, 164.4. ms: m/z (relative intensity): 250 (M^+) (100), 221 (77), 205 (26), 177 (15), 157 (10), 43 (10).

Ethyl-5,6-dihydroxy-7-methoxy-2-methylbenzofuran-3-carboxylate (**10c**).

Ir (potassium bromide) 3501, 3326, 2983, 1667, 1619, 1517, 1458, 1311, 1208, 1149, 1087, 846, 784, 685 cm^{-1}. ^{1}H nmr (DMSO-d_6) δ (ppm) 1.35 (t, 3H, methyl); 2.67 (s, 3H, methyl); 3.94 (s, 3H, methyl); 4.32 (q, 2H, methylene); 7.00 (s, 1H, aromatic); 8.61 (broad, 1H, hydroxyl); 9.12 (broad, 1H, hydroxyl). ^{13}C nmr (DMSO-d_6) δ (ppm) 14.6, 14.7, 56.4, 67.3, 104.4, 110.2, 124.5, 127.2, 137.6, 138.8, 141.3, 146.3, 148.8. ms: m/z (relative intensity): 266 (M^+) (100), 237 (60), 221 (30), 205 (10), 108 (30).

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