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# An Efficient Electrochemical Method for the Synthesis of Quinoxaline-dione Derivatives from Oxidation of Catechols in the Presence of $N^1$, $N^2$-dibenzylethane-1,2-diamine

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A series of 1,4-dibenzyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione derivatives (**6a-6c**) were electrosynthesized. In the present work, electrochemical oxidation of catechols **1a-1d** in the presence of the $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) as a nucleophile, has been studied in aqueous solutions using cyclic voltammetry and controlled-potential coulometry (CPC) methods. Various parameters such as the applied potential, pH of the electrolytic solution, cell configuration and also purification techniques, were carried out to optimize the yields of corresponding products. New quinoxaline-6,7-dione derivatives were synthesized in excellent yield using an electrochemical procedure coupled with a Schiff base as a facile, efficient and practical method.
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Organic electrochemical synthesis in aqueous medium provides an alternative strategy for the transformation of *o*-benzoquinones. Because most of *o*-benzoquinones are unstable, they are generally prepared in situ from their precursors, namely, catechols and 2-methoxyphenols. Catechols can be oxidized electrochemically to the corresponding highly active *o*-benzoquinones, followed by a Michael addition reaction when nucleophiles are present in the system.[1] Tabakovic and co-workers have shown that *o*-benzoquinone can react with nucleophiles such as 4-hydroxycoumarin and dimedone to form the heterocyclic compounds.[2,3] Moreover, Zhang and Dryhurst have reported that *o*-benzoquinone derived from oxidation of tetrahydropapaveroline can be attacked by glutathione to yield the mono and bis-glutathionyl compounds.[4] In this direction, we have shown that electrochemically generated *o*-quinones can be attacked by a variety of nucleophiles such as barbituric acid derivatives,[5] acetylacetone,[6] 2-mercaptobenzoxazole,[7] azide ion,[8] 3-hydroxy-1*H*-phenalen-1-one,[9] and Meldrum's acid derivatives[10] and described the efficient and one-pot electrochemical methods for the synthesis of some new organic compounds.

Heterocyclic quinones containing a nitrogen atom are known to possess antibacterial[11–13] antifungalous,[14–16] antioxidant,[17] anticarcinogenic[18,19] and cytotoxic activities.[20,21] Quinoxaline derivatives are nitrogen-containing heterocyclic compounds, and their importance has been reported in the literature. Quinoxaline derivatives constitute the basis of many insecticides, fungicides and herbicides and are important in human health and as receptor antagonists.[22–24] These are useful as intermediates for many target molecules in organic synthesis and as synthons. Many synthetic routes have been developed for the synthesis of quinoxaline derivatives. The most common method is the condensation of an aromatic 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid.[25] However, many improved methods have been reported for the synthesis of quinoxalines using a microwave,[26,27] solid phase synthesis[28,29] and electrochemical methods electrochemical methods.[30,31] In addition, bi-catalyzed (bismuth and copper) syntheses were also reported.[32] Many of these methods suffer from one or more limitations such as harsh conditions, long reaction times, critical product isolation procedures, co-occurrence of several side products and low yields.

The development of an effective method for the electrochemical synthesis of quinoxalines is still an important challenge. There have been several reports[33–36] on some quinoxalinedione derivatives that exhibit antibacterial[33] and antimalarial[34] effects and antiasthmatic and antiallergic activity.[35] In view of the vast biological importance of quinoxaline-6,7-dione derivatives, we decided to synthesize new quinoxaline-6,7-dione derivatives in excellent yield using an electrochemical procedure coupled with a Schiff base as a facile, efficient and practical method.

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## Experimental

*Apparatus.*— Cyclic voltammetry (CV) and controlled-potential coulometry were performed using an Autolab model PGSTAT 302N potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disk from France Radiometer Analytical (1.8 mm diameter). The glassy carbon was polished with polishing cloth before each measurement. A platinum wire was used as a counter electrode and the reference was a saturated calomel electrode (SCE). All electrodes for CV experiments were from France Radiometer Analytical. An undivided cell was used for CPC.[37] The working electrode potentials versus the SCE were measured. The SCE references and carbon rods were placed together, and their distance from the counter electrode was approximately 20 mm. The applied potential throughout CPC vs. SCE was controlled by the potentiostat. During electrolysis, a magnetic stirrer was used.

*Reagents.*— The catechols (catechol, 3-methoxycatechol, 3-methylcatechol and 3,4-dihydroxybenzoic acid) were reagent-grade materials from Aldrich. The $KH_2PO_4$, $K_2HPO_4$ and other acids and bases were of pro-analysis grade from E. Merck. Benzaldehyde, 99% and ethylenediamine were purchased from Aldrich. These chemicals were used without further purification. The reagents and solvents used in this study were of analytical grade and were used without further purification.

*Organic synthesis of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**).*— In a typical procedure, benzaldehyde (2.12 g, 20 mmol) and ethylenediamine (0.60 g, 10 mmol) were mixed in an appropriate beaker in 100 mL MeOH. The obtained mixture was stirred overnight at room temperature, and then sodium borohydride (3.02 g, 80 mmol) was added. The mixture was refluxed for 2–3 hours, cooled and poured into 250 mL of $H_2O$. The solution was removed by filtration off and evaporated to dryness. The residue was then extracted with water-chloroform. The organic layer was separated and dried over anhydrous $Na_2SO_4$. The solvent was evaporated to yield yellow oil. The product **3** was characterized as a pure compound by $^1$H NMR, $^{13}$C NMR, ESI-MS$^2$ and IR.[38–41]

*Electro-organic synthesis of **6a-6c**.*— An aqueous solution of phosphate buffer (pH 7.0, 0.20 M) was pre-electrolyzed at the chosen potentials in Table I. Appropriate amounts of catechols (**1a-1d**) and $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) (Table I) were added to the undivided cell, which was equipped with a graphite anode (an assembly of twelve rods, 6 mm diameter and 11 cm length) and a

**Table I. Electroanalytical and preparative data.**

| Conversion | Concentration[a] (mmol) | Applied potential (V) (SCE) | Product yield (%) |
|---|---|---|---|
| **1a→6a** | 0.25 | 0.45 | 94.8 |
| **1b→6b** | 0.35 | 0.29 | 93.2 |
| **1c→6c** | 0.50 | 0.30 | 92.6 |
| **1d→6a** | 0.50 | 0.35 | 95.5 |

[a]Appropriate amounts of catechols (**1a-1d**) and $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) were added to the cell.

large platinum gauze cathode[37] at room temperature. The process was interrupted during the electrolysis, and the graphite anode was washed in acetone to reactivate it. At the end of electrolysis, the solids that separated were filtered, washed with water and then dried by sodium sulfate. After purification, products were characterized by $^1$H NMR, $^{13}$C NMR, ESI-MS$^2$ and IR.

*Characteristic of products (3, and 6a-6c)—$N^1$,$N^2$-dibenzylethane-1,2-diamine ($C_{16}H_{20}N_2$) (**3**).*— Isolated yield = 67.6%, $^1$H NMR, δ ppm (600 MHz $CDCl_3$): 2.01 (s, 2H amine), 2.76 (s, 4H methylene), 3.77 (s, 4H methylene), 7.24–7.25 (t, 4H aromatic), 7.27–7.31 (t, 2H aromatic), 7.32–7.34 (t, 4H, aromatic). $^{13}$C NMR, δ ppm (150 MHz $CDCl_3$): 48.6, 53.9, 126.9, 128.2, 128.45, 140.3. ESI-MS$^2$: *m/z*, 263.1 ($M^+$+Na), 241.1 ($M^+$+1). $IR_{(KBr)}$: 3304, 3084, 3061, 3027, 2924, 2829, 1950, 1877, 1811, 1603, 1584, 1494, 1452, 1407, 1358, 1202, 1108, 1074, 1054, 1028, 982, 911, 820, 736, 698 and 591 cm$^{-1}$.

*1,4-dibenzyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{22}H_{20}N_2O_2$) (6a).*— Isolated yield = 94.8%, $^1$H NMR, δ ppm (600 MHz $CDCl_3$): 3.56 (s, 4H), 4.53 (s, 4H), 5.57 (s, 2H), 7.25 (t, 4H), 7.32 (t, 4H), 7.38 (t, 2H). $^{13}$C NMR, δ ppm (150 MHz $CDCl_3$): 47.0, 56.2, 99.8, 127.0, 128.3, 129.2, 134.0, 149.5, 179.0. ESI-MS$^2$: *m/z*, 367.1 ($M^+$+Na), 345.1 ($M^+$+1). $IR_{(KBr)}$: 3060, 3024, 3002, 2979, 2917, 1597, 1542, 1483, 1451, 1442, 1362, 1323, 1300, 1245, 1156, 1130, 1091, 1077, 1027, 916, 886, 786, 748, 735, 703, 597 and 460 cm$^{-1}$.

*1,4-dibenzyl-5-methyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{23}H_{22}N_2O_2$) (6b).*— Isolated yield = 93.2%, $^1$H NMR, δ ppm (600 MHz $CDCl_3$): 2.03 (s, 3H, methyl), 3.35 (d, 2H), 3.44 (d, 2H), 4.55 (s, 2H), 4.61 (s, 2H), 5.51 (s, 1H), 7.18-7.19 (d, 2H), 7.31 (t, 2H), 7.35 (t, 2H), 7.40 (t, 4H). $^{13}$C NMR, δ ppm (150 MHz $CDCl_3$): 13.6, 46.2, 46.4, 56.0, 58.3, 96.1, 113.0, 126.8, 127.7, 128.1, 128.2, 129.1, 129.2, 134.1, 136.2, 149.4, 154.5, 177.9, 181.2. ESI-MS$^2$: *m/z*, 381.1 ($M^+$+Na), 359.1 ($M^+$+1). $IR_{(KBr)}$: 3368, 3032, 2873, 2371, 2345, 1597, 1536, 1496, 1450, 1364, 1352, 1318, 1260, 1234, 1155, 1070, 1027, 953, 893, 820, 734, 697 and 464 cm$^{-1}$.

*1,4-dibenzyl-5-methoxy-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{23}H_{22}N_2O_3$) (6c).*— Isolated yield = 92.6%, $^1$H NMR, δ ppm (600 MHz $CDCl_3$): 3.40 (d, 2H), 3.51 (d, 2H), 3.62 (s, 3H, methyl), 4.54 (s, 2H), 4.91 (s, 2H), 5.42 (s, 1H), 7.19 (d, 4H), 7.29 (m, 2H), 7.36 (m, 4H). $^{13}$C NMR, δ ppm (150 MHz $CDCl_3$): 46.9, 47.3, 56.6, 58.0, 60.5, 96.2, 126.8, 127.2, 127.8, 128.3, 128.9, 129.2, 133.9, 134.7, 136.7, 139.7, 152.6, 175.6, 177.3. ESI-MS$^2$: *m/z*, 397.1 ($M^+$+Na), 357.1 ($M^+$+1). $IR_{(KBr)}$: 3061, 3026, 2982, 2935, 1952, 1602, 1529, 1467, 1422, 1361, 1317, 1277, 1193, 1171, 1155, 1096, 1087, 1026, 969, 952, 931, 839, 819, 797, 756, 728, 693, 609, 589, 545, 509 and 460 cm$^{-1}$.

## Results and Discussion

*Chemical synthesis of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**).*— The synthesis of a Schiff base is a classical reaction. It is often carried out with catalysis and generally by refluxing a mixture of an aldehyde (or ketone) and an amine.[42,43] The chemical synthesis of compound **3** was achieved using a Schiff base chemical reaction between benzaldehyde with ethylenediamine in a methanol solution under reflux conditions. In this experiment, a Schiff base compound **3** that potentially contains a nitrogen-containing heterocycle has been easily prepared.[44–48]

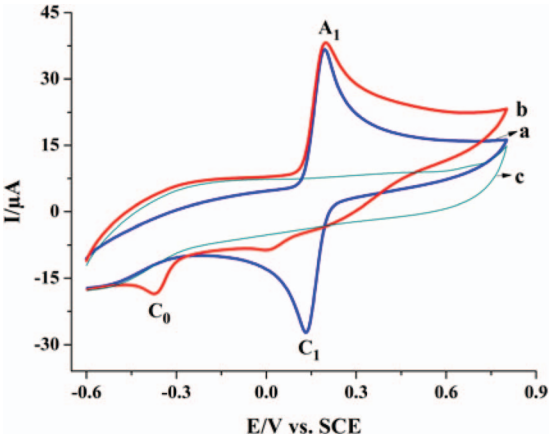



**Figure 1.** Cyclic voltammograms of: (a) 1.0 mM catechol (**1a**); (b) 1.0 mM catechol (**1a**) in the presence of 1.0 mM $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**); (c) 1.0 mM $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**), at a glassy carbon electrode (1.8 mm diameter) in the phosphate buffer solution $KH_2PO_4/K_2HPO_4$ (0.2 M, pH 7). Scan rate: 50 mVs$^{-1}$; T = 25 ± 1°C.

A two-step mechanism can be presented based on the Schiff base reaction for the preparation of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**).[49] The first step in the reaction is reversible, progressing through a carbinolamine intermediate and requires the removal of water, often by azeotropic distillation with benzene, to achieve high yields. The reaction is acid catalyzed, but catalysts are not generally required when aliphatic amines are involved. The second step of the reaction involves the reduction of the resulting compound containing two azomethine groups (C=N) to the product **3** using sodium borohydride. According to our results, the analytical and spectral data are completely consistent with the proposed formulation.

*Electrochemical oxidation of catechol (**1a**) in the presence of (**3**).*— The electrochemical behavior of catechol (**1a**) was investigated by cyclic voltammetry at room temperature in an aqueous solution containing 0.2 M phosphate buffer (pH 7.0) as the supporting electrolyte system. As shown in Fig. 1 (curve a), upon scanning anodically, the catechol exhibited one, well-defined oxidation wave ($A_1$) at +0.19 V (vs. SCE) corresponding to the transformation of catechol (**1a**) to *o*-benzoquinone (**2a**), which was reduced in the cathodic sweep ($C_1$) at +0.13 V (vs. SCE). Previously,[1–10] it has been concluded that the number of electrons involved in the oxidation of catechol and its simple derivatives is two. The oxidation of catechol (**1a**) in the presence of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) as a nucleophile was studied in some detail. When an equivalent amount of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) was added in aqueous solution containing 0.2 M phosphate buffer (pH 7.0), the cathodic counterpart $C_1$ of the anodic peak $A_1$ disappeared (Fig. 1 curve (b)). Additionally, in the negative scan, the voltammogram exhibited a new cathodic peak ($C_0$) at −0.37 V vs. SCE. In the second cycle, a new anodic peak ($A_0$) appeared with an $E_p$ value of −0.28 V vs. SCE (Fig. 2 curve (b)). This peak is related to oxidation of intermediate **5a**.

Furthermore, it was observed that the height of $C_1$ peak increased proportional to the augmentation of the potential sweep rate (Fig. 3 curve (a-g). A similar situation was observed when the $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) to **1a** concentration ratio decreased. The variation of the peak current ratio ($I_{pC1}/I_{pA1}$) versus the scan rate for a mixture of catechol (**1a**) and $N^1$,$N^2$-dibenzylethane-1,2-diamine confirms the reactivity of **2a** toward $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**), appearing as an increase in the ($I_{pC1}/I_{pA1}$) ratio at higher scan rates.

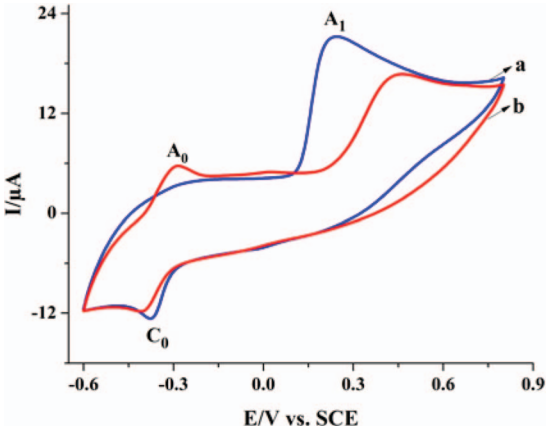



**Figure 2.** Cyclic voltammograms of: (a) first cycle and (b) second cycle of 1.0 mM catechol (**1a**) in the presence of 1.0 mM $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**), at a glassy carbon electrode (1.8 mm diameter) in the 0.2 M phosphate buffer solution ($KH_2PO_4/K_2HPO_4$) pH = 7. Scan rate: 25 $mVs^{-1}$; T = 25 ± 1°C.

Cyclic voltammograms of 1.0 mM catechol (**1a**) in the presence of 1.0 mM of **3** at various pHs are shown in Fig. 4. As is shown, with increasing pH, the height of the anodic peak ($A_1$) increases, the height of cathodic peak ($C_1$) decreases and a new cathodic peak ($C_0$) appears at more negative potentials. This behavior is related to deprotonation of **3** and its activation toward a Michael addition reaction with **3** that leads to formation of the product with more negative oxidation potential. The rate of this intermolecular Michael addition increases with increasing pH. As shown in Fig. 4, at neutral pHs desired reaction is adequately fast. The height of the cathodic peaks also shows that reaction is in the transition region between the diffusion and kinetic situations and suitable for voltammetric study. In basic solutions, the coupling of anionic or dianionic forms of catechols with *o*-benzoquinone **2a** (dimerization reaction) competes with Michael addition of **3** *o*-benzoquinone **2a**.[50] Because of the decrease in the rate of the dimerization reaction and the increase in the rate of the Michael addition reaction between **3** and *o*-benzoquinone **2a** the solution containing phosphate buffer (pH 7.0, $c = 0.2$ M) was selected as the medium for a detailed electrochemical study.

Controlled-potential coulometry was performed in aqueous solution containing 0.2 M phosphate buffer (pH 7), 0.25 mmol of **1a** and

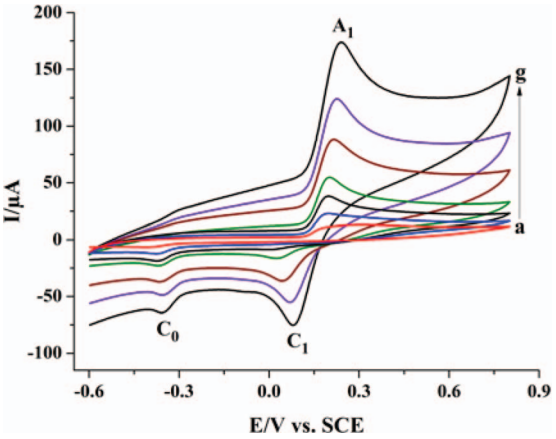



**Figure 3.** Typical cyclic voltammograms of 1.0 mM catechol (**1a**) in the presence of 1.0 mM $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) in water containing of 0.2 M phosphates ($KH_2PO_4/K_2HPO_4$) as the buffer and supporting electrolyte (pH = 7); at a glassy carbon electrode and at various scan rates. Scan rate from (a) to (g) are 10, 25, 50, 100, 250, 500 and 1000 $mVs^{-1}$, respectively. T = 25 ± 1°C.

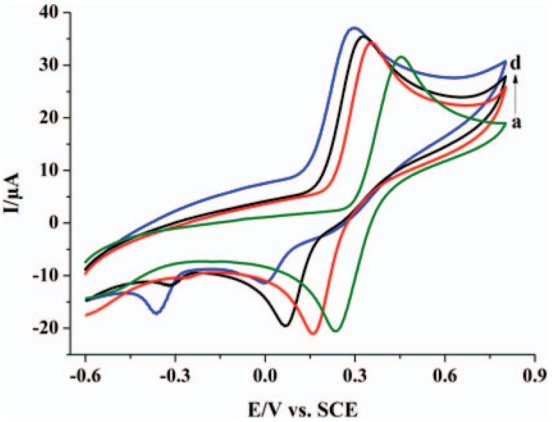
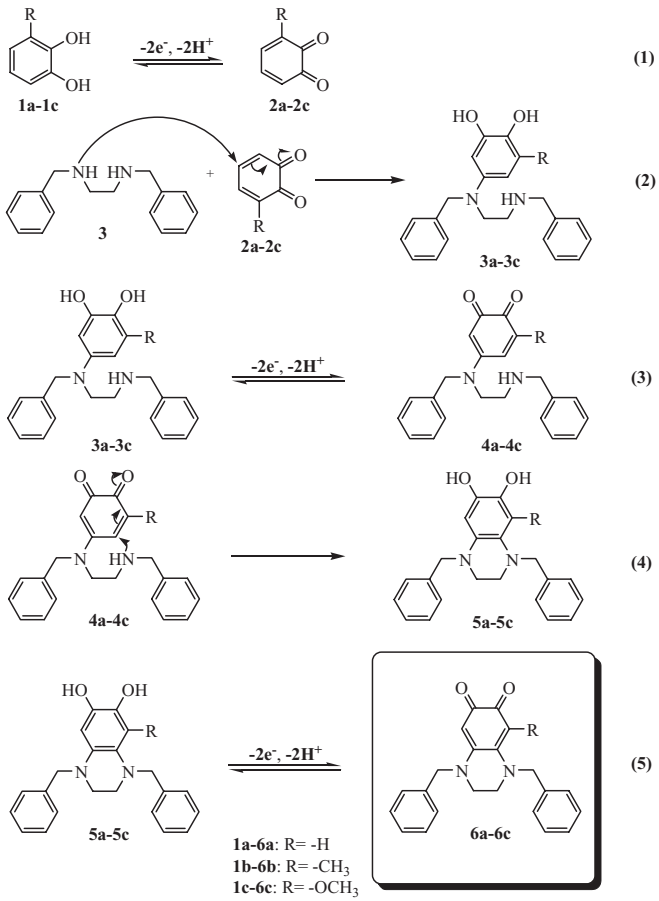
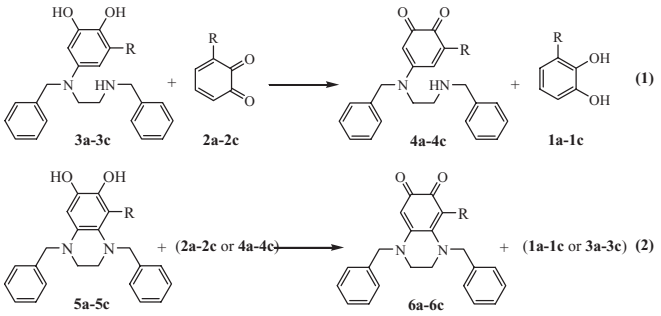



**Figure 4.** Cyclic voltammograms of 1.0 mM catechol in the presence of 1.0 mM $N^1$,$N^2$-dibenzylethane-1,2-diamine in buffered solutions with various pHs. pH from (a) to (d) are 3, 5, 6 and 7, respectively. Ionic strength; 0.2 M. Scan rate: 100 $mVs^{-1}$; T = 25 ± 1°C.

0.25 mmol of **3** at controlled potential (0.45 V vs. SCE). Based on our controlled-potential coulometric analysis (consumption of $6e^-$ per molecule of catechol) we assumed that the anodic oxidation of catechols in the presence of $N^1$,$N^2$-dibenzylethane-1,2-diamine follows the *ECECE* mechanism.[31] These observations allow us to propose the pathway illustrated in Scheme 1 for the electrooxidation of **1a** in the presence of **3**. According to the obtained results, it seems that the Michael addition reaction of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) to *o*-quinone (**2a**) (Scheme 1, Eq. (2)) is faster than other secondary




**Scheme 1.** Proposed mechanism for the electrooxidation of catechols (**1a-1c**) in the presence of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**).

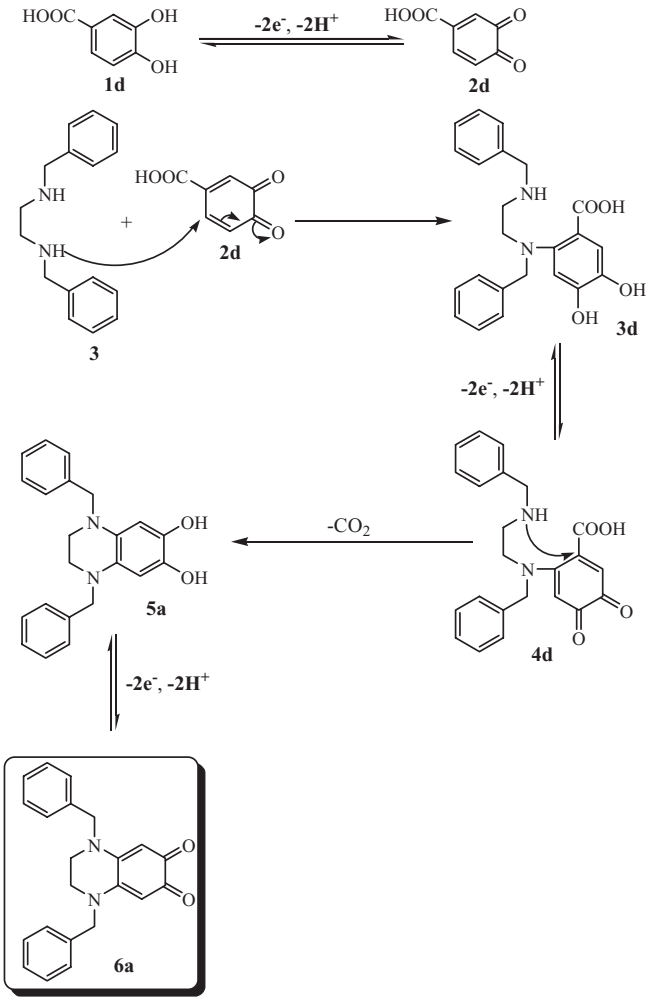



**Scheme 2.** The possible oxidation of **3a**-**3c** and **5a**-**5c** through a solution electron transfer (SET) reaction.

reactions, leading to the adduct **3a**. The adduct **3a** then undergoes the abstraction of a second pair of electrons, leading to *o*-benzoquinone **4a**. The intramolecular addition of **3** to **4a** leads to the formation of the quinoxalinediol derivative **5a,** and further oxidation of this compound produces the final product **6a**. Moreover, the oxidation of **3a** and **5a** may take place through a solution electron transfer (SET) reaction (Scheme 2, Eqs. (1) and (2)).

*Electrochemical oxidation of other catechol derivatives (**1b,1c**) in the presence of **3**.*— The electrooxidation of **1b** and **1c** in the presence of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) proceeds in a way similar to that of **1a**. The *o*-benzoquinone formed via oxidation can act as a Michael acceptor toward nucleophiles yielding substituted catechols. In the cases of **1b** and **1c**, the presence of a methyl or methoxy group as an electron-donating substituent on the molecular ring causes a diminution in activity of *o*-quinones **2b** and **2c** as Michael acceptors toward the 1,4-addition of **3**. These reactions can be followed by cyclic voltammetry.

*Electrochemical oxidation of 3,4-dihydroxybenzoic acid (**1d**) in the presence of **3**.*— For the study of the effect of the presence of a carboxylic group in a reactive site of catechol ring, the electrochemical oxidation of 3,4-dihydroxybenzoic acid (**1d**) has been studied in the presence of **3**. Cyclic voltammogram of 3,4-dihydroxybenzoic acid **1d** in phosphate buffer solution (pH 7.0, 0.20 M,) in the presence of **3** shows the same condition as reported for catechol. Also, other voltammetry and coulometry data are as same as previous case. According to obtained electrochemical data in accompany with spectroscopic data of final product, we propose an *ECECE* mechanism with an electro-decarboxylation reaction for the electrooxidation of **1d** in the presence of **3** (Scheme 3).




**Scheme 3.** Proposed mechanism for the electrooxidation of 3,4-dihydroxybenzoic acid (**1d**) in the presence of $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**).

## Conclusions

The importance of quinoxalinedione derivatives as valuable drugs[33–36] prompted us to synthesis a number of these compounds. The important features of this paper, the synthesis of valuable compounds in aqueous solution instead of toxic solvents, high-energy efficiency, room temperature conditions and using the electrode as an electron source instead of toxic reagents, are in accord with the principle of green chemistry. The results of this work show that electrochemically generated *o*-benzoquinones (**2a**-**2d**) from the oxidation of catechols (**1a**-**1d**), are attacked by $N^1$,$N^2$-dibenzylethane-1,2-diamine (**3**) as a nucleophile. Final products (**6a**-**6c**) are obtained after intermolecular and intramolecular additions of **3** and via an *ECECE* mechanism, after consumption of $6e^-$ per molecule of **1a**-**1d**.

## Acknowledgments

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