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Chemical and electrochemical procedures for the synthesis of diisopropyltetrahydroquinoxalinedione derivatives

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ABSTRACT

Diisopropyltetrahydroquinoxalinedione derivatives are synthesized from the reaction of various catechols with *N,N′*-diisopropylethylenediamine. Both chemical and electrochemical methods give the same products. While the chemical synthesis is faster, the electrochemical synthesis provides higher yields.

1. Introduction

Quinoxalinediones have been used extensively as drugs in medicinal chemistry,[1–4] epilepsy, Parkinson's, schizophrenia, stroke, head trauma, pain and drug addiction.[5–7] Achieving water solubility of quinoxalinediones without loss of selectivity and potency profiles is a major challenge for medicinal chemistry.[8] Most of the reported syntheses describe 1,4- or 2,3-quinoxalinedione derivatives.[9,10]

The quinoxaline-6,7-diones produced in this work are water soluble and might be useful for the treatment of some diseases. Our work is based on the addition of different diamines to quinone derivatives and formation of new nitrogen-containing heterocycles. This work has led to the development of easy and environmentally friendly methods for the synthesis of several new quinoxalinedione derivatives.

In continuation of our studies on the synthesis of quinoxalinediones,[11] herein we describe a convenient method for the chemical and electrochemical synthesis of several new diisopropylquinoxalinedione derivatives from the reaction of catechols **1a–c** with *N,N′*-diisopropylethylenediamine (DIPEDA) (Scheme 1).

2 Electrochemical study of catechol

Cyclic voltammograms of **1a** in the absence (curve a) and presence (curve b) of DIPEDA in a phosphate buffer solution (PBS),[12] pH 7, $c = 0.15$ are shown in Figure 1. A cyclic voltammogram of **1a** in the absence of DIPEDA (curve a) shows one anodic peak (A_1) at 0.20 V and the corresponding cathodic peak (C_1) at 0.13 V, which correspond to the transformation of **1a** to *o*-benzoquinone (**2a**) and vice versa within a quasi-reversible two-electron process.[13] Under these conditions, the peak-current ratio ($I_p^{C_1}/I_p^{A_1}$) is near unity; which can be considered a criterion for the stability of **2a** produced at the surface of the electrode under the experimental conditions.[14] In other words, hydroxylation[15–17] or dimerization[18,19] reactions are too slow to be observed on the time scale of cyclic voltammetry.[20]

Figure 1 (curve b) shows the first cyclic voltammogram obtained for a 1.0 mM solution of **1a** in the presence of 1.0 mM of DIPEDA. The voltammogram exhibits two cathodic peaks C_1 and C_0 (−0.42 V vs. SCE). In the second cycle, a new peak (A_0) appears with an E_p value of −0.34 V versus SCE. This new peak is related to the electrooxidation of intermediate **5a**. Furthermore, it is seen that, proportional to the augmentation of the potential sweep rate and in parallel with a decrease in the height of C_0, the height of C_1 increases. In other words, the variation of peak current ratios ($I_p^{C_1}/I_p^{A_1}$) and ($I_p^{Co}/I_p^{C_1}$) versus scan rate for a mixture of **1a** and DIPEDA confirms the reactivity of **2a** towards DIPEDA, appearing as an increase in the ($I_p^{C_1}/I_p^{A_1}$) ratio and a decrease in the ($I_p^{Co}/I_p^{C_1}$) ratio at higher scan rates.

Constant-current coulometry was performed in an aqueous solution containing 0.25 mmol of **1a** and 0.25 mmol of DIPEDA in an undivided cell, under a low constant-current density (1 mA/cm^2).[21] Monitoring of the electrolysis progress was carried out by cyclic voltammetry. It is shown that, proportional to the

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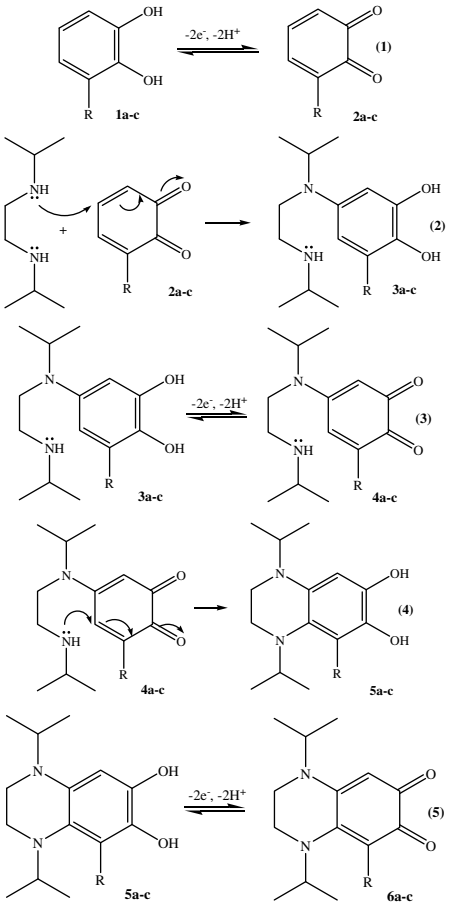
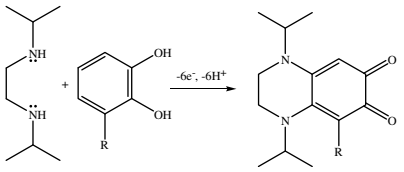


The Overall Reaction:



Scheme 1. The overall reaction: **a**: R=H, **b**: R=CH_3, **c**: R=OCH_3.

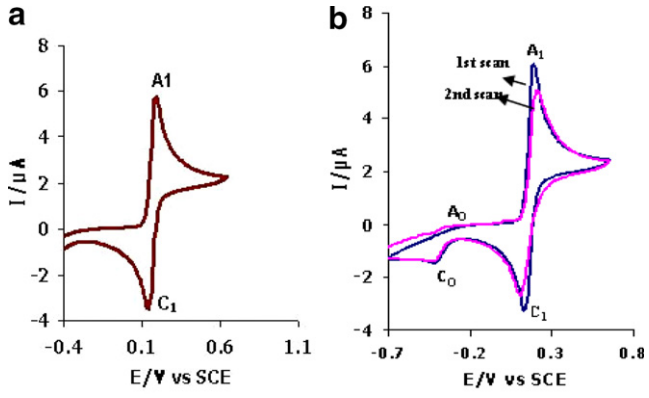


Figure 1. CVs of (a) **1a** (1.0 mM) and (b) first and second cycles of **1a** (1.0 mM) in the presence of DIPEDA (1.0 mM) at a glassy carbon electrode in PBS. Scan rate: 10 mV s^{-1}, T = 25 ± 1 °C.

advancement of the coulometry and in parallel with the decreasing height of the anodic peak A_1, the heights of A_0 and C_0 increase

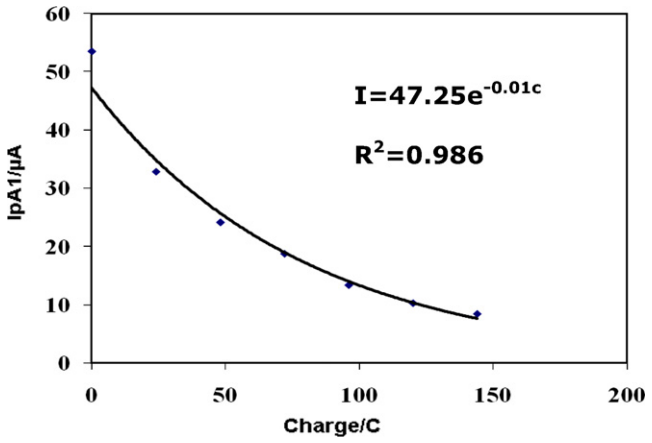


Figure 2. Variation of peak current I_{pA1} versus charge consumed during constant-current coulometry. Scan rate: 50 mV s^{-1}, T = 25 ± 1 °C.

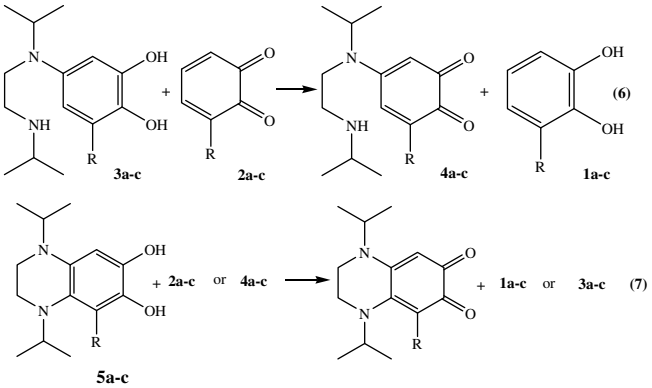
(Fig. 2). A characteristic feature of electrolysis is that a low-current density is required. The current efficiency and yield of product decrease on increasing the current density.[21]

Controlled-potential coulometry, performed in an undivided cell using the above-mentioned conditions, showed that proportional to the advancement of the coulometry,[22] the anodic peak A_1 and its counterpart (C_1) decreased and disappeared when the charge consumption was about $6e^-$ per molecule of **1a**. These observations allow us to propose the ECECE pathway illustrated in Scheme 1 for the electrooxidation of **1a–c** in the presence of DIPEDA.[14]

Formation of **2a–c** was followed by a 1,4-Michael addition of DIPEDA to the quinone to produce the adducts **3a–c**. These adducts then undergo abstraction of a second pair of electrons, leading to quinones **4a–c**. Intramolecular addition produces catechol derivatives **5a–c** and further oxidation of these compounds led to formation of the final products **6a–c**. Oxidation of the intermediates **3a–c** and **5a–c** is easier than oxidation of the parent starting molecules **1a–c** by virtue of the presence of the electron rich amine group(s) on the quinone ring.

Besides, it is possible that the oxidation of **3a–c** and **5a–c** takes place through a single electron transfer (SET) reaction (Scheme 2, Eqs. 6 and 7).

According to our results, the anodic peaks of the voltammograms presented in Figure 1 (A_1 and A_0) are related to the oxidation of **1a** and 1,4-diisopropyl-1,2,3,4-tetrahydroquinoxaline-6,7-diol (**5a**) to **2a** and 1,4-diisopropyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione (**6a**), respectively. Obviously, the cathodic peaks C_1 and C_0 shown in Figure 1 can also correspond to the reduction of **2a** and



Scheme 2. **a**: R=H, **b**: R=CH_3, **c**: R=OCH_3.

6a, respectively. Due to the fast intramolecular Michael addition reaction (Scheme 1, Eq. 4), the anodic and cathodic counterpart peak for the oxidation of **3a–c** were not observed.

Electrooxidation of 3-methylcatechol (**1b**) or 3-methoxycatechol (**1c**) in the presence of DIPEDA in PBS occurs in a manner similar to that of **1a**.

3. Electrochemical study of 3,4-dihydroxybenzoic acid (1d) in the presence of DIPEDA

In order to study the effects of different groups on the reactive sites of the catechol ring, the electrochemical oxidation of **1d** was studied in the presence of DIPEDA. Voltammetry and coulometry data were the same as in the previous cases.[20] According to the obtained electrochemical data, along with the spectroscopic data of the final product, an ECECE mechanism is proposed along with an electro-decarboxylation reaction of **1d** in the presence of DIPEDA.

Cyclic voltammetry and controlled-potential coulometry were performed using an Auto lab model PGSTAT 20 potentiostat/galvanostat. A glassy carbon electrode (GCE) of 1.8 mm^2 was used as the working electrode and a stainless steel wire was used as the counter electrode. The working electrode used in the controlled-potential coulometry and macroscale electrolysis was an assembly of four graphite rods (31 cm^2, from KIGCO, Mashhad, Iran), placed as single rods at the edges of a square at a distance of 3 cm apart, and a large stainless steel gauze cylinder (25 cm^2 area) constituted the counter electrode. The working electrode potential was measured versus SCE (all electrodes from Azar Electrode).

4. Electrochemical synthesis of 6a

A PBS (80 mL) solution containing **1a** (1.0 mmol) and DIPEDA (1.0 mmol) was electrolyzed in an undivided cell equipped with a graphite anode (an assembly of four rods, 6 mm in diameter and 6 cm in length) and a large stainless steel gauze cathode at 25 °C under a constant-current density of 1 mA/cm^2. The quantity of electricity passed was determined using the exponential curve and related equation in Figure 2. The process was interrupted several times during the electrolysis[13] and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis (20 h), the product was extracted with CH_2Cl_2 (2 × 25 mL) and the solvent evaporated. The product **6a** was purified by recrystalization from a*n*-hexane/acetone mixture (20:80) and characterized by IR, ^{1}H NMR, ^{13}C NMR and MS. The residue did not dissolve in any solvent which could be attributed to the formation of oligomers or polymers of catechols.

The same method as above was applied for the synthesis of **6b–c**.

5. Chemical synthesis of 6a

To a stirred PBS (50 mL) solution DIPEDA (1.0 mM) and K_3FeCN_6[23] (6.0 mM) were added. A solution of **1a** (1 mmol) dissolved in PBS (10 mL) was added dropwise over 15 min during which time the solution became dark, and a solid precipitated. After 24 h, the mixture was filtered and the filtrate was extracted with CH_2Cl_2 (2 × 25 mL). The combined organics were dried and evaporated, and the resulting brown precipitate was crystallized from *n*-hexane/acetone mixture (20:80) and characterized by IR, ^{1}H NMR, ^{13}C NMR and MS. The residue did not dissolve in any solvent which could be attributed to the formation of oligomers or polymers of catechols.

The same method as above was applied for the synthesis of **6b–c** (Supplementary data).

6. 1,4-Diisopropyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{14}H_{20}N_2O_2$, 6a)

Isolated yields 33% (electrochemical) and 28% (chemical synthesis), mp = 182–183 °C, $IR_{(KBr)}$: 2974, 1598, 1526, 1463, 1444, 1370, 1299, 1102, 782 and 557 cm^{-1}. ^{1}H NMR, δ ppm (90 MHz $CDCl_3$): 1.16 (d, J = 5 Hz, 12H isopropyl), 3.28 (s, 4H methylene), 4.0 (m, 2H isopropyl), 5.50 (s, 2H quinone). ^{13}C NMR, δ ppm (22.5 MHz $CDCl_3$): 18.8, 39.1, 49.8, 98.6, 149.8, 179.3. MS: *m/e* (relative intensity): 250 (M+2H)[11] (40), 220 (55), 207 (48), 163 (100), 136 (35), 41 (26), 27 (16).

7. 1,4-Diisopropyl-5-methyl-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{15}H_{22}N_2O_2$, 6b)

Isolated yields 25% (electrochemical) and 20% (chemical synthesis), mp = 112–113 °C, $IR_{(KBr)}$: 2926, 1586, 1522, 1353, 1313, 1178, 1083 and 732 cm^{-1}. ^{1}H NMR, δ ppm (90 MHz $CDCl_3$): 1.03 (d, J = 5 Hz, 6H isopropyl), 1.17 (d, J = 5 Hz, 6H isopropyl), 1.90 (s, 3H methyl), 3.23 (t, J = 7 Hz, 4H methylene), 3.99 (m, 1H isopropyl), 4.77 (m, 1H isopropyl), 5.39 (s, 1H quinone). ^{13}C NMR, δ ppm (22.5 MHz $CDCl_3$): 7.8, 20.5, 39.1, 51.5, 78.5, 157.5, 168, 180. MS: *m/e* (relative intensity): 264 (M+2H) (10), 221 (17), 124 (93), 78 (100), 77 (48), 51 (32), 39 (40), 27 (26).

8. 1,4-Diisopropyl-5-methoxy-1,2,3,4-tetrahydroquinoxaline-6,7-dione ($C_{15}H_{22}N_2O_3$, 6c)

Isolated yields 40% (electrochemical) and 35% (chemical synthesis), mp = 177–178 °C (dec), $IR_{(KBr)}$: 3415, 2924, 2852, 1604, 1520, 1439, 1360, 1090, 753 and 605 cm^{-1}. ^{1}H NMR, δ ppm (90 MHz $CDCl_3$): 1.23 (d, J = 5 Hz, 12H isopropyl), 3.24 (s, 4H methylene), 3.68 (s, 3H methyl), 4.03 (m, 1H isopropyl), 4.70 (s, 1H isopropyl), 5.36 (s, 1H quinone). ^{13}C NMR, δ ppm (22.5 MHz $CDCl_3$): 19.07, 20.4, 39.1, 39.3, 50.2, 52.4, 60.1, 94.6, 142, 176, 178. MS: *m/e* (relative intensity): 280 (M+2H) (80), 265 (75), 237 (100), 191 (78), 163 (77), 149 (30).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.049.

References and notes

1. Deur, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4599–4603.
2. Hicks, C. A.; Ward, M. A.; Ragumoorthy, N.; Ambler, S. J.; Dell, C. P.; Dobson, D.; O'Neill, M. J. *Brain Res.* **1999**, *819*, 65–74.
3. Lutfy, K.; Doan, P.; Nugyen, M.; Weber, E. *Pharmacol. Res.* **1998**, *38*, 453–460.
4. Tandon, V. K.; Maurya, H. K.; Yadav, D. B.; Tripathi, A.; Kumarb, M.; Shuklab, P. K. *Bioorg. Med. Chem.* **2006**, *14*, 6120–6126.
5. Popik, P.; Kozela, E.; Pilc, A. *Brit. J. Pharmacol.* **2000**, *130*, 1425–1431.
6. Cha, S.; Sekine, T.; Kushuhara, H.; Yu, E.; Kim, Y. J.; Kim, D. K.; Endon, H. *J. Biol. Chem.* **2000**, *275*, 4507–4512.
7. Bittner, S.; Meenakshi, C.; Temstin, G. *Tetrahedron* **2001**, *57*, 7423–7429.
8. Turski, L.; Huth, A.; Sheardown, M.; McDonald, F.; Neuhaus, R.; Schneider, H. H.; Dirnagl, U.; Wiegand, F.; Jacobsen, P.; Ottow, E. *Proc. Natl. Acad. Sci.* **1998**, *95*, 10960–10965.
9. Song, X.-Q.; Yu, Y.; Liu, W.-S.; Dou, W.; Zheng, J.-R.; Yao, J.-N. *J. Solid State Chem.* **2007**, *180*, 2616–2624.
10. Katayama, S.; Ae, N.; Nagata, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4295–4299.
11. Nematollahi, D.; Hesari, M. *J. Electroanal. Chem.* **2005**, *577*, 197–203.
12. Habibi, D.; Nematollahi, D.; Seyyed-Alhoseini, Z.; Dehdashtian, S. *Electrochim. Acta* **2006**, *52*, 1234–1239.

13. (a) Bayandori Moghaddam, A.; Kobarfard, F.; Hosseiny Davarani, S. S.; Nematollahi, D.; Shamsipur, M.; Fakhari, A. R. *J. Electroanal. Chem.* **2006**, *586*, 161–166; (b) Hawley, M. D.; Tatawawadi, S. V.; Piekarski, S.; Adams, R. N. *J. Am. Chem. Soc.* **1967**, *89*, 447–450; (c) Sternson, A. W.; McCreery, R.; Feinberg, B.; Adams, R. N. *J. Electroanal. Chem.* **1973**, *46*, 313–321; (d) Grujic, Z.; Tabakovic, I.; Trkovnik, M. *Tetrahedron Lett.* **1976**, 4823–4824; (e) Tabakovic, I.; Grujic, Z.; Bejtovic, Z. *J. Heterocycl. Chem.* **1983**, *20*, 635–638.
14. Golabi, S. M.; Nematollahi, D. *J. Electroanal. Chem.* **1997**, *430*, 141–146.
15. Papouchado, L.; Petrie, G.; Adams, R. N. *J. Electroanal. Chem.* **1972**, *38*, 389–395.
16. Papouchado, L.; Petrie, G.; Sharp, J. H.; Adams, R. N. *J. Am. Chem. Soc.* **1968**, *90*, 5620–5621.
17. Young, T. E.; Griswold, J. R.; Hulbert, M. H. *J. Org. Chem.* **1974**, *39*, 1980–1982.
18. Ryan, M. D.; Yueh, A.; Chen, W.-Y. *J. Electrochem. Soc.* **1980**, *127*, 1489–1495.
19. Nematollahi, D.; Rafiee, M.; Samadi-Maybodi, A. *Electrochim. Acta* **2004**, *49*, 2495–2502.
20. Nematollahi, D.; Habibi, D.; Rahmati, M.; Rafiee, M. *J. Org. Chem.* **2004**, *69*, 2637–2640.
21. Nematollahi, D.; Hesari, M.; Hosseiny Davarani, S. S. *ARKIVOC* **2006**, 129–136.
22. Nematollahi, D.; Hesari, M. *J. Anal. Chem.* **2001**, *56*, 1278–1281.
23. Nematollahi, D.; Habibi, D.; Alizadeh, A.; Hesari, M. *J. Heterocycl. Chem.* **2005**, *42*, 289–291.