Electrooxidation of Catechol in the Presence of 1,3-Dimethylbarbituric Acid at Graphite Anode and Nickel Hydroxide Electrode

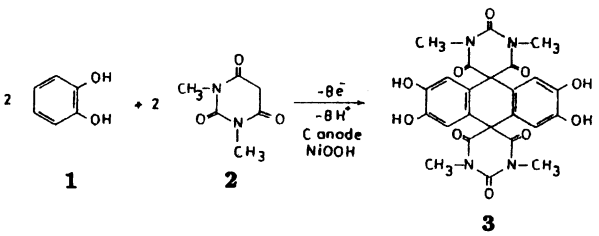
Magdi ABDEL AZZEM,* Magdi ZAHRAN, and Ezzat HAGAGG
Chemistry Department, Faculty of Science, Menoufia University, Egypt
(Received September 30, 1993)

The controlled potential anodic oxidation of catechol in the presence of 1,3-dimethylbarbituric acid was carried out in aqueous solution containing sodium acetate in an undivided cell at graphite anode and nickel hydroxide electrode. In a sequence of Michael addition of the barbiturate to the anodically formed benzoquinone, dispiropyrimidine derivative has been obtained in moderate yield (35—36%). A mechanism has been proposed and confirmed on the basis of CPE product, identification through IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopy.

Catecholamines are a class of neutrotransmitters in the brain.[1] Therefore they occupy a central position in contemporary neutropharmacology. They have been implicated in various types of mental diseases such as depression, schizophrenia, and other psychotic disorders.[2] Although simple *o*-benzenediol such as catechol has no biological significance, it is important to understand its electrochemistry in order to compare the behavior of its biological activity with catecholamines. Because electrochemical oxidation very often paralles the cytochrome P450 catalyzed oxidation in liver microsomes, it was interesting to study the anodic oxidation of catechol in the presence of the barbiturate as CH-acidic nucleophile. The barbiturates are of particular interest, since they are known to have hyponotic properties and they are used as long active on central nervous system (CNS).[3] We now present a simple and facile electrochemical process for the anodic oxidation of catechol **1** using controlled potential electrolysis (CPE) in the presence of 1,3-dimethylbarbituric acid **2** as nucleophile to synthesis 2′,3′.6′,7′-tetrahydroxy-1,1″,3,3″-tetramethyldispiro[pyrimidine-5(2*H*), 9′(10′)-anthracene-10′,5″(2″*H*)-pyrimidine]-2,2″,4,4″,6,6″-hexone **3** (Scheme 1). The electrochemical synthesis is carried out in aqueous solution containing sodium acetate as supporting electrolyte in an undivided cell at a graphite anode and nickel hydroxide electrode. This electrochemical method has the additional advantage that work up is easy since the product is insoluble in the electrolysis medium.

Experimental

Material. 1,3-Dimethylbarbituric acid (**2**) is prepared according to the literature.[4] Sodium acetate (The British Drug Houses Ltd., London N. I.) and catechol (Aldrich Chemical Co., Ltd.) are used without further purification.



Scheme 1.

Apparatus. Cyclic voltammetry was carried out using a Cypress computer measuring system for electrochemical analysis model CYSY-1B. Current–voltage curves were recorded on Hewlett–Packard model 7440A X,Y-recorder. Analytical cell model C-1A (Bioanalytical System) was used together with a glassy carbon electrode (3.0 mm dia) as working electrode, a platinum counter electrode and an Ag/AgCl reference electrode. Controlled potential electrolysis (CPE) was carried out using a stabilized current source model NTN 700 M-200 (FUG, Rosenheim) modified as potentiostat together with a digital coulometer. An undivided beaker type cell (200 cm^3) equipped with a graphite anode (24 cm^2), Pt cathode (4 cm^2) Ag/AgCl reference electrode and a magnetic stirrer was used for a preparative electrolysis. In case of using nickel hydroxide electrode, six nickel rods (0.2×10 cm) were connected together and suspended in the electrolysis solution as anode with stainless steel plate as cathode and SCE as reference electrode. IR spectra were recorded on a Perkin–Elemer model 1430, ^{1}H NMR on Brucher WH-90 (90 MHz), ^{13}C NMR on Bruker AC-200 (50.3 MHz). Mass spectra were obtained at 70 eV.

CPE Procedure at Graphite Anode, Separation, and Identification of the Resulting Product. Catechol (1.0 mmol) was dissolved in 150 cm^3 of an aqueous solution containing 0.15 M sodium acetate (1 M=1 mol dm^{-3}) as supporting electrolyte. The potential was fixed at 0.5 V vs. Ag/AgCl, resulting in a current of 110 mA. After the consumption of few coulombs, 1,3-dimethylbarbituric acid (1.0 mmol) was added, and the current increased to 120 mA. After about two hours, the current dropped to 10 mA. After the consumption of about 4 F mol^{-1}, the electrolysis solution was kept in the refrigerator for about four hours. The precipitated solid was collected by filtration and recrystallized from methanol–water to give 0.35 mmol of **3** (yield 35%), mp>300 °C. IR (KBr) ν 3670, 3600 (OH), 1710, 1650 (CO), and 1430 cm^{-1} (C=C). ^{1}H NMR (DMSO-d^6) δ=3.3 (s, 12H, N-CH$_3$), 6.6 (S, 4H, aromatic CH), 9.4 (b, 4H, 4OH). UV λ_{max} in DMF, 242 nm.

Elemental analysis: Calcd for $C_{24}H_{20}N_4O_{10}$: C, 55.01; H, 3.84; N, 10.68%, M, 524. Found: C, 54.71; H, 3.60; N, 10.52%. MS *m/z* 524 (M^+, 20%), 438 (M^+ – ($CH_3NCONCH_3$) 36%), 410 (M^+ – [($CH_3NCONCH_3$) – CO] 68%), 382 (M^+ – [($CH_3NCONCH_3$) – 2CO] 100%),

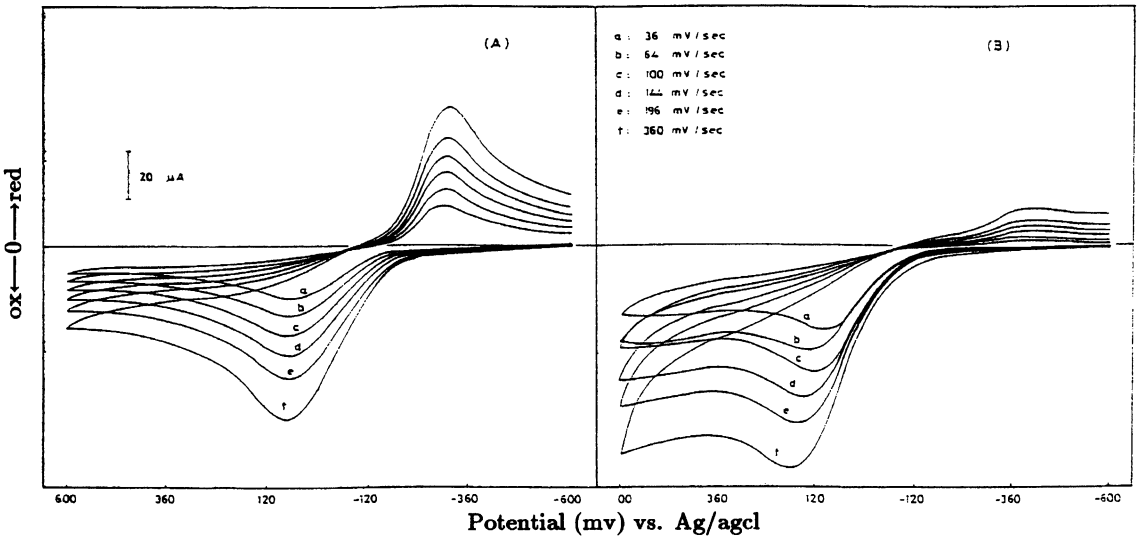
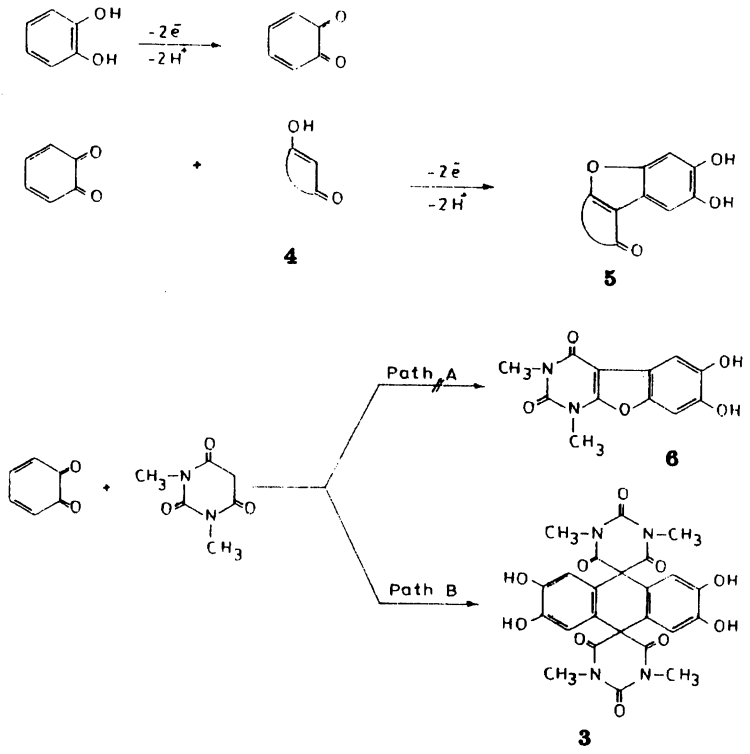


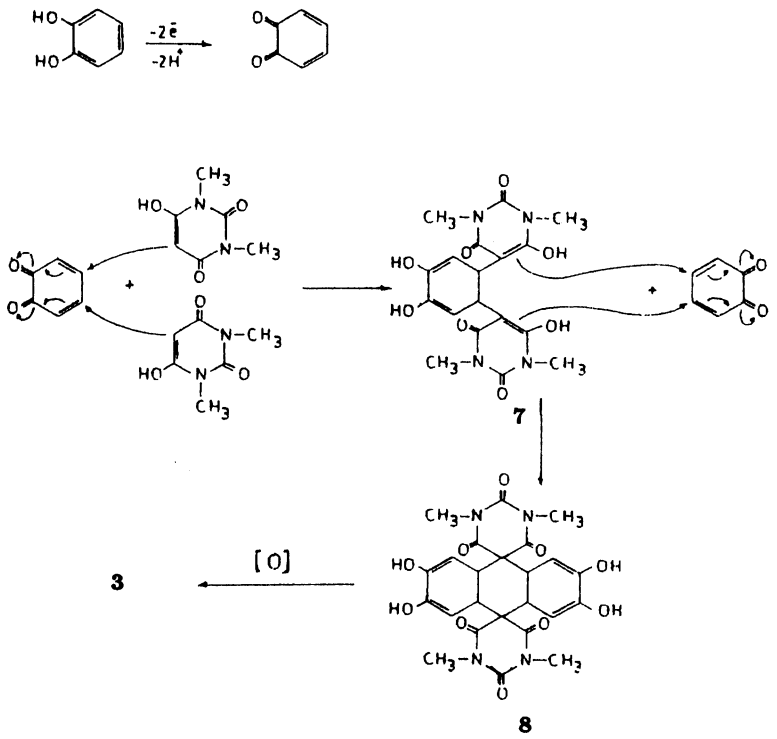
Fig. 1. Cyclic voltammograms of catechol in the absence and presence of 1,3-dimethylbarbituric acid (**2**) in 0.1 M sodium acetate. (A) : 0.016 mmol catechol, (B) : 0.016 mmol catechol–0.016 mmol compound **2**.



Scheme 2.

354 ($(M^+ - [(CH_3NCONCH_3) - 3CO]$ 20%), 296 ($M^+ - [(CH_3NCONCH_3) - 3CO - 2NCH_3]$ 19%), 268 ($M^+ - [2\text{-}(CH_3NCONCH_3) - 3CO - 2NCH_3]$ 5%), 240 ($M^+ - [2\text{-}(CH_3NCONCH_3) - 4CO - 2NCH_3]$14%), 211 (10%), 150 (15%), 57 (90%), 44 (78%), and 32 (22%). ^{13}C NMR (cf. below Chart 1).

CPE Procedure at Niclel Hydroxide Electrode. Catechol (2.0 mmol) was dissolved in 150 cm^3 of aqueous solution containg 0.15 M sodium acetate as supporting electrolyte. The reaction potential was fixed at 0.5 V vs. SCE. After the consumption of few coulombs, 2 mmol of 1,3-dimethylbarbituric acid was added. The termination of electrolysis was detected by TLC (toluene/ethyl acetate/methanol 6 : 3 : 1). After electrolysis, the solution was kept in the refrigerator for about five hours. The precipitated solid was collected by filtration and recrystallized from methanol–water to give 0.3 mmol of **3** (35%). The resulting product has the same spectral data as that which was separated at graphite anode.



Scheme 3.

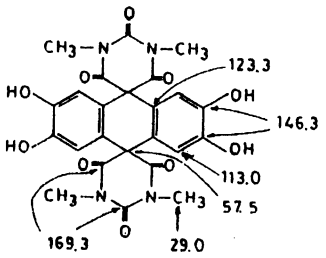


Chart 1.

Results and Discussion

The cyclic voltammetry (CV) of catechol **1** in the presence and absence of 1,3-dimethylbarbituric acid **2** was studied as a function of the scan rate in a solution of 0.15 M sodium acetate (pH 7.4) as shown in Fig. 1A. In the absense of the barbiturate, the typical quasi-reversible behavior for the quinone/hydroquinone system is obtained.[5,6] The formed *o*-benzoquinone can act as Michael-acceptor toward nuclephiles[7,8] yielding disubstituted catechols.[5,9,10] This reaction can be followed by CV. In the presence of one equivalent of barbiturate (Fig. 1B), the cathodic peak for the reduction of *o*-quinone is absent at low scan rates and considerably diminished at higher scan rates. This behavior is clear for the reaction of *o*-benzoquinone with barbiturate. As the barbiturate itself is oxidized at more positive potentials (Fig. 2), the nucleophilic attack of barbiturate to *o*-benzoquinone during the anodic oxidation of catechol in the presence of barbiturate can be predicted. It is well documented in literature[11,12] that

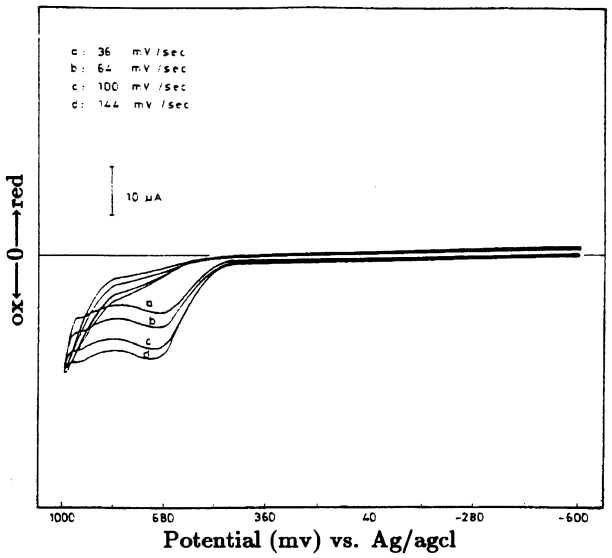
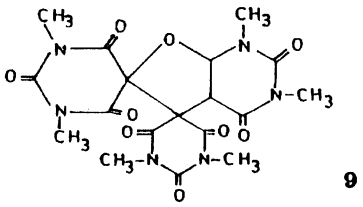


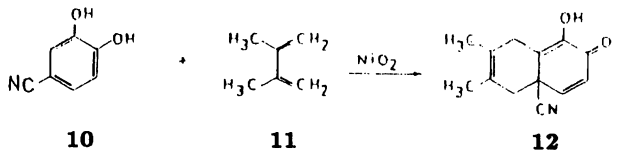
Fig. 2. Cyclic voltammograms of 0.016 mmol of compound **2** in 0.1 M sodium acetate.

the electrooxidation of catechol in the presence of CH-acidic 1,3-dicarbonyl compounds with the general formula (**4**) will give the corresponding benzofuran derivatives **5** (Scheme 2). In the presence of barbiturate, the expected product, therefore would be **6** (Scheme 2, path A). Controlled potential electrolysis of catechol **1** in the presence of barbiturate **2** in sodium acetate at 0.5 V vs. Ag/AgCl with the consumption of 4 F mol^{-1} was carried out. The resulting product is precipitated and recrystallized. IR, ^{1}H NMR, ^{13}C NMR, and mass spec-



9

Chart 2.



10 11 12

Scheme 4.

tra did not fit with the expected structure **6** but it fits with structure **3** (Scheme 2, path B). Proposed reaction pathways for the formation of compound **3** is shown in Scheme 3. Addition of two molecules of the barbiurate to insitu formed *o*-benzoquinone presumably leads to the intermediate disubstituted compound **7**. The latter intermediate will react with another *o*-benzoquinone to give compound **8** which was not separated but was further oxidized under the reaction conditions to give compound **3**. It is reported[13] that the electrolysis of 1,3-dimethylbarbituric acid leads to the formation of a trimeric compound **9**. This observation supports our interpretation as it shows that barbiturates may undergo anodically induced spiro-anellation (Chart 2). On the other hand, the oxidation of 4-cyanocatechol **10** using nickel peroxide is reported to give rise to an *o*-quinone intermediate which has been trapped in the presence of 2,3-dimethylbutadiene **11** to give the adduct[14] **12** as shown in Scheme 4. This reaction attracted our attention, since it has been found that reactions taking place on powderd nickel peroxide can also take place on nickel hydroxide electrode[15] where the nickel hydroxide electrode resembles in its applications and selectivity, the chemical oxidant nickel peroxide.[16] Therefore, CPE of catechol in the presence of 1,3-dimethylbarbituric acid in sodium acetate at 0.5 V vs. SCE at nickel hydroxide electrode was carried out. The resulting product was separated and recrystallized giving the dispiropyrimidine **3** in 36% yield. This means that changing the electrode from graphite to nickel hydroxide electrode did not improve the yield of the product **3**. But the advantages of using NiOOH electrode as an indirect method of oxidation are known.[15,17] It is important to mention that CPE was carried out under the same experimental conditions in the absence of catechol, 1,3-dimethylbarbituric acid showed no activity towards the nickel hydroxide electrode.

The authors wish to express their thanks to Professor E. Steckhan for fruitful discussions suggestions made, revision of the manuscript, which contributed to improvement the paper. The Deutscher Akademischer Austauschdient (DAAD) for a short visit fellowship (M. A.) is gratefully acknowledged.

References

1) R. N. Adams, *Anal. Chem.*, **48**, 1126A (1976).
2) G. Dryhurst, K. M. Kadish, F. Scheller, and R. Renneberg, in "Biological Electrochemistry," Academic Press, New York (1982), Vol. 1, Chap. 2.
3) D. J. Brown in "Comprehensive Heterocyclic Chemistry," ed by A. R. Katritzky, Pergamon Press, Oxford (1984), Vol. 2, p. 150.
4) W. Pflediderer and K. H. Schündehütte, *Justus Liebigs Ann. Chem.*, **612**, 158 (1958).
5) L. Papouchado, G. Petrie, and R. N. Adams, *J. Electroanal. Chem. Interfacial Electrochem.*, **38**, 389 (1972).
6) M. D. Ryan, A. Yuehand, and W. Y. Chen, *J. Electrochem. Soc.*, **127**, 1489 (1980).
7) A. W. Sternson, R. McCreery, B. Feinberg, and R. N. Adams, *J. Electoanal. Chem. Interfacial Eelctrochem.*, **46**, 313 (1973).
8) M. D. Hawely, S. V. Tatawawadi, S. Piekarski, and R. N. Adams, *J. Am. Chem. Soc.*, **89**, 447 (1967).
9) G. Sivaramiah and V. R. Krishman, *Indian J. Chem.*, **4**, 541 (1967).
10) F. R. Hewgill, T. J. Stone, and W. A. Waters, *J. Chem. Soc.*, **1964**, 408.
11) Z. Grujic, I. Tabakovic, and M. Trkovnik, *Tetrahedron Lett.*, **1976**, 4823.
12) I. Tabakovic, Z. Grujić, and Z. Bejtovic, *J. Heterocycl., Chem.*, **20**, 635 (1983).
13) S. Kato, M. Poling, D. van der Helm, and G. Dryhurst, *J. Am. Chem. Soc.*, **96**, 5255 (1974).
14) M. F. Ansell and A. F. Gosden, *J. Chem. Soc., Chem. Commun.*, **1965**, 520.
15) H. J. Schäfer, *Top. Curr. Chem.*, **142**, 102 (1987).
16) M. V. George and K. S. Balachandran, *Chem. Rev.*, **75**, 491 (1975).
17) J. Kaulen and H. J. Schäfer, *Synthesis*, **7**, 513 (1979).