

Electrochemical Studies and Antioxidant Activity of Heterocyclic Nitrate Systems

Amlil A^{1,2}, Yassine H¹, Akhramez S¹, Touzara S², Ayad H³, Elabbadi N³, Chtaini A², Hafid A¹ and Khouili M^{1*}

¹Faculty of Science and Technology, Laboratory of Organic and Analytical Chemistry, University Sultan Moulay Slimane, Morocco

²Faculty of Science and Technology, Laboratory of Molecular Electrochemistry and Inorganic Materials, University Sultan Moulay Slimane, Morocco

³Faculty of Science and Technology, Laboratory of Biochemistry, University Sultan Moulay Slimane, Morocco

Abstract

A nitration by penta-hydrated bismuth $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (eq) was carried out on two commercial molecules, methoxynaphthalene 1 and naphthalen-2-ol 2. The compounds produced from this organic synthesis (1.a, 1.b, 1.c and 2') as well as the starting molecules 1 and 2 have undergone a study on their antioxidant capacity, using two methods: electrochemical cyclic voltammetry CV and DPPH biologically. The experimental results of the two methods confirm that the antioxidant power of these aromatic molecules is canceled in the case of nitration or by replacement of the hydroxyl group (molecule 2) by the methoxy group (molecule 1).

Keywords: Nitration; Naphthalene; Cyclic voltammetry; Antioxidant activity

Introduction

Nitration is one of the oldest and most important unit reactions in organic synthesis. It is a key reaction for the production of dyes, plastics and basic chemical reagents. Conventional nitration is generally carried out in a strongly acidic medium, such as nitric acid and concentrated sulfuric acid [1,2]. This method is associated with many drawbacks, which are due to excessive loss of acid. This loss is harmful to the environment. In addition to that, its treatment is difficult, with exorbitant cost. Because of the problems associated with mixed acids, alternative methods were to be a field of research. In this case, various nitrating agents have been studied under different conditions [3].

Most of these agents have drawbacks, such as the regio-selectivity of nitration and the oxidation of competitive substrates. Therefore, there is a need for the development of new methods of nitration of aromatic compounds [4]. In the shed of this work, we present an efficient and easy-to-use protocol for the nitration of aromatics. This is achieved in the presence of bismuth nitrate, which is a widely used reagent in organic synthesis. It is better known as a polyvalent oxidant. In addition to that, it is used as weak Lewis acid in various transformations, and often under microwave irradiation [5-7].

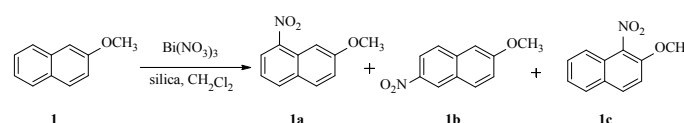
In the other side, the molecules containing the nitro group have been under investigation for a long time because of their important biological activity and specifically their antioxidant activities.

Despite wide application in organic synthesis, the utility of bismuth nitrate ($\text{Bi}(\text{NO}_3)_3$), as a nitrating agent, is relatively unexplored and may be underestimated. Previous studies have shown that bismuth nitrate ($\text{Bi}(\text{NO}_3)_3$) is effective for the nitration of phenolic compounds in the presence of a Lewis acid, in organic solvents and under microwave irradiation. Other authors have studied the nitration of arenes in the presence of bismuth nitrate and a catalyst such as silica. Furthermore, the operating conditions using silica with sulfuric acid, and silica in THF as a solvent under microwave, have been described in the literature Schemes 1 and 2 [8-10].

On our part, we used the nitrate of bismuth pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$), in the presence of silica. In this case, several tests were carried out on 2-methoxynaphthalene 1, while varying the amounts of the reagents (Table 1). All nitrated products were characterized by the usual spectroscopic methods (^1H , ^{13}C NMR and mass spectrometry).

Entry	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (eq)	Silica (eq)	Time	Yield (%)		
				1a	1b	1c
1	0.5	1	6h	12	14	57
2	0.95	1	6h	11.7	9.3	82
3	1.2	1	6h	7	18	74
4	2	1	4h	12	11	64
5	3	1	4h	11.5	9	48.8

Table 1: Results of the nitration reaction on methoxy-naphthalene.



Scheme 1: Nitration reaction of methoxynaphthalene with bismuth pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$)

Several researchers have shown the utility of the detection of nitrated organic products by physicochemical methods. In the literature, glassy carbon electrodes GCP and carbon fiber microelectrode CFME, represent the main electrochemical sensors used in the follow-up analyzes of these nitro compounds, such as Methyl parathion (MPT), para-nitrophenol (PNP) and o-nitrophenol (2-nitrophenol). This choice is due to their qualities of selectivity, efficiency, stability and reproducibility [11-13].

In order to increase the detection sensitivity of the nitro compounds, a modification of the surface of the electrodes mentioned above has been made. However, a passivation problem has occurred at a given concentration of micro pollutants, which represents the limit of detection of the electrodes used. This problem is solved for the GCP

*Corresponding author: Khouili M, Faculty of Science and Technology, Laboratory of Organic and Analytical Chemistry, University Sultan Moulay Slimane, Morocco, Tel: 00212661057943; E-mail: aminamlil@yahoo.fr

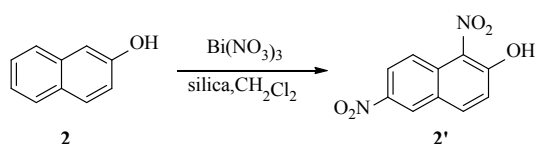
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electrode, followed by a protocol for polishing and rinsing its surface, which lasts for 20 minutes.

Our work consists of studying the electrochemical behavior of the different heterocycles synthesized from methoxynaphthalene 1 and naphthalen-2-ol 2 in order to understand the nucleophilic substitution reactions at different positions of these compounds by the Nitro group.



Scheme 2: Nitration reaction of naphthalen-2-ol with bismuth pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$)

The chosen electrode in our case is the CPE carbon paste electrode. This electrode is not disposable and not expensive and this is characterized by an immediate renewal of its surface, which solves the problem of passivation encountered at the level of other electrodes.

After the electrochemical analysis of the nitrated molecules, a biological study was carried out. In this part, an analysis of the antioxidant activity of the parent molecules as well as the nitrated organic molecules was carried out in order to compare the effect of nitration on the antioxidant power.

Experimental Section

Instrumentation

General synthetic methods: All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis by using silica gel (60 F254) plates. Compounds were visualized by UV irradiation at 256 or 365 nm. Column Chromatography was performed on silica gel 60. Melting points ($^{\circ}\text{C}$) were taken on samples in open capillary tubes. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 300 (300 MHz for ^1H spectra; 75 MHz for ^{13}C spectra). Chemical shifts are given in parts per million (ppm) from tetramethylsilane (TMS) as internal standard in CDCl_3 , and the residual peak of DMSO in $[\text{D}_6]$ DMSO. The following abbreviations are used for the ^1H NMR spectra multiplicities: br. s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet. Coupling constants (J) are reported in Hertz [Hz].

Synthesis of nitrated organic molecules: a) Nitration reaction of methoxy-naphthalene with bismuth pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$) 2-Methoxynaphthalene (0.5 g, 3.164 mmol) and silica (500 mg) were added to a suspension in CH_2Cl_2 (20 ml) of 1.2 equivalents of bismuth pentahydrate nitrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$) (1.84 g, 3.777 mmol). The mixture was refluxed for 6 h. After cooling to room temperature, the reaction mixture was filtered and washed with CH_2Cl_2 , the resulting filtrate was concentrated, and the resulting residue was purified by column chromatography using EtOAc-hexane (1: 9 v / v). The products were obtained (1.a, 1.b and 1.c) with a total yield of 99%.

7-methoxy-1-nitronaphthalene 1.a: Yield: 7%; yellow powder; mp 64-66 $^{\circ}\text{C}$; ^1H NMR (DMSO, 300 MHz): δ (ppm) 8.24-8.35 (m, 2H, Ar-H), 8.07 (d, 1H, Ar-H, $J=9\text{Hz}$), 7.79 (d, 1H, Ar-H, $J=2.4\text{Hz}$), 7.52 (t, 1H, Ar-H, $J=7.8\text{Hz}$), 7.36 (dd, 1H, Ar-H, $J=9\text{Hz}$, $J=2.4\text{Hz}$), 3.90 (s, 3H, OCH₃); ^{13}C NMR (DMSO, 75 MHz): δ 160.6, 145.1, 135.4, 131.2, 130.1, 126.3, 125.6, 122.7, 120.3, 101.6, 55.8.

2-methoxy-6-nitronaphthalene 1.b: Yield: 18 %; yellow powder; mp 130-132 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO): δ 8.89 (d, 1H, Ar-H), 8.17 (dd, 2H, Ar-H, $J=9\text{Hz}$, $J=2.4\text{Hz}$); 8.00 (d, 1H, Ar-H, $J=9.3\text{Hz}$); 7.51 (d, 1H, Ar-H, $J=2.4\text{Hz}$); 7.34 (dd, 1H, Ar-H, $J=9.3\text{Hz}$, $J=2.7\text{Hz}$); 3.92 (s, 3H, OCH₃); ^{13}C NMR (DMSO, 75 MHz): δ 160.9, 143.6, 138.1, 132.3, 128.7, 127.2, 125.0, 121.2, 120.1, 106.8, 56.1.

2-methoxy-1-nitronaphthalene 1.c: Yield: 74%; crystalline yellow powder (ref Acta Cryst E); mp 110-112 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO): δ 8.20 (d, 1H, Ar-H, $J=9\text{Hz}$), 8.02 (d, 1H, Ar-H, $J=8.4\text{Hz}$), 7.71-7.47 (m, 4H, Ar-H), 4.01 (s, 3H, OCH₃); ^{13}C NMR (DMSO, 75 MHz): δ 148.7, 133.1, 129.9, 128.8, 128.0, 125.6, 125.0, 119.8, 114.5, 57.6.

b) Nitration reaction of naphthalen-2-ol with bismuth pentahydrate ($\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$)

2-Naphthol (0.5 g, 3.37 mmol) and silica gel (500 mg) were added to a suspension of bismuth nitrate pentahydrate (1.2 eq) (1.96 g, 4.044 mmol) in CH_2Cl_2 . The mixture was refluxed for 24 hours. After cooling to room temperature, the reaction mixture was filtered and washed with CH_2Cl_2 , the resulting filtrate was evaporated under vacuum, and the resulting residue was purified by column chromatography using EtOAc-hexane (1:9 v/v).

Preparation of the carbon paste electrode (CPE)

The carbon paste electrode has been developed according to the protocol cited in reference [14]. The graphite carbon powder was mixed with the paraffin oil in previously defined proportions. The resulting paste is inserted into the electrode cavity of 0.258 cm^2 section, a carbon rod is used to provide electrical conduction.

Electrochemical materials: The electrochemical measurements were invested by a Palm-Sens Em-Stat potentiostat. The electrochemical cell is equipped with three electrodes: a reference electrode (ECS), working electrode (CPE) and the counter electrode (platinum plate).

Results and Discussion

Electrochemical characterization of nitrated molecules

The electrochemical characterization of these molecules was carried out through two stages:

- Characterization of the parent molecule before its nitration.
- Characterization of molecules produced after nitration of the parent molecule.

The nitration of methoxynaphthalene produced three molecules that differ in the position of the NO_2 group.

- 1.a: The nitro group NO_2 is in position 8.
- 1.b: The nitro group NO_2 is in position 6.
- 1.c: The NO_2 nitro group is in position 1.

The electrochemical studies were invested by cyclic voltammetry (CV), in an acetic buffer solution of pH=5.2, at ambient temperature and without stirring. The detected concentration of these molecules is estimated at 8×10^{-4} M in a volume of 40 ml of the acetic buffer.

Electrochemical characterization of the parent molecule 1 before its nitration

As seen before, the electrode used for this study is the CPE carbon paste electrode, this electrode has been electrochemically characterized

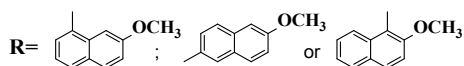
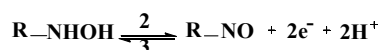
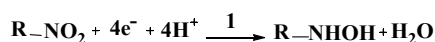
before and after the addition of the molecule in the electrolytic medium. The results obtained are shown in Figure 1.

The presence of methoxynaphthalene in the medium is characterized by the appearance of a peak of reduction towards approximately -0.5V/ECS, this isolated peak corresponds to the irreversible reduction of methoxynaphthalene.

Electrochemical characterization of the nitrated molecules produced from the parent molecule 1

a) Analysis of the EPC modified by 1.a. The molecule 1.a was introduced into the carbon paste in powder form; the resulting electrode is introduced into the measuring cell containing the buffer solution.

We find, at the first scan, in the direction of the negative potential, the presence of a reduction peak P_1 at the potential -0.815V/ECS and an oxidation peak P_2 in the direction of the positive scanning at the potential +0.13V/ECS. The second cycle shows a reduction peak P_3 at the potential +0.09V/ECS at cathodic scanning and the peak P_2 already obtained at the previous anodic scanning. The peak P_1 is irreversible and the peaks P_2 and P_3 represent a reversible oxidation-reduction phenomenon. P_4 is the oxidation peak of the methoxy group (-OCH₃). The electrochemical detection of 1.a is based on two redox systems. Indeed, at first it is reduced in an irreversible way, according to the equation (1). The product of this first reduction (R-NHOH) oxidizes reversibly according to equation (2) (Figure 2) [11].



b) Analysis of the EPC modified by 1.b:

The voltammogram recorded by the carbon paste electrode modified by the molecule 1.b Figure 3 shows the same behavior recorded for the molecule 1.a with a displacement of the potentials of the three peaks

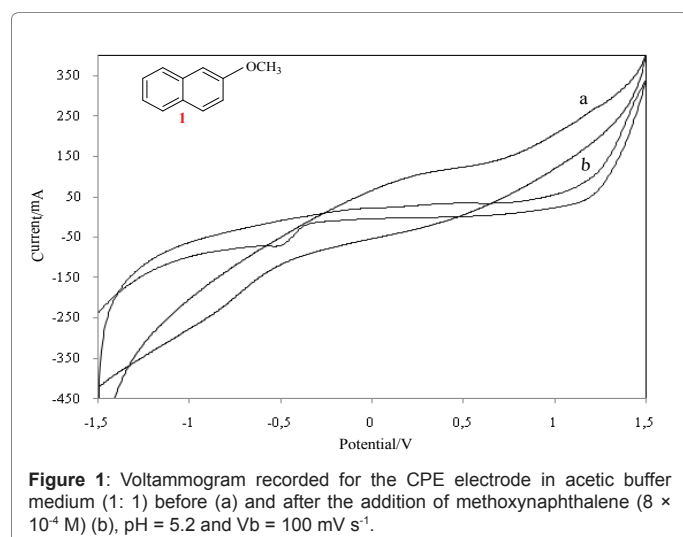


Figure 1: Voltammogram recorded for the CPE electrode in acetic buffer medium (1: 1) before (a) and after the addition of methoxynaphthalene (8×10^{-4} M) (b), pH = 5.2 and $V_b = 100$ mV s⁻¹.

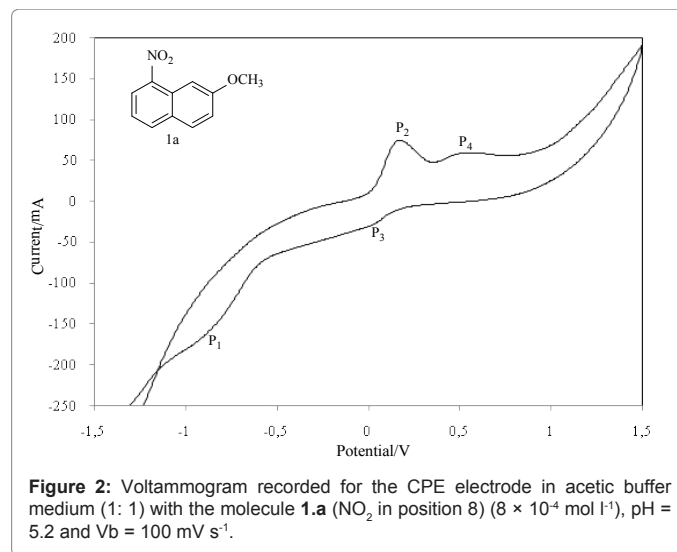


Figure 2: Voltammogram recorded for the CPE electrode in acetic buffer medium (1: 1) with the molecule 1.a (NO_2 in position 8) (8×10^{-4} mol l⁻¹), pH = 5.2 and $V_b = 100$ mV s⁻¹.

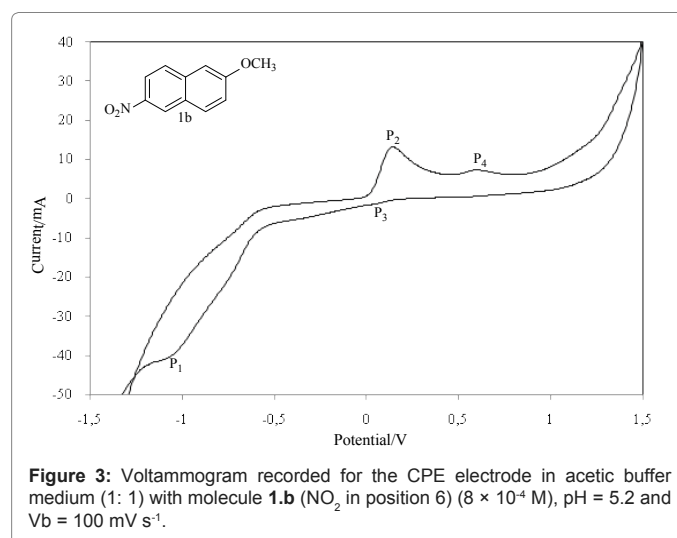


Figure 3: Voltammogram recorded for the CPE electrode in acetic buffer medium (1: 1) with molecule 1.b (NO_2 in position 6) (8×10^{-4} M), pH = 5.2 and $V_b = 100$ mV s⁻¹.

characteristic of the oxidation-reduction of the grouping nitro (NO_2) which is due to the position of the nitro group (NO_2) relative to the methoxy group (-OCH₃). We observe that the reduction peak P_3 is less visible for this molecule.

c) Analysis of the EPC modified by 1.c:

The voltammograms below show the electrochemical response obtained when the working electrode is the carbon paste modified by the molecule 1.c. The voltammogram has the same speed as those obtained by the other electrodes, except that the potentials of the peaks are shifted towards the positive values (Figure 4).

Results Summary

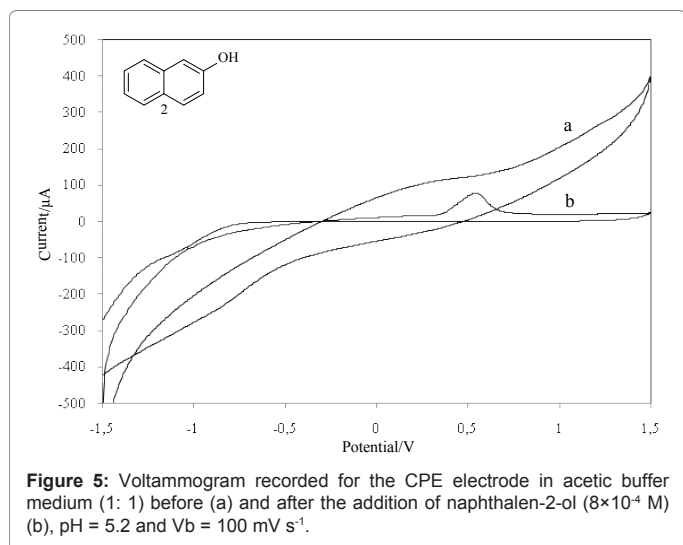
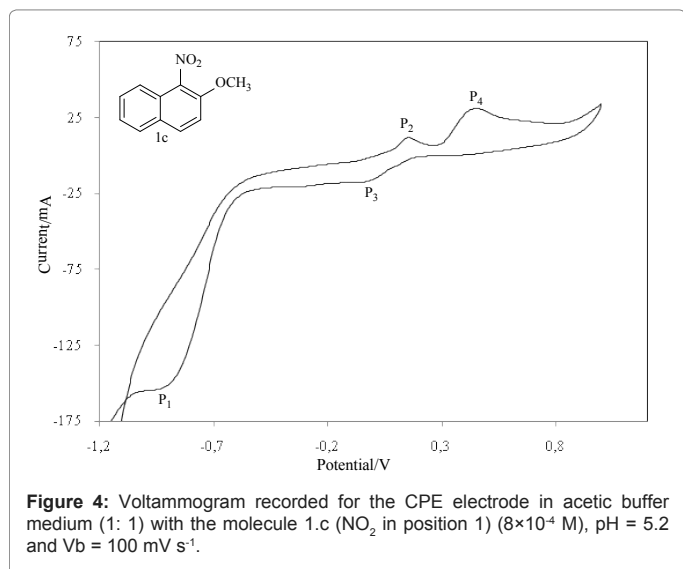
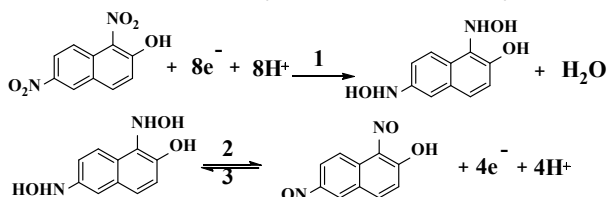
Electrochemical characterization of the parent molecule 2 before its nitration

In the light of these studies, two molecules of naphthalene were nitrated. The difference exists in the group attached to each molecule. The parent molecule 1 has a methoxy group (-OCH₃) and the parent molecule 2 has an alcohol group (OH). The electrochemical characterization of the parent molecule 1 shows no oxidation-reduction

peak (Figure 1), whereas the characterization of the parent molecule 2 exhibits an oxidation peak at the 0.5 V potential (Figure 5).

Electrochemical characterization of the nitrated molecule produced from the parent molecule 2

The peaks P_1 , P_2 , P_4 , P_3 and P_5 are even thinner compared to the peaks of the molecules of the reaction 1. We also note the presence of a single peak of reduction P_1 at the potential -0.66 V/ECS which characterizes the reduction of the two nitro groups (NO_2). On the other hand, we have two redox couples (P_2, P_3) and (P_4, P_5) which characterizes the oxidation-reduction of the groups (NHOH/NO) (Figure 6).



As it is described in Tables 2 and 3 we note that the potentials of the three characteristic peaks of the oxidation-reduction concerning the nitro group are compatible with the results seen in the bibliography.

In order to broaden our vision of the link between antioxidant and oxidoreduction, we will study the electrochemical responses of two other commercial molecules, naphthalene A and 1,2-benzenediol B, due to their chemical structures close to molecules studied during this work. Plus ascorbic acid (Vitamin C) which has a very high antioxidant activity (Figure 7).

The cyclic voltammogram of naphthalene does not represent any oxidation or reduction peak (Figure 8).

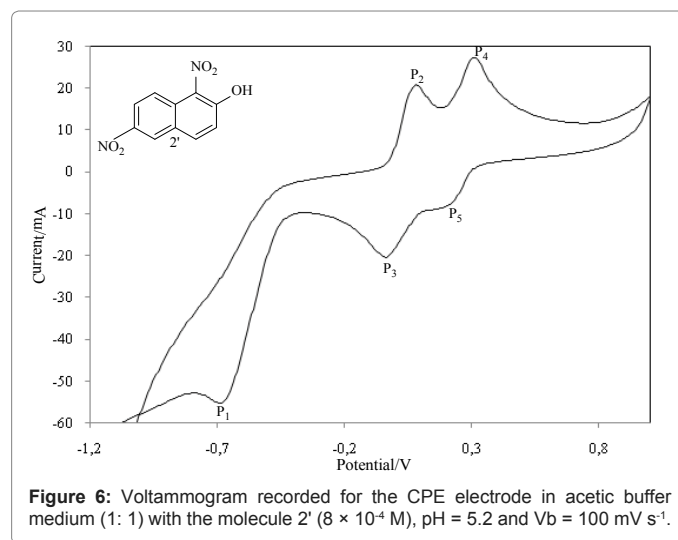
A single peak of reduction appears on the 1,2-benzenediol CV at -0.12 V/ECS potential (Figure 9). On the CV of ascorbic acid appears an oxidation peak at the potential 0.7 V/ECS.

The analysis of the electrochemical results obtained shows that the antioxidant properties of these molecules are based on two principles:

- Principle 1: The molecule has an antioxidant power, if it has stronger oxidizing properties than the molecule having the free radical.
- Principle 2: The molecule has antioxidant power, if it has stronger reducing properties than the target molecule.

We therefore deduce that:

- Molecules with oxidizing properties and reversible reducing properties (1.a, 1.b, 1.c and 2') at the liver do not have antioxidant properties because they are not part of either principle.

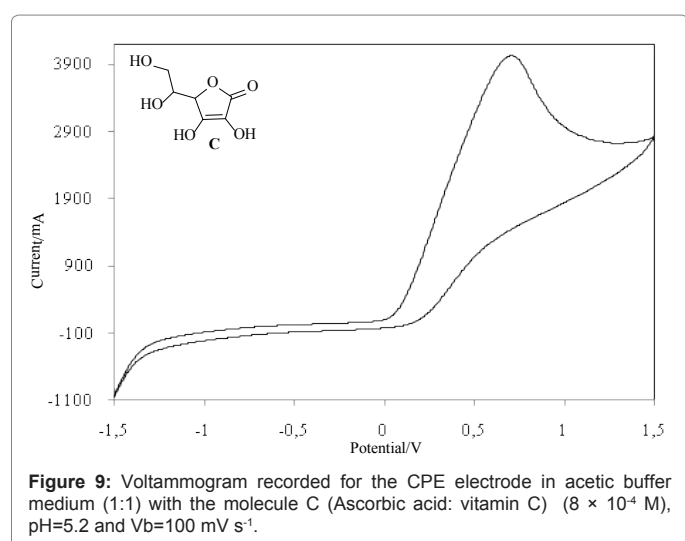
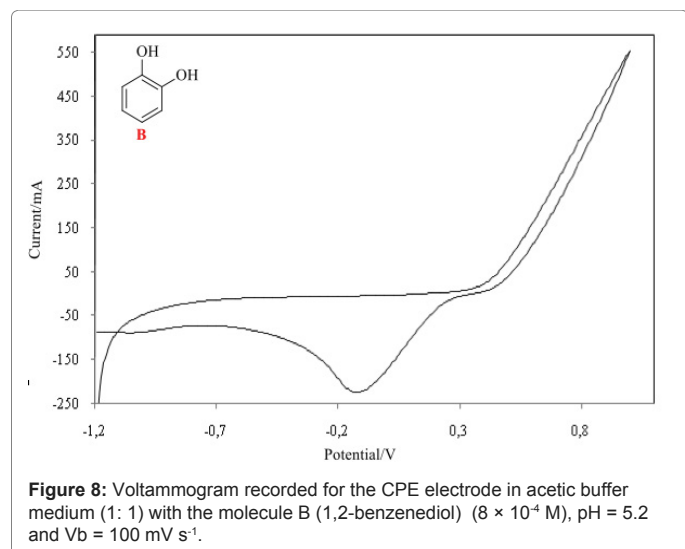
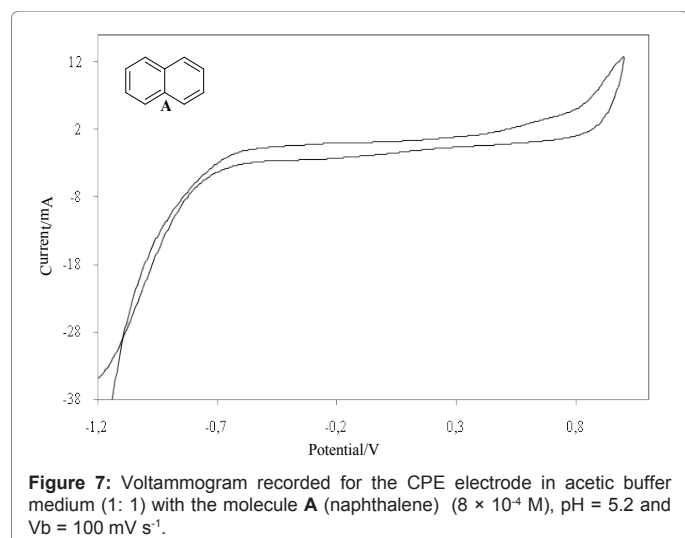


Molecule	1.a	1.b	1.c
Ep_1 (V)	-0,815	-1	-0,87
Ep_2 (V)	+0,13	+0,105	+0,03
Ep_3 (V)	+0,09	+0,11	+0,11

Table 2: The potentials of the three peaks for each nitrated molecule.

Molecule	2'
Ep_1 (V)	-0,66
Ep_2 (V)	+0,05
Ep_3 (V)	-0,01
Ep_4 (V)	+0,28
Ep_5 (V)	+0,05

Table 3: The potentials of the five peaks of the nitro molecule 2'.



- Molecules 2 and B have potential antioxidant properties:

- Molecule 2 has stronger oxidative properties than the target molecule, which follows principle 2.
- Molecule B, on the other hand, has stronger reducing properties than the free radical, which inhibits the reducing properties of the latter.

Antioxidant activity of heterocyclic nitrate systems

The free radical scavenging potentials of commercial or synthesis compounds and ascorbic acid at different concentrations were evaluated by using DPPH method. Antioxidants react with DPPH, which is a nitrogen-centered radical with a characteristic absorption at 517 nm and convert to 1,1-diphenyl-2-picryl hydrazine. The degree of discoloration indicates the scavenging potentials of the antioxidant compounds. The results showed that 2-naphthol as well as 1,2-benzenediol reduced the DPPH radical in dose dependent manner and the IC_{50} was found to be $50 \mu\text{g/ml}$ and $20 \mu\text{g/ml}$, respectively Figure 7 and Table 4.

Code of the molecule	Structure of the molecule	Classifications	IC_{50} Value ($\mu\text{g/ml}$)
1		methoxynaphthalene	>1600
1.a		7-methoxy-1-nitronaphthalene	>1600
1.b		2-methoxy-6-nitronaphthalene	>1600
1.c		2-methoxy-1-nitronaphthalene	>1600
2		2-naphthol	50 ± 4
2'		1,6-dinitronaphthalen-2-ol	>1600
A		naphthalene	>1600
B		1,2-benzenediol	20 ± 2
C		ascorbic acid : vitamin C	5 ± 0.5

Table 4: Antioxidant effect was evaluated by DPPH method.

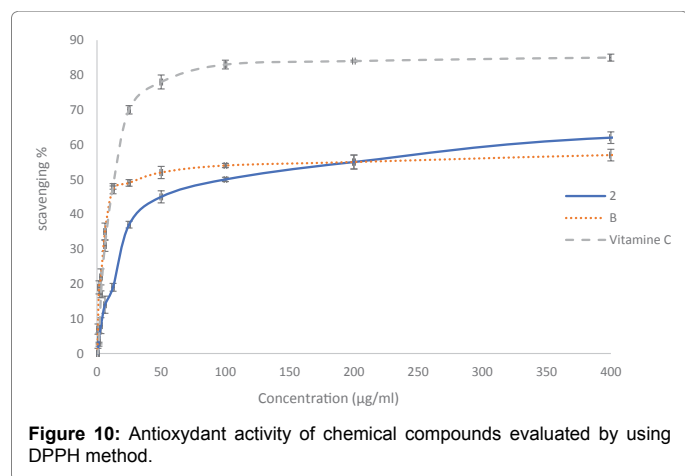


Figure 10: Antioxidant activity of chemical compounds evaluated by using DPPH method.

Compounds were prepared in DMSO then diluted in methanol at appropriate concentrations (see method section). Then 150 µl of methanolic solution of DPPH (40 µg/ml) was added to each well, shaken and the test plate was allowed to stand in the dark at 37°C for 30 min. Absorbance was measured at 517 nm using a test plate reader (ELISA).

It is noteworthy that these phenolic compounds are as active as the standard ascorbic acid ($IC_{50}=5 \mu\text{g/ml}$) used. Nitration of 2-naphtol in position 1 and 6 by bismuth penta-hydrate reagent was carried out as described in method section and the identified compound 1,6-dinitronaphtalen-2-ol was completely inactive on DPPH radical, even at highest concentrations (1,6 mg/ml) Table 4. As expected naphthalene as well as the methoxy-naphtalene series were not able to react positively with DPPH radical in our experiment conditions (Table 4 and Figure 10).

Phenolic compounds were able to scavenge radicals and to chelate metals while ascorbic acid can play a pro-oxidant role in the presence of transition metals. However, when the hydroxyl group was substituted for methoxy or when nitration on aromatic molecular part was occurred, the antioxidant power was drastically cancelled, pointing out the relationship between the capacity of hydrogen to move from hydroxyl group (phenolic) and the scavenging potentials of the antioxidant compounds. Indeed, the antioxidant capacity of the phenolic compounds is mainly due to their redox properties, which allow them to act as reducing agents, hydrogen donors and singlet oxygen quenchers, or decomposing peroxides [15,16]. The ability of some compounds to scavenge free radicals in DPPH tests does not mean that these compounds will perform readily where complex mechanisms are operating such as those in physiological substrates. For this reason, there is a need to verify the antioxidant effect in scavenging specific species such as superoxide anion radical ($O_2^{\cdot-}$), hydroxyl radical ($\cdot OH$) and hydrogen peroxide (H_2O_2). These oxygen species are often generated in organisms by diverse cellular processes, such as the electron transport chain in mitochondria, in microsomes and through enzymes like xanthine oxidase and NADPH oxidase or from exogenous factors. These reactive species, which can be increased as part of certain pathologies [17], cause oxidative damage in reactions with almost every molecule found in living cells [18,19].

Conclusion

Our work has been divided into two parts, the first one devoted to the organic synthesis of new nitrated organic molecules (1.a, 1.b, 1.c

and 2'). The second studies the antioxidant power of molecules 1 and 2, before and after nitration and other commercial molecules, in two ways: electrochemical and biological. According to the electrochemical results obtained, the molecules having at the same time the oxidizing properties and the reversible reducing properties (1.a, 1.b, 1.c and 2') have no antioxidant power, because they are not part of neither of the two principles. While, molecules 2 and B have important antioxidant properties. This has been confirmed by the biological results.

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