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An investigation of nucleophilic substitution reactions of 2,3-dichloro-1,4-naphthoquinone with various nucleophilic reagents

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Abstract: Novel *N*-, *N,S*- and *N,O*-substituted naphthoquinone compounds were prepared by the reactions of 2,3-dichloro-1,4-naphthoquinone (**1**) and the corresponding nucleophiles in the presence of chloroform and triethylamine or an ethanolic solution of Na₂CO₃. The structures of the novel naphthoquinone compounds were characterized by microanalysis, FT-IR, ¹H-NMR, ¹³C-NMR, MS and cyclic voltammetry.

Keywords: 1,4-naphthoquinone; thioethers; amine; indolylquinones.

INTRODUCTION

The synthesis of novel quinone derivatives have been receiving great attention because of the bright colors and pharmaceutical properties of quinones.^{1–3} Quinone-type drugs systems are also being developed and many of the clinically approved drugs are quinone related compounds.^{4–7} Antibacterial and antifungal activities of some novel naphthoquinone derivatives were reported previously in the literature.^{8–10}

2,3-Dichloro-1,4-naphthoquinone (**1**) was selected as the starting material because it is reasonably stable, readily available and is known as a key synthetic intermediate in organic, medicinal and industrial chemistry. The aim of this study was the synthesis of derivatives of the quinone and their characterization with spectral methods.

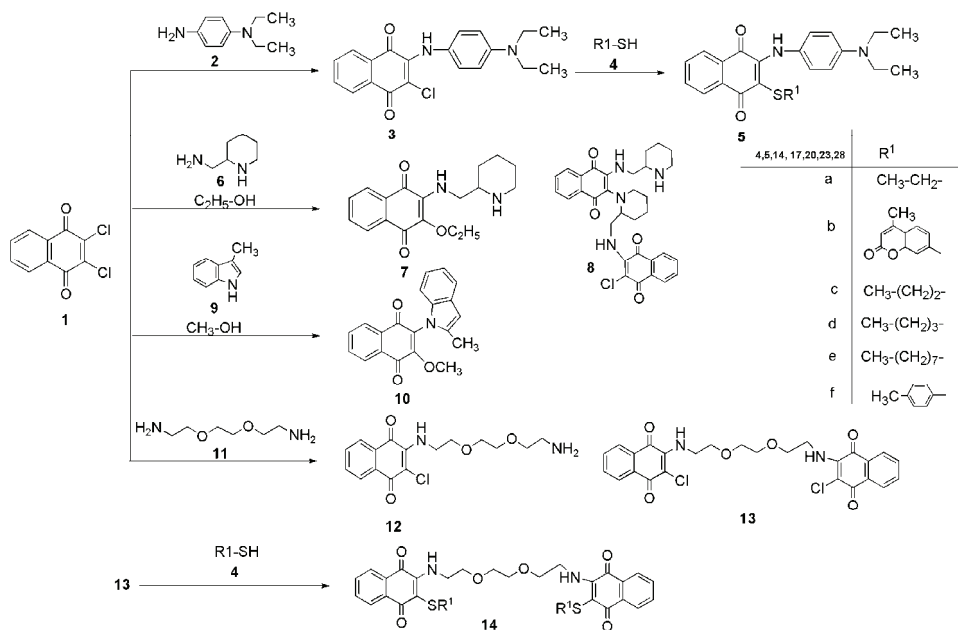
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RESULTS AND DISCUSSION

Chemistry

The reactions of 2,3-dichloro-1,4-naphthoquinone (**1**) with various N- or S-nucleophiles resulted in the substitution of one or both of the chlorine atoms.^{11,12} The reaction occurs according to the addition–elimination mechanism.¹³ Some novel indolylquinones were also synthesized using 3-substituted indole derivatives and *N*-substituted quinonyl derivatives were obtained. These substitution reactions of *p*-chloranil are known from the literature.^{14,15}

Compound **3**¹⁶ was obtained by reaction of **1** with **2** in chloroform with triethylamine (Et₃N). The novel *N*-, *S*-substituted naphthoquinones **5a–e** were obtained by the reactions of compound **3**¹⁶ and various thiols **4a–e**. The synthetic strategy for the novel compounds is illustrated in Scheme 1. The ¹³C-NMR spectrum of compound **5a** gave two carbon signals for C=O groups at 179.6 and 179.7 ppm due to the naphthoquinone unit. In the IR spectra of compound **5b**, the lactone carbonyl group was seen at 1734 cm⁻¹, while the quinone carbonyl group appeared at 1666 cm⁻¹. In the mass spectrum of compounds **5c** and **5d**, the accurate mass measurements of the molecular ion peaks were registered at *m/z* 395 and 409 [M+H]⁺, respectively. The S-CH₂ protons of **5e** appeared in the ¹H-NMR spectrum as triplets at 2.50 ppm.



Scheme 1. Synthetic pathway for the synthesis of the novel substituted naphthoquinone derivatives.

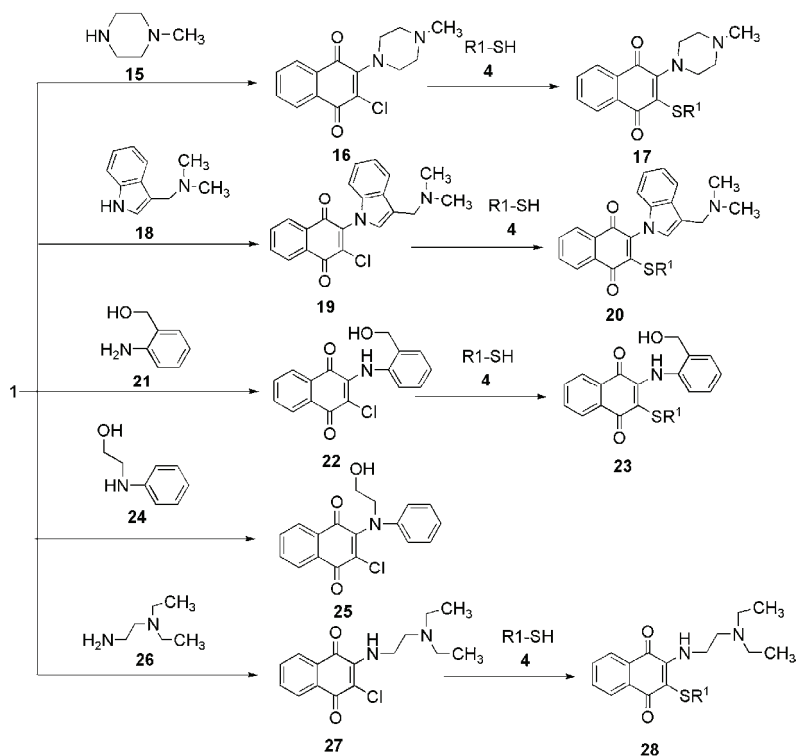
N- and ethoxy-substituted naphthoquinone **7** was obtained by reaction of **1** and an equivalent number of moles of **6** in an ethanolic solution of Na₂CO₃. The –OCH₂ protons of **7** appeared in the low-field region of the ¹H-NMR spectrum as multiplets at 4.57–4.60 ppm. The interesting *N,N*-substituted dinaphthoquinone derivative **8** was synthesized by the reaction of **1** and the equivalent number of moles of **6** in chloroform with triethylamine. The derivative **8** was obtained as a stable brown solid in good yield. In the mass spectrum of compound **8**, the accurate mass of the molecular ion peak as the sodium adduct ion was observed at *m/z* 595 [M+Na]⁺.

The reaction of **1** with indole **9** in methanol resulted in the *N*- and methoxy-substituted compound **10**. The –OCH₃ protons of compound **10** appeared in the ¹H-NMR spectrum as singlet at 4.10 ppm. In this reaction, methanol behaved as a nucleophile and attacked the naphthoquinone to give the addition reaction. The indole-substituted quinone derivatives were colored stable compounds.

The known compound **13**¹⁷ and the novel compound **12** were obtained by reaction of **1** with diamine **11**. The mass spectrum of compound **12** in the positive ion mode of the ESI technique confirmed the proposed structure; the protonated molecular ion peak was identified at *m/z* 339 [M+Na]⁺. The reactions of **13**¹⁷ with thiols **4d** and **e** gave the interesting *N,S*-substituted dinaphthoquinone derivatives **14d** and **14e**, which were obtained in high yields. In the ¹³C-NMR spectrum of compound **14d**, two carbonyl carbon signals were observed at 179.1 and 180.3 ppm. In the mass spectrum of compound **14e**, the accurate mass of the molecular ion peak was registered at *m/z* 749 [M+H]⁺. The known compound **16**¹⁸ was obtained by reaction of naphthoquinone **1** with amine **15** in chloroform in the presence of Et₃N. The reaction of compound **16**¹⁸ with thiols **4d–f** gave the novel *N,S*-naphthoquinone derivatives **17d–f**. In the ¹H-NMR spectrum of compound **17d**, the –SCH₂ protons gave a triplet at 2.96 ppm and the C–CH₃ for compound **17f** gave multiplets at 1.40–1.45 ppm (Scheme 2).

The *N*-substituted naphthoquinone **19** was synthesized by reaction of **1** with **18** in chloroform in the presence of Et₃N. The ¹H-NMR spectrum of compound **19** showed the –NCH₂ protons as a singlet at 3.37 ppm. The compound **20d** was obtained by the reaction of compound **19** with **4d** in ethanol with Na₂CO₃. In the ¹³C-NMR spectrum of the *N,S*-substituted compound **20d**, two carbonyl carbon signals were observed at 179.4 and 180.5 ppm. The novel compound **22** was obtained by reaction of **1** with amine **21**. The IR spectrum of compound **22** showed a characteristic amine band (–NH) at 3365 cm^{–1}. The *N,S*-naphthoquinone substituted **23c** and **d** were obtained by reaction of **22** with **4c** and **d** in ethanol containing Na₂CO₃. In the mass spectrum of compounds **23c** and **d**, the accurate mass measurements of the molecular ion peaks were registered at *m/z* 366 [M+H]⁺ and 354 [M–H][–], respectively. The *N*-substituted naphthoquinone **25** was obtained in the reaction of **1** with *N*-(2-hydroxyethyl)aniline **24** in chloro-

form in the presence of Et₃N. The -NCH₂ protons of **25** appeared in the low-field region of the ¹H-NMR spectrum as triplets at 3.80 ppm.



Scheme 2. Synthesis of novel *N*- and *N,S*-substituted naphthoquinone derivatives.

The reaction of the known compound **27**¹⁹ with **4d** and **e** gave the *N,S*-substituted naphthoquinones **28d** and **e**. The mass spectrum of compounds **28d** and **e** gave molecular ion peaks at m/z 361 [M]⁺ and 417 [M+H]⁺, respectively.

Electrochemical assay

Some of the novel naphthoquinone derivatives were studied by cyclic voltammetry in aprotic media (DMF) using tetrabutylammonium perchlorate (0.10 M) as the supporting electrolyte at 100 mV s⁻¹ on a glassy carbon electrode. The electrochemical parameters, including cathodic peak potentials (E_{pc1} and E_{pc2}), the half-wave peak potentials ($E_{1,1/2}$) and the difference between the first oxidation and reduction processes (ΔE_p) are given in Table I.

The cyclic voltammogram of 2,3-dichloro-1,4-naphthoquinone (**1**) gave two monoelectronic waves. The first (c_1) and second (c_2) cathodic peaks corresponded to the semiquinone (Q/Q⁻) and dianion (Q⁻/Q²⁻) pairs, respectively.

TABLE I. Half-wave potentials (for the 1st wave) and electrochemical data for some of the naphthoquinone derivatives ($c = 1.0 \times 10^{-3}$ M) in 0.1 M DMF/TBAP; $\Delta E_{p1} = E_{pa1} - E_{pc1}$; $E_{1,1/2} = (E_{pa1} + E_{pc1})/2$

Compound	E_{pc1} / V	E_{pc2} / V	$\Delta E_{p1} / mV$	$E_{1,1/2} / V$
2,3-Dichloro-1,4-naphthoquinone (1)	-0.4038	-1.1620	235	-0.2862
3 ¹⁶	0.3133	-0.6661	265	0.4459
5a	0.2483	-0.7499	300	0.3984
5c	-0.3043	-0.7171	252	0.1262
5d	0.2953	-0.7361	133	0.1337
5e	0.2444	-0.7530	303	0.3960
8	-	-0.9873	-	-
14d	-0.2203	-0.7709	102	-0.2712
14e	-0.2774	-0.7980	-	-
19	-0.6961	-1.235	128	-0.6323
20d	-0.7550	-1.3580	88	0.7112
22	-0.5286	-0.7391	-	-
27 ¹⁹	-0.4737	-0.7410	-	-
28d	-0.7839	-0.7201	84	-0.7520
28e	-0.7988	-	99	-0.7494

The reduction mechanism changed when 2,3-dichloro-1,4-naphthoquinone (**1**) was substituted with *N*-nucleophiles. Additional cathodic and anodic peaks were detected in the voltammograms because of the various type of substituents.²⁰ During the electrochemical study of the *N*-substituted compound **3** and the *N,S*-substituted compounds **5a**, **5c–5e**, **14d** and **14e**, the CV displayed a different profile that did not follow the typical two monoelectronic reversible charge transfer process occurring for 2,3-dichloro-1,4-naphthoquinone (**1**). Three peaks were observed in both cathodic and anodic regions of the CV. The potential in the first reduction step for compound **5a** was seen at $E_p(c_1) = 0.2483$ V. This could be related the acidity level of the proton settled on the nitrogen atom.²¹ The first cathodic peak was not observed in the CV for the dinaphthoquinone compound **8**. The resulting voltammogram of compound **19** showed two typical successive one-electron reduction processes that could be observed for quinones in aprotic media. This can be related to the absence of a proton in the molecule. The *N*-substituted compound **27** gave three cathodic peaks in the CV. The resulting voltammogram of the *N,S*-substituted compounds **28d** and **e** showed a decrement in the peak intensities.

EXPERIMENTAL

Chemistry

The melting points were measured on a Buchi B-540 melting point apparatus. The elemental analyses were realized on a Thermo Finnigan Flash EA 1112 Elemental Analyser. The infrared (IR) spectra were recorded in KBr pellets on a Perkin Elmer Precisely Spectrum One FTIR spectrometer. ¹H- and ¹³C-NMR spectra were recorded on a Varian UNITYINOVA

instrument operating at 500 MHz for ^1H -NMR and 126 MHz for ^{13}C -NMR spectra. The mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer according to ESI probe. The products were isolated by column chromatography on silica gel (Merck Silica gel 60, particle size 63–200 μm). TLC plates silica 60F₂₅₄ (Merck, Darmstadt), detection with ultraviolet light (254 nm). All chemicals were of reagent grade and used without further purification.

The analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

Cyclic voltammetry measurements were performed in a conventional three-electrode cell using a computer-controlled Gamry Reference 600 Model potentiostat/galvanostat. A glassy carbon disc was used as the working electrode. The surface of the working electrode was polished with alumina before each run. A platinum wire served as the counter electrode. The reference electrode was an Ag/AgCl electrode. Electrochemical grade tetrabutylammonium perchlorate (TBAP) in extra pure DMF was employed as the supporting electrolyte at a concentration of 0.10 M. Prior to each run, the solutions were purged with nitrogen. Measurements were made over a potential range between 1.0 and -2.0 V with a step rate of 0.1 V s^{-1} .

General procedures

Procedure 1. 1.0 g (4.4 mmol) 2,3-dichloro-1,4-naphthoquinone (**1**) and the corresponding nucleophile were stirred in CHCl_3 (30 mL) with triethylamine (3 mL) solution for 2–3 h at room temperature. The color of the solution quickly changed and the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4×30 mL), and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

Procedure 2. 1.0 g (4.4 mmol) 2,3-dichloro-1,4-naphthoquinone (**1**) and the corresponding nucleophile were stirred in EtOH (65 mL) solution of Na_2CO_3 (1.52 g) for 2 to 3 h at room temperature. The color of the solution quickly changed and the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4×30 mL), and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

Procedure 3. 1.0 g (4.4 mmol) 2,3-dichloro-1,4-naphthoquinone (**1**) and 8.86 mmol nucleophile were stirred in a methanolic (65 mL) solution of Na_2CO_3 (1.52 g) for 2 to 3 h at room temperature. The color of the solution quickly changed and the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4×30 mL), and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

CONCLUSIONS

Novel substituted naphthoquinone compounds were synthesized from the reactions of **1** and related nucleophiles in different reaction media. The structures of novel compounds were characterized by microanalysis, FT-IR, ^1H -NMR, ^{13}C -NMR, MS and cyclic voltammetry.

SUPPLEMENTARY MATERIAL

The analytical and spectral data of the synthesized compounds are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

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ИЗВОД

ИСПИТИВАЊЕ РЕАКЦИЈЕ НУКЛЕОФИЛНЕ СУПСТИТУЦИЈЕ
2,3-ДИХЛОР-1,4-НАФТОХИНОНА СА РАЗЛИЧИТИМ НУКЛЕОФИЛИМА

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Синтетисани су нови *N*-, *N,S*- и *N,O*-супституисани деривати нафтохинона реакцијом 2,3-дихлор-1,4-нафтохинона (**1**) са одговарајућим нуклеофилима у хлороформу у присуству триетиламина или у етанолу у присуству Na₂CO₃. Структуре нових једињења одређене су микро-анализом, FT-IR, ¹H-NMR, ¹³C-NMR, MS и цикличном волтаметријом.

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