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**Research Article**

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# A new method for the synthesis of juglone

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**ABSTRACT**

*In the present study, an appropriate synthetic route was adopted to produce the target synthesis of Juglone. In the first of these objectives, 5-nitro-1,4-naphthoquinone had been synthesized by direct nitration of 1,4-naphthoquinone in the presence of water and sulfuric acid. Then the intermediate synthesis of 5-amino-1,4-naphthoquinone was obtained by the reduction of nitro. Finally, Juglone was produced after the hydrolysis of diazonium salt of 5-amino-1,4-naphthoquinone. The chemical structure of the product obtained by the process of the present study was verified by IR and $^1$H NMR. The data accord well with those recorded on literatures.*

**Keywords**: Juglone; 5-Nitro-1,4-naphthoquinone; 5-Amino-1,4-naphthoquinone; Diazonium salt; Nitro reduction; Hydrolysis.

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## INTRODUCTION

Juglone, 5-hydroxy-1,4-naphthoquinone, obtained from the shells of unripe walnuts, exhibits a wide spectrum of pharmaceutical activities including antibacterial and antitumor properties. Due to the ability to create dark orange-brown stains, it has also found use as a dye for textile and as a coloring agent for foods and cosmetics. Nowadays, Juglone and its derivatives are also exploited as a valuable precursor for the synthesis of potential anti-cancer drugs and redox intermediates in fuel-cell [1]. Thus, economic and ecological considerations are increasingly focusing interest at the present time on the efficient chemical synthesis of Juglone instead of extracting from green walnuts skin.

Heretofore, it is known that Juglone can readily be obtained by the oxidation of 1,5-dihydroxynaphthalene with various oxidants [2,3,4] . However, the traditional route of oxidation using chromic acid [2,3] and peroxyacetic acid [4] suffer from the disadvantages of high capital cost, low yield and formation of by-product of 5-hydroxy-1,2-naphthoquinone [4]. In addition, other methods for its synthesis often require starting materials which are not readily available [5].

An object of the present study is to provide a novel process for the production of Juglone by hydrolysis of diazonium salt of 5-amino-1,4-naphthoquinone (ANQ) . Another object of the present study is to overcome the above-mentioned drawbacks by using such compounds and processes and to provide a process whereby the inexpensive material of 1,4-naphthoquinone.

The intermediate of ANQ obtained by the process of the present study is not necessarily isolated from the reaction mixture but can be diazotized directly in the same medium. In this study, three basic principles including nitration, reduction and oxidation were employed to produce the synthesis of ANQ. Their formulae are shown in Fig. 1

It is generally known that when a solution of a diazonium salt is heated, nitrogen is evolved and the diazo group is replaced by a hydroxyl group in an $S_N1$ type of displacement reaction [6]. In order to obtain corresponding phenol, the diazonium sulphate is used in preference to the diazonium chloride, since the present of chloride ions gives rise

to small quantities of the aryl chloride as a by-product [6]. Accordingly, it is essential to avoid the side reaction of coupling reaction between unreacted diazonium salt and the phenol [6], so the reaction is usually carried out by adding the solution of a diazonium salt to a large volume of boiling dilute sulphuric acid. This type of reaction provides a ready method of replacing the amino group by the hydroxy group. Thus, Juglone can be easily obtained by the hydrolysis of diazonium sulphate of ANQ.

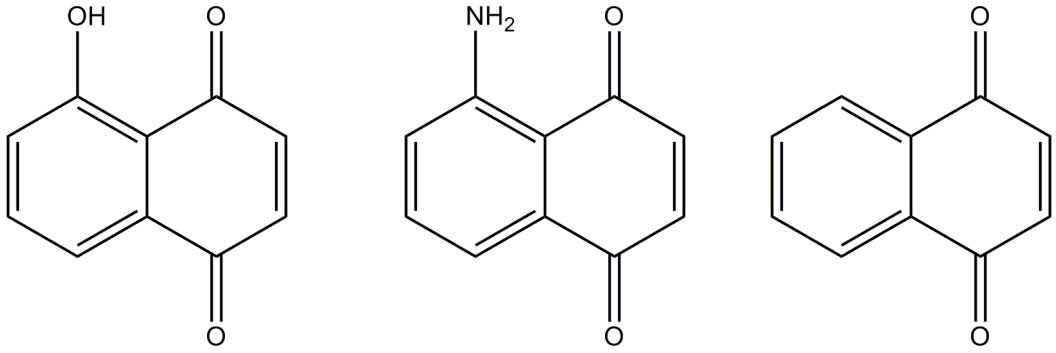


**Fig. 1 Formulae of Juglone, ANQ and 1,4-Naphthoquinone**

## EXPERIMENTAL SECTION

Materials

Reagents and solvents used in the experiments were purchased reagent grade and used without further purification unless otherwise stated. Infrared spectra were obtained using a Perkin-Elmer FT instrument. $^1$H NMR spectra was acquired on a Varian Unity-300 spectrometer at 300 MHz and. Spectra were recorded in deuterated chloroform ($CDCl_3$), using chloroform as internal standard.

Procedures

5-nitro-1,4-naphthoquinone

A 100 ml beaker was charged with 2.8 g of water, 59.5 g of sulfuric acid and 7.7 g of nitric acid. The temperature of the mixture was kept below 5 °C, and to it added 10 g of 1,4-naphthoquinone. The mixture was maintained at 15 °C for about 1 hour with stirring to effect reaction until all of the 1,4-naphthoquinone had disappeared (Fig. 2). Poured the mixture into a 1 L beaker set in ice-water, stirred to precipitate the product of 5-nitro-1,4-naphthoquinone. The precipitate was then filtered, and dried under reduced pressure to obtain 10.8 g of a yellow-colored product. On recrystallization twice from methanol the pure substance was obtained in beautiful, fine yellow needles.

FTIR (KBr) ($cm^{-1}$): 1545 and 1303 ($NO_2$); 1640 (C=O); $^1$H NMR ($CDCI_3$) δ (ppm): 8.32 (1H, H-6); 7.85 (2H, H-7 H-8); 7.06 (2H, H-2 and H-3).

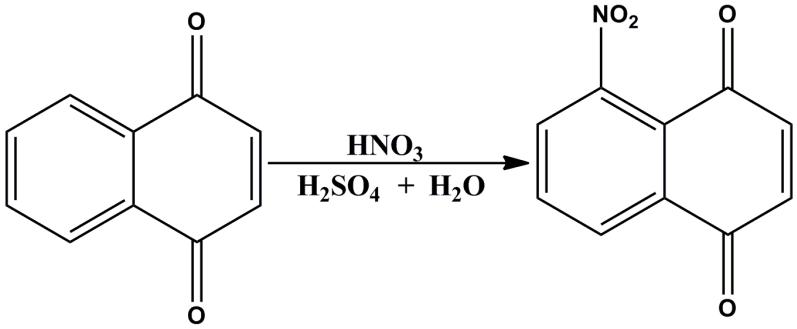


**Fig.2 Synthesis of 5-nitro-1,4-naphthoquinone**

5-Amino-1,4-naphthoquinone

150 ml of acetic acid in a 500 ml beaker was heated to 50 °C, and to it was added 10 g of 5-nitro-1,4-naphthoquinone with stirring. 40 g of sodium hydrosulfite was added to the mixture, and the mixture was then maintained at 100 °C for about 90 min with stirring to effect reaction until all of sodium hydrosulfite had disappeared. This operation led to 5-amino-l,4-dihydroxynaphthalene (Fig. 3). Then the mixture was cooled to 15 °C. The 5-amino-l,4-dihydroxynaphthalene need not be isolated but reoxidized directly in the same medium by adding 34 g of hydrogen peroxide (30%). The resulting reaction mixture was stirred for 10 min during which the dark green solution turned into a dark red solution. This operation led to ANQ (Fig. 3). A particularly advantageous

embodiment of this process is that the followed product need not be isolated from the reaction mixture, because it would be used to diazotize in the next step without further purification.

The data of IR and $^1$H NMR of the ANQ obtained by this process of the present study were in accord with those of authentic 5-amino-1,4-naphthoquinone.

FTIR (KBr) (cm$^{-1}$): 3294 and 3404 ($NH_2$); 1635 (C=O). $^1$H NMR ($CDCI_3$) δ (ppm):7.38 (1H, H-8); 7.36 (1H, H-6); 6.95 (1H, H-7); 6.92 (2H, H-2 and H-3); 6.90 (2H, $NH_2$).

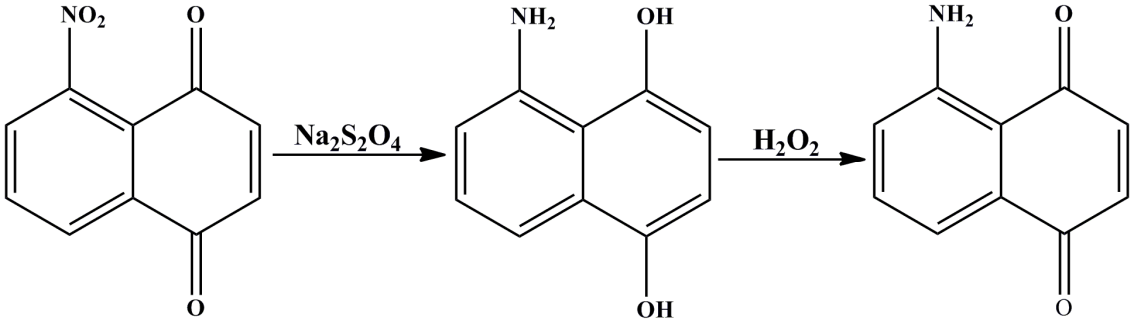


**Fig.3 Synthesis of ANQ**

5-hydroxy-1,4-naphthoquinone

50 g of concentrated sulfuric acid in a 500ml beaker was cooled to 0 °C, and to it was added, slowly and with stirring, an amount of dry powdered sodium nitrite equivalent to 3.5 g of pure $NaNO_2$ [7]. The temperature of the mixture was kept below 7 °C. Stirring was continued for about 5 minutes after all of the nitrite had been added, and then the beaker was transferred to a water bath. When the temperature of the mixture had reached that of the water bath, very gradual heating was started and continued until the temperature had reached 70 °C. The mixture was then stirred at this temperature until all of the nitrite had dissolved. When a clear solution was finally obtained [7], it was cooled in water to about 20 °C, and the above-mentioned reaction mixture of ANQ was added in small portions. The mixture was maintained at 25 °C for about 10 min with stirring to effect reaction. This operation led to the diazonium sulphate of ANQ. This reaction mixture was then boiled in a solution of copper sulfate (6 g) and water (100 ml) for 5 min. Poured the mixture into a 2 L beaker set in ice-water, and stirred vigorously to obtain the product of Juglone (Fig. 4). When cold, filtered and washed with ice-water. On recrystallization twice from benzene the pure substance of Juglone (6.1 g , 70%) was obtained in beautiful, fine orange-red needles.

FTIR (KBr) (cm$^{-1}$): 3436 (-OH); 1645 (C=O). $^1$H NMR ($CDCI_3$) δ (ppm):6.96 (2H, H-2 and H-3); 7.27 (1H, H-6); 7.60(1H, H-7); 7.65 (1H, H-8); 11.89 (1H,-OH).

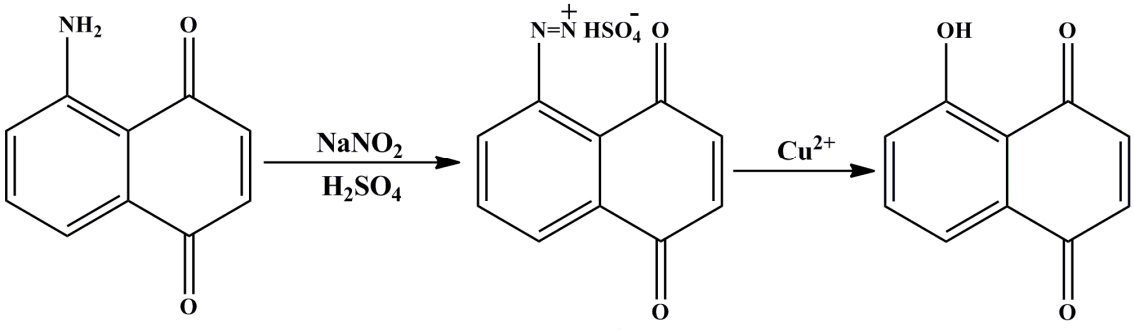


**Fig.4 Synthesis of ANQ**

## RESULTS AND DISCUSSION

(1) It is known that, when 1,4-naphthoquinone is subjected to direct nitration with nitric acid, there occur decomposition or side reactions because the quinonoid ring is unstable and reactive. However, in the present study the product of 5-nitro-1,4-naphthoquinone is obtained by nitrating 1,4-naphthoquinone with nitric acid in the presence of water and sulfuric acid, even though the l,4-naphthoquinone was not protected in the 2-and 3-position at all. One possible reason is that water in the system improved the selectivity of nitro group and the sulfuric acid played a role as solvent when the nitration of 1,4-naphthoquinone carried out in the presence of water and sulfuric acid.

(2) The selective reduction of aryl nitro compounds in the presence of carbonyl which is a sensitive functionality,

stannous chloride in concentrated hydrochloric acid is one of the classic reagents for reduction of nitro to the target amine, because stannous chloride fails to reduce carbonyl group under the condition of reduction of nitro.

However, the introduction of chloride ions would give rise to the aryl chloride as a by-product when the diazonium compounds of ANQ began formed, since chloride ions is a stronger nucleophile than hydrogen sulfate. Thus, in the present study the ANQ was prepared indirectly by the reduction of 5-nitro-1,4-naphthoquinone with sodium hydrosulfite, thereby avoiding the introduction of other strong nucleophile into the reaction system. Reduction with sodium hydrosulfite led to the formation of transitional product of 5-amino-l,4-dihydroxynaphthalene since both carbonyl and nitro groups were reduced. The synthesis of ANQ was obtained by the reoxidation of 5-amino-l,4-dihydroxynaphthalene with hydrogen peroxide which would not introduce any impurities into the system but also can be used to oxidate sodium bisulfite produced by the reduction of sodium hydrosulfite according to Eq. 1. The naphthol molecule was converted to the naphthoquinone form by the loss of two electrons resulting in the change of the color of the solution according to Eq. 2.

**Eq. 1**


**Eq. 2**

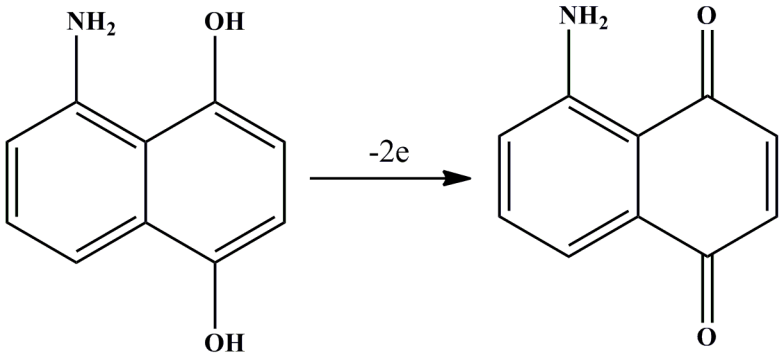


**Fig.5 Eq. 1 and Eq. 2**

(3) The solution of sodium nitrite in concentrated sulphuric acid was a particularly effective and very valuable diazotising medium [6] for the product of ANQ, because it not only provide a nitrosonium hydrogen sulphate reagent [6] but also avoid the by-product of aryl chloride resulting from diazonium chloride and the side reaction of coupling reaction between unreacted diazonium salt and the phenol. The diazo group was lost as molecular nitrogen and was replaced by hydroxyl group [6] when the aqueous solution of the diazonium sulphate of ANQ was heated to about 100°C. The copper sulfate was employed to accelerate the decomposition of diazonium sulphate. The mechanism is shown in Fig.6.

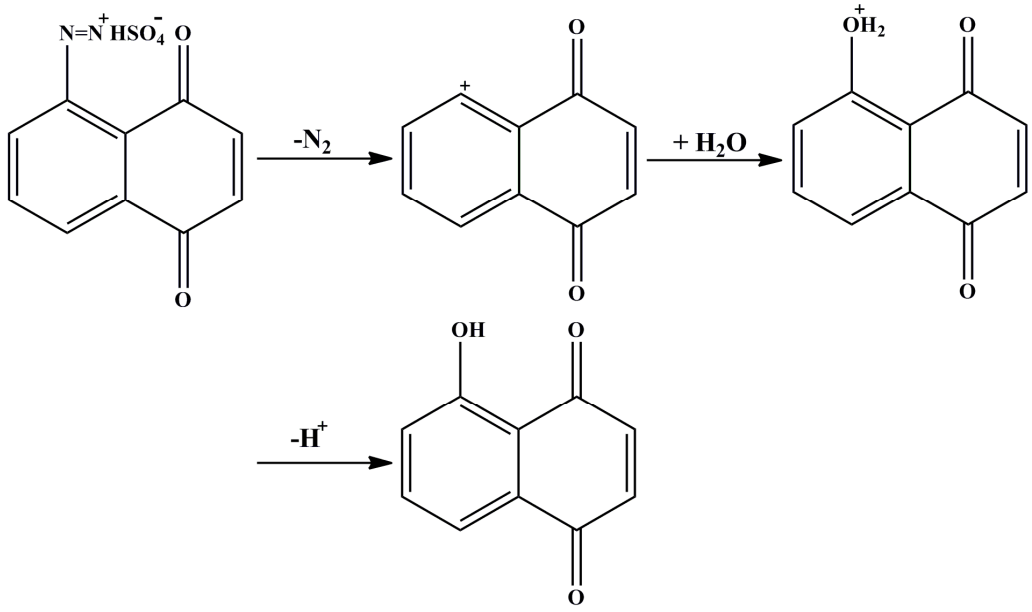


**Fig.6 The mechanism of hydrolysis of diazonium sulphate of ANQ**

## CONCLUSION

An effective and efficient method for the synthesis of Juglone based on 1,4-naphthoquinone has been reported. The hydrolysis of diazonium salt of the ANQ provides an accessible and simple procedure to obtain the target product. Additionally, the use of inexpensive and environmentally reagents makes this an attractive and advantageous method for the synthesis of Juglone.

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