PREPARATION OF ALKOXY DERIVATIVES OF 2-CHLORO-1,

4-NAPHTHOQUINONE AND 2-CHLORO-5(8?)-

NITRO-1,4-NAPHTHOQUINONE

APPROVED:

Lois Smith

Major Professor

David F. Dawson

Minor Professor

J. L. Carrico

Director of the Department of Chemistry

Robert B. Toulouse

Dean of the Graduate School

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THESIS

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By

Kenneth T. Hern, B. A.

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CHAPTER I

INTRODUCTION

For many years it has been known that compounds, based on a 1,4-naphthoquinone nucleus, possess varying degrees of usefulness as chemotherapeutic agents. During these years the synthesis and identification of such compounds have been of interest to such investigators as Dam (11,12,13,14), Almquist (1,2,3,4,5,6), Fieser (18,19,20, 21,22), and Doisy (15,16). Dam was the earliest investigator of such compounds and through his experiments in 1926 (11) he called attention to the therapeutic possibilities of naphthoquinones. His work showed that chicks raised on a specific synthetic diet developed a hemorrhagic condition with a prolonged blood clotting time. Continuing his work along this same line he discovered and reported in 1935 (11) that a new vitamin substance was the factor guarding against this condition of prolonged bleeding. Dam suggested calling this new substance vitamin K.

Dam continued his experiments with this newly discovered substance and presented a series of articles during

the next four years. These articles contained further evidence that vitamin K was indeed the antihemorrhagic factor. Dam terminated his work in 1939 (13) with the reported isolation of vitamin K from alfalfa.

Immediately following Dam's original paper, work was begun in the laboratories of H. J. Almquist and his co-workers. These people reported the results of their experiments in a series of papers from 1935 to 1937 (1,2,3,4, 5). They showed vitamin K to be the antihemorrhagic factor and the presence of this substance in fish meal and in alfalfa.

E. A. Doisy and his associates, in 1939, also reported the isolation of vitamin K from both alfalfa and fish meal, but they noted that the vitamin K obtained from alfalfa was not the same vitamin K obtained from fish meal. They assigned the name vitamin K_1 to the substance in alfalfa and vitamin K_2 to the substance in fish meal (16). Doisy and his co-workers synthesized phthiocol, 2-methyl-3-hydroxy-1,4-naphthoquinone, and observed that it possessed vitamin K activity. Using this newly discovered fact they were able to determine the structure of the naturally occurring K vitamins. During this same year Almquist (4) and L. F. Fieser (18) obtained similar results independently.

Various other workers turned their interest to the synthesis and isolation of other compounds having potential vitamin K activity. One compound of particular interest was menadione, 2-methyl-1,4-naphthoquinone. Several investigators, including Ansbacher and Fernholz (17), Campbell (8), and Stahmann and others (27), reported that this compound had an activity equivalent to if not greater than vitamin K itself.

Using 1,4-naphthoquinone as the basic material, many, many other compounds have been prepared in an effort to obtain useful chemotherapeutic agents. The compounds under consideration in this paper are 1,4-naphthoquinones with alkoxyl groups in the two or three positions. These compounds have been studied by many investigators and have been shown to be chemotherapeutic agents of varying degrees. For instance, Hayashi (24) found that the activity against gram-positive bacteria could be increased by substitution of the quinone nucleus with such groups as the methoxy group. This compound would be 2-methoxy-1,4-naphthoquinone, a compound which had been synthesized and studied as early as 1926 by Fieser (17). Fieser synthesized both the methoxy and ethoxy compounds from the silver

salt of lawsome, 2-hydroxy-1,4-naphthoquinone,and methyl iodide.

Garrara and Lorenzini (23) studied a variety of compounds to determine their antibacterial activity. One of these, 2-methoxy-3-hydroxy-1,4-naphthoquinone, along with a few others, showed considerable activity.

Colwell and McCall (10) studied the antibacterial and antifungal properties of 2-methyl-1,4-naphthoquinone, 2-methyl-3-chloro-1,4-naphthoquinone, and 2-methyl-3-methoxy-1,4-naphthoquinone in the presence of an excess of mercapto compounds. They demonstrated that the antibacterial and antifungal properties were destroyed in all of these agents except 2-methyl-3-methoxy-1,4-naphthoquinone.

Sakai, Minoda, Saito, and Fumiko (25) studied a group of quinone derivatives in a search for chemotherapeutic agents that would have activity against cancer. Their experiment consisted of cutting NF sarcoma tissue into small fragments of about 1 mm. in diameter. These fragments were immersed in a physiological salt solution and kept there for twenty-four hours at 4-7° C. At the end of this period the tissue fragments were implanted into subcutaneous tissue of mice, and the growth of tumors was observed

for two weeks. The different compounds were then tested and it was found that 2-chloro-3-ethoxy-1,4-naphthoquinone was tumorcidal at concentrations of 0.05 per cent.

Many other alkoxy compounds too numerous to mention have also been studied as chemotherapeutic agents, and from the work cited above it becomes quite obvious that the alkoxy derivatives of 1,4-naphthoquinones have considerable potentiality as chemotherapeutic agents.

The principal starting material used in this work was 2,3-dichloro-1,4-naphthoquinone. It was chosen because it could be obtained commercially at a reasonable cost, and the synthesis of alkoxy derivatives from this particular compound had been shown to be relatively straightforward.

Nitration of 2,3-dichloro-1,4-naphthoquinone with nitric acid in the presence of sulfuric acid (26) yields 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone, the other starting material.

In preparing the various alkoxy compounds, 2,3-dichloro-1,4-naphthoquinone, and 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone were refluxed with stirring in methanol, ethanol, 1-propanol, and 2-propanol in the presence of anhydrous sodium acetate. These compounds were very light-sensitive.

They turned from bright yellow to brown when exposed to light. To prevent this oxidation the purified compounds were stored in brown sample bottles.

This work was sponsored by the National Cancer Institute of the U. S. Public Health Service. The testing of these compounds is being arranged by the Cancer Chemotherapy National Service Center.

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CHAPTER II

EXPERIMENTAL

2-Methoxy-3-chloro-1,4-naphthoquinone

A mixture of 5 g (0.022 mole) of 2,3-dichloro-1,4-naphthoquinone, 1.9 g. (0.022 mole) of anhydrous sodium acetate, and 100 cc. of anhydrous methyl alcohol was refluxed with stirring for one hour on a steam bath. Long, yellow needle-like crystals were formed during the course of the reaction. Fifteen milliliters of water were added to precipitate the product and the mixture was allowed to stand for one hour. The product was then filtered, washed with dilute sodium bicarbonate solution until all of the red color disappeared, and then with water. The product, when dried over night, yielded 4.6 g. (88 per cent) and melted at 146-147°. Recrystallization from methanol caused no change in the melting point.

Anal. Calc. for $C_{11}H_7O_3Cl$: Cl, 15.94; Found: Cl, 15.78.

2-Ethoxy-3-chloro-1,4-naphthoquinone

A reaction mixture similar to that described by Fieser (1) was prepared by adding a mixture of 5 g. (0.022 mole) of 2,3-dichloro-1,4-naphthoquinone and 1.9 g. (0.022 mole of anhydrous sodium acetate, to 100 cc. of anhydrous ethyl alcohol. The mixture was refluxed with stirring for one hour on a steam bath. The reaction mixture was poured into a 250 ml. beaker and diluted with ten milliliters of water. The mixture was allowed to stand for three hours. The bright yellow crystals which separated from the solution were filtered, washed with dilute sodium bicarbonate solution, and then with water. After drying in a desicator over night the yield was 3.8 g. (70 per cent) and the melting point was 95-98°. Recrystallization from ethanol and water raised the melting point to 98-99°.

Anal. Calc. for $C_{12}H_9O_3Cl$: Cl, 14.96; Found: Cl, 14.81.

2-Propoxy-3-chloro-1,4-naphthoquinone

A mixture of 5 g. (0.022 mole) of 2,3-dichloro-1,4-naphthoquinone, 1.9 g. (0.022 mole) of anhydrous sodium acetate, and 150 cc. of n-propyl alcohol was added to a

two-necked, 250 ml. flask. Upon mixing the reactants the immediate appearance of the red coloration did not occur. The mixture was then refluxed with stirring and at the end of one hour began to turn red. Refluxing was continued for ten hours. At the end of the refluxing period the mixture was immediately filtered and the filtrate diluted with 50 cc. of water. The resulting solution was then allowed to stand over night. The product, which separated as a yellow solid, was washed with dilute sodium bicarbonate solution and then with water. The crude product weighed 2.1 g. (37 per cent) and melted at 69-78°. Recrystallization from a mixture of ethanol and water raised the melting point to 88-90°.

Anal. Calc. for $C_{13}H_{11}O_3Cl$: Cl, 14.15; Found: Cl, 13.08.

2-Isopropoxy-3-chloro-1,4-naphthoquinone

A mixture of 5 g. (0.022 mole) of 2,3-dichloro-1,4-naphthoquinone, 1.9 g. (0.022 mole) of anhydrous sodium acetate, and 150 cc. of isopropyl alcohol was refluxed with stirring for a total of ten hours. The resulting mixture was filtered immediately and the filtrate diluted

with 50 cc. of water. The diluted solution was allowed to stand over night. The product was filtered and washed with dilute sodium bicarbonate solution until all of the red color disappeared, and then with water. The crude product weighed 2.2 g. (38 per cent) and melted at 57-61°. Recrystallization from ethanol and water raised the melting point to 67-69°.

Anal. Calc. for $C_{13}H_{11}O_3Cl$: Cl, 14.15; Found: Cl, 12.98.

Nitration of 2,3-Dichloro-1,4-naphthoquinone

The nitration of 2,3-dichloro-1,4-naphthoquinone was carried out in a manner similar to that described by Imray (2). To a mixture of 200 cc. of concentrated sulfuric acid and 30 g. (0.134 mole) of 2,3-dichloro-1,4-naphthoquinone was added 150 cc. of concentrated nitric acid in 100 cc. of concentrated sulfuric acid. The nitric acid mixture was added at such a rate that the temperature did not exceed 100°. The total time for the reaction was five hours. At the end of this period, 300 cc. of water was added and the diluted mixture was cooled in an ice bath for two hours. The product was then filtered, washed with

water, and recrystallized from acetic acid. The yield was 22 g. of long yellow needles. The melting point of the recrystallized product was 175-177°.

2-Methoxy-3-chloro-5(8?)-nitro-1,4-naphthoquinone

A mixture of 5 g. (0.0183 mole) of 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone, 1.6 g. (0.0186 mole) of anhydrous sodium acetate, and 100 cc. of methyl alcohol was refluxed with stirring on a steam bath for one hour. The reaction mixture was then cooled for two hours during which time the product separated as a very bright yellow crystal. The product was filtered, washed with dilute sodium bicarbonate solution until all of the red color disappeared and then with water. The weight of the product was 4.1 g. (81 per cent) and the melting point was 110-111°. Recrystallization from methanol caused no change in the melting point.

Anal. Calc. for $C_{11}H_6O_5NCl$: Cl, 13.26; Found: Cl, 13.11.

2-Ethoxy-3-chloro-5(8?)-nitro-1,4-naphthoquinone

A mixture of 5 g. (0.0183 mole) of 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone, 1.6 g. (0.0186 mole) of anhydrous sodium acetate, and 100 cc. of anhydrous ethyl alcohol was refluxed one hour with stirring. At the end of the reflux period the reaction mixture was poured into a 250 ml. beaker and diluted with 10 cc. of water. The diluted mixture was allowed to stand for two hours. The bright yellow needles were filtered and washed with dilute sodium bicarbonate solution and water. The weight of the product was 3.5 g. (67 per cent) and the melting point of the product unrecrystallized was 92-97°. Recrystallization from ethanol and water raised the melting point to 96-98°.

Anal. Calc. for $C_{12}H_8O_3NCl$: Cl, 12.59; Found: Cl, 12.35.

2-Propoxy-3-chloro-5(8?)-nitro-1,4-naphthoquinone

A mixture of 5 g. (0.0183 mole) of 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone, 1.6 g. (0.0186 mole) of anhydrous sodium acetate, and 100 cc. of anhydrous 1-propanol was refluxed three hours with stirring. At the end of this

reflux period the mixture was diluted with 30 cc. of water and allowed to stand for three hours. The product separated as a yellow crystal. The product was filtered and washed with a dilute solution of sodium bicarbonate and with water. The yield was 2.8 g. (50 per cent). The melting point of the product after recrystallization from ethanol and water was 106-107°.

Anal. Calc. for $C_{13}H_{11}O_5NCl$: Cl, 11.94; Found: Cl, 11.78.

2-Isopropoxy-3-chloro-5(8?)-nitro-1,4-naphthoquinone

A mixture of 5 g. (0.0183 mole) of 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone, 1.6 g. (0.0186 mole of anhydrous sodium acetate, and 100 cc. of anhydrous isopropyl alcohol was refluxed three and one-half hours with stirring. At the end of the reflux period the reaction mixture was diluted with 40 cc. of water and allowed to stand for four hours. At the end of this time the product was filtered and washed with a dilute solution of sodium bicarbonate and water. The product was recrystallized from methanol and water. It was a bright yellow crystal melting at 96-98°. The yield was 2.2 g. (40 per cent).

Anal. Calc. for $C_{13}H_{10}O_5NCl$: Cl, 11.94; Found; Cl, 11.66.

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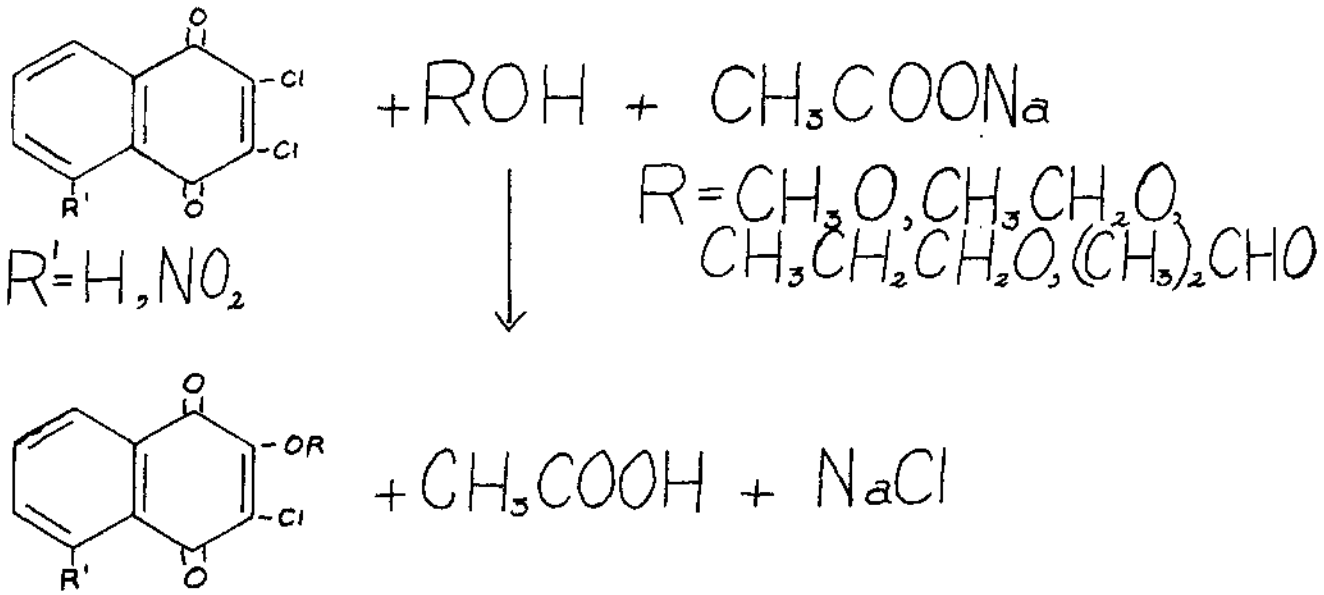
CHAPTER III

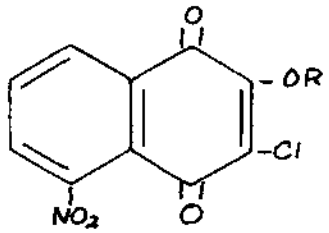
DISCUSSION

It was the purpose of this investigation to prepare alkoxy derivatives of 2,3-dichloro-1,4-naphthoquinone and 2,3-dichloro-5(8?)-nitro-1,4-naphthoquinone by displacing one of the chlorines with different alkoxy groups. The reactions were carried out in much the same manner as that described by Fieser (1). He reacted 2,3-dichloro-1,4-naphthoquinone with ethanol in the presence of sodium acetate and obtained 2-ethoxy-3-chloro-1,4-naphthoquinone. The general equation for the reaction would be as follows:

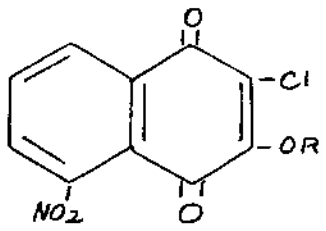


It is obvious from the equations just cited that when $R' = NO_2$ there is a possibility for two products to be formed. These would be either 2-alkoxy-3-chloro-5-nitro-1,4-naphthoquinone (I) or 2-chloro-3-alkoxy-5-nitro-1,4-naphthoquinone (II).

I



II



In the experiments conducted, however, no evidence was demonstrated that could lead to the isolation or separation of the two isomers.

Several other reactions were also run in an attempt to synthesize alkoxyl compounds by the same procedure as

the one used throughout this work. Larger alcohols were used in an effort to synthesize naphthoquinones with larger alkoxyl groups in the two or three position. Some of the alcohols used were 1-butanol, 2-butanol, and cyclohexanol. Each of these alcohols, when refluxed with the naphthoquinone in the presence of anhydrous sodium acetate, produced the characteristic red color of the reaction; but the desired product was always unobtainable.

The analysis for the per cent chlorine is the only analytical data reported, although the per cent nitrogen was also determined for some of the nitrated quinones. The nitrogen percentage is not used because, in some instances, the difference in the per cent nitrogen present in the starting material and the alkoxy product was not sufficiently large to merit its use. The nitrogen analysis was by the micro Dumas method and the chlorine analysis was by the Parr bomb method. All melting points reported are uncorrected and were taken on a Thomas Hoover apparatus.

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