PYRIDINIUM AND PYRAZINIUM DERIVATIVES OF

2,3-Dichloro-1,4-naphthoquinone

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THESIS

Presented to the Graduate Council of the
North Texas State College in Partial
Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

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Denton, Texas
June, 1956

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CHAPTER I

INTRODUCTION

The structure of the anti-hemorrhagic vitamin K_1 was proved to be 2-methyl-3-phytyl-1,4-naphthoquinone by Almquist (1, 2), Dam (7, 8), Doisy (9, 10), and Fieser (13, 14, 15), and that of vitamin K_2 was found to be 2-methyl-3-difarnesyl-1,4-naphthoquinone by Doisy (12).

Since then the interest in 1,4-naphthoquinone derivatives has increased, and many natural occurring and synthesized naphthoquinone derivatives have been studied for their anti-hemorrhagic, anti-respiratory, bacteriostatic, and bactericidal activities.

Doisy (9) isolated vitamin K_1 from alfalfa and vitamin K_2 from putrefied sardine meal.

Almquist and Klose (2) purified or synthesized and tested a number of naphthoquinones and related compounds and found that 2-methyl-1,4-naphthoquinone, like phthiocol and similar compounds, was capable of maintaining the prothrombin level of chick blood at a normal value when a sufficient amount is given. They (2) also prepared and purified 2-methyl-3-phytyl-1,4-naphthoquinone by condensation of 2-methyl-1,4-naphthoquinone with phytol. This compound showed some anti-hemorrhagic activity. It was also

synthesized by Fieser (14) by heating equivalent amounts of phytol and 2-methyl-1,4-naphthoquinone in dioxane solution in the presence of anhydrous oxalic acid. This compound was compared with vitamin K_1 obtained from alfalfa and found to be identical with it according to Fieser (15).

Thayer (28) found the most active anti-hemorrhagic compound was 1,4-dihydroxy-2-methylnaphthalene, which was prepared by the hydrogenation of 2-methyl-1,4-naphthoquinone. The later was selected to be a standard compound for vitamin K potency, since its potency agrees with the value assigned to the natural K_1, namely, 1000 units per milligram. 2-methyl-1,4-naphthoquinone was also found to be as active as vitamin K_1 by Tishler and Simpson (29). Fernholz and coworkers showed that none of the 1,4-naphthoquinones carrying longer chains in the 2- or the 3- positions approaches 2-methyl-1,4-naphthoquinone in activity.

Pthiocol, 2-methyl-3-hydroxy-1,4-naphthoquinone, was the first completely identified form of vitamin K (11). It has been isolated as the yellow pigment of Mycobacterium tuberculosis (human) and synthesized by Anderson and coworkers (3).

Many compounds, formed by the reaction of 2-methyl-1, 4-naphthoquinone with various metallic or amine bisulfites, were made by Moore (22). These compounds were highly water-soluble and possessed a degree of vitamin K activity equivalent to that of the 2-methyl-1,4-naphthoquinone.

Meunier, Mentzer, and Buu-Hoï (20) found that 3-methyl-1,4-naphthoquinone and 2-hydroxyl-3-methyl-1,4-naphthoquinone showed vitamin K activity, while 3-chloro-1,4-naphthoquinone and 2-hydroxy-3-chloro-1,4-naphthoquinone showed a weak hemorrhagic activity.

It has been shown (5) that synthetic vitamin K was among the few vitamins that influence acid formation in fermenting saliva-sugar solutions. This marked inhibitory effect is probably not associated with its vitamin activity, but may be due to its bactericidal properties.

Woolley (31) found that 2,3-dichloro-1,4-naphthoquinone was toxic to mice and yeasts, although it can be regarded as an analog to vitamin K.

Fieser and others (16) prepared hydrolapachol, 2-isopentyl-3-hydroxy-1,4-naphthoquinone, which was found to be active against malaria. Fieser and Heymann (17) studied the anti-respiratory activities of 82 different naphthoquinones relative to compound M-1916 which is 2-phenyl-propyl-3-hydroxy-1,4-naphthoquinone.

Buu-Hoï (4) prepared several arylamine derivatives of 2,3-dichloro-1,4-naphthoquinones which are capable of inhibiting the growth of the tubercle bacillus. Kimler (18) reported that the tetrasodium-2-methyl-1,4-naphthoquinone diphosphoric acid ester and other related compounds are active against Mycobacterium tuberculosis var. hominis.

Among the 15 naphthoquinone compounds tested by Lloyd (19) against the tubercle bacillus in vitro only one, 3-sulfanilyl-1,4-naphthoquinone, showed sufficient promise.

Sjögren and Berlin (26) found that 2-sulfanilamido-1,4-naphthoquinone is active against Pneumococcus and E. coli in vitro, and its activity is equal to that of sulfapyridine (Schreiber, 25).

Platas (24) prepared some 2-(4-alkylpyridine) derivatives of 2,3-dichloro-1,4-naphthoquinone by the method of Ullman and Ettisch (30), which were found to be active against the tubercle bacillus. Miller (21) continued this work by preparing other pyridinium derivatives of naphthoquinone by the Knoevenagal Condensation of aromatic aldehydes with 3-hydroxy-1,4-naphthoquinone-2-(4-methylpyridinium) anhydride. A series of pyridinium derivatives of naphthoquinone similar to those reported by Platas (24) were prepared by Talbott (27), through the condensation of pyridine-N-oxides and 2,3-dichloronaphthoquinone.

This investigation deals with the synthesis of 2-alkylpyridine and 2-alkylpyrazine derivatives of 2,3-dichloro-1,4-naphthoquinone. These compounds will be tested for physiological activity by Parke-Davis and Company.

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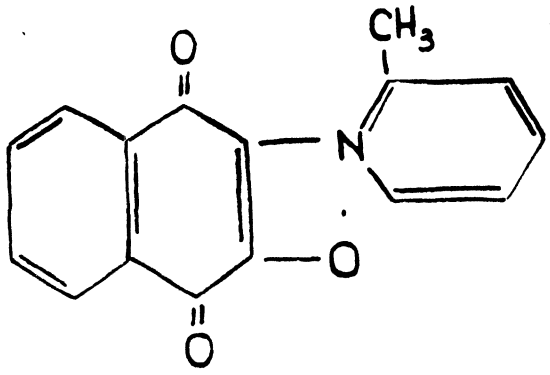
CHAPTER II

EXPERIMENTAL

3-Hydroxy-1,4-naphthoquinone-2-(2-picolinium) Anhydride



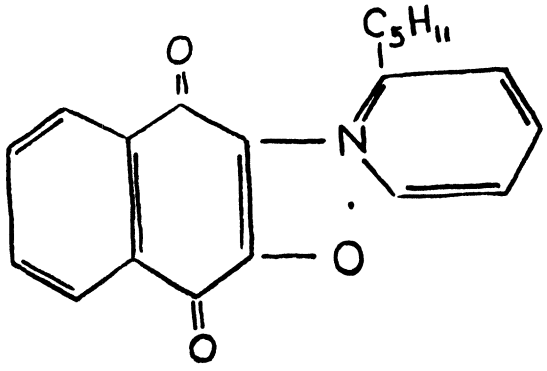
A mixture of 5 grams (0.022 moles) of 2,3-dichloro-1, 4-naphthoquinone and 6.04 grams (0.66 moles) of 2-picoline in 50 ml. (0.87 moles) of glacial acetic acid was refluxed for five hours in a 200-ml., round-bottomed flask fitted with a reflux condenser. The mixture turned to a deep brown solution which was cooled and filtered. To the clear filtrate 10 ml. of concentrated hydrochloric acid were added, followed by the addition of 200 ml. of cold water. The brown solid, which was removed by filtration and recrystallized from hot 95% ethanol, melted at 160-161° C. No more precipitation was obtained on further dilution of the clear filtrate.

Analysis: Calculated for $C_{16}H_{11}O_3N$: N, 5.28%

found: N, 5.4%

3-Hydroxy-1,4-naphthoquinone-2-(2-n-pentyl-pyridinium)

Anhydride



A suspension of 15 grams (0.066 moles) of 2,3-dichloro-1,4-naphthoquinone and 29.5 grams (0.198 moles) of 2-n-pentylpyridine in 125 ml. (1.97 moles) of glacial acetic acid was refluxed for five hours. The mixture turned to a deep red solution from which a red solid was separated after diluting with 300 ml. of cold water and cooling.

The red solid was recrystallized from hot 95% ethanol and melted at 171-172° C.

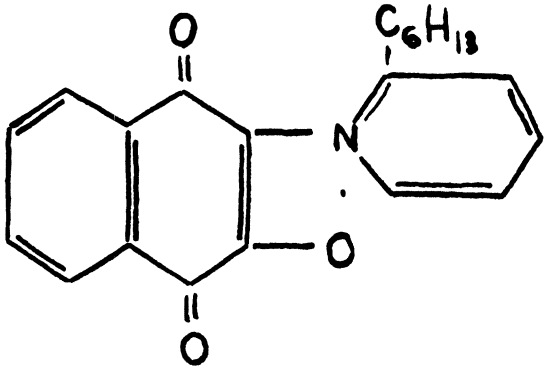
The red solid can be dissolved in concentrated hydrochloric acid, filtered, and diluted with water in order to obtain the purified form which melts at 171-172° C.

Analysis: Calculated for $C_{20}H_{19}O_3N$: N, 4.38%

found: N, 3.49%

3-Hydroxy-1,4-naphthoquinone-2-(2-n-hexyl-pyridinium)

Anhydride



A mixture of 20 grams (0.088 moles) of 2,3-dichloro-1,4-naphthoquinone and 150 ml. (2.61 moles) of acetic acid was refluxed for 25 minutes, then 43.00 grams (0.264 moles) of 2-n-hexylpyridine were added and the refluxing was continued for five hours. The solution was then deep purple in color. The reaction solution was cooled, filtered, and diluted with 350 ml. of cold water. The solid was filtered and recrystallized from hot 95% ethanol. Crystals were formed and melted at 184-185° C.

The original filtrate was further diluted and cooled, and more of the solid was obtained.

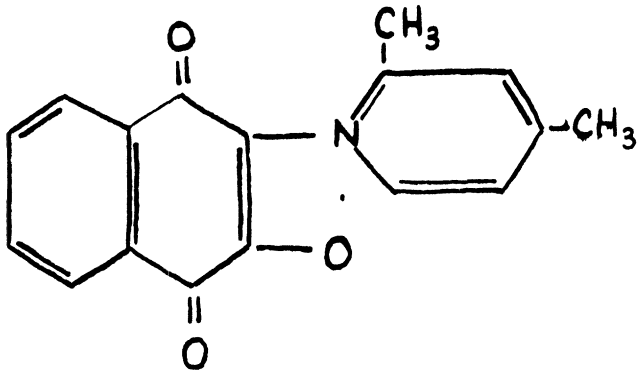
A total of 16.8 grams, which is 60% of the theoretical amount, was obtained.

Analysis: Calculated for $C_{21}H_{21}O_3N$: N, 4.18%

found: N, 3.8%

3-Hydroxy-1,4-naphthoquinone-2-(2,4-lutidinium)

Anhydride



A mixture of 15 grams (0.066 moles) of 2,3-dichloro-1,4-naphthoquinone and 125 ml. (1.97 moles) of glacial acetic acid was placed in a 500-ml., round-bottomed flask provided with a condenser.

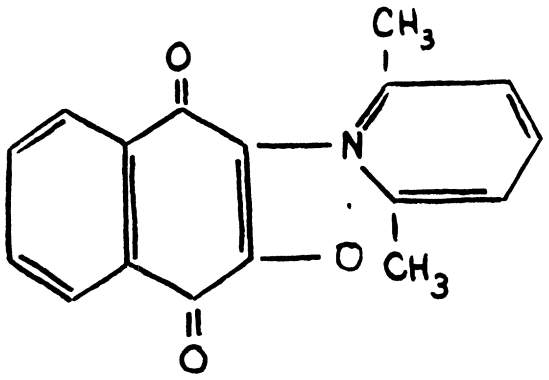
The mixture was heated to the reflux temperature, and then 21-6 ml. (0.198 moles) of 2,3-lutidine were added. The mixture was heated under reflux for five hours. The mixture was diluted with 300 ml. of cold water. The red solid was removed by filtration and recrystallized from hot 95% ethanol. Its melting point was 161-163° C.

Analysis: Calculated for $C_{17}H_{13}O_3N$: N, 5.00%

found: N, 4.00%

3-Hydroxy-1,4-naphthoquinone-2-(2,6-lutidinium)

Anhydride



A suspension of 20 grams (0.088 moles) of 2,3-dichloro-1,4-naphthoquinone in 150 ml. of glacial acetic acid was heated to the reflux temperature in a 500-ml., round-bottomed flask fitted with a condenser. Then 28.8 ml. (0.264 moles) of 2,6-lutidine were added, and the heating was continued for five hours.

The yellow suspension turned to a brown solution to which 10 ml. of concentrated hydrochloric acid were added followed by the addition of 350 ml. of cold water.

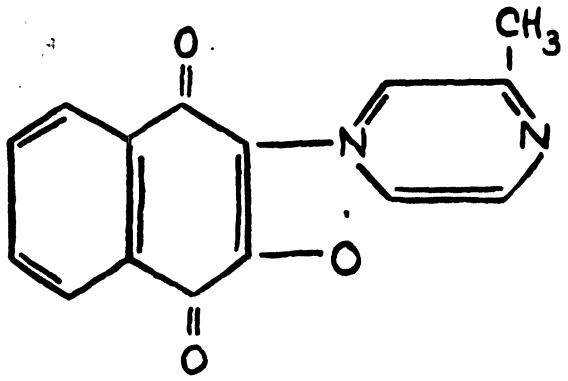
Brown solid was separated by filtration and recrystallized from hot 95% ethanol. The solid melted at 172-173° C.

Analysis: Calculated for $C_{17}H_{13}O_3N$: N, 5.00%

found: N, 4.3%

3-Hydroxy-1,4-naphthoquinone-2-(3-methylpyrazinium)

Anhydride



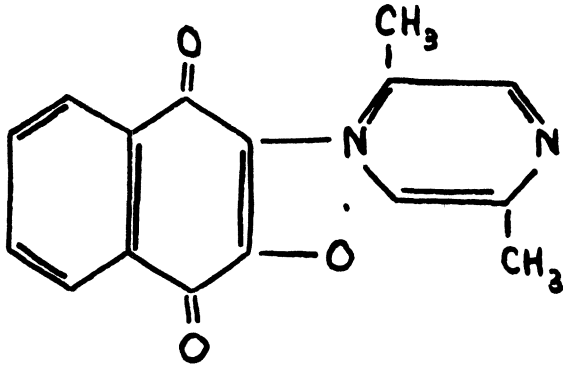
Twenty grams (0.88 moles) of 2,3-dichloro-1,4-naphthoquinone were placed in a 500- ml., round-bottomed flask, then 24.84 grams (0.264 moles) of 2-methylpyrazine were added. The mixture color became red after a short time. One hundred fifty ml. (2.61 moles) of glacial acetic acid were added and a condenser was fitted to the mouth of the flask. The mixture was heated to reflux temperature for one hour, cooled to the room temperature, and filtered. Then 350 ml. of cold water were added to the clear filtrate. Golden crystals were formed which on filtration gave a dull brown solid. This solid was recrystallized from hot 95% ethanol and bright bronze leaf crystals, whose melting point was 187-188° C., were obtained.

Analysis: Calculated for $C_{15}H_{10}O_3N_2$: N, 10.52%

found: N, 11.7%

3-Hydroxy-1,4-naphthoquinone-2-(,5-dimethylpyrazinium)

Anhydride



A mixture of 20 grams (0.88 moles) of 2,3-dichloro-1,4-naphthoquinone, 26 grams (0.264 moles) of 2,5-dimethylpyrazine, and 125 ml. (1.97 moles) of acetic acid were refluxed for two hours. The brown solution was cooled to the room temperature and filtered. Three hundred fifty ml. of cold water were added to the clear filtrate, and the brown-red solid was removed by filtration. Brown-red crystals, whose melting point was 210-212° C., were obtained on recrystallization from hot 95% ethanol.

Analysis: Calculated for $C_{16}H_{12}O_3N_2$: N, 10.00%

found: N, 9.3%

CHAPTER III

DISCUSSION

An extensive work has been done concerning the condensation reaction between pyridines and 2,3-dichloro-1,4-naphthoquinone. The starting material was 2,3-dichloro-1,4-naphthoquinone in almost all such investigations, because of its commercial availability and the ease by which it undergoes condensation reaction with the pyridine nucleus.

It was in 1921 when Ullman and Ettisch (5) prepared and gave the mechanism for the reaction of 2,3-dichloro-1,4-naphthoquinone and pyridine. They did not use any solvent for the reaction, and the product obtained was recrystallized from methanol.

In 1954, Platas (3) prepared a series of pyridine derivatives of 1,4-napthoquinone by causing pyridine and several 4-n-alkylpyridine derivatives to undergo condensation reaction with 2,3-dichloro-1,4-naphthoquinone in glacial acetic acid as a solvent. The yield was found to be, to some extent, better than what Ullman and Ettisch (5) obtained.

Many other investigators like Mahon (1), Miller (2), and Talbott (4) continued, individually, the preparation of pyridine derivatives of 1,4-naphthoquinone using glacial acetic acid as a solvent. This is the only satisfactory

solvent for this reaction. Other solvents give only tarry material.

It was the purpose of this investigation to prepare 2-n-alkylpyridine and 2-methylpyrazine derivatives of 1,4-naphthoquinone. All of the compounds described in this paper were prepared by using glacial acetic acid as the reaction solvent. All of the 2,3-dichloro-1,4-naphthoquinone and the various pyridine derivatives were mixed in molar ratios of one to three respectively. It was noticed that the time needed for the completion of the reactions described in this paper was longer than that needed for the reactions reported by Platas (3), except in case of 2-methylpyrazine and 2,3-dichloro-1,4-naphthoquinone where no difficulty was encountered. This may lead to the suggestion that the substituent group in the 2- position on the pyridine or on the pyrazine nucleus presents a steric hindrance effect to some extent. The presence of two nitrogen atoms in the pyrazine nucleus gives the reasonable explanation for the readiness of the reaction between 2-methylpyrazine and 2,3-dichloro-1,4-naphthoquinone. The nitrogen atom which is far away from the methyl group in the 2-methylpyrazine molecule will condense with the naphthoquinone ring, and the steric effect is no longer valid.

The compounds described here are different from the corresponding 4-n-alkylpyridine derivatives of 1,4-naphtho-

quinone. In general, they have lower melting points and they are deeper in color.

The mechanism by which these reactions proceed is entirely analogous to the mechanism proposed by Ullman and Ettisch (5) for the reaction between pyridine and 2,3-dichloro-1,4-naphthoquinone, since it does not involve the alpha position on the pyridine or on the pyrazine rings. The nitrogen atom of the pyridine or of the pyrazine molecules forms a quaternary salt with the chlorine atom of the 2,3-dichloro-1,4-naphthoquinone. Under the action of water or the acid solvent, and under the influence of heat, the excess of the pyridine or that of the pyrazine acts as a base and permits the quaternary salt to lose hydrogen chloride rapidly to form either one of two intermediates. In one intermediate, a chlorine atom is located on the nitrogen atom of the pyridine or on that of the pyrizine nucleus in the form of a quaternary salt, and a hydroxyl group is attached to the naphthoquinone ring in the 3- position. In the other intermediate the situation is simply reversed. These intermediates lose HCl rapidly and give rise to the desired compound.

The nitrogen analysis were made by the micro-Dumas method. All of the melting points reported were uncorrected.

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