SYNTHESIS OF SOME 1-SUBSTITUTED-2-METHYL-
NAPHTHIMIDAZOLE-4,9-DIONES

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THESIS

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By

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. EXPERIMENTAL</td>
<td>5</td>
</tr>
<tr>
<td>III. DISCUSSION</td>
<td>16</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>18</td>
</tr>
</tbody>
</table>
CHAPTER I

INTRODUCTION

Imidazole derivatives of 1,4-naphthoquinones are found to have biological activity which interferes with the utilization of vitamin K or of the purines since they have groups common to these two classes of compounds.

A number of 1,4-naphthoquinones have been shown to be metabolic antagonists and their activity was neutralized by the addition of vitamin K or 2-methyl-1,4-naphthoquinone. 2,3-Dichloro-1,4-naphthoquinone has been found to be a powerful fungicide (7), and alkylthio derivatives of 1,4-naphthoquinone are used as fungicides (6). Amine derivatives of 2-chloro-1,4-naphthoquinone have been found to be inhibitors of certain acid forming bacteria (1).

2-Methoxy- and 2-chloro-1,4-naphthoquinones display some antibiotic activity (4). Certain 2-alkyl-3-hydroxy-1,4-naphthoquinones have considerable antimalarial activity (2).

Benzimidazole and 5(6)-aminobenzimidazole were found to exhibit a bacteriostatic action which could be reversed by the addition of guanine or adenine (3).

The above reports and that of the preparation of a number of 1-H-naphthimidazole-4,9-diones (5) suggested the
preparation of some 1-substituted-naphthimidazole-4,9-diones for possible biological activity.

The method used to prepare these compounds was first reported by Fries and Billig (3). They observed that 2-acetylamino-3-arylamino-1,4-naphthoquinones were converted to the corresponding imidazoles on treatment with acid or base. The general procedure was similar to that used by Hoover and Day (5) in preparing 1-H-naphthimidazole-4,9-diones and is outlined by the following steps starting with 2,3-dichloro-1,4-naphthoquinone.
Where $R = \text{Phenyl}$

- p-Tolyl
- o-Tolyl
- p-Bromophenyl
- n-Butyl
- Benzyl
- n-Tetradecyl
BIBLIOGRAPHY

CHAPTER I


CHAPTER II

EXPERIMENTAL

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

To a refluxing mixture of 25.68 g. (0.10 mole) of 2,3-dichloro-1,4-naphthoquinone and 300 ml. of methanol, 75 ml. of concentrated aqueous ammonium hydroxide was added dropwise. The refluxing was continued an additional two hours. The mixture was then cooled, filtered and dried yielding 22.4 g. (95 per cent) of orange product which melted at 200-201°. This melting point checked with that reported by Fries and Ochwat (2) and by Hoover and Day (4).
2-Acetylamo-3-chloro-1,4-naphthoquinone

To a beaker containing 35 ml. of acetic anhydride and 22.4 g. of 2-amino-3-chloro-1,4-naphthoquinone was added 12 drops of concentrated sulfuric acid and the mixture was then heated slightly while stirring until the bright orange color changed to a dull yellow. The mixture was diluted with 300 ml. of water, filtered and washed with water and ether. The product was dissolved in hot ethanol, decolorizing carbon was added and the solution was filtered while hot. Upon cooling and filtering the solution yielded 15.55 g. (58 per cent) of small yellow platelets which melted at 217°. A melting point of 219° was reported by Ullman and Btish (5) and Hall (3).
2-Acetylamino-3-substituted-1,4-naphthoquinones

2-Acetylamino-3-anilino-1,4-naphthoquinone

To a 125 ml. flask was added 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone and 50 ml. of ethanol. The mixture was heated to reflux and 5.60 g. (0.06 mole) of aniline was added to the resulting green solution. The mixture was refluxed for twenty minutes, then diluted with 50 ml. of water, cooled, filtered, and dried. The product was 8.10 g. of reddish-purple solid which melted at 203°. The crude product was recrystallized twice from ethanol. Seven and seven-tenths grams was obtained. The melting point checked with that reported by Fries and Billig (1) and Hall (3).

2-Acetylamino-3-o-toluidino-1,4-naphthoquinone

To a 125 ml. flask was added 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone and 50 ml. of ethanol and the mixture was heated to reflux. To the hot mixture was added 6.40 g. (0.06 mole) of o-toluidine, 10 ml. of dioxane and 50 ml. of water. The mixture was then cooled, filtered and dried yielding 5.80 g. (72 per cent) of brown solid which melted at 195°. The product was recrystallized twice from a solution of 40 ml. of ethanol and 10 ml. of dioxane yielding 5.30 g. of pure product.

Anal. Calcd. for C_{19}H_{16}N_{2}O_{3}: N, 8.74; Found: N, 8.89.
**2-Acetylamino-3-p-toluidino-1,4-naphthoquinone**

A mixture of 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone and 50 ml. of ethanol was heated to reflux in a 125 ml. flask. To this hot mixture was added 6.40 g. (0.06 mole) of p-toluidine. The mixture was diluted with 50 ml. of water, cooled, filtered and dried. The resulting yield was 8.0 g. (85 per cent) of brownish-black solid. Recrystallization from 40 ml. of ethanol yielded 7.65 g. which melted at 194°.

**Anal.** Calcd. for C_{19}H_{16}N_{2}O_{3}: N, 8.74; Found: N, 9.11.

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**2-Acetylamino-3-p-bromoanilino-1,4-naphthoquinone**

A mixture of 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone and 50 ml. of ethanol was heated in a 125 ml. flask fitted with a reflux condenser. To this hot mixture was added 10.4 g. (0.06 mole) of p-bromoaniline. The mixture was diluted with 50 ml. of water, then cooled, filtered and dried yielding 9.4 g. (90 per cent) of glistening brown solid. The product was recrystallized from 53 ml. of ethanol yielding 8.0 g. of pure product which melted at 200°.

**Anal.** Calcd. for C_{18}H_{13}N_{2}O_{3}Br: N, 7.27; Found: N, 7.17.
2-Acetylamino-3-benzylamino-1,4-naphthoquinone

To a 125 ml. flask was charged 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone in 50 ml. of ethanol. To this mixture was added 6.40 g. (0.06 mole) of benzylamine. After the vigorous reaction subsided, 50 ml. of water was added and the reaction cooled. The mixture was filtered and dried. Seven and seven-tenths grams of glistening orange crystals was obtained. The product was recrystallized from 70 ml. of ethanol. The pure product weighed 7.5 g. (78 per cent). The compound melted at 200°.

Anal. Calcd. for C_{19}H_{16}N_{2}O_{3}: N, 8.745; Found: N, 8.92.

2-Acetylamino-3-(1-butylamino)-1,4-naphthoquinone

To a 125 ml. flask was charged 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone in 50 ml. of ethanol. To this mixture was added 4.40 g. (0.06 mole) of 1-butylamine. After the vigorous reaction subsided, 50 ml. of water was added and the reaction cooled. An immediate separation of bright crystalline flakes occurred. The crystals were filtered and dried yielding 5.70 g. of golden-red product. After recrystallization from 35 ml. of ethanol, 5.20 g. (65 per cent) was obtained. The pure product melted at 177°.

Anal. Calcd. for C_{16}H_{18}N_{2}O_{3}: N, 9.784; Found: N, 9.84.
2-Acetylamino-3-(1-tetradecylamino)-1,4-naphthoquinone

To a 125 ml. flask was charged 7.45 g. (0.03 mole) of 2-acetylamino-3-chloro-1,4-naphthoquinone in 50 ml. of ethanol. To this mixture was added 12.7 g. (0.06 mole) of 1-tetradecylamine. After the vigorous reaction subsided, 50 ml. of water was added and the reaction cooled. The mixture was filtered and dried. The orange crystals weighed 10.5 g. After recrystallization from 35 ml. of ethanol, the yield obtained was 9.40 g. (95 per cent). The melting point of the pure product was 129°.

Anal. Calcd. for C_{26}H_{38}N_{2}O_{3}: N, 6.567; Found: N,
1-Substituted-2-methylnaphthimidazole-4,9-diones

1-Phenyl-2-methylnaphthimidazole-4,9-dione

One gram (0.033 mole) of 2-acetylamino-3-anilino-1,4-naphthoquinone was placed in a 125 ml. flask with 80 ml. of ethanol and the mixture was heated. Six and seven-tenths milliliters of 2 N sodium hydroxide was added immediately. The hot solution developed a green color. The mixture was heated for twenty minutes, then poured into 200 ml. of water containing 6.70 ml. of 2 N hydrochloric acid. The resulting mixture was heated and ethanol added gradually until the yellow imidazole which had separated was dissolved. The product which separated on cooling was recrystallized from 100 ml. of ethanol. The yield was 0.60 g. (63 per cent) of yellow crystalline solid which melted at 239-241°.

Fries and Billig (1) reported this compound to melt at 239°.

Anal. Calcd. for C_{18}H_{12}O_{2}N_{2}: N, 9.73; Found: N, 9.59.

1-p-Tolyl-2-methylnaphthimidazole-4,9-dione

A mixture of 8.4 g. (0.026 mole) of 2-acetylamino-3-p-toluidino-1,4-naphthoquinone and 366 ml. of ethanol was heated in a 600 ml. beaker. After the yellowish-green solution became hot, 42 ml. of 2 N sodium hydroxide was added and heating continued for fifteen minutes. The resulting solution was poured into 1260 ml. of water containing 42 ml. of 2 N hydrochloric acid. The mixture was then
heated and 188 ml. of ethanol added gradually until the imidazole, which had separated, was redissolved. The hot solution was treated with decolorizing carbon, filtered and cooled. The mixture was then reheated, cooled and filtered yielding 2.80 g. (40 per cent) of yellowish-green solid which melted at 263°.

**Anal.** Calcd. for $C_{19}H_{14}N_2O_2$: N, 9.266; Found: N, 9.19.

1-o-Toly1-2-methylnaphthimidazole-4,9-dione

To a 600 ml. beaker was added 5.85 g. (0.025 mole) of 2-acetylamino-3-o-toluidino-1,4-naphthoquinone and 233.6 ml. of ethanol. Heat was applied until the solution became hot and 29.20 ml. of 2 N sodium hydroxide was added. The heating was continued for twenty minutes. The hot solution was poured into 876 ml. of water containing 29.2 ml. of 2 N hydrochloric acid. The resulting mixture was heated and 75 ml. of ethanol added gradually until the imidazole redissolved. The solution was cooled, filtered, and dried. The yield was 1.79 g. (24 per cent) of pale yellow solid which melted at 181°.

**Anal.** Calcd. for $C_{19}H_{14}N_2O_2$: N, 9.266; Found: N, 9.41.
**1-p-Bromophenyl-2-methylnaphthimidazole-4,9-dione**

To a hot solution of 8.0 g. (0.02 mole) of 2-acetylamino-3-p-bromoanilino-1,4-naphthoquinone in 320 ml. of ethanol was added 20 ml. of 2 N sodium hydroxide. The mixture was heated for twenty minutes. The coloration changed while heating. The solution was poured into 1200 ml. of water containing 40 ml. of 2 N hydrochloric acid. The product which separated from the cool solution was filtered and dried yielding 6.0 g. (82 per cent) of dull yellow solid which melted at 244° after one recrystallization from ethanol.

**Anal.** Calcd. for C_{18}H_{11}N_{2}O_{2}Br: N, 7.63; Found: N, 7.47.

**1-(1-Butyl)-2-methylnaphthimidazole-4,9-dione**

One gram (0.035 mole) of 2-acetylamino-3-(1-butylamino)-1,4-naphthoquinone was added to 40 ml. of ethanol and the mixture was heated. To the hot mixture was added 2.5 ml. of 2 N sodium hydroxide and heating was continued for twenty minutes. The hot solution was poured into 200 ml. of water containing 5 ml. of 2 N hydrochloric acid. The resulting mixture was heated and ethanol added gradually until the product dissolved. The solution was cooled and the product filtered and dried. The yield was 0.7 g. (75 per cent) of yellow product which melted at 117°.

**Anal.** Calcd. for C_{16}H_{16}O_{2}N_{2}: N, 10.44; Found: N, 10.26.
**1-Benzyl-2-methylnaphthimidazole-4,9-dione**

Two grams (0.06 mole) of 2-acetylamino-3-benzylamino-1,4-naphthoquinone was added to 80 ml. of ethanol and the mixture was heated. To the hot mixture was added 5.0 ml. of 2 N sodium hydroxide and heating was continued for twenty minutes. The hot solution was poured into 300 ml. of water containing 10 ml. of 2 N hydrochloric acid. The resulting mixture was heated and ethanol added gradually until the product dissolved. The solution was cooled and the product filtered and dried. The yield was 1.5 g. (83 per cent) of greenish-yellow product which melted at 198°.

**Anal.** Calcd. for C₁₈H₁₄O₂N₂: N, 9.27; Found: N, 9.06.

**1-(1-Tetradecyl)-2-methylnaphthimidazole-4,9-dione**

One gram (0.024 mole) of 2-acetylamino-3-(1-tetradecylamino)-1,4-naphthoquinone was added to 40 ml. of ethanol and the mixture was heated. To the hot mixture was added 2.5 ml. of 2 N sodium hydroxide and heating was continued for twenty minutes. The hot solution was poured into 200 ml. of water containing 5.0 ml. of 2 N hydrochloric acid. The resulting mixture was heated and ethanol added gradually until the product dissolved. The solution was cooled and the product filtered and dried. The yield was 0.7 g. (72 per cent) of yellowish-green product which melted at 72-73°.

**Anal.** Calcd. for C₂₅H₃₆O₂N₂: N, 6.86; Found: N, 6.7.
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CHAPTER III

DISCUSSION

The method used in making the intermediate compounds was that of Fries and Ochwat (2). The method of Fries and Billig (1) for making the imidazole using acid was found to be unsatisfactory; however, the method described by Hoover and Day (3) using base was found to give satisfactory results.

Reactions between 2-acetylamino-3-chloro-1,4-naphthoquinone and p-propionaniline, 2,5-dichloroaniline, and taurine (2-aminoethylsulfonic acid) were attempted but no products were obtained.

These imidazoles are basic and will dissolve in excess acid. They are ether and alcohol soluble but only slightly soluble in water; therefore, they are readily recrystallized from ethanol-water mixtures.

All melting points are given in degrees Centigrade and are uncorrected. All analyses were by the micro Dumas method.
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