QUINOLINES FROM ARYLOXYKETONES AND ISATIN

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A THESIS

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Georgia School of Technology

In Partial Fulfillment

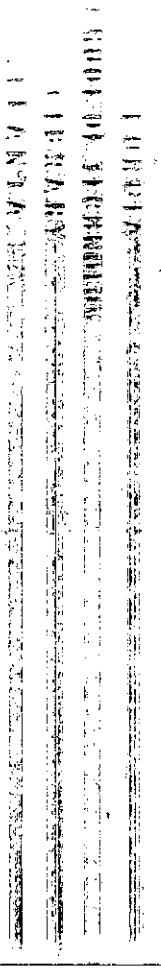
of the Requirements for the Degree

Master of Science in Chemistry

by

Arthur Maultsby Dowell, Jr.

June 1947



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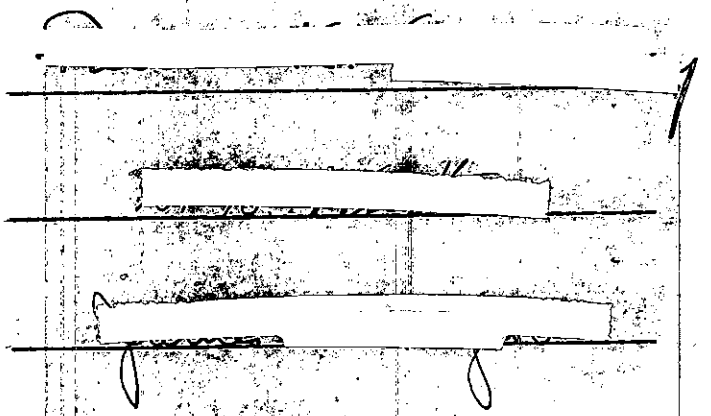

Date Approved by Chairman May 20, 1947

ACKNOWLEDGEMENTS

On completion of this work I wish to express my sincerest appreciation and gratitude to Dr. P. K. Calaway, not only for his suggestion of the problem, but also for his most valuable aid and guidance during its prosecution.

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QUINOLINES FROM ARYLOXYKETONES AND ISATIN

CHAPTER I

THE PFITZINGER REACTION

The preparation of quinoline derivatives from isatin and 5-methylisatin may be attributed to Pfitzinger, who prepared 6-methyl-4-quinaldinecarboxylic acid by the condensation of 5-methylisatin with acetone.[1,2]

The Pfitzinger reaction has been extended by workers in this laboratory to include the condensation of aryloxyketones and arylthioketones with isatin.[3,4,5]

The chief product of the reaction of isatins with unsymetrical ketones will normally have the larger group in the 3-position.[6,7]

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[1]Pfitzinger, J. prakt. Chem., 33, 100 (1886)

[2]Pfitzinger, J. prakt. Chem., 38, 584 (1888)

[3]Calaway and Henze, J. Am. Chem. Soc., 61, 1355 (1939)

[4]Knight, Porter, and Calaway, J. Am. Chem. Soc., 66, 1893 (1944)

[5]Newell and Calaway, J. Am. Chem. Soc., 69, 116 (1947)

[6]Pfitzinger, J. prakt, Chem., 56, 283 (1897)

[7]Von Braun, Gmelin, and Schulthesis, Ber., 56, 1344 (1923)

CHAPTER II

THE PURPOSE OF THIS INVESTIGATION

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The availability of aryloxyketones from chloroacetone and substituted phenols suggested their condensation with isatins since Newell and Calaway[5] have utilized the tolylthiopropanones in this manner. The use of tolyloxypropanones was therefore of interest.

Experiments have proven that the quinoline group in quinine possesses marked anti-malarial properties. Plasmochin, cinchophen, and atoquinol are substituted quinolines whose effectiveness has been proven.

The compounds reported in this thesis are all substituted cinchoninic acids, and are therefore related in structure to these chemotherapeutic agents.

CHAPTER III

EXPERIMENTAL

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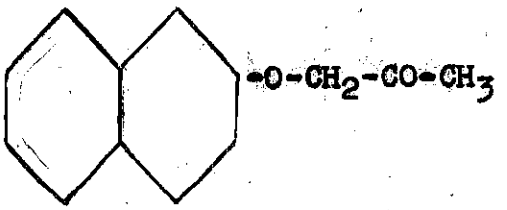
The Preparation of 1-(β-Naphthoxy)-2-propanone (I)



1-(β-Naphthoxy)-2-propanone (I) was prepared from chloroacetone and β-naphthol by the method of Hurd and Perlitz.[8]

Fifty grams (0.54 mol.) of chloroacetone and 50 grams of acetone (previously dried over anhydrous calcium chloride) were mixed in a 125 ml. separatory funnel and 3 grams of potassium iodide was added. The mixture was shaken and allowed to stand overnight.

In a three necked, one liter flask equipped with a mechanical stirrer, a reflux condenser, and a drying tube was placed a solution of 59 grams (0.41 mol.) of β-naphthol in 150 ml. of dry acetone. The stirrer was started and 57 grams (0.41 mol.) of anhydrous potassium carbonate was added. The chloroacetone mixture was added slowly over

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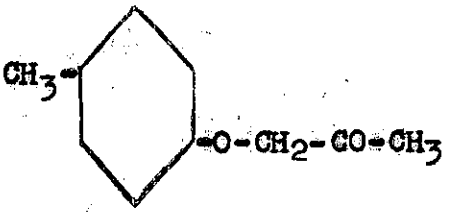
[8]Hurd and Perlitz, J. Am. Chem. Soc., 68, 38 (1946)

a period of one hour and the reaction mixture was refluxed with stirring on a hot water bath for six hours after which stirring was continued at room temperature for twenty hours.

The resulting mixture was filtered, the precipitate washed well with acetone, and the filtrate and washings combined. Upon the addition of water, the crude ketone precipitated. This was filtered and air dried overnight to remove the acetone. Purification was accomplished by dissolving the crude product in a boiling solution of 800 ml. of methyl alcohol and 200 ml. of water, cooling to room temperature, filtering the precipitate, and drying in air. A pale yellow, waxy product was obtained.

The melting point of the 1-(β-naphthoxy)-2-propanone (I) was 73 degrees C. (corrected). The yield was 80 grams, or 97 per cent of the theoretical. The oxime was a white solid melting at 123 degrees C. (corrected).

The Preparation of 1-(p-Tolyloxy)-2-propanone (II)



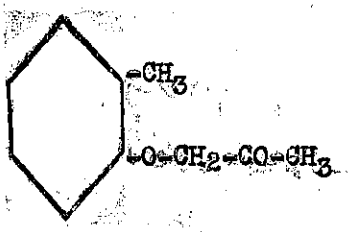
1-(p-Tolyloxy)-2-propanone (II) was prepared by the method of Hurd and Perlitz.[8]

Fifty grams (0.54 mol.) of chloroacetone, 3 grams of powdered potassium iodide, and 50 ml. of dry acetone were mixed in a 125 ml. separatory funnel and allowed to stand overnight. The resulting solution was slowly added to a mixture of 44.3 grams (0.41 mol.) of p-cresol, 57 grams (0.41 mol.) of anhydrous potassium carbonate, and 150 ml. of dry acetone, in a three necked flask fitted with a mechanical stirrer and a reflux condenser. As in the preparation of 1-(β-naphthoxy)-2-propanone (I), the reaction mixture was refluxed with stirring for six hours, and stirring was continued for twenty hours at room temperature.

After the reaction was completed, the potassium chloride was filtered off and washed with dry acetone. The filtrate and washings were combined and concentrated by evaporation on a hot water bath at 80 degrees C. and under a pressure of 35 mm. to remove the excess acetone. The residue was distilled under a pressure of 6 mm. A small fraction of chloroacetone distilled over from 40 to 65 degrees C. 1-(p-Tolyloxy)-2-propanone (II), a pale yellow liquid, distilled over

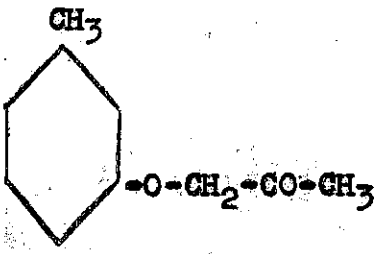
from 108 to 112 degrees C. Distillation was discontinued when the distillate became dark in color and the column head temperature rose suddenly. Thirty-nine grams of product (58 per cent yield) was obtained.

The Preparation of 1-(o-Tolyloxy)-2-propanone (III)



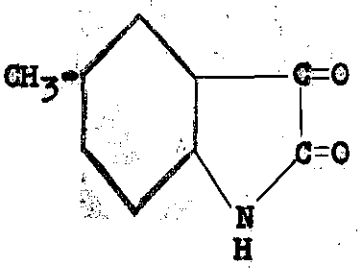
This compound was prepared by the method outlined for 1-(p-tolyloxy)-2-propanone (II), but was obtained in higher yield (71 per cent of the theoretical) as a yellow oil boiling at 106 degrees (5 mm.). The 2,4-dinitrophenylhydrazone of this ketone was a light orange solid melting at 153 degrees.

The Preparation of 1-(m-Tolyloxy)-2-propanone (IV)



By the same general procedure 1-(m-tolyloxy)-2-propanone (IV) was prepared in 57 per cent yield as a dark amber liquid boiling at 111 degrees (5 mm.). Redistillation gave a pale yellow liquid that turned dark upon cooling. The 2,4-dinitrophenylhydrazone was an orange solid melting at 132 degrees.

The Preparation of 5-Methylisatin[9] (V)



Ninety grams (0.54 mol.) of chloral hydrate was dissolved in 1200 ml. of water in a five liter round bottom flask, and 1300 grams of crystalline sodium sulfate was added. A solution of 54 grams (0.5 mol.) of p-toluidine in 300 ml. of water and 43 ml. (0.52 mol.) of concentrated hydrochloric acid was added to the chloral hydrate solution, and this was followed by 110 grams (1.58 mol.) of hydroxylamine hydrochloride in 500 ml. of water. The flask was then heated at such a rate as to produce boiling in forty-five to fifty minutes. The liquid was allowed to boil for two minutes, cooled, filtered, and the p-methyl-isonitrosoacetanilide air dried for twenty-four hours.

Six hundred grams (328 ml.) of concentrated sulfuric acid was warmed to 50 degrees in a one liter three necked flask fitted with a mechanical stirrer, and the p-methyl-isonitrosoacetanilide was added with stirring at such a rate as to keep the temperature between 50 and 60 degrees C. After the addition of the isonitroso

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[9]Gilman, Organic Synthesis-Collective Volume I, p. 321

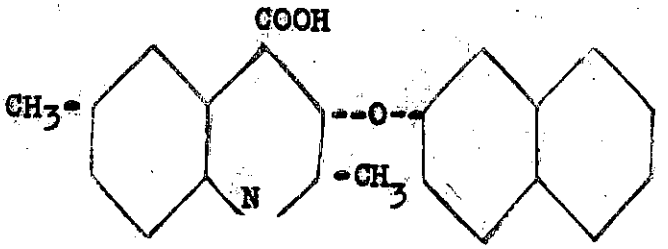
compound was complete, the solution was heated to 80 degrees for a period of ten minutes, cooled under running water, poured over five liters of cracked ice, and allowed to stand until the ice melted.

The crude 5-methylisatin (V) which separated out was filtered and washed free of sulfuric acid with cold water. The yield of the crude product was 74 grams (82 per cent of the theoretical).

The product was purified by two different methods during the course of this investigation. The first method consisted of dissolving the crude product in three times its weight of boiling glacial acetic acid, filtering, and cooling the filtrate in an ice bath. The 5-methylisatin (V) precipitated as dark red needles. Yield from this method of purification was approximately 30 to 35 per cent.

In the second method of purification 5-methylisatin (V) was suspended in 400 ml. of hot water and enough 30 per cent sodium hydroxide added to put the crude substance into solution. Dilute hydrochloric acid (1:3) was added until a slight precipitate appeared. The solution was immediately filtered, the precipitate rejected, and the filtrate made acid to congo red paper with dilute hydrochloric acid. The solution was cooled in an ice bath; the 5-methylisatin (V) was filtered off and dried in air. The yield from this purification process was 80 to 90 per cent.

The Preparation of 6-Methyl-3-(β-naphthoxy)-4-quinaldine-carboxylic acid (VI)



Eighteen and seven-tenths grams (0.116 mol.) of 5-methylisatin (V) was dissolved in 200 ml. of 33 per cent potassium hydroxide and placed in a three necked flask fitted with a mechanical stirrer. Twenty-three and two-tenths grams of 1-(β-naphthoxy)-2-propanone (I) was added and the mixture was refluxed with stirring on a steam bath for eight hours. At the end of this time a dark colored liquid layer separated on the top of the potassium hydroxide solution. Upon cooling, this liquid solidified to form a cake. The liquid was drawn off and acidified with dilute (1:1) acetic acid. No precipitate formed, even upon standing, and the solution was discarded.

The solid cake was broken up and dissolved in 300 ml. of boiling water. All of the precipitate dissolved, forming a dark amber solution. From this behavior it was decided that the cake consisted of the potassium salt of 6-methyl-3-(β-naphthoxy)-4-quinaldinecarboxylic acid (VI) that had been salted out of solution by the high concentration of potassium hydroxide. This was verified by the addition of 33 per cent potassium hydroxide to a small portion of the hot solution. The solution was boiled with Nuchar for five minutes, filtered hot, allowed

to cool, and then made acid to litmus with 120 ml. of 1:1 acetic acid. After standing for several hours, the solution was filtered, the solid suspended in 3.75 liters of hot water, and enough 33 per cent potassium hydroxide added to put all of the material into solution. After treating with Nuchar again, the solution was made acid to litmus with 1:1 acetic acid. An olive grey precipitate separated. This was filtered off, washed with cold water, and suspended in 1200 ml. of water to wash free of potassium acetate and acetic acid. The product was then filtered and air dried. The yield was 18.6 grams, or 46.8 per cent of the theoretical.

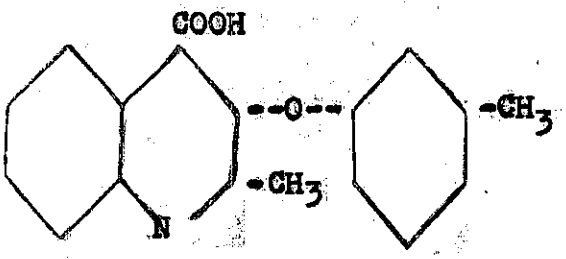
The compound was soluble in hot methanol, ethanol, ethylene glycol, and glacial acetic acid. It was almost completely insoluble in water, but the addition of a little acetic acid to the water greatly increases the solubility. All attempts to recrystallize the compound from these solvents and mixtures of these solvents were failures.

The compound darkened at 178 degrees and melted with decomposition at 233 degrees C. The darkening at 178 degrees is evidently a decarboxylation, since carbon dioxide was evolved at this temperature. It was found that the melting point varied with the rate of heating.

A quantitative nitrogen determination gave a value of 3.59 per cent, as compared with the theoretical value of 3.70 per cent (for the dihydrate). It is probable that the acid retained two molecules of water of hydration as similar results have been obtained in earlier work in this laboratory.[5] This water was lost by drying over phosphorus pentoxide. The neutral equivalent of the dehydrated acid was

found to be 341.5, whereas the theoretical is 343.4.

The Preparation of 3-(m-Tolyloxy)-4-quinaldine-carboxylic acid (VII)



Seven and thirty-five hundredths grams (0.05 mol.) of isatin was dissolved in 125 ml. of 33 per cent potassium hydroxide and placed in a three necked flask fitted with a mechanical stirrer and a reflux condenser. Eight and two tenths grams (0.05 mol.) of 1-(m-tolyloxy)-2-propanone (IV) was added, and the mixture was refluxed with stirring on a steam bath for six hours.

The reaction mixture was allowed to cool, and the solid cake separated from the liquid by decantation. This liquid yielded no precipitate upon acidification with dilute acetic acid. The solid material was broken into small pieces and dissolved in 500 ml. of hot water, boiled with Nuchar, filtered, and the crude 3-(m-tolyloxy)-4-quinaldinecarboxylic acid (VII) precipitated by the addition of 1:1 acetic acid to the cold solution. The solid was filtered off, suspended in 500 ml. of hot water, and enough 33 per cent potassium hydroxide added to put the material into solution. As in the case of 6-methyl-3-(β-naphthoxy)-4-quinaldinecarboxylic acid (VII), the potassium salt was salted out by the high concentration of potassium hydroxide. The solution was treated with Nuchar again, filtered and

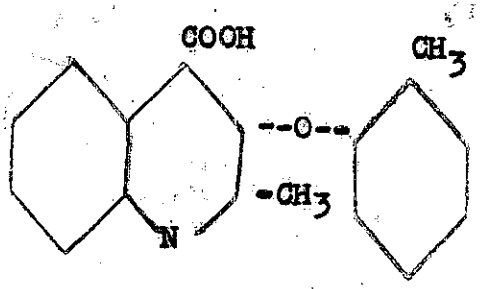
the acid precipitated by the addition of dilute acetic acid. The precipitate was filtered, washed twice with 100 ml. portions of cold water, and placed in a one liter beaker with 400 ml. of water. The suspension was boiled for forty-five minutes and filtered hot. A small amount of acid went into solution but was recovered by cooling the filtrate. The purified acid was a light biege color.

The yield was 9.78 grams, or 66.7 per cent of the theoretical.

The acid melted with decomposition at 224 degrees, but began to darken at 185 degrees.

A nitrogen analysis gave a value of 4.24 per cent, as compared with a theoretical value of 4.25 per cent on the basis of the dihydrate.

The Preparation of 3-(o-Tolyloxy)-4-quinaldine-carboxylic acid (VIII)

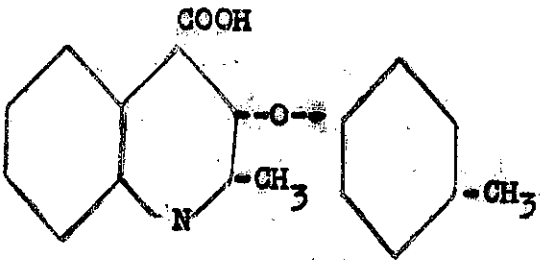


This compound was prepared by the method outlined for the m-isomer, but was obtained in slightly lower yield (64.8 per cent of the theoretical) as a pale yellow solid.

The 3-(o-tolyloxy)-4-quinaldinecarboxylic acid (VIII) darkened at 197 degrees C. and melted with decomposition at 229 degrees C.

Analysis of a sample previously dried over phosphorus pentoxide gave a nitrogen content of 4.73 per cent. The calculated value is 4.77 per cent nitrogen.

The Preparation of 3-(p-Tolyloxy)-4-quinaldine-carboxylic acid (IX)



3-(p-Tolyloxy)-4-quinaldinecarboxylic acid (IX) was prepared by the same general procedure as the meta-isomer. The yield was 58 per cent of the theoretical.

The compound is a pale yellow solid melting with decomposition at 206 degrees after darkening at 176 degrees.

A quantitative nitrogen analysis of a sample previously dried over phosphorus pentoxide gave a result of 4.91 per cent. The theoretical is 4.77 per cent.

CHAPTER IV

DISCUSSION OF RESULTS

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The Pfitzinger reaction has been extended to include the condensation of 5-methylisatin with 1-(β-naphthoxy)-2-propanone (I) in the usual manner.

The tolyloxypropanones have been utilized in the synthesis of three new substituted cinchoninic acids from isatin.

The highest yield (66.7 per cent) was obtained in the preparation of 3-(m-tolyloxy)-4-quinaldinecarboxylic acid (VII), and the lowest (46.8 per cent) in the preparation of 6-methyl-3-(β-naphthoxy)-4-quinaldinecarboxylic acid (VI).

The potassium salts of all of the quinaldinecarboxylic acids prepared possess soap like properties. They tend to foam in water solution, and are salted out by high concentrations of potassium hydroxide.

Decarboxylation of the compounds occured around 176 degrees. The melting point was not taken to be characteristic of the compound because it was found to be dependent to a large extent upon the rate of heating and the extent of darkening of the compound.

All of the quinoline acids showed a tendency to hold water of crystallization. This water was removed by drying in a vacuum desiccator over phosphorus pentoxide.

CHAPTER V

SUMMARY

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The following compounds have been prepared and some study made of their properties:

1. Ketones

   1-(β-Naphthoxy)-2-propanone (I); 1-(p-tolyloxy)-2-propanone (II); 1-(o-tolyloxy)-2-propanone (III); and 1-(m-tolyloxy)-2-propanone (IV).

2. Ketone Derivatives

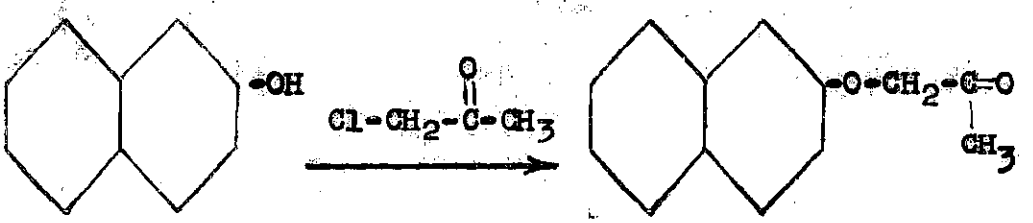
   The 2,4-dinitrophenylhydrazone of 1-(o-tolyloxy)-2-propanone; the 2,4-dinitrophenylhydrazone of 1-(m-tolyloxy)-2-propanone; and the oxime of 1-(β-naphthoxy)-2-propanone.

3. Substituted Quinoline Acids

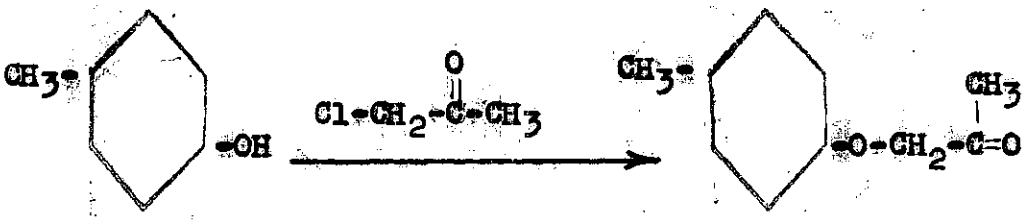
   6-Methyl-3-(β-naphthoxy)-4-quinaldinecarboxylic acid (VI); 3-(m-tolyloxy)-4-quinaldinecarboxylic acid (VII); 3-(o-tolyloxy)-4-quinaldinecarboxylic acid (VIII); and 3-(p-tolyloxy)-4-quinaldinecarboxylic acid (IX).

FIGURE I

The Preparation of 1-(β-Naphthoxy)-2-propanone (I)
and 1-(p-Tolyloxy)-2-propanone (II)



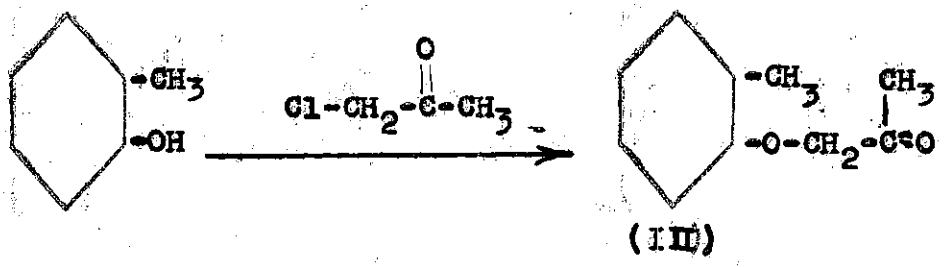
(I)



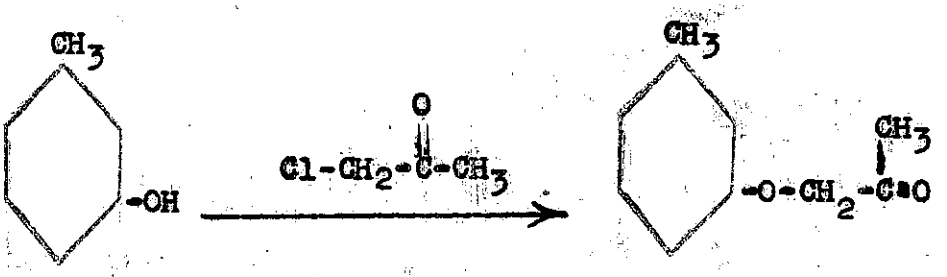
(II)

FIGURE II

The Preparation of 1-(o-Tolyloxy)-2-propanone (III)
and 1-(m-Tolyloxy)-2-propanone (IV)



(III)



(IV)

FIGURE III

The Preparation of 5-Methylisatin (V)

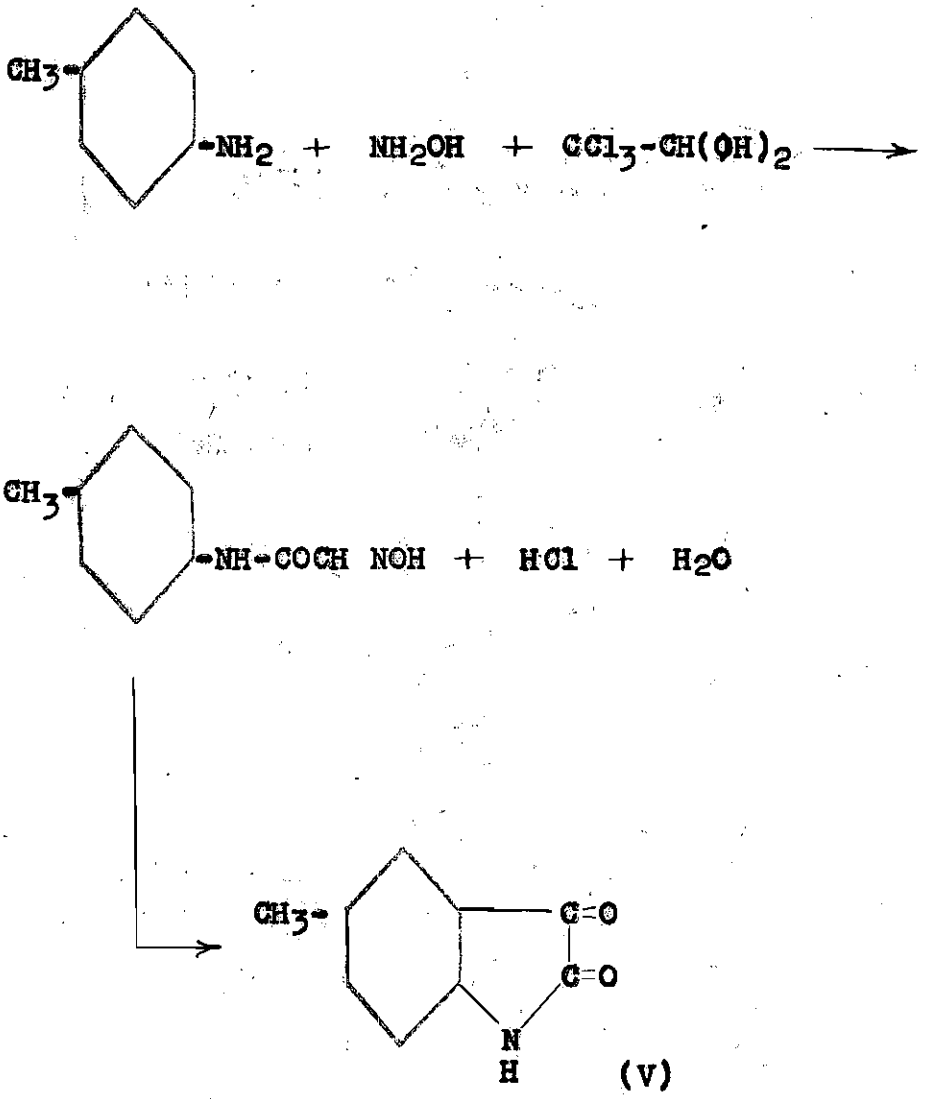


FIGURE IV

The Preparation of 6-Methyl-3-(β-naphthoxy)-4-quinaldinecarboxylic acid (VI)

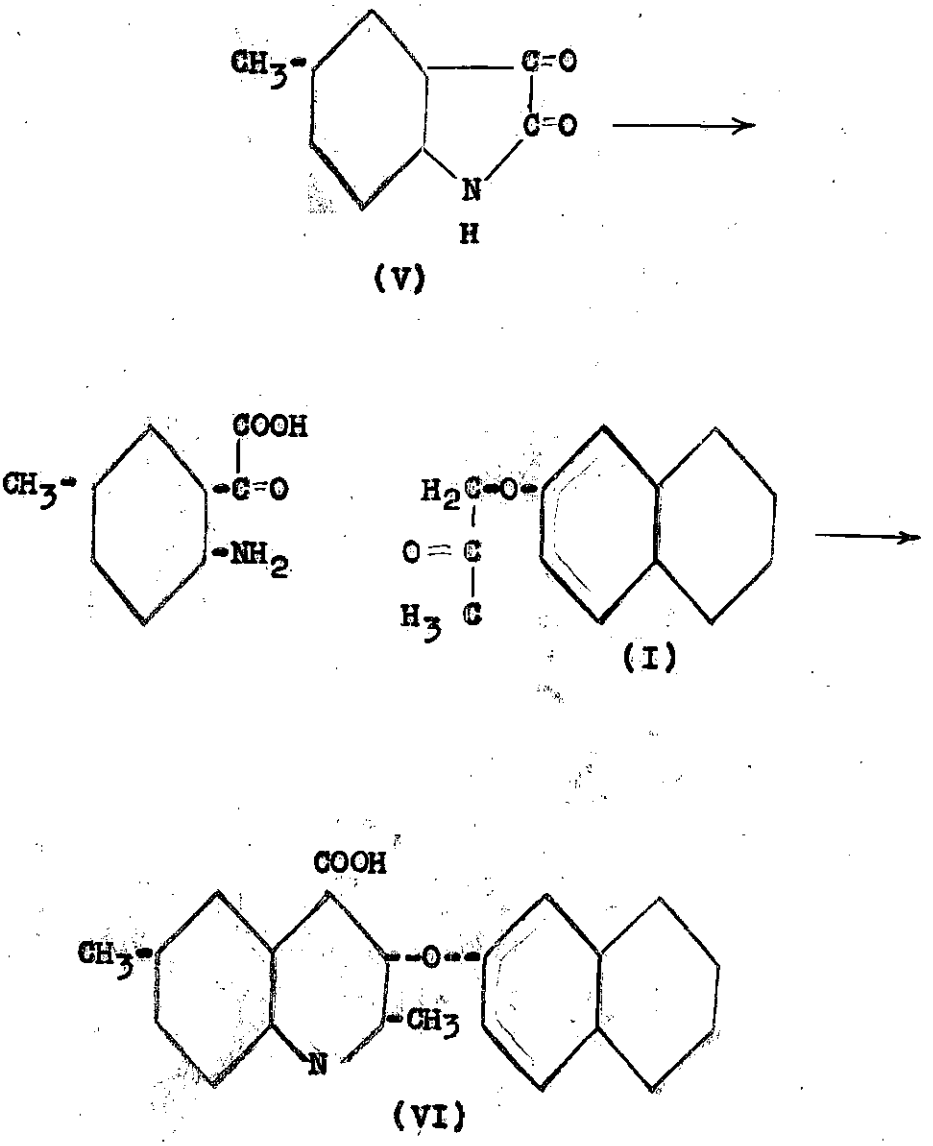
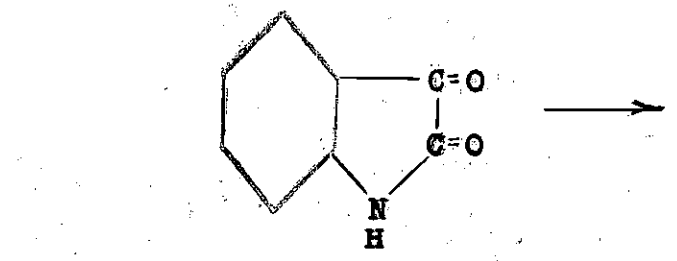
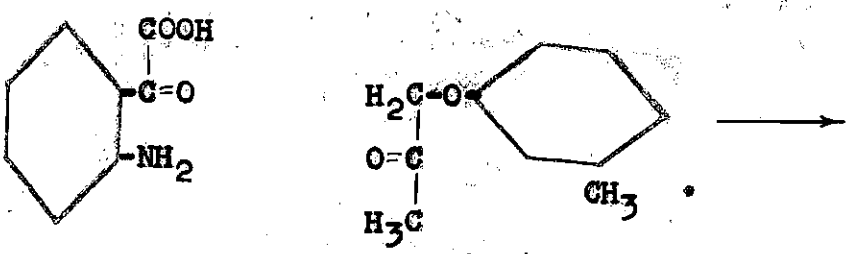


FIGURE V

The Preparation of 3-(m-Tolyloxy)-4-quinaldine-carboxylic acid (VII)





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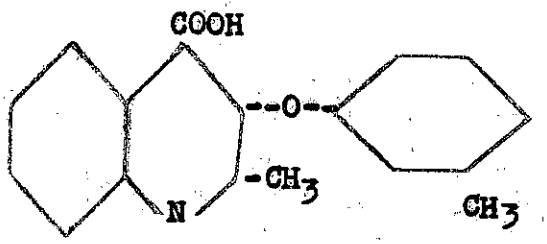


(VII)

FIGURE VI

The Preparation of 3-(o-Tolyloxy)-4-quinaldine-carboxylic acid (VIII)

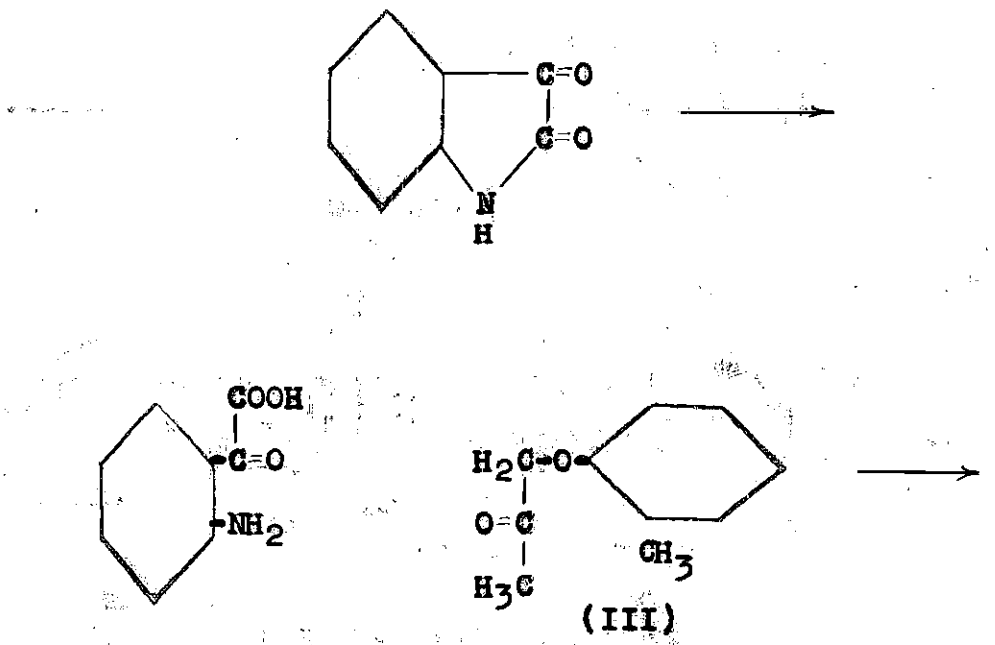
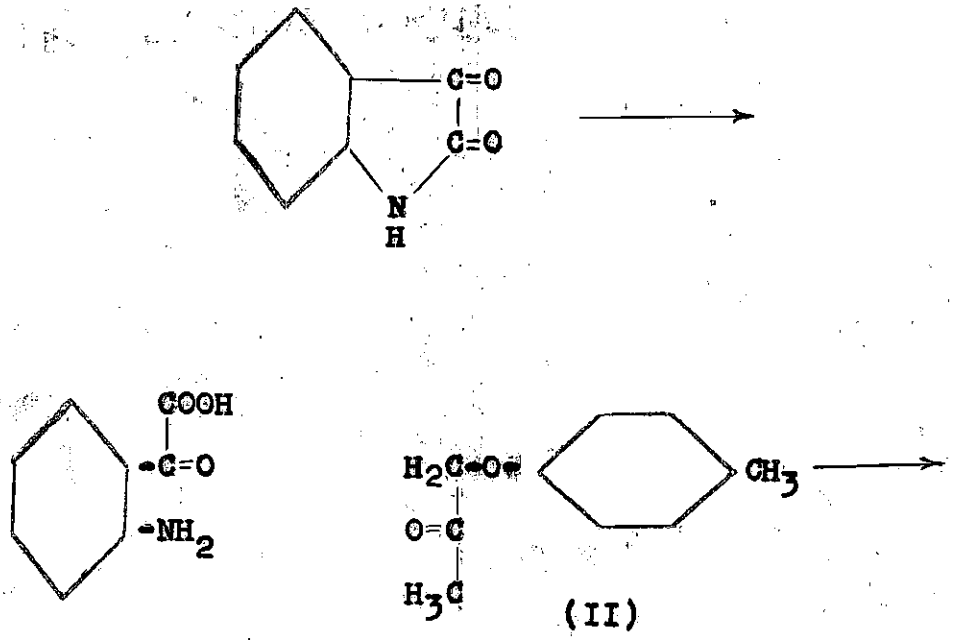


FIGURE VII

The Preparation of 3-(p-Tolyloxy)-4-quinaldine-carboxylic acid (IX)



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