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QUINALDINECARBOXYLIC ACIDS BY THE
PFITZINGER REACTION

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A THESIS

Presented to

the Faculty of the Division of Graduate Studies

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In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Chemistry

by

Howard Smith McCullough

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QUINALDINECARBOXYLIC ACIDS BY THE
PFITZINGER REACTION

Approved:

D. V. L. ...

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Date Approved by Chairman 15 March 1948

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Upon completion of this work, I wish to express my sincerest appreciation and gratitude to Dr. P. K. Calaway for his suggestion of the problem and invaluable aid and inspiration during its prosecution.

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CHAPTER I
PFITZINGER REACTION

QUINALDINECARBOXYLIC ACIDS BY THE PFITZINGER REACTION

CHAPTER I

THE PFITZINGER REACTION

The condensation of 5-methylisatin with acetone to form 6-methyl-4-quinaldinecarboxylic acid in 1886 by Pfitzinger gave use to the general reaction between isatins and ketones which now bears his name^{1,2}.

Calaway and co-workers have extended the Pfitzinger Reaction to include the condensation of aryloxyketones, arylthioketones, and alkoxyaryloxyketones with isatins^{3,4,5,6,7}.

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

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

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

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

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

⁶Dowell, McCullough, and Calaway, J. Am. Chem. Soc., 70, 226 (1948)

⁷Sublett, Georgia School of Technology, Master's Thesis, (1947)

The chief product of the condensation of unsymmetrical ketones with isatins will normally have the larger group in the 3-position^{8,9}.

⁸Pfitzinger, J. prakt. Chem., 56, 283 (1897)

⁹Von Braun, Gmelin, and Schulthesis, Ber., 56, 1344 (1923)

CHAPTER II

THE PURPOSE OF THIS INVESTIGATION

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The quinoline nucleus with various substituents has exhibited therapeutic value in a number of cases. Examples are cinchophen, for rheumatic fever and gout; yatren, for amebic dysentery; vioform, as a substitute for iodoform; and plasmochin and quinine, as anti-malarials¹⁰.

The substituted cinchoninic acids reported in this thesis are closely related in structure to these chemotherapeutic agents, and there is a possibility that they may be of some value as therapeutic agents.

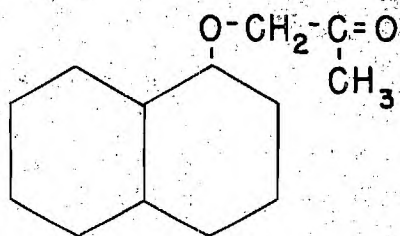
The availability of aryloxyketones from chloroacetone and substituted phenols suggested their condensation with various isatins as a continuation of the work of Henze, Calaway^{3,4,5,6,7} and co-workers.

¹⁰Jenkins and Hartung, Chemistry of Organic Medicinal Products, John Wiley and Sons, Inc., New York, N.Y. (1943), second edition, pp. 498-501.

CHAPTER III
EXPERIMENTAL

CHAPTER III

EXPERIMENTAL

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

(I)

1-(α -Naphthoxy)-2-propanone (I) was prepared from chloroacetone and α -naphthol by the method developed by Hurd and Perletz.¹¹

Fifty grams (.54 mole) of chloroacetone and 62.5 ml. of acetone, previously dried over calcium chloride, were placed in a separatory funnel. To these were added 3 grams of potassium iodide, and the mixture was thoroughly shaken and allowed to stand overnight at room temperature.

To 59 grams (.41 mole) of α -naphthol, in a 500 ml. round bottom, three-necked flask, equipped with a mechanical stirrer and a reflux condenser, was added 59 grams (.43 mole) of anhydrous potassium

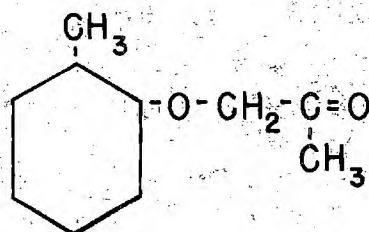
¹¹Hurd and Perletz, J. Am. Chem. Soc., 68, 38 (1946)

carbonate and 150 ml. of dry acetone. A drying tube was inserted in the condenser, and the mixture was refluxed with stirring for fifteen minutes. The chloroacetone mixture was then added dropwise with continued refluxing and stirring over a period of thirty minutes. After the addition of chloroacetone, the mixture was refluxed and stirred for six hours. At the end of this time, the mixture was stirred for twenty hours at room temperature.

The mixture was filtered, the precipitate washed well with acetone, and the filtrate and washings combined and concentrated under reduced pressure (aspirator) on a hot water bath. The crude product was distilled at 3 mm. pressure.

1-(α -Naphthoxy)-2-propanone (I), a pale yellow liquid, distilled over from 142 to 148 degrees C. Distillation was discontinued when the distillate showed signs of discoloration and the temperature in the column head rose suddenly. The yield was 48 grams, corresponding to 58.5 per cent of the theoretical. The 2,4 dinitrophenylhydrazone was a deep yellow solid melting sharply at 189 degrees C. (corr.). The density was 1.1437 and the index of refraction was 1.6043, both observed at 20 degrees C. The molar refraction was found to be 60.13 from observations, as compared to 59.87; calculated.

The Preparation of 1-(o-Toloxyl)-2-propanone (II)



(II)

Fifty grams (.54 mole) of chloroacetone was added to a mixture of 62.5 ml. of dry acetone and 3 grams of powdered potassium iodide in a 125 ml. separatory funnel. After shaking, the mixture was allowed to stand overnight.

In a three-necked, round bottom flask, equipped with a reflux condenser with drying tube and a mechanical stirrer, was placed 44.3 grams (.41 mole) of previously dried o-cresol, 150 ml. dry acetone and 59 grams (.43 mole) of potassium carbonate. The mixture was heated to reflux, and the chloroacetone mixture was added, with stirring, over a period of thirty minutes. The refluxing was continued for six, and the stirring for twenty, hours.

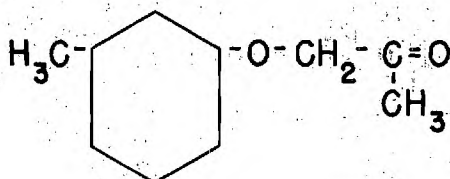
The solid material was removed by filtering and washed with several portions of acetone. The filtrate and washings were combined and concentrated on a hot water bath under reduced pressure (aspirator). Almost all the acetone and chloroacetone were removed by this

process. The crude product was then distilled under 3 mm. pressure.

The first distillate, up to 94 degrees C., was chloroacetone. The second fraction, boiling from 94 degrees to 97 degrees at 3 mm., was identified as 1-(o-toloxo)-2-propanone (II). Forty-nine and six-tenths grams, a yield of 73.7 per cent of the theoretical, was collected as a pale yellow liquid.

The 2,4-dinitrophenylhydrazone was prepared and its melting point determined as 152 degrees C. (corr.). The index of refraction and density at 20 degrees C. were found to be 1.5175 and 1.0585, respectively. From these, the molar refraction was calculated to be 46.88, as compared to the theoretical value of 46.44.

The Preparation of 1-(m-Toloxyl)-2-propanone (III)

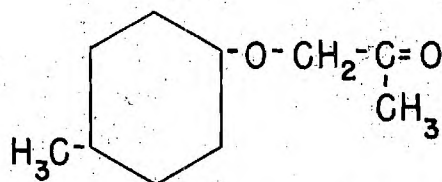


(III)

This compound was prepared by the same general procedure as used for the preparation of 1-(o-toloxyl)-2-propanone (II), except that the starting material was 44.3 grams (.41 mole) of m-cresol. The fraction distilling under 3 mm. pressure between 92-95 degrees C. was a yellow, viscous liquid and weighed 49 grams, a yield of 73 per cent of the theoretical value.

The observed density and index of refraction (20 degrees C.) were 1.0587 and 1.5182, respectively. The theoretical molar refraction was 46.44, and the experimental value, 46.95. The 2,4-dinitrophenylhydrazone melted at 141 degrees C. (corr.).

The Preparation of 1-(p-Toloxyl)-2-propanone (IV)

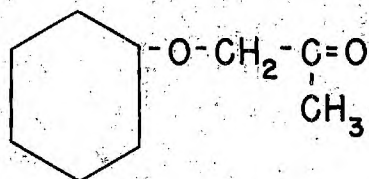


(IV)

The same procedure used previously was followed in preparing 1-(p-toloxyl)-2-propanone (IV), for which the starting material was 44.3 grams (.41 mole) of p-cresol. The product was obtained as a clear, almost colorless liquid in the amount of 49 grams (72.5 per cent of theoretical), with a boiling point of 90 degrees C. (corr.) under 3 mm. pressure.

The molar refraction, as calculated from the experimental values of density and index of refraction of 1.0558 and 1.5165 (20 degrees C.), respectively, was found to be 46.96. The theoretical value is 46.44. The 2,4-dinitrophenylhydrazone was an orange-yellow solid melting at 133 degrees C.

The Preparation of 1-Phenoxy-2-propanone (V)



(V)

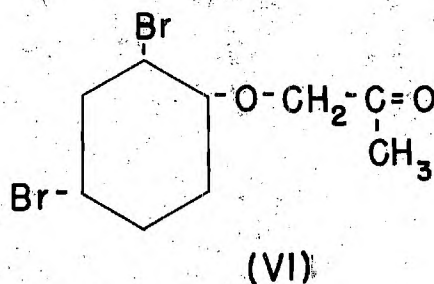
This compound was prepared in the same manner as outlined for 1-(o-toloxyl)-2-propanone (II), starting with 38.5 grams (.41 mole) of phenol. 1-phenoxycyclohexyl 2-propanone (V) was obtained as a water clear liquid boiling at 75 degrees C. under 2 mm. pressure and in a yield of 48 grams, which was 85 per cent of theoretical.

Whitney and Henze¹² reported this compound in 1938 as having a density of 1.0903 and index of refraction of 1.5228, both at 20 degrees C. From these data, the molar refraction was determined to be 42.27, while from the theoretical values, 41.82 was found.

The 2,4-dinitrophenylhydrazone was a yellow solid, melting at 128 degrees C.

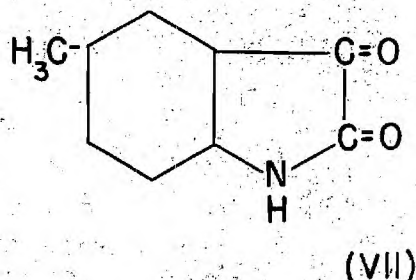
¹²W. B. Whitney and H. R. Henze, J. Am. Chem. Soc., 60, 1148 (1938)

The Preparation of 1-(2,4-Dibromophenoxy)-2-propanone (VI)



The method of Hurd and Perletz¹¹ was used in preparing this compound, and 17.3 grams (0.1 mole) of 2,4-dibromophenol was used as starting material. However, it was found that, after concentrating the filtrate from the reaction mixture and the washings, chilling caused a precipitate to form. Cold water was added and the precipitate was collected and washed with several portions of cold water. The product, when air dried for twenty-four hours, was a waxy yellow solid which, when purified by recrystallization from cyclohexane, melted sharply at 94 degrees C. The yield was 26.3 grams, which was 85 per cent of theoretical. The 2,4-dinitrophenylhydrazone melted at 156 degrees C.

The Preparation of 5-Methylisatin (VII)¹³



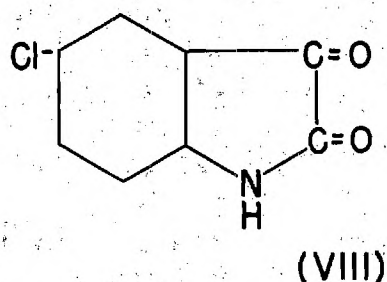
Ninety grams (0.54 mole) of chloral hydrate was dissolved in 1200 ml. of water in a five liter round bottom flask, and 1300 grams of crystalline sodium sulfate was added. Fifty-four grams (0.5 mole) of p-toluidine was dissolved in 300 ml. of water to which had been added 43 ml. (0.52 mole) of concentrated hydrochloric acid. This solution was then added to the flask, followed by 110 grams (1.58 moles) of hydroxylamine hydrochloride in 500 ml. of water. The mixture was then heated so as to boil within forty-five to fifty minutes. After boiling for two minutes, it was then cooled under running water. The p-methylisonitrosoacetanilide was filtered off as a straw colored solid and air dried for twenty-four hours.

Seven hundred and fifty grams (410 ml.) of concentrated sulfuric acid was warmed to 50 degrees C. in a one liter round bottom flask

¹³Gilman, Organic Synthesis, John Wiley and Sons, Inc., New York, N.Y. (1932), Vol. I, p. 321

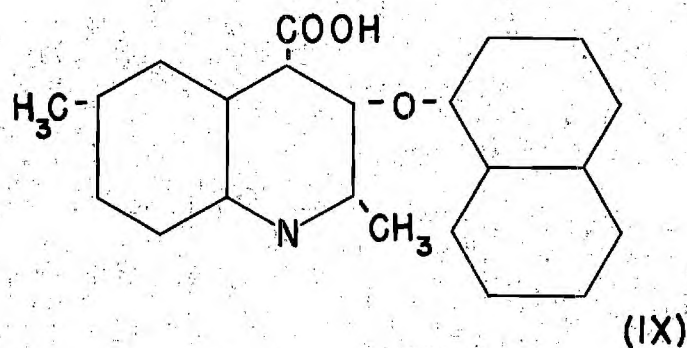
equipped with a mechanical stirrer. The p-methylisonitrosoacetanilide was added at such rate as to keep the temperature of the acid between 50 and 60 degrees C. After the addition of the p-methylisonitrosoacetanilide was completed, the solution was warmed to 80 degrees C. for ten minutes, care being taken not to let the temperature go higher, then cooled under running water, and poured over five volumes of crushed ice. The crude 5-methylisatin separated out as a red-orange solid, and was filtered, washed free of sulfuric acid with cold water, and air dried for twenty-four hours. The yield was 74 grams (82 per cent of theoretical). The crude product was suspended in 400 ml. of hot water and enough 33 per cent potassium hydroxide was added to effect solution. Dilute hydrochloric acid was added until there was a slight precipitation. This was filtered off, and the remaining solution was made acid to congo red paper with more dilute hydrochloric acid. There was a heavy precipitation; the mixture was cooled in an ice bath, and the 5-methylisatin filtered off and dried in air. The yield of purified 5-methylisatin (VII) varied for several batches between 80 and 90 per cent.

The Preparation of 5-Chloroisatin (VIII)



The procedure for the preparation of 5-chloroisatin (VIII) was essentially the same as for 5-methylisatin (VII). The starting material was 63.75 grams (0.5 mole) of p-chloroaniline. The yield on purification was slightly lower, 62 grams (67 per cent of theoretical). The purified 5-chloroisatin (VIII), after drying, was an orange-red powder melting at 235 degrees C.

The Preparation of 6-Methyl-3-(α -naphthoxy)-4-quinoline-carboxylic Acid (IX)



Thirteen and seven-tenths grams (0.085 mole) of 5-methylisatin (VII) was dissolved in 120 ml. of 33 per cent aqueous potassium hydroxide solution and placed in a round bottom flask fitted with a mechanical stirrer. Seventeen grams (0.085 mole) of 1-(α -naphthoxy)-2-propanone (I) was added, and the mixture was heated on a water bath and stirred for seven hours. When the mixture was cooled, a solid cake separated and was removed. The residual liquid was treated with dilute acetic acid until it tested acid to litmus. No precipitate separated from the liquid, even upon prolonged standing and chilling; therefore, it was discarded.

The solid cake, disintegrated and dissolved in 300 ml. of hot water, gave a dark brown solution. A small portion was made acid with dilute acetic acid (1:1) and a light tan precipitate separated out. Addition of a small amount of 33 per cent potassium hydroxide caused

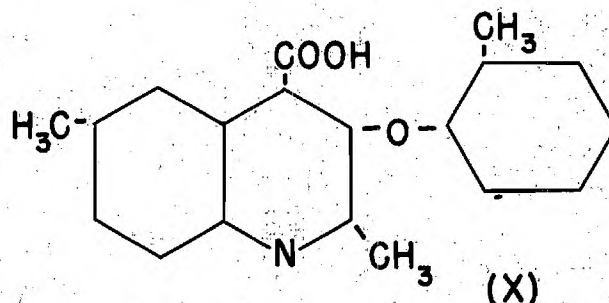
the acid to go into solution again, giving a dark brown color. By this test, it was decided that the solid cake was the potassium salt of 6-methyl-3-(α -naphthoxy)-4-quinaldinecarboxylic acid (IX), salted out by the high concentration of potassium hydroxide. The remainder of the solution from the solid cake was treated with Nuchar, boiled for five minutes, filtered and made acid with dilute acetic acid (1:1). The light tan precipitate was taken up again in water, placed in solution with a small amount of 33 per cent potassium hydroxide, treated with Nuchar, boiled, filtered, and the solution again made acid to litmus with dilute acetic acid (1:1). The precipitate, 6-methyl-3-(α -naphthoxy)-4-quinaldinecarboxylic acid (IX), was lighter in color after this second treatment. In order to remove inorganic salts, the product was taken up in 600 ml. of hot water, boiled for five minutes, cooled to room temperature, and filtered. The yield was 12 grams (40 per cent of theoretical).

It was found that the compound, upon heating, darkened around 190 degrees C., began to lose carbon dioxide, and finally melted at 238 degrees C. (dec.). However, this melting point is not too important, as it was found that the rate of heating affected the melting point greatly.

A quantitative determination of the nitrogen content by the Dumas method gave 3.9 per cent for a sample dried over phosphorous pentoxide for two to three days as compared to 4.08 per cent theore-

tical. Other samples, air dried and dried over calcium chloride, gave percentages of nitrogen which indicated that the acid held two molecules of water of hydration.

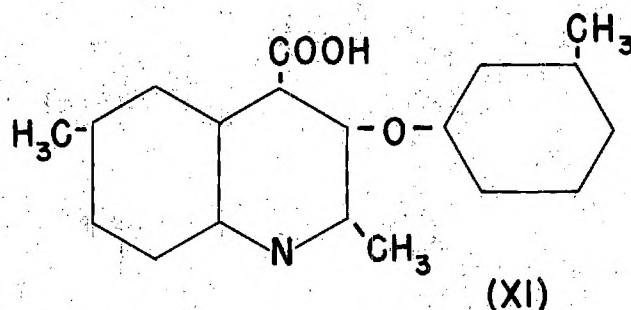
The Preparation of 6-Methyl-3-(o-toloxo)-4-quinaldine-
carboxylic Acid (X)



Twenty-four and seven-tenths grams (0.15 mole) of 1-(o-toloxo)-2-propanone (II) was reacted with 5-methylisatin by the same procedure as outlined for the preparation of 6-methyl-3-(α -naphthoxy)-4-quinaldinecarboxylic acid (IX). The yield of 6-methyl-3-(o-toloxo)-4-quinaldinecarboxylic acid (X) was 37.2 grams, or 80.8 per cent of the theoretical value.

A nitrogen determination of a sample dried over phosphorous pentoxide gave 4.24 per cent nitrogen, while the calculated value was 4.54 per cent. This compound darkened around 178 degrees C. and melted at 225 degrees C. (dec.).

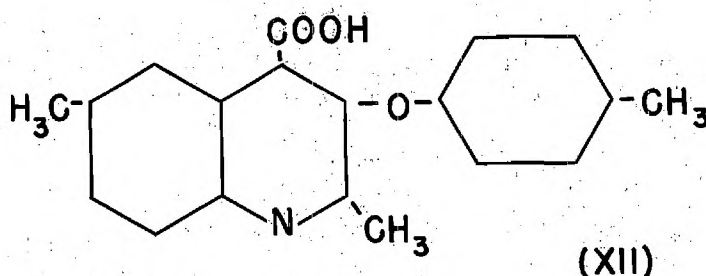
The Preparation of 6-Methyl-3-(m-toloxyl)-4-quinoline-
carboxylic Acid (XI)



This compound was prepared by the general method outlined before, and 16.4 grams (.1 mole) of 1-(m-toloxyl)-2-propanone (III) gave 22.5 grams (73.2 per cent of theoretical) of 6-methyl-3-(m-toloxyl)-4-quinolinecarboxylic acid (XI) as a pale yellow solid.

This compound melted at 231 degrees C. (dec.), but started darkening at 185 degrees C. The calculated percentage nitrogen was 4.54 per cent, while that found by analysis was 4.35 per cent.

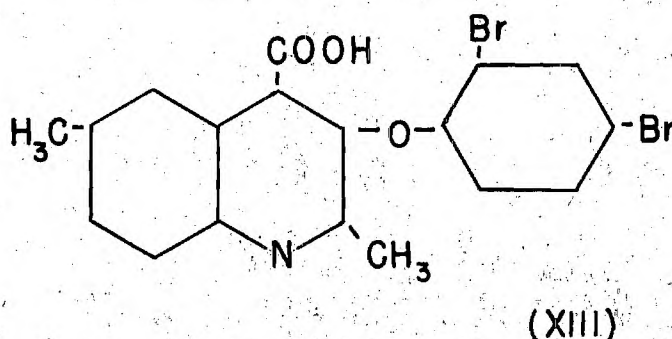
The Preparation of 6-Methyl-3-(p-toloxo)-4-quinaldine-
carboxylic Acid (XII)



Starting with 19.7 grams (.12 mole) of 1-(p-toloxo)-2-propanone (IV) and using the general method outlined, 6-methyl-3-(p-toloxo)-4-quinaldinecarboxylic acid (XII) was prepared in a yield of 22.3 grams (72.6 per cent). The slightly colored solid darkened at 171 degrees C. and melted at 202 degrees C. (dec.).

The theoretical per cent nitrogen was 4.54 per cent, as compared to 4.42 per cent found by analysis of a sample dried over phosphorous pentoxide.

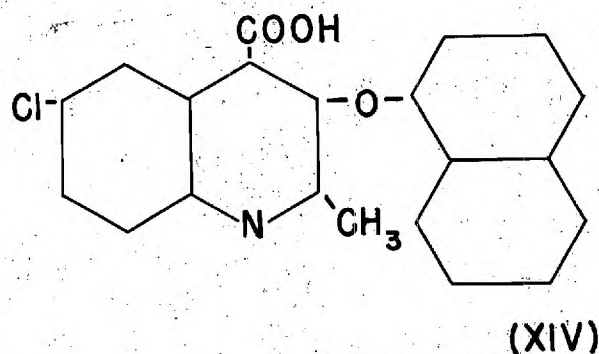
The Preparation of 6-Methyl-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic Acid (XIII)



The general procedure used previously was used to prepare 6-methyl-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic acid (XIII) except that the starting material was 5.08 grams (0.0166 mole) of 1-(2,4-dibromophenoxy)-2-propanone (VI). The product, a very slightly colored solid, was obtained in a yield of 4.54 grams, 60 per cent of the theoretical.

The compound, when heated, darkened around 175 degrees C. and melted at 223 degrees C. (dec.). A nitrogen determination gave 3.18 per cent as compared to the theoretical per cent of 3.10.

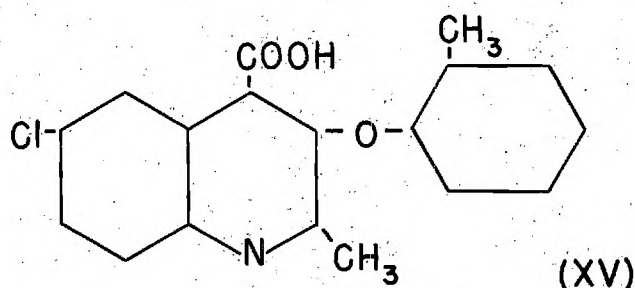
The Preparation of 6-Chloro-3-(α -naphthoxy)-4-quinoline-
carboxylic Acid (XIV)



Ten grams (0.05 mole) of 1-(α -naphthoxy)-2-propanone (I) was condensed with 9.25 grams of 5-chloroisatin (VIII) by the usual method. It was found that this reaction proceeded much faster than the condensations previously described, and that the time on the steam bath could be reduced from seven hours to one hour.

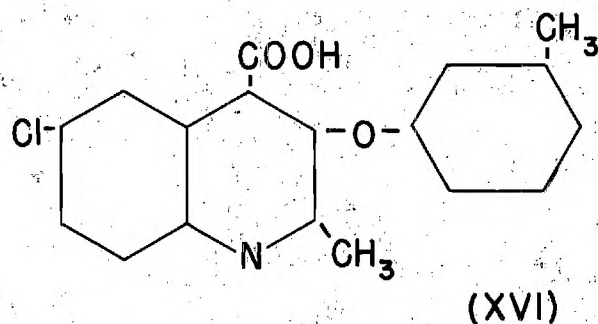
The yield was unusually low for this condensation, 3.35 grams (18.6 per cent of theoretical). The melting point was 238 degrees C. (dec.), with darkening beginning at 203 degrees C. The calculated percentage of nitrogen was 3.85, as compared to 3.63 per cent found by analysis.

The Preparation of 6-Chloro-3-(o-toloxo)-4-quinaldine-
carboxylic Acid (XV)



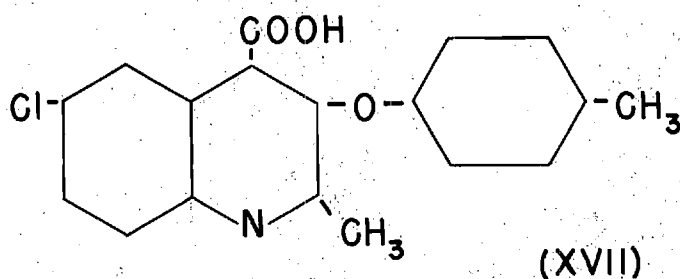
By the general method outlined previously, 6-chloro-3-(o-toloxo)-4-quinaldinecarboxylic acid (XV) was prepared from 8.2 grams (.05 mole) of o-toloxo-2-propanone (II). The yield was 11.0 grams, 67 per cent of theoretical, and the melting point was observed at 241 degrees C. (corr.) (dec.). A nitrogen determination of a sample dried over phosphorous pentoxide gave 4.27 per cent as compared to the theoretical of 4.30 per cent.

The Preparation of 6-Chloro-3-(m-toloxo)-4-quinaldine-
carboxylic Acid (XVI)



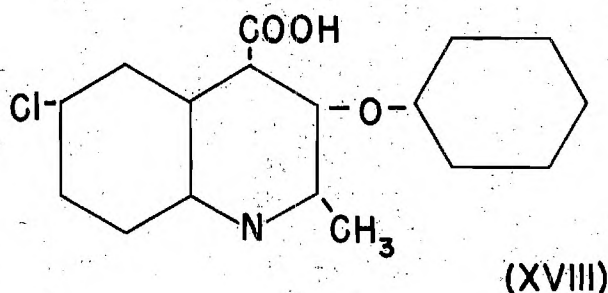
This acid was prepared by the same general procedure, starting with 8.2 grams (.05 mole) of m-toloxo-2-propanone (III). The yield of 6-chloro-3-(m-toloxo)-4-quinaldinecarboxylic acid (XVI), a light tan solid, was 10 grams, or 61 per cent of the theoretical. The melting point was found to be 230 degrees C. (corr.) (dec.). The percentage nitrogen was found to be 4.45, as compared to the theoretical value of 4.27.

The Preparation of 6-Chloro-3-(p-toloxo)-4-quinaldine-
carboxylic Acid (XVII)



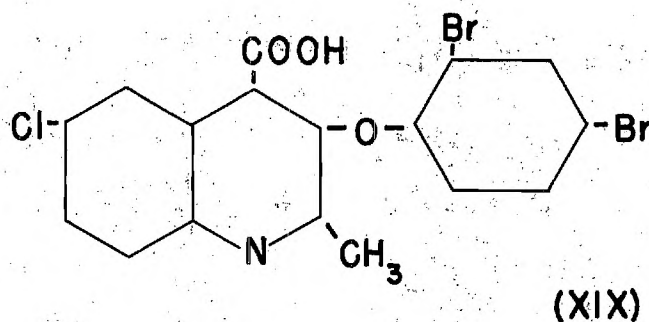
By the general method outlined previously, 6-chloro-3-(p-toloxo)-4-quinaldinecarboxylic acid (XVII) was prepared with 8.2 grams (.05 mole) of p-toloxo-2-propanone (IV). The yield was 13.7 grams, 83.7 per cent of theoretical, and the melting point was found to be 227 degrees C. (dec.). A nitrogen determination of a sample previously dried over phosphorous pentoxide gave 4.14 per cent while the theoretical percentage is 4.27.

The Preparation of 6-Chloro-3-phenoxy-4-quinaldine-
carboxylic Acid (XVIII)



By the method used previously, 6-chloro-3-phenoxy-4-quinaldinecarboxylic acid (XVIII) was prepared from 2.25 grams (.015 mole) of 1-phenoxy-2-propanone (V). The yield was 1.5 grams, a yield of 32 per cent of theoretical. The melting point was 248 degrees C. (corr.) (dec.). The theoretical per cent of nitrogen was 4.46 as compared to 4.61 per cent found by analysis of a sample previously dried over phosphorous pentoxide.

The Preparation of 6-Chloro-3-(2,4-dibromophenoxy)-4-
quinaldinecarboxylic Acid (XIX)



Using the same method outlined previously, 6-chloro-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic acid (XIX) was prepared from 4.62 grams (.015 mole) of 2,4-dibromophenoxy-2-propanone (VI). The yield was 5.88 grams, 83.1 per cent of theoretical, and the melting point was 243 degrees C. (corr.) (dec.). A nitrogen determination gave 3.08 per cent, as compared to the theoretical value of 2.97 per cent.

CHAPTER IV

GENERAL DISCUSSION OF RESULTS

CHAPTER IV

GENERAL DISCUSSION OF RESULTS

The preparation of aryloxyketones by the method of Hurd and Perletz¹¹ has been extended to include various substituted aryloxyketones. The compounds thus prepared were all high boiling liquids with the exception of 1-(2,4-dibromophenoxy)-2-propanone (VI), which was a pale yellow solid. The color of the liquids immediately upon distillation was water-clear, but darkened considerably upon standing. This was due to decomposition as was proved by Tarbell¹⁴, who found that 4-methyl phenoxyacetone, or 3-(p-toloxo)-2-propanone (IV), upon $2\frac{1}{2}$ hours heating at 250-260 degrees C. gave 10 per cent p-cresol and 73 per cent starting material. All ketones prepared gave a marked change in color and odor after standing for a period of four months.

The refractive index was determined with an Abbe' Refractometer with the temperature adjusted to 20 degrees C. The density was determined with a goose-neck pycnometer of 1.4 ml. capacity. In calculating the actual molar refraction, the formula of Lorentz and Lorenz was used, while the theoretical values were determined using

¹⁴Tarbell, J. Org. Chem., 7, 251 (1942)

those given by Cohen¹⁵ and Gilman¹⁶. The actual values varied from the theoretical values only slightly, the maximum being 1.1 per cent.

The aryloxyketones were condensed with 5-methylisatin and 5-chloroisatin. It was found that the time required for condensation of 5-methylisatin with the ketones was greater than the time needed for completion of the reaction when 5-chloroisatin was used. The yields averaged between sixty and eighty per cent of the theoretical. Lower yields are probably due to several factors, i.e., decomposition of the ketone by the strong alkali, increased solubility of the quinoline acid in water. It was noted that the substitution of a chloro group in the 6-position increased the solubility over the 6-methyl compound.

The potassium salts of the acids, salted out of the condensation mixture by the high concentration of potassium hydroxide, were soluble in hot water, and possessed soap-like properties, as indicated by a tendency to foam when agitated.

Upon heating, the quinoline acids began to darken at about 175 degrees C. This darkening was accompanied by decarboxylation. The melting point varied with the rate of heating and, as a consequence, is of little or no value as a characteristic of the compound.

¹⁵Cohen, Organic Chemistry for Advanced Students, Part II, fifth edition, Edwd. Arnold and Co., London, (1928), pp. 25-34

¹⁶Gilman, Organic Chemistry, Vol. 2, second edition, John Wiley and Sons, Inc., New York, N.Y., (1943), pp. 1750-1752

For nitrogen determination, the semi-micro method of Dumas was used. As the 6-chloro compounds burned easily, it was necessary to use a very low flame at the beginning of the combustion.

CHAPTER V

SUMMARY

CHAPTER V

SUMMARY

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

1. Ketones

- 1-(α -naphthoxy)-2-propanone (I)
- 1-(o-toloxo)-2-propanone (II)
- 1-(m-toloxo)-2-propanone (III)
- 1-(p-toloxo)-2-propanone (IV)
- 1-phenoxy-2-propanone (V)
- 1-(2,4-dibromophenoxy)-2-propanone (VI)

2. Ketone Derivatives

The 2,4-dinitrophenylhydrazones of:

- 1-(α -naphthoxy)-2-propanone (I)
- 1-(o-toloxo)-2-propanone (II)
- 1-(m-toloxo)-2-propanone (III)
- 1-(p-toloxo)-2-propanone (IV)
- 1-phenoxy-2-propanone (V)
- 1-(2,4-dibromophenoxy)-2-propanone (VI)

3. Substituted Quinoline Acids

6-methyl-3-(α -naphthoxy)-4-quinaldinecarboxylic acid (IX)

6-methyl-3-(o-toloxo)-4-quinaldinecarboxylic acid (X)

6-methyl-3-(m-toloxo)-4-quinaldinecarboxylic acid (XI)

6-methyl-3-(p-toloxo)-4-quinaldinecarboxylic acid (XII)

6-methyl-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic acid (XIII)

6-chloro-3-(α -naphthoxy)-4-quinaldinecarboxylic acid (XIV)

6-chloro-3-(o-toloxo)-4-quinaldinecarboxylic acid (XV)

6-chloro-3-(m-toloxo)-4-quinaldinecarboxylic acid (XVI)

6-chloro-3-(p-toloxo)-4-quinaldinecarboxylic acid (XVII)

6-chloro-3-phenoxy-4-quinaldinecarboxylic acid (XVIII)

6-chloro-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic acid (XIX)

APPENDIX I

APPENDIX I

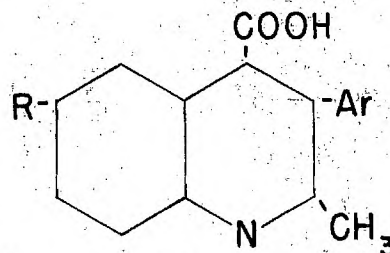
TABLE I: Substituted Aryloxypropanones

	ArO in ArOCH ₂ COCH ₃	Yield %	B.P./ 3mm. Degrees C.	2,4-Dinitro- phenylhydrazone	n_D^{20}	d_4^{20}	Molar Refraction ^{15,16}	
							Theoretical	Actual
I.	α -Naphthoxy	59	142-8	189	1.6043	1.1437	59.87	60.13
II.	o-Toloxo	74	94-7	152	1.5175	1.0585	46.44	46.88
III.	m-Toloxo	60	95-96	141	1.5182	1.0587	46.44	46.95
IV.	p-Toloxo	73	90-91	133	1.5165	1.0558	46.44	46.96
V.	Phenoxy	85.0	75 (2 mm.)	128	1.5228 ⁽¹²⁾	1.0903 ⁽¹²⁾	41.82	42.27 ^a
VI.	2,4-Dibromo- phenoxy	85.0	94 (m.p.)	156	---	---	---	---

^aCalculated from ref. 12.

APPENDIX I

TABLE II: 3-Aryloxy-4-quinaldinecarboxylic Acids



	R	Ar	Yield %	M.p. Degrees C.	% Nitrogen	
					Calcd.	Found
IX.	CH ₃	α -Naphthoxy	40	238	4.08	3.90
X.	CH ₃	o-Toloxo	80.8	225	4.54	4.24
XI.	CH ₃	m-Toloxo	73.2	231	4.54	4.35
XII.	CH ₃	p-Toloxo	72.6	202	4.54	4.42
XIII.	CH ₃	2,4-Dibromo- phenoxy	60	223	3.10	3.18

	R	Ar	Yield %	M.p. Degrees C.	% Nitrogen	
					Calcd.	Found
XIV.	Cl	α -Naphthoxy	18.6	238	3.85	3.63
XV.	Cl	o-Toloxo	67	241	4.27	4.30
XVI.	Cl	m-Toloxo	61	230	4.27	4.45
XVII.	Cl	p-Toloxo	83.7	227	4.27	4.14
XVIII.	Cl	Phenoxy	32	248	4.46	4.61
XIX.	Cl	2,4-Dibromo- phenoxy	83.1	243	2.97	3.08

APPENDIX II

FIGURE 1

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

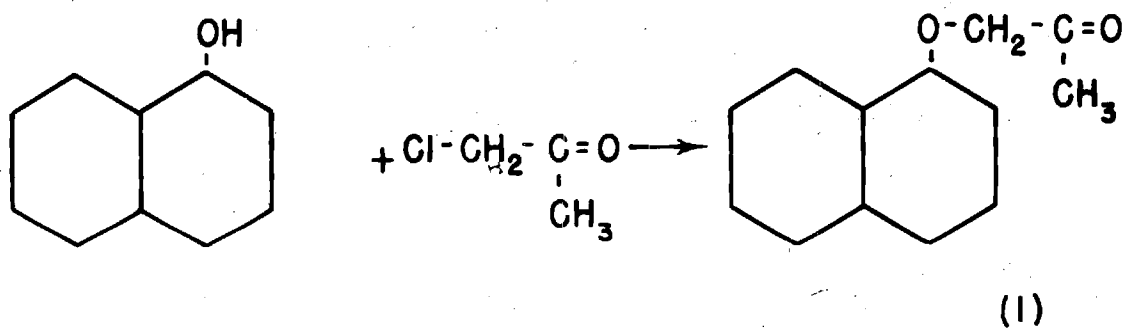


FIGURE 2

The Preparation of 1-(*o*-Toloxo)-2-propanone (II)

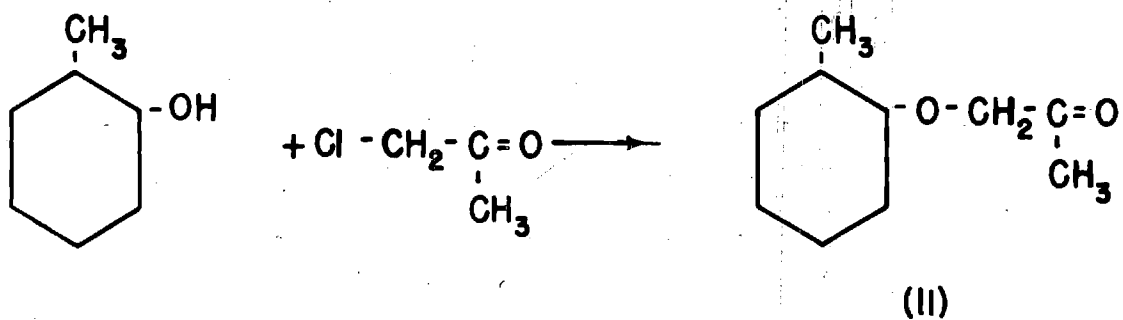


FIGURE 3

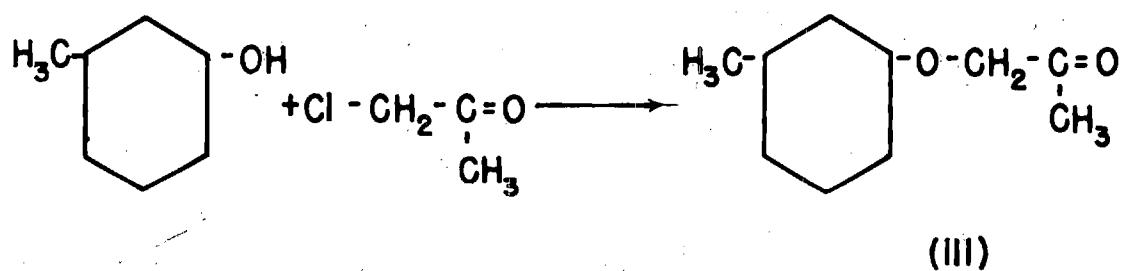
The Preparation of 1-(*m*-Toloxyl)-2-propanone (III)

FIGURE 4

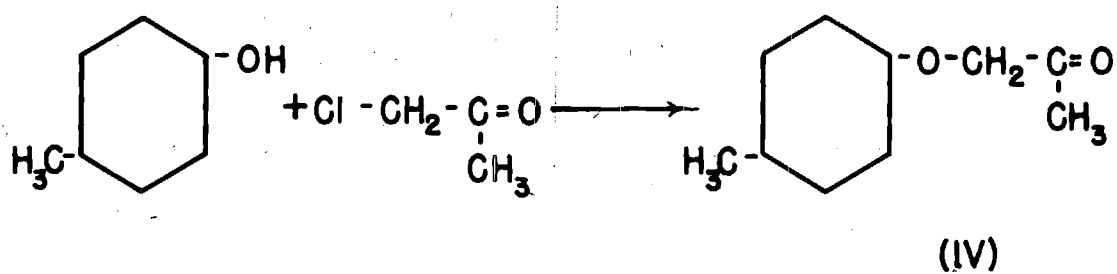
The Preparation of 1-(*p*-Toloxyl)-2-propanone (IV)

FIGURE 5

The Preparation of 1-Phenoxy-2-propanone (V)

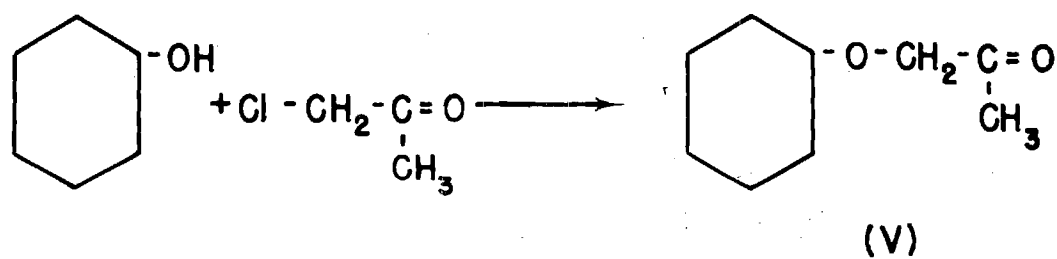


FIGURE 6

The Preparation of 1-(2,4-Dibromophenoxy)-2-propanone (VI)

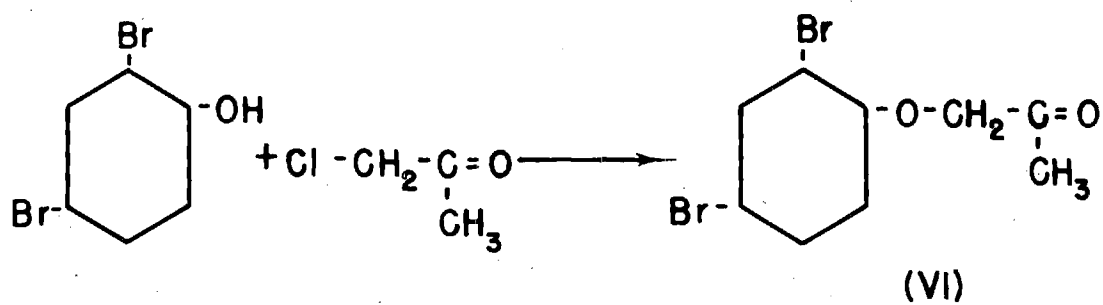


FIGURE 7

The Preparation of 5-Methylisatin (VII)

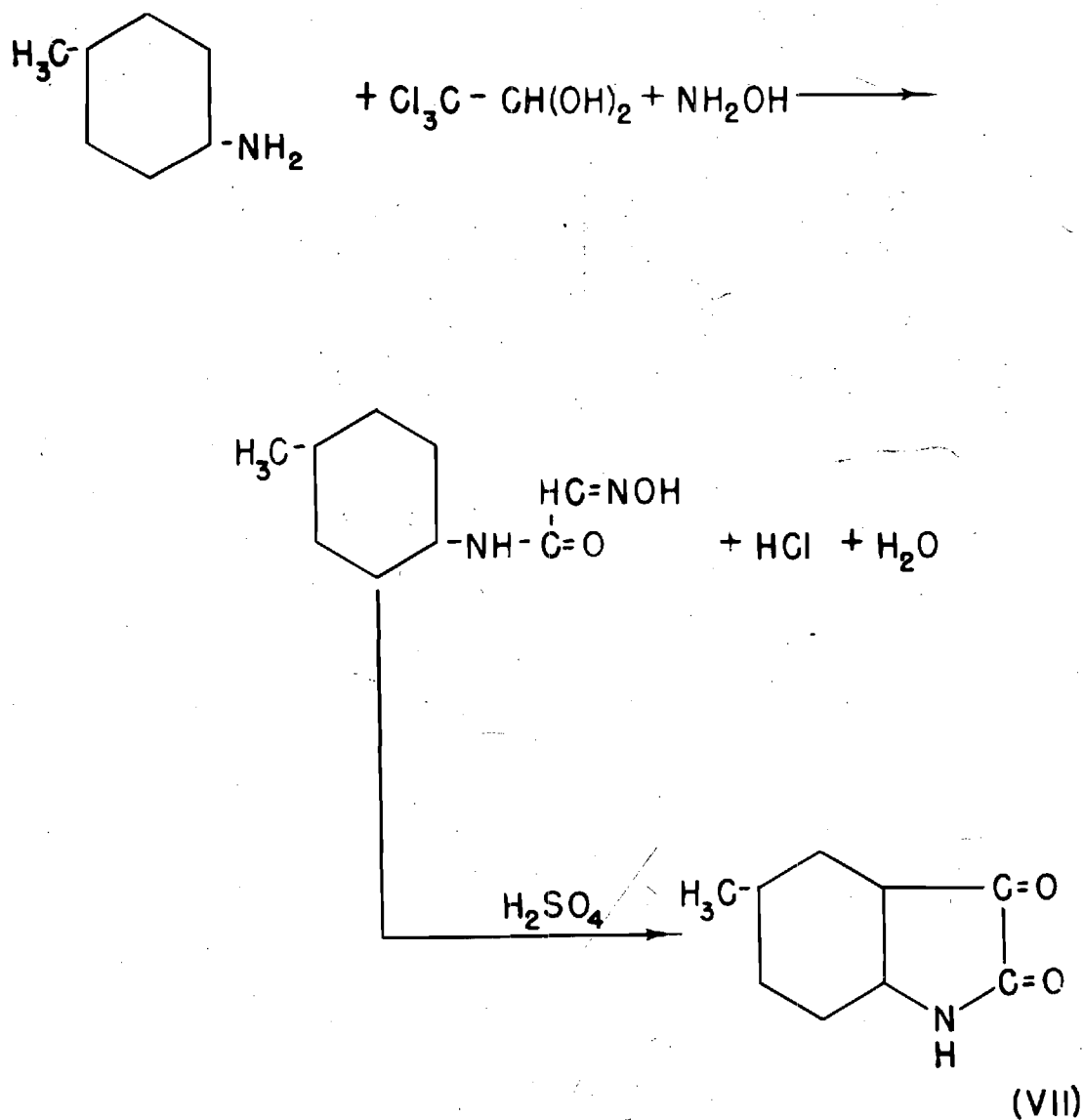


FIGURE 8

The Preparation of 5-Chloroisatin (VIII)

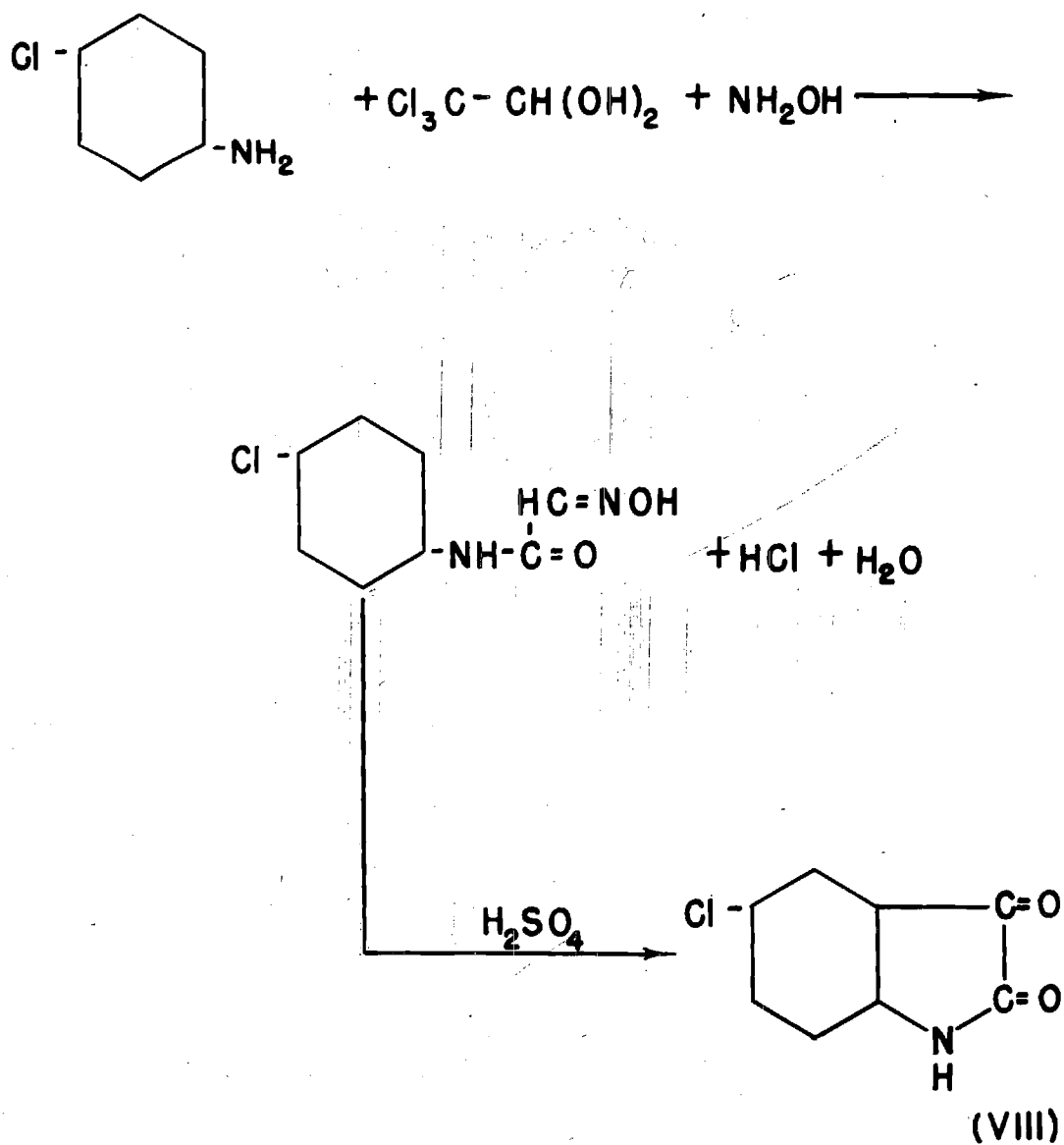


FIGURE 9

The Preparation of 6-Methyl-3-(α -naphthoxy)-4-quinaldinecarboxylic Acid (IX)

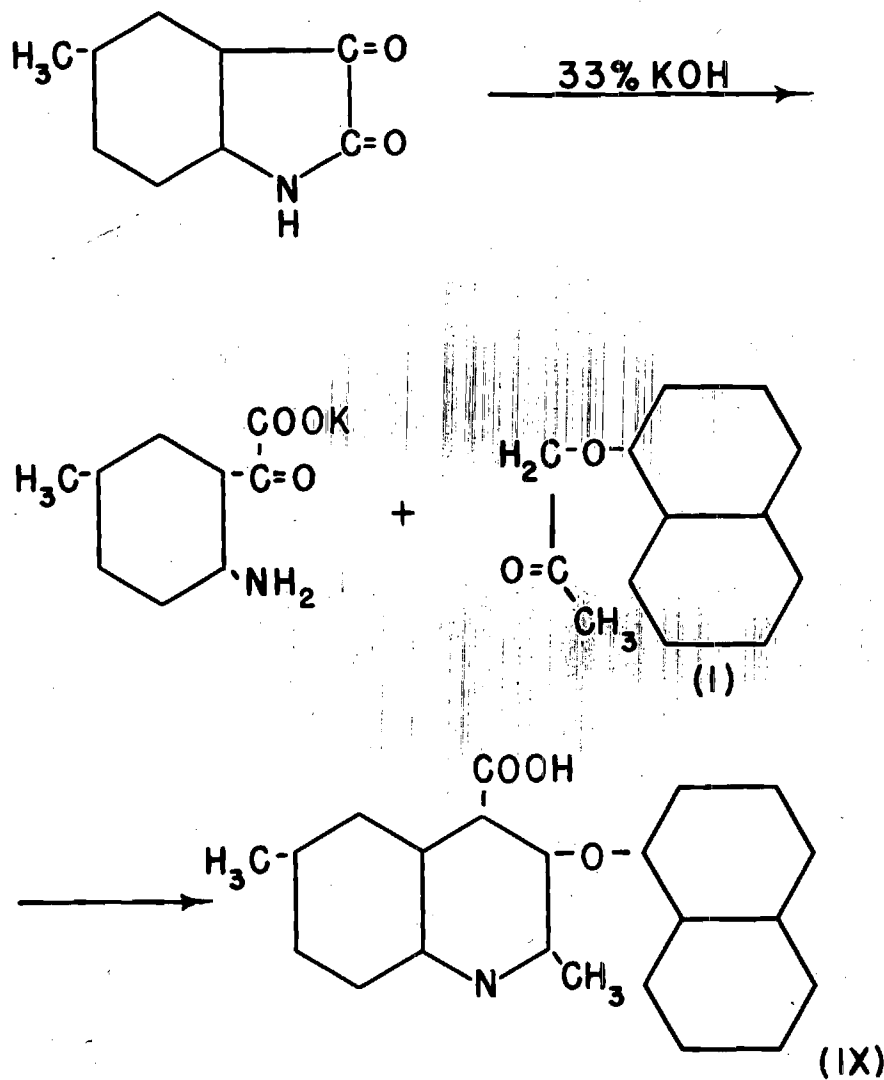


FIGURE 10

The Preparation of 6-Methyl-3-(*o*-toloxy)-4-quinaldinecarboxylic Acid (X)

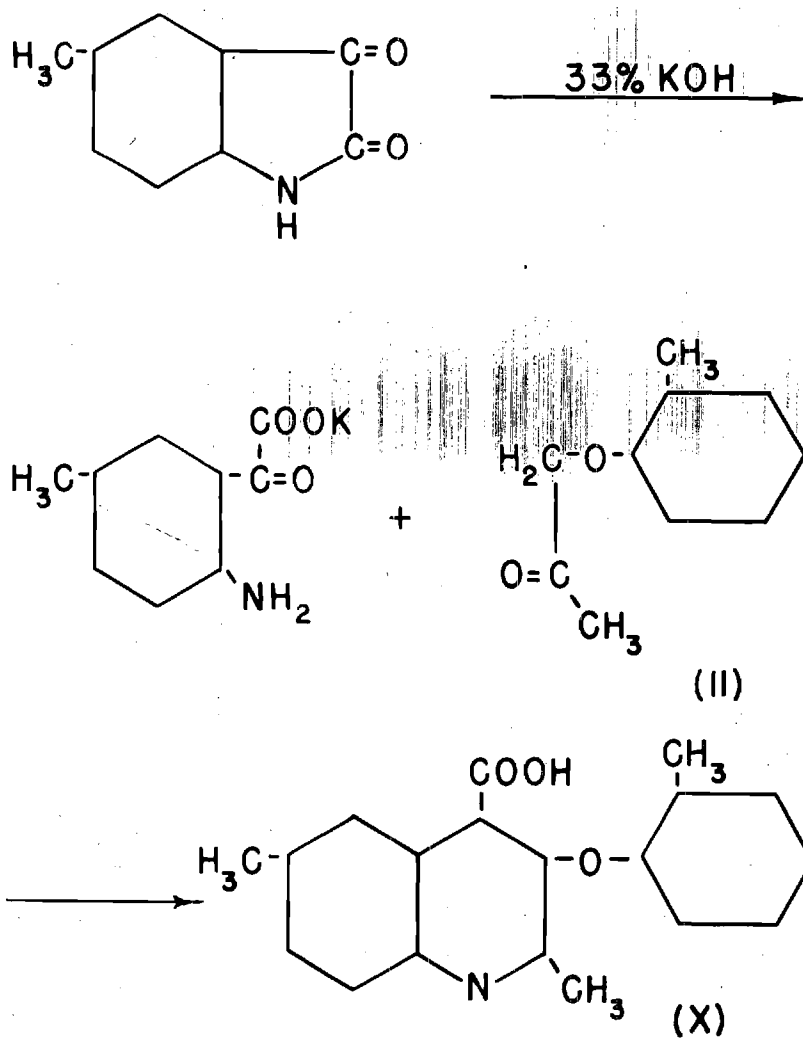


FIGURE II

The Preparation of 6-Methyl-3-(*m*-toloxy)-4-quinaldinecarboxylic Acid (XI)

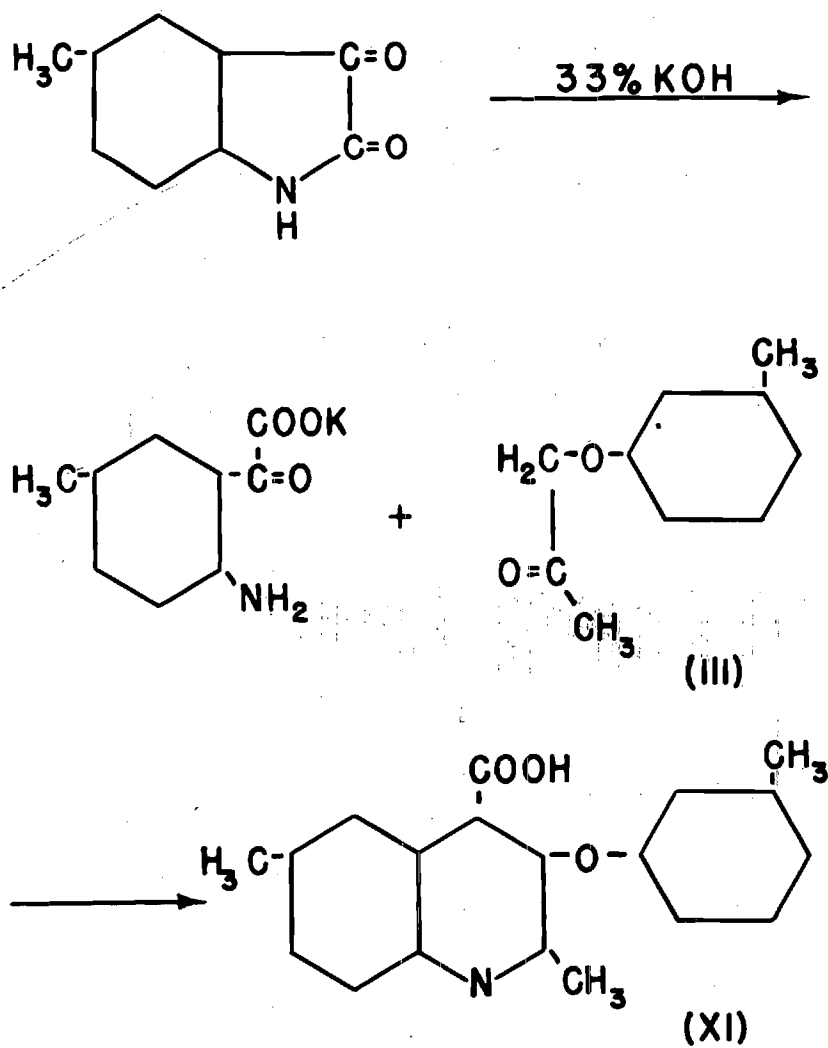


FIGURE 12

The Preparation of 6-Methyl-3-(*p*-toloxy)-4-quinaldinecarboxylic Acid (XII)

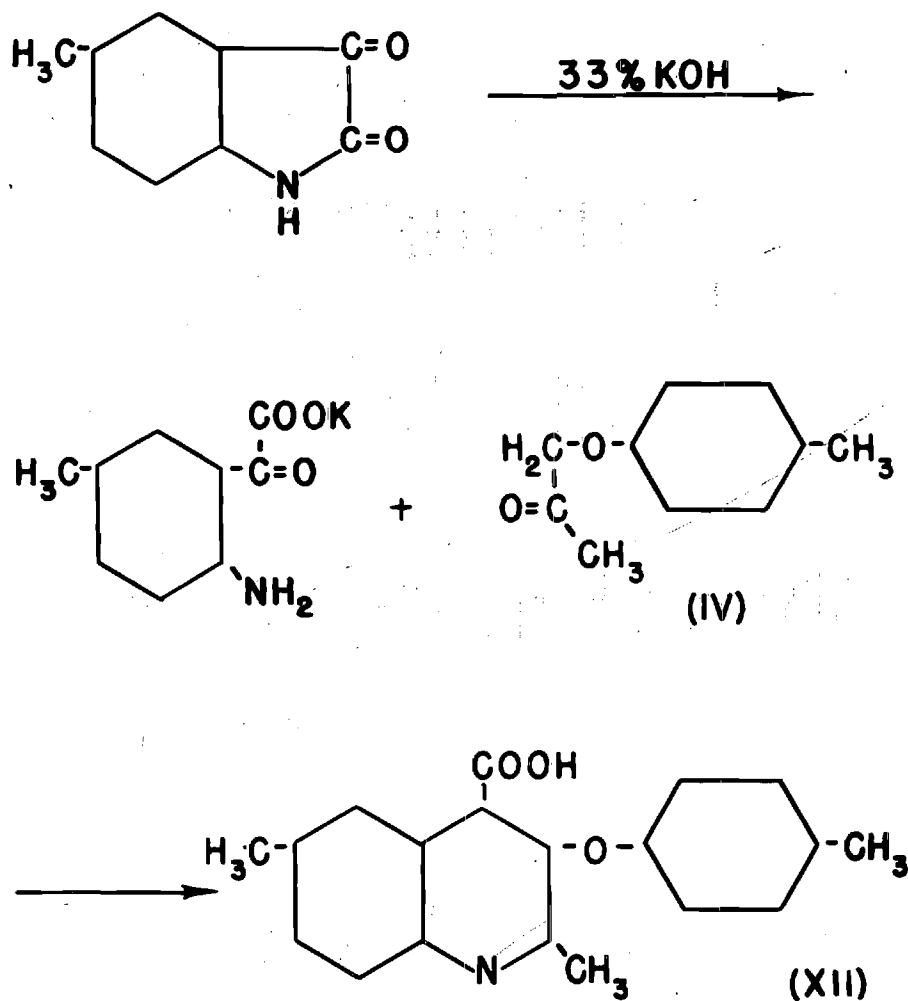


FIGURE 13

The Preparation of 6-Methyl-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic Acid (XII)

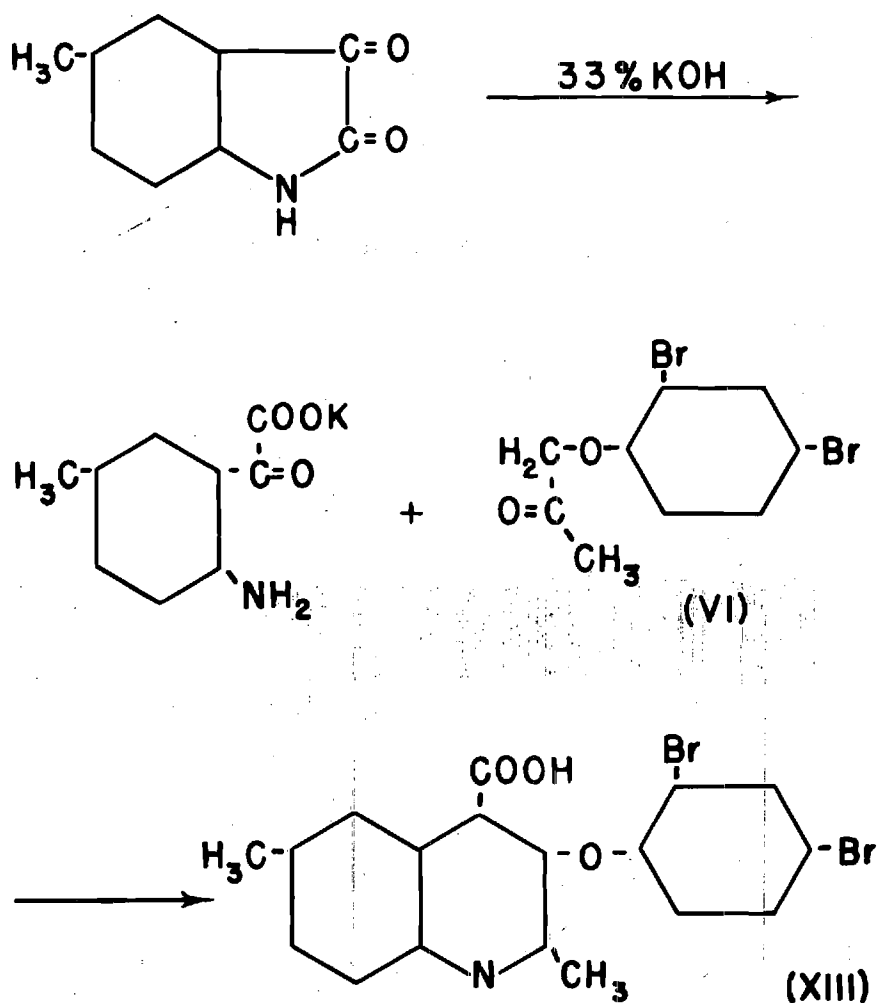


FIGURE 14

The Preparation of 6-Chloro-3-(α -naphthoxy)-4-quinaldinecarboxylic Acid (XIV)

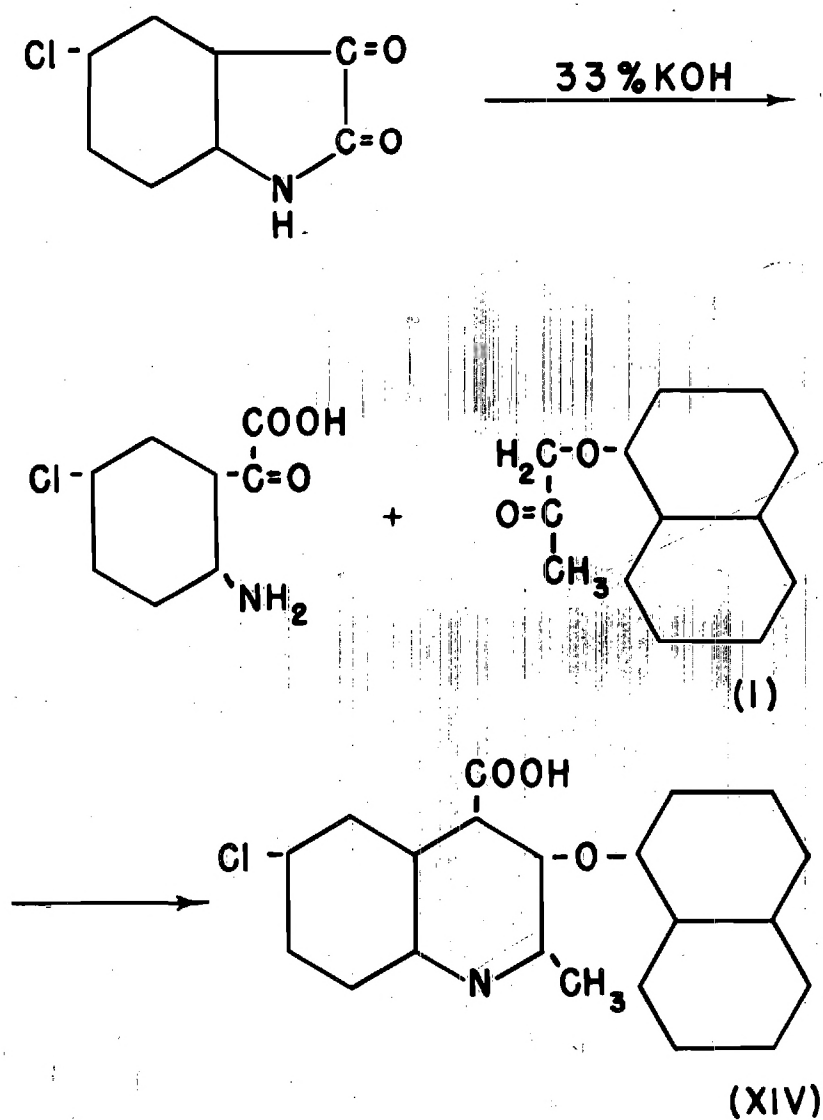


FIGURE 15

The Preparation of 6-Chloro-3-(*o*-toloxy)-4-quinaldinecarboxylic Acid (XV)

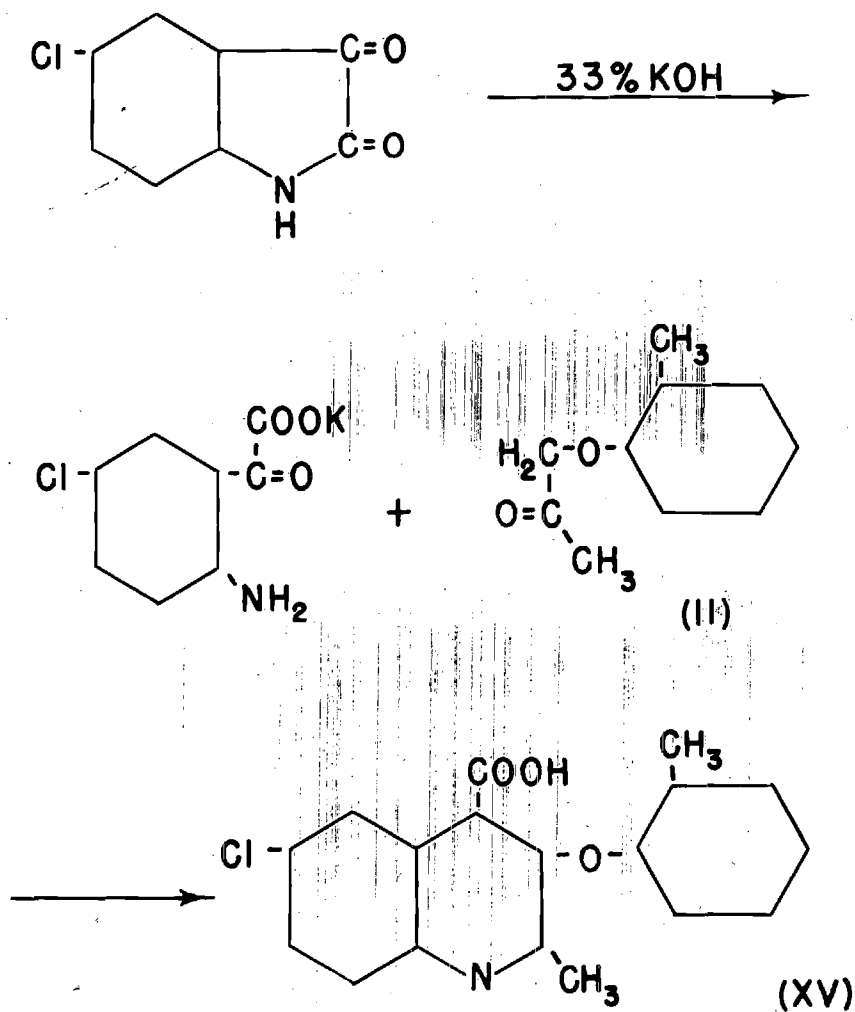


FIGURE 16

The Preparation of 6-Chloro-3-(*m*-toloxy)-
4-quinaldinecarboxylic Acid (XVI)

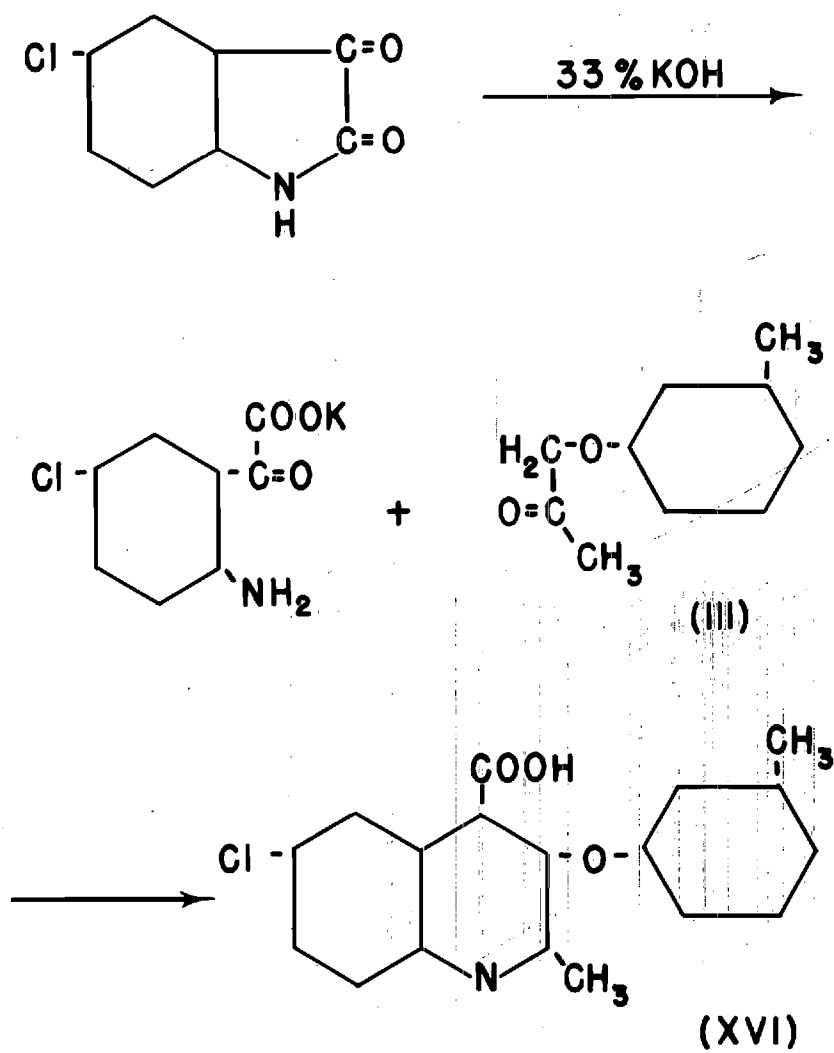


FIGURE 17

The Preparation of 6-Chloro-3-(*p*-toloxy)-4-quinaldinecarboxylic Acid (XVII)

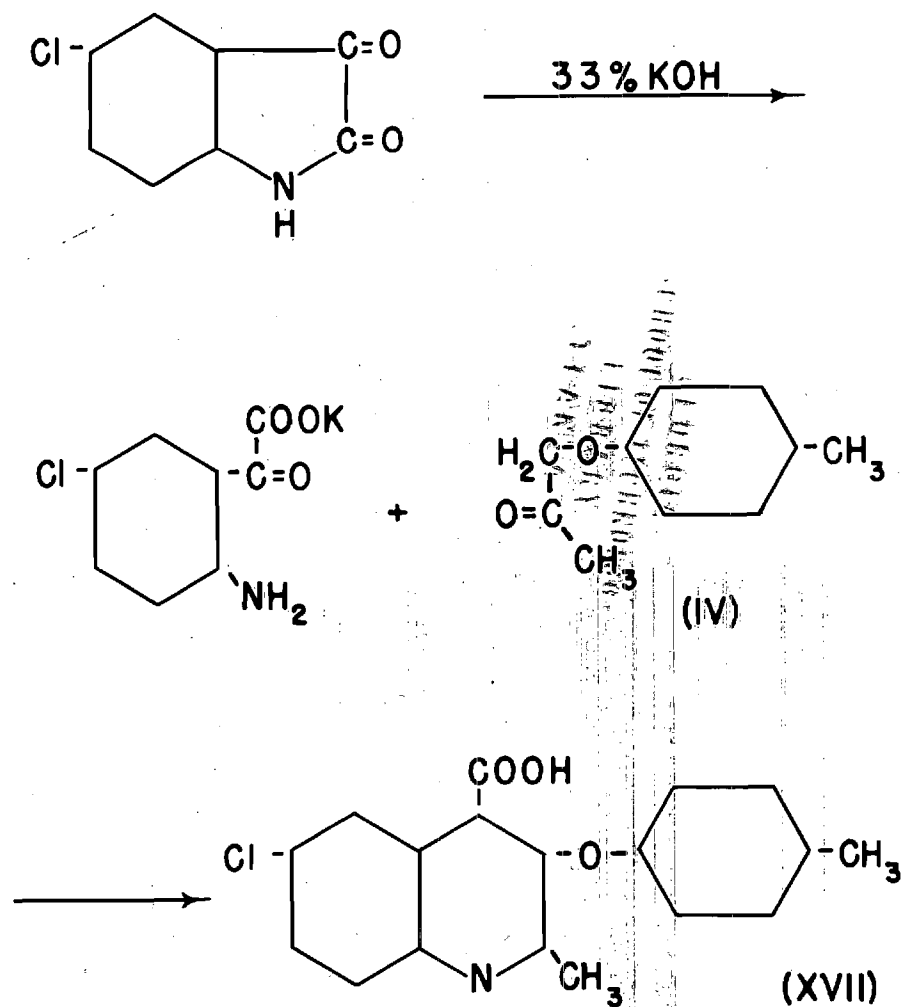


FIGURE 18

The Preparation of 6-Chloro-3-phenoxymethyl-4-quinolinecarboxylic Acid (XVIII)

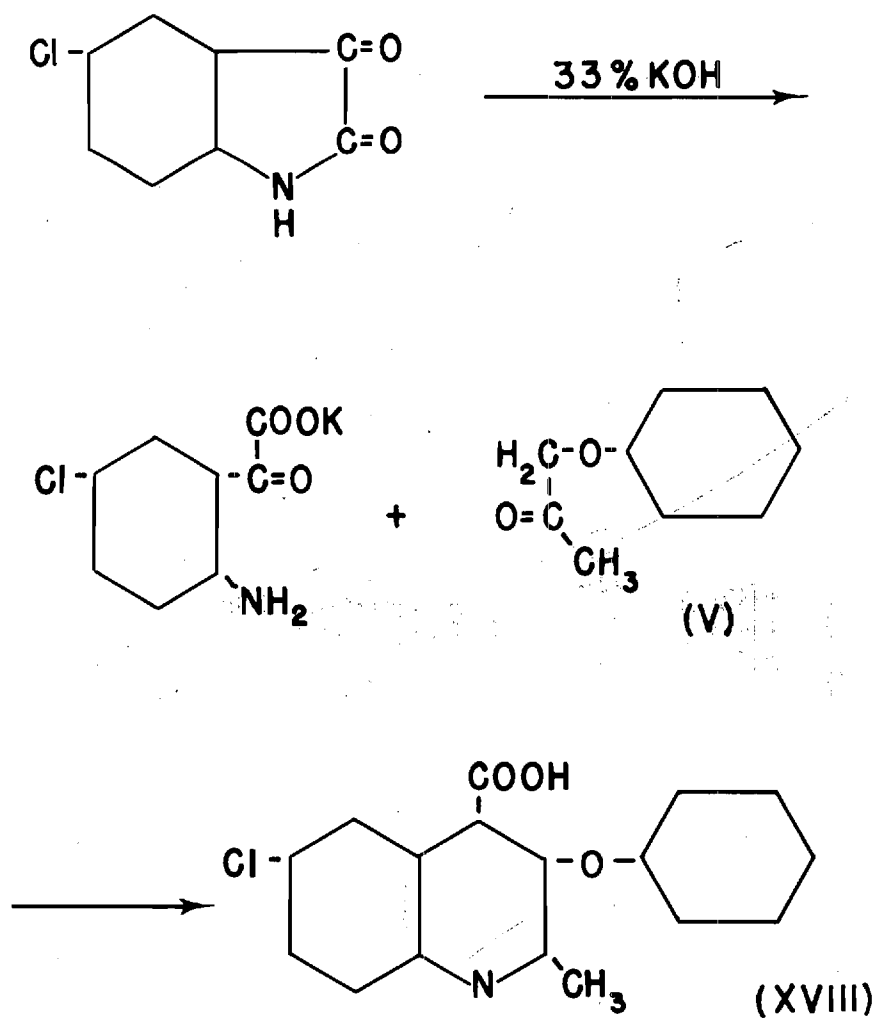
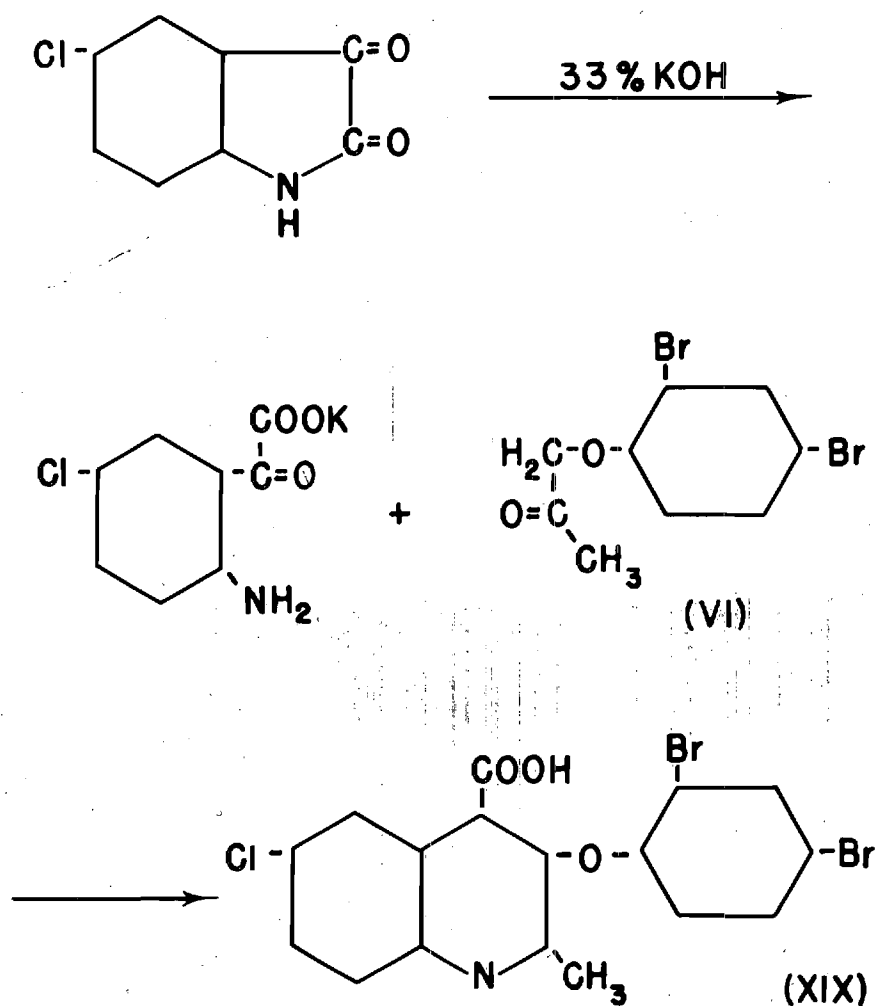


FIGURE 19

The Preparation of 6-Chloro-3-(2,4-dibromophenoxy)-4-quinaldinecarboxylic Acid (XIX)



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