SUBSTITUTED QUINOLINES AND ACRIDINES FROM
5-ETHYL ISATIN BY THE PFITZINGER
REACTION

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by

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6-DEETHYL ATML BY THE PRITZINGER
REACTION

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[Signature]

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CHAPTER I

THE PFITZINGER REACTION
SUBSTITUTED QUINOLINES AND ACRIDINES FROM 5-METHYL ISATIN BY THE PFITZINGER REACTION

CHAPTER I

THE PFITZINGER REACTION

The preparation of quinolines derivatives from isatin and 5-methyl isatin may be attributed to Pfitzinger, who prepared 2,6-dimethyl-cinchoninic acid (II) by the condensation of 5-methyl isatin (I) with acetone in the presence of 33 percent aqueous potassium hydroxide.\textsuperscript{1,2}

\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H}_2\text{CH} \\
\text{C}=\text{O} & \quad \text{C}=\text{CCH}_3 \\
\text{C}=\text{O} & \quad \text{COOH} \\
\end{align*}

By the use of aldehydes in the same type of reaction, one might expect to synthesize cinchoninic acids substituted in the 2-position.

\textsuperscript{1} Pfitzinger, \textit{J. prakt. Chem.}, 33, 100 (1886)

\textsuperscript{2} Pfitzinger, \textit{J. prakt. Chem.}, 38, 584 (1888)
In like manner ketones which are unsymmetrical should yield isomers substituted in the 2- and 3- positions. An illustration is afforded by the reaction between isatin (III) and the ketone RCH₂COCH₂R' where R is an alkyl or aryl group and R' is an alkyl or aryl radical or hydrogen atom. The mechanism of the reaction was formulated as follows by Halberkann:

Pfitzinger reported that the reaction between isatin (III) and methyl-ethyl-ketone resulted in 2,3-dimethyl-cinchoninic acid (IV), but it was later demonstrated that a small amount of 2-ethyl-cinchoninic was produced.

---

3 Halberkann, Ber., 54, 3090 (1921)
4 Pfitzinger, J. prakt. Chem., 56, 283 (1897)
5 Von Braun, Gmelin, and Schulthesis, Ber., 56, 1844 (1923)
In general, the chief product of the reaction of isatin with unsymmetrical ketones will have the smaller group affixed to the 2-position.

Modification of the Pfitzinger method have been introduced in which aryloxy ketones and thioaryloxy ketones were used in place of the usual aliphatic and aromatic ketones. The mechanism of the reaction showing the main product is as follows:

---

7. Porter, Georgia School of Technology, Master's Thesis (1942)
CHAPTER II

PURPOSE OF THIS INVESTIGATION
CHAPTER II

PURPOSE OF THIS INVESTIGATION

The availability of 5-methyl isatin from p-toluidine and of cyclic, aryloxy and thioaryloxy ketones suggested employing the Pfitzinger reaction in the preparation of substituted quinolines and acridines.

Biological experiments have proved that the quinoline group in quinine possesses marked anti-malarial properties. Plasmoquin, cinchophen and atoquinol are a few among this class of compounds whose effectiveness has been proven. Atebrin, used in the treatment of malaria, is a derivative of acridine.

The compounds reported in this thesis are either substituted acridines or substituted quinolines, and as such may be of chemotherapeutic interest.
CHAPTER III

EXPERIMENTAL
Nineety grams of chloral hydrate was dissolved in 1200 cc of water in a five liter round bottomed flask, and 1300 grams of crystallized sodium sulfate was added. To this mixture was introduced a solution of 54 grams (0.5 mol) of p-toluidine in 300 cc of water and 51.2 grams of concentrated hydrochloric acid. A solution of 110 grams (1.58 mol) of hydroxylamine hydrochloride in 500 cc of water was then added, and the flask heated at such a rate as to produce boiling in forty-five to fifty minutes. The reaction was complete after two minutes of vigorous boiling. The solution was cooled, filtered, and the product air-dried.

Six hundred grams (326 cc) of concentrated sulfuric acid was warmed to 50 degrees in a one liter three-necked flask fitted with an
efficient stirrer, and to this the isonitrosoaceto-\text{-p-}toluidine was added at such a rate as to keep the temperature between 50-60 degrees. After the addition of the isonitroso compound was completed, the reaction mixture was heated to 80 degrees and kept at this temperature for about ten minutes. The solution was then cooled to room temperature and poured over ten to twelve times its volume of cracked ice. The mixture was allowed to stand for about thirty minutes and filtered. The product was washed several times with cold water and air-dried. The yield was 62 grams, or 80 percent of the theoretical. The melting point of the crude product was 177-179 degrees (uncorr.).
The Preparation of Phenoxyacetone $^2$ (VII)

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{O} \\
\text{O} & \quad \text{C}-\text{CH}_3
\end{align*}
\]

Thirty four and eight tenths grams (0.3 mol) of sodium phenoxide was suspended in 200 cc of benzene in a 500 cc three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel. Twenty seven and eight tenths grams (0.3 mol) of chloroacetone was added slowly with vigorous agitation. After the addition of the chloroacetone, the solution was refluxed for fourteen hours. The mixture was cooled, filtered, and the benzene removed by distillation over a water bath at a pressure of 35-40 mm.

The residue was transferred to a 50 cc distilling flask and fractionated under a pressure of 1-2 mm. The fraction boiling between 67-72 degrees was collected. The yield was 11.5 grams, or 28 per cent of the theoretical yield.

Twenty seven and a half grams (0.25 mol) of thiophenol was added to 200 cc of benzene in a 500 cc three-necked flask equipped with a mechanical stirrer, a reflux condenser and a dropping funnel. Five and six tenths grams (0.25 mol) of sodium wire was added slowly with efficient stirring. The mixture was refluxed until all the sodium had dissolved, and the sodium thiophenoxide has separated out as a white solid. Twenty three and one tenth grams of chloroacetone was added slowly with vigorous agitation. After twenty five hours refluxing, the sodium chloride was filtered from the mixture, and the benzene removed by distillation over a water bath at a pressure of 35-40 mm. The residue was fractionated and the portion boiling at 168-171 degrees (35-38 mm) was collected. The oil had a slight greenish tinge and solidified upon cooling. The melting point was 34 degrees, and the yield was 20 grams, representing 40 percent of the theoretical.

3Borsche, Ann., 377, 119 (1910)

4Porter, Georgia School of Technology, Master's Thesis (1942)
The Preparation of \( \text{2-methyl-5-phenyl-9-trimethylene-9-quinolinecarboxylic acid (IX)} \)

Twenty four and three tenths grams of 5-methyl isatin (0.15 mol) was dissolved in 33 percent aqueous potassium hydroxide and placed in a 500 cc three-necked flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. The mixture was heated to reflux and twelve and six tenths grams of cyclopentanone (0.15 mol) was added over a period of an hour with continuous stirring. Refluxing was continued for an additional thirty hours. The basic solution was diluted with 200 cc of water, treated with Nuchar, cooled in an ice bath, and neutralized with dilute acetic acid. A dark yellow precipitate formed, which was purified by washing with boiling ethyl alcohol.

This general procedure was followed in the condensation of the other ketones with 5-methyl isatin.

The yield of the crude product (IX) was 12.9 grams representing 57 percent of the theoretical yield.

The melting point of the compound was 304.6 degrees C. (corr.) (dec.).
The neutral equivalent was found to be 221.5, whereas, the calculated molecular weight is 227.3.

A nitrogen analysis gave a value of 6.18 percent, which compared favorably with the theoretical percentage of 6.17.
The quantities used were 0.1 mol each of 5-methyl isatin and cyclohexanone. The mixture was refluxed for a period of four hours, and the product was purified by treatment of the basic solution with Nuchar and precipitating the acid (X) by neutralization with dilute acetic acid. The yield was 12 grams of the pure product, or 43.3 percent of the theoretical.

The melting point of the compound was 299.3 degrees C. (corr.) (dec.).

The neutral equivalent was found to be 273.6. If two molecules of water of crystallization are assumed, the theoretical molecular weight is 277.3.

The nitrogen determination gave a value of 5.47 percent, whereas the theoretical, with two molecules of water of crystallization, is 5.06 percent.

A weighed sample of the compound was placed over P₂O₅ in a
vacuum desiccator. After three weeks, the weight became constant and the percentage loss in weight was 13.5. The theoretical percentage of water is 13.0.

The melting point of the anhydrous compound was 296.2 degrees C. (corr.)(dec.).

The neutral equivalent was found to be 240.9, whereas the calculated value is 241.3.

A quantitative nitrogen determination showed 6.12 percent, as compared with a theoretical value of 5.81 percent.
The Preparation of 7-methyl-1,2,3,4-tetrahydroacridine (XI)

Three grams of the 7-methyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid was placed in a 25 cc distilling flask connected to an air condenser. The pressure was reduced to 1-2 mm and the compound heated in an oil bath until it melted. Carbon dioxide was given off, which solidified upon cooling. The solid (XI) was dissolved in dilute hydrochloric acid, warmed over a steam bath and treated with Nuchar. The solution was cooled and made slightly basic by the addition of aqueous potassium hydroxide. A white precipitate formed, which was filtered off, washed with cold water and placed in the desiccator to dry.

A nitrogen determination showed 7.26 percent as compared with a theoretical value of 7.06 percent.

The melting point was 56 degrees C.

The picrate was prepared and purified by the usual method and its melting point determined as 191.8 degrees C. (corr.).
One tenth mol each of o-methyl cyclohexanone and 5-methyl isatin was used. The solution was refluxed for twenty five hours, diluted with 100 cc of water, cooled and neutralized with dilute acetic acid. A yield of 14 grams of the crude product was obtained, or 51 percent of the theoretical.

The crude acid (XII) was purified by treatment of the basic solution with Nuchar, and precipitating the product by neutralizing the solution with dilute acetic acid. The pure compound was dried in a desiccator.

The melting point was 260.2 degrees C. (corr.)(dec.).

The neutral equivalent was found to be 287.5, which if two molecules of water of crystallization are assumed checks fairly closely with the theoretical molecular weight of 291.3.

The nitrogen content was found to be 4.76 percent, whereas the calculated value is 4.81 percent.

A weighed sample of the product (XII) was placed over P₂O₅ in a
vacuum desiccator. After three weeks, the weight became constant, and the loss in weight was 12.4 percent, whereas the calculated percentage of water is 12.3.

The melting point of the anhydrous compound was 251.2 degrees C. (corr.)(dec.).

The neutral equivalent was determined as 255.8 as compared with the calculated molecular weight of 255.3.

The nitrogen content was found to be 5.66 percent, whereas the theoretical value is 5.49 percent.
Two and one half grams of 1,7-dimethyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid was placed in a 25 cc distilling flask attached to an air condenser. The compound was heated in an oil bath at a pressure of 1-2 mm. Upon melting, carbon dioxide was given off and a red, viscous liquid distilled over, which did not solidify upon cooling.

The liquid was dissolved in dilute hydrochloric acid, treated with Nuchar, filtered and made slightly basic by addition of potassium hydroxide. A colorless oil separated.

A quantitative nitrogen analysis showed a value of 6.85 percent as compared with the calculated value of 6.63 percent.

The picrate was prepared and purified and the melting point determined as 154 degrees C. (corr.).
The Preparation of 3,7-dimethyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid (XIV)

One tenth molar quantities of p-methyl cyclohexanone and 5-methyl isatin were used. The solution was refluxed for three hours, cooled, and neutralized with dilute acetic acid. The yield of the crude acid (XIV) was 23.3 grams, representing 85 percent of the theoretical yield.

The product was purified by treatment of the basic solution with Nuchar, and precipitating the compound by neutralization with dilute acetic acid.

The melting point was 320.8 degrees C. (corr.) (dec.).

The neutral equivalent was found to be 253.1, whereas the calculated value is 255.3.

A quantitative nitrogen determination showed 5.76 percent nitrogen as compared with the theoretical value of 5.49 percent.
The Preparation of 3,7-dimethyl-1,2,3,4-tetrahydro-
acridine (XV)

Two and one half grams of 3,7-dimethyl-1,2,3,4-tetrahydro-
5-acridinecarboxylic acid was placed in a 25 cc boiling flask connected
to an air condenser. The pressure was reduced to 1-2 mm and the com-
pound heated in an oil bath. The mass melted at 290-295 degrees C.
and carbon dioxide was evolved. A clear liquid distilled over which
solidified upon cooling. It was purified by recrystallization from
ethyl alcohol.

The melting point of the compound was 103.6 degrees C. (corr.)
(dec.).

The nitrogen content was found to be 7.03 percent as compared
with the theoretical percentage of 6.63.

The picrate was prepared and purified in the usual manner, and
its melting point was determined as 207.4 degrees C. (corr.)(dec.).
The quantities used were 0.078 mol each of 5-methyl isatin and phenoxyacetone. The mixture was refluxed for about thirty hours over a steam bath, diluted with 200 cc of water, treated with Nuchar and made slightly acid with dilute acetic acid. After about twelve hours the acid (XVI) was filtered off and further purified by washing with boiling ethyl alcohol. The yield of the crude product was 42 percent of the theoretical value.

The melting point of the compound was 267.5 degrees C. (corr.) (dec.).

A quantitative nitrogen analysis showed 4.74 percent nitrogen as compared with the theoretical value of 4.78 percent.
The preparation of 6-methyl-3-thiophenoxy-4-quinaldinecarboxylic acid (XVII)

The quantities used were 0.1 mol each of thiophenoxyacetone and 5-methyl isatin. The solution was refluxed for thirty hours over a steam bath, diluted with 400 cc of water, and treated with Nuchar. The basic solution was cooled and made slightly acid with dilute acetic acid. The cream colored solid which separated was purified by recrystallizing from ethyl alcohol. After drying in a desiccator, the yield was 18.5 grams, or 60 percent of the theoretical value.

The melting point of the compound was 290.8 degrees C.(corr.) (dec.).

The neutral equivalent was determined as 308.9 as compared with the theoretical value of 309.4.

The nitrogen content was found to be 4.61 percent, whereas the calculated value is 4.53 percent.

A sulfur determination by the Carius method showed a value of 10.34 percent. The sulfur content is theoretically 10.35 percent.
Three grams of 6-methyl-3-thiophenoxy-4-quinaldine-carboxylic acid was placed in a 25 cc boiling flask attached to an air condenser. The pressure was reduced to 1-2 mm and the mass heated in an oil bath. When the temperature of the bath reached 270 degrees C. the acid melted and carbon dioxide was evolved. A liquid distilled over which solidified upon cooling. The crude product (XVIII) was purified by re-crystallization from ethyl alcohol.

The melting point of the compound was 79.8 degrees C. (corr.).

The nitrogen determination was one percent higher than the theoretical value.

The picrate was prepared and purified and its melting point was 217.5 degrees C. (corr.).
CHAPTER IV

DISCUSSION OF RESULTS
CHAPTER IV

DISCUSSION OF RESULTS

The feasibility of the use of substituted isatin in the Pfitzinger reaction has been extended as the condensation of 5-methyl isatin with the ketones used in this study proceeded in the usual manner.

The highest yields were obtained from the condensation of 5-methyl isatin with p-methyl cyclohexanone and thiophenoxyacetone. The yields were 85 and 60 percent respectively. The lowest yield was 42 percent from the reaction of phenoxyacetone and 5-methyl isatin.

The attempts to decarboxylate the acids-(X); (XII); (XIV); (XVII)- were successful, giving substituted acridines in each. The picrates of each of the acridines were prepared.

The neutral equivalents and nitrogen determinations of 7-methyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid and 1,7-dimethyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid gave results which check with the theoretical if two molecules of water of crystallization are assumed. After drying over phosphorus pentoxide, the percentage loss in weight of each compound compared favorably with the calculated percentage of water, and the nitrogen analyses and neutral equivalents gave values which check with the anhydrous compounds.
CHAPTER V

SUMMARY
The following acids have been prepared and their properties studied: 7-methyl-$\alpha,\beta$-trimethylene-9-quinoline-carboxylic acid (IX); 7-methyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid (XII); 3,7-dimethyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid (XIV); 6-methyl-3-phenoxy-4-quinaldinecarboxylic acid (XVI); and 6-methyl-3-thiophenoxy-4-quinaldinecarboxylic acid (XVII).

The acids numbered (X), (XII), (XIV), and (XVII) were decarboxylated, yielding the substituted acridines: 7-methyl-1,2,3,4-tetrahydro-acridine (XI); 1,7-dimethyl-1,2,3,4-tetrahydro-acridine (XIII); 3,7-dimethyl-1,2,3,4-tetrahydro-acridine (XV); and 6-methyl-3-thiophenoxy-quinaldine (XVIII). The picrates of the substituted acridines were prepared.
FIGURE I

The Preparation of 5-methyl isatin (VI)

\[
\begin{align*}
\text{H}_3\text{C} & + \text{NH}_2\text{CH} + \text{CCl}_3\text{CH(OH)}_2 & \rightarrow \\
\text{H}_3\text{C} & + \text{NH}_2\text{COCH = NOH} + \text{HCl} + \text{H}_2\text{O} & \\
\text{H}_3\text{C} & + \text{NH}_2\text{C} = \text{O} + \text{NH}_4\text{HSO}_4
\end{align*}
\]
FIGURE II

The Preparation of Phenoxyacetone (VII) and Thiophenoxyacetone (VIII)

(VII)

(VIII)
FIGURE III

Reaction between Thiophenoxyacetone and 5-methyl isatin
FIGURE IV

Derivatives from 6-methyl-3-thiophenoxy-4-quinolinesalicylic acid

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{COOH} \quad \text{S-CH}_3 \\
\text{N} & \quad \text{S-C}_6\text{H}_5 \\
\text{N} & \quad \text{CH}_3 \\
\end{align*}
\]

\[-\text{CO}_2 \rightarrow \]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S-C}_6\text{H}_5 \\
\text{N} & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S-C}_6\text{H}_5 \\
\text{N} & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S-C}_6\text{H}_5 \\
\text{N} & \quad \text{CH}_3 \\
\end{align*}
\]
FIGURE V

Reaction between Cyclohexanone and 5-methyl isatin
FIGURE VI

Derivatives from 7-methyl-1,2,3,4-tetrahydro-5-acridinecarboxylic acid
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