The Preparation of Cinchoninic Acids and Related Compounds

Thesis by
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In Partial Fulfillment of the Requirements
for the Degree of Master of Science

California Institute of Technology
Pasadena, California
1 9 4 5

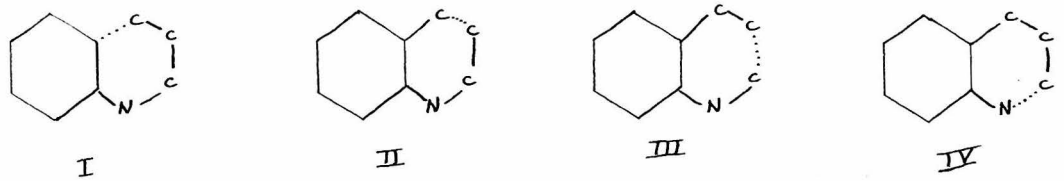
Acknowledgement

I wish to express my sincere thanks for the help and guidance of Dr. E. R. Buchman, under whose direction this research was carried out. Also, I appreciate the suggestions and help of Dr. H. Sargent, Dr. D. R. V. Golding, Dr. C. M. McCloskey, Mr. D. R. Howton, and Mr. T. C. Myers.

Theoretical

The experiments described in this Thesis were carried out in connection with a research program which had as its aim the synthesis of potential antimalarials. The compounds under consideration were analogs of quinine, the synthesis of which has been effected (1) starting from quininic acid (6-methoxycinchoninic acid). The synthesis of other cinchoninic acids (quinoline-4-carboxylic acids) thus has an obvious part in a program designed to prepare substances related to quinine.

In the literature some thirty methods by which quinoline derivatives may be obtained have been described. Some of these are only slight variations of others, but almost all require a derivative of aniline as a starting material. In other words, the nitrogen of the quinoline ring is already joined to the benzene nucleus. The problem, therefore, resolves itself into a ring closure between the nitrogen and the ortho position of the benzene ring. According to some authorities (2), there are only four fundamental syntheses--all others being variations of these. The following diagrams represent these syntheses graphically. The dotted lines indicate the two atoms which must be united to complete the hetero ring.



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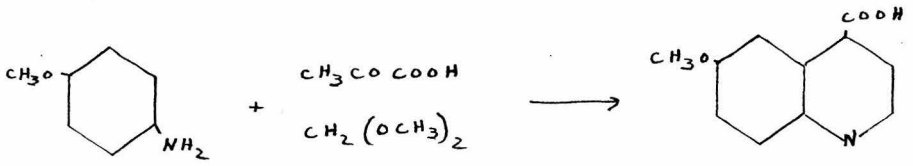
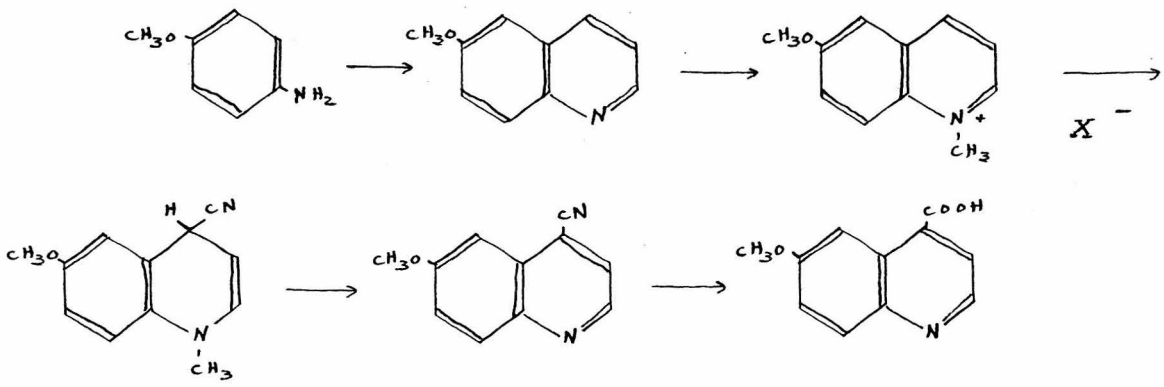
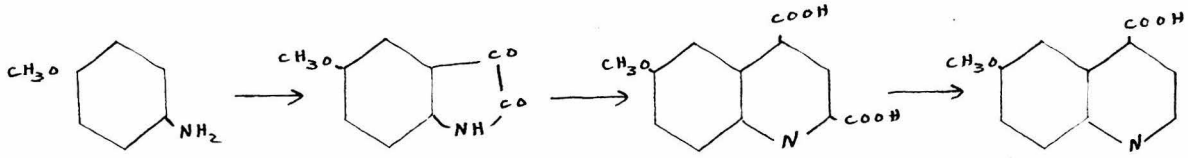
Based on the above principles, a number of cinchoninic acid syntheses have been developed. Quininic acid, for example has been synthesized by Pictet and Misner (3) by the following reaction:



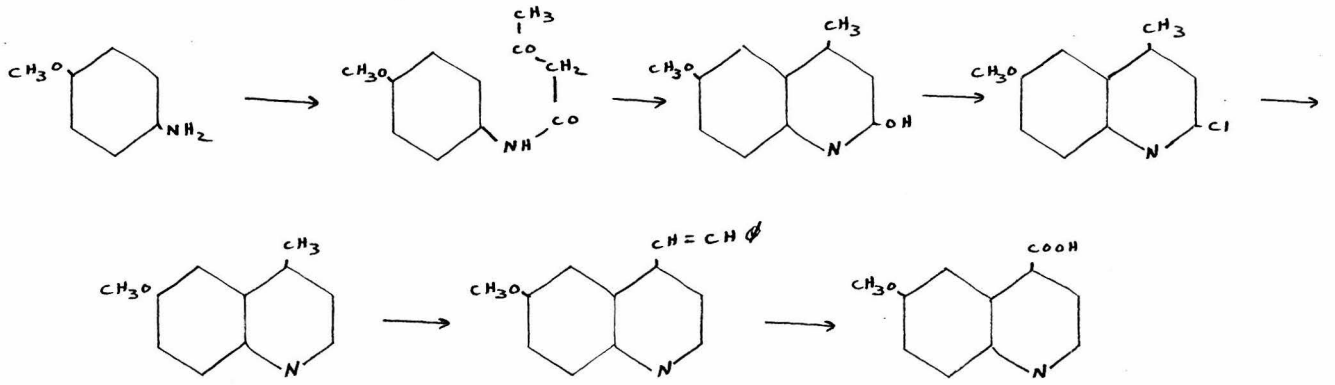
A second synthesis due to Kaufmann and Peyer (4) proceeded by a series of steps:



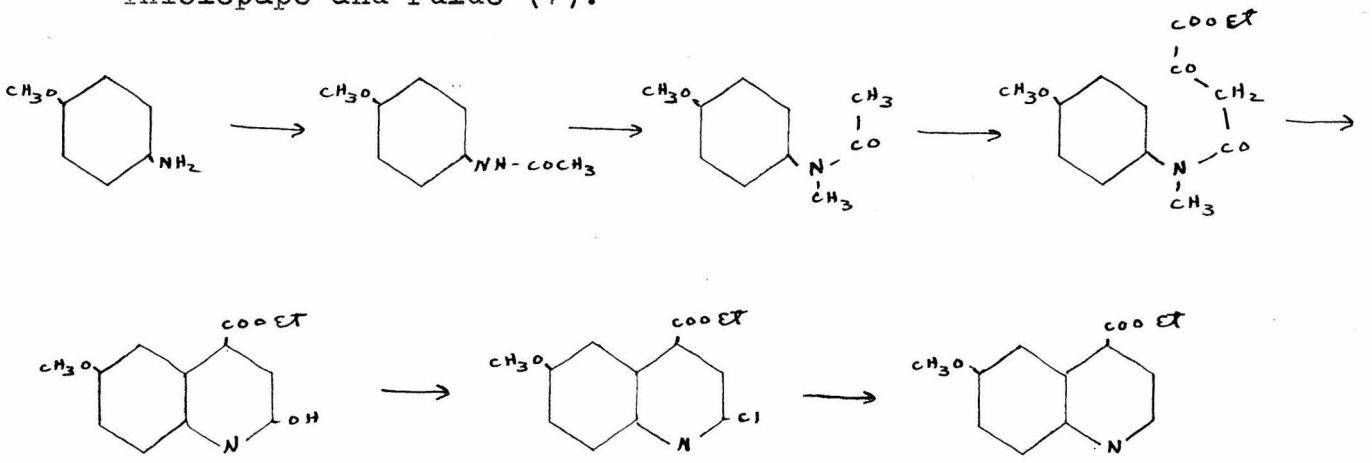
A third synthesis was described by Halberkann(5).



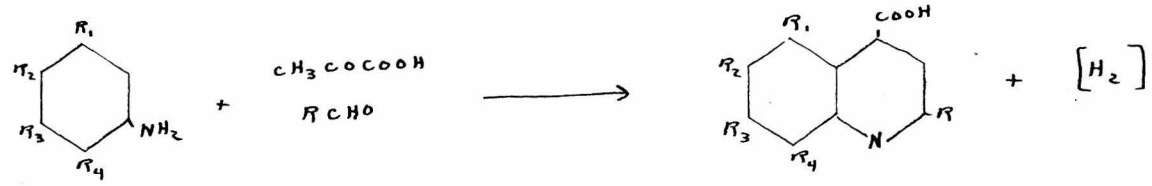
Rabe and coworkers (6) made use of still another several-step procedure:



Finally, another type of synthesis was worked out by Thielepape and Fulde (7):

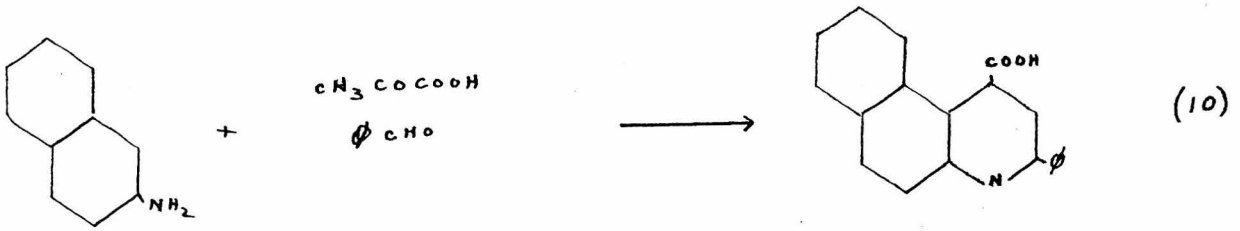


A synthesis used in the present investigation was the one of Doebner and v. Miller (8). In this reaction an aniline derivative may be refluxed with an aldehyde and pyruvic acid in ethanol solution (compare the Pictet-Misner synthesis of quininic acid). The resulting product is a 2-substituted quinoline-4-carboxylic acid.



Borsche (9) has shown that benzalaniline in boiling alcohol first forms an addition compound with pyruvic acid, which easily yields 2-phenylquinoline-4-carboxylic acid. The extra two atoms of hydrogen are not eliminated but are utilized in the reduction of some reactant.

Several applications of the Doebner and v. Miller reaction to the preparation of benzoquinoline derivatives were studied. The reactions carried out are illustrated below.



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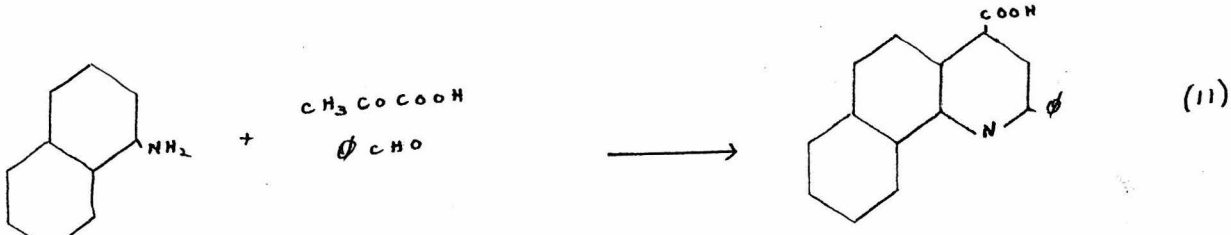

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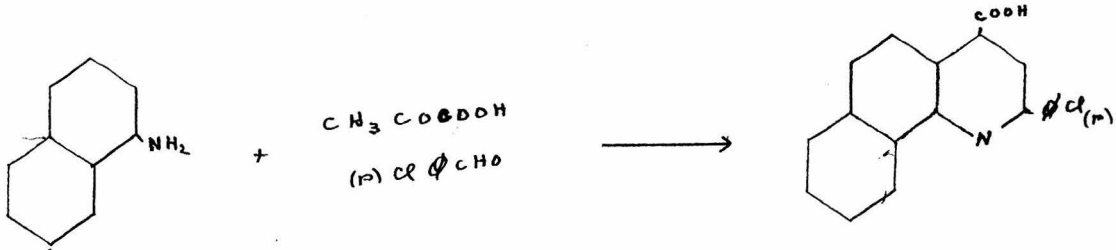
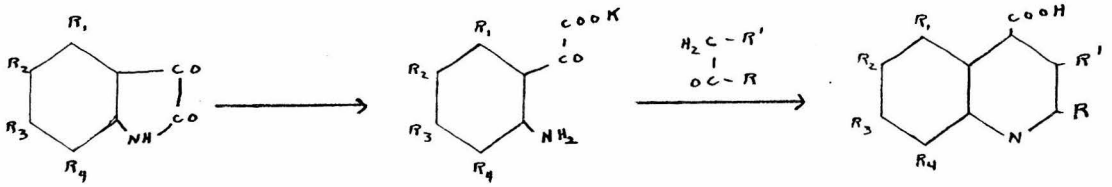


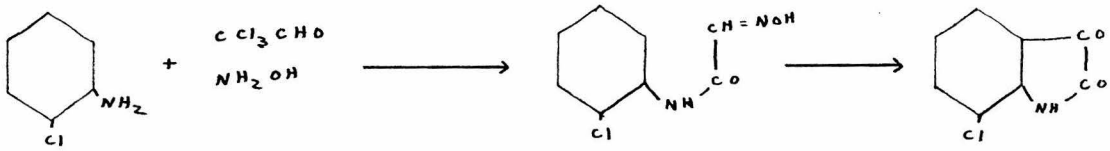
A standard method for the preparation, especially of 2-substituted cinchoninic acids, is that of Pfitzinger (12) (applied above by Halberkann). This synthesis utilizes an isatin as starting material. The isatin, after conversion to the potassium salt of the corresponding isatinic acid, is condensed with pyruvic acid and a carbonyl derivative containing the $-CH_2-CO-R$ grouping to yield a 2-R-quinoline-4-carboxylic acid.



Where R = -COOH, a quinoline-2,4-dicarboxylic acid is formed which, on partial decarboxylation (cf. Halberkann), is converted to a cinchoninic acid.

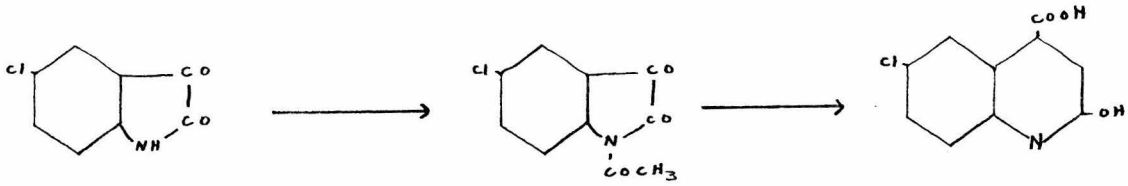
In the present work, application of the Pfitzinger reaction was made to the synthesis of 6-chlorocinchoninic acid (13) (from 5-chloroisatin and pyruvic acid and subsequent decarboxylation) and to the syntheses of 8-chlorocinchoninic acid (from 7-chloroisatin in a similar manner) and of 8-chloro-2-phenylcinchoninic acid (from 7-chloroisatin and acetophenone). The condensation of 5-bromoisatin with acetone and with pyruvic acid was also carried out. The extention of the Pfitzinger reaction to 5-nitroisatin (14) was attempted without success (see Experimental).

The 5-substituted isatins employed in the above experiments were made by direct halogenation or nitration of isatin (15). 7-chloroisatin (16) was made by the usual Sandmeyer method:



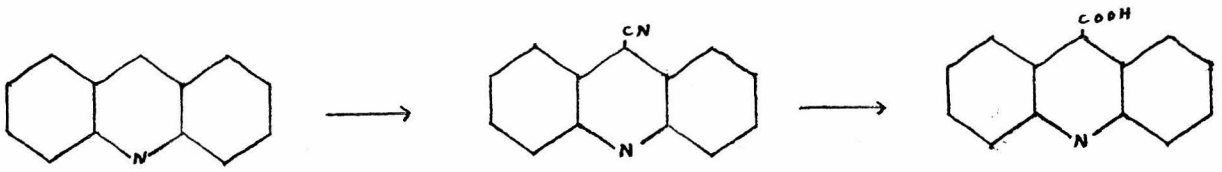
Although the literature (17) indicates that the Sandmeyer synthesis does not apply to the preparation of 7-nitroisatin, it was found possible to prepare the substance in approximately 80% yield by ring closure of o-nitroisonitrosoacetanilide.

Yet another method used in this investigation for the synthesis of a cinchoninic acid was the reaction illustrated below. Camps (18) had prepared 2-hydroxycinchoninic acid in this manner.



Since acridine can be considered a 2,3-benzoquinoline, it was of interest to synthesize acridine-9-carboxylic acid. This was accomplished by known methods (19)

starting from acridine.



Experimental[1]

Preparation of Ethyl 2-Phenyl-5,6-Benzoquinoline-4-carboxylate

2-Phenyl-5,6-benzoquinoline-4-carboxylic acid (10). In a 22-l., round-bottomed flask equipped with an efficient stirrer were placed 506 g. of β-naphthylamine, 6250 ml. of absolute ethanol, 428 g. of benzaldehyde, and 642 ml. of 50% pyruvic acid (Calco Chemical Company technical grade). The mixture was heated to boiling with stirring which led to the formation of a crystalline precipitate. After heating to boiling for 1 hour, the mixture was cooled and the precipitate filtered off, washed first with absolute ethanol, and then with ether. The product was first air-dried and then dried in the vacuum oven at 70°, yield 759.5 g. In another experiment 280 g. of β-naphthylamine, 3500 ml. of absolute ethanol, 240 g. of benzaldehyde and 360 ml. of 50% pyruvic acid were treated in a similar fashion, yielding 268.5 g. of yellow powder as product.

Ethyl 2-phenyl-5,6-benzoquinoline-4-carboxylate. Preliminary experiments indicated that it was not feasible to esterify 2-phenyl-5,6-benzoquinoline-4-carboxylic acid by heating with absolute alcohol in the presence of concentrated sulfuric acid. By this method

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1) All melting points are corrected. I am indebted to Dr. G. Oppenheimer and her staff for microanalyses.

esterification proceeded very slowly (undoubtedly due to steric hindrance); practically all of the starting acid was recovered unchanged, and only enough of the ethyl ester was obtained for a satisfactory identification of the characteristic picrate, m.p. and mixed m.p. 192°.

In a 2-l., round-bottomed flask equipped with a reflux condenser and protected from atmospheric moisture by a calcium chloride tube was placed 261.6 g. of crude 2-phenyl-5,6-benzoquinoline-4-carboxylic acid and 330 ml. of thionyl chloride (purified over raw linseed oil) was added; there was a small heating effect and some gas evolved. The mixture was heated on a steam bath for 3.5 hours, at the end of which time suction was applied to the yellow-colored slurry. After removal of thionyl chloride by continuing to heat from a steam cone while maintaining the aspirator vacuum, the product was a solid cake which was broken up into a nearly dry powder. To this was added 500 ml. of absolute alcohol, and the mixture refluxed for 2 hours. It was then diluted with about 700 ml. of water and basified by the addition of 15 N ammonium hydroxide. The crude ester, an oily solid, was extracted with ether, the ether solution dried and solvent evaporated. The resulting crystals were recrystallized from absolute ethanol, yielding 205.7 g. of pearly flakes, m.p. 82-83°; an additional 22.5 g. of less pure ester was obtained from the mother

liquors. A portion of the ester was recrystallized from ethanol for analysis, pearly flakes, m.p. 83.5-84.5°.

Anal. Calc'd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28
Found: C, 80.58; H, 5.12; N, 4.43

The ester can be distilled, b.p. ca. 200° at 2 mm., and gives a picrate, m.p. 192.0-192.5°, analysis for $C_{28}H_{20}N_4O_9$.

The aqueous solution made basic with ammonia in the above experiment was heated to boiling, and allowed to cool after adding glacial acetic acid to pH 3. The yellow crystalline precipitate was filtered, rinsed with alcohol, then with ether, and dried, yield 34.0 g.

Methyl 2-phenyl-5,6-benzoquinoline-4-carboxylate was made from the acid chloride and methanol in the same way as the above ethyl ester. It was obtained as a crystalline solid, needles from a mixture of ethanol and isopropanol, m.p. 126.5-126.7°.

Preparation of Ethyl 2-Phenyl-7,8-Benzoquinoline-4-carboxylate

2-Phenyl-7,8-benzoquinoline-4-carboxylic acid (11). In a 12 l., round-bottomed flask equipped with a stirrer were placed 300 g. of α-naphthylamine (Eastman Kodak white label grade), 223 g. of benzaldehyde, 185 g. of 50% pyruvic acid (Calco Chemical Company technical grade), and 3750 ml. of absolute ethanol. The mixture was

heated over a water bath and maintained at the boiling point for 4.5 hours. After cooling, the product was filtered off, washed with absolute ethanol and air-dried, yield 231 g. of yellow crystalline solid. A second similar run with the same amounts of materials gave only 148 g. of product; esterification of this, however, gave higher yields of ester.

Ethyl 2-phenyl-7,8-benzoquinoline-4-carboxylate. In a 5 l., round-bottomed flask equipped with a Friedricks condenser protected by a soda-lime tube were placed 4.5 l. of absolute ethanol, 250 ml. of concentrated sulfuric acid, and 148 g. of crude 2-phenyl-7,8-benzo-quinoline-4-carboxylic acid. The mixture was refluxed for 62 hours, after which the excess ethanol was removed by heating on a steam cone using aspirator vacuum. The solution was then cooled, ice and water added to make the volume 3 l. and then finally made basic with aqueous ammonia. The ester was removed by extraction with three portions of benzene and the benzene extracts were combined and dried over anhydrous potassium carbonate. After removal of solvent and evaporation from a steam cone in vacuo., the residue was recrystallized from 1 l. of absolute ethanol. The yield was 128.3 g. of light yellow solid, m.p. 96°. For analysis a sample was recrystallized several times from absolute ethanol.

Anal. Calc'd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28
Found: C, 80.62; H, 5.18; N, 4.24

Preparation of Ethyl 2-p Chlorophenyl-7,8-Benzoquinoline-4-carboxylate

2-p Chlorophenyl-7,8-benzoquinoline-4-carboxylic acid. In a 22 l., round-bottomed flask, equipped with a large capacity reflux condenser, were placed 572.8 g. (4.0 moles) of Eastman Kodak white label grade ∝-naphthylamine, 562.4 g. (4.0 moles) of p-chlorobenzaldehyde, 704 g. (4.0 moles) of 50% technical pyruvic acid and 10 l. of denatured 95% ethanol. The mixture was refluxed for 18 hours. (After the first 20 minutes of boiling, a yellow crystalline compound was formed.) After refluxing was completed, the mixture was placed in the cold room at 5° overnight. The crystals were then filtered off, washed with 95% ethanol and air-dried. The yield was 746.2 g. of crude acid. A portion, after two recrystallizations from glacial acetic acid (yellow microneedles), melted at 308-309°.

Anal. Calc'd for $C_{20}H_{12}ClNO_2$: C, 71.97; H, 3.63; N, 4.20
Found: C, 70.83; H, 3.91; N, 4.19

Ethyl 2-p chlorophenyl-7,8-benzoquinoline-4-carboxylate. In a 22 l., round-bottomed flask, equipped with an efficient reflux condenser, were placed 705 g. of crude 2-p chlorophenyl-7,8-benzoquinoline-4-carboxylic acid, 9 l. of absolute ethanol, and 400 ml. of concentrated sulfuric acid. The mixture was refluxed together for

41 hours. The acid dissolved completely after 21 hours of boiling. After refluxing was complete, the excess ethanol was removed over a steam bath in vacuo to a volume of 2 l. The thick gummy residue was poured over cracked ice and extracted three times with benzene (total benzene used, 3.5 l.). The benzene was extracted with 1 l. of 1 N sodium hydroxide, dried over anhydrous sodium sulfate, filtered, and evaporated over a steam bath in vacuo to a very thick oil. After recrystallization from 950 ml. of ethanol plus 600 ml. of benzene, the yield was 167.3 g. of light yellow needles, m.p. 124-125°. A portion, recrystallized from ethanol-benzene, formed dense tufts of tan bars, m.p. 127.4-127.8°.

Anal. Calc'd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87
Found: C, 72.86; H, 4.76; N, 3.89

Preparation of Ethyl 6-Chloroquinoline-4-carboxylate

5-Chloroisatin (15). In a 12 l., round-bottomed flask, equipped with a glass stirrer, a gas inlet tube, and an outlet tube, were placed 250 g. of isatin (Eastman Kodak white label grade) and 10 l. of water. Chlorine gas was bubbled into the mixture with vigorous stirring. The color-change from red to yellow determined the end of the reaction. The slurry was filtered on a large

Buchner with suction, washed with water, and air-dried. Purification was accomplished by adding to the dried crude product 1 l. of absolute ethanol; the resulting mixture was then heated to boiling for 30 minutes, cooled, filtered, and air-dried. The yield was 145 g. of product melting at 250.5-252.5°. (literature (15) 246°)

6-Chloroquinoline-2,4-dicarboxylic acid (13). In a large beaker was placed a solution of 1200 g. of potassium hydroxide in 3 l. of water. This was heated practically to the boiling point. Then the crude damp 5-chloroisatin from 300 g. of isatin was added with stirring. The color changed first to deep red, then to green. After all of the 5-chloroisatin dissolved, 648 g. of 50% technical pyruvic acid was added. The mixture was allowed to stand at room temperature for 14 hours, then heated on a hot plate for 30 minutes. While boiling hot, 1 l. of 12 N hydrochloric acid was added as rapidly as possible; then a second liter, drop by drop with stirring. (Unless the mixture was acidified while hot, the half potassium salt precipitated.) When cool, the 6-chloroquinoline-2,4-dicarboxylic acid was filtered with suction, washed first with water, then with a small amount of cold ethanol, and air-dried. The yield was 320.2 g. of a product melting at 265-266°

with decarboxylation and immediate resolidification; the melting point was observable only when the heating was rapid.

Anal. Calc'd for $C_{11}H_6ClNO_4$: C, 52.26; H, 2.40; N, 5.54
Found: C, 52.30; H, 2.98; N, 5.51

6-Chloroquinoline-4-carboxylic acid (13). In a 3 l., round-bottomed flask, equipped with an efficient stirrer, were placed 308 g. of the above crude 6-chloroquinoline-2,4-dicarboxylic acid and 800 ml. of freshly redistilled nitrobenzene. These were heated together in a wax bath, with vigorous stirring, to 195° for 4.5 hours, during which time a large amount of carbon dioxide was evolved. After cooling to room temperature, the partially decarboxylated acid was filtered on a Buchner filter with suction, washed with ethyl ether until free of nitrobenzene, and air-dried. The yield of crude 6-chloroquinoline-4-carboxylic acid was 220 g. A recrystallized sample melted at 313° dec. (literature (13) 302°).

Ethyl 6-chloroquinoline-4-carboxylate. In a 3 l., round-bottomed flask were placed the above 220 g. of 6-chloroquinoline-4-carboxylic acid and 2 l. of absolute ethanol. 150 ml. of concentrated sulfuric acid was added very slowly. The mixture was refluxed for 40 hours, using a soda-lime protected Friedricks condenser. After the esterification was complete, suction was applied and the excess ethanol removed. The resulting

sirup was cooled, diluted with ice and water, and filtered. The filtrate was made alkaline with potassium carbonate and extracted with ethyl ether. After removal of the ether, this material was combined with the precipitate above. It was found that this crude ester consisted of a mixture of the desired 4-carbethoxy-6-chloroquinoline with 2,4-dicarbethoxy-6-chloroquinoline. In order to separate these two, the picrate of the monoethyl ester was precipitated from ethanol. The diethyl ester does not form a picrate. The free ester was then regenerated and recrystallized from 60-70° petroleum ether. The yield was 90 g. of ester melting at 63-64°.

Anal. Calc'd for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.28; N, 5.94
Found: C, 61.00; H, 4.29; N, 6.04

The 2,4-dicarbethoxy-6-chloroquinoline which occurred as an impurity was also partially characterized. It crystallized from isopropyl ether in two forms: needles and blocky prisms, both of which melted at 93-93.5°.

Anal. Calc'd for $C_{15}H_{14}ClNO_4$: C, 58.50; H, 4.55; N, 4.55
Found: C, 58.34; H, 5.77; N, 4.82

Preparation of 2-Methyl-6-Chloroquinoline-4-carboxylic Acid

3.0 g. of 5-chloroisatin (prepared as described above) was added to a hot solution of 10.6 g. of potassium

hydroxide in 21 ml. of water. After the isatin was completely dissolved, the solution was cooled and 8 ml. of acetone was added, plus a small amount of water to bring about a one-phase system. This mixture was allowed to stand at room temperature for 18 hours; then was heated for 20 minutes and neutrallized with hydrochloric acid. The precipitated acid was filtered, washed with water, and air-dried. The crude 2-methyl-6-chloroquinoline-4-carboxylic acid was recrystallized from 50% ethanol. The yield was 1.92 g. of acid melting at 170.5-171.5°.

Anal. Calc'd for $C_{11}H_8ClNO_2$: C, 59.60; H, 3.64; N, 6.32
Found: C, 59.33; H, 3.63; N, 6.10

Preparation of Ethyl 2-Hydroxy-6-Chloroquinoline-4-carboxylate and of Ethyl 2,6-Dichloroquinoline-4-carboxylate

N-Acetyl-5-chloroisatin. 8 g. of 5-chloroisatin (prepared as above) and 36 ml. of freshly distilled acetic anhydride were mixed together and refluxed for 1.5 hours on a wax bath at 160°. One drop of sulfuric acid seemed to be necessary to start the reaction. The yellow crystals which formed on cooling were filtered off and washed with ethyl ether. After two recrystallizations from an isopropyl ether-n-butanol mixture the product weighed 4.12 g. The melting point was 168-169°.

Anal. Calc'd for $C_{10}H_6ClNO_2$: C, 53.70; H, 2.70; N, 6.26
Found: C, 53.57; H, 2.66; N, 6.49

2-Hydroxy-6-chloroquinoline-4-carboxylic acid.

In a small round-bottomed flask were mixed 3.0 g. of acetyl-5-chloroisatin, 82 ml. of distilled water, and 1.37 g. of sodium hydroxide. These were refluxed together on a wax bath at 130° for 50 minutes. After cooling, the clear yellow solution was brought to pH 2 with hydrochloric acid. The precipitate was centrifuged and extracted with sodium bicarbonate solution. The 5-chloroisatin recovered weighed 0.9 g. The sodium bicarbonate-soluble portion, after acidification, centrifuging, washing, and air-drying, yielded 1.5 g. of 2-hydroxy-6-chloroquinoline-4-carboxylic acid melting above 315°. Recrystallization was effected from acetic acid.

Anal. Calc'd for $C_{10}H_6ClNO_2$: C, 53.70; H, 2.70; N, 6.26
Found: C, 53.75; H, 2.76; N, 6.00

Ethyl 2-hydroxy-6-chloroquinoline-4-carboxylate.

In a 200 ml., round-bottomed flask was placed 100 ml. of absolute ethanol, 2 ml. of concentrated sulfuric acid, and 1.4 g. of 2-hydroxy-6-chlorocinchoninic acid. These were refluxed together for 41 hours. Upon cooling, fine matted yellow crystals immediately began to form. These were filtered, washed with absolute ethanol, then with ether, and dried. After recrystallization from ethanol the product melted at 236.5°.

Anal. Calc'd for $C_{12}H_{10}ClNO_3$: C, 57.30; H, 4.01; N, 5.57
Found: C, 57.27; H, 4.25; N, 5.73

Ethyl 2,6-dichloroquinoline-4-carboxylate. In a 5 ml., round-bottomed flask were placed 0.50 g. of ethyl 2-hydroxy-6-chloroquinoline-4-carboxylate and 1.25 ml. of phosphorous oxychloride. These were refluxed together on a wax bath at 140° for 35 minutes. The product was cooled and washed well with water. Recrystallization from ethanol gave long white needles melting at 132.5-132.8°.

Anal. Calc'd for $C_{10}H_9Cl_2NO_2$: C, 53.30; H, 3.35; N, 5.18
Found: C, 53.55; H, 3.33; N, 4.93

Preparation of Ethyl 8-Chloroquinoline-4-carboxylate

o-Chloroisonitrosoacetanilide (16). In a 22 l., round-bottomed flask equipped with an efficient stirrer were placed 9600 ml. of distilled water, 590 g. of chloral hydrate, and 3750 g. of technical anhydrous sodium sulfate. The mixture was stirred and warmed to 40° to secure complete solution. At that temperature a slurry of 411 g. of Monsanto o-chloroaniline, 1900 ml. of distilled water, and 282 ml. of 12 N hydrochloric acid was added. A white turbidity appeared at this point. A solution of 710 g. of hydroxylamine hydrochloride in 1200 ml. of water was added, and the mixture was heated to boiling in 53 minutes by the use of four Fisher burners. Boiling was continued for 3 minutes,

after which the reaction mixture was allowed to cool. The solid was filtered, washed with water, and dissolved in 6600 ml. of 5% sodium hydroxide. This was filtered from a small amount of insoluble material and made acid with 12 N hydrochloric acid. The precipitate was filtered and washed with water. To remove water, the filter cake was extracted with 2 l. of ether, the extracts dried and the ether removed by distillation, yield 422 g. of o-chloroisonitrosoacetanilide.

7-Chloroisatin (16). In a 5 l., round-bottomed flask, equipped with a stirrer, and supported only at the top, was placed 2 l. of concentrated sulfuric acid. This was heated to 80° and 200 g. of o-chloroisonitroso-acetanilide was added. The temperature rose spontaneously and was controlled by cooling with a water bath. The temperature was kept at 95° for 17 minutes by appropriate heating and cooling. At the end of that time, the solution was cooled and poured over an excess of cracked ice. It was allowed to stand for 1 hour, and was then filtered, washed with water, and air-dried. The yield was 139.2 g.

8-Chloroquinoline-2,4-dicarboxylic acid. The crude 7-chloroisatin from 790 g. of isonitroso compound was condensed in four approximately equal portions as follows: approximately 139 g. of 7-chloroisatin was added with stirring to a hot solution of 425 g. of

potassium hydroxide in 1550 ml. of water. The mixture was heated and stirred for 30 minutes; then 290 g. of 50% technical pyruvic acid was added and the reaction mixture was allowed to stand at room temperature for 18 hours. At the end of this time it was heated to the boiling point and 6 N hydrochloric acid was dropped in slowly with stirring until the mixture was acid. After cooling it was filtered, washed with water, then a little methanol, and finally with ether. The yield from all four batches was 412 g.

8-Chloroquinoline-4-carboxylic acid. In a 3 l., round-bottomed flask were placed the above 412 g. of 8-chloroquinoline-2,4-dicarboxylic acid and 1 l. of freshly redistilled nitrobenzene. The slurry was stirred and heated to 180-186° for 7 hours. After cooling, the reaction mixture was diluted with 1 l. of 60-70° petroleum ether, filtered, washed with petroleum ether, and air-dried. The yield was 341 g.

Ethyl 8-chloroquinoline-4-carboxylate. In a 12 l., round-bottomed flask, equipped with a reflux condenser, were placed 8 l. of absolute ethanol, 400 ml. of concentrated sulfuric acid, and the above 341 g. of crude 8-chlorocinchoninic acid. These were refluxed together for 23 hours. The excess ethanol was removed with suction to a volume of 2 l. After cooling, ice and 500 ml. of concentrated aqueous ammonia were added. The precipitated oil was extracted twice with benzene,

dried over anhydrous sodium sulfate, and filtered. The benzene was removed on a steam cone under suction. The ester was then crystallized from 1 l. of absolute ethanol by cooling to minus 35°. The yield was 270 g. of ethyl 8-chloroquinoline-4-carboxylate, melting at 36-37°.

Anal. Calc'd for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.28; N, 5.94
Found: C, 61.01; H, 4.17; N, 5.59

Preparation of Ethyl 2-Phenyl-8-Chloroquinoline-4-carboxylate

2-Phenyl-8-chloroquinoline-4-carboxylic acid. 123 g. of 7-chloroisatin (prepared as above) was dissolved in 410 ml. of hot 30% potassium hydroxide solution and stirred vigorously for 30 minutes. Then a solution of 153.5 g. of acetophenone (Eastman Kodak white label grade) in 800 ml. of absolute ethanol was added and the mixture was refluxed together for 24 hours. The excess ethanol was boiled off under suction and the resulting sirup was diluted with four times its volume of water. This solution was extracted three times with isopropyl ether to remove excess acetophenone, then acidified with hydrochloric acid. The precipitated acid was filtered, washed with water, and air-dried. The yield was 162 g. of 2-phenyl-8-chloroquinoline-4-carboxylic acid.

Ethyl 2-phenyl-8-chloroquinoline-4-carboxylate. In a 5 l., round-bottomed flask, equipped with a soda-lime protected reflux condenser, were placed the above 162 g. of 2-phenyl-8-chloroquinoline-4-carboxylic acid, 2 l. of absolute ethanol, and 150 ml. of concentrated sulfuric acid. These were refluxed together for 35 hours. The excess ethanol was removed on a steam cone under aspirator vacuum. The residue was cooled, diluted with ice and water to a volume of 1.5 l., made basic with aqueous ammonia, and extracted twice with benzene. The benzene extract was dried over anhydrous sodium sulfate, then the solvent removed on a steam cone. The ester was recrystallized from 1 l. of hot ethanol. The yield was 140 g. of ethyl 8-chloroquinoline-4-carboxylate, melting at 98-98.5°.

Anal. Calc'd for $C_{18}H_{14}ClNO_2$: C, 69.40; H, 4.53; N, 4.49
Found: C, 69.80; H, 4.46; N, 4.01

Preparation of Ethyl 6-Bromo-2-Methylquinoline-4-carboxylate

5-Bromoisatin (15). In a 2 l., 3-necked flask equipped with stirrer, addition funnel and outlet tube were placed 10 g. of isatin (Eastman Kodak white label) and 1 l. of distilled water. To the stirred suspension was added 4.2 ml. of bromine at such a rate that the bromine was distributed in small droplets throughout the mixture. After all of the bromine had reacted,

the suspension was filtered and the product washed with water and air-dried, yield 15.1 g., m.p. 251.5-254.5°. On recrystallization from 1 l. of absolute ethanol, 6 g. was recovered in the first crop and 3 g. in the second, m.p. 257-258°. In runs conducted on a larger scale and using only 300 ml. of water per 10 g. of isatin the reaction mixture became filled with yellow solid and was difficult to stir; after about 2 hours the mixture became thinner and thorough mixing was again possible. The crude bromoisatin was suitable for use in the following experiments.

6-Bromo-2-methylquinoline-4-carboxylic acid. The crude 5-bromoisatin obtained by bromination of 37.5 g. of isatin was dissolved in hot potassium hydroxide solution (200 g. of potassium hydroxide in 500 ml. of water). The resulting greenish-brown solution was allowed to cool, 160 ml. of acetone was added, mixed and allowed to stand overnight. The reaction mixture was further heated on a hot plate for 25 minutes and neutralized slowly with hydrochloric acid. After cooling, the mixture was filtered and the precipitate washed thoroughly with water, air-dried, and then dried in the oven at 110°, yield 60.5 g. In another experiment the bromoisatin from 112.5 g. of isatin gave 188 g. of product.

A sample was recrystallized from ethanol for analysis, m.p. 272-273°.

Anal. Calc'd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.03; N, 5.26
Found: C, 49.81; H, 3.21; N, 5.10

Ethyl 6-bromo-2-methylquinoline-4-carboxylate.

In a 3 l., round-bottomed flask equipped with addition funnel and reflux condenser were placed 188 g. of crude 6-bromo-2-methylcinchoninic acid and 1200 ml. of absolute ethanol. Through the separatory funnel was added 100 ml. of concentrated sulfuric acid and the mixture refluxed overnight from a boiling water bath. After removal of excess ethanol on a steam cone under aspirator vacuum, the residue was cooled to 0° and neutralized with 6 N ammonium hydroxide. The product was filtered off and recrystallized from absolute ethanol, yield 158 g. of light tan crystals, m.p. 110-111°.

Anal. Calc'd for $C_{13}H_{12}BrNO_2$: C, 53.09; H, 4.11; N, 4.78
Found: C, 52.58; H, 4.13; N, 4.61

Preparation of Ethyl 6-Bromoquinoline-2,4-dicarboxylate

6-Bromoquinoline-2,4-dicarboxylic acid. 2.75 g. of 5-bromoisatin (prepared as above) was added to a hot solution of 10.6 g. of potassium hydroxide in 21 ml. of water. To this solution was added 7.2 g. of 50% pyruvic

acid (technical grade) and the mixture was allowed to stand at room temperature for 18 hours. It was then heated for 20 minutes and acidified with hydrochloric acid. The product was filtered, washed, and air-dried. After recrystallization from ethanol, the yield was 1.54 g. of 6-bromoquinoline-2,4-dicarboxylic acid, melting (with decomposition) at 314°.

Ethyl 6-bromoquinoline-2,4-dicarboxylate. Crude damp 5-bromoisatin from 200 g. of isatin (prepared as above) was condensed in two portions with 440 g. of technical 50% pyruvic acid in the presence of 33% aqueous potassium hydroxide (800 g. of potassium hydroxide, 1600 ml. of distilled water). The condensation product was worked up as above. This crude dicarboxylic acid was added with stirring in approximately 100 g. portions to redistilled nitrobenzene, heated to 200° for 1 hour, then cooled and filtered. The first portion was converted to the potassium salt, steam distilled to remove the nitrobenzene, then reprecipitated with hydrochloric acid. The last three portions were washed free from nitrobenzene with ethyl ether. The combined crude acid (300 g.) was placed in a 5 l., round-bottomed flask together with 2.5 l. of absolute ethanol and 300 ml. of concentrated sulfuric acid and the mixture refluxed together for 13 hours. The excess ethanol was removed under suction. The resulting sirup was

cooled, then diluted with ice and water. This was basified with aqueous ammonia and extracted with isopropyl ether. After evaporation of the isopropyl ether, the crude ester was recrystallized twice from isopropyl ether. The yield was 56.3 g. of ester melting at 108-109°. 27 g. of unesterified acid was recovered. The analysis indicates that 6-bromo-2,4-dicarbethoxyquinoline was obtained rather than the monocarbethoxy derivative.

Anal. Calc'd for $C_{15}H_{14}BrNO_4$: C, 51.13; H, 4.02; N, 4.05
Found: C, 51.31; H, 4.16; N, 4.37

5-Nitroisatin Studies

5-Nitroisatin (15). In a 200-milliliter, round-bottomed flask were placed 100 ml. of concentrated sulfuric acid and 10 g. of isatin (Eastman Kodak white label grade) and the mixture was cooled to 0° in an ice bath. To this solution was added slowly with stirring 6.87 g. of potassium nitrate. The mixture was allowed to warm to room temperature and stand for 18 hours. It was then poured over cracked ice, filtered, washed free of acid, and air-dried. The yield was 12.4 g. After recrystallization from a large amount of ethanol the 5-nitroisatin melted at 250-251° (literature (15) 245°).

Larger runs caused no difficulty; 70 g. of isatin when nitrated gave 81.5 g. of crude 5-nitroisatin; 200 g. of isatin gave 226 g. of product.

Condensation of 5-nitroisatin with acetophenone (14). In a 2 l., round-bottomed flask was placed a solution of 48 g. of potassium hydroxide in 500 ml. of water, 38.4 g. of 5-nitroisatin, 48 g. of acetophenone, and 360 ml. of absolute ethanol. These were refluxed together for 14 hours, then cooled to 0°. A bright yellow potassium salt crystallized which was filtered, washed with 50 ml. of cold water, and air-dried, yield 10.0 g. This was dissolved in a minimum of hot 50% ethanol, filtered, and acidified with 10% acetic acid. The bright yellow acid was filtered and washed with boiling water. The yield was 7.4 g. It was not found possible to recrystallize this acid. Attempts to esterify it by refluxing with ethanol plus sulfuric acid also failed. Under other conditions an acidic condensation product was obtained which could in part be esterified by refluxing with ethanol and sulfuric acid. 11 g. of 5-nitroisatin was dissolved in 60 ml. of 33% aqueous potassium hydroxide. A solution of 15 ml. of acetophenone in 90 ml. of ethanol was added and the mixture refluxed for 15 hours. The excess ethanol was distilled out from a steam cone under suction. The reaction mixture was cooled, then diluted with 4 times its

volume of water and ice. After three extractions with isopropyl ether to remove the excess acetophenone, the solution was acidified with hydrochloric acid. The dark precipitate was filtered and washed with water, then dissolved in dilute sodium hydroxide, heated with Norite for 0.5 hours, and filtered again. The filtrate was made acid with hydrochloric acid, filtered, washed, and dried, yield, 15.1 g. of dark material of indefinite melting point. Esterification with ethanol and sulfuric acid gave an ester melting at 107-108°. The carbon and hydrogen analyses did not give concordant results; the analytical figures for nitrogen (Found: N, 9.69, 9.65) did not agree with those calculated for 6-nitro-2-phenyl-4-carbethoxyquinoline (Calc'd for $C_{18}H_{14}N_2O_4$: N, 8.65).

Condensation of 5-nitroisatin with acetone. In a 250 ml. beaker was placed 60 ml. of 33% potassium hydroxide and 11.0 g. of 5-nitroisatin. 5.0 g. of acetone and 90 ml. of absolute ethanol were added to the resulting potassium salt. After standing at room temperature for 50 hours, the mixture was diluted with 200 ml. of water and acidified with hydrochloric acid. The acidic product was filtered, washed first with water, then with a little ethanol, and air-dried. The yield was 7.2 g. of tan acid. Attempts to crystallize it failed. It was not found possible to esterify this acid by refluxing with ethanol and sulfuric acid.

7-Nitroisatin Studies

o-Nitroisonitrosoacetanilide. In a 5 l., round-bottomed flask, equipped with a stirrer and a thermometer were placed 2 l. of distilled water, 750 g. of technical anhydrous sodium sulfate and 108 g. (0.65 moles) of Merck reagent grade chloral hydrate. The mixture was stirred and heated to 40° to obtain complete solution. With a mortar and pestle 90 g. (0.65 moles) of o-nitroaniline and 150 ml. of 12 N hydrochloric acid were triturated together. This was added with stirring to the above solution. A solution of 142 g. of hydroxylamine hydrochloride in 500 ml. of distilled water was then added. The mixture was heated with vigorous stirring as rapidly as was possible with two Fisher burners. The reaction mixture came to the boiling point in 35 minutes and was then boiled for 15 minutes. When cool, it was filtered. The solid was stirred up with 1 l. of 5% sodium hydroxide for 2 hours and then filtered. The filtrate was made acid with hydrochloric acid, filtered, washed with water, and air-dried. The yield was 65 g. of product melting at 142.5-143.0°. An analytical sample was obtained by taking up in isopropyl ether-60-70° petroleum ether, filtering from insoluble material, evaporating solvent

and finally recrystallizing from benzene, m.p. 145.5-146.0°.

Anal. Calc'd for $C_8H_7N_3O_4$: C, 45.93; H, 3.37; N, 20.10
Found: C, 46.16; H, 3.44; N, 19.95

7-Nitroisatin. In a 2 l., round-bottomed flask, equipped with a stirrer and thermometer and supported only at the top, was placed 650 ml. of concentrated sulfuric acid. This was heated to 80° and the finely powdered o-nitroisonitrosoacetanilide was added. A spontaneous rise in temperature was observed. The temperature was kept at 95-100° for 15 minutes by appropriate heating or cooling. Cooling was accomplished by bringing a water bath up around the flask. After the reaction was complete, the mixture was allowed to cool. It was then poured over an excess of cracked ice. To insure complete precipitation, this mixture was allowed to stand for 2 hours before filtering. After washing free from sulfuric acid and air-drying, the yield was 40.7 g. of tan powder. After recrystallization from acetic acid the melting point was 232-233°.

Anal. Calc'd for $C_8H_4N_2O_4$: C, 50.02; H, 2.10; N, 14.57
Found: C, 49.79; H, 2.35; N, 14.80

An attempt to condense this 7-nitroisatin with acetophenone in the presence of 33% aqueous potassium hydroxide gave an insoluble acid (compare 5-nitroisatin condensation) which on esterification with ethanol and sulfuric acid yielded an ester, m.p. 129.5-130.5° from ethanol (Found: N, 7.85, 7.64).

Preparation of Ethyl Acridine-9-carboxylate

9-Cyanoacridine (19). In a 5 l., round-bottomed flask (in a hood), equipped with a stirrer and a reflux condenser, were placed 1650 ml. of absolute ethanol, 132 g. of glacial acetic acid, and 372 g. of acridine (Reilly Tar and Chemical Corp.). The mixture was warmed and stirred until complete solution occurred. A solution of potassium cyanide (207 g. in 290 ml. of water) was added at 25° and the mixture refluxed over a boiling water bath for 1.5 hours. The liquid was poured into a large evaporating dish on a steam bath. After the solvent was evaporated, the crystals were spread out on a paper to air-dry and oxidize. Complete oxidation was assumed when a green color did not develop upon addition of concentrated hydrochloric acid to an ethanolic solution of the 9-cyanoacridine. The oxidized product was stirred vigorously in boiling water for 3 hours to dissolve inorganic material, cooled, filtered, washed with water, and air-dried. The yield was 397 g.

Acridine-9-carboxylic acid (19). In a 5 l., round-bottomed flask were placed 379 g. of 9-cyanoacridine (from the above preparation) and 3800 ml. of 90% sulfuric acid (3390 ml. of concentrated sulfuric acid plus 410 ml. of water). The mixture was heated on a boiling

water bath with vigorous stirring for 18 hours. The hydrolyzed product was cooled in an ice-salt bath and divided into two equal portions, each in 4 l. beakers. To each portion was slowly added with stirring 264 g. of reagent grade sodium nitrite. The mixtures were kept carefully at 0° until the evolution of gas ceased (1 to 2 minutes). The reaction mixtures were permitted to warm to room temperature, then were heated in a hot water bath for 2 hours, cooled, and poured over cracked ice. The resulting mixtures were warmed to approximately 40° and, when frothing ceased, they were filtered, washed with water and air-dried. To purify the product it was dissolved in dilute sodium hydroxide, filtered from insoluble impurities, acidified with hydrochloric acid, filtered, washed with water, and air-dried. The combined yield was 297 g.

Ethyl acridine-9-carboxylate. Preliminary experiments indicated that acridine-9-carboxylic acid could not readily be esterified by heating with ethanol and sulfuric acid. In a 100 ml., round-bottomed flask were placed 3.1 g. of acridine-9-carboxylic acid (prepared as above) and 13 ml. of thionyl chloride (freshly redistilled over linseed oil). These were refluxed together over a hot water bath, using a calcium chloride protected Friedricks condenser, for 1.5 hours. A complete

solution resulted at the end of that time. The excess thionyl chloride was removed *in vacuo*. The lumps of acid chloride were crushed to a powder rapidly and 25 ml. of absolute ethanol was added. The mixture was refluxed overnight. Excess ethanol was removed on a steam cone *in vacuo*. The resulting thick sirup was cooled, ice was added, and the reaction mixture made basic with aqueous ammonia. It was extracted three times with benzene. The benzene was dried over anhydrous potassium carbonate, filtered, and evaporated, yield 2.7 g. of crude ester, m.p. 67-70°. Purification was accomolished by recrystallization from isopropyl ether. The melting point of the purified ester was 78.5-79.5°.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.58
Found: C, 76.22; H, 5.40; N, 5.69

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