[From the Department of Organic Chemistry, Research Division, Sharp and Dohme, Inc.]

# THE SYNTHESIS OF 3-HYDROXY-2-PHENYLQUINOLINE-4,8-DICARBOXYLIC ACID AND CERTAIN OF ITS DERIVATIVES

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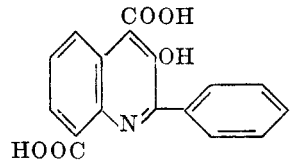
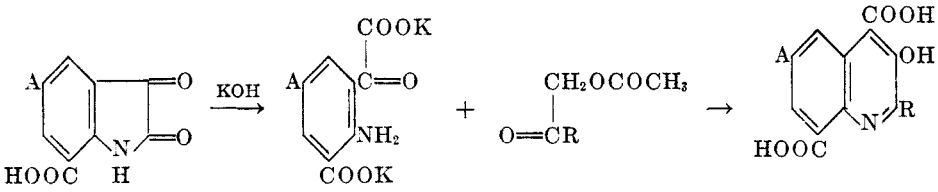
Marshall and co-workers (2, 12, 20) and others (11, 17) have reported the synthesis and pharmacological properties of a number of derivatives of 3-hydroxycinchoninic acid. One of the most interesting compounds of the series was 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (I). In view of the activity

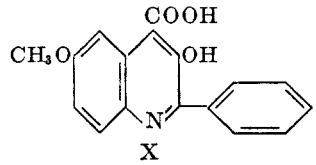


I

of I, a study of some of its derivatives was undertaken. Since both cinchophen (2-phenylcinchoninic acid) and salicylic acid have certain structural and, perhaps, pharmacological characteristics similar to I, the extensive knowledge of the relation of structure to activity in these compounds served as a basis for the choice of some of the derivatives of I.

The Pfitzinger reaction (13) is generally applicable to the synthesis of 3-hydroxycinchoninic acids (12, 3) and in the present study the reaction of the appropriate 7-carboxyisatin with substituted phenacyl acetates led to derivatives of I. The isatins used were 7-carboxyisatin, 7-carbomethoxy-5-chloroisatin, and 7-carboxy-5-methoxyisatin. The presence of a chloro or a methoxy group in the benzenoid nucleus of either naturally-occurring or synthetic quinolines that have found a place in medicine guided the choice of these particular isatins. Furthermore, it has been found in this laboratory that the introduction of a methoxy group in the 6-position of 3-hydroxy-2-phenylcinchoninic acid (HPC) considerably reduced the toxicity for mice (see compound X).





X

The carboxyisatins were readily prepared by the method of Sandmeyer (14); however, their purification proved to be quite difficult. In fact, it was necessary to use crude 7-carboxy-5-methoxyisatin in the Pfitzinger reaction because of the difficulty encountered in its purification.

Although phenacyl halides have been successfully used in this type of reaction (5), the yields of 3-hydroxycinchoninic acids are better and the products are purer when the phenacyl acetates are used. The Pfitzinger reaction was carried out using 7-carboxyisatin with each phenacyl acetate recorded in Table I. The expected product was isolated in each case except when 3,4-dihydroxyphenacyl

TABLE I

PHENACYL CHLORIDES AND ACETATES

$$RH + ClCOCH_2Cl \rightarrow \underset{\textbf{A}}{RCOCH_2Cl} \rightarrow \underset{\textbf{B}}{RCOCH_2OCOCH_3}$$

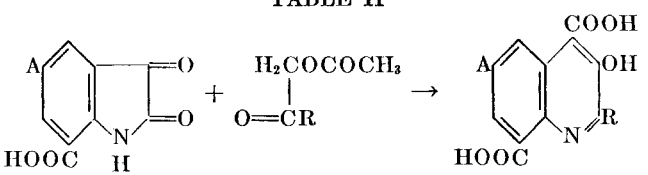
| R | PRODUCT A | | | PRODUCT B | | |
|---|---|---|---|---|---|---|
| | Yield,[a] % | M.P.,[b] °C. | LITERATURE REF. | YIELD,[a] % | M.P.,[b] °C. | LITERATURE REF. |
| $C_6H_5$- | [c] | — | — | 59 | 48.5–49.5 | (19) |
| *p*-$ClC_6H_4$- | 75 | 100–103 | (10) | 67 | 70–72 | (15) |
| *p*-$BrC_6H_4$- | [c] | — | — | 89 | 81–82 | (6) |
| *p*-$CH_3CONHC_6H_4$- | 90 | 172–173 | (10) | 88 | 151–155 | (9) |
| *p*-$C_6H_5C_6H_4$- | [d] | — | — | 60 | 104–107 | (8) |
| 2,4-$(CH_3)_2C_6H_3$- | [d] | — | — | 70 | 43–45[f] | [e] |
| 3,4-$(HO)_2C_6H_3$- | 58 | 171–172 | (10) | 83 | 157–160[f] | [g] |
| *p*-$CH_3OC_6H_4$- | 50 | 96–100 | (16) | 58 | 59–61 | (7) |

[a] The yields are given for the once-distilled or once-recrystallized material. [b] The melting points are the uncorrected values for the once-recrystallized or once-distilled material unless otherwise indicated. [c] The required phenacyl bromide, purchased from Eastman Kodak, was used in this case. [d] The required phenacyl chloride was purchased from Eastman Kodak in this case. [e] This compound has not been reported in the literature; the details of the preparation are given in the experimental section. [f] This is the m.p. of the pure compound. [g] This compound has not been described in the literature. It was prepared in the conventional manner and purified by recrystallization from water. *Anal.* Calc'd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.31; H, 4.47.

acetate was used. In this case, even when an atmosphere of nitrogen was maintained, only polymeric material was obtained. When *p*-acetylaminophenacyl acetate was used, hydrolysis of the acetyl group occurred during the reaction and the corresponding amino analog was isolated.

In most cases the Pfitzinger reaction gave excellent yields of crude product. Purification of the 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acids was difficult because no solvent satisfactory for crystallization was found. Fractional precipitation by gradual acidification of a solution of the sodium or ammonium salt proved to be the most profitable method of purification. Table II presents a summary of the substituted 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acids prepared in this study.

TABLE II



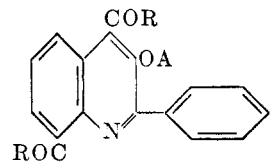

| No. | R | A | YIELD[a] % | M.P.,[b] °C. | EMPIRICAL FORMULA | ANALYSIS[c] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Carbon | | Hydrogen | | Nitrogen | |
| | | | | | | Calc'd | Found | Calc'd | Found | Calc'd | Found |
| I | $C_6H_5$— | H | 58 | 305–307[d] | $C_{17}H_{11}NO_5$ | 66.02 | 65.58 | 3.58 | 3.57 | 4.53 | 4.62 |
| II | *p*-$ClC_6H_4$— | H | 31 | 347–350[d] | $C_{17}H_{10}ClNO_5$ | 59.41 | 59.26 | 2.93 | 3.19 | 4.08 | 4.08 |
| III | *p*-$BrC_6H_4$— | H | 25 | 323–327[d] | $C_{17}H_{10}BrNO_5$[e] | 52.60 | 52.51 | 2.60 | 2.61 | 3.61 | 3.69 |
| IV | *p*-$CH_3OC_6H_4$— | H | 47 | 320–322[d] | $C_{18}H_{13}NO_6$ | 63.72 | 63.47 | 3.86 | 3.96 | 4.13 | 4.09 |
| V | *p*-$NH_2C_6H_4$— | H | 25 | >350[d] | $C_{17}H_{12}N_2O_5$ | 62.96 | 63.24 | 3.73 | 3.92 | 8.64 | 8.64 |
| VI | *p*-$C_6H_5C_6H_4$— | H | 28 | 320[d] | $C_{23}H_{15}NO_5$ | 71.68 | 71.34 | 3.92 | 3.98 | 3.64 | 3.56 |
| VII | *2,4*-$(CH_3)_2C_6H_3$— | H | 17 | 308–310[d] | $C_{19}H_{15}NO_5$ | 67.65 | 67.56 | 4.48 | 4.65 | 4.15 | 4.15 |
| VIII | $C_6H_5$— | $CH_3O$— | 11 | 310–312[f] | $C_{18}H_{13}NO_6$ | 63.72 | 64.33 | 3.86 | 4.06 | 4.13 | 4.26 |
| IX | $C_6H_5$— | Cl[g] | 29 | 337–338[d] | $C_{17}H_{10}ClNO_5$ | 59.41 | 59.13 | 2.93 | 3.02 | 4.08 | 4.21 |

[a] The yields reported are for the purified products. [b] The melting points are uncorrected values obtained on the pure material. [c] The found values are the average of duplicate analyses. [d] Purification was carried out by repeated fractional precipitation by gradual acidification of a solution of the sodium or ammonium salt. [e] *Anal.* Calc'd: Br, 20.59. Found: Br, 20.71. [f] Purification was carried out as in [d] followed by recrystallization from a mixture of 2-methoxyethanol and dimethylformamide. [g] 7-Carbomethoxy-5-chloroisatin was used in this preparation.

Several functional derivatives of I were also prepared. Three 3-acyloxy derivatives were obtained by heating I with the appropriate acid anhydride. Two esters and the diamide of I were synthesized using conventional methods. Data concerning these compounds is summarized in Table III.

3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (I) was readily decarboxylated under conditions that were employed in the decarboxylation of 3-hydroxycinchoninic acid (3) and 2-phenyl-3-hydroxycinchoninic acid. However, only the 4-carboxy group was lost and the product was 3-hydroxy-2-phenylquinoline-8-

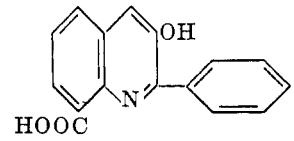
TABLE III




| No. | R | A | YIELD,[a] % | M.P.,[b] °C. | EMPIRICAL FORMULA | ANALYSIS[c] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Carbon | | Hydrogen | | Nitrogen | |
| | | | | | | Calc'd | Found | Calc'd | Found | Calc'd | Found |
| XI | $OCH_3$ | H | 88 | 118–120 | $C_{19}H_{15}NO_5$ | 67.65 | 67.62 | 4.48 | 4.49 | 4.15 | 4.15 |
| XII | $OC_2H_5$ | H | 79 | 111–113 | $C_{21}H_{19}NO_5$ | 69.03 | 69.09 | 5.24 | 5.23 | 3.83 | 3.85 |
| XIII | $NH_2$ | H | 95 | 257–258 | $C_{17}H_{13}N_3O_3$ | 66.44 | 66.42 | 4.26 | 4.26 | 13.68 | 13.63 |
| XIV | OH | $COCH_3$ | 80 | 222–223 | $C_{19}H_{13}NO_6$ | 64.96 | 64.20 | 3.73 | 3.87 | 3.99 | 3.93 |
| XV | OH | $CO(CH_2)_2CH_3$ | 89 | 204–205 | $C_{21}H_{17}NO_6$ | 66.49 | 66.25 | 4.52 | 4.83 | 3.68 | 3.61 |
| XVI | OH | $CO(CH_2)_4CH_3$ | 76 | 185.5–187.5 | $C_{23}H_{21}NO_6$ | 67.80 | 67.78 | 5.20 | 5.29 | 3.44 | 3.39 |

[a] The yields reported are for the crude products before recrystallization. [b] The melting points are uncorrected values obtained on the purified material. [c] The found values are the average of duplicate analyses.

carboxylic acid (XVII), an isomer of the 3-hydroxy-2-phenylcinchoninic acid (HPC) originally studied by Marshall, *et al.* Six derivatives of I were decarboxyl-




XVII

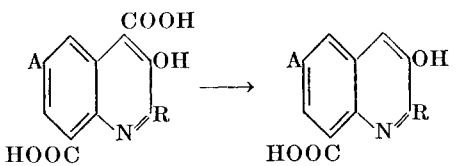
ated to the corresponding analogs of XVII; these reactions are summarized in Table IV.

## EXPERIMENTAL

### ISATINS

*7-Carboxyisatin* was prepared from anthranilic acid by a modification (3) of the method of Sandmeyer (14).

TABLE IV




| No. | R | A | YIELD,[a] % | M.P.,[b] °C. | EMPIRICAL FORMULA | ANALYSIS[c] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Carbon | | Hydrogen | | Nitrogen | |
| | | | | | | Calc'd | Found | Calc'd | Found | Calc'd | Found |
| XVII | $C_6H_5$— | H | 99 | 316–318[d] | $C_{16}H_{11}NO_3$ | 72.44 | 72.36 | 4.18 | 4.15 | 5.28 | 5.26 |
| XVIII | *p*-$ClC_6H_4$— | H | 95 | 340–342[d] | $C_{16}H_{10}ClNO_3$ | 64.12 | 63.75 | 3.36 | 3.51 | 4.67 | 4.58 |
| XIX | *p*-$BrC_6H_4$— | H | 80 | 326–327[d] | $C_{16}H_{10}BrNO_3$ | 55.83 | 55.97 | 2.93 | 3.17 | 4.07 | 4.01 |
| XX | *p*-$CH_3OC_6H_4$— | H | 96 | 318–319[d] | $C_{17}H_{13}NO_4$ | 69.14 | 69.12 | 4.44 | 4.58 | 4.74 | 4.71 |
| XXI | *p*-$C_6H_5C_6H_4$— | H | 91 | 329–331[d] | $C_{22}H_{15}NO_3$ | 77.40 | 77.07 | 4.43 | 4.46 | 4.10 | 4.05 |
| XXII | 2,4-$(CH_3)_2C_6H_3$— | H | 71 | 281–282[e] | $C_{18}H_{15}NO_3$ | 73.70 | 73.55 | 5.15 | 5.19 | 4.78 | 4.74 |
| XXIII | $C_6H_5$— | Cl | 74 | 344–345[d] | $C_{16}H_{10}ClNO_3$ | 64.12 | 63.49 | 3.36 | 3.66 | 4.67 | 4.62 |

[a] The yields reported are for the crude product before purification. [b] The melting points are uncorrected values obtained on the purified material. [c] The found values are the average of duplicate analyses. [d] Purification was effected by recrystallization from diethylene glycol monoethyl ether. [e] Purification was carried out by recrystallization from *n*-propyl alcohol.

*7-Carbomethoxy-5-chloroisatin* which has not been described in the literature was prepared as follows:

*Methyl 2-amino-5-chlorobenzoate* was prepared from 2-amino-5-chlorobenzoic acid (Eastman Kodak) using methanol and hydrogen chloride according to the method of Freudler (4). The yield was 77%, m.p. 68–69°.

*Methyl 2-isonitrosoacetamido-5-chlorobenzoate.* Chloral hydrate (65.6 g., 0.4 mole) was dissolved in water (1.28 l.). The solution was stirred mechanically and treated with a solution of methyl 2-amino-5-chlorobenzoate (70 g., 0.38 mole )in concentrated hydrochloric acid (69 ml., 0.8 mole) and water (400 ml.). A solution of hydroxylamine hydrochloride (87 g., 1.26 moles) in water (560 ml.) was added and the mixture was stirred rapidly and heated to boiling. Boiling was continued for 20 minutes, then the mixture was cooled and the solid that separated was removed. The product was washed with water and dried. The yield was 65 g. (67%), m.p. 201–205°. Two recrystallizations from methanol gave fine white needles, m.p. 219–221°.

*Anal.* Calc'd for $C_{10}H_9ClN_2O_4$: C, 46.80; H, 3.53; N, 10.92.

Found: C, 46.89; H, 3.58; N, 10.90.

*7-Carbomethoxy-5-chloroisatin.* Concentrated sulfuric acid (120 ml., *d.* 1.84) was mechanically stirred and heated to 85°. 2-Carbomethoxy-5-chloroisonitrosoacetanilide (55 g., 0.215 mole) was added portionwise over about 30 minutes while the temperature was maintained at 85°. After the addition was complete, the temperature was raised to 100° for 15 minutes. The mixture was cooled and poured onto crushed ice (1 kg.). After 2 hours, the solid that separated was removed, washed with water, and dried. The yield was 12 g. (23%) of crude ester. A sample of the crude ester recrystallized once from benzene and twice from dimethylethylcarbinol afforded tan-colored needles, m.p. 232–234°.

*Anal.* Calc'd for $C_{10}H_6ClNO_4$: C, 50.12; H, 2.52; N, 5.85.

Found: C, 49.92; H, 2.37; N, 6.00.

Addition of a large volume of conc'd sulfuric acid to the filtrate gave 25 g. (50%) of a tan solid which is impure 7-carboxy-5-chloroisatin.

*7-Carboxy-5-methoxyisatin.* 2-Amino-5-methoxybenzoic acid was prepared by the oxidation of 5-methoxyisatin with hydrogen peroxide according to the method of Bachman and Picha (1). The yield was 62%, m.p. 147–148°.

*2-Isonitrosoacetamido-5-methoxybenzoic acid.* Chloral hydrate (57.9 g., 0.35 mole) and sodium sulfate (400 g.) were dissolved in water (1 l.) and the solution was stirred mechanically. A solution prepared from 2-amino-5-methoxybenzoic acid (57.7 g., 0.34 mole), water (300 ml.), and concentrated hydrochloric acid (45 ml. of 35% material) was added. The mixture was then treated with a solution of hydroxylamine hydrochloride (69.5 g., 0.1 mole) and rapidly heated to boiling. The precipitate that separated upon cooling was removed, washed with water, and dried.

The crude product was suspended in water, the solid was dissolved by adding the minimum quantity of sodium hydroxide, and the resulting solution was filtered. Acidification of the filtrate gave 73.8 g. (93%) of crude product, m.p. 210–212°. Recrystallization from a mixture of methanol and water gave a crystalline product, m.p. 214–216°.

*Anal.* Calc'd for $C_{10}H_{10}N_2O_5$: N, 11.76. Found: N, 11.85.

*7-Carboxy-5-methoxyisatin.* Concentrated sulfuric acid (200 ml., *d.* 1.84) was stirred mechanically and heated to 85°. 2-Carboxy-4-methoxyisonitrosoacetanilide (35.7 g., 0.15 mole) was added portionwise over 30 min., maintaining the temperature at 85–90° during the addition. After the addition was complete, the mixture was heated at 90–95° for 15 min., then cooled and poured onto crushed ice (1 kg.). After two hours, the precipitate was removed, suspended in hot water, and dissolved by adding 40% sodium hydroxide. The solution was kept warm for 30 min., then neutralized with dilute hydrochloric acid (*p*H 7.0), treated with decolorizing charcoal, and filtered. The filtrate was made acid to Congo Red paper with hydrochloric acid and the precipitate was removed, washed with water, and dried. The yield was 20.5 g. (62%), m.p., 210° (dec.).

Attempts to purify this crude material were unsuccessful; however, when it was employed in subsequent reactions, products giving satisfactory analyses were obtained.

*5-Methoxyisatin* was prepared from *p*-anisidine by a modification (3) of the method of Bachman and Picha (1).

### PHENACYL DERIVATIVES

Substituted phenacyl halides were either prepared by the Friedel-Crafts reaction, using chloracetyl chloride and the appropriate benzene derivative, or else they were purchased. Table I summarizes the important data concerning these syntheses.

Phenacyl acetates were prepared in the conventional manner by the reaction of the phenacyl halides with sodium or potassium acetate. The data concerning these syntheses are summarized in Table I. A typical preparation follows:

*2,4-Dimethylphenacyl acetate.* A solution of sodium acetate trihydrate (27.2 g., 0.2 mole), water (100 ml.), and glacial acetic acid (10 ml.) was added to a solution of 2,4-dimethylphenacyl chloride (36 g., 0.2 mole) in ethyl alcohol (200 ml.) and the mixture was refluxed for 24 hours. The solution was chilled and the solid that separated was removed, washed with 50% aqueous ethanol, and dried. The yield was 27 g. (66%) m.p. 42–44°. Two recrystallizations of a sample from petroleum ether (b.p. 30–60°) gave white needles, m.p. 43–45°.

*Anal.* Calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.
Found: C, 69.85; H, 6.99.

### 3-HYDROXY-2-PHENYLCINCHONINIC ACID DERIVATIVES

*3-Hydroxy-6-methoxy-2-phenylcinchoninic acid* (X). 5-Methoxyisatin (17.7 g., 0.1 mole) was dissolved in 6 *N* potassium hydroxide (100 ml.) and heated on a steam-bath. A solution of phenacyl acetate (22.2 g., 0.125 mole) in warm ethanol (100 ml.) was added portionwise over a period of an hour. The mixture was refluxed for four hours after the addition was complete and then the alcohol removed by evaporation on a steam-bath. The residue was diluted with water (500 ml.), treated with decolorizing charcoal, and filtered. The filtrate was acidified with excess dilute hydrochloric acid and the product was separated, washed with water, and dried. The yield was 29.5 g. (100%).

The crude product was suspended in water (1.5 l.), the solid was dissolved by the addition of sodium bicarbonate, the solution was filtered, and the filtrate was acidified with excess hydrochloric acid. The product was removed, washed with water, and dried. The yield was 27.9 g. (95%), m.p. 196–197° (dec.). A second reprecipitation gave a good recovery of yellow solid which melted at 202–203° (dec.), resolidified then remelted at 224–225°.

*Anal.* Calc'd for $C_{17}H_{13}NO_4$: N, 4.74. Found: N, 4.68.

*Substituted 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acids* were prepared from the appropriate 7-carboxyisatin and substituted phenacyl acetate. In general, little difficulty was encountered in the reactions and the crude products were readily isolated. However, no convenient method of purification was discovered and it was necessary in most cases to resort to fractional precipitation. A summary of the reactions that were carried out appears in Table II. A typical preparation follows:

*3-Hydroxy-2-(p-methoxyphenyl)quinoline-4,8-dicarboxylic acid* (IV). 7-Carboxyisatin (31.0 g., 0.16 mole) was dissolved in 6 *N* potassium hydroxide (165 ml.). To this solution was added *p*-methoxyphenacyl acetate (45.0 g., 0.22 mole) dissolved in warm ethanol (125 ml.) and the mixture was refluxed for 10 hours. The reaction mixture was evaporated (to about 100 ml.) on a steam-bath and the residue was diluted with water (600 ml.). The solution was treated with decolorizing charcoal, filtered, and the filtrate was acidified with an excess of concentrated hydrochloric acid.

The gelatinous product was removed, suspended in water (1 l.), and dissolved by the addition of concentrated ammonium hydroxide (50 ml. of 28% $NH_3$). The resulting solution was filtered and 6 *N* hydrochloric acid (about 30 ml.) was added dropwise with vigorous mechanical stirring (a "Waring blendor" gives excellent results). The small quantity of precipitate that separated was removed and discarded. The addition of more 6 *N* hydrochloric acid (85 ml.) to the filtrate precipitated the bulk of the product, probably as the mono-ammonium salt. The solid was removed, suspended in water (500 ml.) and 6 *N* hy-

drochloric acid (25 ml.) was added slowly with stirring as before. The mixture was allowed to stand several hours, then filtered and the product was washed with water and dried.

After a second reprecipitation in the same manner, the product was dried, triturated with a small volume of cold ethanol, filtered, and dried. The yield of bright yellow powder was 22.5 g. (47%), m.p. 320–322° (dec.).

*Functional derivatives of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid.* A summary of these derivatives is given in Table III.

*Dimethyl 3-hydroxy-2-phenylquinoline-4,8-dicarboxylate* (XI). 3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (30.9 g., 0.1 mole) was added slowly with stirring and cooling to concentrated sulfuric acid (100 ml., *d.* 1.84). Absolute methanol (400 ml.) was added with cooling and the solution was refluxed for 24 hours. The mixture was cooled and poured onto crushed ice (2 kg.). The orange-yellow product was removed and washed with water. This solid was suspended in water (500 ml.) and aqueous sodium bicarbonate was added until the evolution of carbon dioxide ceased and the solution reacted basic to litmus paper. The insoluble material was removed, washed with water, and dried; the yield was 29 g. (88%). Two recrystallizations of a sample from methanol gave orange-yellow needles, m.p. 118–120°.

*Diethyl 3-hydroxy-2-phenylquinoline-4,8-dicarboxylate* (XII). The reaction involving 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (31.3 g., 0.098 mole), concentrated sulfuric acid (100 ml.), and absolute ethanol (400 ml.) was carried out in a fashion similar to that described for the dimethyl ester; yield, 28.7 g. (79%). Recrystallization from ethanol, then from cyclohexane, and finally from ethanol gave light yellow needles, m.p. 111–113°.

*3-Hydroxy-2-phenylquinoline-4,8-dicarboxamide* (XIII). Dimethyl 3-hydroxy-2-phenylquinoline-4,8-dicarboxylate (23.5 g., 0.07 mole) was dissolved in 7 *N* ammoniacal methanol (187 ml.). The mixture was heated in a steel autoclave at 100° for 24 hours. After cooling, the solid that separated was removed, washed with methanol, and dried. The yield was 20.5 g. (95%), m.p. 255–258°. Recrystallization after decolorization with charcoal of a sample using 2-methoxyethanol as a solvent gave pale yellow crystals, m.p. 257–258°.

*3-Acetoxy-2-phenylquinoline-4,8-dicarboxylic acid* (XIV). A suspension of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (21.65 g., 0.07 mole) in acetic anhydride (250 ml.) was stirred and slowly heated to boiling. Heating was continued until solution was effected (10 min.). The solution was cooled, refrigerated for 15 hours, and the nearly white solid removed. The product was washed with a little acetic anhydride, then with ether, and finally dried in a vacuum desiccator over potassium hydroxide. The yield was 21.5 g. (88%), m.p. 224–225° (dec.) when placed in a preheated bath at 205° and heated 1° per 10 seconds.

Attempts to purify this material further were not very successful. Two recrystallizations from acetic anhydride gave about 80% recovery for each operation; the product melted at 222–223° when determined as previously described. It was very difficult to free the product from acetic anhydride. Even after drying at 125° at reduced pressure over potassium hydroxide, poor analytical results were obtained.

*3-Butyryloxy-2-phenylquinoline-4,8-dicarboxylic acid* (XV). A suspension of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (21.05 g., 0.07 mole) in butyric anhydride (100 ml.) was stirred at 165° until solution was effected (10 minutes). The solution was filtered, cooled, and the product isolated in a manner similar to that described for the acetoxy derivative. The yield was 23.5 g. (89%), m.p. 204–205° when inserted in a bath preheated to 190° and heated 1° per 10 seconds. Attempts to purify this material were not very profitable. Recrystallization from butyric anhydride gave an 85% recovery of light yellow powder with the melting point unchanged.

*3-Caproyloxy-2-phenylquinoline-4,8-dicarboxylic acid* (XVI). 3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (24 g., 0.08 mole) was suspended in caproic anhydride (89 g., 0.41 mole) (18). The mixture was stirred and heated at 150° until solution was effected. The product was isolated in a manner similar to that described for the acetoxy derivative. The yield was 25 g. (76%), m.p. 184–186°. Recrystallization from ethyl acetate gave pale yellow crystals, m.p. 185.5–187.5°.

3-HYDROXY-2-PHENYLQUINOLINE-8-CARBOXYLIC ACIDS

These compounds were prepared by decarboxylation of the appropriate 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acids. The reactions which were carried out are summarized in Table IV. A typical run follows:

*3-Hydroxy-2-phenylquinoline-8-carboxylic acid* (XVII). 3-Hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (20 g., 0.065 mole) was suspended in nitrobenzene (170 ml.) and the mixture was refluxed. The solid dissolved quickly with the evolution of carbon dioxide. A yellow solid soon began to separate. After 15 to 30 minutes the mixture was cooled, filtered, and the solid washed with ether. The yield was 17 g. (99%), m.p. 314–315°. Recrystallization first from dimethylformamide (85 ml.), then from diethylene glycol monoethyl ether (Carbitol) (350 ml.) gave 12.6 g. of yellow plates, m.p. 316–318°.

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SUMMARY

Six 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acids containing *p*-chloro-, *p*-bromo-, *p*-amino-, *p*-methoxy-, *p*-phenyl-, and 2,4-dimethyl- substituents in the phenyl ring were prepared. Derivatives containing a chloro or a methoxy group in the 6- position of the quinoline nucleus were also synthesized. These quinoline derivatives were prepared by the Pfitzinger reaction using the appropriate 7-carboxyisatin and substituted phenacyl acetate. Two diesters, the diamide, and three 3-acyloxy derivatives of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid were prepared by conventional methods. Seven of the 3-hydroxy-2-phenylquinoline-4,8-carboxylic acids were decarboxylated to give the corresponding 3-hydroxy-2-phenylquinoline-8-carboxylic acids.

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