190–193° (dec.); 37 g. of 7-chlorocinchoninic acid was recovered after the hydrolysis.

A sample of the dihydrobromide crystallized from dilute hydrobromic acid decomposed at 184–186°.

Anal. Calcd. for $C_{15}H_{16}ON_2ClBr\cdot 2HBr$: C, 34.8; H, 3.5; N, 5.4. Found: C, 35.2; H, 3.7; N, 5.1.

7-Chloro-α-(2-piperidyl)-4-quinolinemethanol (SN 8153).[15]—Ring closure was carried out on 141 g. of the crude bromoketone dihydrobromide from the last experiment and the product was reduced under the conditions described elsewhere[4,7] to give 30.1 g. of crude carbinol dihydrochloride. The product was recrystallized from methanol after treatment with Norite to give 23.2 g. of colorless wedge-like crystals m. p. 206–209° (dec.) representing an over-all yield of 16.3% on the basis of cinconinic ester consumed.

Anal. Calcd. for $C_{15}H_{17}ON_2Cl\cdot 2HCl$: C, 51.5; H, 5.5; N, 8.0. Found: C, 51.1; H, 5.4; N, 7.8.

The free base, prepared from the dihydrochloride and recrystallized from 95% ethanol, melted at 173–174° with some change in crystal form around 130°.

Anal. Calcd. for $C_{15}H_{17}ON_2Cl$: C, 65.1; H, 6.2; N, 10.1. Found: C, 65.2; H, 6.5; N, 10.2.

5-Chloroquinoline-2,4-dicarboxylic Acid.—This acid was prepared from 4-chloroisatin (207 g.) by the Pfitzinger reaction in the manner described previously for the 7-chloro isomer, care being taken to avoid isolation of a monosodium salt. The dicarboxylic acid (86 g.) was obtained in 30% yield and an analytical sample, recrystallized from acetic acid, melted at 218–219° (dec.).

Anal. Calcd. for $C_{11}H_6O_4NCl$: C, 52.5; H, 2.4; N, 5.6. Found: C, 52.5; H, 2.5; N, 5.3.

5-Chlorocinchoninic Acid.—The decarboxylation of 58 g. of the above dicarboxylic acid was carried out as previously described to give 36.2 g. (76%) of crude 5-chlorocinchoninic acid, a sample of which when recrystallized from methanol had m. p. 254–255°.

Anal. Calcd. for $C_{10}H_6O_2NCl$: C, 57.8; H, 2.9; N, 6.8. Found: C, 57.8; H, 3.1; N, 6.5.

Ethyl 5-Chlorocinchoninate.—5-Chlorocinchoninic acid (34.3 g.) was refluxed with 220 ml. of purified thionyl chloride for two and one-half hours. The excess thionyl chloride was distilled off and the crystalline residue refluxed with 250 ml. of absolute ethanol. The ester was then isolated and distilled, b. p. 136–139° (0.2 mm.), to give 29.2 g. (75%) of material m. p. 64–65°. A sample crystallized from ligroin (60–70°) melted at 65–65.5°.

Anal. Calcd. for $C_{12}H_{10}O_2NCl$: C, 61.2; H, 4.3; N, 5.9. Found: C, 60.9; H, 4.5; N, 5.8.

Attempts to condense this ester with ε-benzamidocaproic ester were unsuccessful.

α-(2-Piperidyl)-4-quinolinemethanol[6] (SN 2549).—The procedure and experimental conditions used were those reported by Sargent[5] for the 6-methoxy analog.

From 250 g. of ethyl cinchoninate[16] and 337 g. of ethyl ε-benzamidocaproate[17] there was obtained 280 g. of bromoketone dihydrobromide. By acidification of the basic aqueous phase after the chloroform extraction, 40 g. of crude cinchoninic acid was recovered. The salt of the bromoketone (195 g.) was converted to 89 g. of the crude carbinol dihydrochloride by ring closure and reduction. The free base (28 g.) was obtained from 40 g. of the salt and melted at 144–145° in agreement with the literature.[6]

Summary

The preparation and characterization of 4-chloro and 6-chloroisatin and their conversion to 5-chloro and 7-chlorocinchoninic acids and esters is described.

The synthesis of 7-chloro-α-(2-piperidyl)-4-quinolinemethanol is reported and the preparation of the previously known α-(2-piperidyl)-4-quinolinemethanol by an improved procedure is noted.

(15) The Survey number, designated SN, identifies a drug in the Records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

(16) Kindly supplied by Dr. R. C. Elderfield, Columbia University.

(17) Kindly supplied by Dr. C. C. Price, the University of Illinois.

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The Synthesis of Potential Antimalarials. 2-Phenyl-α-(2-piperidyl)-4-quinolinemethanols[1,2]

BY M. M. RAPPORT,[2a] A. E. SENEAR, J. F. MEAD AND J. B. KOEPFLI

The design of more effective antimalarials has of necessity been largely based on empiricism, and any biological information which might suggest a more rational approach has been worth exploring. Such a lead was furnished by the isolation of a crystalline product from the *in vivo* action of rabbit liver on quinine by Kelsey, Geiling, *et al.*,[3] and the evidence presented by Mead and Koepfli,[4] that the product was a carbostyril analog of quinine resulting from oxidation at the 2-position of the quinoline portion of the molecule. Furthermore, some early plasma-level studies by Shannon and collaborators[5] could be interpreted as indicating cinchonine to be *inherently* a more potent antimalarial than quinine, though of about equal potency for practical purposes because of its more rapid degradation *in vivo*. This suggested the possibility of increasing the effectiveness of the cinchonine type of antimalarial by the introduction of a substituent into the 2-position of the quinoline ring, precluding oxidation to a carbostyril. Experiments leading to the preparation of a "blocked" dihydrocinchonine will be described in a forthcoming report.[6]

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

(2) Presented in part at the program of the Division of Medicinal Chemistry at the Atlantic City meeting of the American Chemical Society, April, 1946.

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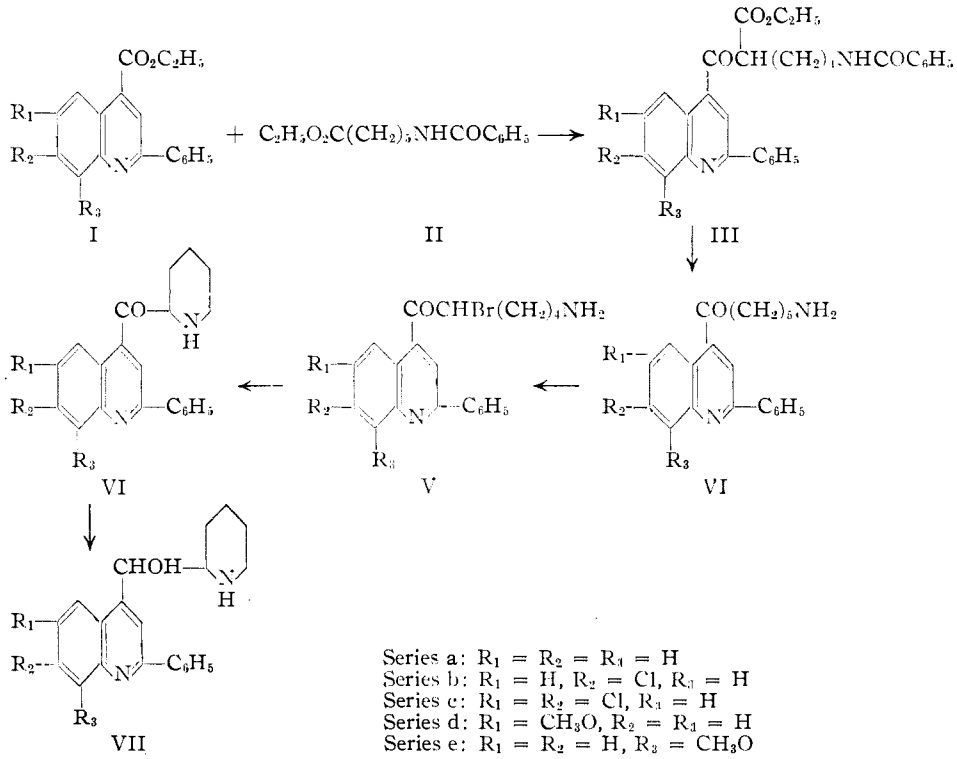
(3) Kelsey, Geiling, Oldham and Dearborn, *J. Pharmacol.*, **80**, 391 (1944).

(4) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(5) Dr. James A. Shannon, private communication.

(6) Mead, Rapport and Koepfli, THIS JOURNAL, **68**, 2704 (1946).



Beginning in 1942, E. R. Buchman and collaborators had begun the exploration of α-(2-piperidyl)-4-quinolinemethanols originally synthesized by Ainley and King[7] and had greatly improved the general method of synthesis,[8] making more accessible these compounds of proven antimalarial efficacy. Difficulties which were being encountered in attempts to introduce a blocking group into the quinoline nucleus of various cinchona alkaloids,[6] together with the fact that the Ainley and King type of compound may be regarded as a simplified quinine, suggested the preparation of the 2-phenylquinolinemethanols described in this report as a means of exploring the effect of a quinoline-2 substituent in drugs resembling quinine.

The preparation of the carbinols VIIa to VIIe followed with some modifications the method of Ainley and King[7] as improved by Sargent.[8] In the 2-phenyl series, the intermediates appear to be more stable than those in the original Ainley and King synthesis and it was not necessary to employ some of the precautions suggested by them and by Sargent.

The 2-phenylcinchoninic esters (I) were obtained by esterifying the corresponding acids by the procedure employed by Ainley and King to esterify cinchoninic acid.[7] The 2-phenylcinchoninic acids, Ib and Ie, were prepared by the Doebner method[9] from substituted anilines. The Pfitzinger procedure,[10] in which an appropriately substituted isatin is condensed with acetophenone, was employed in the case of the acids corresponding to the esters Ia, Ic, and Id, and as a check on the structure of Ib.

The procedure reported in the patent literature[11] for the preparation of 5,6-dichloroisatin was not practical and one reported by Sandmeyer[12] led to a mixture, difficult to separate, in which the 4,5-isomer predominated. Therefore 5,6-dichloroisatin was prepared in good yield by the direct chlorination of 6-chloroisatin[13] and the structure confirmed by oxidation[14] to 4,5-dichloroanthranilic acid.

The esters (I) were condensed with ethyl ε-benzamidocaproate (II) in the presence of sodium amide. The crude condensation mixture (containing III) was hydrolyzed with a strong acid to give the aminoketones (IV), isolated as the hydrobromides; these salts were brominated in warm hydrobromic acid to give the α-bromoketone (V) hydrobromides. The ring closure (V → VI) was effected by shaking the α-bromoketone (V) hydrobromides with aqueous-ethanolic sodium carbonate. The α-2-piperidyl ketones (VI) were not isolated, but the reaction mixture was hydrogenated directly with Adams catalyst to give the desired carbinols (VII). In certain cases 2-

(7) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).
(8) Sargent, THIS JOURNAL, **68**, 2688 (1946).
(9) Doebner, *Ann.*, **249**, 105 (1888).
(10) Pfitzinger, *J. prakt. Chem.*, **56**, 283 (1897).
(11) German Patent 281,052 (July 20, 1913).
(12) Sandmeyer, *Helv. Chim. Acta*, **2**, 241 (1919).
(13) Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946).
(14) Sumpter and Jones, *ibid.*, **65**, 1802 (1943).

phenylcinchoninic acids, from unreacted I, were recovered after the hydrolysis step (III → IV) and taking these recoveries into account, the over-all yields of the dihydrochlorides of the carbinols VIIa, VIIb and VIId, from the esters (I) were 30–39%; that of the free base of VIIe, 35%, and of the free base of VIIc, 3.1%.

No diastereomers of the carbinols (VII) have been detected among the products of hydrogenation of the α-2-piperidyl ketones (VI), although both isomers predicted by the presence of two centers of asymmetry in the carbinols have been isolated in cases where the quinoline-2 position was unsubstituted.[8]

The 8-hydroxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol was obtained directly from VIIe in 90% yield by hydrolysis.

An attempt was made to prepare the 5-chloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol isomeric with VIIb. The requisite 5-chloro-2-phenylcinchoninic acid was prepared from 4-chloroisatin[13] by the Pfitzinger procedure.

As in analogous instances[13,15] where the quinoline nucleus is substituted in the 5-position, esterification of the cinchoninic acid could only be effected through the acid chloride and the ester would not condense with II.

The antimalarial activity of the carbinols (VII) will be reported elsewhere[16] but it may be stated that the activity of 2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIa), the first of this series to be prepared, proved to be many times that of the unsubstituted α-(2-piperidyl)-4-quinolinemethanol[7,13] and warranted the further exploration of quinolinemethanols featuring a quinoline-2 substituent. Although the hypothesis which led to this series of drugs envisioned a "blocking" effect in the quinoline-2 position, there is no reason to suppose that some other mechanism may not be responsible for the increased antimalarial activity.

Experimental[17]

In order to avoid needless repetition, a detailed experimental procedure will be given for Series a, and only the pertinent modifications of this procedure for the subsequent series.

Series a

ε-(2-Phenylcinchoninyl)-*n*-amylamine (IVa) Dihydrobromide.—To 38 g. (1.65 mole) of powdered sodium amide (prepared according to Sargent[8]) in a 3-necked, 5-liter flask equipped with a Hirshberg stirrer and a condenser protected with a soda-lime tube, a solution of 360 g. (1.30 mole) of ethyl 2-phenylcinchoninate (Ia)[10,18] and 345 g. (1.31 mole) of ethyl ε-benzamidocaproate (II)[19] in 675 ml. of dry, thiophene-free benzene was added. The flask was then heated at 90° for twenty-two hours with constant stirring.

The reaction mixture was cooled in an ice-water-bath while a solution of 1.2 l. of concentrated hydrochloric acid and 1 l. of water was added. The stirrer was then replaced with a stillhead, and the benzene steam distilled until the temperature of the vapors reached 108°. After substituting a condenser for the stillhead, refluxing was continued for forty hours. The solution was then cooled and made alkaline (*p*H 10–12) with 50% (by weight) sodium hydroxide solution (920 ml.). The ketone was extracted with 1.5 l. of chloroform in several portions. After drying over sodium sulfate the chloroform layer was extracted with 750 g. of 40% hydrobromic acid. The chloroform was removed from the hydrobromic acid layer by heating on a steam-bath and stirring for thirty minutes. The increase in weight of the solution was then found to be 304 g.

Upon chilling, crystals of the ketone IVa dihydrobromide separated out and a small sample was isolated. After two recrystalizations from 96% ethanol, it was obtained as yellow clusters of needles, m. p. 225–227° (dec.).

Anal. Calcd. for $C_{21}H_{22}ON_2 \cdot 2HBr$: C, 52.5; H, 5.0; N, 5.8. Found: C, 52.8; H, 5.1; N, 5.7.

ε-Bromo-ε-(2-phenylcinchoninyl)-*n*-amylamine (Va) Dihydrobromide.—The hydrobromic acid suspension of the salt of the ketone IVa in the last experiment was heated to 85°, and, with mechanical stirring, a solution of 138 g. of bromine (90% of the theoretical required by the increase in weight) in 275 ml. of 40% hydrobromic acid was added over a twenty-minute period. The temperature was kept at 85–90°; the product began to crystallize out before all the bromine was added. The mixture was heated to the boiling point and 250 ml. of 40% hydrobromic acid was added, but the product did not dissolve. The reaction mixture was chilled, and the product crystallized as a solid mass. It was collected on a sintered glass funnel, washed by suspension in isopropanol to remove hydrobromic acid, then with acetone until the filtrate was colorless, and finally with ether. After drying *in vacuo* over sodium hydroxide, 334.5 g. of a light yellow powder was obtained, m. p. 210.5–212° (dec.). An additional crop of 41 g., m. p. 210–211°, was obtained by concentration of the mother liquors to half the volume. The total yield was 375 g. (52%).

A sample recrystallized for analysis from methanol–isopropyl ether was obtained as yellow prisms, m. p. 197–198° (dec.).

Anal. Calcd. for $C_{21}H_{21}ON_2Br \cdot 2HBr$: C, 45.1; H, 4.2; N, 5.0. Found: C, 45.1; H, 4.4; N, 4.9.

By acidifying the aqueous phase from the chloroform extraction of the ketone and washing the precipitate with ethanol to remove benzoic acid, 96 g. of crude cinchophen was recovered.

2-Phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIa), (SN-8538).[16]—To a suspension of 140 g. (0.25 mole) of the salt of the bromoketone Va in 2.2 l. of absolute ethanol in a 4-liter bottle, 735 ml. of 15% (by weight) sodium carbonate solution was added. After displacing the air with nitrogen, the bottle was stoppered and shaken mechanically for fifty minutes; 3.0 g. of platinum oxide was then added, and the bottle filled with hydrogen. The reduction, at room temperature under atmospheric pressure of hydrogen, was allowed to proceed for four hours, at which time the rate of hydrogen absorption had fallen from 100 ml./min. initially to 1 ml./min. The total uptake was 6.7 l., theory required 7.1.

The catalyst and precipitated salts were filtered off, and the ethanol was removed under reduced pressure. After decanting the aqueous phase, the residual oil was rinsed with water and dissolved in 1 l. of absolute ethanol. This solution was filtered and 50 ml. of concentrated hydrochloric acid added. The precipitate was filtered, washed with acetone, and dried to give 71 g. of a light pink powder, m. p. 226–228° (dec.). Recrystallization was effected as follows. Twenty-five grams of crude product was dissolved in 190 ml. of boiling water containing 3 ml. of con-

(15) Buchman and Howton, *ibid.*, **68**, 2718 (1946).

(16) The Survey number, designated SN, identifies a drug in the Records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

(17) All melting points are corrected. The microanalyses were performed by Dr. Gertrude Oppenheimer and Mr. G. A. Swinhart.

(18) Dr. R. C. Elderfield, Columbia University, kindly supplied additional quantities of this material.

(19) All of this material was kindly supplied by Dr. C. C. Price of the University of Illinois.

centrated hydrochloric acid. 1.15 Liters of acetone was added, and the solution chilled overnight to give 18.2 g. of pure, almost colorless prisms of dihydrochloride hemihydrate, m. p. 230–230.5° (dec.).

Anal. Calcd. for $C_{21}H_{22}ON_2 \cdot HCl \cdot 1/2H_2O$: C, 63.0; H, 6.3; N, 7.0. Found: C, 62.8; H, 6.8; N, 6.9.

From 86% ethanol the compound crystallized as stout, colorless prisms of the monohydrochloride monohydrate, m. p. 221–222° (dec.).

Anal. Calcd. for $C_{21}H_{22}ON_2 \cdot HCl \cdot H_2O$: C, 67.6; H, 6.8; N, 7.5. Found: C, 67.7; H, 6.4; N, 7.3.

The free base VIIa was obtained by neutralizing an alcoholic suspension of the dihydrochloride with 5 *N* sodium hydroxide, removing the solvent, and crystallizing the dry residue from isopropyl ether. The crystals were either colorless needles or flat prisms, m. p. 141.5–143°.

Anal. Calcd. for $C_{21}H_{22}ON_2$: C, 79.2; H, 7.0; N, 8.8. Found: C, 79.4; H, 7.2; N, 8.9.

From methanol the compound crystallized beautifully as colorless long prisms containing one molecule of solvent and melting with effervescence at 91–94°.

Anal. Calcd. for $C_{21}H_{22}ON_2 \cdot CH_3OH$: C, 75.4; H, 7.5; N, 8.0. Found: C, 75.3; H, 7.3; N, 8.2.

Series b

Ethyl 7-Chloro-2-phenylcinchoninate (Ib).—A large-scale preparation of 7-chloro-2-phenylcinchoninic acid using the Doebner reaction as described by Borsche[20] was carried out and the acid m. p. 249–254° (after sintering at 190°) obtained in 35% yield. Since the possibility existed that the Doebner reaction with *m*-chloroaniline, benzaldehyde and pyruvic acid might lead to the 5-chloro isomer the 7-chloro-2-phenylcinchoninic acid was also prepared from 6-chloroisatin[13] by the Pfitzinger reaction in 45% yield. The acids obtained by the two methods were identical and were esterified in the usual way with sulfuric acid in absolute ethanol to yield the same ester Ib (73%) which after recrystallization from ethanol melted at 89–90°.

Anal. Calcd. for $C_{18}H_{14}O_2NCl$: C, 69.4; H, 4.5; N, 4.5. Found: C, 69.6; H, 4.6; N, 4.2.

ε-(2-Chloro-2-phenylcinchonyl)-*n*-amylamine (IVb) Dihydrobromide.—The condensation of 134 g. of ethyl 7-chloro-2-phenylcinchoninate (Ib)[18] and 118 g. of the caproic ester II[19] in benzene (250 ml.) with sodium amide from 12.5 g. of sodium was carried out in the usual way. However 245 ml. of concentrated sulfuric acid in 350 ml. of water was used for the hydrolysis of IIIb and when 33% (by weight) sodium hydroxide was used to bring the solution to alkalinity it was necessary to add additional water to prevent the precipitation of sodium sulfate.

The chloroform solution (500 ml.) of the ketone (corresponding to IVb) was not dried but added directly to 600 ml. of 20% hydrobromic acid. A yellow solid crystallized out of the two-phase mixture which was filtered off, washed with acetone and dried to give 99.4 g. (45%) of yellow crystals melting at 264–269°. A sample of the ketone IVb dihydrobromide recrystallized from methanol melted at 262–263°.

Anal. Calcd. for $C_{21}H_{21}ON_2Cl \cdot 2HBr$: C, 49.0; H, 4.5; N, 5.5. Found: C, 49.0; H, 4.8; N, 5.5.

The aqueous solution remaining after the previous chloroform extraction was acidified and extracted with ether to yield 64 g. of 7-chloro-2-phenylcinchoninic acid.

ε-Bromo-ε-(7-chloro-2-phenylcinchonyl)-*n*-amylamine (Vb) Dihydrobromide.—The ketone IVb dihydrobromide (96 g.) in 1 l. of 48% hydrobromic acid was brominated with 30 g. of bromine in 100 ml. of 48% hydrobromic acid under the conditions described for Series a except that additional hydrobromic acid was not added. The crude yellow crystalline (m. p. 264–267°) dihydrobromide of the bromoketone Vb weighed 101 g. (91%) and a sample recrystallized from methanol-isopropyl ether had m. p. 245–248° (dec.).

Anal. Calcd. for $C_{21}H_{20}ON_2Cl \cdot 2HBr$: C, 42.5; H, 3.7; N, 4.7. Found: C, 43.0; H, 3.8; N, 4.3.

7-Chloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIb), (SN 10,286).—Ring closure was carried out on 97.2 g. of the bromoketone Vb dihydrobromide in 1 l. of ethanol by means of 420 ml. of saturated sodium carbonate solution. The product was reduced after addition of 2.3 g. of platinum oxide (compare Series a). Instead of decanting the aqueous phase after removal of the ethanol, the residual red oil was taken up in chloroform. The chloroform after being dried and filtered was removed and the residual oil taken up in 100 ml. of absolute ethanol. The addition of 200 ml. of 5.9 *N* ethanolic hydrogen chloride precipitated the crude pink crystalline salt of VIIb, which after being washed with ethanol and acetone and dried weighed 27.7 g. and melted at 221–222° (dec.). For purification, the crude salt in 500 ml. of boiling methanol was precipitated with 900 ml. of isopropyl ether to give 24.7 g. (36%) of slightly colored crystalline dihydrochloride of VIIb, m. p. 225–226° (dec.).

Anal. Calcd. for $C_{21}H_{21}ON_2Cl \cdot 2HCl$: C, 59.2; H, 5.4; N, 6.6. Found: C, 59.3; H, 5.7; N, 6.4.

A sample of the above dihydrochloride was suspended in ethanol and treated with sodium hydroxide solution. The resulting precipitate was recrystallized several times from ethanol to give the colorless crystalline free base VIIb, m. p. 190–191°.

Anal. Calcd. for $C_{21}H_{21}ON_2Cl$: C, 71.5; H, 6.0; N, 7.9. Found: C, 71.6; H, 6.1; N, 7.6.

A sample of the dihydrochloride of VIIb from a preliminary experiment was converted to the free base as described. In this instance the product recrystallized from ethanol melted at 100°, resolidified and then melted at 151–152°. The analysis was for an ethanolate of the free base VIIb.

Anal. Calcd. for $C_{21}H_{21}ON_2Cl \cdot C_2H_5OH$: C, 69.2; H, 6.8; N, 7.0. Found: C, 69.3; H, 6.5; N, 6.8.

On examination it was found that the ethanolate of the free base VIIb changed to the non-solvated form on standing several weeks or after drying *in vacuo* at 78° for four hours; it was not possible, however, to convert the non-solvated to the solvated form by crystallization from ethanol.

Series c

5,6-Dichloroisatin.—A suspension of 30.0 g. (0.165 mole) of powdered (60 mesh) 6-chloroisatin[13] in 400 ml. of glacial acetic acid in a round-bottomed, 3-necked, 1-liter flask fitted with a mechanical glass stirrer, a gas inlet tube that dipped below the surface of the liquid, and an outlet tube, was cooled in a water-bath at 18–20°. Then, with vigorous stirring, chlorine was passed in for three hours, while keeping the bath at the above temperature. The chlorination was stopped, and air was passed through the reaction mixture for thirty minutes to remove some of the excess chlorine. Glacial acetic acid (200 ml.) was then added, and the solid was dissolved by refluxing. On cooling, the product crystallized in large orange-red prisms. After filtering, washing with acetic acid and ligroin and drying in the vacuum oven at 70°, 19.2 g. (54%) was obtained, m. p. 266–272° (dec.). After another crystallization from acetic acid, the melting point was 274–277° (literature,[11] 273–275°).

A sample of the above isatin was oxidized with 3% hydrogen peroxide to an anthranilic acid, m. p. 213.5–214.5°. The literature[21] gives the m. p. of 4,5-dichloroanthranilic acid as 213–214°, whereas the 3,4-isomer melts at 237–238°.

6,7-Dichloro-2-phenylcinchoninic Acid.—To a suspension of 75.1 g. (0.35 mole) of 5,6-dichloroisatin in 415 ml. of absolute ethanol, 50 g. (0.42 mole) of acetophenone was added followed by 208 ml. of 33% (by weight) potassium hydroxide. The deep purple reaction mixture was refluxed for eight hours in a water-bath at 95°. The solvents were then removed by evaporating overnight in a large dish on a hot water-bath. The solid cake was almost

(20) Borsche, *Ber.*, **41**, 3884 (1908).

(21) Villiger, *Ber.*, **42**, 3543 (1909).

completely dissolved in 2 l. of hot water, and, after cooling to 40°, the mixture was extracted with 1.25 l. of isopropyl ether in two portions. After removal of the dissolved ether at 100°, the hot solution was strongly acidified with concentrated hydrochloric acid. The deep orange-colored precipitate was filtered, washed with water, suspended in 2 l. of water, and dissolved by adding concentrated ammonium hydroxide. The solution was stirred until almost clear and then suction filtered from an insoluble, deep red by-product. The filtrate was heated to 100° and acidified with concentrated hydrochloric acid, and the precipitate collected and washed by suspension in 1 l. of water. Drying on clay and then at 100° under reduced pressure gave 95 g. (86%), m. p. 275–276° (dec.). For analysis, a sample was recrystallized from ethanol to give almost colorless clusters of prisms, m. p. 277–278° (dec.).

Anal. Calcd. for $C_{16}H_9O_2NCl$: C, 60.4; H, 2.9; N, 4.4. Found: C, 60.1; H, 3.0; N, 4.5.

The deep red by-product mentioned above, after three recrystallizations from ethanol, was obtained as flat, red prisms, m. p. 238° and would appear to be the result of condensation between two molecules of acetophenone and one of dichloroisatin with loss of one molecule of water.

Anal. Calcd. for $C_{24}H_{17}O_3NCl_2$: C, 65.7; H, 3.7; N, 3.4. Found: C, 65.8; H, 3.9; N, 3.2.

Ethyl 6,7-Dichloro-2-phenylcinchoninate (Ic).—To a suspension of 54 g. (0.17 mole) of 6,7-dichlorocinchophen in 270 ml. of absolute ethanol, 27 ml. of concentrated sulfuric acid was added and the mixture refluxed for 21 hours. The ester Ic (46.3 g.) (79%) was isolated in the usual way and an analytical sample, prepared by crystallization from ligroin (86–100°) and then ethanol, melted at 115°.

Anal. Calcd. for $C_{18}H_{13}O_2NCl_2$: C, 62.4; H, 3.8; N, 4.1. Found: C, 62.2; H, 4.1; N, 4.1.

ε-(6,7-Dichloro-2-phenylcinchoninyl)-*n*-amylamine (IVc) Hydrobromide.—The ester, Ic (70.1 g., 0.20 mole) and 57.3 g. (0.22 mole) of the caproic ester II[19] in 125 ml. of benzene was condensed in the presence of sodium amide from 9.2 g. (0.40 mole) of sodium as in Series a.

To the cold reaction mixture, a warm (50°) solution of 150 ml. of concentrated sulfuric acid and 300 ml. of water was added. The stirrer was replaced with a stillhead, and the benzene was steam distilled. After substituting a condenser for the stillhead and replacing the 40 ml. of aqueous distillate with an equal volume of water, refluxing was continued for eighty-nine hours. The reaction mixture was then diluted with 1.25 l. of water and heated to the boiling point, giving an insoluble dark oil and a yellow-brown solution. The oil was removed by suction filtering through a steam-jacketed funnel, and the filtrate was chilled and made alkaline with 50% (by weight) sodium hydroxide, keeping the temperature below 40° by cooling in an ice-bath. The ketone was extracted with chloroform; the chloroform layer was then washed with 500 ml. of water, dried over sodium sulfate, and evaporated to dryness under reduced pressure to give 15.9 g. of a dark brown oil. To this oil 15 ml. of 40% hydrobromic acid and 50 ml. of acetone were added. A clear solution was obtained by gently warming for fifteen minutes, and the solvents were then completely removed under reduced pressure. The residue was crystallized from 50 ml. of 69% ethanol. Filtering, washing with ethanol, then acetone and ether, and drying in the vacuum oven at 70° gave 10.9 g. of yellow needles.

The residue from the sulfuric acid extraction, which hardened on cooling, was reëxtracted with eight 500-ml. portions of 10% (by volume) sulfuric acid and worked up in the manner described to give an additional 20.2 g. of yellow needles, the total yield being 31.1 g.

The melting points of the various batches varied from 162–165° for the first crop to 168–174° for later crops but the material was used for the next step without further purification.

A sample of the compound, recrystallized from 96% ethanol to constant melting point, was obtained as faintly colored needles, m. p. 168–181°. Recrystallization from acetonitrile or acetic acid did not improve the melting point. The analysis was approximately correct for a monohydrobromide monohydrate.

Anal. Calcd. for $C_{21}H_{20}ON_2Cl_2 \cdot HBr \cdot H_2O$: C, 51.9; H, 4.8. Found: C, 52.4; H, 5.1.

ε-Bromo-ε-(6,7-dichloro-2-phenylcinchoninyl)-*n*-amylamine (Vc) Dihydrobromide.—To 130 ml. of 48% hydrobromic acid, 18.0 g. (0.037 mole) of the salt of ketone IVc was added. The mixture was heated to the boiling point and a solution of 5.9 g. (0.037 mole) of bromine in 12 ml. of 48% hydrobromic acid was added dropwise over a twenty-minute period with constant stirring. The mixture became so thick due to crystallization of the product that 45 ml. of 48% hydrobromic acid was added during the addition. When all the bromine had been added, the reaction mixture was heated at the boiling point for ten minutes. After chilling overnight, the product was filtered, pressed as dry as possible, and then washed abundantly with acetone. After drying *in vacuo* over phosphorus pentoxide, 21.4 g. (90%) of yellow prisms was obtained, m. p. 227–228° (dec.). Recrystallization of a sample from acetic acid did not alter the melting point.

Anal. Calcd. for $C_{21}H_{19}ON_2Cl_2Br \cdot 2HBr$: C, 40.2; H, 3.4. Found: C, 40.1; H, 3.5.

6,7-Dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIc), (SN 10,282).—To a suspension of 18.5 g. (0.029 mole) of the salt of the bromoketone Vc in 370 ml. of water and 740 ml. of ether in a 2-liter bottle, 220 ml. of 15% (by weight) sodium carbonate was added. After displacing the air with nitrogen, the bottle was stoppered and shaken mechanically for fifty minutes, giving an orange ether layer and a colorless aqueous layer. Considerable pressure had developed. The ether layer was dried over sodium sulfate and evaporated to dryness at reduced pressure under nitrogen, and the 10.5 g. of residue was taken up in 200 ml. of absolute ethanol and reduced in the usual manner with 0.7 g. of platinum oxide. After two and one-half hours the hydrogen uptake was 765 ml., the rate having fallen to 0.5 ml./min. from the 70 ml./min. initially; theory required 925 ml. The ethanol solution was filtered and concentrated under reduced pressure to 80 ml. and 3 ml. of 6 *N* ethanolic hydrochloric acid added. After standing overnight, the light pink precipitate which separated was filtered, washed with ethanol, acetone, and ether, and dried to give 2.25 g. (17%) of the dihydrochloride, m. p. 227° (dec.).

This material was suspended in 100 ml. of 96% ethanol, and, at the boiling point, 0.6 ml. of 50% (by weight) sodium hydroxide added. The solution was filtered with Norite and chilled overnight. The crystals which separated were collected, washed with ethanol, and dried to give 1.5 g. of light buff-colored flat prisms, m. p. 202–206° at 1°/min. from 185° after effervescence and resolidification. A sample of VIIc recrystallized for analysis from 96% ethanol, was obtained as colorless prisms, m. p. 204–206° under the conditions recorded above.

Anal. Calcd. for $C_{21}H_{20}ON_2Cl_2 \cdot C_2H_5OH$: C, 63.7; H, 6.1; N, 6.5. Found: C, 64.0; H, 6.4; N, 6.3.

Drying at 100° *in vacuo* removed the ethanol of crystallization from VIIc.

Anal. Calcd. for $C_{21}H_{20}ON_2Cl_2$: C, 65.1; H, 5.2; N, 7.2. Found: C, 64.8; H, 5.5; N, 7.0.

The monohydrochloride of VIIc crystallized as pale greenish-yellow needles from an ethanolic solution of the base to which one or two equivalents of ethanolic hydrochloric acid had been added, m. p. 235.5–237° (dec.) at 0.7°/min. from 200°.

Anal. Calcd. for $C_{21}H_{20}ON_2Cl_2 \cdot HCl \cdot 1/2H_2O$: C, 58.3; H, 5.1; N, 6.5. Found: C, 58.7; H, 5.1; N, 6.1.

The dihydrochloride of VIIc was obtained as light yellow microcrystalline needles, m. p. 229–230° (dec.) at 1°/min. from 205°, when a large excess of hydrochloric acid was added to an ethanolic solution of the base.

Anal. Calcd. for $C_{21}H_{20}ON_2Cl_2 \cdot 2HCl$: C, 54.8; H, 4.8; Ionic Cl, 15.4. Found: C, 55.2; H, 5.0; Ionic Cl, 15.2.

Series d

ε-Bromo-ε-(6-methoxy-2-phenylcinchoninyl)-*n*-amylamine (Vd) Dihydrobromide.—The condensation of 276 g. (0.90 mole) of ethyl 6-methoxy-2-phenylcinchoninate (Id)[13,22] and 237 g. (0.90 mole) of caproic ester II[19] in benzene (500 ml.) with sodium amide from 26 g. (1.13 mole) of sodium was carried out in the usual way. The hydrolysis was carried out after the addition of 700 ml. of concentrated hydrochloric acid and 500 ml. of water, the solution was then adjusted to *p*H 7.5 with 50% (by weight) sodium hydroxide and the ketone extracted with 2 l. of chloroform (128 g. of 2-phenylquininic acid was recovered from the aqueous phase). After drying over sodium sulfate, the chloroform solution was concentrated under reduced pressure to 750 ml. and extracted with 760 g. of 40% hydrobromic acid. Chloroform was removed from the aqueous phase by warming and stirring, and the increase in weight was then found to be 160 g.

To this solution of the ketone, 64.5 g. of bromine (88% of that required by the increase in weight) in 130 ml. of 40% hydrobromic acid was added rapidly at 80–85° with mechanical stirring. The reaction mixture was stirred in ten minutes, heated to the boiling point, rapidly filtered through a sintered glass funnel to remove some free acid (25 g.), and chilled in the cold room overnight. The product was collected on a sintered glass funnel, washed with isopropanol, acetone and ether, and then dried to give 101 g. of a light yellow powder, m. p. 170–171° (dec.). By concentration of the mother liquors a second crop of 27 g. decomposing 8° lower was obtained. The total yield was 128 g. (23%).

A sample of the dihydrobromide of Vd recrystallized twice from methanol–isopropyl ether was obtained as light yellow clusters of needles, m. p. 174–175° (dec.).

Anal. Calcd. for $C_{22}H_{23}O_2N_2Br \cdot 2HBr \cdot 2H_2O$: C, 42.3; H, 4.7; N, 4.5. Found: C, 42.5; H, 4.7; N, 4.4.

6-Methoxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIId), (SN 9848).—Ring closure was carried out on 104 g. (0.167 mole) of the salt of the bromoketone Vd in 1.75 l. of ethanol by means of 490 ml. of 15% (by weight) sodium carbonate solution. The product was reduced after addition of 2.5 g. of platinum oxide (compare Series a).

The catalyst and precipitated salts were filtered off, and the ethanol was removed under reduced pressure. A solid separated which was washed with water and dissolved in ethanol. The addition of excess ethanolic hydrochloric acid precipitated the yellow dihydrochloride which was washed with ethanol and acetone and dried to give 48.8 g., m. p. 240° (dec.).

Purification could be effected only through the free base which was obtained by neutralizing an alcoholic suspension of the dihydrochloride with 5 *N* sodium hydroxide, removing the solvent, and recrystallizing the residue from methanol. The crystals were stout rods or flat prisms containing one molecule of solvent and softening from 88–95°, partially fusing from 95–105°, then resolidifying and melting at 176.5–177.5°.

Anal. Calcd. for $C_{22}H_{24}O_2N_2 \cdot CH_3OH$: C, 72.6; H, 7.4; N, 7.4. Found: C, 72.8; H, 7.7; N, 7.6.

From isopropanol the free base VIId crystallized unsolvated as clusters of colorless, feathery needles, m. p. 175.5–176.5°.

Anal. Calcd. for $C_{22}H_{24}O_2N_2$: C, 75.8; H, 6.9; N, 8.0. Found: C, 75.5; H, 7.2; N, 8.2.

The monohydrobromide of VIId crystallized from 96% ethanol as colorless clusters of needles, m. p. 213.5–215° (dec.).

Anal. Calcd. for $C_{22}H_{24}O_2N_2 \cdot HBr$: C, 61.5; H, 5.9; N, 6.5. Found: C, 61.5; H, 6.4; N, 6.4.

(22) This ester was prepared from 2-phenylquininic acid in 73% yield [see Claus and Brandt, *Ann.*, **282**, 106 (1894)]. The 2-phenylquininic acid was prepared in 95% yield by the Pfitzinger reaction from 5-methoxyisatin (prepared by method of D. R. V. Golding, unpublished); it had previously been prepared [Doebner, *Ann.*, **249**, 105 (1888)] from *p*-anisidine in about 50% yield.

The dihydrochloride of VIId, precipitated from ethanol as small clusters of yellow needles, melted at 240.5–241° (dec.), and analyzed for a hemihydrate.

Anal. Calcd. for $C_{22}H_{24}O_2N_2 \cdot 2HCl \cdot 1/2H_2O$: C, 61.4; H, 6.3; N, 6.5. Found: C, 61.4; H, 6.4; N, 6.8.

Series e

Ethyl 8-Methoxy-2-phenylcinchoninate (Ie).—8-Methoxy-2-phenylcinchoninic acid, prepared from *o*-anisidine by the method of Doebner[9] in 27% yield, was esterified in the usual way. The ester Ie was obtained in 81% yield in the form of large, pale yellow prisms from absolute ethanol and melted at 106.5–107.5°.

Anal. Calcd. for $C_{19}H_{17}O_3N$: C, 74.3; H, 5.6; N, 4.6. Found: C, 74.6; H, 5.6; N, 4.8.

ε-(3-Methoxy-2-phenylcinchoninyl)-*n*-amylamine (IVe) Dihydrobromide.—The ester Ie (291 g., 0.95 mole) and 252 g. (0.95 mole) of the caproic ester II[19] in 560 ml. of benzene were condensed in the presence of sodium amide from 33.5 g. (1.46 mole) of sodium as in Series a.

The reaction mixture was cooled in an ice–water-bath while a solution of 725 ml. of concentrated hydrochloric acid and 500 ml. of water was added. The stirrer was then replaced with a stillhead, and the benzene was steam distilled until the temperature of the vapors reached 108°. After substituting a condenser for the stillhead and replacing the 225 ml. of aqueous distillate with an equal volume of 6 *N* hydrochloric acid, refluxing was continued for 29 hours. The solution was then cooled, diluted with 500 ml. of water, made alkaline (*p*H 9) with 50% (by weight) sodium hydroxide, and the ketone was extracted with 1.35 l. of chloroform. The chloroform extract was washed twice with equal volumes of dilute sodium hydroxide solution to remove 8-methoxycinchophen, small quantities of 50% sodium hydroxide being added to the aqueous phase until it retained a permanent deep yellow color after shaking with the chloroform. After drying over sodium sulfate, the chloroform layer was evaporated to dryness under reduced pressure to give 235 g. of a dark brown oil. Upon addition of 150 ml. of 48% hydrobromic acid to the oil, a large quantity of chloroform boiled off. Acetone (500 ml.) was added, and the solution obtained by warming was evaporated almost to dryness under reduced pressure. Upon standing, the residual oil slowly crystallized. The solid was collected on sintered glass, washed with acetone, isopropanol, and again acetone, and dried over calcium chloride and sodium hydroxide *in vacuo* to give 177 g. of a deep yellow powder, m. p. 102–108° with sintering from 95–101°. From the mother liquors and washings, by similar treatment, a second crop of 42 g. was obtained to give a total yield of 219 g. (44%).

A sample of 0.101 g. of the salt of the ketone IVe required 19.40 ml. of 0.0200 *N* silver nitrate to completely precipitate the bromine. The product was therefore the dihydrobromide of IVe, 0.101 g. of which would require 19.60 ml. of silver nitrate.

Recrystallization from 10% hydrobromic acid by addition of acetone gave yellow clusters of prisms, m. p. 103–111°. The compound was not further analyzed.

By acidifying the aqueous phase from the chloroform extraction and recrystallizing the precipitate from 1 l. of ethanol, 84 g. of 8-methoxycinchophen was recovered.

ε-Bromo-ε-(8-methoxy-2-phenylcinchoninyl)-*n*-amylamine (Ve) Dihydrobromide.—To a solution of 219 g. (0.43 mole) of the salt of the ketone IVe in 200 ml. of 48% hydrobromic acid at 100°, 63.5 g. (0.40 mole) of bromine in 100 ml. of 48% hydrobromic acid was added dropwise with mechanical stirring over a fifteen-minute period. The reaction mixture was then heated to boiling and allowed to cool overnight. The large clusters of yellow prisms which separated were collected on a sintered glass funnel, washed once with water, then abundantly with acetone, and finally with ether. After drying over calcium chloride and sodium hydroxide at 30 mm., 194 g. (70%) of a deep yellow powder was obtained, m. p. 141.5–142° (dec.). After three recrystallizations from 10% hydrobromic acid, a sample dried at room temperature was obtained as clusters

of long, yellow prisms, m. p. 146.5–147° (dec.). The analysis showed it to be a tetrahydrate.

Anal. Calcd. for $C_{22}H_{23}O_2N_2Br \cdot 2HBr \cdot 4H_2O$: C, 40.0; H, 5.0. Found: C, 40.2; H, 5.1.

The loss of water by further drying caused the compound to become orange in color and the decomposition point to be depressed 2°. The analysis then showed that only two molecules of water of crystallization remained.

Anal. Calcd. for $C_{22}H_{23}O_2N_2Br \cdot 2HBr \cdot 2H_2O$: C, 42.3; H, 4.7; Ionic Br, 38.3. Found: C, 41.9; H, 5.3; Ionic Br, 38.1.

8-Methoxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIe), (SN 12,240).—Ring closure was carried out on 110 g. (0.167 mole) of the salt of the bromoketone Ve in 1.8 l. of ethanol with 490 ml. of sodium carbonate solution. The product was reduced after addition of 1.0 g. of platinum oxide (see Series a). The reduction was allowed to proceed for 4.5 hours, at which time the rate of hydrogen absorption had fallen from 360 ml./min. initially to 0.3 ml./min. The total uptake was 5.3 l.; theory required 4.6 l.

The catalyst and precipitated salts were filtered off, the ethanol removed under reduced pressure and the solid which separated filtered and washed with ethanol, water, ethanol, and ether. After drying, VIIe weighed 40.3 g., m. p. 195–198° at 1.5°/min. from 180°. A second crop of 6.2 g. was obtained from the mother liquors to give a total yield of 46.5 g. (80%). Recrystallization from 96% ethanol gave colorless needles, m. p. 196–200° at 1°/min. from 180°. Further recrystallizations from several different solvents gave crystals of variable melting point in the range of 193–205°, depending upon the particular sample of VIIe at hand. Analytical samples were obtained melting at 194–196° and 197–202° at 1°/min.

Anal. Calcd. for $C_{22}H_{24}O_2N_2$: C, 75.8; H, 6.9; N, 8.0. Found: for sample, m. p. 194–196°, C, 75.9; H, 7.1; N, 8.0. Found: for sample, m. p. 197–202°, C, 76.1; H, 7.2; N, 8.2.

The monohydrobromide of VIIe crystallized from 96% ethanol as colorless clusters of needles, m. p. 215–217° (dec.) at 1°/min. from 190°.

Anal. Calcd. for $C_{22}H_{24}O_2N_2 \cdot HBr$: C, 61.5; H, 5.9; N, 6.5. Found: C, 61.5; H, 6.2; N, 6.8.

8-Hydroxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (SN 14,183).—The 8-methoxy-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (VIIe) (23.5 g.) was refluxed with 120 ml. of 48% hydrobromic acid for twenty-four hours. The reaction mixture was cooled, and the crystals which separated were collected, washed with water and acetone, and dried to give 27.0 g. of the dihydrobromide salt of the 8-hydroxycarbinol. This material was suspended in 1.35 l. of hot 96% ethanol, 10 ml. of 50% (by weight) sodium hydroxide was added, and the resulting solution filtered and concentrated at atmospheric pressure to 700 ml. On chilling overnight, rosets of yellow needles of the sodium salt separated which were filtered off, washed with ethanol and ether, and dried in the vacuum oven at 70° to give 17.6 g., m. p. above 320° (dec.). Concentration of the mother liquors gave an additional 4.6 g. of product, the total yield being 22.2 g. (*ca.* 90%). Analysis gave inconsistent results.

17.6 g. of the sodium salt was suspended in 400 ml. of 96% ethanol, and, at the boiling point, 53 ml. of 0.92 *N* hydrochloric acid was added. On boiling for one minute crystals began to separate from the clear solution. After chilling overnight, the pale yellow needles were collected, washed with ethanol, and dried to give 11.4 g., m. p. 200–202°. After recrystallization from ethanol, a sample of the free base melted at 201–202°. A dark green color reaction was obtained with ferric chloride.

Anal. Calcd. for $C_{21}H_{22}O_2N_2$: C, 75.4; H, 6.6; N, 8.4. Found: C, 75.5; H, 6.8; N, 8.3.

The monohydrochloride crystallized from 38% ethanol as clusters of long prisms, m. p. 227.5–228° (dec.) at 1.5°/min. from 220°.

Anal. Calcd. for $C_{21}H_{22}O_2N_2 \cdot HCl$: C, 68.0; H, 6.3; Ionic Cl, 9.6. Found: C, 68.0; H, 6.1; Ionic Cl, 9.8.

5-Chloro-2-phenylcinchoninic Acid.—A Pfitzinger reaction, carried out in the usual manner, with 183 g. of 4-chloroisatin[13] and 220 g. of acetophenone yielded 163 g. (57%) of 5-chloro-2-phenylcinchoninic acid in the form of colorless rectangular prisms (from methanol), m. p. 234–235° (dec.).

Anal. Calcd. for $C_{16}H_{10}O_2NCl$: C, 67.78; H, 3.55; N, 4.94. Found: C, 67.93; H, 3.57; N, 4.73.

Ethyl 5-Chloro-2-phenylcinchoninate.—5-Chloro-2-phenylcinchoninic acid could not be esterified in the usual way with ethanol and concentrated sulfuric acid. Accordingly 163 g. of the acid was converted through the acid chloride (compare esterification of 5-chlorocinchoninic acid[13]) to the crude ester which distilled at 194° (0.14 mm.) to give 122 g. (68%) of white crystalline solid melting at 57–59°. A sample for analysis crystallized from methanol in large white prisms, m. p. 59.5–60.5°.

Anal. Calcd. for $C_{18}H_{14}O_2NCl$: C, 69.35; H, 4.53; N, 4.49. Found: C, 69.49; H, 4.23; N, 4.19.

All attempts to condense ethyl 5-chloro-2-phenylcinchoninate with the caproic ester II[19] under a variety of conditions were unsuccessful (compare Buchman, *et al.*,[15] and Senear, *et al.*[13]).

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Summary

A number of new cinchoninic acids and esters have been prepared and improvements reported in the preparation of several previously known.

Six 2-phenyl-α-(2-piperidyl)-4-quinolinemethanols or substituted Ainley and King type compounds have been prepared; the increase in antimalarial activity of this type of compound occasioned by the quinoline-2 substituent has been noted.

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