Anal. Calcd. for $C_{15}H_{19}ClN_2O$: C, 64.62; H, 6.87; N, 10.05. Found: C, 64.64; H, 7.02; N, 9.76.

A solution of 131 g. (0.287 mole) of IIIb in 120 ml. of 48% hydrobromic acid was heated to about 50°, treated with a solution of 48 g. (0.3 mole) of bromine in 20 ml. of the same solvent, and maintained near the boiling point for five minutes (the further addition of bromine gave a crystalline compound, presumably perbromide). The solution was then concentrated *in vacuo* and the viscous residue diluted with *i*-propanol; after standing for a few hours, IVb was filtered off and washed with *i*-propanol; yield, 116 g. (78% calculated as dihydrobromide) of tan fluffy needles, m. p. 194° dec. A portion recrystallized from ethanol–water formed wedge-shaped crystals, m. p. 187–188° dec. The analysis (Found: C, 35.6; H, 3.4; N, 5.7) indicates a partial loss of hydrogen bromide.

IVb (103 g. = 0.2 mole) together with 2.5 liters of absolute ethanol, 400 ml. of 14% aqueous sodium carbonate and 100 g. of powdered anhydrous sodium carbonate was cyclized (two hours) and reduced (2.0 g. of catalyst, three hours) and the product worked up as in series a. Its solution in 55 ml. of ethanol was saturated with dry hydrogen chloride, diluted with 10 ml. of water and allowed to stand; yield of Vb dihydrochloride, 21.5 g. (27.3% from IVb, 9.6% over-all from Ib). This colorless solid was recrystallized from ethanol–water, needles, m. p. (prior sintering) 205–215° dec., analysis for $C_{15}H_{17}ClN_2O \cdot 2HCl \cdot 2.5H_2O$. Regeneration of Vb gave well-formed cube-like crystals, m. p. 175–176° from butanone–methanol (analysis for methanolate).

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot CH_3OH$: C, 62.23; H, 6.86; N, 9.07. Found: C, 62.27; H, 6.72; N, 9.47.

6,8-Dichloroquinolyl-4)-α-piperidylcarbinol (Vc) (SN-10278).[24]—Ic (190 g. = 0.703 mole) was condensed (twenty hours) and the product hydrolyzed (twenty-four hours) as in series a. The chloroform extracts were dried over anhydrous potassium carbonate and evaporated. To the residue (107.5 g.) was added 115.7 g. of 48% hydrobromic acid and the dark solution, on standing overnight at 0°, was transformed to a yellow crystalline mass. The solid (tiny yellow needles) was filtered off and washed with acetone until the washings were colorless; yield 71.1 g. plus 25.8 g. of a gray yellow powder recovered from the mother liquors (27% from Ic). After recrystallization from 48% hydrobromic acid, IIIc melted at 205–206° dec.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O \cdot 2HBr \cdot 2H_2O$: C, 35.39; H, 4.36; N, 5.50. Found: C, 35.08; H, 4.48; N, 5.09.

To a solution of 25.8 g. (0.508 mole) of IIIc in 28 ml. of water and 28 ml. of 48% hydrobromic acid, 8.75 g. (0.0547 mole) of bromine in an equal weight of 48% hydrobromic acid was slowly added, keeping the solution near the boiling point. On standing the mixture became filled with a bright yellow, granular mass which was filtered off and washed thoroughly with acetone, yield 21.3 g. (75.7%). After recrystallization from 48% hydrobromic acid, the tiny orange needles (IVc) melted at 209–210°.

Anal. Calcd. for $C_{15}H_{15}BrCl_2N_2O \cdot 2HBr$: C, 32.64; H, 3.11; N, 5.07. Found: C, 33.12; H, 3.44; N, 5.04.

A 5.51-g. (0.01-mole) portion of IVc was cyclized (*cf.* series b, four hours) and reduced (0.1 g. of catalyst, two hours) and the product taken up in chloroform as usual. Evaporation of solvent yielded an oil (4.2 g.) which (since a crystalline hydrochloride could not be obtained directly) was treated with 2.94 g. of oxalic acid and the resulting mixture was taken up in the minimum amount of boiling ethanol. Colorless needles formed on standing; acetone was added, and the oxalate was filtered and washed thoroughly with acetone; yield 1.35 g. (29.7%; over-all yield 6% from Ic). A portion was recrystallized from water, tiny colorless needles, m. p. 193–195° dec., analysis for $C_{15}H_{16}Cl_2N_2O \cdot C_2H_2O_4 \cdot 3H_2O$. The oxalate was treated with aqueous sodium hydroxide and the base extracted with chloroform; Vc crystallized from ethanol in fine colorless needles, m. p. 199.5–200.5°.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O$: C, 57.89; H, 5.18; N, 9.00. Found: C, 58.16; H, 5.11; N, 9.00.

Vc hydrochloride was precipitated from an ethanolic solution of the free base by passing in dry hydrogen chloride. The mixture was heated to boiling and water added until a clear solution was obtained. On standing, colorless needles formed which were rinsed with ethanol and dried, m. p. 197.5–200.5°, analysis for $C_{15}H_{16}Cl_2N_2O \cdot 2HCl \cdot H_2O$.[28]

Summary

(6-Chloroquinolyl-4)-α-piperidylcarbinol, (8-chloroquinolyl-4)-α-piperidylcarbinol and (6,8-dichloroquinolyl-4)-α-piperidylcarbinol have been prepared.

A number of halogenated cinchoninic acid derivatives have been described.

(28) Ultraviolet absorption spectrum, see Buchman and Golding, unpublished.

PASADENA 4, CALIF. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1043]

The Synthesis of Potential Antimalarials. 7-Chloro-α-(2-piperidyl)-4-quinolinemethanol[1]

BY A. E. SENEAR, HERBERT SARGENT,[2] J. F. MEAD[3] AND J. B. KOEPFLI

The work reported in this paper had as its objective the preparation of the 5-chloro and 7-chloro substituted α-(2-piperidyl)-4-quinolinemethanols, an extension of the exploration of the effect of halogen substituents in the benzene-ring portion of the Ainley and King type antimalarial.[4]

(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) Present address: U. S. Rubber Co., Passaic, New Jersey.

(3) Present address: Occidental College, Los Angeles, California.

(4) Buchman, Sargent, Meyers and Seneker, THIS JOURNAL, **68**, 2692 (1946).

The 7-chloro-α-(2-piperidyl)-4-quinolinemethanol was obtained in good yield from the requisite cinchoninic ester by the improved[5] Ainley and King procedure.[6] However the 5-chloro isomer could not be obtained, due no doubt to the steric effect of the 5-substituent. This same inability to effect condensation between a 5-substituted cinchoninic ester and ε-benzamidocaproic ester in the presence of sodamide has been encountered in other instances.[7]

(5) Sargent, *ibid.*, **68**, 2688 (1946).

(6) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(7) Buchman and Howton, THIS JOURNAL, **68**, 2718 (1946).

Of importance to this investigation was the development of suitable laboratory syntheses of 4-chloroisatin and 6-chloroisatin. Sandmeyer[8] has described the preparation from *m*-chloroaniline of a mixture of these two isomers which he did not attempt to separate. The Sandmeyer synthesis proved to be very satisfactory when carried out on a large scale under conditions similar to those described by Marvel and Hiers[9] for the preparation of isatin. A method for the separation of the two isomers, based on a fractional precipitation with acid, was worked out and it was found that they occur in about equal amounts in the mixture. The identity of each of the isomers was established by oxidation to the corresponding known anthranilic acid by the method of Sumpter and Jones.[10]

The 5-chloro and 7-chlorocinchoninic acids were prepared from the 4-chloro and 6-chloroisatins by the well-known Pfitzinger reaction in good yield. The ethyl ester of 7-chlorocinchoninic acid was obtained in the usual way by heating the acid with ethanolic hydrogen chloride; however, in the case of the 5-chlorocinchoninic acid, this method failed, presumably because of the steric effect of the halogen in the 5-position. The ethyl 5-chlorocinchoninate was therefore prepared via the acid chloride of the 5-chlorocinchoninic acid.

A considerable quantity of α-(2-piperidyl)-4-quinolinemethanol, originally prepared by Ainley and King,[6] was needed for pharmacological and clinical investigation and a short description is included in the experimental section of the preparation of this compound from ethyl cinchoninate in an over-all yield of 44% by the improved procedure.[5]

Experimental[11]

Separation of 4-Chloro and 6-Chloroisatin.—To a solution of 490 g. of chloral hydrate and 3.11 kg. of anhydrous sodium sulfate in 8 l. of water was added a solution of 342 g. of *m*-chloroaniline in 1.6 liters of water and 235 ml. of concentrated hydrochloric acid followed by a solution of 590 g. of hydroxylamine hydrochloride in 1 liter of water. The resulting suspension was heated to boiling and then cooled and extracted with 4 l. of ether. The ether was evaporated in an open pan leaving 493 g. (93%) of crude isonitroso-*m*-chloroacetanilide.[8] The finely ground crude material was added in small portions with stirring over a period of twenty minutes to 2.5 liters of concentrated sulfuric acid maintained at 80–85°. The reaction mixture was heated for fifteen minutes at 90–95° and poured over cracked ice. The red precipitate was filtered off and the filter cake suspended in 5 liters of water and brought into solution with the addition of 1 liter of 3 *N* sodium hydroxide. The deep red solution was filtered through Celite and the clear filtrate cautiously neutralized with concentrated hydrochloric acid during vigorous stirring. At the point where precipitation commenced (about *p*H 8) 100 ml. of concentrated hydrochloric acid in 500 ml. of water was added and the crude isatin which precipitated, filtered off after five minutes. Upon addition of an additional 500 ml. of concentrated hydrochloric acid to the filtrate, a second precipitate in the form of small orange plates was collected.

4-Chloroisatin.—The first precipitate above weighed 224 g., a yield of 46% from *m*-chloroaniline, and melted at 238–248°. Although this material contained a small amount of the isomer it was sufficiently pure for most purposes. A sample for analysis was obtained after several recrystallizations from acetic acid as red needles, m. p. 256.5–258°.

Anal. Calcd. for $C_8H_4O_2NCl$: C, 52.9; H, 2.2; N, 7.7. Found: C, 52.6; H, 2.3; N, 7.6.

A sample of the recrystallized isatin was oxidized[10] with hydrogen peroxide to an acid m. p. 140–141°. Cohn[12] gives 146–147° for the melting point of 6-chloroanthranilic acid.

6-Chloroisatin.—The second precipitate above weighed 145 g., a yield of 30% based on *m*-chloroaniline, and melted at 253–257° and was practically free from the 4-isomer. A sample from analysis for acetic acid melted at 258–259°.

Anal. Calcd. for $C_8H_4O_2NCl$: C, 52.9; H, 2.2; N, 7.7. Found: C, 53.0; H, 2.2; N, 8.0.

A sample was oxidized[10] in 76% yield to an anthranilic acid m. p. 237–238°. Cohn[12] gives 235–236° as the melting point of 4-chloroanthranilic acid. The acetyl derivative of this acid melted at 212–215° (literature,[12] 214°).

7-Chloroquinoline-2,4-dicarboxylic Acid.—Finely ground 6-chloroisatin (63.4 g.) was treated with 127 g. of 50% pyruvic acid in sodium hydroxide solution by the Pfitzinger procedure.[4,13] The resulting product, 83.1 g. (95%) melted at 282–284° with previous evolution of gas at 228–233°. A sample of the dicarboxylic acid crystallized from acetic acid in thin rectangular platelets m. p. 285–290° (dec.) with sintering at 238°.

Anal. Calcd. for $C_{11}H_5O_4NCl$: C, 52.5; H, 2.4; N, 5.6. Found: C, 52.5; H, 2.5; N, 5.7.

The dimethyl ester was prepared and crystallized from ethanol in poorly formed plates, m. p. 130–131°.

Anal. Calcd. for $C_{13}H_{10}O_4NCl$: C, 55.8; H, 3.6; N, 5.0. Found: C, 55.7; H, 3.6; N, 5.2.

The diethyl ester[14] melted at 95–96°.

Anal. Calcd. for $C_{15}H_{14}O_4NCl$: C, 58.6; H, 4.6; N, 4.6. Found: C, 58.7; H, 4.8; N, 4.4.

7-Chlorocinchoninic Acid.—The 7-chloroquinoline-2,4-dicarboxylic acid (83.1 g.) was decarboxylated by refluxing in nitrobenzene for one hour in 84% yield. A sample for analysis crystallized from acetic acid in colorless long platelets m. p. 290–291° (dec.).

Anal. Calcd. for $C_{10}H_6O_2NCl$: C, 57.8; H, 2.9; N, 6.8. Found: C, 57.8; H, 3.3; N, 6.3.

Ethyl 7-Chlorocinchoninate.—The above cinchoninic acid (55.4 g.) was esterified with ethanolic hydrogen chloride. The crude ester was crystallized from 300 ml. of ligroin (60–70°), after treatment with Norite, by cooling for several days at −5° and was obtained in 77% yield as large prisms, m. p. 33–35°. The ester, b. p. 145° (0.7 mm.), was recrystallized for analysis and melted at 35–36°.

Anal. Calcd. for $C_{12}H_{10}O_2NCl$: C, 61.2; H, 4.3; N, 5.9. Found: C, 60.9; H, 4.4; N, 5.6.

The picrate of this ester, crystallized from ethanol, melted at 173–174°.

Anal. Calcd. for $C_{18}H_{13}O_9N_4Cl$: C, 46.5; H, 2.8. Found: C, 46.2; H, 2.9.

ε-Bromo-ε-(7-chlorocinchoninyl)-*n*-amylamine Dihydrobromide.—Ethyl 7-chlorocinchoninate (138 g.)[14] and ethyl ε-benzamidocaproate (138 g.) were condensed in the presence of sodium amide (prepared from 16.5 g. of sodium) and the product was hydrolyzed and the resulting ketone brominated as described for analogous cases.[4,7] The salt of the bromoketone weighed 141 g. (47%) and had m. p.

(8) Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(9) Marvel and Hiers, "Organic Syntheses," Coll. Vol. I, 1941, p. 327.

(10) Sumpter and Jones, THIS JOURNAL, **65**, 1802 (1943).

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

(12) Cohn, *Chem. Zentr.*, **72**, II, 580 (1901).

(13) Pfitzinger, *J. prakt. Chem.*, **56**, 283 (1897).

(14) Prepared by Mr. Kurt Mislow.

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[6] 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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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1042]

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.

(2a) Present address: Cleveland Clinic, Cleveland, Ohio.

(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).