lization from methyl alcohol with the addition of a drop of 48% hydrobromic acid plus a few drops of water, bunches of colorless, rectangular plates, m. p. 197–213°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2 \cdot 2HBr$: C, 52.68; H, 5.38; N, 5.34. Found: C, 52.53; H, 5.40; N, 5.15.

The regenerated free base was an ether-soluble oil which did not crystallize even on long standing. With ethereal picric acid an oily picrate was obtained which crystallized from dioxane–water in square plates of indefinite melting point.

(6 - Methoxyquinolyl - 4) - α - N - (β - hydroxyethyl) - piperidylcarbinol (SN8284).[15]—In a tightly-stoppered bottle was placed 15.0 g. of VIII together with 70 ml. of methanol and 12.5 ml. of ethylene oxide (addition made at 0°). The mixture was allowed to stand at room temperature for three and one-half hours, at the end of which time the contents of the bottle were evaporated on a steam-bath to remove solvent. A slight excess, 22 g., of 48% hydrobromic acid was added to the residue, giving a crystalline mass which was diluted with hot ethanol, treated with Norite and centrifuged. The solution deposited sword-like needles which were filtered off and washed with *i*-propanol; yield, 11.0 g. A further purification was obtained by dissolving in hot methanol, again treating with Norite and evaporating solvent on the steam-bath; this yielded cube-like crystals, m. p. 152° (rapid heating; m. p. 184–221° on slow heating).

Anal. Calcd. for $C_{18}H_{24}N_2O_3 \cdot 2HBr \cdot 1.5H_2O$: C, 44.37; H, 5.59; N, 5.75. Found: C, 44.43; H, 5.56; N, 6.05.

A portion of this salt dissolved in a small amount of water was redeposited as needles m. p. 143–149°, resolidifying, and melting again at *ca.* 184–215°.

The free base was regenerated as a colorless viscous oil, very soluble in ether; from a solution of the base in ethanol the dihydrochloride was prepared, rectangular plates, m. p. 194–215°, analysis for $C_{18}H_{24}N_2O_3 \cdot 2HCl \cdot 1.5H_2O$.

Summary

A study has been made of the Ainley and King synthesis of (6-methoxyquinolyl-4)-α-piperidylcarbinol (VIII). Modifications of this synthesis have been developed which permit the convenient preparation of VIII in considerably improved over-all yield. The isomeric racemate, β-VIII, and several N-substituted derivatives have been described.

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Potential Antimalarials. (Chloroquinolyl-4)-α-piperidylcarbinols[1]

BY E. R. BUCHMAN, H. SARGENT, T. C. MYERS AND J. A. SENEKER

A study[2] made in this Laboratory of the Ainley and King[3] synthesis of V (R = 6-methoxyquinolyl-4) resulted in an improved preparative-scale method for this substance. In an extension of this work, we have now prepared Va,[4] Vb and Vc *via* the intermediates shown.

$$\underset{\text{I}}{RCOOC_2H_5} + \underset{\text{II}}{C_2H_5OOC(CH_2)_5NHCOC_6H_5} \longrightarrow$$

$$\underset{\text{III}}{RCO(CH_2)_5NH_2 \cdot 2HBr} \longrightarrow$$

$$\underset{\text{IV}}{RCOCHBr(CH_2)_4NH_2 \cdot 2HBr} \longrightarrow \underset{\text{V}}{RCHOH\text{-}\alpha\text{-piperidyl}}$$

Series a R[5] = 6-chloroquinolyl-4
b R = 8-chloroquinolyl-4
c R = 6,8-dichloroquinolyl-4

The esters (I) were prepared from appropriate chloroisatins by a method which had been employed by Work[6] to obtain 6-chlorocinchoninic acid. In addition to the intermediates required in this research, a number of other halogenated cinchoninic acid derivatives are described in the Experimental Part.

The authors are grateful to Dr. D. R. Howton for aid in preparing the manuscript.

Experimental[7]

Halogenated Cinchoninic Acid Derivatives

Ethyl 6-Chlorocinchoninate (Ia).[8]— 5-Chloroisatin (VIa)[9] (m. p. 252.5–254.5°) from chlorination[10] of 300 g. (2.04 moles) of isatin was condensed[6] with pyruvic acid.[11] The reaction mixture, after standing for fourteen hours, was heated to boiling for one-half hour and then made strongly acid by addition of 12 *N* hydrochloric acid (half potassium salt precipitates first). The crude 6-chloroquinoline-2,4-dicarboxylic acid (VIIa)[6] was filtered off and washed with water; yield 320 g. (62% from isatin). A sample was recrystallized from 50% ethanol; m. p. (rapid heating) 265° dec. and resolidification; on slow heating, this m. p. was not observed.

Anal. Calcd. for $C_{11}H_6ClNO_4$: C, 52.50; H, 2.40; N, 5.57. Found: C, 52.30; H, 2.98; N, 5.51.

Crude VIIa (308 g. = 1.22 moles) was decarboxylated (five hours at *ca.* 200°; see under Ib) and the resulting crude 6-chlorocinchoninic acid (VIIIa)[6] esterified.[8] After excess ethanol was removed *in vacuo*, the residual sirup was cooled and treated with ice and water (precipitation

(1) The work described in this paper 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) Sargent, THIS JOURNAL, **68**, 2688 (1946).

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

(4) In series a-c, only one of the two diastereoisomeric racemic forms of V was isolated; the other form (*cf.* ref. 2) was presumably formed but in relatively smaller amount.

(5) Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946), describe the preparation of V (R = 7-chloroquinolyl-4); Campbell and Kerwin[8] have reported carbinolamines $RCHOHCH_2NR'_2$ in which R = 6-chloroquinolyl-4.

(6) Work, *J. Chem. Soc.*, 426 (1942).

(7) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver 2, Colorado.

(8) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946).

(9) Lit. in Sumpter, *Chem. Rev.*, **34**, 404 (1944).

(10) Liebermann and Krauss, *Ber.*, **40**, 2500 (1907).

(11) A technical product (*ca.* 50% aqueous solution) supplied by the Calco Chemical Division of the American Cyanamid Company was used directly.

of VIIa diethyl ester[12] together with some Ia). The solution was made alkaline with potassium carbonate, extracted with ethyl ether and the extracts were freed of ether. The monoester picrate was precipitated in ethanolic solution; a sample was recrystallized, thin needles from ethanol, m. p. 160.1–160.6°, analysis for $C_{18}H_{13}ClN_4O_9$. Ia was regenerated and recrystallized from 60–70° petroleum ether; yield 90 g. (19.5% from isatin), m. p. 63–64° (lit.[8] m. p. 68–69°); b. p. (2 mm.) 160–165°, analysis for $C_{12}H_{10}ClNO_2$.

To establish the position of the carbethoxy group in Ia, a sample (0.15 g.) was mixed with 0.15 g. of a palladium-on-barium-carbonate catalyst and 0.15 g. of anhydrous potassium carbonate in 15 ml. of ethanol and the mixture was shaken with moist hydrogen at atmospheric pressure and room temperature; 19.4 ml. was absorbed in one hour. After centrifuging, the solution was evaporated, and the residue taken up in isopropyl ether and converted to the picrate, m. p. 186.3–187.0°[13] from ethanol, unchanged after mixing with authentic ethyl cinchoninate[14] picrate.

Ethyl 2,6-Dichlorocinchoninate (XI).—Eight grams of VIa and 36 ml. of acetic anhydride plus a drop of sulfuric acid were refluxed for one and one-half hours; on cooling yellow crystals formed which were filtered off and recrystallized from *i*-propyl ether–*n*-butanol, yield 4.1 g., m. p 168–169° (analysis see below). Three grams of this N-acetyl-VIa gave[15] 1.5 g. of 2-hydroxy-6-chlorocinchoninic acid (IX); a portion was recrystallized from acetic acid, m. p. above 315°.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.70; N, 6.26. Found (N-acetyl-VIa): C, 53.57; H, 2.66; N, 6.49. Found (IX): C, 53.75; H, 2.76; N, 6.00.

Ethyl 2-hydroxy-6-chlorocinchoninate (X) was obtained by refluxing IX (1.4 g.) with 100 ml. of ethanol and 2 ml. of sulfuric acid for forty hours. On cooling, fine matted yellow needles formed which were filtered off and recrystallized from ethanol, m. p. 236.5°.

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

A mixture of 0.5 g. of X and 1.2 ml. of phosphorus oxychloride was refluxed for one-half hour (bath at 140°) and the product cooled, poured into water, washed with dilute alkali and recrystallized from ethanol, long white needles, m. p. 132.5–132.8°.

Anal. Calcd. for $C_{12}H_9Cl_2NO_2$: C, 53.36; H, 3.36; N, 5.19. Found: C, 53.55; H, 3.33; N, 4.93.

The catalytic reduction of XI (conditions see under Ia; interrupted after *ca.* one molecular equivalent of hydrogen had been absorbed) gave a mixture from which ethyl cinchoninate was isolated as the picrate.[13]

6-Chloro-2-methylcinchoninic acid was obtained by a procedure based on that[16] for 2-methylcinchoninic acid, m. p. 170.5–171.5° from 50% ethanol.

Anal. Calcd. for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.33; H, 3.63; N, 6.10.

Ethyl 6-Bromo-2-methylcinchoninate.—Crude 5-bromoisatin[9] (obtained in nearly theoretical yield on adding the requisite amount of bromine to a stirred aqueous suspension of isatin) was converted[19] to 6-bromo-2-methylcinchoninic acid,[17] m. p. 272–273° from ethanol.

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

The ester was obtained in the usual manner, m. p. 110–111° from ethanol.

Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 52.81; H, 4.08; N, 4.61.

Ethyl 6-Bromoquinoline-2,4-dicarboxylate.—6-Bromoquinoline-2,4-dicarboxylic acid, m. p. 314° dec. (prepared from 5-bromoisatin and pyruvic acid) was esterified with ethanolic sulfuric acid; m. p. 108–109° from *i*-propyl ether.

Anal. Calcd. for $C_{15}H_{14}BrNO_4$: C, 51.15; H, 4.00; N, 3.98. Found: C, 51.13; H, 4.06; N, 4.16.

Ethyl 8-Chlorocinchoninate (Ib).—7-Chloroisatin (VIb)[18] was prepared by a method based on that for isatin.[19] In a representative run, 411 g. (3.22 moles) of o-chloroaniline[20] gave crude o-chloroisonitrosoacetanilide (XII) which was purified by reprecipitation with hydrochloric acid from its solution in warm 5% sodium hydroxide. The wet filter cake was dissolved in ethyl ether, the aqueous phase was separated and the ether was removed by distillation; yield 398 g. (61%). This dry XII (200 g. = 1 mole) was added[19] to 2 liters of C. P. sulfuric acid at 80°[18] and the solution maintained at 95°[18] for fifteen minutes. The product was worked up in the usual manner[19]; yield of crude dry VIb 139.2 g. (76.7%).

The crude wet VIb from 790 g. (3.98 moles) of XII was condensed in four portions with pyruvic acid[11] (see under Ia). The crude dicarboxylic acid (412 g.) was mixed with 1 liter of nitrobenzene and the slurry stirred and heated at *ca.* 185° for seven hours. The reaction mixture was diluted with 1 liter of petroleum ether (60–70°), filtered and the solid washed with petroleum ether. The product (341 g.) was refluxed for twenty-three hours with 8 liters of ethanol and 400 ml. of concentrated sulfuric acid. After concentrating *in vacuo* to 2 liters, ice and 500 ml. of concentrated aqueous ammonia were added. The precipitated oil was taken up in benzene and, after removal of solvent (steam bath *in vacuo*), the residue was recrystallized from 1 liter of ethanol at −35°; yield of Ib, 270 g. of powdery crystals (28.8% from XII), m. p. 36–37°.

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

5,7-Dichloroisatin (VIc).[9,21]—Three hundred grams (2.04 moles) of isatin was placed in a 5-liter 3-necked flask together with 10 g. of sodium iodide and 3500 ml. of water; the flask was equipped with a "Lightnin" stirrer and placed in a bath at approximately −10°. Chlorine was passed into the vigorously stirred mixture (maintained at about 0°) as rapidly as it could be absorbed until the absorption was negligible (about nine hours; it is essential that chlorination be complete). The temperature of the mixture was allowed to approach gradually that of the room and the unstable 1,5-dichloroisatin was filtered off, rinsed well with water, sucked dry, and spread out to air-dry (one–two days).

The dry material was added with effective stirring to 1.2 liters of C. P. concentrated sulfuric acid while maintaining the temperature at about 10°. The cooling bath was then removed and the mixture allowed to stand for twelve hours (temperature rose at first to *ca.* 45°). Excess ice was then added and, when crystallization was complete (one hour), the crude VIc was filtered off, washed well with water and spread to dry (crude m. p. *ca.* 185–205°); two to four recrystallizations[22] from boiling glacial acetic acid were necessary to bring the m. p. to 226°;

(12) Arising from VIIa half potassium salt unconverted to free VIIa and unchanged during the decarboxylation step. 2,4-Dicarbethoxy-6-chloroquinoline crystallized from *i*-propyl ether in two forms, needles and blocky prisms, both melting at 93.0–93.5°. *Anal.* Calcd. for $C_{15}H_{14}ClNO_4$: C, 58.54; H, 4.58; N, 4.55. Found: C, 58.34; H, 4.77; N, 4.82. The diester is markedly less basic than Ia; the latter yields a rather insoluble picrate while the diester does not.

(13) *Cf.* Koelsch, THIS JOURNAL, **65**, 2463, footnote 12 (1943).

(14) Supplied by Dr. R. C. Elderfield (Columbia University).

(15) Compare conversion of N-acetylisatin to 2-hydroxycinchoninic acid, ref. 3, p. 73.

(16) *Cf.* Pfitzinger, *J. prakt. Chem.*, [2] **56**, 283 (1897).

(17) Kalle and Co., German Patent 489,458 (Schmidt and Krieger, inventors) [*Chem. Zentr.*, **101**, **I**, 1699 (1930); *Friedländer*, **16**, 2661].

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

(19) Marvel and Hiers in "Organic Syntheses," Coll. Vol. 1, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, page 327.

(20) Supplied by the Monsanto Chemical Company.

(21) Bayer and Co., German Patents 255,772, 255,774 [*Chem. Zentr.*, **84**, **I**, 478 (1913); *Friedlander*, 11, 280, 282].

(22) VIa (plates from glacial acetic acid) may be present; under these recrystallization conditions, a VIa solution tends to supersaturate so that VIc may readily be obtained pure.

yield of recrystallized material 200–246 g. (45–55%). VIc crystallized from glacial acetic acid in hollow orange rectangular tubes, m. p. 230° (lit.[21] m. p. 221°).

Ethyl 6,8-Dichlorocinchoninate (Ic).—To 215 g. (1 mole) of VIc, dissolved in a boiling solution of 621 g. of potassium hydroxide in 2 liters of water, was added cautiously 380 g. of *ca.* 50% pyruvic acid[11] (spontaneous boiling and separation of solid). The mixture was heated with *ca.* 500 ml. of water (until the solid was nearly dissolved) and acidified (see under Ia). The crude 6,8-dichloroquinoline-2,4-dicarboxylic acid (VIIc), yield 277 g. after drying at 100°, contained considerable inorganic matter. A portion was recrystallized from water; small colorless needles, m. p. 279.5–280.5° dec.

Anal. Calcd. for $C_{11}H_5Cl_2NO_4 \cdot 0.5H_2O$: C, 44.77; H, 2.05; N, 4.75. Found: C, 44.54; H, 2.21; N, 4.42.

The crude VIIc, in enough nitrobenzene to form a stirrable slurry, was heated at 185–205° for six hours. The reaction mixture was cooled, treated with 600 ml. of 60–70° petroleum ether and filtered. After washing with petroleum ether, the filtrate and washings were extracted with two 400 ml. portions of 6 *N* sodium hydroxide, and the filter cake was boiled with this sodium hydroxide solution. The resulting tarry solution was filtered (with Celite), the filtrate brought to *p*H 3 and the almost clay-like precipitate was filtered off and the solid dried at 100°, yield 252.4 g. This material was esterified and worked up as in the preparation of Ib; the crude Ic, after complete removal of benzene, was taken up in 300 ml. of *i*-propyl ether and the solution treated with 2 liters of 60–70° petroleum ether. The precipitated tar was filtered off (with Celite), the filtrate evaporated and the residue was recrystallized from 225 ml. of *i*-propyl ether; total yield (after reworking mother liquors) 151 g. (56% from VIc) of colorless Ic, m. p. *ca.* 70°; a portion was recrystallized from ethanol, needles, m. p. 73.5–74.5°.[23]

Anal. Calcd. for $C_{12}H_9Cl_2NO_2$: C, 53.36; H, 3.36; N, 5.19. Found: C, 53.55; H, 3.53; N, 5.18.

Piperidylcarbinols

6-Chloroquinolyl-4)-α-piperidylcarbinol (Va) (SN-8534).[24]—Following the procedure[2] for V (R = 6-methoxyquinolyl-4), Ia (31.3 g. = 0.133 mole) was condensed with II[25] (seventeen hours) and the product hydrolyzed (twenty hours). The bases were taken up in chloroform and the extracts were dried over anhydrous potassium carbonate and shaken with 120 g. of 40% hydrobromic acid. The aqueous phase was separated, heated to about 60° and nitrogen bubbled through it to free of solvent; gain in weight 25.3 g. Cooling this hydrobromic acid solution yielded a crystalline cake, *ca.* 1 g. of which was removed, freed of mother liquor, and recrystallized from methanol. The micro needles of ε-(6-chlorocinchoninyl)-*n*-amylamine dihydrobromide (IIIa) were rinsed with *i*-propanol until colorless, m. p. 233–235°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot 2HBr$: C, 41.07; H, 4.37; N, 6.39. Found: C, 41.00; H, 4.49; N, 6.42.

The bulk of the crystalline cake was warmed to about 100° and treated with a solution of 13 g. of bromine in an equal weight of 48% hydrobromic acid; the reaction was apparently instantaneous and a mass of fine needles began to separate during the addition. The solution was cooled, filtered and the product washed with acetone, colorless crystals, yield 37 g.; evaporation of the mother liquors and dilution with acetone gave a second crop (3.5 g.); total yield 56.5% from Ia (78% taking into account recovered VIIIa). ε-Bromo-ε-(6-chlorocinchoninyl)-*n*-amylamine dihydrobromide (IVa) crystallized from methanol as a monohydrate, m. p. 185–186°; this salt turned orange *in vacuo* (3 mm.) and became colorless again on exposure to moist air.

Anal. Calcd. for $C_{15}H_{16}BrClN_2O \cdot 2HBr \cdot H_2O$: C, 33.64; H, 3.76; N, 5.23. Found: C, 33.31; H, 4.14; N, 4.94.

A mixture of 73 g. (0.136 mole) of IVa and 950 ml. of methanol was treated with a solution of 90 g. of anhydrous potassium carbonate in 200 ml. of water. Air was swept from above the dark orange mixture with nitrogen and it was mechanically shaken for thirty minutes. Adams catalyst (1.5 g.) was then added and on reduction, 6.21 liters of hydrogen (calcd. *ca.* 3.53 liters)[26] was taken up; the initially rapid rate of absorption became negligible after about two and one-half hours. After heating the solution to the boiling point, inorganic solids were filtered off and washed (methanol); the filtrate was freed of methanol on a steam-bath and the residue was extracted with chloroform. The extracts were in turn freed of solvent and the residue was dissolved in 75 ml. of ethanol and treated with dry hydrogen chloride; the crystalline precipitate was filtered off, washed with isopropanol and ether, yield 14.2 g.[27] This was recrystallized from water (with Norite), giving 9.5 g. (19.0% from IVa; 10.8% over-all from Ia) of colorless Va salt. A sample, recrystallized from water containing a few drops of hydrochloric acid, yielded hexagonal plates, m. p. 233–234° dec., analysis for $C_{15}H_{17}ClN_2O \cdot 2HCl \cdot H_2O$. Va was crystallized from ethanol–isopropyl ether, bars, m. p. 183.1–183.6°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O$: C, 65.09; H, 6.19; N, 10.12. Found: C, 65.24; H, 6.22; N, 10.02.

(8-Chloroquinolyl-4)-α-piperidylcarbinol (Vb) (SN-10276).[24]—As in series a, 315 g. (1.34 moles) of Ib was condensed (twenty hours) and hydrolyzed (twenty-five hours). After removal of chloroform, the crude bases (231.2 g.) were treated with 500 ml. of *i*-propanol, followed by 280 g. of 48% hydrobromic acid. On standing, IIIb crystallized out, was filtered off and rinsed with *i*-propanol; yield, 276 g. (45.1%) of tan powder, m. p. 187–194°. A portion was recrystallized from *i*-propanol–aqueous hydrobromic acid, needles, m. p. 189–190°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot 2HBr \cdot H_2O$: C, 39.45; H, 4.63; N, 6.14. Found: C, 39.79; H, 4.91; N, 5.94.

The corresponding dihydrochloride was prepared by treating a solution of the base in absolute ethanol with anhydrous hydrogen chloride; needles from ethanol–water, m. p. 173° dec., analysis for $C_{15}H_{17}ClN_2O \cdot 2HCl \cdot 2H_2O$.

IIIb (2.5 g.) in 50 ml. of ethanol plus 10 ml. of water was basified with sodium hydroxide, 0.1 g. of Adams catalyst added, and the mixture shaken with moist hydrogen. Absorption was negligible until acetic acid had been added; approximately the theoretical amount was then taken up in fifteen minutes. The solution was basified, the solvent removed and the residue extracted with chloroform. Evaporation gave α-(8-chloroquinolyl-4)-ζ-amino-*n*-hexanol, colorless bars, m. p. 143.5–144.5° after recrystallization from butanone–*i*-propanol.

(23) Ic was later prepared in this Laboratory by Dr. D. R. V. Golding who separated it from concurrently formed 2,4-dicarbethoxy-6,8-dichloroquinoline by distillation. Ic, b. p. 155–158° at 1 mm., crystallized from 60–70° petroleum ether in well formed prisms, m. p. 78–79°, did not form an ether-insoluble picrate and was soluble in 6 *N* hydrochloric acid but not in 3 *N* acid. The diester boiled at about 170° at 1 mm., was less soluble in ligroin, *i*-propyl ether, or ethanol than Ic, and was insoluble in 10 *N* hydrochloric acid; it formed light yellow needles from acetonitrile, m. p. 172.8–173.5°. *Anal.* Calcd. for $C_{15}H_{13}Cl_2NO_4$: C, 52.65; H, 3.83; N, 4.09. Found: C, 52.37; H, 3.76; N, 4.04.

(24) 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 the Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(25) Furnished by Dr. E. B. Hartshorn (Dartmouth College), by Dr. R. C. Elderfield (Columbia University) and by Dr. C. C. Price University of Illinois).

(26) In series a, c, 160–175% of the theoretical amount of hydrogen was absorbed (in the corresponding chloro-2-phenyl series, *cf.* Buchman, Sargent, Myers and Howton, THIS JOURNAL, **68**, 2710 (1946), absorption approximated the theoretical.

(27) From the mother liquors was obtained 3.0 g. of a substance, m. p. 228°; regeneration gave a non-crystalline base.

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.

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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]

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]

(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.

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

(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).