The free base IIIb, prepared from the salt and crystallized from ethanol as colorless prisms, melted at 169–170°.

Anal. Calcd. for $C_{15}H_{24}ON_2$: C, 76.0; H, 8.5; N, 9.9. Found: C, 75.7; H, 8.5; N, 10.0.

Series c

2-Cyclohexylcinchoninic Acid and Ethyl Ester.—The acid was prepared in 66% yield as described by John and Pietsch[7] from isatin and methyl cyclohexyl ketone.[15] The crude acid (140 g.) was esterified in the usual way to give 120 g. of ethyl ester, b. p. 165–168° (0.3 mm.); a picrate of this ester melted at 155–157°, the value given by John and Pietsch. A sample of the ester was saponified and the resulting acid, after several recrystallizations from absolute ethanol, melted at 180–184° (John and Pietsch report 189°); after crystallization from 50% ethanol, the acid melted at 134–141° in a manner suggesting solvation (Skita and Wulff[5] give 137° as the m. p. of the acid prepared by the Doebner method).

ε-Bromo-ε-(2-cyclohexylcinchoninyl)-*n*-amylamine Dihydrobromide (IIc).—Ethyl 2-cyclohexylcinchoninate (89.5 g.) and ethyl ε-benzamidocaproate (86.5 g.) were condensed in the presence of sodium amide (from 11.5 g. of sodium) in the usual way. After hydrolysis and bromination the hydrobromic acid solution of IIc was evaporated *in vacuo* and the residual oil taken up in isopropanol, from which solution crystallized 56.2 g. of IIc, m. p. 145–150°. A sample for analysis crystallized from isopropanol in rosets of colorless crystals, m. p. 145–147° (dec.), which contained one mole of isopropanol of crystallization.

Anal. Calcd. for $C_{21}H_{27}ON_2Br \cdot 2HBr \cdot C_3H_8O$: C, 46.1; H, 6.0. Found: C, 45.8; H, 5.8.

2-Cyclohexylcinchoninic acid (40.7 g.) was recovered in the usual manner from the hydrolysate of the last experiment.

2-Cyclohexyl-α-(2-piperidyl)-4-quinolinemethanol (IIIc), (SN 10,749).—The dihydrochloride IIc (55 g.) was suspended in 600 ml. of ethanol and treated in the usual fashion to close the ring and effect reduction. After removing the ethanol the product was taken up in chloroform, the chloroform evaporated to dryness and the residue dissolved in 75 ml. of ethanol. The addition of 70 ml. of 6 *N* ethanolic hydrogen chloride precipitated the crude dihydrochloride of IIIc (30 g.) which crystallized from ethanol as microcrystals of m. p. 177–180°.

The free base (IIIc) was prepared from the dihydrochloride and recrystallized from acetonitrile in the form of long, silky needles, m. p. 157–159°.

Anal. Calcd. for $C_{21}H_{30}ON_2$: C, 77.7; H, 8.7; N, 8.6. Found: C, 77.5; H, 8.7; N, 8.5.

A sample of the dihydrochloride of IIIc for analysis was prepared from the free base in ethanol by precipitation with ethanolic hydrogen chloride; the salt was hydrated and melted at 178–181°.

Anal. Calcd. for $C_{21}H_{28}ON_2 \cdot 2HCl \cdot H_2O$: C, 60.7; H, 7.8. Found: C, 61.0; H, 7.9.

2-*t*-Butylcinchoninic Acid and Ethyl Ester.—Condensation between isatin and pinacolone, in the manner of the Pfitzinger reaction, resulted in recovery of the starting materials, even though the conditions were varied considerably.

Trimethylacetaldehyde (20 g.),[16] pyruvic acid (18 g.) and aniline (18 g.) were condensed under the usual conditions of the Doebner reaction. The resulting crude acid, after two crystallizations from ethanol and one from benzene, was obtained as light yellow prisms (5 g.), m. p. 147–149°.

Anal. Calcd. for $C_{14}H_{15}O_2N$: N, 6.1. Found: N, 6.1.

The crude acid (12 g.) was esterified in the usual way to give 10 g. of semi-crystalline material which was distilled at 115–118° (0.2 mm.) to yield 7.5 g. of light yellow crystalline ethyl ester, m. p. 47–48°.

Anal. Calcd. for $C_{16}H_{19}O_2N$: C, 74.7; H, 7.4; N, 5.4. Found: C, 74.9; H, 7.5; N, 5.4.

Summary

The synthesis of three 2-alkyl-α-(2-piperidyl)-4-quinolinemethanols as well as the requisite cinchoninic esters is described.

(15) Nenitzescu and Cioranescu, *Ber.*, **69**, 1821 (1936).

(16) Campbell, THIS JOURNAL, **59**, 1980 (1937).

PASADENA, CALIFORNIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1047]

Potential Antimalarials. (Chloro-2-phenylquinolyl-4)-α-piperidylcarbinols[1]

BY E. R. BUCHMAN, H. SARGENT, T. C. MYERS AND D. R. HOWTON

Koepfli and co-workers[2] have reported the synthesis of (2-phenylquinolyl-4)-α-piperidylcarbinol; a variety of substituted derivatives have also been prepared.[2,3] The present paper describes the preparation of additional analogs containing chlorine in the molecule.

Cinchoninic esters (I) used as starting materials were made from appropriate chlorinated isatins[4] *via* the Pfitzinger reaction.[5] From these the carbinols (V) were synthesized by the conventional Ainley and King[6] method employing modifications suggested by Sargent.[7] Only one of the diastereoisomeric racemic forms[7] of V was obtained in each series.

$$\underset{\text{I}}{RCOOC_2H_5} + \underset{\text{II}}{C_2H_5OOC(CH_2)_5NHCOC_6H_5} \longrightarrow \underset{\text{III}}{RCO(CH_2)_5NH_2 \cdot xHBr} \longrightarrow \underset{\text{IV}}{RCOCHBr(CH_2)_4NH_2 \cdot xHBr} \longrightarrow \underset{\text{V}}{RCHOH\text{-}\alpha\text{-piperidyl}}$$

Series a. R[8] = 6-chloro-2-phenylquinolyl-4
b. R = 8-chloro-2-phenylquinolyl-4
c. R = 6,8-dichloro-2-phenylquinolyl-4
d. R = 6,8-dichloro-2-(*p*-chlorophenyl)-quinolyl-4

(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) Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

(3) Brown, Jacobs, Winstein, *et al.*, *ibid.*, **68**, 2705 (1946).

(4) See Buchman, Sargent, Myers and Seneker, *ibid.*, **68**, 2692 (1946).

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

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

(7) *Cf.* Sargent, THIS JOURNAL, **68**, 2688 (1946); also refs. 2, 3, 4.

(8) Other (chloro-2-phenylquinolyl-4)-α-piperidylcarbinols have been synthesized, refs. 2, 3 and Koepfli and co-workers, unpublished. Vb, Vc and Vd analogs of the type $RCHOHCH_2NR'_2$ have been prepared, Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946).

Experimental[9]

2-Phenylcinchoninic Esters[10]

Ethyl 6-Chloro-2-phenylcinchoninate (Ia).—6-Chloro-2-phenylcinchoninic acid (VIa)[11] was prepared from 224 g. (1.23 moles) of 5-chloroisatin,[4] yield 338 g.; a reprecipitated sample melted at 245–246° (lit.[11] m. p. 243°). The crude VIa was refluxed for fifty hours with 3.3 liters of ethanol containing 200 ml. of concentrated sulfuric acid. After removing the bulk of the ethanol, Ia was precipitated by adding ice and ammonium hydroxide and recrystallized from ethanol; yield 268 g. (69.6% from 5-chloroisatin). A sample was recrystallized from ethanol, m. p. 81.0–81.5°.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.34; H, 4.53; N, 4.49. Found: C, 69.61; H, 5.04; N, 4.12.

Ethyl 8-Chloro-2-phenylcinchoninate (Ib)[12] was prepared similarly from 123 g. (0.678 mole) of 7-chloroisatin,[4] yield of crude acid (VIb), 162 g. Ib was extracted with benzene and recrystallized from ethanol, yield 140 g. (66.3% from 7-chloroisatin), m. p. 98.0–98.5° after an additional recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.34; H, 4.53; N, 4.49. Found: C, 69.80; H, 4.63; N, 4.01.

Ethyl 6,8-Dichloro-2-phenylcinchoninate (Ic).—6,8-Dichloro-2-phenylcinchoninic acid (VIc) was prepared from 150 g. (0.694 mole) of 5,7-dichloroisatin,[4] yield 221 g. Recrystallization of a sample from methanol gave a mixture of stout swords and fine needles; these were shown to be dimorphs, m. p. of either form 266–267°.

Anal. Calcd. for $C_{18}H_9Cl_2NO_2$: C, 60.40; H, 2.85; N, 4.40. Found: C, 60.49; H, 2.67; N, 4.33.

VIc sodium salt crystallized from water as a hydrate, tan plates, m. p. 251.5–253.5°, analysis for $C_{18}H_8Cl_2NNaO_2 \cdot 1.5H_2O$. Crude VIc (218 g.) was esterified in the usual way. Recrystallization of Ic from benzene–ethanol (3:2) gave 205 g. (86.5% from dichloroisatin) of colorless needles, m. p. 131.7–132.7°; a recrystallized portion melted at 132.3–132.8°.

Anal. Calcd. for $C_{18}H_{13}Cl_2NO_2$: C, 62.44; H, 3.78; N, 4.05. Found: C, 62.89; H, 3.84; N, 4.37.

Ethyl 6,8-Dichloro-2-(*p*-chlorophenyl)-cinchoninate (Id).—The reaction of 246 g. (1.14 moles) of 5,7-dichloroisatin[4] with excess of *p*-chloroacetophenone (Eastman Kodak Co. Practical) gave 409 g. of 6,8-dichloro-2-(*p*-chlorophenyl)-cinchoninic acid (VId); a portion was recrystallized from methanol, fine colorless needles, m. p. 269.5–270.5°.

Anal. Calcd. for $C_{16}H_8Cl_3NO_2$: C, 54.50; H, 2.29; N, 3.97. Found: C, 54.42; H, 2.25; N, 3.90.

Crude VId (406.8 g.) was esterified (eighty hours) and the ester was extracted with benzene and recrystallized from ethanol–benzene, yield 302.4 g. (69.7% from dichloroisatin). Id crystallized from *i*-propyl ether–benzene in straw-colored needles or hexagons; both forms melted at 140.0–141.5° (no mixed m. p. depression).

Anal. Calcd. for $C_{18}H_{12}Cl_3NO_2$: C, 56.79; H, 3.18; N, 3.68. Found: C, 56.94; H, 3.37; N, 3.89.

Piperidylcarbinols

The usual procedures[7] were followed; some modifications were, however, necessary in the hydrolysis step. After the condensation was completed, the reaction mixture was allowed to cool nearly to room temperature and a suitable quantity of 54–60% sulfuric acid (hydrochloric acid was not suitable) added rapidly. On thorough mixing, the temperature rose to about 60° and the mixture separated into two or three phases. The benzene was distilled off, new stoppers were then fitted to the flask and the mixture was heated under reflux. During a period of from thirty to sixty-five hours, the insoluble viscous gum slowly dissolved, giving a deeply colored solution with an occasional small quantity of suspended solid.

The crude hydrolyzate was poured directly onto a large quantity of ice and basified by addition of aqueous sodium hydroxide keeping the temperature of the liquid below 35–40°; the precipitated yellow-brown gum was then extracted with chloroform or benzene. Chloroform extractions were often complicated by the separation of finely divided solid (the sodium cinchoninate), the crystallization of which seemed to be induced by this solvent; with benzene, on the other hand, the sodium salt generally oiled out of the aqueous phase and remained in this state during the comparatively easy removal of the benzene phase. Any sodium salts which had separated from the aqueous phase were dissolved and on acidification (preferably with acetic acid), substantial quantities of VI were recovered. The ketone extracts were dried over sodium sulfate and freed of solvent in a tared flask. The residual brown sirup could be worked up as the crystalline anhydroketones (see series d); usually a quantity of 48% hydrobromic acid equivalent to the weight of the crude product was slowly added followed by dilution with ethanol, acetone, or *i*-propanol, to yield III.

ε-(6-Chloro-2-phenylcinchoninyl)-*n*-amylamine Hydrobromide (IIIa).[13]—A solution of Ia (238.8 g. = 0.767 mole) and 204 g. (0.776 mole) of ethyl benzamidocaproate (II)[14] in 400 ml. of benzene was added to sodamide from 21.8 g. (0.948 mole) of sodium and the mixture heated for nineteen hours. After refluxing with 575 ml. of 12 *N* hydrochloric acid and 400 ml. of water for four days, some oil was still present; 40 ml. of concentrated sulfuric acid was added and the mixture refluxed for four days longer. The solution was then basified, extracted with 1 liter of chloroform and the extract concentrated to an oil, which was poured into 180 g. (1.06 moles) of 48% hydrobromic acid. On standing overnight at 0° the mixture set to a yellow crystalline mass; the solid (yellow flakes) was filtered off and washed with *i*-propanol; yield 133.5 g. (33.8% calculated as dihydrobromide).

ε-Bromo-ε-(6-chloro-2-phenylcinchoninyl)-*n*-amylamine Dihydrobromide (IVa).—This 133.5 g. (*ca.* 0.26 mole) of IIIa was dissolved (with heating) in 400 ml. of 48% hydrobromic acid plus 950 ml. of water. Then, with vigorous stirring and heating to prevent the formation of perbromide, 44.6 g. (0.273 mole) of bromine in 44.6 g. of 48% hydrobromic acid was added slowly to the solution; crystallization began soon after the start of the addition. IVa was filtered off, washed with acetone, and dried *in vacuo* (yellow needles which dried into cottony clusters), weight 84.6 g. The mother liquors yielded an additional 19.7 g.; total yield 22.2% from Ia. After recrystallization from methanol plus 48% hydrobromic acid, IVa melted at 211–212° dec.

Anal. Calcd. for $C_{21}H_{20}BrClN_2O \cdot 2HBr \cdot H_2O$: C, 41.26; H, 3.96; N, 4.58. Found: C, 41.17; H, 4.10; N, 4.46.

(6-Chloro-2-phenylquinolyl-4)-α-piperidylcarbinol (Va) (SN9848).[15]—IVa (103 g. = 0.168 mole) was dissolved in 3075 ml. of ethanol and 410 ml. of 14% sodium carbonate was added. After shaking for one-half hour, 1 g. of Adams catalyst was added, and the mixture reduced

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

(10) The 2-phenylcinchoninic acids (VI) were prepared essentially according to the method given[5] for preparation of the parent acid. *i*-Propyl ether was used to extract unreacted acetophenone; under the conditions of the reaction, VIc potassium salt, for instance, had an appreciable solubility in ethyl ether.

(11) Borsche, *Ber.*, **41**, 3891 (1908).

(12) Prepared by Mr. J. A. Seneker.

(13) Ketones (III and IV) with chlorine in the 8-position of the quinoline rest (series b, c, d) gave monohydrobromides (*cf.* Lutz, *et al.*[8]) while IVa formed a dihydrobromide; *cf.* also Buchman and Howton, THIS JOURNAL, **68**, 2718 (1946).

(14) Supplied by Dr. C. C. Price (University of Illinois) and by Dr. R. C. Elderfield (Columbia University).

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

(*ca.* six hours) until the rate of hydrogen up-take was negligible; hydrogen absorbed was 4.6 liters (calcd. 4.0 liters). The solution was then filtered and concentrated on the steam-bath; the residue, on cooling, gave a crystalline mass plus a small amount of oil. After adding alcohol until the oil dissolved, the mixture was filtered and the product rinsed with ethanol, colorless homogeneous crystalline rhombs, weight 35 g. (52.1% (as ethanolate); 11.5% over-all from Ia). A portion recrystallized from water plus enough methanol for solution melted at 194–195° (slow heating; on rapid heating m. p. 128° with resolidification).

Anal. Calcd. for $C_{21}H_{21}ClN_2O \cdot CH_3OH$: C, 68.65; H, 6.55; N, 7.28. Found: C, 68.93; H, 6.43; N, 6.72.

A 7-g. portion of Va was suspended in 20 ml. of 96% ethanol and dry hydrogen chloride passed in; the hydrochloride was filtered off and washed with ethanol; yield 7.5 g., m. p. 241–242° dec. from ethanol–water (4:1), analysis for $C_{21}H_{21}ClN_2O \cdot HCl$.

(6-Chloro-2-phenylquinolyl-4)-α-N-methylpiperidylcarbinol (SN11370).[15]—Va (3.5 g.) was dissolved in 125 ml. of C. P. benzene and 1.70 g. of anhydrous potassium carbonate, 7.0 ml. of water and 1.39 g. of dimethyl sulfate were added. The mixture was shaken mechanically for twelve hours; the benzene phase was separated and the solvent removed by evaporating. The product was taken up in 12 ml. of ethanol and converted to the salt by addition of 1.6 ml. of 12 *N* hydrochloric acid; yield 3.7 g. A portion was recrystallized from ethanol–water, colorless rectangular plates, m. p. 210.5–211.0° dec.

Anal. Calcd. for $C_{22}H_{23}ClN_2O \cdot 2HCl \cdot 1.5H_2O$: C, 56.60; H, 6.05; N, 6.00. Found: C, 56.97; H, 5.83; N, 6.02.

ε-Bromo-ε-(8-chloro-2-phenylcinchoninyl)-*n*-amylamine Hydrobromide (IVb).—Ib (93.6 g. = 0.3 mole) and II (78.8 g. = 0.3 mole) were condensed (0.37 mole of sodamide, 180 ml. of benzene, twenty-one hours) and the product was hydrolyzed by refluxing with a solution of 156 ml. of concentrated sulfuric acid in 224 ml. of water for fifty hours. The crude bases were taken up in chloroform and the extracts were freed of solvent (steam-cone, *in vacuo*); yield 73.4 g. of oil. Treatment with 70 g. of 48% hydrobromic acid yielded an insoluble portion (9.8 g. = 0.031 mole of unchanged Ib). Cautious dilution of the aqueous phase until an oil began to separate, then scratching and allowing to stand gave an impure solid; it was shaken with 70 ml. of 48% hydrobromic acid and 50 ml. of chloroform, yielding 2.8 g. of a bright yellow insoluble material.[16] The aqueous portion of the filtrate was treated with a 50% solution of 15.0 g. of bromine in 48% hydrobromic acid and, after removal of solvent *in vacuo* (steam-bath), the residual sirup was dissolved in 50 ml. of ethanol. On cooling, 30.2 g. of tiny, bright yellow needles deposited, m. p. 171° dec.; concentration and cooling gave 20.2 g. more of IVb; total yield 29.2% from Ib (67% taking into account recovered VIb and Ib). Recrystallization of IVb from boiling ethanol–48% hydrobromic acid did not appreciably change the melting point.

Anal. Calcd. for $C_{21}H_{20}BrClN_2O \cdot HBr \cdot 3.5H_2O$: C, 43.81; H, 4.90; N, 4.87. Found: C, 43.67; H, 4.52; N, 5.09.

(8-Chloro-2-phenylquinolyl-4)-α-piperidylcarbinol (Vb) (SN10281).[15]—IVb (39.6 g. = 0.0688 mole) was cyclized (see under Va, one hour) and reduced (0.75 g. of catalyst, seventy minutes, theoretical amount of hydrogen absorbed). The resulting colorless mixture was heated to boiling on the steam-bath and 300 ml. of butanone was added to dissolve the white organic solid which had separated during reduction; inorganic solids were filtered off and the filtrate evaporated to dryness on the steam-bath. The residue was shaken with 200 ml. of chloroform and 100 ml. of water and filtered, yield 11.6 g. of Vb; recrystallization from a small amount of pyridine gave compact, colorless clusters, m. p. 217.7–218.6° on slow heating.

Anal. Calcd. for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94. Found: C, 71.15; H, 6.08; N, 8.10.

The chloroform phase from the above filtrate was freed of solvent, 50 ml. of ethanol added and the resulting slurry saturated with anhydrous hydrogen chloride; the solid dissolved and then another separated out which, after cooling, was filtered off and washed with isopropanol, yield 7.38 g. (melting point not appreciably raised by recrystallization); a portion was crystallized from ethanol–water as faintly colored, transparent bars, m. p. 231.5–232.4° dec., analysis for $C_{21}H_{21}ClN_2O \cdot HCl$. The free base liberated from this hydrochloride was identical with Vb. Together, Vb and Vb hydrochloride represent a yield of 75.4% from IVb, or 22% from Ib (50.5% from Ib taking into account recoveries).

ε-(6,8-Dichloro-2-phenylcinchoninyl)-*n*-amylamine Hydrobromide (IIIc).—Four large scale runs were carried out; in each of these a solution of 511.2 g. (1.475 moles) of Ic[17] and 423.6 g. (1.61 moles) of II in 900 ml. of benzene was added to sodamide (from 45.6 g. (1.98 moles) of sodium) and the mixture heated at *ca.* 100° for sixteen hours. Each oily product was hydrolyzed by refluxing for fifty hours with 1080 ml. of concentrated sulfuric acid and 1200 ml. of water; the hydrolyzates were basified and shaken, each with 2 liters of benzene, giving a three-phase system. The aqueous layers were discarded; the combined heavy intermediate oily layers from two runs were diluted with 2.5 l. of chloroform, allowed to stand until the sodium salt of VIc had crystallized and then filtered, yield of crude sodium salt 449 g. (the free acid was regenerated and esterified giving 156.5 g. of Ic; the second pair of runs gave 202 g.). The chloroform filtrates (from the first pair of runs) were combined with the benzene layers (from these same runs), dried over anhydrous potassium carbonate and freed of solvent on the steam-bath *in vacuo*. The crystalline residue (689.3 g.) was crushed in a mortar under *i*-propanol, heated nearly to boiling in 2.5 liters of *i*-propanol, treated with 200 ml. of 48% hydrobromic acid and the mixture stirred vigorously for one hour to insure complete conversion to IIIc. After cooling to 5°, the resulting stiff paste was filtered and rinsed with *i*-propanol, yield 626 g.; mother liquors were evaporated to *ca.* 500 ml. and the crystals filtered and rinsed with acetone, yield 48.9 g. The total yield of IIIc was 48.8% (57.4% taking into account recovered Ic); in the second pair of runs, the corresponding figures were 43.1 and 53.7%. IIIc crystallized from 40% aqueous hydrobromic acid upon addition of isopropanol, pearly yellow flakes, m. p. 236–237° dec.

Anal. Calcd. for $C_{21}H_{20}Cl_2N_2O \cdot HBr$: C, 53.86; H, 4.52; N, 5.98. Found: C, 54.17; H, 4.76; N, 6.00.

A small portion was treated with aqueous sodium hydroxide and the liberated base extracted with benzene and recrystallized twice from isopropanol (with Norite), tiny swords, m. p. 172.6–173.1°.

Anal. Calcd. for $C_{21}H_{18}Cl_2N_2$[18]: C, 68.30; H, 4.91; N, 7.59. Found: C, 68.03; H, 5.24; N, 7.49.

(6,8-Dichloro-2-phenylquinolyl-4)-α-piperidylcarbinol (Vc) (SN10275).[15]—Since, in preliminary runs, the bromination of IIIc yielded gummy products, the following procedure was developed: a mixture of 82.5 g. (0.176 mole) of IIIc and 180 ml. of 48% hydrobromic acid was warmed to about 80°, giving a clear yellow-brown solution; then, with swirling, a solution of 28.2 g. (0.176 mole) of bromine in 20 ml. of 48% hydrobromic acid was added over a period of one–two minutes. The resulting solution was heated to the boiling point and allowed to cool; a slurry formed which was dispersed in 1 liter of ethanol

(16) This was recrystallized from ethanol–48% hydrobromic acid and the bright-yellow, hexagonal plates washed with acetone (treatment with water or alcohols gave a white solid, m. p. 263°), m. p. 160–163° dec. This substance in warm 48% hydrobromic acid, on treatment with bromine vapors, apparently gave a hydrated IVb, clusters of light-orange needles from ethanol–48% hydrobromic acid, m. p. 171–174° dec., analysis for $C_{21}H_{20}BrClN_2O \cdot HBr \cdot 1.5H_2O$.

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

(18) Free ketones of type III apparently lose water easily; III is readily regenerated by treatment of the anhydro-ketone with acid.

(previously cooled to *ca.* −30° by addition of Dry Ice). The mixture was introduced into 2 liters of similarly cooled ethanol and, while maintaining the temperature well below room temperature, 280 ml. of 9 *N* sodium hydroxide was added with vigorous swirling, followed by 82.5 g. of anhydrous sodium carbonate. The flask was tightly stoppered (stopper wired on) and mechanically shaken for about twelve hours. Inorganic solids were then filtered from the orange-brown suspension and the filter cake was washed with 500 ml. of ethanol. The filtrate, after addition of 3.0 g. of platinum oxide (American Platinum Works) was reduced; the hydrogen-absorption rate was negligible after about twelve hours when 6.6 liters of gas had been taken up (calcd. 5.1 liters). Solids were filtered from the mixture, washed with a little ethanol, and the filtrate evaporated to dryness on a steam-bath. The residue was washed with water, air-dried, dispersed in 300 ml. of acetone, treated with 15 ml. of 12 *N* hydrochloric acid, and allowed to stand for about five hours; Vc hydrochloride was then filtered off and washed with acetone, crude yield, 11.0–30.0 g. Accumulated catalyst from 13.5 runs of this size was extracted with a mixture of glacial acetic and 12 *N* hydrochloric acid (1:1) until the extracts were colorless; these extracts yielded 39.0 g. of crude Vc hydrochloride. This material, together with other crude Vc salt from these runs, was dissolved in 750 ml. of the same solvent (acetic–hydrochloric acid), treated with about 5 g. of Norite, washed through a filter with 150 ml. of the same solvent, and diluted with 1570 ml. of methanol–water (4:1). The resulting crystals were filtered off and washed with methanol, yield 264.0 g. of slightly colored solid, m. p. 249° dec., analysis for $C_{21}H_{20}Cl_2N_2O \cdot HCl \cdot 1.5H_2O$.[19] The mother liquors, on concentration and cooling, gave three additional crops[20]; total yield of Vc salt, 340.5 g. (31.5% from IIIc; 14.4% from Ic; 17.4% over-all taking into account recovered Ic). Vc crystallized from *i*-propanol in tiny colorless needles, m. p. 231.0–231.5°.

Anal. Calcd. for $C_{21}H_{20}Cl_2N_2O$: C, 65.12; H, 5.21; N, 7.24. Found: C, 64.93; H, 5.03; N, 6.93.

Recrystallization of Vc from glacial acetic acid gave an acetate, large, colorless rhombs of sharp, reproducible m. p. 231–232° (slight dec.).

ε-(6,8-Dichloro-2-(*p*-chlorophenyl)-cinchoninyl)-*n*-amylamine Hydrobromide (IIId).—Id (305.8 g. = 0.80 mole) and 212 g. (0.807 mole) of II in 430 ml. of benzene (slurry at 35°) were heated with 1.01 moles of sodamide for twenty-three hours. The hydrolysis was carried out with a solution of 560 ml. of concentrated sulfuric acid in 660 ml. of water, refluxing for sixty-four hours. The crude bases were taken up in chloroform, freed of solvent, again taken up in benzene and the solution was filtered (filter aid) from tar. The filtrate was concentrated to a sirup and diluted to about 900 ml. with ethanol. The crystals which formed on seeding were filtered off (126 g., 38.9%) and used directly for preparation of IVd. A portion was recrystallized twice from ethanol–benzene (Norite), colorless needles, m. p. 155.6–156.0°.

Anal. Calcd. for $C_{21}H_{17}Cl_3N_2$[18]: C, 62.47; H, 4.25; N, 6.94. Found: C, 62.49; H, 4.42; N, 6.78.

The mother liquors were concentrated giving 132 g. of oil; 80 g. of 48% hydrobromic acid was added and the mixture diluted with acetone to *ca.* 1 liter. After standing in the ice box for twelve hours, the resulting yellow solid was filtered off, yield 47.0 g. (regeneration gave the anhydro-base); total yield (anhydro-base plus salt) 50.5% from Id. A portion of the salt was recrystallized from 48% hydrobromic acid and washed with acetone, clusters of tiny greenish-yellow needles, m. p. 267.5–271.5° dec.

Anal. Calcd. for $C_{21}H_{19}Cl_3N_2O \cdot HBr$: C, 50.17; H, 4.01; N, 5.57. Found: C, 49.90; H, 4.08; N, 5.89.

Hydrolysis with a mixture of acetic acid and hydrochloric acid failed to remove the benzoyl group. The condensation product from 30 g. (0.0787 mole) of Id was refluxed with a mixture of 150 ml. of glacial acetic acid and 100 ml. of concentrated hydrochloric acid for five days. The chloroform soluble bases were treated with 13.2 g. of 48% hydrobromic acid and the solution warmed and diluted with 100 ml. of acetone; a yellow powder (9.3 g.) precipitated, m. p. 246–248° dec. The regenerated free base was recrystallized from ethanol–benzene, colorless diamond-shaped crystals, m. p. 183.5–184.0° (analysis for N-benzoyl-ε-(6,8-dichloro-2-(*p*-chlorophenyl)-cinchoninyl)-*n*-amylamine).

Anal. Calcd. for $C_{28}H_{23}Cl_3N_2O_2$: C, 63.95; H, 4.41; N, 5.33. Found: C, 64.03; H, 4.47; N, 5.61.

ε-Bromo-ε-(6,8-dichloro-2-(*p*-chlorophenyl)-cinchoninyl)-*n*-amylamine Hydrobromide (IVd).—A 90-g. (0.223-mole) portion of crude anhydro-base was brominated in 400 ml. of 48% hydrobromic acid at about 90° with 36 g. (0.225 mole) of bromine in 40 ml. of 48% hydrobromic acid. After boiling for five minutes, water was slowly added to the hot solution, throwing out a crystalline solid. After the mixture had cooled to about 40°, the solid was filtered, washed with water, and air-dried. The material was stirred with a small amount of boiling glacial acetic acid and the paste thus formed was slowly cooled, filtered off and washed (first with acetic acid, then with acetone), yield 82.5 g. (63.7%) of dark yellow powder. A portion was recrystallized from glacial acetic acid (with Norite), fine, long yellow needles, m. p. 197° dec.

Anal. Calcd. for $C_{21}H_{18}BrCl_3N_2O \cdot HBr$: C, 43.37; H, 3.29; N, 4.82. Found: C, 43.37; H, 3.58; N, 4.61.

Bromination of IIId normally gave IVd; in the following experiment ε,ε-dibromo-IIId was obtained. IIId (47 g. = 0.0935 mole) was dissolved in 235 ml. of 48% hydrobromic acid, the solution heated nearly to boiling and 15.0 g. (0.0935 mole) of bromine in 15 g. of the same solvent added quickly. The solution was boiled for a few minutes and, on cooling, orange needle clusters crystallized; these were filtered off and air-dried, yield 33.6 g. of bright yellow powder, m. p. 176–179° dec. After two recrystallizations from 48% hydrobromic acid, yellow needle clusters were obtained which were filtered and washed with water, yellow-orange powder, m. p. 166–167° dec.

Anal. Calcd. for $C_{21}H_{17}Br_2Cl_3N_2O \cdot HBr \cdot 2H_2O$: C, 36.21; H, 3.18; N, 4.02. Found: C, 36.20; H, 3.60; N, 4.03.

(6,8-Dichloro-2-(*p*-chlorophenyl)-quinolyl-4)-α-piperidylcarbinol (Vd) (SN11445).[15]—An 81.5-g. (0.14-mole) portion of crude IVd was dissolved in 2.8 liters of boiling ethanol, 280 ml. of 14% sodium carbonate was added with shaking, and then 70 g. of anhydrous potassium carbonate. After shaking for one and one-half hours, 2.25 g. of catalyst was added, and the mixture reduced (six and one-half hours; 3.71 liters of hydrogen (theory 4.03 liters)). The solution was filtered, the yellow filter cake boiled with benzene and with ethanol, and the extracts were combined with the main filtrate; evaporation gave a crystalline mass which was triturated with water. The solid was filtered off, washed thoroughly with water and dried at 60°; the resulting brown powder (53 g.) was stirred with cold ethanol, filtered, washed with acetone, with ethanol, and with ether, yield 18.5 g. of greyish powder (washings see below). This crude Vd was dissolved in a mixture of 140

(19) As noted in other cases (*cf.* Vd salts) Vc hydrochloride crystallized under different conditions as salts of different melting points differing in extent of hydration; adding one equivalent of 12 *N* hydrochloric acid to a suspension of crude Vc in absolute ethanol gave colorless plates, m. p. 274–275°, analysis for Vc·HCl; the latter was recrystallized from water–acetic acid, hexagons, m. p. 250.5° dec., analysis for Vc·HCl·0.5H₂O.

(20) Basification of the mother liquors from the last crop of Vc hydrochloride gave an oily precipitate which solidified and was washed with water, stirred with warm ethanol and filtered; yield 21.3 g. Recrystallization from benzene gave colorless microneedles, m. p. 189.0–189.5°. *Anal.* Calcd. for $C_{23}H_{25}ClN_2O_2$: C, 69.59; H, 6.35; N, 7.06; Cl, 8.93. Found: C, 69.57; H, 6.38; N, 7.11; Cl, 8.89. Probably the replacement of chlorine by ethoxyl took place during the condensation step and the resulting small amount of impurity in IIIc gave rise to this (6(or 8)-ethoxy-8-(or 6)-chloro-2-phenylquinolol-4)-α-piperidylcarbinol.

ml. of glacial acetic acid and 28 ml. of 12 *N* hydrochloric acid; the solution was heated rapidly to boiling, treated with *ca.* 2 g. of Norite, filtered, and the cake washed with 57 ml. of glacial acetic acid. The amber-colored filtrate was diluted with its own volume of methanol and allowed to stand; Vd hydrochloride came down as a mass of well-formed microneedles, which were filtered off after an hour, rinsed with methanol, then ether, and air-dried, yield 15.9 g. of pale cream powder, m. p. 258–259° dec. The ethanol–acetone–ether washings (above) were concentrated to a sirup and dissolved in 80 ml. of glacial acetic acid and 16 ml. of 12 *N* hydrochloric acid and the solution diluted with twice its volume of methanol; an additional 8.7 g. of reasonably pure hydrochloride was obtained, total yield *ca.* 36.8% (11.8% over-all from Id). A portion was recrystallized from a mixture of acetic acid and water, light tan needle clusters, m. p. 227–229°, analysis for $C_{21}H_{19}Cl_3N_2O \cdot HCl \cdot H_2O$. Vd hydrochloride was found to have several melting points, depending on recrystallization conditions; the forms (probably solvated) were interchangeable, and all could be regenerated to the same free base. Vd was recrystallized from benzene, tiny, colorless needles, m. p. 241–242° dec.

Anal. Calcd. for $C_{21}H_{19}Cl_3N_2O$: C, 59.80; H, 4.54; N, 6.64. Found: C, 59.97; H, 4.64; N, 6.65.

Crude dibromo-IIId was ring-closed and reduced in the same manner; 33.6 g. (0.0482 mole) in 1.2 liters of ethanol was treated with 120 ml. of 14% sodium carbonate solution and 30 g. of anhydrous potassium carbonate. After shaking for one and one-half hours, 0.45 g. of catalyst was added, and the mixture reduced (five and one-half hours, 1.52 liters of hydrogen (2.57 one calcd.)); 4.2 g. (20.7%) of Vd was isolated.

Summary

(6 - Chloro - 2 - phenylquinolyl - 4) - α - piperidylcarbinol (and its N-methyl derivative), (8-chloro - 2 - phenylquinolyl - 4) - α - piperidylcarbinol, (6,8-dichloro-2-phenylquinolyl-4)-α-piperidylcarbinol and (6,8-dichloro-2-(*p*-chlorophenyl)-quinolyl-4)-α-piperidylcarbinol have been prepared.

PASADENA 4, CALIF. RECEIVED APRIL 5, 1946

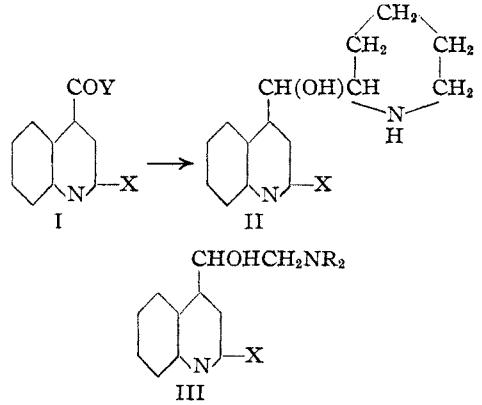
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

α-Piperidyl-4-quinolinemethanols Substituted in the 2-Position[1]

BY S. WINSTEIN, THOMAS L. JACOBS, EDWARD F. LEVY, DEXTER SEYMOUR, GUSTAVE B. LINDEN AND ROBERT B. HENDERSON

In exploring further variations[2] in the nature of the substituent blocking the 2-position of α-piperidyl-4-quinolinemethanol[3] II (X = H) we have prepared several such quinolinemethanols with so-called "negative" substituents. The aminoalcohols II contained either the 2-dialkylamino group (X = piperidino, morpholino and dibutylamino) which proved somewhat less effective than a phenyl group,[4] or the 2-hydroxyl group which produced complete loss of antimalarial activity as anticipated.[5] The preparation of the analogous 2-amino, 2-ethoxy and 2-phenylthio piperidylcarbinols was attempted and abandoned when it proved relatively easier to prepare the corresponding ethanolamines III.[6]

The general method of preparation of these α-piperidyl-4-quinolinemethanols was, as previously,[2] the one used by Ainley and King[3] and improved by Sargent,[4,7] the over-all yields from the appropriate cinchoninic ester I (Y = OC_2H_5) being approximately 10–20%, not allowing for recovered acid I (Y = OH).



Nucleophilic displacements of a group such as chloride proceed well at the 2-carbon atom in the quinoline nucleus. This was convenient in connection with the preparation of cinchoninic acids or derivatives of the type I, but troublesome in other phases of the work. 2-Chlorocinchoninic acid I (X = Cl, Y = OH), readily available[3,8] from N-acetylisatin by way of the 2-hydroxycinchoninic acid I (X = OH, Y = OH), was readily converted by heating with the appropriate amine, to the 2-piperidino-, morpholino-, dibutylamino- and novalaminocinchoninic acids.

The 2-aminocinchoninic acid I (X = NH_2, Y = OH) was prepared by treatment of the 2-chlorocinchoninic acid with ammonia and am-

(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 University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

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(4) Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

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

(6) Winstein, Jacobs, Linden, Seymour, Levy, Day, Robson, Henderson and Florsheim, THIS JOURNAL, **68**, 1831 (1946).

(7) Sargent, *ibid.*, **68**, 2088 (1946).

(8) Camps, *Arch. Pharm.*, **237**, 659 (1899).