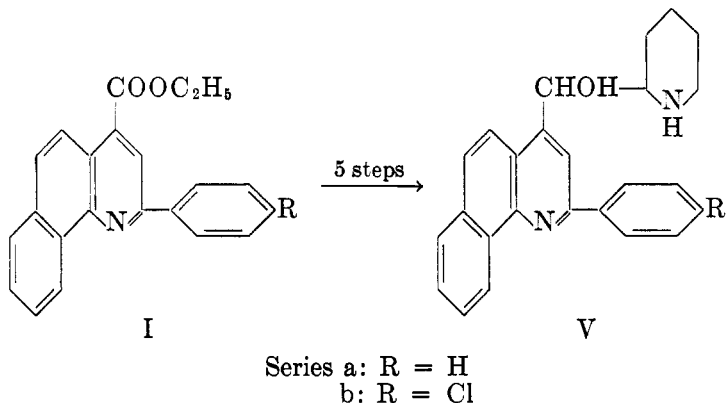


POTENTIAL ANTIMALARIALS. (2-PHENYL-7,8-BENZOQUINOLYL-4)- α -PIPERIDYLCARBINOLS¹

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(2-Phenyl-7,8-benzoquinolyl-4)- α -piperidylcarbinols Va and Vb were prepared in the usual manner (1) starting from the corresponding esters Ia and



Ib which were obtained via the Doebner reaction. The antimalarial activities of Va (SN 10,534) and of Vb (SN 12,895) are tabulated in the Wiselogle Monograph (2).

A preliminary attempt was made to synthesize carbinols in the 5,6-benzoquinolyl-4 series; it was found that, undoubtedly due to the steric effect of the 5-substituent (3), ethyl 2-phenyl-5,6-benzocinchoninate (VI) did not condense smoothly with ethyl benzamidocaproate (II).

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EXPERIMENTAL³

BENZOCINCHONINIC ESTERS

Ethyl 2-phenyl-7,8-benzocinchoninate (Ia) (4). The Doebner condensation (4) was carried out in ethanol, heating for four hours; a 50% aqueous pyruvic acid (supplied by the Calco

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³ All melting points are corrected.

Chemical Division of the American Cyanamid Company) was used. The crude acid, after washing with ethanol, was esterified with ethanolic sulfuric acid. The reaction mixture was poured into ice-water and basified; the ester was extracted with benzene and recrystallized from ethanol, m.p. 96° [lit. (4) m.p. 103°], yield 18.6% from α -naphthylamine.

Ethyl 2-(p-chlorophenyl)-7,8-benzocinchoninate (Ib). A mixture of 572.8 g. (4 moles) of α -naphthylamine, 562.4 g. (4 moles) of *p*-chlorobenzaldehyde, 704 g. (ca. 4 moles) of 50% aqueous pyruvic acid, and 10 l. of 95% ethanol was refluxed for ca. sixteen hours. The crude product was washed with 95% ethanol and dried, yield 705 g.; a portion, on recrystallization from glacial acetic acid, gave yellow microneedles, m.p. 308–309°.

Anal. Calc'd for $C_{20}H_{12}ClNO_2$: N, 4.20. Found: N, 4.19.

This acid was refluxed for forty-one hours with 9 l. of ethanol and 400 ml. of concentrated sulfuric acid and the solution evaporated *in vacuo* to ca. 2 l. The residual sirup was poured on ice and the ester extracted with benzene. The extracts were washed with 1 *N* sodium hydroxide and evaporated to a thick oil which was taken up in 600 ml. of ethanol. On cooling, crude tarry ester separated (470 g.) which was recrystallized from a mixture of 940 ml. of ethanol and 610 ml. of benzene; yield (after washing with ethanol) 167.3 g. (11.5% from α -naphthylamine), m.p. 124–126°. A portion was recrystallized from ethanol-benzene, dense tufts of tan bars m.p. 127.4–127.8°.

Anal. Calc'd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87.

Found: C, 72.86; H, 4.76; N, 3.89.

Ethyl 2-phenyl-5,6-benzocinchoninate (VI). β -Naphthylamine (280 g., 1.95 moles) was condensed (4) in ethanol with benzaldehyde and 50% pyruvic acid (one hour) and the mixture was cooled to ca. 60° and filtered. The crude acid was washed with ethanol and dried, yield 268.5 g. Since esterification with ethanolic sulfuric acid proceeded too slowly to be feasible, 261.6 g. of this acid was converted to the acid chloride (heating on steam-bath for three and one-half hours with 330 ml. of purified thionyl chloride; removing excess of latter on steam-bath *in vacuo*) and this was refluxed for two hours with 500 ml. of ethanol. After diluting the mixture with water and making basic with 15 *N* ammonium hydroxide, the ester was extracted with ether and recrystallized from ethanol, yield 205.7 g. (m.p. 82–83°) plus 22.5 g. from the mother liquors (36.5% from β -naphthylamine). A portion of VI was recrystallized from ethanol, pearly flakes, m.p. 83.5–84.0°.

Anal. Calc'd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28.

Found: C, 80.58; H, 5.12; N, 4.43.

Simon and Mauguin (5) claim to have prepared VI by the action of ethyl pyruvate on benzal- β -naphthylamine but report no characterization. VI boils at ca. 200° at 2 mm. and gives a *picrate*, m.p. 192.0–192.5°.

Anal. Calc'd for $C_{28}H_{20}N_4O_9$: C, 60.43; H, 3.62; N, 10.07.

Found: C, 60.39; H, 3.65; N, 10.13.

The corresponding methyl ester was made from the acid chloride and methanol, needles, m.p. 126.5–126.7° from ethanol-isopropanol [lit. (6) m.p. 125°, 128°].

PIPERIDYLCARBINOLS

Except where otherwise noted, the general procedures were those employed in a previous publication (1d).

*ε-(2-Phenyl-7,8-benzocinchoninyl)-*n*-amylamine hydrobromide (IIIa)*. A solution of 201 g. (0.615 mole) of Ia and 161 g. of II in 370 ml. of benzene was heated with sodamide (from 17.7 g. of sodium) for twenty-eight hours. After hydrolysis by refluxing for thirty-seven hours with a solution of 319 ml. of sulfuric acid in 457 ml. of water, the reaction mixture was made basic and extracted with chloroform. The extracts were freed of solvent (steam-bath, *in vacuo*) and the residue (160.5 g.) treated with 71 g. of 48% hydrobromic acid and ca. 250 ml. of isopropanol. When crystallization was complete, the product (crude IIIa) was filtered off, washed with isopropanol, and air-dried; yield 119.2 g., m.p. 218–221°. From a portion, the free base (compare 1c) was liberated and taken up in benzene; after removal of solvent it was obtained crystalline by moistening with ligroin and scratching, m.p. 69–72°. Another portion of the salt was recrystallized from ethanol—48% hydrobromic

acid, clusters of tiny, bright yellow needles (possibly dihydrobromide), m.p. 225–226° dec. (slow heating; on rapid heating m.p. 237° sl. dec.). An analytical sample was prepared by recrystallizing crude IIIa from glacial acetic acid, clusters of yellow-brown needles, m.p. 206–207°.

Anal. Calc'd for $C_{25}H_{24}N_2O \cdot HBr$: C, 66.81; H, 5.61; N, 6.24.

Found: C, 66.64; H, 5.77; N, 6.19.

ϵ -Bromo- ϵ -(2-phenyl-7,8-benzocinchoninyl)-*n*-amylamine hydrobromide⁴ (IVa). Crude IIIa (94.3 g.) was dissolved in 105 ml. of 48% hydrobromic acid at 60° and treated rapidly with a solution of 33.6 g. of bromine in 27 ml. of the same solvent. An oil precipitated which rapidly dissolved on heating; on subsequent cooling a crystalline cake was obtained. To the mixture was added 275 ml. of 48% hydrobromic acid, 520 ml. of isopropanol, 815 ml. of ethanol, and 320 ml. of water and the cake was dissolved by heating to boiling. After cooling overnight, the resulting mass of orange-yellow needles was filtered off, washed with ethanol, and air-dried; yield 99.6 g. (36.3% from Ia), m.p. 196° dec.; a sample was analyzed directly.

Anal. Calc'd for $C_{25}H_{23}BrN_2O \cdot HBr \cdot 2H_2O$: C, 53.21; H, 5.00; N, 4.97.

Found: C, 53.50; H, 4.84; N, 4.93.

IVa dihydrate was recrystallized from glacial acetic acid, orange-yellow clusters, m.p. 191.8–192.2° (sample inserted in m.p. bath at 170°).

Anal. Calc'd for $C_{25}H_{23}BrN_2O \cdot HBr$: C, 56.83; H, 4.58; N, 5.30.

Found: C, 56.75; H, 4.63; N, 5.11.

(2-Phenyl-7,8-benzoquinolyl-4)- α -piperidylcarbinol (Va). A mixture of 60.9 g. (0.108 mole) of IVa dihydrate, 1500 ml. of ethanol, and 232 ml. of 14% aqueous sodium carbonate was shaken for eighty minutes. After reduction (0.75 g. of catalyst, twenty-five hours, 3.05 l. of hydrogen) the suspension was heated together with 300 ml. of butanone and 450 ml. of benzene and inorganic solids were filtered off and washed with hot benzene and ethanol. The filtrates were evaporated on the steam-bath, the residue was treated with water-chloroform and undissolved organic solids were combined with the chloroform phase. The chloroform suspension was freed of solvent (finally by boiling off small portions of 95% ethanol from the residue), 100 ml. of 95% ethanol was added, and the mixture was saturated with dry hydrogen chloride; the precipitate was filtered off, washed with isopropanol, and air-dried, yield 50.7 g., m.p. 266°. This product was recrystallized from 100 ml. of water plus 190 ml. of 12 *N* hydrochloric acid using Norit, large clusters of well-formed needles, m.p. 258° dec., yield 50.6 g. (quantitative from IVa; 36.3% over-all from Ia, 63.1% taking into account recovered cinchoninic acid).

Anal. Calc'd for $C_{25}H_{24}N_2O \cdot 2HCl \cdot 1.5H_2O$: C, 64.10; H, 6.24; N, 5.98.

Found: C, 64.16; H, 6.26; N, 5.81.

Va was liberated from the salt by suspending the latter in pyridine-benzene and boiling with 4 *N* sodium hydroxide; the base was taken up in benzene-pyridine and, after evaporation of solvent, was recrystallized from pyridine, compact clusters of tiny needles, m.p. 226.8–227.5°.

Anal. Calc'd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60.

Found: C, 81.23; H, 6.38; N, 7.88.

ϵ -(2-*p*-Chlorophenyl)-7,8-benzocinchoninyl)-*n*-amylamine hydrobromide (IIIb). Ib (173 g., 0.478 mole) was condensed with II (twenty-four hours) and the product hydrolyzed (forty-two hours). The hydrolyzate was basified in the presence of benzene, the mixture was filtered using Celite, and the filter cake was washed with hot benzene. After removal of solvent (steam-bath, *in vacuo*) from the combined benzene extracts, the residue (134.7 g.) was treated with 260 ml. of isopropanol, 50 ml. of acetone, and 90.3 g. of 48% hydrobromic acid. The solution obtained on warming was allowed to cool and the resulting mass of fine

⁴ Published studies (7) have made it seem possible to generalize regarding the salt-forming properties of 8-substituted 2-phenylquinoline derivatives. However, in the present work, it was found that IVb (but not IVa) was isolated as a dihydrobromide while Va (but not Vb) formed a stable dihydrochloride.

needle-clusters filtered and washed with isopropanol and with acetone; yield of bright yellow first crop (IIIb) 42.0 g., m.p. 264–265°. The mother liquors plus some ethanol were evaporated to ca. 150 ml. and diluted with an equal volume of benzene to give a second crop, 34.7 g., m.p. 245–247°; in the same way a third crop of 27.7 g. was obtained. From samples of these crude salts, the free base (compare Series a) corresponding to IIIb was prepared, m.p. 134–136° after scratching with isopropanol-ligroin; it crystallized slowly even when seeded. A portion of first-crop material was recrystallized from aqueous acetic acid, tan flakes, m.p. 190–191° (m.p. bath heated slowly from 184°; m.p. varies with rate and extent of heating); the analysis indicates *IIIb monohydrate* as a possible formula.

Anal. Calc'd for $C_{25}H_{23}ClN_2O \cdot HBr \cdot H_2O$: C, 59.83; H, 5.22; N, 5.58.

Found: C, 60.44; H, 5.54; N, 5.78.

Experiments with recrystallized and unrecrystallized material showed that it was advantageous to brominate crude first-crop and second-crop IIIb directly. Third-crop IIIb (22.0 g.) was purified by conversion to the free base which was taken up in benzene and the solution freed of solvent [solids difficultly soluble in benzene (m.p. 194–197°) were discarded]; crude yield 11.8 g.

ε-Bromo-ε-(2-(p-chlorophenyl)-7,8-benzocinchoninyl)-n-amylamine hydrobromide (IVb). Second-crop IIIb (29.1 g.) was suspended in 120 ml. of nearly boiling 48% hydrobromic acid and treated slowly with 9.6 g. of bromine in 12 ml. of the same solvent. The latter was added in portions with heating after each addition until the initially precipitated oil had dissolved. The solution was slowly diluted with 150 ml. of isopropanol and filtered hot (using Celite). The filtrate, on cooling, deposited a bright yellow solid which was filtered off and washed with isopropanol-ether, yield 25.4 g. A portion was recrystallized from glacial acetic acid, tiny, rough, bright yellow bobbins, m.p. 189° dec.

Anal. Calc'd for $C_{25}H_{22}BrClN_2O \cdot 2HBr \cdot H_2O$: C, 45.38; H, 3.96; N, 4.23.

Found: C, 45.63; H, 4.07; N, 4.19.

First-crop IIIb (4.84 g.) gave on bromination 5.78 g. of crude IVb, m.p. 170°. The crude base (11.8 g.) from third-crop IIIb gave 15.0 g. of crude IVb.

(2-(p-Chlorophenyl)-7,8-benzoquinolyl-4)-α-piperidylcarbinol (Vb). Crude IVb (14.6 g.) from third-crop IIIb, 400 ml. of ethanol, and 58 ml. of 14% aqueous sodium carbonate were shaken for eighty minutes and reduced (3.0 g. of catalyst, eleven hours, 1.47 l. of hydrogen). The mixture, after the addition of 160 ml. of benzene, was heated to boiling and filtered and the filter cake was extracted with 50 ml. of boiling benzene. The combined solutions were freed of solvent and the crystalline residue washed well with water and dried. The product (8.8 g.) was taken up in 25 ml. of boiling pyridine and the solution was diluted with 50 ml. of hot benzene and allowed to crystallize. Yield, 6.0 g. of fine white needle-clusters, m.p. 224.9–225.5° (sintering from 223°).

Anal. Calc'd for $C_{25}H_{23}ClN_2O$: C, 74.52; H, 5.75; N, 6.95.

Found: C, 74.93; H, 6.01; N, 6.66.

Crude IVb (4.77 g.) from first-crop IIIb gave on reduction 1.93 g. of recrystallized Vb; 25.4 g. of IVb from second-crop IIIb gave 7.2 g. of recrystallized carbinol. These figures indicate an 18.2% over-all yield from Ib. A solution of 17.8 g. of Vb in 103 ml. of glacial acetic acid and 80 ml. of 12 N hydrochloric acid was diluted with 700 ml. of methanol and then, with swirling, 27 ml. of water was added. The finely-divided solid which separated was filtered off, washed with aqueous methanol, and dried; yield 17.2 g., m.p. 256–258° (slow heating from 242°).

Anal. Calc'd for $C_{25}H_{23}ClN_2O \cdot HCl \cdot 0.5H_2O$: C, 66.96; H, 5.62; N, 6.25.

Found: C, 66.57; H, 5.69; N, 6.13.

SUMMARY

(2-Phenyl-7,8-benzoquinolyl-4)-α-piperidylcarbinol and [2-(p-chlorophenyl)-7,8-benzoquinolyl-4]-α-piperidylcarbinol have been prepared.

PASADENA 4, CALIF.

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