Preparation of Certain Benzo[*h*]quinolinemethanols as Potential Antimalarial Agents (1)

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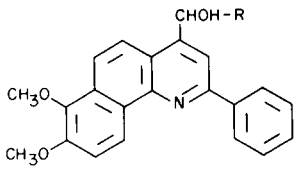
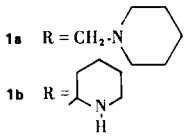
The purpose of the work reported herein was the preparation of dimethoxy 2-phenylbenzo[*h*]quinolinemethanols (**1a-c**) possessing amino functions on the substituent at position 4 and which have been shown in simpler quinoline systems to confer antimalarial potency.



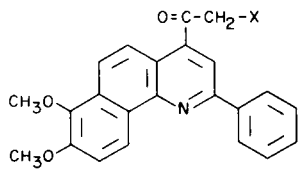


1a R = CH_2-N

1b R =

1c R = CH_2-N(n-C_4H_9)$_2$

7,8-Dimethoxy-2-phenylbenzo[*h*]cinchoninic acid was prepared by the Doebner pyruvic acid synthesis on 5,6-dimethoxy-1-naphthylamine. The cinchoninic acid was converted *via* its acid chloride to the chloromethyl- or the bromomethyl ketones (**2a** and **b**).

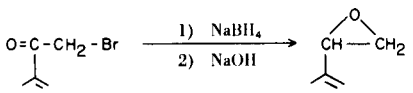


2a X = Cl

2b X = Br

It was proposed to prepare **1a** and **1c** by displacement of the halogen of **2a** or **2b** with a variety of amines, followed by reduction of the ketonic group. Gobeil and Hamilton (2) observed low yields (30-35%) in amination of non-methoxylated analogs of **2a** and **2b** with piperidine in benzene solution. In the present work, yields of piperidinomethyl 2-phenyl-4-benzo[*h*]quinolyl ketone could be increased to 60% by use of chloroform as the solvent and by use of equimolecular amounts of haloketone and amine, rather than a twofold excess of amine. However, the yields in this modification using the dimethoxylated systems (**2a** and **b**) were low, and the product was difficult to purify.

Compound **2b** was smoothly converted to the epoxide (**3**) by borohydride reduction followed by basic workup (3):



2b **3**

Treatment of **3** with piperidine and with di-*n*-butylamine gave acceptable yields of **1a** and **1c**.

Compound **1b** was prepared from 7,8-dimethoxy-2-phenylbenzo[*h*]cinchoninoyl chloride by the two step method of Boykin and co-workers (4).

None of the benzoquinolinemethanols (**1a-c**) demonstrated antimalarial activity in screening tests on mosquitos (5).

EXPERIMENTAL (6)

7,8-Dimethoxy-2-phenylbenzo[*h*]cinchoninic Acid (4).

To a refluxing solution of 3.92 g. (0.037 mole) of benzaldehyde in absolute ethanol was added in one portion 7.5 g. (0.037 mole) of 5,6-dimethoxy-1-naphthylamine (7). After refluxing for 5 minutes, 3.25 g. (0.037 mole) of pyruvic acid in 15 ml. of absolute ethanol was added dropwise over 20 minutes, and refluxing was continued for a total of 3 hours. After approximately 20 minutes, the deep red solution became lighter and an orange solid separated. The mixture was stirred at room temperature for 6 hours and then the solid was collected and washed with absolute ethanol. Yield, 4.9 g. (37%), m.p. 280-282°. A sample for analysis was recrystallized from acetone-methanol, m.p. 281-283°. IR (potassium bromide), 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.52; H, 4.80; N, 3.90. Found: C, 74.05; H, 4.60; N, 4.28.

7,8-Dimethoxy-2-phenylbenzo[*h*]cinchoninoyl Chloride (5).

A mixture of 2 g. (0.0055 mole) of **4** and **5** ml. of thionyl chloride was heated on a steam bath for 5 minutes. The mixture turned a deep red; an additional 5 ml. of thionyl chloride was added and refluxing was continued for another 5 minutes. The excess thionyl chloride was removed by azeotroping with benzene, and the reddish-yellow crystalline residue was recrystallized from benzene-*n*-hexane to yield 0.9 g. (50%) of reddish needles, m.p. 164-166°. IR (potassium bromide), 1770 cm^{-1} (COCl).

Anal. Calcd. for $C_{22}H_{16}ClNO_3$: C, 69.94; H, 4.27; Cl, 9.38; N, 3.71. Found: C, 69.93; H, 4.30; Cl, 9.81; N, 3.84.

Bromomethyl 7,8-dimethoxy-2-phenyl-4-benzo[*h*]quinolyl Ketone (2b).

A modification of the method of Lutz *et al.* (8) was employed. To a stirred methylene chloride solution of diazomethane (40 ml. of 0.5 *M*) at -5° was added 1.9 g. (0.005 mole) of **5** at such a rate that the temperature did not rise above 0°. After maintaining the temperature at 0° for 10 minutes, the mixture was permitted to

come to room temperature overnight; to this solution was added 15 ml. of 48% hydrobromic acid, and the resulting mixture was stirred for 0.5 hour. The organic layer was separated and the aqueous layer was extracted with three 20 ml. portions of methylene chloride. The combined organic solutions were washed with two 20 ml. portions of water, dried (magnesium sulfate), and the solvent was removed at room temperature under reduced pressure. The solid residue was recrystallized from benzene-*n*-hexane to yield 1.8 g. (86%) of material, m.p. 158-160°. A sample for analysis was recrystallized repeatedly from benzene-*n*-hexane, m.p. 160-162°. IR (potassium bromide), 1685 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{18}BrNO_3$: C, 63.31; H, 4.16; N, 3.22. Found: C, 63.73; H, 4.28; N, 3.17.

Chloromethyl 7,8-dimethoxy-2-phenyl-4-benzo[*h*]quinolyl Ketone (**2a**).

The procedure was that for the bromoketone (**2b**), in which 10 ml. of concentrated hydrochloric acid replaced the hydrobromic acid. Compound **5** (0.5 g., 0.00132 mole) gave rise to 0.3 g. (59%) of product, m.p. 157-158° (from benzene-*n*-hexane). IR (potassium bromide), 1695 cm. 1 (C=O).

Anal. Calcd. for $C_{23}H_{18}ClNO_3$: C, 70.50; H, 4.63; Cl, 9.05; N, 3.57. Found: C, 70.64; H, 4.67; Cl, 8.98; N, 3.55.

7,8-Dimethoxy-2-phenyl-4-benzo[*h*]quinolylethylene Oxide (**3**).

A modification of the method of Atkinson and Puttick (3) was employed. To a solution of 3.0 g. (0.0068 mole) of **2b** in 65 ml. of ethylene glycol monomethyl ether cooled to 0° was added with stirring 0.5 g. (0.013 mole) of sodium borohydride over 10 minutes. The solution was stirred an additional 15 minutes at 0°. Sodium hydroxide (2 g. in 10 ml. of water) was added dropwise with stirring and the reaction mixture was stirred 0.5 hour. The white precipitate which separated was washed twice with ethylene glycol monomethyl ether and then once with water. It was dried under reduced pressure to yield 1.87 g. (74%) of material, m.p. 141-142°. A sample for analysis recrystallized from benzene-*n*-hexane as clusters of needles, M.P. 142-143.5°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.43; H, 5.44; N, 4.06.

Piperidinomethyl 7,8-Dimethoxy-2-phenyl-4-benzo[*h*]quinolyl Ketone Hydrobromide (**6**).

A solution of 0.109 g. (0.0025 mole) of **2b** and 0.2 g. (0.0025 mole) of piperidine in 3 ml. of chloroform was refluxed for 13 hours. The yellow solid which separated was collected and washed repeatedly with chloroform and was recrystallized from chloroform-methanol to yield 0.039 g. (30%) of a yellow, microcrystalline powder, m.p. 262-263°. IR (potassium bromide), 1695 cm^{-1} (C=O).

Anal. Calcd. for $C_{28}H_{29}BrN_2O_3$: C, 64.49; H, 5.61; Br, 15.33; N, 5.37. Found: C, 64.56; H, 5.49; Br, 15.54; N, 5.29.

2-Pyridyl 7,8-Dimethoxy-2-phenyl-4-benzo[*h*]quinolyl Ketone (**7**).

The method of Boykin *et al.* (4) was employed. To an ether solution containing 0.001 mole of 2-pyridyllithium (prepared from *n*-butyllithium and 2-bromopyridine) and maintained at -60° was added with stirring 0.18 g. (0.0005 mole) of finely powdered **4** under a stream of nitrogen. After 5 minutes, 25 ml. of anhydrous ether was added and stirring was continued for 3 hours at -60° under nitrogen. The reaction was then brought to 0° and 25 ml. of moist ether was added, followed by 25 ml. of water. The red organic layer was separated, the solvent was removed under reduced pressure, and the residue was crystallized from ethanol to yield 0.120 g. (50%) of bright yellow crystals, m.p. 182-183°. IR (potassium bromide), 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.80; H, 4.83; N, 6.53.

7,8-Dimethoxy-α(2-piperidyl)-2-phenyl-4-benzo[*h*]quinolinemethanol (**1b**).

The method of Boykin *et al.* (4) was employed. A solution of 0.575 g. (0.00137 mole) of **7** in 225 ml. of ethanol and 0.5 ml. of concentrated hydrochloric acid was hydrogenated in the presence of 0.2 g. of platinum black at a maximum pressure of 45 psig until the theoretical amount of hydrogen was absorbed (1 hour). This mixture was filtered with *Celite*, the filtrate was concentrated to approximately 10 ml. under reduced pressure, and was poured into 100 ml. of ice-water containing 2.5 g. of sodium bicarbonate. The resulting flocculent precipitate was extracted with several portions of ether; the combined extracts were washed with water, dried (magnesium sulfate), and the ether was evaporated. The resinous residue was recrystallized several times from acetonitrile to yield 0.190 g. (32%) of material, m.p. 131-133°.

Anal. Calcd. for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 76.04; H, 6.65; N, 6.64.

7,8-Dimethoxy-α(1-piperidinomethyl)-2-phenyl-4-benzo[*h*]quinolinemethanol Dihydrochloride (**1a**).

A solution of 0.357 g. (0.001 mole) of **3** and 0.175 g. (0.002 mole) of piperidine in 10 ml. of dimethylformamide was heated at 95-100° for 24 hours. The solution was poured into ice-water and the resulting mixture was extracted with three 40 ml. portions of ethyl acetate. The combined extracts were washed with 25 ml. of water, dried (magnesium sulfate), and the solvent was removed. The oily residue was taken up in a small volume of methanol and the hydrochloride salt was formed by the addition of ethereal hydrogen chloride. The reddish-yellow paste which separated solidified on standing and was recrystallized repeatedly from methanol-ether to yield 0.190 g. (37%) of yellow crystals, m.p. 175-178°.

Anal. Calcd. for $C_{28}H_{32}Cl_2N_2O_3$: C, 65.24; H, 6.26; Cl, 13.76; N, 5.43. Found: C, 65.23; H, 6.37; Cl, 13.84; N, 5.39.

7,8-Dimethoxy-α(di-*n*-butylaminomethyl)-2-phenyl-4-benzo[*h*]quinolinemethanol Dihydrochloride (**1c**).

A solution of 0.357 g. (0.001 mole) of **3** and 0.258 g. (0.002 mole) of di-*n*-butylamine in 5 ml. of dimethylformamide was heated at 110-115° for 24 hours. The solution was poured over crushed ice, and the resulting mixture was extracted with three 50 ml. portions of ether. The combined extracts were dried (magnesium sulfate), the solvent removed, and the residue was converted to its hydrochloride salt which was recrystallized repeatedly from methanol-ether to yield 0.200 g. (36%) of yellow cubes, m.p. 180-181.5°.

Anal. Calcd. for $C_{31}H_{40}Cl_2N_2O_3$: C, 66.54; H, 7.21; Cl, 12.67; N, 5.01. Found: C, 66.85; H, 7.49; Cl, 12.60; N, 5.33.

REFERENCES

(1) This work was performed under Contract DA-49-193-2944 with the U. S. Army Medical Research and Service Command, Office of the Surgeon General under the Army Research Program on Malaria.

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(5) Screening was performed through the antimalaria program of the Walter Reed Army Institute of Research.

(6) Melting points are corrected and were taken on a Thomas-Hoover apparatus in open capillaries. Elemental analyses were by Huffman Laboratories, Wheatridge, Colorado. Infrared spectra were recorded on a Beckman IR-10 instrument.

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