

KUMAMOTOSHI, JAPAN

(23) A. C. Cope, H. R. Nace, W. R. Hatchard, W. H. Jones, M. A. Stahmann and R. B. Turner, *ibid.*, **71**, 554 (1949).

iso-Pamaquine. The testing of 8-(3-dimethylamino-1-methylpropylamino)-6-quinolinol sulfate trihydrate as an antimalarial has been summarized^{18,19,24}; it is of little value in experimental *T. cruzi* infections.²⁰

8-(4-Diethylamino-1-methylbutylamino)-6-quinolinol has been inadequately described in the literature.^{17a,25,26} We have prepared the dihydriodide and methylene 1,1'-bis-(2-hydroxy-3-naphthoate) from Pamaquin.

Experimental²⁷

4-Dimethylamino-2-butanol (II).—4-Dimethylamino-2-butanone (I) was obtained in 43–59% yields by a Mannich reaction on acetone, much as has been described.^{28,29} The ketone was conveniently reduced using a copper anode and lead cathode. The catholyte was a mixture of 493 g. (4.3 moles) of ketone (I), 230 cc. of concentrated sulfuric acid and 950 g. of ice; the anolyte consisted of 45% sulfuric acid. Reduction was done below 30° (cooling coils required) and was complete with consumption of 230 amp. during six hours.³⁰ The catholyte was filtered, basified in the cold with 35% sodium hydroxide, the oil separated and the aqueous layer extracted well with ether. The combined organic layer was dried (potassium carbonate) and fractionated; the portion boiling 40–57° (12 mm.) was twice fractionated to give 312.4 g. (62.5% yield) of 4-dimethylamino-2-butanol (II), as a colorless liquid, b.p. 49–52° (12 mm.). This compound has been reported earlier.^{17a,28}

3-Bromo-N,N-dimethylbutylamine Hydrobromide (III).—4-Dimethylamino-2-butanol (167 g., 1.42 moles) was treated with 410 cc. of 70% hydrobromic acid during one hour and then heated 12 hours in a bath at 80° (internal temperature, 74–75°). A light tan residue (302–323 g., 80–85% yield) of (III) was obtained by evaporation *in vacuo* at 70°. The crude hydrobromide was crystallized from ethyl acetate–dioxane (2:1) to give white microcrystals, m.p. 139.5–141° dec. (lit.^{17a} m.p. 150–151°).

Anal. Calcd. for $C_8H_{14}BrN \cdot HBr$: N, 5.37. Found: N, 5.51.

8-(3-Dimethylamino-1-methylpropylamino)-6-methoxyquinoline (V).—A mixture of 197 g. (0.75 mole) of hydrobromide (III), 261 g. (1.5 moles) of 8-amino-6-methoxyquinoline (IV) and 200 cc. of water was subjected to reaction after the manner of Pamaquine manufacture (*cf.* procedure B in ref. 31). The yield of (V) was 120.5–128.5 g. (58–63%); it was a viscous, golden oil which boiled at 168–173° (0.1 mm.). This compound has been claimed^{17c} to solidify slowly.

Anal. Calcd. for $C_{16}H_{20}N_2O$: N, 15.50. Found: N, 15.95.

8-(3-Dimethylamino-1-methylpropylamino)-6-quinolinol (VI).—Seven-tenths mole (182.4 g.) of (V) and 1200 cc. of

55% hydrobromic acid were heated under reflux in a bath at 120–125° until a test portion was completely soluble in 35% sodium hydroxide solution; this required *ca.* three hours. The residue remaining after *in vacuo* removal of most water and acid was dissolved in its own weight of hot water and basified strongly. The cooled garnet solution was extracted well with benzene to remove any (V), and then acidified promptly with 10% hydrochloric acid. The base (VI) was liberated in the cold by addition of 10% aqueous sodium carbonate and extracted with benzene. In turn, these were extracted with a total of 675 cc. of 2 N sulfuric acid, and the extracts warmed to 65–70° before adding propanol-2 to incipient cloudiness. Prolonged chilling and rubbing caused the sulfate of (VI) to separate in the form of golden leaflets. The salt was collected, washed with propanol-2, dissolved in 300 cc. of water at 75° and stirred with 5 g., each, of Darco G-60 and Filter-cel for 10 minutes before filtration. Propanol-2 was added to the hot filtrates to incipient precipitation and seed crystals added. The product was collected after prolonged chilling, washed with propanol-2, acetone, and ether before air-drying. A yield of 202.4 g. of golden orange leaflets resulted; this sample of sulfate contained 16.0% moisture. After drying over activated alumina, the 8-(3-dimethylamino-1-methylpropylamino)-6-quinolinol sulfate, m.p. 118–120°, gave analyses corresponding to the trihydrate (SN-191).

Anal. Calcd. for $C_{15}H_{21}N_2O \cdot H_2SO_4 \cdot 3H_2O$: base, 63.0; H_2SO_4 , 23.9; H_2O , 13.1. Found: base, 62.7; H_2SO_4 , 23.9; H_2O , 13.4.

8-(4-Diethylamino-1-methylbutylamino)-6-quinolinol. (a) Dihydriodide.—One hundred grams (0.3 mole) of 94.5% pure Pamaquine base was mixed with 1200 cc. of 45% hydriodic acid and stirred at 110–115°. The reaction was essentially complete (no more methyl iodide collected) in *ca.* two hours, and then the water and excess acid distilled *in vacuo*. The last amounts of water were removed azeotropically, leaving an orange-red viscous oil which solidified partially after nearly two years (most of the time at 20–30°, some while at 5–10°). This material was thrice triturated with, each time, 200 cc. of anhydrous acetone and a workable product resulted. The gummy solid was triturated with 1:1 acetone–ether, then extracted with boiling 2:1 acetone–ether to obtain an orange solid. This substance (39.0 g., m.p. 153–155°) was 8-(4-diethylamino-1-methylbutylamino)-quinolinol dihydriodide of 96% purity (*ca.* 22% yield). Three crystallizations of the crude from ethanol–ether afforded 31.3 g. of pure compound, m.p. 162–164°.

Anal. Calcd. for $C_{18}H_{27}N_2O \cdot 2HI$: C, 38.80; H, 5.24; N, 7.54; I, 45.55. Found: C, 38.70; H, 5.16; N, 7.51; I, 45.12.

(b) Methylene 1,1'-Bis-(2-hydroxy-3-naphthoate).—Pamaquine base was refluxed with a large excess of 55% hydrobromic acid after the manner described for (V); a 50–63% yield of base, b.p. 200–208° (0.8 mm.), resulted. The viscous golden oil became a vitreous solid on standing; this base has been reported previously.^{17a,25,26}

Anal. Calcd. for $C_{18}H_{27}N_2O$: N, 13.94. Found: N, 14.35.

A solution of 24.0 g. of 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol in 61 cc. of 10% hydrochloric acid was diluted to 500 cc. with water and this was added, simultaneously with a solution of 29.5 g. of 94.6% pure disodium methylene 1,1'-bis-(2-hydroxy-3-naphthoate) in 400 cc. of water, to 300 cc. of water which was stirred vigorously. The orange solid which precipitated was washed with hot alcohol and dried at 100°. Despite prolonged drying, the salt (51.5 g., m.p. 250°) contained 6% moisture.

Anal. Calcd. for $C_{18}H_{27}N_2O \cdot C_{22}H_{16}O_6$: base, 43.7; acid, 56.3. Found (dry basis): base, 43.1; acid, 57.2.

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RENSSELAER, N. Y.

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(27) All melting points are corrected values whereas boiling points are not.

(28) C. Mannich, *Arch. pharm.*, **255**, 261 (1917); C. Mannich and K. Curtaz, *ibid.*, **264**, 741 (1926).

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(30) As a test for completion, a 2-cc. sample from the cathode compartment was basified with 50% caustic. The oil which separated was dissolved in 10 cc. of absolute ethanol and a pellet of sodium hydroxide added, then the mixture boiled for a few minutes. If much ketone were present, a brown color soon developed, but only a straw color if reduction were nearly complete.

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