A Short Synthesis of 5,7-Bis(dialkylamino)-2-methyl-8-hydroxyquinolines

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The bromine atoms of the title compound were replaced by the requisite amino compound to afford the desired derivatives in high yields. Thus, six target compounds viz- bis(diethylamino)-, bis(dibutylamino)-, bis(dicyclohexylamino)-, dipyrrolidino-, dipiperidino-, and dipiperazino-derivatives were obtained and characterized by spectral and elemental analyses.

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Several derivatives of the quinoline nucleus have found use as antiseptic agents but have limited clinical application because of toxicity. The use of quinoline-based agents began with the isolation of alkaloids of cinchona bark, prominent among which were quinine and cinchonine. Structural modifications resulted in potent antimalarial agents such as chloroquine and primaquine [1]. Further modifications gave rise to clioquinol **1**, broxyquinoline **2**, broxaldine **3** and brobenzoxaldine **4** which have been used as topical anti-infective agents. In our continued efforts to prepare target compounds for antimalarial screening it was desirable to prepare derivatives of **3** by replacing the bromine atoms with various alkylamino substituents. The requisite atoms appear suitably activated by the electronic and structural disposition of **3** for the desired modifications. It was found that when **3** was treated with the amine at elevated temperatures or a mixture of the two dissolved in a suitable solvent and heated under reflux that the corresponding derivatives were obtained in high yields [2,3]. Thus, under suitable conditions **3** gave the following derivatives, **5 - 10** as shown.

These compounds have significant activities to varying extent against both Gram positive and Gram negative microorganisms. Their antimicrobial activities were investigated against selected Gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, Gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*, and yeast *Candida albicans*. All the compounds showed significant activity against the test microorganisms, from 5 – 30 times compared to the title compound. It was observed that all the derivatives were more effective against Gram positive bacteria. No correlation has been established between the minimum inhibitory concentrations (MIC) of the derivatives and the structural modifications [4].

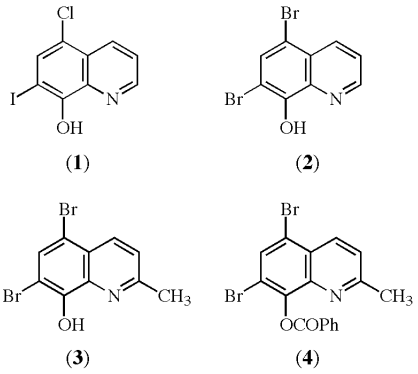
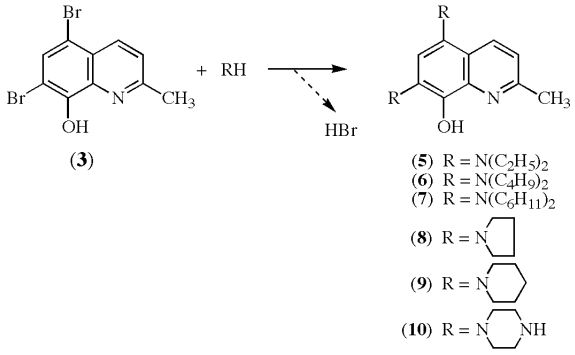


Figure 1

Scheme 1



EXPERIMENTAL

Melting points were determined with a Gallenkamp electrically heated block and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer, incorporated with a data station, for nujol mulls on sodium chloride plates, unless stated otherwise. The ^{1}H nmr spectra were recorded on a Bruker WM 250 (250 MHz), a Nicolet NT 200 (200 MHz) or a Perkin Elmer R 32 (90 MHz) spectrometer. The data are recorded as the chemical shifts (δ) in parts per million (ppm) followed by integral and multiplicity of the particular proton. Mass spectra were recorded with a micromass instrument 16F, incorporated with a data system Vg 2000, at 35 and 70 electron volts. Thin-layer chromatography (tlc) was conducted with Merck 60GF254 pre-coated silica gel plates. Drying and/or purification of organic solvents was done as described by Riddick and Bunger [5].

General Procedure for the Preparation of the Diamino-derivatives **5 – 10**.

Method A.

The amine (18.93 mmoles, *ca* 6 molar equivalents) was added dropwise to 5,7-dibromo-2-methyl-8-hydroxyquinoline **(3)** (1.00 g, 3.16 mmoles) in such a way to contain the initial

exothermic reaction and heated at a suitable temperature (normally at 110° - 115°) for five hours or until reaction was complete as indicated by tlc. The reaction mixture was then allowed to cool to room temperature and the excess amine removed *in vacuo*. The solid residue was washed with a little cold water and dried in air and recrystallized from the solvent indicated.

Method B.

The amine (18.93 mmoles, *ca* 6 molar equivalents), if solid was crushed and powdered, and mixed with 5,7-dibromo-2-methyl-8-hydroxyquinoline **(3)** (1.00 g, 3.16 mmoles) in such a way as to control the initial exothermic reaction and dissolved in absolute alcohol. The resulting solution was heated under reflux for four hours and allowed to cool to room temperature. Any precipitated solid was removed by filtration and solution reduced to a small volume until crystals began to appear or persistent cloudiness was observed. Crystallization was allowed to proceed at room or reduced temperature. The crystalline product was then further purified by recrystallization from the indicated solvent. Generally, if an intractable gummy solid was obtained it was found that preparative tlc run in methanol:acetone:water:ammonia 6:2:2:1 afforded products pure enough for recrystallization.

The following dialkylamino derivatives were thus obtained by method A unless otherwise indicated:

5,7-Bis(*N,N*'-Diethylamino)-2-methyl-8-hydroxyquinoline (**5**).

Diethylamine (2.00 ml, 18.93 mmoles) gave **5** in 70% yield (0.67 g), mp 115 – 116° from acetone; ir: ν_{max} 3400 (OH), 1620 (C=N), 1600 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): δ 1.20 (12H, t, CMe x 4), 2.33 (3H, s, Ar-Me), 2.85 (8H, q, CH_2-N x 4), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 301 (10) (M^+), 157 (100), 140 (22), 125 (12).

Anal. Calcd. for $C_{18}H_{27}N_3O$: C, 71.83; H, 9.03; N, 13.94. Found: C, 71.75; H, 8.97; N, 13.74.

5,7-Bis(*N,N*'-Dibutylamino)-2-methyl-8-hydroxyquinoline (**6**).

Dibutylamine (2.69 ml, 18.93 mmoles) gave **6** in 70% yield (0.91 g), mp 87- 88° from methanol; ir: ν_{max} 3400 (OH), 1645 (C=N), 1600 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): δ 1.13 (12H, t, CMe x 4); 1.43 (16H, m, CH_2 x 8), 2.33 (3H, s, Ar-Me), 2.55 (8H, t, CH_2-N x 4), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 414 (14) (M^+), 157 (100), 140 (6), 125 (10).

Anal. Calcd. for $C_{26}H_{43}N_3O$: C, 75.50; H, 10.48; N, 10.16. Found: C, 75.25; H, 10.20; N, 9.84.

5,7-Bis(*N,N*'-Dicyclohexylamino)-2-methyl-8-hydroxyquinoline (**7**).

Dicyclohexylamine (3.77 ml, 18.93 mmoles) gave **7** in 50% yield (0.82 g), mp 112 – 113° from methanol; ir: ν_{max} 3400 (OH), 1630 (C=N), 1595 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): δ 1.34 (40H, m, CH_2 x 20), 2.33 (3H, s, Ar-Me), 2.55 (4H, t, NCH x 4), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 518 (11) (M^+), 157 (100), 140 (49), 125 (21).

Anal. Calcd. for $C_{34}H_{51}N_3O$: C, 78.87; H, 9.93; N, 8.12. Found: C, 79.10; H, 10.21; N, 8.26.

5,7-Dipyrrolidino-2-methyl-8-hydroxyquinoline (**8**).

Pyrrolidine (1.58 ml, 18.93 mmoles) gave **8** in 70% yield (0.66 g), mp 166- 168° from acetone; ir: ν_{max} 3300 (OH), 1640 (C=N), 1601, 1589 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): 1.34 (8H, m, CH_2 x 4), 2.33 (3H, s, Ar-Me), 2.75 (8H, t, CH_2-N x 4), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 297 (15) (M^+), 157 (100), 125 (25).

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.42; H, 7.65; N, 13.82.

5,7-Dipiperidino-2-methyl-8-hydroxyquinoline (**9**).

Piperidine (1.58 ml, 18.93 mmoles) gave **9** in 80% yield (0.82 g), mp 132 – 134° from acetone; ir: ν_{max} 3300 (OH), 1640 (C=N), 1601, 1589 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): 1.34 (12H, m, CH_2 x 6), 2.33 (3H, s, Ar-Me), 2.75 (8H, t, CH_2-N x 4), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 325 (15) (M^+), 157 (100), 140 (25), 125 (6).

Anal. Calcd. for $C_{20}H_{27}N_3O$: C, 73.81; H, 8.36; N, 12.91. Found: C, 73.50; H, 8.21; N, 12.65.

5,7-Dipiperazino-2-methyl-8-hydroxyquinoline (**10**).

Using method B, piperazine (1.63 g, 18.93 mmoles) gave **10** in 64% yield (0.66 g), mp 162 – 163° from ethanol; ir: ν_{max} 3400-br (N-H), 3300 (OH), 1640 (C=N), 1601, 1589 (C=C), 1250 cm^{-1} (C-O); ^1H nmr (DMSO-d_6): 2.33 (3H, s, Ar-Me), 2.75 (16H, t-br, CH_2-N x 8), 4.50 (2H, s-br, NH x 2), 5.10 (1H, s, Ar-OH), 7.20 (1H, d, Ph, H-3), 7.28 (1H, s, H-6) 8.11 (1H, d, Ph, H-4); ms: m/z 327 (11) (M^+), 157 (100), 140 (49), 125 (10).

Anal. Calcd. for $C_{18}H_{25}N_5O$: C, 66.03; H, 7.70; N, 21.39. Found: C, 65.95; H, 7.40; N, 21.08.

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