Preparation of 7-Aminoquinolines as Candidate Antiparasitic Agents

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A series of ten 7-quinolinediamines were prepared and evaluated for potential antiparasitic activity against *P. berghei, P. cynomolgi, L. donovani* and *T. rhodesiense. Compounds* **1d** and **8** showed activity being slightly effective against *L. donovani* in hamsters.

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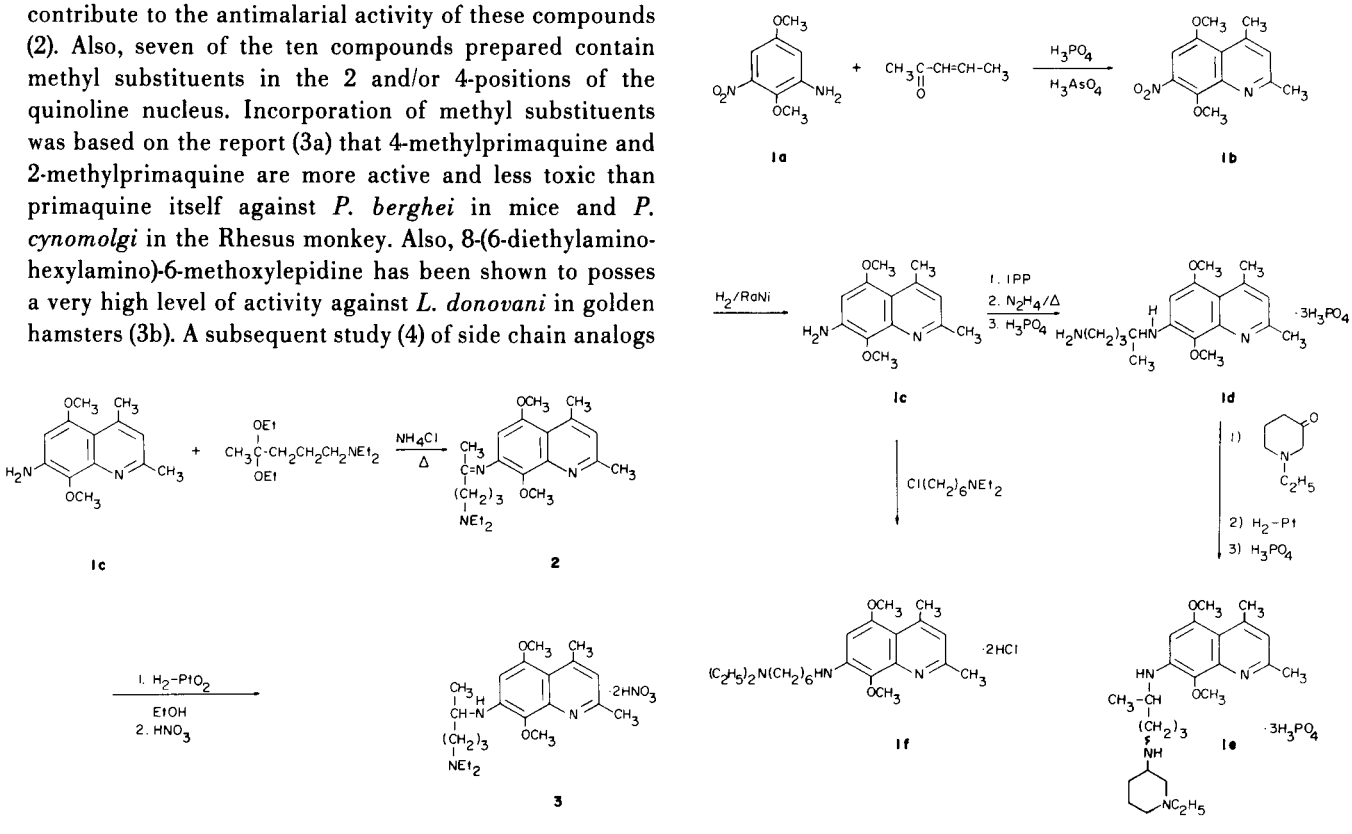
In a preceeding paper (1), we reported the preparations of selected 3 and 5-quinolinediamines for evaluation as potential antimalarials. None of the compounds was active against *P. berghei* in mice; one example was moderately active against *P. cynomolgi* in the Rhesus monkey. In a continuing effort to develop new leads in the aminoquinoline area we undertook the synthesis of ten examples in the 7-quinolinediamine series. To our knowledge very few compounds of this type have been evaluated to date and we felt that the test results obtained for such compounds would shed further light on the effects of the postion of the diamine side chain upon the antiparasitic acitivity of the aminoquinolines. The ten examples prepared all contain methoxy substituents in the 5 and 8 positions of the quinoline nucleus based in part on the controversial theory that quinoid intermediates resulting from *in vivo* transformations of the 8-aminoquinolines contribute to the antimalarial activity of these compounds (2). Also, seven of the ten compounds prepared contain methyl substituents in the 2 and/or 4-positions of the quinoline nucleus. Incorporation of methyl substituents was based on the report (3a) that 4-methylprimaquine and 2-methylprimaquine are more active and less toxic than primaquine itself against *P. berghei* in mice and *P. cynomolgi* in the Rhesus monkey. Also, 8-(6-diethylaminohexylamino)-6-methoxylepidine has been shown to posses a very high level of activity against *L. donovani* in golden hamsters (3b). A subsequent study (4) of side chain analogs of this highly acitive compound indicated that the 6-diethylaminohexylamino side chain appeared to be optimum and three examples in the 7-quinolinediamine series, all containing this effective side chain, were evaluated as potential antileishmanial agents.

Chemistry.

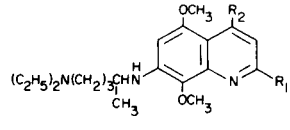
The first four examples (**1d, 1e, 1f,** and **3**) are alkylated analogs of 7-amino-5, 8-dimethoxy-2,4-dimethylquinoline. The preparations of the first three examples **1d, 1e,** and **1f** are shown in Scheme 1. 2,5-Dimethoxy-3-nitroaniline (**1a**) was prepared essentially *via* the procedure described by Burger and Fitchett (5). Condensation of **1a** and 3-penten-2-one under standard Skraup conditions afforded the desired 7-nitroquinoline **1b** which upon catalytic

Scheme I

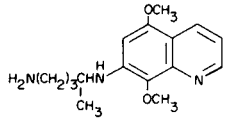


reduction with Raney nickel (6) afforded 7-aminoquinoline **1c**. Condensation of **1c** with 4-iodo-1-phthalimidopentane under conditions previously described (6) afforded the phthalimido-protected 7-quinolinediamine which upon hydrazinolysis afforded the target diamine **1d**. Treatment of **1d** with *N*-ethyl-3-piperidone (7) followed by catalytic reduction of the intermediate Schiff base afforded the second target compound **1e** in this series. Condensation of **1c** with 6-diethylaminohexylchloride under conditions previously described (4) afforded analog **1f**. The fourth example (**3**), bearing the 4-diethylamino-1-methylbutylamino side chain (Pamaquine type) was prepared as shown below.

Attempted introduction of diethylaminopentyl side chain by condensation of compound **1c** with 5-diethylamino-2-pentanone in the presence of mercuric chloride catalyst failed. In view of this, a modified approach, based on the work of Elderfield (8) and Shiho (9) was investigated. The diethylaminopentanone was converted to the diethyl ketal which was condensed with 7-aminoquinoline **1c** using ammonium chloride as catalyst. The condensation proceeded to near completion in 2 hours at 155°. The crude imine **2** was hydrogenated over platinum oxide in ethanol to yield the target diamine **3**. The fifth example (**4**) is the 2-desmethyl analog of **3** and was prepared *via* the procedure described for **3** substituting methyl vinyl ketone for 3-penten-2-one in the Skraup ring closure step. Examples **5,6**, and **7d** are 2,4-desmethyl analogs. The requisite 5,8-dimethoxy-7-nitroquinoline was prepared by treating aniline **1a** with acrolein. Target diamines **5** and **6** were prepared *via* the procedures described for **1d** and **3**, respectively.



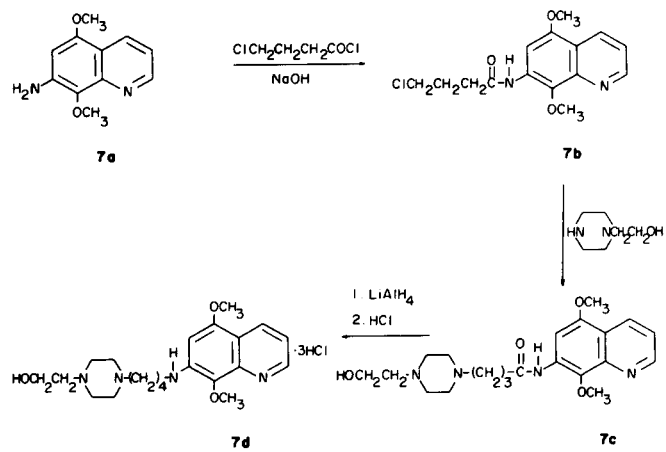
4, R_1 = H, R_2 = CH_3
6, R_1 = R_2 = H



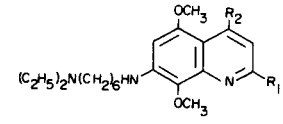
5

Example **7d**, contains a linear side chain bearing a hydroxyethylpiperazinyl moity at the terminus. Condensation of 5,8-dimethoxy-7-aminoquinoline (**7a**) with chlorobutryl chloride afforded the butyramide **7b**. Reaction with commercially-available piperazine ethanol, followed by reduction of the intermediate amide **7c** with lithium alumiunm hydride, afforded the target compound **7d** shown below.

Analogs of **8** and **9** are the 2-desmethyl and 4-desmethyl analogs of **1f** and were prepared *via* condensation of the appropriate 7-aminoquinoline with 6-diethylaminohexyl chloride as described for **1f**.



7a **7b** **7c** **7d**



8, R_1 = H, R_2 = CH_3
9, R_1 = CH_3, R_2 = H

Biology.

The target compounds were submitted to the Walter Reed Army Institute of Research for evalution as potential antiparasitic agents. Compounds **3, 4** and **6** were tested for suppressive antimalarial activity against *P. berghei* in mice (10). All were inactive and not-toxic at 640 mg/kg, the highest dosage tested. Compounds **1d** and **5** were tested for radical curative antimalarial activity against *P. cynomolgi* in the Rhesus monkey (11). Both were inactive. In addition, compounds **1d, 1e, 1f, 5, 7d, 8,** and **9** were tested for antileishmanial activity against *L. donovani* in the hamster (12). Only compounds **1d** and **8** were active with 34% and 26% suppression respectively at a dosage of 208 mg/kg. Finally, examples **1e** and **7d** were tested for antitrypanosomal activity against *T. rhodesiense* in mice (13). Both were inactive.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. The nmr spectra were determined on a Varian Model T60A spectrometer. Ethanol used in this work was specially denatured Grade 3A alcohol (90% ethanol, 5% 2-propanol and 5% methanol by volume). Commercial Raney nichel was purchased from W. R. Grace Co. (No. 30). Silica gel was purchased from EM Labs (70-230 mesh).

2,4-Dimethyl-5,8-dimethoxy-7-nitroquinoline (**1b**).

A mixture of 2,5-dimethoxy-3-nitroaniline (5) (10 g, 0.05 mole), arsenic acid (14.2 g, 0.1 mole) and phosphoric acid (95%, 50 ml) was heated in an oil bath to 100° (internal temperature). The oil bath was removed and 3-penten-2-one (80% pure by vpc, 7.9 g, 0.075 mole) was added dropwise

with vigorous stirring at such a rate that the reaction was maintained at 100 +2°. The resulting mixture was heated at 100° with stirring for an additional hour. The mixture was then poured into ice water (200 ml) and the aqueous solution was made alkaline (*p*H 8) with ammonium hydroxide. The precipitated solid was collected and dried *in vacuo* at 70° overnight. The dried solid was extracted (using a Soxhlet) overnight with boiling cyclohexane. Concentration of the extract yielded 10.9 g of crude product, mp 130-134°. Recrystallization from ethyl acetate (Norit A) gave the title quinoline isolated in two crops, 7.7 g, mp 134-136° and 1.4 g, mp 134-135°, (69%).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.78; H, 5.50; N, 10.84.

The following 7-nitroquinolines were prepared similarly.

5,8-Dimethoxy-4-methyl-7-nitroqinoline.

This compound was obtained in a yield of 48%, mp 156-158° (acetic acid-ethyl acetate).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.29; H, 5.00; N, 11.30.

5,8-Dimethoxy-7-nitroquinoline.

This compound was obtained in a yield of 30%, mp 150-151° (ethyl acetate).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.31; N, 11.96. Found: C, 56.39; H, 4.36; N, 12.17.

5,8-Dimethoxy-2-methyl-7-nitroquinoline.

This compound was obtained in a yield of 40%, mp 147-149° (ethyl-acetate)

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.11; H, 4.99; N, 11.29.

7-Amino-5,8-dimethoxy-2,4-dimethylquinoline (**1c**).

5,8-Dimethoxy-2,4-dimethyl-7-nitroquinoline (**1b**) (9 g, 0.037 mole) was suspended in ethanol (180 ml) and hydrogenated in a Parr apparatus (initial pressure 50 psig) for 30 minutes over active Raney nickel catalyst (4 g wet weight). The solution was filtered (celite) to remove the catalyst. The filtrate was concentrated to dryness and the solid residue was recrystallized from benzene to yield 7.6 g (95%) of the title compound, mp 166-168°.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.30; H, 6.87; N, 12.24.

The following 7-aminoquinolines were prepared similarly.

7-Amino-5,8-dimethoxy-4-methylquinoline.

This compound was obtained in a yield of 97%, mp 139-142° (benzene).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.17; H, 6.46; N, 12.72.

7-Amino-5,8-dimethoxyquinoline (**7a**).

This compound was obtained in a yield of 79%, mp 156-158° (benzene).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.44; H, 6.29; N, 13.66. Found: C, 64.67; H, 6.00; N, 13.70.

7-Amino-5,8-dimethoxy-2-methylquinoline.

This compound was obtained in a yield of 81%, mp 120.5-122° (benzene).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.35; N, 12.61.

7-(4-Amino-1-methylbutylamino)-5,8-dimethoxy-2,4-dimethylquinoline Triphosphate (**1d**).

7-Amino-5,8-dimethoxy-2,4-dimethylquinoline (**1c**) was condensed with 4-iodo-1-phthalimidopentane in the presence of triethylamine as described earlier (6). The yield was 30%, mp 233-235° (methanol).

Anal. Calcd. for $C_{18}H_{27}N_3O_2 \cdot 3H_3PO_4$: C, 35.35; H, 5.93; N, 6.87; P, 15.19. Found: C, 35.29; H, 6.10; N, 6.95; P, 14.98.

7-(4-Amino-1-methylbutylamino)-5,8-dimethoxyquinoline Diphosphate (**5**).

This compound was similary prepared and was obtained in a yield of 28%, mp 200-203° (ethanol).

Anal. Calcd. for $C_{16}H_{29}N_3C_{10}P$: C, 39.59; H, 6.02; N, 8.66; P, 12.76. Found: C, 39.25; H, 6.27; N, 8.54; P, 12.54.

5,8-Dimethoxy-2,4-dimethyl-7-[5-(1-ethyl-3-piperidylamino)-2-pentylamino]quinoline Triphosphate (**1e**).

To a solution of **1d** (3.2 g, 0.01 mole) in ethanol (100 ml) was added *N*-ethyl-3-piperidone (7) (1.67 g, 0.013 mole) in ethanol (10 ml). The mixture was hydrogenated at 50 psig for 6 hours over platinum oxide. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in ether and acidified with ehtanolic phosphoric acid (10% phosphoric acid in ethanol). The yellow solid was separated and crystallized from ethanol to give the title compound (3.3 g, 44%), mp 110-114°.

Anal. Calcd. for $C_{25}H_{40}N_4O_2 \cdot 3H_2O$: C, 38.51; H, 7.49; N, 7.18; P, 11.91. Found: C, 38.42; H, 7.70; N, 7.05; P, 12.09.

7-(6-Diethylaminohexylamino)-5,8-dimethoxy-2,4-dimethylquinoline Dihydrochloride (**1f**).

A mixture of **1c** (5 g, 0.02 mole) and 6-diethylaminohexyl chloride (5 g, 0.0236 mole) was stirred at 120-125° for 16 hours. Additional 6-diethylaminohexyl chloride (2.5 g) was added and the mixture was heated for an additional 3 hours. The resulting gummy solid was dissolved in hot chloroform (3 × 50 ml), cooled, and 20% sodium hydroxide (150 ml) was added. The aqueous layer was extracted with chloroform (2 × 150 ml). The combined chloroform layer was washed with water (2 × 200 ml), brine (200 ml) and dried (sodium sulfate). Concentration *in vacuo* afforded a dark brown oil (8.5 g). The crude product was chromatographed over silica gel (500 g), and eluted with chloroform-methanol-ammonium hydroxide (650:150:3) to afford recovered 2,4-dimethyl-5,8dimethoxy-7-aminoquinoline (2.5 g), pure alkylation product (2.4 g) and an additonal quantity of fairly pure product (0.3 g). The pure base (2.4 g) was treated with hydrogen chloride-2-propanol (3.06 *N*, 3.8 ml) to afford pure title compound (1.3 g, 30% yield based on recovered starting material), mp 214-216°.

Anal Calcd. for $C_{23}H_{39}Cl_2N_3O_2$: C, 59.99; H, 8.59; Cl, 15.40; N, 9.13. Found: C, 60.05; H, 8.30; Cl, 15.15; N, 9.16.

The following compounds were prepared similarly.

7-(6-Diethylaminohexylamino)-5,8-dimethoxy-4-methylquinoline Dihydrochloride (**8**).

This compound was obtained in a yield of 39%, mp 205-207° (acetonitrile).

Anal. Calcd. for $C_{22}H_{37}Cl_2N_3O_2$: C, 59.18; H, 8.29; Cl, 15.88; N, 9.41. Found: C, 58.93; H, 8.37; Cl, 15.69; N, 9.15.

7-(6-Diethylaminohexylamino)-5,8-dimethoxy-2-methylquinoline Dinitrate (**9**).

This compound was obtained in a yield of 30%, mp 185-187° (2-propanol).

Anal. Calcd. for $C_{22}H_{37}N_5O_8$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.11; H, 4.99; N, 11.29.

5-Diethylamino-2,2-diethoxypentane.

Hydrogen chloride was slowly passed with stirring into a cold (ice-bath) mixture of 5-diethylamino-2-pentanone (78.5 g, 0.5 mole), triethyl orthoformate (90 ml, 0.5 mole) and anhydrous ethanol (105 ml, 1.7 mole) until the brown solution became red-purple in color indicating that the solution was acidic (*ca.* *p*H 2). The resulting mixture was refluxed on a steam bath for 1 hour, cooled and treated with aqueous sodium hydroxide (25 g in 200 ml of water). The mixture was extracted with ether (2 × 100 ml), and the combined extracts were dried (potassium carbonate) and evaporated. The residue was distilled under reduced pressure to afford 100 g (86%, 95% pure by vpc, 6 ft. 10% Carbowax 20 M on Chromosorb W) of

the title compound, bp 60-68°/0.25 mm. (lit (14), bp 117°/14 mm).

7-(4-Diethylamino-1-methylbutylamino)-5,8-dimethoxy-2,4-dimethylquinoline Dinitrate (**3**).

A mixture of **1c** (16 g, 0.07 mole), 5-diethylamino-2,2-diethoxypentane (24 g, 0.1 mole) and ammonium chloride (0.1 g) was heated (oil bath) with stirring at 155° (internal temperature) for 2 hours. Ethanol (5.9 g, 92%) was allowed to distill from the reaction mixture during this period. The oily residue was taken up in anhydrous ethanol (175 ml) and hydrogenated (50 psig) for 20 hours over prereduced platinum oxide (0.32 g). The mixture was filtered, the solvent was removed under aspirator pressure and excess diethyl ketal was removed by distillation under reduced pressure. The residue was taken up in petroleum ether and filtered. The filtrate was evaporated to give 26 g of the crude product as the free base. The crude product (25 g) was repeatedly chromatographed over silica gel (250 g, eluted with benzene-ethanol, 5:1, then ethanol). A total of 12.9 g of pure product was isolated. Treatment with ethereal nitric acid gave 16 g of dinitrate salt, np 230-232°/dec. The crude salt was recrystallized once from ethanol and once from methanol-ethyl acetate to yield 13.5 g (39%) of the title compound, mp 238°/dec.

Anal. Calcd. for $C_{22}H_{37}N_5O_8$: C, 52.89; H, 7.47; N, 14.02. Found: C, 52.68; H, 7.31; N, 13.98.

The following 7-quinolinediamines were prepared similarly.

7-(4-Diethylamino-1-methylbutylamino)-5,8-dimethoxy-4-methylquinoline Dinitrate (**4**).

This compound was obtained in a yield of 64%, mp 209-210° (ethanol).

Anal. Calcd. for $C_{21}H_{35}N_5O_8$: C, 52.06; H, 7.07; N, 14.45. Found: C, 51.89; H, 7.26; N, 14.19.

7-(4-Diethylamino-1-methylbutylamino)-5,8-dimethoxyquinoline Dinitrate (**6**).

This compound was obtained in a yield of 46%, mp 177-179° (ethanol-ethyl acetate).

Anal. Calcd. for $C_{20}H_{33}N_5O_8 \cdot H_2O$: C, 49.07; H, 7.21; N, 14.31. Found: C, 49.08; H, 6.95; N, 14.15.

7-(4-Chlorobutyramido)-5,8-dimethoxyquinoline (**7b**).

To a solution of 5,8-dimethoxy-7-aminoquinoline (6.1 g, 0.03 mole) in benzene (150 ml), 4-chlorobutyryl chloride (4.7 g, 0.033 mole) and sodium hydroxide (1.6 g, 0.04 mole in 50 ml of water) were added simultaneously from two dropping funnels. After the addition was complete, the mixture was stirred for 2 hours. The organic layer was separated, washed with water, dried (potassium carbonate) and the solvent was evaporated under reduced pressure. The crude product was recrystallized from benzene-petroleum ether to give pale yellow crystals (6.3 g, 68%), mp 140-142°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; Cl, 11.48; N, 9.02. Found: C, 58.13; H, 5.83; Cl, 11.46; N, 8.81.

5,8-Dimethoxy-7-[4-[(2-hydroxyethyl)-1-piperazinyl]-1-butyramido]quinoline Trihydrochloride (**7c**).

The above intermedate **7b** (3.08 g, 0.01 mole) and *N*-(2-hydroxyethyl)piperazine (2.86 g, 0.22 mole) in benzene (100 ml) were refluxed for 24 hours. The solvent was evaporated under reduced pressure. The residue was slurried with chloroform (150 ml) and washed with cold water (3 × 10 ml). The organic layer was dried (potassium carbonate), treated with charcoal (Norit) and concentrated *in vacuo*. The residual yellow oil was dissolved in ethanol (10 ml) and acidified with ether-hydrogen chloride. The yellow solid was separated and crystallized from ethanol (× 3) to give the title compound (3.3 g, 65%), mp 230-233°.

Anal. Calcd. for $C_{21}H_{30}N_4O_4 \cdot 3HCl \cdot H_2O$: C, 47.60; H, 6.60; Cl, 20.06; N, 10.57. Found: C, 47.65; H, 6.61; Cl, 19.90; N, 10.42.

5,8-(Dimethoxy-7-[4-[(2-hydroxyethyl)-1-piperazinyl]-1-butylamino]-quinoline Trihydrochloride (**7d**).

The above trihydrochloride (5.3 g, 0.01 mole) was suspended in chloroform and made alkaline with 40% sodium hyroxide. The organic layer was dried (potassium carbonate) and concentrated. The residual free base (4 g) was dissolved in tetrahydrofuran (100 ml) and slowly added to a suspension of lithium aluminum hydride (1.5 g) in ether (100 ml). The suspension was refluxed for 24 hours and the solvents were partly distilled. Fresh ether was added (200 ml) and excess lithium aluminum hydride was decomposed by careful addition of ice-cold water (20 ml). The solids were separated, washed with ether and the organic layer was evaporated to dryness. The residue was suspended in ether (100 ml), filtered and acidified with ether-hydrogen chloride. The precipitate was separated and recrystallized from ethanol-ether to give the title compound (3.1 g, 60%), mp 120-123°.

Anal. Calcd. for $C_{21}H_{35}Cl_3N_4O_3 \cdot 2H_2O$: C, 47.24; H, 7.26; Cl, 19.91; N, 10.49. Found: C, 47.36; H, 6.90; Cl, 19.82; N, 10.69.

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