Reduced 8-Aminoquinoline Analogues as Potential Antimalarial Agents

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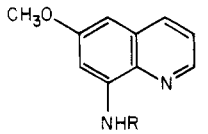
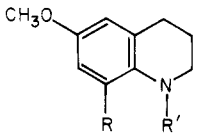
The synthesis of 1-alkyl-8-(aminoalkylamino)-6-methyl-1,2,3,4-tetrahydroquinolines, 8-(4′-amino-1′-methylbutylamino)-6-methoxy-1-methyl-1,2-dihydroquinoline, 5-substituted 8-(4′-amino-1′-methylbutylamino)-1-methyl-1,2-dihydroquinolines, 8-alkylamino-1-(2-*N*,*N*-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinolines, 1-(2-*N*,*N*-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline, 1-(2-*N*,*N*-diethylaminoethyl)-8-(2-*N*,*N*-diethylaminoethylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline, and 2-substituted 8-methoxy-5,6-dihydro-4-imidazo[*i*,*j*]quinolines is described. These compounds as well as most of the intermediates used in their preparation were tested against *Plasmodium berghei* in mice, and a few compounds were tested for prophylactic activity against *Plasmodium cynomolgi* in rhesus monkeys.

The 8-aminoquinolines such as pamaquine (**1a**) and primaquine (**1b**) are highly active against the primary exoerythrocytic forms of *Plasmodium vivax* and *Plasmodium falciparum* and against the gametocytes of all four species of plasmodia that infect man.[1-3] In fact, the main clinical value of these drugs derives from their ability to destroy the exoerythrocytic forms of both *P. vivax* and *Plasmodium malariae*, a property not common to any other group of compounds so far tested.

The effect of variation of the nuclear substituent as well as the position-8 side chain in the 8-aminoquinolines has been extensively investigated and summarized.[2,3] In addition, 8-(5-diethylamino-2-pentylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline (**2a**, tetrahydropamaquine), a reduced analogue of pamaquine, was shown to possess an activity of 30 Q[4] in *Plasmodium lophurae* in duck (suppressive test) and an activity of 15 Q in *Plasmodium gallinaceum* in chick (suppressive test).[5a] In latter studies Gray and Hill reported that tetrahydropamaquine (**2a**) was approximately one-fourth as active as the parent compound against *P. gallinaceum* in chicks and *Plasmodium relictum* in canaries.[6] In clinical trials tetrahydropamaquine was found to be both less active and less toxic than pamaquine against *P. falciparum* gametocytes.[5,6] The 1-substituted analogue, 1-(9-diethylaminononyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (**2b**), was active against *P. lophurae* in turkeys (prophylactic test).[5b] To

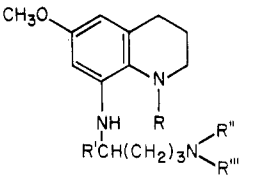


1a, R = $-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
b, R = $CH(CH_3)(CH_2)_3NH_2$



2a, R = $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$; R′ = H
b, R = H; R′ = $(CH_2)_9N(C_2H_5)_2$

our knowledge no other reduced analogues have been tested. In the present paper we describe the preparation and test results obtained on some 1-alkyl-8-(aminoalkylamino)-6-methoxy-1,2,3,4-tetrahydroquinolines (**3**), 8-(alkylamino)-1-(2-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinolines (**4**), 1-alkyl-8-(aminoalkylamino)-6-methoxy-1,2-dihydroquinolines (**5**), and 2-substituted 8-methoxy-5,6-dihydro-4-imidazo[*i*,*j*]quinolines (**6**).



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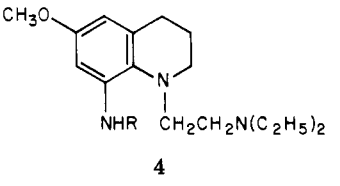

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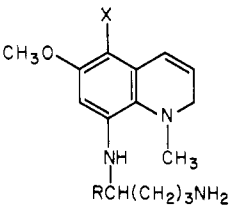

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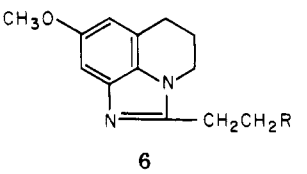

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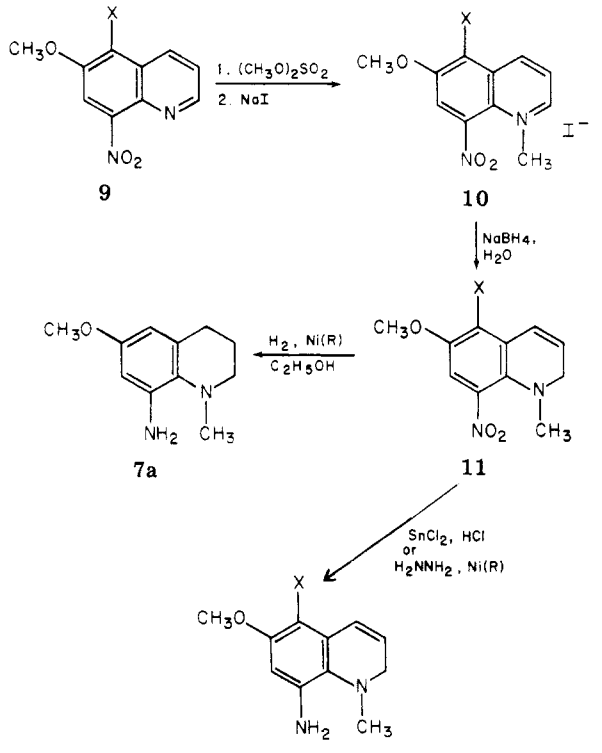
Chemistry. In order to achieve the synthesis of the desired 1-alkyl-8-(aminoalkylamino)-6-methoxy-1,2,3,4-tetrahydroquinolines (**3** and **4**) and the 1-alkyl-8-(aminoalkylamino)-6-methoxy-1,2-dihydroquinolines (**5**), it was necessary to devise synthetic schemes for the preparation of 1-alkyl-8-amino-6-methoxy-1,2,3,4-tetrahydroquinolines (**7**) and 1-alkyl-8-amino-6-methoxy-1,2-dihydroquinolines (**8**), followed by the incorporation of an appropriate side chain at position 8.

A synthetic procedure for the preparation of 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**) and 8-amino-6-methoxy-1-methyl-1,2-dihydroquinoline (**8**) was developed and is shown in Scheme I. Conversion of the appropriate 6-methoxy-8-nitroquinoline (**9**) to the methiodides (**10**)[7] followed by reduction of **10** with sodium borohydride yielded the corresponding 6-methoxy-1-methyl-8-nitro-1,2-dihydroquinoline (**11**). The 8-nitro compounds **11a–c** gave **8a–c** on reduction with stannous chloride or hydrazine in the presence of Raney nickel and **11a** afforded 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**) on catalytic reduction with Raney nickel catalyst. Since the alkylation of **9a** to give 1-butyl-6-methoxy-8-nitroquinolinium salts occurred in only very low yield, we developed a different procedure for the preparation of **7b** and **7c** which is shown in Scheme II. Reduction of **9** with sodium borohydride in acetic acid gave the dihydro derivative **12**[8] which on butyrylation gave **13**. Treatment of **13** with diborane followed by treatment with acetic acid effected both reduction of the 3,4 double bond and the amide group to give **14**. Reduction of **14a** and **14b** with Raney nickel and hydrazine gave the desired amine **7b** and **7c**, respectively.

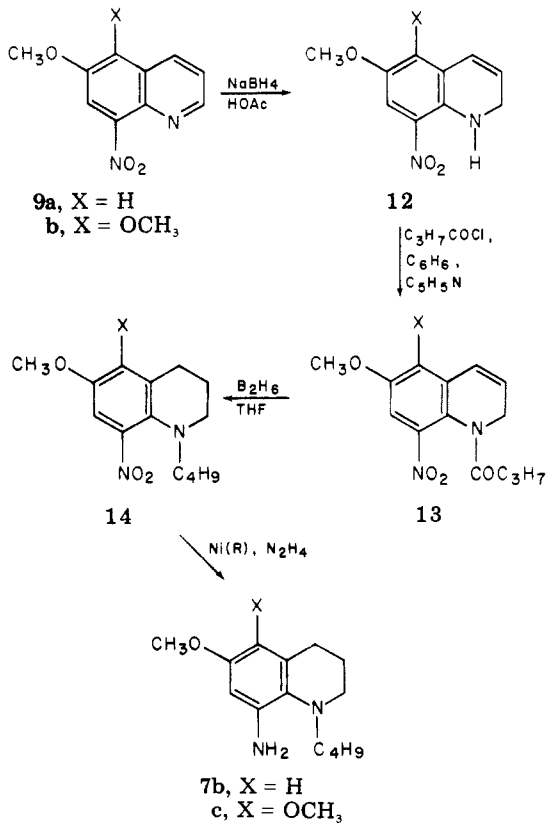
The second phase of these syntheses involved the attachment of side chains to the amines **7** and **8**. The 4-*N*,*N*-diethylaminobutyl side chain was attached to **7a** and **7b** as shown in Scheme III. Condensation of **7a** and **7b**

Scheme I



a, X = H
b, X = CH_3O
c, X = *p*-ClC_6H_4S

Scheme II



with *N,N*-diethylsuccinamic acid (prepared from succinic anhydride and diethylamine) using DCI as the coupling agent gave the corresponding amides **15a** and **15b**. Reduction of **15a** and **15b** with diborane or sodium bis(2-methoxyethoxy)aluminum hydride yielded 8-(4-diethylaminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**3a**) and 1-butyl-8-(4-diethylaminobutylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline (**3b**), respectively.

We devised two methods for adding the 4-aminobutyl side chain to **7a** which are also outlined in Scheme III. In one scheme **7a** was condensed with *N*-benzylsuccinamic acid (prepared from succinic anhydride and benzyl amine) in the presence of DCI to give **15c**. Reduction of **15c** with diborane afforded 8-(4′-benzylaminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**3c**) which also served as an intermediate for the preparation of the 8-(4-aminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**3d**). This conversion was effected by catalytic debenzylation of **15c** using palladium-on-carbon catalyst in ethanol containing hydrochloric acid. An alternate synthesis of **3d** involved the alkylation of **7a** with *N*-(4-bromobutyl)phthalimide to give **16a** followed by removal of the phthaloyl-protecting group with hydrazine.[9] If **7a** and **8a–c** were alkylated with 4-bromo-1-phthalimidopentane in the presence of a base, the protected derivatives **16a–e** were obtained. Treatment of **16** with hydrazine in ethanol gave the primaquine analogue **3e**, **5a**, and **5b**.

The synthesis of the 8-alkylamino-1-(2-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinolines (**4**) is shown in Scheme IV. Acylation of **17** with butyryl chloride or ethyl chloroformate yields **18a** and **18b** which on reduction gave **19a** and **19b**, respectively. Treatment of **19a** and **19b** with sodium and alcohol afforded **20a** and **20b** which yielded 8-butylamino-1-(2-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (**4a**) and 1-(2-diethylaminoethyl)-6-methoxy-8-methylamino-1,2,3,4-tetrahydroquinoline (**4b**), respectively, on alkylation with diethylaminoethyl chloride.

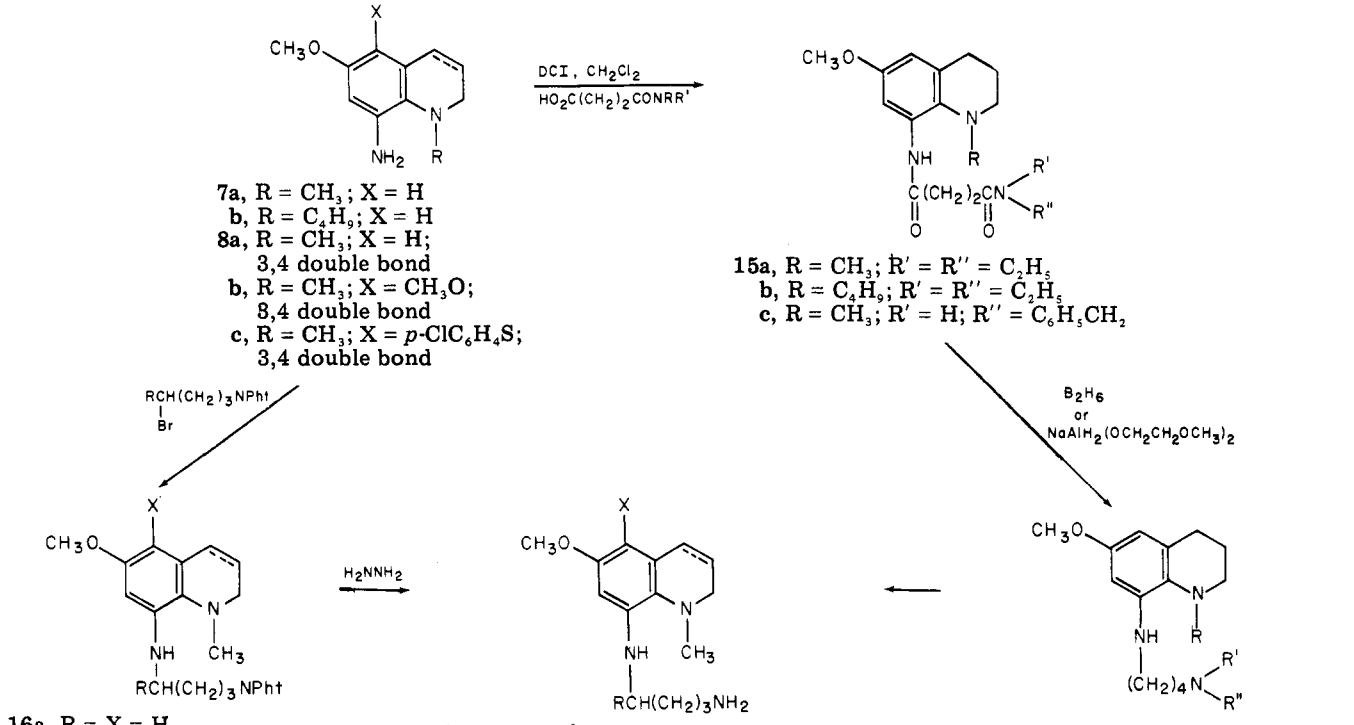
8-(2-*N,N*-Diethylaminoethylamino)-1-(2-*N,N*-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (**4c**) was obtained by the route shown in Scheme V. Alkylation of **17** with *N,N*-diethylaminoethyl chloride followed by reduction with sodium and alcohol afforded **22** which yielded **4c** on treatment with *N,N*-diethylaminoethyl chloride.

Scheme VI outlines the reaction schemes used to prepare 2-(*n*-propyl)-8-methoxy-5,6-dihydro-4-imidazo[*i,j*]quinoline (**6a**), 2-[2′-(*N,N*-diethylcarbimido)ethyl]-8-methoxy-5,6-dihydro-4-imidazo[*i,j*]quinoline (**6b**), and 2-(3-diethylaminopropyl)-8-methoxy-5,6-dihydro-4-imidazo-[*i,j*]quinoline (**6c**). Catalytic reduction of **18a** or **18c**, prepared by coupling **17** with *N,N*-diethylsuccinamic acid, with Adams catalyst in acetic acid or ethanol gives **6a** and **6b**, respectively. Similar compounds have been prepared by Elderfield and Kreysa[10] using a different route. Reduction of **6b** with diborane gave **6c**.

Biological Activity. Compounds **3a–e**, **4a–c**, **6a–c**, **7a,b**, **11a**, **15c**, **18a**, and **22** were tested for antimalarial activity against mice infected with *P. berghei*.[11,12] None of the compounds tested caused any significant increase in mean survival time. Compound **4a** which showed an increase in life span of 5.5 days was the most active compound. The compounds tested were nonlethal to mice at dose levels as high as 640 mg/kg.

Compounds **3e**, **5a**, and **5b** were tested for prophylactic antimalarial activity against *P. cynomolgi* in rhesus monkeys. The results obtained are listed in Table I. Test results were carried out by Dr. L. H. Schmidt, Southern Research Institute, Birmingham, Ala.[13] In this test animals are given an iv injection of 100 000–500 000 sporozoites

Scheme III



7a, R = CH_3; X = H
b, R = C_4H_9; X = H
8a, R = CH_3; X = H; 3,4 double bond
b, R = CH_3; X = CH_3O; 3,4 double bond
c, R = CH_3; X = *p*-ClC_6H_4S; 3,4 double bond

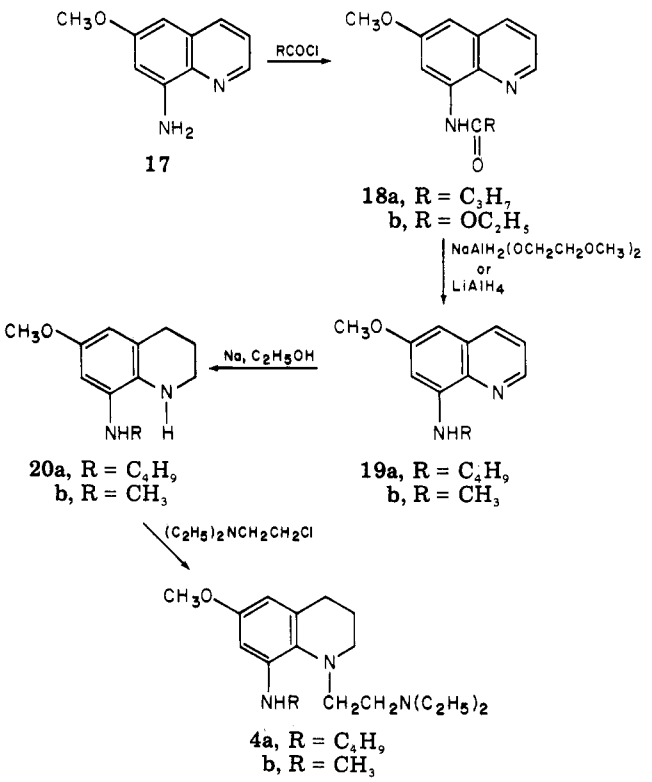
15a, R = CH_3; R' = R'' = C_2H_5
b, R = C_4H_9; R' = R'' = C_2H_5
c, R = CH_3; R' = H; R'' = $C_6H_5CH_2$

16a, R = X = H
b, R = CH_3; X = H
c, R = CH_3; X = H; 3,4 double bond
d, R = CH_3; X = CH_3O; 3,4 double bond
e, R = CH_3; X = *p*-ClC_6H_4S; 3,4 double bond

3d, R = X = H
e, R = CH_3; X = H
5a, R = CH_3; X = H; 3,4 double bond
b, R = CH_3; X = CH_3O; 3,4 double bond

3a, R = CH_3; R' = R'' = C_2H_5
b, R = C_4H_9; R' = R'' = C_2H_5
c, R = CH_3; R' = H; R'' = $C_6H_5CH_2$

Scheme IV



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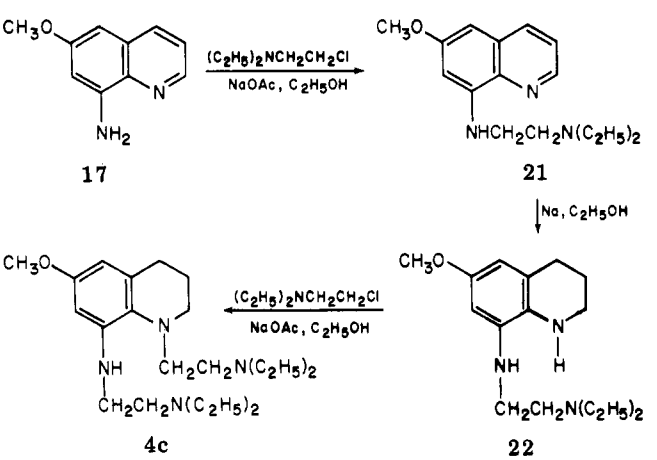
18a, R = C_3H_7
b, R = OC_2H_5

20a, R = C_4H_9
b, R = CH_3

19a, R = C_4H_9
b, R = CH_3

4a, R = C_4H_9
b, R = CH_3

Scheme V



17

21

4c

22

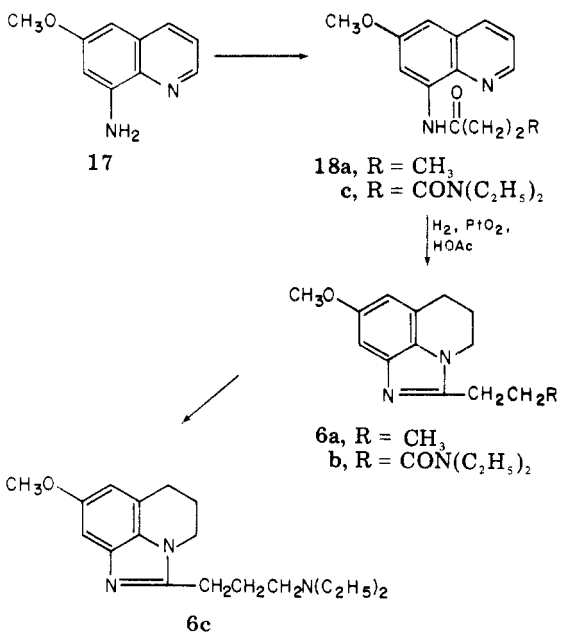
Table I. Antimalarial Test Results against *P. cynomolgi*[a]

Compd[b]	Dose, mg/kg	No. of animals	Cures[c]	Relapses[d]
3e	10	1	0	1 (13)
	1	1	0	1 (10)
5a	10	1	1	0
	1	1	0	1 (11)
5b	10	1	1	0
	1	1	0	1 (12)

[a] Data supplied through courtesy of Dr. E. A. Steck. [b] Compounds were tested as their fumarate salts. [c] Monkeys that do not relapse in 90 days are considered cured. [d] The number in parentheses is the relapse day.

prepared from a homogenate of *A. freeborni* mosquito salivary glands infected with the Bastianelli strain of *P. cynomolgi*. The test compound is administered for nine consecutive days beginning on the day before sporozoite inoculation. Blood examinations are made on the last day of drug administration and are repeated until parasitemia

Scheme VI



is found. If patency is not observed within 60 days after challenge, the compound used is scored as having prophylactic activity. Untreated control monkeys are consistently patent on the eighth day after inoculation. Primaquine serves as a baseline in this test; at 1.0 mg/kg relapse occurs about 12 days post-medication. The two dihydro derivatives, **5a** and **5b**, were curative at a dose level of 10 mg/kg but were inactive at 1.0 mg/kg.

The above data indicate that reduction or partial reduction of the heterocyclic ring of 8-aminoquinidine antimalarials combined with the addition of an alkyl group to the heterocyclic nitrogen either eliminates or lessens their antimalarial activity against *P. berghei* in mice and *P. cynomolgi* in rhesus monkeys.

Experimental Section[15]

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

6-Methoxy-1-methyl-8-nitroquinoline Methiodide (10a). The title compound was prepared by the procedure reported by Mislow and Koepfli.[7] The yield of **10a** was 90–95% of theory, mp 155–157° (lit.[7] mp 149°).

6-Methoxy-1-methyl-8-nitro-1,2-dihydroquinoline (11a). To a solution of 32 g (0.092 mol) of **10a** in 960 ml of water was added 32 g of a sodium borohydride portionwise. Immediate evolution of hydrogen occurred, and a dark red color developed. After 0.5 h the solution was extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to give 19.7 g (97%) of **11a** as dark red crystals. The analytical sample was prepared by recrystallization from an ether and hexane mixture: mp 56–61° (resolidified and melted at 174–180°); ir (CH_2Cl_2) 1565 (C=C), 1518 and 1336 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2.68 (s, >NCH_3), 3.73 (s, CH_3O–), 4.13 (q, NCH_2C=C–), 5.89 (m, ArCH=C*H*–), 6.38 (m, ArC*H*=CH–), 6.67 (d, 5 H, J = 2.8 Hz), and 7.08 ppm (d, 7 H); MS (70 eV) m/e 220. Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

8-Amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (7a). A solution of 0.5 g (2.27 mmol) of **11a** in 35 ml of ethanol containing Raney nickel was hydrogenated in a Parr hydrogenator until hydrogen ceased to be absorbed. The catalyst was removed by filtration. The solid obtained on concentration of the filtrate was recrystallized from a methylene chloride and hexane mixture to give 0.30 g (69%) of **7a**: mp 74–75° (with sublimation); ir (CH_2Cl_2) 3322 and 3418 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 1.88 (m, $3CH_2$), 2.60 (s, CH_3N<), 2.72 (t, $2CH_2$), 3.04 (m, $4CH_2$), 3.68 (s, CH_3O), 6.03 and 6.16 ppm (2 d, 5 and 7 H). Anal. ($C_{11}H_{14}N_2O$) C, H, N.

6-Methoxy-8-nitro-1,2-dihydroquinoline (12a). To an ice-cooled solution of 10 g of 6-methoxy-8-nitroquinoline (**9a**) in 300 ml of acetic acid was added sodium borohydride in small portions until no more starting material remained in the reaction mixture (by TLC analysis). The mixture was diluted with H_2O and extracted with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4). Recrystallization, of the residue obtained on concentration, from a methylene chloride and hexane mixture gave 8.95 g of crystals, mp 145–147°. The analytical sample prepared by recrystallization from the same solvent system had mp 147–148 °C; ir ($CHCl_3$) 3325 (NH) and 1512 and 1319 cm^{-1} (nitro); NMR ($CDCl_3$) δ 3.70 (s, OCH_3), 4.48 (m, NCH_2–), 5.75 (m, 3 H), 6.21 (m, 4 H), 6.57 (d, 5 H, J = 3 Hz), 7.18 (d, 7 H), and 8.11 ppm (broad s, NH). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

1-Butyryl-6-methoxy-8-nitro-1,2-dihydroquinoline (13a). To a solution of 2.06 g (0.01 mol) of 6-methoxy-8-nitro-1,2-dihydroquinoline (**12a**) in 30 ml of dry benzene containing 4 ml of pyridine was added 3.12 g (0.03 mol) of butyryl chloride, and the mixture was refluxed for 1.5 h. The cooled reaction mixture was diluted with water and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and concentrated to a waxy solid. The solid was extracted into hot hexane. On concentration and cooling 2.25 g (81%) of crystalline **13a** separated, mp 115–117°. The analytical sample was prepared by recrystallization from a methylene chloride and hexane mixture: mp 118–119 °C; ir ($CHCl_3$) 1670 (amide C=O), 1535 cm^{-1} (nitro); NMR ($CDCl_3$) δ 0.98 (t, CH_2CH_3), 2.48 [m, $-C(=O)CH_2$], 3.82 (s, OCH_3), 4.32 (m, NCH_2–), 6.22 (m, 3 H), 6.55 (d, 4 H), 6.83 (d, 5 H), and 7.27 ppm (d, 7 H). Anal. ($C_{14}H_{16}N_2O_4$) C, H, N.

8-Amino-1-butyl-6-methoxy-1,2,3,4-tetrahydroquinoline (7b). To a suspension of 6.52 g (0.02 mol) of 1-butyryl-6-methoxy-8-nitro-1,2-dihydroquinoline (**13a**) in 50 ml of sodium-dried ether under nitrogen was added a solution of 25 ml of 1 M diborane–tetrahydrofuran complex in tetrahydrofuran at 25°. The mixture was then stirred for 4.5 h at 25°. The excess diborane was destroyed by slow addition of excess acetic acid. The mixture was heated on a steam bath for 0.5 h, cooled, diluted with H_2O, and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and concentrated to give 4.8 g of an oil. The product was chromatographed on alumina III (250 g) using chloroform as the eluent. The product fraction was collected and concentrated to give 3.3 g of **14a** as a red oil: ir (CH_2Cl_2) 1505 and 1305 cm^{-1} (nitro); NMR ($CDCl_3$) δ 0.85 (t, CH_2CH_3), 3.70 (s, OCH_3), 6.70 (d, 5 H), and 7.02 ppm (d, 7 H).

A mixture of 300 mg (1.14 mmol) of 1-butyl-6-methoxy-8-nitro-1,2,3,4-tetrahydroquinoline (**14a**), 10 ml of absolute alcohol, and 1.5 ml (large excess) of hydrazine was stirred with a catalytic amount of Raney nickel (approximately 50 mg) until the evolution of gas stopped and the red solution turned colorless. The catalyst was removed by filtration. The residue obtained after concentration of the filtrate on a rotary evaporator was dissolved in chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The solid obtained was recrystallized from hexane to give 225 mg (84%) of **7b**, mp 61–63 °C. The analytical sample prepared by recrystallization from hexane had mp 63–64 °C; ir (CH_2Cl_2) 3430 and 3300 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 0.95 (t, $-CH_3$), 2.71 (t, $-NCH_2$), 3.02 (m, $4-CH_2$), 3.68 (s, $-OCH_3$), 6.00 (d, 5 H), and 6.12 ppm (d, 7 H). Anal. ($C_{14}H_{22}N_2O$) C, H, N.

5,6-Dimethoxy-8-nitro-1,2-dihydroquinoline (12b). To an ice-cooled solution of 10 g (0.0428 mol) of 5,6-dimethoxy-8-nitroquinoline (**9b**)[14] in 300 ml of acetic acid was added sodium borohydride in small portions until no more starting material remained in the mixture (by TLC analysis). The reaction mixture was diluted with 300 ml of water and extracted with chloroform. The chloroform extract was washed thoroughly with water, dried (Na_2SO_4), and concentrated to dryness. The solid obtained was recrystallized from a methylene chloride and hexane mixture to give 9.85 g (97%) of product, mp 116–118 °C. The analytical sample prepared by crystallization from a methylene chloride–hexane mixture had mp 118–119 °C; ir ($CHCl_3$) 3345 (NH) and

1505 and 1312 cm^{-1} (nitro); NMR ($CDCl_3$) δ 3.77 (s, 5-OCH_3), 3.84 (s, 6-OCH_3), 4.45 (m, $-NCH_2-$), 5.71 (m, 3 H), 6.60 (m, 4 H), 7.27 (s, 7 H), and 8.22 ppm (broad s, NH). Anal. ($C_{11}H_{11}N_2O_4$) C, H, N.

1-Butyryl-5,6-dimethoxy-8-nitro-1,2-dihydroquinoline (13b). To a solution of 2.34 g (0.01 mol) of 5,6-dimethoxy-8-nitro-1,2-dihydroquinoline (**12b**) and 4 ml of pyridine in 30 ml of dry benzene was added 3.12 g (0.03 mol) of butyryl chloride. The mixture was refluxed for 4.5 h. The cooled reaction mixture was diluted with 150 ml of H_2O and extracted with chloroform. The organic extracts were washed with water, dried (Na_2SO_4), and concentrated to a waxy residue. The material was extracted with hot hexane. On concentration and cooling 2.05 g (71%) of **13b** as orange-red crystals was obtained, mp 79–81 °C. The analytical sample prepared by recrystallization from an ether and hexane mixture had mp 81–82 °C; ir ($CHCl_3$) 1675 (amide C=O) and 1530 and 1340 cm^{-1} (nitro); NMR ($CDCl_3$) δ 0.98 (t, CH_2CH_3), 2.47 [m, $C(=O)CH_2-$], 2.47, 3.89 (2 s, 5- and 6-OCH_3), 6.25 (m, 3 H), 6.88 (d, 4 H), and 7.38 ppm (s, 7 H). Anal. ($C_{15}H_{18}N_2O_5$) C, H, N.

8-Amino-1-butyl-5,6-dimethoxy-1,2,3,4-tetrahydroquinoline (7c). To a suspension of 1.25 g (0.004 mol) of 1-butyryl-5,6-dimethoxy-8-nitro-1,2-dihydroquinoline (**13b**) in 25 ml of sodium-dried ether under nitrogen was added a solution of 10 ml of 1 M diborane–tetrahydrofuran complex in tetrahydrofuran at 25°. The mixture was then stirred overnight at 25°. The excess diborane was destroyed by slow addition of excess acetic acid. The mixture was heated on a steam bath for 0.5 h, cooled, diluted with H_2O, and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and concentrated to give 1.05 g of an oil. The product was chromatographed on alumina III (50 g) using chloroform as the eluent. The product fraction was collected and concentrated to give 0.85 g (71%) of **14b** as a red oil: ir ($CHCl_3$) 1517 cm^{-1} (nitro).

A solution of 0.85 g (0.003 mol) of 1-butyl-5,6-dimethoxy-1,2,3,4-tetrahydroquinoline (**14b**) in 7.5 ml of alcohol was stirred with 0.5 ml of hydrazine (97.8%) and Raney nickel (approximately 1.0 g of the wet catalyst). The reaction was completed within a period of 1.5 h. The catalyst was removed by filtration; the filtrate was concentrated to a small volume, diluted with water, and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and evaporated to dryness. The solid obtained was extracted with hexane. Concentration of the hexane gave 0.54 g (65%) of **7c** as a waxy solid. The analytical sample prepared by recrystallization from hexane had mp 86–87°. Anal. ($C_{14}H_{22}N_2O$) C, H, N.

8-Amino-6-methoxy-1-methyl-1,2-dihydroquinoline (8a). To a solution–suspension of 9.53 g of granular tin, 304 g of $SnCl_2$, 600 ml of concentrated HCl, and 351 ml of ethanol cooled to 0° was added 75 g (0.34 mol) of 6-methoxy-1-methyl-8-nitro-1,2-dihydroquinoline (**11a**) portionwise, such that the temperature never exceeded 10°. After the addition, the temperature was brought to 10° for 1 h and then 25° for 1 h, whereupon the reduction was complete. The reaction was basified (with cooling) and extracted with methylene chloride. The extracts were washed (H_2O), dried (Na_2SO_4), and concentrated to give 38.4 g of a dark oil. Chromatography on alumina III, eluting with 5% THF–C_6H_6, gave 17.6 g (27%) of **8a** as a yellow oil which crystallized on cooling: ir (CH_2Cl_2) 3450 and 3375 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 2.46 (s, CH_3N), 3.57 (m, $2CH_2$), 3.70 (s, CH_3O), 5.76 (m, 3 H), 6.03 and 6.16 (2 d, 5 and 7 H), and 6.43 ppm (m, 4 H). Anal. ($C_{11}H_{11}N_2O$) C, H, N.

5,6-Dimethoxy-1-methyl-8-nitro-1,2-dihydroquinoline (11b). A mixture of 4.68 g (0.02 mol) of 5,6-dimethoxy-8-nitroquinoline (**9b**)[14] and 8 ml of dimethyl sulfate was heated on a steam bath for about 4 h. The mixture was allowed to cool and diluted with 20 ml of H_2O, and excess sodium iodide was added. A red oily liquid separated. The mixture was extracted with chloroform and washed with a small amount of H_2O. Concentration of the dried (Na_2SO_4) extracts gave **10b** as a red liquid which was used without further purification.

Compound **10b** was suspended in water and treated with sodium borohydride portionwise until the reduction was complete (by TLC analysis). The reaction mixture was extracted with ether, washed with water, dried (Na_2SO_4), and concentrated to give 2.4 g of crude product. The product was chromatographed on alumina III (150 g) using chloroform as the eluent. The product fractions were collected, concentrated to dryness, and recrystallized from an ether and hexane mixture to give 1.85 g (37%) of **11b**, mp 80–84°. The analytical sample prepared by recrystallization from an ether–hexane mixture had mp 84–85 °C; ir ($CHCl_3$) 1562 and 1330 cm^{-1} (NO_2); NMR ($CDCl_3$) 2.70 (s, $CH_3N<$), 3.80 and 3.84 (2 s, 5- and 6-CH_3O), 4.08 (m, $NCH_2CH=CH-$), 5.89 (m, $ArCH=CH$), 6.23 (m, $ArCH=CH$), and 7.20 ppm (s, 7 H). Anal. ($C_{12}H_{14}N_2O_4$) C, H, N.

8-Amino-5,6-dimethoxy-1-methyl-1,2-dihydroquinoline (8b). A mixture of 0.5 g (0.002 mol) of **11b**, 10 ml of absolute ethanol, and 1 ml of 95% hydrazine was stirred with 1 g of Raney nickel until the evolution of gas stopped. The catalyst was removed by filtration. The residue obtained after concentration of the filtrate was dissolved in chloroform. The extracts were washed with water, dried (Na_2SO_4), and concentrated on a rotary evaporator. The solid obtained was recrystallized from hexane to give 0.32 g (67%) of **8b** as pale white crystals, mp 83–85°. The analytical sample prepared by sublimation had mp 85–86°; ir (CH_2Cl_2) 3650 and 3345 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 2.44 (s, NCH_3), 3.54 (m, NCH_2), 3.70 and 3.75 (2 s, 5- and 6-CH_3O), 5.79 (m, 3 H), 6.20 (s, 7 H), 6.80 ppm (m, 4 H). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

5-(*p*-Chlorophenylthio)-6-methoxy-8-nitroquinoline (9c). To a solution of 0.10 g (about 4.5 mmol) of sodium dissolved in 5 ml of methanol was added 150 mg (1.04 mmol, 5% excess) of *p*-chlorothiophenol and 283 mg (1 mmol) of 6-methoxy-5-bromo-8-nitroquinoline,[16] and the mixture was refluxed for 0.5 h. The reaction was cooled and diluted with 2 ml of H_2O. The precipitate formed on cooling was recrystallized from absolute ethanol to give 256 mg (75%) of **9c**: mp 156–157 °C; ir ($CHCl_3$) 1612 (aromatic), 1533 and 1322 cm^{-1} (nitro); NMR ($CDCl_3$) δ 3.97 (s, CH_3O), 7.03 (A_2B_2 pattern for *p*-chlorophenylthio group), 7.49 (m, 3 H), 7.79 (s, 7 H), 8.78 (m, 4 H), and 8.89 ppm (m, 2 H). Anal. ($C_{16}H_{11}ClN_2O_3S$) C, H.

5-(*p*-Chlorophenylthio)-6-methoxy-1-methyl-8-nitro-1,2-dihydroquinoline (11c). A mixture of 346 mg (1 mmol) of **9c** and 0.5 ml of dimethyl sulfate was heated on a steam bath for 2 h. The cooled reaction mixture was diluted with 10 ml of MeOH and treated with $NaBH_4$ until no more **9c** remained. The resulting mixture was diluted with H_2O and extracted with chloroform. The extracts were washed with NaCl solution and concentrated to give 0.5 g of dark wax-like substance. The whole mass was chromatographed on an alumina II column (150 g), eluting with benzene. The red fraction was collected to give 250 mg (72%) of **11c** as a red oil: ir ($CHCl_3$) 1560 and 1331 cm^{-1} (nitro); NMR ($CDCl_3$) δ 2.69 (s, NCH_3), 3.68 (s, CH_3O), 4.08 (m, NCH_2-), 5.96 (m, 3 H), 7.02 (m, 4 protons of the *p*-chlorophenylthio group and the 4 H and 7 H on the quinoline ring). This material was used without further purification.

8-Amino-5-(*p*-chlorophenylthio)-6-methoxy-1-methyl-1,2-dihydroquinoline (8c). The reduction of **11c** to **8c** was conducted to the same manner as described for the reduction of **11a** to **8a** using 14 g (0.39 mol) of **11c**, 200 ml of absolute alcohol, 10 ml of 95% hydrazine, and 15 g of wet Raney nickel. The chromatographed (alumina III) product was recrystallized from a methylene chloride and hexane mixture to give 9.02 g (62%) of **8c**, mp 129–130°. The analytical sample prepared by recrystallization from the same solvent had mp 130–131°; ir ($CHCl_3$) 3370 and 3475 (NH_2) and 1595 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 2.44 (s, NCH_3), 3.54 (m, methylene protons of the ring), 3.71 (s, 6-CH_3O), 4.28 (broad s, NH_2), 5.85 (m, 3 H), 6.26 (s, 7 H), 6.91 (m, 4 H), and 6.98 ppm (A_2B_2 pattern for *p*-chlorophenylthio group). Anal. ($C_{16}H_{13}ClNOS$) C, H, Cl, N, S.

8-(4-Diethylamino-1,4-dioxobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (15a). Diethylamine (3.05 g, 41.6 mmol) was added to a suspension of 4.16 g (41.6 mmol) of succinic anhydride in 100 ml of methylene chloride. After 2 h, 8.0 g (41.6 mmol) of 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**) was added followed by 9.44 g (45.8 mmol) of dicyclohexylcarbodiimide. The reaction mixture was stirred at 25° for 2 days. The dicyclohexylurea which had formed was removed by filtration and washed with cold methylene chloride. The oil obtained after concentration of the filtrate was dissolved in dilute hydrochloric acid and extracted with ether. The acid solution was neutralized with 1 N sodium hydroxide solution and extracted with methylene chloride. The dried (Na_2SO_4) extracts

were concentrated to 12.74 g of an oil. Chromatography on alumina III using 5% THF-C_6H_6 as the eluent gave 3.03 g (28%) of **15a** as an oil which crystallized on standing. The analytical sample prepared by recrystallization from benzene-hexane had mp 68–73°; ir (CH_2Cl_2) 3345 (NH), 1678 (amide I), 1630 (amide C=O), and 1522 cm^{-1} (amide II); NMR ($CDCl_3$) δ 1.10 and 1.19 (2 t, $CONCH_2CH_3$), 1.88 (m, 3-CH_2), 2.57 (s, CH_3N), 3.02 (m, 4-CH_2), 3.20–3.50 (2 q, $COCH_2CH_2$–), 3.72 (s, OCH_3), 6.31 and 7.78 (2 d, 5 H and 7 H), and 8.28 ppm (broad s, NH). Anal. ($C_{19}H_{29}N_3O_3$) C, H, N.

8-(4-*N*,*N*-Diethylaminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (3a) Diresorcylate. A three-necked flask equipped with drying tube, septum, and nitrogen inlet was purged with nitrogen and then charged with 3.0 g (8.7 mmol) of **15a** and 40 ml of ether (dried over sodium). Diborane (50 ml of a 1 M solution in THF) was added via a syringe. After stirring overnight, 6 N hydrochloric acid solution was added cautiously followed by 1 N sodium hydroxide solution, and the mixture was extracted with ether. Concentration of the dried (Na_2SO_4) ether extract gave 2.01 g of **3a** as an oil: ir (CH_2Cl_2) 3345 cm^{-1} (NH) and the absence of amide bands; NMR ($CDCl_3$) δ 1.01 (t, CH_2CH_3), 2.56 (s, CH_3N), 3.73 (s, OCH_3), 5.94 and 6.04 ppm (2 d, 5 H and 7 H).

A 1.49-g (4.67 mmol) sample of **3a** was converted to 2.80 g (95%) of the diresorcylate salt. Recrystallization from acetone–hexane followed by recrystallization from ether–hexane gave the analytical sample, mp 91–94° dec. Anal. ($C_{33}H_{45}N_3O_9 \cdot H_2O$) C, H, N.

1-Butyl-8-(4-*N*,*N*-diethylaminobutylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline (3b) Fumarate. Compound **3b** was prepared in a manner analogous to that described for the preparation of **3a**. Starting with 4.68 g (0.02 mol) of **7b**, 3.95 g of **15b** was obtained which was reduced with Vitride [70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene] instead of diborane to give 1.85 g of **3b**.

The fumarate salt was prepared and recrystallized from ethyl acetate: mp 99–101°. Anal. ($C_{26}H_{43}O_5$) C, H, N.

8-(4-Benzylamino-1,4-dioxobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (15c). To a suspension of succinic anhydride (1.56 g, 15.6 mmol) in 200 ml of methylene chloride was added benzylamine (1.83 g, 15.6 mmol). After stirring 1 h, 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**, 3.0 g, 15.6 mmol) was added, followed by dicyclohexylcarbodimide (3.39 g, 16.4 mmol). The reaction mixture was stirred at 25° for 2 days. The dicyclohexylurea which formed was removed by filtration and washed with methylene chloride. The filtrate was concentrated to 8.04 g of an oil. Chromatography on alumina III eluting with 40% THF-C_6H_6 gave 5.81 g of an oil. Recrystallization from acetone–hexane gave 2.94 g (48%) of **15c**, mp 148–150°. The analytical sample prepared by recrystallization from acetone–hexane followed by drying at 140° had mp 150–152°; ir (CH_2Cl_2) 3440 and 3340 (NH), 1670 and 1520 cm^{-1} (amide C=O). Anal. ($C_{22}H_{27}N_3O_3$) C, H, N.

8-(4-Benzylaminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (3c) Dihydrochloride. A three-necked flask equipped with drying tube, nitrogen inlet, and septum was purged with nitrogen and then charged with 6.65 g (17.5 mmol) of **15c** and 125 ml of ether (dried over sodium). Diborane (125 ml of a 1 M solution in tetrahydrofuran) was added via a syringe. The reaction was stirred overnight at 25° and then quenched by cautious addition of 6 N hydrochloric acid solution, followed by 1 N sodium hydroxide solution. The basic solution was extracted with ether, and the extracts were dried (Na_2SO_4) and concentrated to 6.4 g of an oil. Chromatography on alumina III eluting with benzene containing 1% diethylamine and 5% tetrahydrofuran gave 4.46 g (72%) of an oil: ir (CH_2Cl_2) 3350 cm^{-1} (NH) and absence of amide bands; NMR ($CDCl_3$) δ 1.78 (m, methylene protons of ring), 2.56 (s, NCH_3), 2.69 (m, $-NHCH_2CH_2CH_2CH_2NH$), 3.06 (m, $NHCH_2CH_2CH_2CH_2NH$), 3.72 (s, OCH_3), 3.78 (s, $CH_2C_6H_5$), 5.96 (d, J = 2.5 Hz, 5, 7 H), 7.27 (m, aromatic protons).

A 2.1-g (5.95 mmol) sample of **3c** was converted to the dihydrochloride. Recrystallization from ethanol–ether gave 2.06 g (81%) of white crystals, mp 178–181°, with softening beforehand. The analytical sample prepared by recrystallization from the same solvent had mp 180–182°; ir (KBr) 2940–2440 cm^{-1} (NH_2^+). Anal. ($C_{22}H_{33}Cl_2N_3O$) C, H, Cl, N.

8-(4-Aminobutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (3d) Fumarate. Method A. A solution–suspension of **15c** (100 mg, 0.283 mmol) and 20 mg of palladium hydroxide on carbon in 12 ml of ethanol containing 5 drops concentrated hydrochloric acid was hydrogenated on a Parr shaker overnight. The catalyst was filtered off and the filtrate concentrated. The residue was basified with 1 N sodium hydroxide solution and extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated to 65 mg (87%) of an oil: NMR ($CDCl_3$) δ 1.78 (m, methylene protons of ring), 2.56 (s, NCH_3), 2.69 (m, $NHCH_2CH_2CH_2CH_2NH$), 3.06 (m, $NHCH_2CH_2CH_2CH_2NH$), 3.72 (s, OCH_3), 5.92 and 6.10 ppm (2 d, J = 2.5 Hz, 5 and 7 H).

The fumarate salt was prepared and recrystallized from an ethanol and ether mixture, mp 148.5–150°. Anal. ($C_{19}H_{29}N_3O_5$) C, H, N.

Method B. A mixture of 2.5 g (13.5 mmol) of 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**), 3.81 g (13.5 mmol) of *N*-(4-bromobutyl)phthalimide, and 2.2 g (27 mmol) of sodium acetate in 35 ml of ethanol was refluxed for 48 h. The reaction mixture was cooled, diluted with H_2O, and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to give 8.55 g of dark oil. Chromatography on alumina, eluting with a gradient system of C_6H_6, 1% THF-C_6H_6, and 2% THF-C_6H_6, gave 1.88 g (35%) of **16a** as an amber oil: NMR ($CDCl_3$) δ 1.79 (m, methylene protons of ring), 2.53 (s, NCH_3), 2.70 [t, CH_2-N-(phthaloyl)], 3.05 [m, $(CH_2)_3NH$], 3.69 (s, OCH_3), 5.89 and 5.98 (2 d, 5, 7 H, J = 2.5 Hz), and 7.70 ppm (m, phthaloyl protons).

To a solution of 1.86 g (4.74 mmol) of **16a** in 30 ml of ethanol was added 3 ml of hydrazine hydrate. The resulting solution was refluxed for 1 h, cooled, and filtered to remove the precipitated hydrazide. The filtrate was concentrated; the residue was dissolved in methylene chloride and filtered to remove last traces of the hydrazide. Concentration of filtrate gave 1.06 g (85%) of a yellow oil. The NMR ($CDCl_3$) of this sample was identical with that of the product obtained by debenzylation of **3c**.

8-(4-Amino-1-methylbutylamino)-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (3e) Fumarate. A mixture of 5.0 g (26.0 mmol) of 8-amino-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline (**7a**), 7.22 g (26.0 mmol) of 2-bromo-5-phthalimidopentane and 3 ml of triethylamine[17] was heated at 135° (under a dry ice condenser) for 8 h. The reaction mixture was cooled, dissolved in acetone, and filtered to remove triethylamine hydrobromide. The filtrate was concentrated to give 11.26 g of a dark oil. Chromatography on alumina eluting with benzene afforded 1.65 g (16%) of **16b** as a yellow oil: ir (CH_2Cl_2) 1710 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 1.18 (d, CH_3CH), 1.70 (m, methylene protons of ring), 2.54 (s, NCH_3), 2.70 [t, CH_2-N-(pht)], 3.00 (t, $CHCH_2CH_2$), 3.69 (s, OCH_3), 6.42 (m, CH_3CHCH_2), 5.85 and 5.96 (2 d, 5, 7 H), 7.72 ppm (m, phthaloyl protons).

In a manner exactly analogous to the preparation of **3d** from **16a**, 1.65 g (4.06 mmol) of **16b** was treated with 3 ml of hydrazine hydrate in 30 ml of ethanol to give 1.00 g (89%) of yellow oil. The oil was converted to the fumarate salt in the standard manner: 1.12 g (93%); mp 169–171°. The analytical sample prepared by recrystallization from ethanol–ether had mp 170–172°; NMR (polysol) δ 1.18 (d, CH_3CH), 1.70 (m, methylene protons of ring), 2.50 (s, NCH_3), 2.65 (t, CH_2NH_2), 2.95 (t, $CHCH_2CH_2$), 3.64 (s, OCH_3), 5.81 and 5.89 (2 d, 5, 7 H), 6.44 (s, CH=CH). Anal. ($C_{18}H_{29}N_3O_3$) C, H, N.

8-(4′-Amino-1′-methylbutylamino)-6-methoxy-1-methyl-1,2-dihydroquinoline (5a) Fumarate. A mixture of 7.42 g (39.1 mmol) of **8a**, 11.6 g (39.1 mmol) of 4-bromo-1-phthalimidopentane, and 4 ml of triethylamine was heated at 135° for 6 h under a dry ice condenser. The reaction was cooled, dissolved in methylene chloride, and filtered to remove triethylamine hydrobromide. The filtrate was concentrated to 18.26 g of a dark oil. The oil was eluted through 750 g of Florisil, using 2% THF-C_6H_6 as the eluent, to give 9.77 g of amber oil. This was chromatographed on 2 kg of alumina III using a gradient eluent of 2 l. of 1% THF-C_6H_6 into 2 l. of C_6H_6, finishing with 2% THF-C_6H_6. A total of 1.55 g (10%) of **16c** was obtained as a yellow oil: ir (CH_2Cl_2) 1775 and 1712 cm^{-1} (imide C=O); NMR ($CDCl_3$) δ 1.18 (d, CH_3CH), 1.68 (m, $CHCH_2CH_2CH_2N$), 2.39 (s, CH_3N), 3.54 (m, $2CH_2$), 3.70 (m, CH_2N), 3.72 (s, CH_3O), 5.72 (m, 3 H), 5.78

and 6.03 (2 d, 5 and 7 H), 6.39 (m, 4 H), and 7.20 ppm (m, phthaloyl).

A solution of 1.55 g (3.84 mmol) of **16c**, 1 ml of hydrazine hydrate, and 20 ml of ethanol was refluxed for 1.5 h. The reaction was cooled and the precipitated hydrazide removed by filtration. The filtrate was concentrated; the residue was dissolved in methylene chloride and filtered again to remove the last traces of the hydrazide. Concentration of the filtrate gave 991 mg (93%) of the free amine. The fumarate salt was prepared in the standard manner in 97% yield. After recrystallization from ethanol–ether, the salt had mp 115–123° dec. The analytical sample prepared by recrystallization from the same solvent had mp 119–123° dec; NMR (polysol) δ 1.14 (d, CH_3CH), 1.68 (m, CHCH_2CH_2CH_2N), 2.37 (CH_3N), 2.84 (m, –CH_2N), 3.50 (m, 2CH_2), 3.68 (s, CH_3O), 5.70 (m, 3 H), 5.90 and 6.01 (2 d, 5 and 7 H), 6.42 (m, 4 H), and 6.49 ppm (s, CH=CH). Anal. ($C_{20}H_{20}N_3O_5 \cdot 0.5H_2O$) C, H, N.

8-(4′-Amino-1′-methylbutylamino)-5,6-dimethoxy-1-methyl-1,2-dihydroquinoline (5b) Fumarate. The reaction was conducted in the same manner as described for the preparation of **5a** using 506 mg (2.3 mmol) of **8b**, 700 mg (2.36 mmol) of 2-bromo-5-phthalimidopentane, and 1 ml of triethylamine. The chromatographed product (alumina III) was obtained as a viscous yellow oil (307 mg) (30.7%) (a larger scale run gave 25% yield): ir ($CHCl_3$) 1705 cm^{-1} (amide carbonyl); NMR ($CDCl_3$) δ 1.18 (d, CH_3CH), 1.75 (m, CHCH_2CH_2CH_2N), 2.37 (s, NCH_3), 3.52 (m, CH_2), 3.65 and 3.80 (2 s, 5- and 6-CH_3O), 5.78 (m, 3 H), 6.12 (s, 7 H), 6.41 (m, 4 H), and 7.71 ppm (m, phthaloyl protons).

A solution of 3.45 g (0.0079 mol) of 5,6-dimethoxy-1-methyl-8-(4′-phthaloylamino-1′-methylbutylamino)-1,2-dihydroquinoline (**16d**) in 100 ml of absolute alcohol containing 2 ml of hydrazine was refluxed for 1 h. The reaction mixture was cooled, and the hydrazide was removed by filtration. The filtrate was concentrated to dryness, dissolved in 20 ml of methylene chloride, and filtered again to remove the last traces of hydrazide. Concentration of the filtrate gave 2.2 g (88%) of 8-(4-amino-1′-methylbutylamino)-5,6-dimethoxy-1-methyl-1,2-dihydroquinoline (**5b**): ir (CH_2Cl_2) 3400 cm^{-1} showed absence of C=O absorption; NMR ($CDCl_3$) δ 1.20 (d, CH_3CH), 2.40 (s, NCH_3), 3.72 and 3.82 (2 s, 5, 6-OCH_3), 5.80 (m, 3 H), 6.13 (s, 7 H), 6.83 ppm (m, 4 H).

The fumarate salt had mp 164–168 °C dec; NMR (polysol) δ 1.15 (d, CH_3CH), 2.33 (s, CH_3N), 3.48 (d, 2 H), 3.61 and 3.76 (2 s, 5- and 6-OCH_3), 6.14 (s, 7 H), 6.43 (s, –CH=CH– of fumarate), 5.8 (m, 3 H), 6.73 (d, 4 H), 3.48 (d, 2 H, 2 H). Anal. ($C_{19}H_{29}N_3O_4 \cdot 0.25H_2O$) C, H, N.

8-Butyrylamino-6-methoxyquinoline (18a). To a solution of 10 g (0.574 mol) of 8-amino-6-methoxyquinoline (**17**) in 250 ml of benzene containing 10 ml of pyridine was added dropwise 6.31 g (59 mmol) of butyryl chloride and the resulting mixture was stirred 16 h at 25°. The dark-colored reaction mixture was diluted with 1 N sodium hydroxide solution, the organic layer was separated, and the aqueous layer extracted with chloroform. The combined organic layers were dried (Na_2SO_4) and concentrated to give 14.1 g of an oil. The oil was dissolved in chloroform and eluted through an alumina III column using chloroform as the eluent. Concentration of the product fraction followed by recrystallization from hexane gave 13 g (93%) of **18a**, mp 61–62°. The analytical sample prepared by recrystallization from hexane had mp 62–62.5°; ir (CH_2Cl_2) 3345 (NH), 1688 (amide I) and 1528 cm^{-1} (amide II); NMR ($CDCl_3$) δ 1.04 (t, CH_3CH_2, J = 6 Hz), 1.84 (m, CH_2CH_2CH_3), an apparent triplet at 2.53 (COCH_2CH_2CH_3), 3.90 (s, CH_3O), 6.74 (d, 5 H, $J_{5,7}$ = 2.8 Hz), 7.34 (q, 3 H, $J_{3,4}$ = 8.3 and $J_{2,3}$ = 4 Hz), 7.99 (q, 4 H, $J_{4,3}$ = 8.3 and $J_{4,2}$ = 1.5 Hz), 8.51 (d, 7 H, $J_{7,5}$ = 2.8 Hz), 8.58 (q, 2 H, $J_{3,2}$ = 4 and $J_{4,2}$ = 1.5 Hz), and 9.72 ppm (s, NH). Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

8-Butylamino-6-methoxyquinoline (19a). To a solution of 8.54 g (0.03 mol) of 8-butyrylamino-6-methoxyquinoline (**18a**) in 50 ml of sodium-dried benzene under N_2 was added dropwise 22 ml (0.07 mol) of Vitride solution in benzene. The mixture was stirred for 1 h and then refluxed for 30 min. The excess of Vitride was destroyed by careful addition of water and the aqueous layer extracted with chloroform. The combined organic fractions were dried (Na_2SO_4) and concentrated to give a pale red oil. The whole mass was chromatographed on alumina III using benzene–chloroform (1:1) as the eluent. The product fraction was concentrated to give 6.83 g (99%) of **19a** as an oil: ir (CH_2Cl_2) 3400 (NH) and 1620 cm^{-1} (Ar). This product was used in the next step without further purification.

8-Butylamino-1-(β-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (4a) Dihydrobromide. To a solution of 4.5 g (0.019 mol) of 8-butylamino-6-methoxyquinoline (**19a**) in 300 ml of refluxing ethyl alcohol was added 9.0 g of sodium (sodium added in small portions over a period of 1.5 h). After the addition of sodium, the mixture was refluxed for another 1.5 h. The cooled reaction mixture was diluted with water and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and concentrated to give 4.0 g of **20a** as a waxy solid.

To a solution of 4.0 g (0.017 mol) of 8-butylamino-6-methoxy-1,2,3,4-tetrahydroquinoline (**20a**) in 50 ml of ethanol was added 3.4 g of *N,N*-diethylaminoethyl chloride hydrochloride and 3.28 g of anhydrous sodium acetate. The resulting mixture was refluxed for 2.5 h. The cooled mixture was diluted with 100 ml of water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The crude gummy material obtained was chromatographed on alumina III (500 g) using benzene–chloroform (6:4) as the eluent to give 2.2 g of the pure product as an oil: NMR ($CDCl_3$) δ 0.96 (t, –CH_2CH_3), 1.03 (t, NCH_2CH_3), 2.62 (m, NC$H_2$$CH_3$), 3.68 (s, CH_3O), 5.82 (d, 5 H), and 5.95 ppm (d, 7 H). The mass spectra showed m/e 333.

The oil was dissolved in ether and saturated with hydrogen bromide gas. The resulting precipitate was filtered under N_2 and recrystallized from an isopropyl alcohol–ether mixture to give 1.85 g of a pale white dihydrobromide of **4a**: mp 199–201 °C; ir (KBr) 3240–2450 cm^{-1} (broad NH^+). Anal. ($C_{20}H_{37}Br_2N_3O$) C, H, Br, N.

8-Ethoxycarbonylamino-6-methoxyquinoline (18b). To a solution of 20.0 g (0.115 mol) of 8-amino-6-methoxyquinoline (**17**) in 500 ml of dry benzene containing 20 ml of dry pyridine was added dropwise 18.0 g (0.183 mol) ethyl chloroformate. After 24 h at room temperature, the reaction mixture was diluted with H_2O and extracted with benzene. The extracts were dried (Na_2SO_4) and concentrated to give 28.25 g of dark solid. Elution through a short alumina column with benzene as the eluent gave 26.5 g of a yellow solid. Recrystallization from a methylene chloride–hexane mixture gave 25.56 g (90%) of **18b** as yellow crystals, mp 82–23°. The analytical sample prepared by recrystallization from the same solvent system had mp 82–83°; ir (CH_2Cl_2) 3360 (NH) and 1725 cm^{-1} (C=O). Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

6-Methoxy-8-methylaminoquinoline (19b). To a suspension of 6.65 g (0.175 mol) of $LiAlH_4$ in 200 ml of THF (distilled from $LiAlH_4$) was added dropwise a solution of 20.31 g (82.5 mmol) of **18b** in 200 ml of distilled THF. The reaction mixture was refluxed for 2.5 h and then cooled. Water was added cautiously followed by sodium potassium tartrate, and the mixture was extracted with chloroform. The extracts were dried (Na_2SO_4) and concentrated to give 16.50 g of dark oil. Chromatography on alumina eluting with benzene gave 5.42 g (35%) of **19b** as a yellow oil: ir (CH_2Cl_2) 3415 cm^{-1} (NH), absence of C=O; NMR ($CDCl_3$) δ 2.97 (s, NCH_3), 3.85 (s, OCH_3), 6.23 and 6.30 (2 d, 5 H and 7 H, $J_{5,7}$ = 2.5 Hz), 7.24 (q, 3 H, $J_{3,4}$ = 8.3 and $J_{3,2}$ = 4 Hz), 7.86 (q, 4 H, $J_{4,3}$ = 8.3 and $J_{4,2}$ = 1.5 Hz) and 8.47 ppm (q, 2 H, $J_{3,2}$ = 5.3 and $J_{4,2}$ = 1.5 Hz). This product was used in the next step without further purification.

1-(β-Diethylaminoethyl)-6-methoxy-8-methylamino-1,2,3,4-tetrahydroquinoline (4b) Fumarate. In a manner analogous to the preparation of 8-butylamino-1-(β-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (**4a**), 6.99 g (37.1 mmol) of **19b** was reduced with 13.98 g of sodium and then alkylated with 6.39 g (37.1 mmol) of β-diethylaminoethyl chloride hydrochloride and 6.08 g (72.4 mmol) of sodium acetate in 300 ml of ethanol to give 1.28 g (12%) of yellow oil. The oil was converted to the fumarate salt in the usual manner. Recrystallization from ethyl acetate gave 1.17 g of crystals, mp 139–141°. The analytical sample prepared by recrystallization from ethyl acetate had mp 139–140.5°; NMR (polysol-*d*) δ 1.13 (t, CH_3CH_2), 1.75 (m, methylene protons of ring), 2.58 (m, CH_2CH_2N), 2.72 (s, NCH_3), 2.86 (m, CH_2CH_2N), 3.64 (s, OCH_3), 5.80 (broad s, 5 H and 7 H), and 6.56 ppm (s, CH=CH). Anal. ($C_{21}H_{33}N_3O_5$) C, H, N.

8-(4-*N*,*N*-Diethylaminoethylamino)-6-methoxyquinoline (21). A solution of 7.9 g (0.05 mol) of **17**, 8.2 g of sodium acetate, and 8.6 g (0.05 mol) of *N*,*N*-diethylaminoethyl chloride hydrochloride in 80 ml of 65% ethanol was refluxed for 3 days with an additional 8.6 g of *N*,*N*-diethylaminoethyl chloride hydrochloride added each day. The solution was diluted with 300 ml of water, made alkaline with potassium hydroxide pellets, saturated with potassium carbonate, and extracted with ether. The ether extract was dried (Na_2SO_4), the solvent removed, and the residue distilled under reduced pressure. The product, 6.3 g (49%), came over as the highest boiling fraction: bp 180–182° (0.10 mm); NMR ($CDCl_3$) δ 1.03 (t, CH_3CH_3, J = 7 Hz), 2.60 (q, CH_3CH_2), 2.81 and 3.23 (t, and q, CH_2CH_2), 3.84 (s, CH_3O), 6.4 (m, 5 H and 7 H), 7.25 (q, 3 H, $J_{3,4}$ = 8.1 and $J_{2,3}$ = 4 Hz), 7.88 (q, 4 H, $J_{4,3}$ = 8.1 and $J_{4,2}$ = 1.9 Hz), and 8.52 ppm (q, 2 H, $J_{3,2}$ = 4 and $J_{4,2}$ = 1.9 Hz). Anal. ($C_{16}H_{23}N_3O$) C, H, N.

8-(β-*N*,*N*-Diethylaminoethylamino)-1-(β-*N*,*N*-diethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (4c). To a solution of 4.7 g (0.018 mol) of **21** in 300 ml of refluxing ethyl alcohol was added 9.0 g of sodium (added in small portions over a period of 1.5 h). After the addition of sodium, the mixture was refluxed for another 1.5 h. The cooled reaction mixture was diluted with 100 ml of water and neutralized with acetic acid, and 3.1 g (0.018 mol) of *N*,*N*-diethylaminoethyl chloride hydrochloride was added. The mixture was refluxed for 3 days with an additional 3.1 g of *N*,*N*-diethylaminoethyl chloride hydrochloride added each day. The solids that had formed were removed by filtration, and the filtrate was concentrated on a rotary evaporator under reduced pressure. The residue was extracted with chloroform, and these extracts were chromatographed on alumina column using C_6H_6–THF (9:1) as the eluent. Two products were obtained. The first product eluted was 8-(4-*N*,*N*-diethylaminoethylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline (**22**) (2.56 g, 54%). The di-*p*-toluoyl-*l*-tartrate salt monohydrate had mp 101–105° dec; NMR (polysol-*d*) δ 1.10 (t, CH_3CH_2, J = 7 Hz), 2.37 (s, $ArCH_3$), 3.61 (s, CH_3O), and 5.85 and 6.09 ppm (two d, 5 H and 7 H). Anal. ($C_{36}H_{45}N_3O_9 \cdot H_2O$) C, H, N.

The second product eluted was **4c**: NMR ($CDCl_3$) δ 0.94–1.16 (two sets of triplets, CH_3CH_2), 2.45–3.30 (complicated multiplets for $-CH_2CH_2-$ and 2 H, 3 H, and 4 H of heterocyclic ring), 3.71 (s, CH_3O), and 5.76 and 5.99 ppm (2 d, 5 H and 7 H). Anal. ($C_{22}H_{40}N_4O$) C, H, N.

8-Methoxy-2-(*n*-propyl)-5,6-dihydro-4-imidazo[*i*,*j*]quinoline (6a). A solution of 1.0 g (4.1 mmol) of 8-butyrylamino-6-methoxyquinoline (**18a**) in 50 ml of acetic acid containing 0.15 g of platinum oxide was hydrogenated in a Parr hydrogenator until hydrogen ceased to be absorbed. The catalyst was removed by filtration, and the filtrate was concentrated by freeze-drying. Recrystallization of the residue from hexane gave 0.90 g (98%) of **6a**, mp 83–84°. The analytical sample prepared by recrystallization from a methylene chloride and hexane mixture had mp 85–86°; ir (CH_2Cl_2) 1500, 1612, and 1632 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (t, CH_3CH_2CH, J = 7 Hz), 3.83 (s, CH_3O), 4.06 (t, $CH_2CH_2CH_3$, J = 6 Hz), 6.62 (d, 7 H, $J_{7,9}$ = 2 Hz), and 7.02 ppm (d, 9 H); MS (70 eV) m/e 230. Anal. ($C_{14}H_{18}N_2O$) C, H, N.

8-(4-Diethylamino-1,4-dioxobutylamino)-6-methoxyquinoline (18c). To a suspension of 8.63 g (0.86 mol) of succinic anhydride in 50 ml of methylene chloride was added 6.3 g (86.3 mmol) of diethylamine. After all of the solid had dissolved, 15.0 g (86.3 mmol) of 8-amino-6-methoxyquinoline was added, followed by 18.6 g (94.9 mmol) of DCI. The reaction was stirred for 2 days at 25° and then filtered to remove dicyclohexylurea. The filtrate was concentrated to give 34.9 g of a dark oil. This was eluted through a short Florisil column with 25% THF–hexane to give 21.49 g of oil. Recrystallization from benzene–hexane gave 13.0 g (46%) of the title compound: mp 101–103°; ir (CH_2Cl_2) 3345 (NH), 1680 and 1630 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 1.09 and 1.19 (2, t, CH_3CH_2), 2.86 (m, $-CH_2CH_2$), 3.38 (q, CH_3CH_2), 3.88 (s, CH_3O), 6.75 and 8.46 (2 d, 5 and 7 H), 7.34 (q, 3 H), 7.89 (m, 4 H), and 8.50 ppm (m, 2 H). Anal. ($C_{18}H_{23}N_3O_3$) C, H.

2-[2′-(*N*,*N*-Diethylcarbimido)ethyl]-8-methoxy-5,6-dihydro-4-imidazo[*i*,*j*]quinoline (6b). A solution of 5.0 g (0.015 mol) of **18c** in 200 ml of acetic acid containing 0.75 g of platinum oxide was hydrogenated on a Parr hydrogenator until hydrogen ceased to be absorbed. The catalyst was removed by filtration, and the filtrate was concentrated by freeze-drying. Recrystallization of the residue from a hexane and acetone mixture gave 3.03 g (64%) of **6b**: mp 73–74°; ir (CH_2Cl_2) 1630 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 0.98–1.3 (2 t, CH_3CH_2), 3.90 (s, CH_3O), 4.16 [$CH_2CH_2CHON(Et)_2$], 6.64 (d, 7 H), and 6.99 ppm (d, 9 H). Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

2-(3-Diethylaminopropyl)-8-methoxy-5,6-dihydro-4-imidazo[*i*,*j*]quinoline (6c) Fumarate. To a solution of 2-[2′-(*N*,*N*-diethylcarbimido)ethyl]-8-methoxy-5,6-dihydro-4-imidazo[*i*,*j*]quinoline (**6b**), 3.68 g (0.012 mol), in 50 ml of benzene was added diborane in THF (1 M, 32 ml) over a period of 1.5 h. The mixture was stirred 17 h at room temperature and then 4 h on a steam bath. The mixture was cooled, and 100 ml of water was added cautiously. The water layer was saturated with NaOH and then the combined benzene and water layers were extracted with Et_2O. The ether was washed with saturated NaCl solution and then dried over Na_2SO_4. The dried ether solution was stripped to leave **6c** as a yellow oily residue, 3.20 g. The fumarate salt was prepared and recrystallized from hot ethanol: mp 161–163°; NMR (CH_3OH-d_4) δ 1.29 [t, $N(CH_2CH_3)_2$], 3.78 (s, CH_3O–), 6.64 (s, $HCCO_2H$), 6.77 and 6.94 ppm (2 d, 5 H and 7 H, J = 2 Hz). Anal. ($C_{28}H_{37}N_3O_{11}$) C, H, N.

The analysis agreed with the NMR integration which indicates the sample contains 2.5 fumarates for each quinoline.

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β-Adrenergic Blocking Agents. 13. (3-Amino-2-hydroxypropoxy)benzamides

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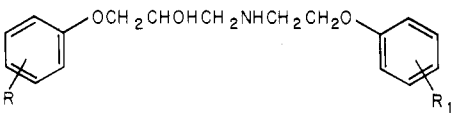
A series of (1-amino-2-hydroxypropoxy)benzamides has been tested in experimental animals. Several of the compounds are potent selective β-blockers; their structure–activity relationships and chemistry are discussed.

The search for cardioselective, β-adrenergic blocking agents, initiated by practolol[1] (Eraldin[2]), has led several groups of workers to examine analogous compounds which contain an amide function. Thus Cox and co-workers[3] have examined a series of compounds of the general structure 1 where R and R_1 represent a variety of amidic



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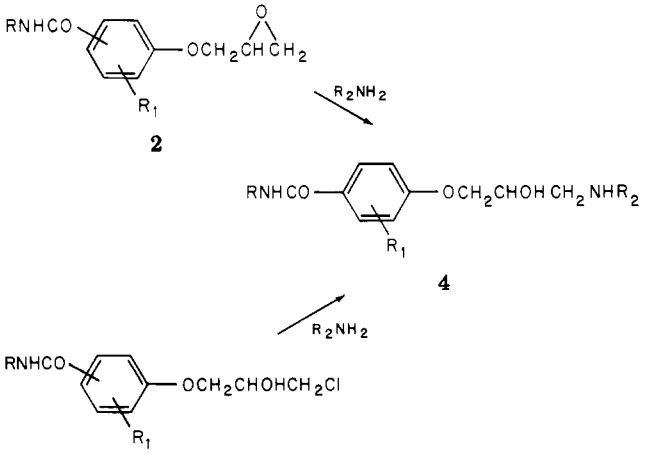
functions, and they have demonstrated a selectivity of action on cardiac vs. tracheal β-receptors. Similarly Shtacher and co-workers[4] found that compounds with a carbamoyl substituent show selectivity for cardiac vs. vascular β-receptors. In an extension of our work on selective β-blocking agents we have prepared a series of analogues in which the aryl residue has a para-substituted carbamoyl group together with an ortho substituent.[5]

We report here the synthesis and biological activity of these compounds, some of which were more potent than practolol and exhibited similar selectivity for myocardial relative to vascular β-receptors. Some conclusions on structure–activity relationships in the series are also included.

Chemistry. The compounds were prepared in a manner analogous to that used for other 1-amino-3-(substituted phenoxy)-2-propanols using the reaction of 1,2-epoxy-3-(substituted carbamoylphenoxy)propane (**2**) or 1-chloro-3-(substituted carbamoylphenoxy)-2-propanol (**3**) with the appropriate amine. The various hydroxy-*N*-



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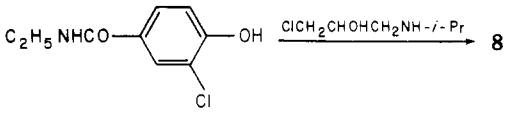
substituted benzamides used as starting material were synthesized by well-known methods, those which are novel are listed in Table II. The epoxide **2** and chlorohydrin **3** intermediates were used without purification in most cases. A marked feature of the series was the difficulty experienced in isolating the final product, TLC separation being necessary for the isolation of one-third of the compounds quoted in Table I. As in previous work[1,6] we surmised that the chloropropanols (used in methods C and D) in the presence of base lost HCl to give the 1,2-epoxypropane. Confirmation that the epoxide ring of **2** opened up in the manner indicated was obtained when *N*-ethyl-3-chloro-4-hydroxybenzamide (**5**) was condensed with 1-chloro-3-isopropylamino-2-propanol in the presence of base to give the same compound (**8**, Table I) as that already obtained by method C. The oxazolidine **6** was formed when the



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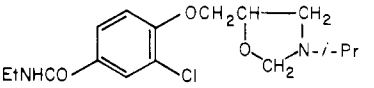
amino alcohol (**8**, Table I) as the free base was treated with formaldehyde in hot EtOH. Resolution of **8** to give the



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dextro and levo enantiomers was effected by the crystallization of the (+)- and (−)-*O,O*-di-*p*-toluoyl tartrate salts.[7]

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using the previously described cat preparation.[8] The results given in Table I are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg, dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Statistical analysis of the results shows that the mean ED_{50} on the log scale for compounds with an average of two to three tests per compound was ±0.12 log units (i.e., a mean error of approximately 30%).

Discussion

The objective of this investigation was to determine whether the carbamoyl moiety, like the acylamino moiety, would confer β_1 cardiac selectivity. The data in Table I show that many of the compounds had a profile of activity similar to that of the practolol series,[1] in that they exhibit