8-(ω-Aminoalkylamino)quinolines as Potential Prophylactic Antimalarials

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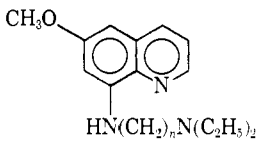
A series of primary and secondary aminoheptyl or aminooctyl derivatives of 8-aminoquinoline was prepared and evaluated for potential prophylactic antimalarial activity. A known tertiary amine derivative was reevaluated and included for comparison. Although retaining characteristic 8-aminoquinoline toxicity, several compounds were "active" as suppressive antimalarials. None showed significant prophylactic activity.

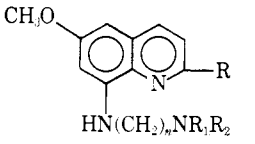
It has been suggested[1] that the 8-aminoquinoline (pamaquine, pentaquine, and primaquine) may act as true prophylactics against both vivax and falciparium infections, as well as achieve radical cure in relapsing malaria.[2] And, since resistance to 8-aminoquinolines does not appear to be a problem, we were encouraged to reexamine this class in an effort to discover members that were potential prophylactic agents. As a class, the 8-aminoquinolines are quite toxic, but results from structure-activity relationship studies[2] suggest a few clues which might help eliminate this obstacle to their wide usage.

An approach derived from the work of Magidson and coworkers[3] appeared to be indicated. Lengthening the basic side chain of 8-(ω-diethylaminoalkylamino)-6-methoxyquinoline (I) affected alternation of the chemotherapeutic index (CI) from the even to odd values of n,[1] the alternation between ethylene (n = 2, CI = 6) and heptamethylene (n = 7, CI = 34) compounds being particularly striking. Since this characteristic was not manifest when results were reported as quinine equivalents, the alternation appears to result from irregular changes in toxicities due to some alternating physical property in the homologous series.[4] Bovet and Demanche[5] also observed that the kind of plasmodicidal activity changed as the number of methylene groups in the basic side chain increased.



I

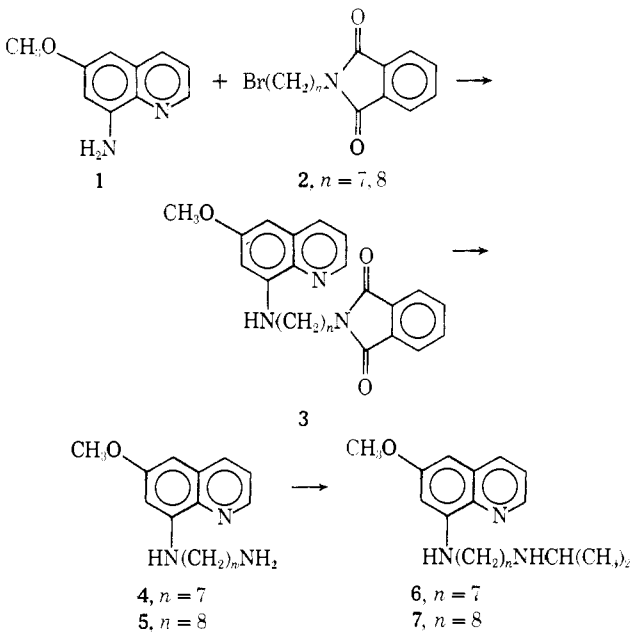
With these observations in mind, as well as the previous indications[1,2] that primary and secondary amine derivatives of the 8-aminoquinolines are less toxic than the tertiary amine analogs, we have prepared a number of compounds (II) for evaluation as potential antimalarials possessing lower toxicity. Two known analogs were resynthesized for evaluation and comparison in mice infected with *Plasmodium berghei*. Since the less toxic 2-benzyloxy analog[6] of primaquine has demonstrated causal prophylactic activity in mice infected with *P. berghei*,† this moiety was also introduced into several of the heptyl and octyl homologs in an attempt to obtain antimalarials with reduced toxicity.



II, NR_1R_2 = NH_2, $NHCH(CH_3)_2$, $N(C_2H_5)_2$; n = 7, 8; R = $-OCH_2C_6H_5$

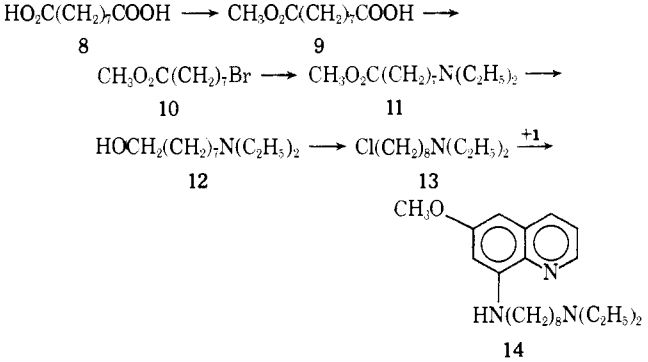
Chemistry. The syntheses of 6-methoxy-8-(ω-aminoalkylamino)quinolines **4** and **5** were accomplished by minor modification of standard procedures (Scheme I).[7,8] Reductive alkylation[9] of **4** and **5** gave the expected secondary amine derivatives **6** and **7** (Table I).

Scheme I



The original procedure[3,10] for the preparation of the tertiary amine derivatives (*e.g.*, **14**) was cumbersome, involving large quantities of expensive intermediates and low-yield reactions resulting in mixtures of products. We selected, therefore, the sequence outlined in Scheme II, utilizing inexpensive azelaic acid‡ as the starting material. The modified Hunsdiecker reaction,[11] employing the thallium carboxylate, was successful for preparation of ethyl bromooctanoate (**10**). (The standard procedure with mercuric oxide also gave satisfactory results with azelaic

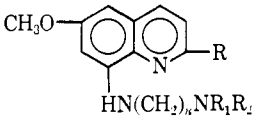
Scheme II



† Personal communication, Walter Reed Army Institute of Research.

‡ Courtesy of Emery Industries, Inc., Cincinnati, Ohio.

Table I. 8-(ω-Aminoalkylamino)quinolines



No.	NR_1R_2	R	n	Mp, °C	Yield, %	Salt	Base:acid	Formula	Analyses
4a	NH_2	H	7	210–211.5	62	Oxalate	2:1	$C_{36}H_{52}N_6O_6$	C, H, N
4b	NH_2	H	7	104–106	52	Maleate	1:2	$C_{25}H_{33}N_3O_9$	C, H, N
20a	NH_2	BzO[a]	7	158–160	44	Maleate	1:1	$C_{28}H_{36}N_3O_6$	C, H, N
5a	NH_2	H	8	207.5–209.5[b]	92	Oxalate	2:1	$C_{38}H_{56}N_6O_6$	C, H, N
5b	NH_2	H	8	93–95	93	Maleate	1:2[c]	$C_{26}H_{37}N_3O_{10}$[d]	C, H, N
20b	NH_2	BzO[a]	8	153.5–155	86	Maleate	1:1	$C_{29}H_{33}N_3O_6$	C, H, N
6a	NH-*i*-Pr	H	7	150–151.5	29	Oxalate	1:1	$C_{22}H_{32}N_3O_5$	C, H, N
6b	NH-*i*-Pr	H	7	97–99	72	Maleate	1:1	$C_{24}H_{34}N_3O_5$	C, H, N
7	NH-*i*-Pr	H	8	186–188	75	HCl	1:2	$C_{21}H_{35}N_3OCl_2$	C, H, N
21	NH-*i*-Pr	BzO[a]	8	114–118	80	Maleate	1:1	$C_{32}H_{43}N_3O_6$	C, H, N
14	$N(C_2H_5)_2$	H	8	113.5–116[e]	50–65	HCl	1:2	$C_{22}H_{37}N_3OCl_2$	

[a]BzO = Benzyloxy. [b]Lit.[7a] 105–108°; base:oxalic acid, 71.9:25.5%. [c]Confirmed by nmr. [d]Hydrate (1 mol of H_2O). [e]Lit.[10] 112–113°.

acid.) Preparation of ethyl 8-diethylaminooctanoate (**11**) was effected by reaction of diethylamine with **10**. Reduction of the amino ester **11** with $LiAlH_4$ gave the amino alcohol **12**, which was converted to the chloride **13**. Reaction of the chloride **13** with **1** gave the known 6-methoxy-8-(8-diethylaminooctylamino)quinoline (**14**). Several intermediates employed in Scheme II should be useful in the synthesis of other tertiary amine homologs of **14**. Since the tertiary amines were not of unique interest in this study, an investigation on the scope of this reaction sequence was not undertaken.

Modification of the published procedure[12] for preparation of 2-benzyloxy derivatives led to significant improvement in overall yield and shortened the sequence (Scheme III). For example, the use of phosphorus oxychloride in the preparation of 2-chloro-6-methoxy-8-nitroquinoline (**16**) led to more consistent results and a cleaner work-up than the phosphorus pentachloride method.[12] A one-step nucleophilic displacement reaction on the chloroquinoline (**16**) replaced the two-step hydrolysis and benzylation procedure.[12] Raney nickel-hydrazine[13] reduction of the nitro group in **17** gave significantly better yields of **18** than iron-acid.[12] Alkylation of the amine **18** *via* the acetate buffer method[7b] gave phthalimidoalkylamino derivatives **19** from which 2-benzyloxy-6-methoxy-8-(ω-aminoalkylamino)quinolines (**20**) could be obtained.

Biological Data. The antimalarial test results were provided by the Walter Reed Army Institute of Research. The activity was assessed against *P. berghei* in mice by the method of Rane and coworkers,[14] and the results are given in Table II. Although several of these agents (**5a, 6a,b, 7,** and **14**) were "active" to varying degrees by the Rane test, the characteristic 8-aminoquinoline toxicities remained. Introduction of the 2-benzyloxy group (**20a,b** and **21**) reduced toxicity as well as activity.

Compounds **5a** and **7** were also tested for suppressive antimalarial effects against *Plasmodium gallinaceum* infections in white Leghorn cockerels.[14] Compound **5a** was "active" at 40, 80, 160, and 320 mg/kg (ΔMST 4.4, 4.8, 5.8, and 8.4, respectively), and compound **7** was "active" at 20, 40, 80, and 160 mg/kg [ΔMST 5.4, 5.8, 6.8, and 7.5 (1T), respectively]. The latter agent gave five toxic deaths at 320 mg/kg.

Eight of the compounds were evaluated for potential prophylactic action in the sporozoite–mouse test system (*P. berghei yoelii* and *Anopheles stephesi*).[15] The compounds were given subcutaneously to a group of five infected mice for 3 consecutive days: the day before, the day of, and the day after sporozoite infection. Results are given in Table III. None of these compounds was as active as primaquine, which gave no evidence of parasitemia at 30 mg/kg, because parasites were found in all or some of the mice.

Compounds **5a, 6b,** and **7** were also evaluated for prophylactic action in chicks.[16] In this test white Leghorn cockerels were parasitized by the intrajugular injection of *P. gallinaceum* sporozites. The compounds were suspended in peanut oil and were administered subcutaneously in a single dose on the day of infection. Prophylactic value was assessed by comparing the maximum survival time of

Scheme III

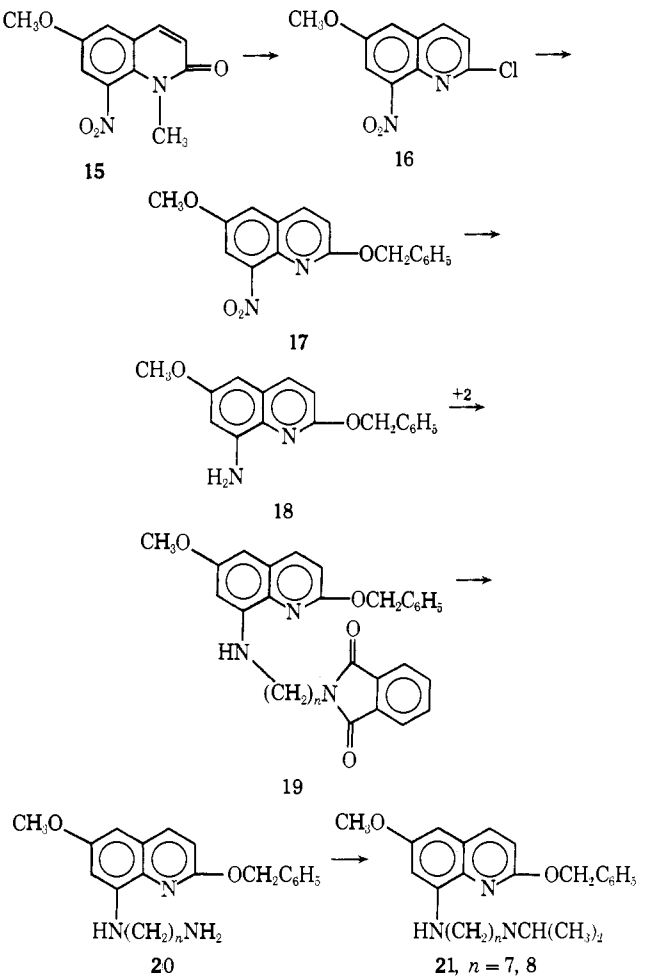


Table II. Antimalarial Activity against *Plasmodium berghei*[a]

Compd	ΔMST (days) after a single sc mg/kg dose					
	20	40	80	160	320	640
4a		0.9		1.4 (1T)		(5T)
4b		1.5		1.9 (1T)		(5T)
20a	0.5	1.5	2.3	3.5	4.3	5.1
5a	0.3	0.7	5.1	7.4 (1T)	9.9 (2T)	(5T)
5b		0.7		1.7		(5T)
20b		0.5		0.7		0.9
6a		3.1	4.1	8.9	9.9 (3T)	(5T)
6b	2.3	3.1	3.5	4.9	9.9 (2T)	13.9 (4T)
7	5.1	12.3	12.5	13.4 (1T)	13.9 (3T)	(5T)
21	0.3	0.5	0.5	0.9	4.5	5.9
14	0.7	3.1	4.7	5.7	5.9 (1T)	13.9 (4T)
P[b]	4.0	5.0	9.4	10.8 (2T)	(5T)	(5T)

[a]Increase in mean survival time (MST) in days of the test group is reported. The mean survival time of untreated mice is 6.1 days. A compound is "active" if ΔMST exceeds 6.1 days. Animals that survive to 60 days postinfection are considered "cured" (C). Deaths from days 2–5 after drug administration are attributed to drug toxicity (T). [b]P = primaquine phosphate, included for comparison.

Table III. Prophylactic Activity in Sporozoite–Mouse Test System[a]

Compd	Parasitemia per five mice at mg/kg dose					
	480	160	120	40	30	10
4a		0/3, 2T/5		5/5		4/5
4b	5T/5		4/5		3/5	
6a		5T/5		1/5		4/5
6b	5T/5		0/5		4/5	
5a		3/5		4/5		5/5
5b	5T/5		5/5		2/4	
7	5T/5		1/5		5/5	
14	5T/5		1/5		3/4	
Primaquine					0/5	

[a]Blood smears for parasite determination are made on days 6, 10, 14, and 21 after infection. Drug effectiveness was evaluated by comparing the mean parasitemia of the drug-treated group to that of the nondrug-treated controls at slide day 14. A value of less than 0.25 of the control value was considered for activity. Primaquine was active under these conditions.

treated sporozoite-infected chicks and the survival time of untreated sporozoite-infected controls. A compound is considered to have potential prophylactic value if it produces a minimum increase of 100% in survival time of the untreated controls. None of the compounds tested in groups of five chicks at graded dose levels (7.5–240 mg/kg) possessed prophylactic activity based on stated criteria.

One compound (**7**) was tested in monkeys by the Schmidt technique[17] for causal prophylactic action and found inactive at 10 mg/kg; primaquine was active at 1 mg/kg. The activity patterns were not considered adequate to justify expanded testing or further extension of the present group.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are corrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Satisfactory ir (Perkin-Elmer 237B grating spectrophotometer, KBr) and nmr (Hitachi Perkin-Elmer R20A high-resolution nmr spectrophotometer and Me_4Si as internal reference) spectra were obtained for all new compounds (DMSO-d_6). Tlc were performed on Eastman chromatogram sheets, type 6060 (silica gel).

Bromophthalimidoalkanes (2). 7-Bromophthalimidoheptane (**2a**)[18] was prepared in 59% yield by the method described for 9-bromophthalimidononane:[19] mp 30–33° (lit.[18] 34°). 8-Bromophthalimidooctane (**2b**) was prepared in 58% yield: mp 49–51° (lit.[7a] 54–55°).

6-Methoxy-8-(8-phthalimidooctylamino)quinoline Hydrobromide (3b).[7a] A mixture of 94 g (0.28 mol) of **2b**, 99 g (0.57 mol) of 6-methoxy-8-aminoquinoline (1), and 600 ml of *i*-PrOH was heated in an open flask at 106–155° for 4 hr (*i*-PrOH evaporated) and at 155° under a slow stream of N_2 for 2 hr. The mixture was digested briefly with 400 ml of benzene and 66 g of 6-methoxy-8-aminoquinoline hydrobromide was obtained by filtration. The hydrobromide was washed with benzene and the combined benzene solutions were concentrated *in vacuo*. The residual oil was dissolved in 600 ml of 95% EtOH and the solution treated with 124 g of 48% HBr. After standing overnight, the mixture was stirred briefly and the orange solid collected by filtration and washed with EtOH: mp 144–147°. Recrystallization from EtOH gave 88 g: mp 146–147°. Cooling of the filtrate gave 13 g of less pure material for a yield of 70%. Repeated recrystallization from EtOH gave the analytical sample: mp 147.5–149°. *Anal.* ($C_{26}H_{30}N_3O_3Br$) C, H, N, Br.

6-Methoxy-8-(7-phthalimidoheptylamino)quinoline (3a). A mixture of 90 g (0.278 mol) of **2a** and 90 g (0.48 mol) of 1 was heated at 155° under N_2 for 2 hr. The mixture was digested with benzene and 59 g of 6-methoxy-8-aminoquinoline hydrobromide was obtained and washed with benzene. The benzene solutions were combined and concentrated *in vacuo*. Treating the residual oil with EtOH gave 84 g (72%) of yellow solid: mp 105–107°. The analytical sample was prepared by recrystallization from EtOH: mp 108.5–110.5°. *Anal.* ($C_{25}H_{27}N_3O_3$) C, H, N.

6-Methoxy-8-(ω-aminoalkylamino)quinolines (Table I, 4 and 5). The procedure of Mosher[8] was slightly modified. A mixture of the appropriate phthalimidoalkylaminoquinoline (base or hydrobromide), 4–5 equiv of 85% hydrazine hydrate, and EtOH was refluxed for 3–4 hr to precipitate the white gelatinous phthalhydrazide. A portion of the solvent was removed *in vacuo* and the residue stirred with Et_2O and 50% aqueous KOH. The Et_2O solution was washed with water and saturated NaCl solution and dried ($MgSO_4$). Et_2O was removed *in vacuo* and the residue dissolved in MeOH or EtOH. This mixture was treated with alcoholic solution of oxalic or maleic acid, and the salts were precipitated with Et_2O.

6-Methoxy-8-(ω-isopropylaminoalkylamino)quinoline (Table I, 6 and 7). The crude hydrazinolysis product was reductively alkylated[9] in anhydrous EtOH with Me_2CO and Adams catalyst on a Parr hydrogenator. The filtered solution was concentrated *in vacuo* and the product isolated as the appropriate salt.

Methyl Hydrogen Azelate (9). The ester acid **9** was prepared in 29% yield (92–93% purity) from dimethyl azelate and azelaic acid by a slight modification of published procedure[20] for monoesterification of dicarboxylic acids. Diglyme was employed as solvent rather than butyl ether. Unreacted starting materials were readily recovered for recycling.

Thallium Methyl Azelate.[11] Thallium ethoxide (22.5 g, 0.09 mol) was pipetted into a stirred mixture of 20.2 g (0.093 mol) of methyl hydrogen azelate and 200 ml of anhydrous Et_2O. Stirring was continued for 20 min and there was obtained 35 g (86%) of thallium salt. Recrystallization from EtOH gave material (70% recovery) melting at 134–136°. (In subsequent experiments the thallium salt was used without purification and with no apparent reduction in yields.)

Methyl 8-Bromooctanoate (10).[11] A mixture of 99 g (0.615 mol) of bromine in 250 ml of CCl_4 was added in 1.0 hr to a stirred

suspension of 178 g (0.4 mol) of thallium methyl azelate in 650 ml of CCl_4. The mixture was stirred 0.5 hr and then refluxed 4.0 hr. The inorganic salt was filtered and washed with CCl_4. The combined CCl_4 solution was successively extracted with 5% bisulfite solution (solid in both phases removed by filtration) and 5% $NaHCO_3$. The dried CCl_4 solution ($MgSO_4$) was passed through alumina in a filter funnel (alumina washed with Et_2O) and concentrated *in vacuo*. The crude bromo ester (88 g, 91.5%) was distilled to yield 69.4 g (71%) of pure methyl 8-bromooctanoate: bp 88–90° (0.1 mm). A similar preparation, without bisulfite and bicarbonate extraction, gave crude and distilled yields of 90 and 68%, respectively.

Methyl 8-Diethylaminooctanoate (11). A mixture of 13.2 g (0.55 mol) of 10 and 35 ml of diethylamine was refluxed 12 hr. Diethylamine hydrobromide (97%) was removed by filtration and washed with Et_2O. The Et_2O and excess diethylamine were removed *in vacuo* and the residue (13 g, 91%) was distilled, giving 11.4 g (80%) of product: bp 78–82° (0.1 mm). The ester was characterized as the hydrochloride salt: mp 76.5–78.5° (Et_2O–MeOH). *Anal.* ($C_{13}H_{28}NO_2Cl$) C, H, N, Cl.

8-Diethylaminooctanol Hydrochloride (12). A mixture of 16.8 g (0.065 mol) of crude methyl 8-diethylaminooctanoate (11) in 40 ml of THF was added in 20 min to 4.0 g (0.108 mol) of $LiAlH_4$ in 50 ml of THF. The magnetically stirred mixture, protected by a nitrogen atmosphere and drying tower, was refluxed for 22 hr and then allowed to stand for 2.0 days. Excess $LiAlH_4$ was destroyed by cautious addition of 4.0 ml of H_2O, 4.0 ml of 15% NaOH, and 12.0 ml of H_2O to the ice-cooled mixture. The precipitate was filtered and washed thoroughly with Et_2O. The filtrate was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was dissolved in anhydrous Et_2O and treated with HCl gas to precipitate 13.8 g (89%) of a hygroscopic solid: mp 88–92°. The analytical sample was recrystallized from Me_2CO: mp 96–98°. *Anal.* ($C_{12}H_{28}NOCl$) C, H, N.

8-Diethylamino-1-chlorooctane Hydrochloride (13). A mixture of 13.8 g (0.058 mol) of 12 and 25 ml of $SOCl_2$ was refluxed (drying tower) for 2 days. Excess $SOCl_2$ was removed *in vacuo* and the residue titurated with anhydrous Et_2O while cooling. The solid was washed with Et_2O and stored *in vacuo* to remove residual Et_2O. There was obtained 12.8 g, which was recrystallized from Me_2CO–Et_2O (1:4) giving 11.0 g (74%): mp 75–78°.

6-Methoxy-8-(8-diethylaminooctylamino)quinoline Dihydrochloride (**Table II**, 14). Compound 14 was prepared in 50–65% yield by the method of Drake and coworkers:[21] mp 113.5–116° (lit.[10] 112–113°).

6-Methoxy-8-nitroquinoline Methiodide. Quaternization was achieved in 94% yield according to the procedure of Mislow and Koepfli,[12] except the salt was washed with a large quantity of Me_2CO and used without further purification: mp 153–154.5° (lit.[12] 149°).

1-Methyl-6-methoxy-8-nitro-1*H*-2-quinolone (15). The methiodide was oxidized by the procedure of Mislow and Koepfli,[12] except the temperature was maintained at 40–50° rather than 30–50°: mp 187–188.5° (lit.[12] 186–187°). The yield was 70% (lit.[12] 58%).

2-Chloro-6-methoxy-8-nitroquinoline (16). This compound (16) was prepared in 40–60% yield by the PCl_5 method[12] and in 70–86% yield by the $POCl_3$ ($POCl_3$–quinoline, 2:1) method:[22] mp 224.5–226.5° (lit.[12] 225–226°).

2-Benzyloxy-6-methoxy-8-nitroquinoline (17). A mixture of 24 g (0.1 mol) of 2-chloro-6-methoxy-8-nitroquinoline (16), 15 g (0.14 mol) of benzyl alcohol, 13.8 g (0.1 mol) of K_2CO_3, and 100 ml of DMF was heated 12 hr at 163° with stirring under a stream of nitrogen. The mixture was diluted with cold H_2O and stirred for 0.5 hr. The filtered solid was washed with H_2O, stirred briefly with 400 ml of 95% EtOH, filtered, and washed again with EtOH. There was obtained 27.9 g (90%): mp 134.5–136.5°. Recrystallization from hot EtOH gave material melting at 137.5–139° (lit.[12] 139–140°).

2-Benzyloxy-6-methoxy-8-aminoquinoline (18). A mixture of 36 g (0.116 mol) of 17, 500 ml of toluene–EtOH (1:1), 50 ml (0.85 mol) of 85% hydrazine hydrate, and 10 g (wet weight, washed with EtOH) of Raney nickel catalyst (W. R. Grace No. 28) was refluxed 5 hr. The condenser was removed and the mixture heated about 0.5 hr (EtOH added) until the vapors were faintly alkaline. A small quantity of hydroquinone was added and the warm mixture filtered with Celite, charcoaled, and concentrated *in vacuo*. The tan solid was swirled with about 100 ml of EtOH and filtered, and the solid was washed with 50 ml of EtOH. There was obtained 27 g of product: mp 85–86.5° (lit.[12] 86–87°). Dilution of the filtrate with H_2O and recrystallization from aqueous EtOH gave another 1.5 g: mp 83–84.5°. The yield was 88%.

2-Benzyloxy-6-methoxy-8-(7-phthalimidoheptylamino)quinoline (**19a**). Compound **19a** was prepared from 18 and **2a** by the acetate buffer method.[7b] The compound was isolated as the HBr salt (65%): mp 138–139.5°. *Anal.* ($C_{32}H_{34}N_3O_4Br \cdot 0.5\ H_2O$) C, H, N.

2-Benzyloxy-6-methoxy-8-(8-phthalimidooctylamino)quinoline (**19b**). Compound **19b** was prepared from 18 and **2b** by the acetate buffer method.[7b] The compound was isolated as the base (mp 80.5–82°) in 37% yield and as the HBr salt (mp 160–162°) in 26% (63% overall yield). An analytical sample of the base was prepared by recrystallization from EtOH: mp 87.5–88.5°. *Anal.* ($C_{33}H_{35}N_3O_4$) C, H, N.

2-Benzyloxy-6-methoxy-8-(aminoalkylamino)quinolines (**Table I**, **20a,b**). These compounds were prepared by the hydrazinolysis method described earlier and isolated as maleate salts.

2-Benzyloxy-6-methoxy-8-(8-isopropylaminooctylamino)-quinoline (**Table I**, 21). The hydrazinolysis product from 9.4 g (0.015 mol) of **19b**·HBr was dissolved in 50 ml of acetone and the mixture stirred 14 hr at ambient temperature with 5 g of 4A molecular sieve. The filtered solution was concentrated *in vacuo*, and the cooled residue was stirred with 100 ml of MeOH while 1.15 g (0.03 mol) of $NaBH_4$ was added in 10 min. MeOH was removed *in vacuo* and the residue diluted with H_2O and extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and treated with maleic acid in methanol. The resulting dark solid (6.8 g, mp 85–94°) was dissolved in MeOH and, after treating with charcoal, reprecipitated with Et_2O. Several recrystallizations from EtOAc gave the greenish maleate: mp 114–118° (melted to a glass which flowed freely at about 130°). *Anal.* ($C_{32}H_{43}N_3O_6$) C, H, N.

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Synthesis and Pharmacological Evaluation of 2,3-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines

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A series of 2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines was synthesized and evaluated for CNS activity. A new antianxiety screen for benzodiazepine-like drugs was used along with the standard anticonvulsant test. Structure-activity relationships were discussed. One compound, 1,3,6,7,8,9-hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one monosulfate (CI-718), is undergoing clinical studies in man.

During the past decade members of the 1,4-benzodiazepine class of compounds have generated considerable interest in the CNS field as psychotherapeutic agents.[1,2] Our laboratories' interest has been mainly centered on the fusion of heterocyclic rings to the seven-member diazepine ring system thus resulting in novel hetero 1,4-diazepines.

Scheme I