Antimalarials. 10. Substituted 3-Halo- and 3-Methoxy-2-aryl-4-quinoline(di-*n*-butylaminomethyl)methanols

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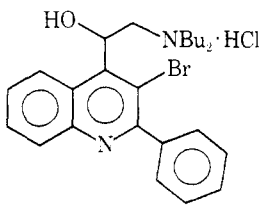
Four 2-aryl-4-quinoline(di-*n*-butylaminomethyl)methanols with Br, Cl, F, or OMe in position 3 were synthesized by modifications of standard reactions. The antimalarial activity decreased with increased size of the 3-substituent. The 3-F-4′,6,8-Cl_3 compound was the most active (at 2.5 mg/kg) and was completely curative at 80 mg/kg against *P. berghei* in mice.

3-Halo- and 3-methoxy-2-aryl-4-quinolineamino alcohols **1–4** were synthesized for comparison with the highly curative antimalarial **7**[2a] to gain further information concerning earlier indications that phototoxicity in 2-aryl types parallels electronegativities of 4′-substituents,[3] Cl > CH_3 > OCH_3, and is decreased by 3-Me and 2′-Cl which must interfere sterically with coplanarity and effectiveness of conjugation of the π systems[3] (e.g., **5**, **8**, **9**[4]). This work was given impetus by the postulate that phototoxicity of a final drug might be anticipated from phototoxicity of the cinchophen from which it was made and from the finding that 3-bromocinchophen (**11**) was not phototoxic.



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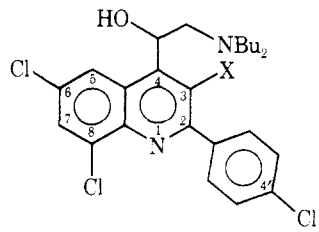
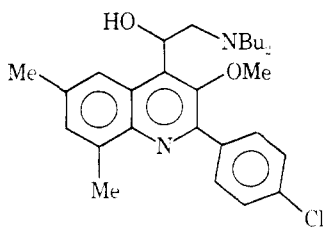


2, X = Cl
3, X = F
5[4]·HCl, X = Me
6,[2a] X = H



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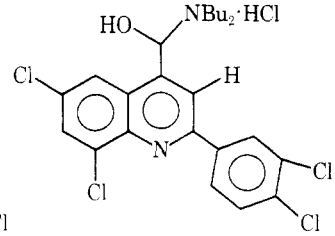
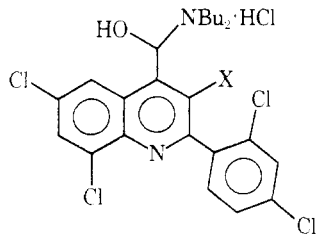


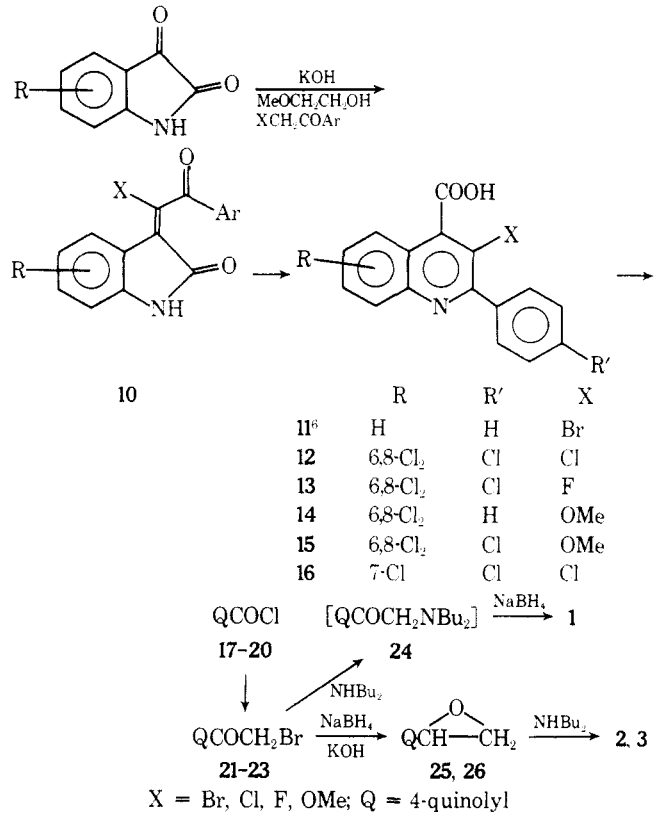
7[2a]



8,[4] X = H
9,[4] X = Me

Chemistry. Attempts first to make 2-piperidyl analogs of 3-halo-2-aryl-4-quinolineamino alcohols by Boykin's procedure[5] failed because 2-PyLi did not react satisfactorily with the cinchophens **11**,[6] **12**, and **12** methyl ester, doubtless due to steric interference by the 3-halogens. The di-*n*-butylamino alcohols **1–3** were therefore synthesized following the classical route[2a] of Scheme I through diazomethylation of the cinchophen acid chlorides **17–19**, hydrobromination of the diazo ketones, condensation of bromo ketone **21** with $NHBu_2$ and $NaBH_4$ reduction to **1**, and $NaBH_4$–KOH reductions of bromo ketones **22** and **23** to epoxides **25** and **26** followed by condensations with $NHBu_2$ to **2** and **3**.

Scheme I



	R	R′	X
11[6]	H	H	Br
12	6,8-Cl_2	Cl	Cl
13	6,8-Cl_2	Cl	F
14	6,8-Cl_2	H	OMe
15	6,8-Cl_2	Cl	OMe
16	7-Cl	Cl	Cl

10

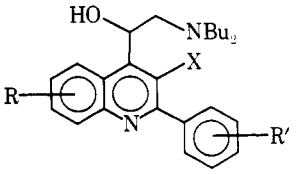
17–20 **24** **1**

21–23 **25, 26** **2, 3**

Attempts to make intermediate cinchophens **12** and **13** from the isatin and the highly reactive 2-haloacetophenones by modified[7] Pfitzinger procedure were unsuccessful, but 3-methoxycinchophens **14** and **15** were obtainable by this method[7c,d] using the less reactive α-methoxyacetophenones. A new procedure was then developed for the reaction with α-haloacetophenones using methoxyethanol as solvent with much smaller amounts of KOH, which gave the 3-halocinchophens **11–13** and **16** in good yields.

Diazomethylation of 3-methoxy-6,8-dichlorocinchophen acid chloride (**20**) followed by hydrobromination failed to give the desired bromomethyl ketone (loss of 3-OMe was shown by ir). A synthetic approach[8] through the 4-hydroxycarbostyryl to 4-quinaldehyde,[9] Scheme II, was then successfully applied to make compound **4**, starting from 6,8-dimethyl-4-hydroxycarbostyryl (**27**) which was chosen instead of the preferred 6,8-Cl_2 analog where reported yields were low.[9c] This involved conversion of **27** into the 2-aminoglyoxal acetal **28**, condensation with $MeOCH_2COPh$-*p*-Cl, hydrolysis of **29** to 4-quinaldehyde **30**, methylenation[10] to epoxide **31**, and condensation with $NHBu_2$.

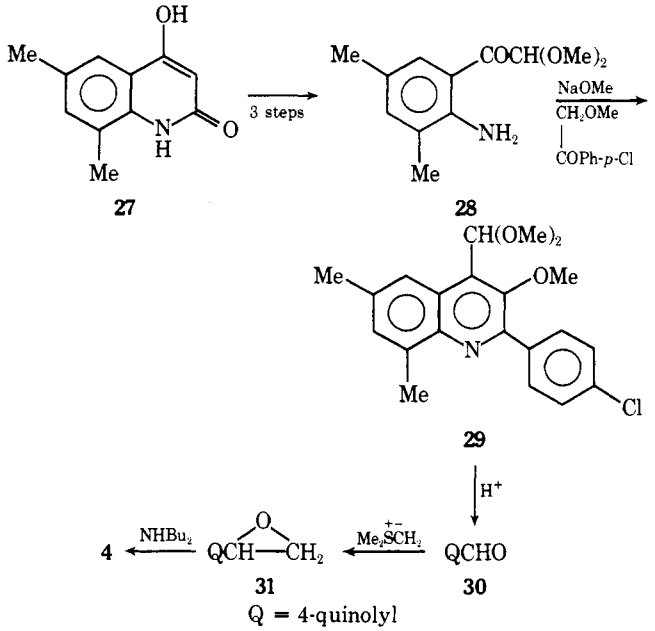
Table I. Antimalarial Activities[a] against *P. berghei* in Mice



Compd	WR no.	Substituents R	R′	X	IMST (days),[b] C (cures),[c,d] dose, mg/kg 10	20	40	80	160	320	Phototoxicity,[e] MED[f] (mice), mg/kg ip
2	140089	6,8-Cl_2	4-Cl	Cl	6.4	8.2	1C	3C	3C	5C	50
3	149105	6,8-Cl_2	4-Cl	F	1C	2C	3C	5C	5C	5C	100
4	157307	6,8-Me_2	4-Cl	OMe	0.7	4.1	6.1	8.1	14.1	4C	100
5[g]	42934	6,8-Cl_2	4-Cl	Me	7.2	10.6	1C	2C	2C	2C	12.5
6[h]	29252	6,8-Cl_2	4-Cl	H	2C	3C	4C	5C	5C	5C	25
6a[h]	28616	6,8-Me_2	4-Cl	H	5.9	10.1	2C	4C	4C	5C	
7[h]	30090	6,8-Cl_2	3,4-Cl_2	H	15	3C	6C	8C	10C	10C	50
8[g]	53188	6,8-Cl_2	2,4-Cl_2	H	1.0	3.5	9.1	2C	3C	4C	12.5
9[g]	63489	6,8-Cl_2	2,4-Cl_2	Me	0.3	1.3	1.7	7.1	1C	2C	100
1	121473	H	H	Br		0.1		0.1		0.3	Neg

[a]See ref 11. [b]IMST = increase in mean survival time in days; compound considered active when IMST is at least twice that of controls (6 days). [c]C = number of cures (mice surviving 60 days) of test groups of five mice. [d]Test groups for 7 were ten mice. [e]Reference 3. [f]MED = minimum effective dose. [g]Reference 4. [h]Reference 2a.

Scheme II



Pharmacology. Test results against *P. berghei* in mice (method of Rane[11]) and photoxicities[3] for the four new 3-substituted 4-quinolineamino alcohols **1–4** and also for the related and previously prepared compounds **5–9**[2,4] are assembled in Table I. The 3-fluoro derivative **3** was the most active (at 2.5 mg/kg), effected cures at 10–40 mg/kg, and was completely curative at 80 mg/kg.

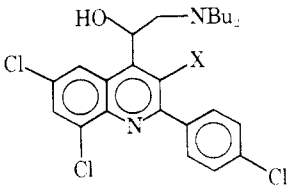
The results for the 6,8-dichloro-2-(*p*-chlorophenyl) and 2,3- and 2,4-dichlorophenyl compounds **2, 3, 5,** and **6** and **7–9** show that as the bulk of the 3-substituent increases, H < F < Cl < Me, the antimalarial activities decrease in that order, **6 > 3 > 2 > 5** and **7 > 8 > 9**, paralleling the Taft steric parameter E_s (Table II) which has been used by Hansch[12] in quantitative multiparameter structure–activity correlations. The relationship can be seen at 10–20 mg/kg and is more pronounced at 40–80 mg/kg. Activity decreases as E_s becomes more negative. The same effect is observed for the isomeric 2-(dichlorophenyl) series **7–9** and **2** with regard to the ortho position of the 2-phenyl ring. A comparison of the activities of **2** and **8** shows that the 3 and 2′ positions are similar in effect for Cl as substituent. One explanation for this is that inhibition of coplanarity of the 2-phenyl and quinoline rings reduces antimalarial activity.[3]

Recently Hansch and Craig[13] reported on the antimalarial structure–activity relationships for a series of phenanthreneamino alcohols as determined by multiple parameter analysis and by additivity methods, and Craig[14] reported on the Free–Wilson analysis of 2-phenyl-4-quinolineamino alcohols. It was concluded that both 1-octanol–water partition coefficients (π) and electronic parameters (σ) could account for most of the biological variation for members of these series. For the quinoline series, the relative magnitudes of these factors were separated according to functional group and position.[14] When the nature and position of all other substituents are held constant for the 3-X-phenylquinoline system, the steric effect of the 3-substituent for compounds **2–6** can be expressed by the equation in Table II using the method described by Hansch.[15] This is the best single parameter equation ($F_{1,3} = 37.2$, $F_{1,3;\alpha\,0.01} = 34.1$) for the limited set of compounds (see Table III).

The methoxy derivative **4** which carries 6,8-dimethyl as substituents (rather than the preferred 6,8-dichloro) has considerably lower antimalarial activity against *P. berghei* than expected for the steric effect of the methoxyl group alone. Obviously this is because 6,8-Cl_2 is a much better auxopharmacophoric combination than 6,8-Me_2.[14] For example, comparison of ED_{50} values for increase in mean survival times by 6,8-Cl_2 compound **6** with those of the 6,8-Me_2 analog **6a** shows the former to be 3.7 times more potent, and the 2-*p*-chlorophenoxy counterpart of the 6,8-Cl_2 compound **6** is 5 times as active as its 6,8-Me_2 analog.[16]

No relationship is obvious between planarity of the total system and animal phototoxicities for any of the analogs except **5, 8,** and **9** (cf. discussion by Rothe and Jacobus[3a]). Furthermore, recent results of clinical trials[2b–e] cast considerable doubt on the correlatability of phototoxicity in animal models with that shown in man because **7** was shown to be both prophylactic and curative[2d] for acute ma-

Table II. Structure–Activity Parameters for 3-X-2-Aryl-4-quinolinemethanols against *P. berghei* in Mice



$\log 1/C = 0.66_1\ (\pm 0.34)\ E_s - 3 + 0.824\ (\pm 0.25)$ n 5 r 0.962 s 0.104

Compd	X	E_s	π	σ_m	σ_p	MR	MW	Log 1/C Obsd	Log 1/C Calcd	Δ log 1/C
6	H	1.24	0	0	0	1.03	1	1.641	1.644	−0.003
3	F	0.78	0.10	0.34	0.06	0.92	19	1.462	1.340	0.122
4	OMe	0.69	−0.33	0.12	−0.27	7.87	31	1.165[a]	1.280	−0.115
2	Cl	0.27	0.59	0.37	0.23	6.03	35	0.955	1.003	−0.048
5	Me	0	0.68	−0.07	0.17	5.65	15	0.867	0.824	0.043

[a] Values calculated for 6,8-Cl_2 analog (3.7 × 4).

laria caused by several strains of *P. falciparum* with no observed adverse side effects and with phototoxicity a minor consideration.[11]

Compound **7** and the new isomer **2** have equal phototoxicities in animals, but **2** has half the antimalarial activity of **7**. On the other hand, the 3-fluoro compound **3** is considerably more active than **7** against *P. berghei* and half as phototoxic; it therefore appears to be a better candidate than was **7** for clinical trial in man.

Experimental Section

Satisfactory spectra were obtained: ir, Perkin-Elmer 337; NMR, Hitachi Perkin-Elmer R-20; mass, Hitachi Perkin-Elmer RMU 6-E. Microanalyses were within ±0.4% of calculated values (Gailbraith Lab. Inc).

4- and 6-chloroisatins[17] were prepared from isonitroso-3-chloroacetanilide by cyclizing (concentrated H_2SO_4, 80°) and separation by fractional precipitation by HCl from basic solution.

2-Methoxy-4′-chloroacetophenone:[18] mp 65–66°; NMR ($CDCl_3$) δ 3.15 (s, 3), 4.69 (s, 2), 7.35–8.10 (m, 4).

New Modification of the Pfitzinger Reaction. 3,4′,6,8-Tetrachlorocinchophen (12) (13 Made Similarily). To a suspension of 21.6 g (0.1 mol) of 5,7-dichloroisatin and 18.9 g (0.1 mol) of α,4′-dichloroacetophenone in 2-methoxyethanol (300 ml, stirred 10 min) was added KOH (48 mg, stirred 18 hr). Slow addition of concentrated HCl (250 ml) followed by EtOH (to suspend precipitate), cooling (30°), basification to pH 11 (10% NaOH), filtration, and acidification to pH 3 (10% HCl) gave **12** (25.3 g, 65%), mp 245–250° dec (use of 2-propanol or DMF–EtOH mixture gave 12–25%).

3-Methoxy-6,8-dichlorocinchophen (14) (cf. ref 7): NMR (Me_2CO-d_6) δ 3.71 (s, 3, CH_3), 6.96 (broad s, concentration dependent, 1, COOH), 7.83 (m, 7, aromatic).

The 2-arylquinoline-4-carbonyl chlorides 17–20[19] were made from **11–14** by excess $SOCl_2$ (1–1.5 g, 10 ml; reflux 2–3 hr), distilling, coevaporating with benzene to remove $SOCl_2$, solution of product in hot CH_2Cl_2, filtration (Celite), evaporation, and cooling.

3-Fluoro-6,8-dichloro-2-(*p*-chlorophenyl)-4-quinolyl Bromomethyl Ketone (23) (21 and 22 Made Similarly). A mixture of 350 ml of Et_2O–CH_2N_2 (0.7 mol) and 5.6 g (0.014 mol) of **19** was stirred (18 hr); then 20 ml of concentrated HBr was added (stirred 3 hr). Washing the Et_2O solution (H_2O), drying ($MgSO_4$), evaporation, and slurrying the residue (petroleum ether, bp 30–60°) gave 5.64 g (87%), mp 153–163° dec. In the case of **22**, Et_2O–CH_2N_2 was added to **18** in CH_2Cl_2 (stirring, 0°). After solution in Me_2CO, evaporation, trituration with MeOH, and crystallization from Me_2CO, the product gave unsatisfactory analysis and was shown to contain at least one important minor compound (TLC, benzene–MeOH); however, spectra showed that the bulk of the mixture was **23** which in the next step gave **26**.

3,6,8-Trichloro-2-(*p*-chlorophenyl)-4-quinoline Ethylene Oxide (25) (26 and 31 Made Similarly). To a solution of **22** (3 g, 6.46 mmol) in 50 ml of THF was added a solution of 1.25 g (3.30 mmol) of $NaBH_4$ in 14.5 ml of 3% KOH–H_2O, followed by 40 ml of THF and 20 ml of EtOH to effect solution (stirred 1 hr); **25** (2.1 g) precipitated.

3,6,8-Trichloro-2-(*p*-chlorophenyl)-4-quinoline(di-*n*-butylaminomethyl)methanol (2) (3 Made Similarly). A mixture of 3.2 g (8.27 mmol) of **25** and 6 ml of $NHBu_2$ was heated (17 hr, 132°). Vacuum evaporation (80°) removed $NHBu_2$, and trituration with hexane and cooling gave **2** (4 g).

3-Bromo-2-phenyl-4-quinoline(di-*n*-butylaminomethyl)-methanol Dihydrochloride (1). Solution of **21** (2 g, 5 mmol) and $NHBu_2$ (1.3 g, 10 mmol) in Et_2O (standing 8 hr, dark, 30°), filtration [removing 6.2 g (94%) of $NHBu_2$·HBr], vacuum evaporation (70°), solution of the residue (EtOH, under N_2), addition of

Scheme III

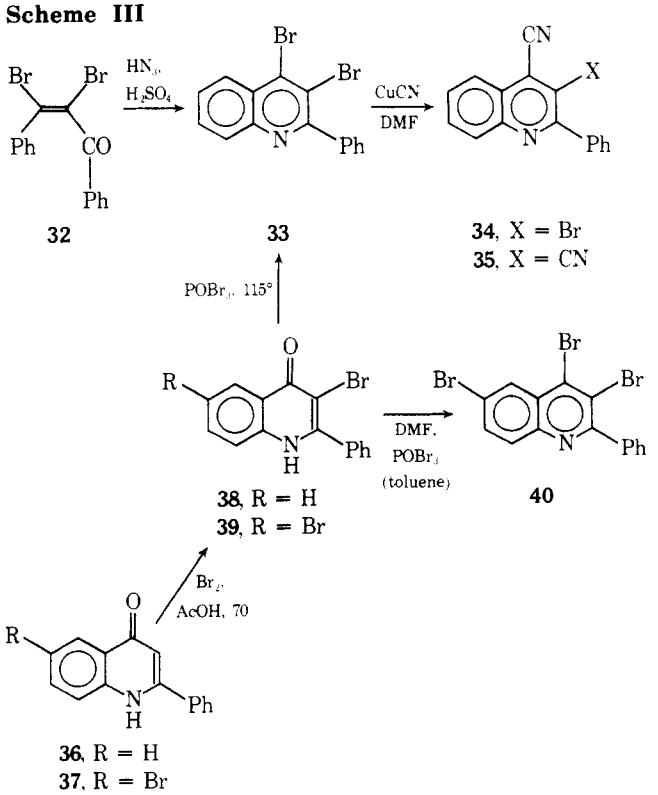
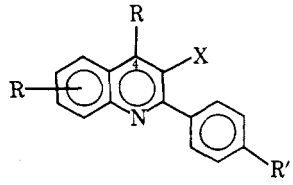
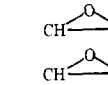
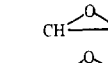
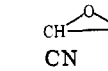


Table III. New Quinoline Derivatives



Compd	R	R′	X	4-R	Yield,[a-o] %	Mp, °C[b-r]	Analyses[s-w]
1	H	H	Br	$CHOHCH_2NBu_2$	20[b]	147 dec	$C_{25}H_{31}BrNO \cdot 2HCl$[t]
2	6,8-Cl_2	Cl	Cl	$CHOHCH_2NBu_2$	96[c]	139.5–141[p,q]	$C_{25}H_{28}Cl_4N_2O$[u]
3	6,8-Cl_2	Cl	F	$CHOHCH_2NBu_2$	87[c]	124–125.5	$C_{23}H_{28}Cl_3FN_2O$[t]
4	6,8-Me_2	Cl	OMe	$CHOHCH_2NBu_2$	59[d]	96–97	$C_{28}H_{37}ClN_2O_2$[t]
5·HCl	6,8-Cl_2	Cl	Me	$CH_2OHCH_2NBu_2$		187–189	$C_{26}H_{32}Cl_4N_2O$[u,x]
8·HCl	6,8-Cl_2	2′,4′-Cl_2	H	$CH_2OHCH_2NBu_2$		193–193.5	$C_{25}H_{21}Cl_5N_2O$[u,x]
9·HCl	6,8-Cl_2	2′,4′-Cl_2	Me	$CH_2OHCH_2NBu_2$		178–180	$C_{26}H_{31}Cl_5N_2O$[u,x]
12	6,8-Cl_2	Cl	Cl	COOH	65[e]	253 dec[p]	$C_{18}H_7Cl_4NO_2$[u]
13	6,8-Cl_2	Cl	F	COOH	81[e]	248–249	$C_{16}H_7Cl_3FNO_2$[u]
14	6,8-Cl_2	H	OMe	COOH	73[f]	217–219 dec	$C_{16}H_{17}Cl_4NO_2$[u]
15	6,8-Cl_2	Cl	OMe	COOH	74[d]	236–237 dec[r]	$C_{17}H_{10}Cl_3NO_3$[t]
16	7-Cl	Cl	Cl	COOH	52[e,g]	272 dec[p]	$C_{18}H_8Cl_3NO_2$[u]
17	H	H	Br	COCl	49[h]	148–149[p,q]	
18	6,8-Cl_2	Cl	Cl	COCl	86[h]	148–150[p]	$C_{16}H_{16}Cl_5NO$[u]
19	6,8-Cl_2	Cl	F	COCl	50[i,j]	168–169.5	$C_{16}H_6Cl_4FNO$[t]
20	6,8-Me_2	H	OMe	COCl	89[h]	155–157	$C_{17}H_{10}Cl_3NO_2$[t]
14 amide	6,8-Cl_2	H	OMe	$CONH_2$	*k*	252–254[p]	$C_{17}H_{12}Cl_2N_2O_2$[t]
12 ester	6,8-Cl_2	Cl	Cl	COOMe	87[i]	207–207.5	$C_{17}H_9Cl_4NO_2$[u]
16 ester	7-Cl	Cl	Cl	COOMe		200–201	$C_{17}H_{10}Cl_3NO_2$[u]
29	6,8-Me_2	Cl	OMe	$CH(OMe)_2$	91[f]	154–155[q]	$C_{21}H_{22}ClNO_3$[t]
30	6,8-Me_2	Cl	OMe	CHO	97[f]	136–137[q]	$C_{19}H_{16}ClNO_2$[t]
21	H	H	Br	$COCH_2Br$	60[l]	95–96	$C_{17}H_{11}Br_2CO$[v]
22	6,8-Cl_2	Cl	Cl	$COCH_2Br$	95[g,m,n]	193–193.5	$C_{17}H_8BrCl_4NO$[w]
23	6,8-Cl_2	Cl	F	$COCH_2Br$	64[g,n,o]	178–180	$C_{17}H_8BrCl_3FNO$[t]
25	6,8-Cl_2	Cl	Cl		83[c]	219–219.5	$C_{17}H_9Cl_4NO$[u]
26	6,8-Cl_2	Cl	F		46[g,n,o]	178–179	$C_{17}H_9Cl_3FNO$[t]
31	6,8-Me_2	Cl	OMe		90[f,n]	101–103[q]	*q*
35	H	H	CN	CN	51.5[e]	203–204	$C_{17}H_9N_3$[t]
38[y]	H	H	Br	(OH)	80[e]	291–294	$C_{15}H_{10}BrNO$[v]
39	6-Br	H	Br	(OH)	83[e]	313–317	$C_{15}H_9Br_2NO$[v]
40	6-Br	H	Br	Br	90[i]	194–195	$C_{15}H_8Br_3N$[v]

[a]Reasonably pure material unless otherwise specified; recrystallized from [b]Me_2CHOH-$(Me_2CH)_2O$; [c]AcOEt; [d]Et_2O; [e]EtOH; [f]Et_2O-hexane; [g]Me_2CO; [h]hexane; [i]CH_2Cl_2-hexane; [j]vacuum sublimed [140° (0.15 mm)]; [k]$CHCl_3$-hexane; [l]cyclohexanone; [m]petroleum ether (bp 65–100°); [n]partially purified; [o]Me_2CO-CH_2Cl_2. [p]Ir (KBr) for **2**, 2960, 2870, 1460, 1380 (CH_3), 2870, 2830, 1460 (CH_2), 1595, 1540, 1490, 1450 cm^{-1} (aromatic); for **12**, 1710, 1960, 2600, 3430 cm^{-1}; for **16** (from **12**, CH_2N_2), 3450, 2525, 1920, 1720 cm^{-1}; for **17**, 1760 cm^{-1}; for **18**, 1760 cm^{-1} (COCl); for **22**, 1450, 1490, 1540, 1600, 1720, 1390, 2960 cm^{-1}; for **25**, 3025, 1240, 905, 828 cm^{-1} (epoxide); for **32** (from **18**, CH_2N_2), 1268 (COC), 1740 (C=O), 2860, 2970 cm^{-1} (OMe); for **34** (from **20**, NH_3), 1760 (C=O), 3180, 3375 cm^{-1} (NH_2); for **36**, 1640 cm^{-1} (γ-quinolone). [q]NMR ($CDCl_3$) δ for **2**, 8.89 (d, 1, *J* = 2 Hz, 5-H), 7.70 (d, 2 H, *J* = 8 Hz, 3′,5′-H_2), 7.68 (d, 1, *J* = 2 Hz, 7-H), 7.46 (d, 2 H, *J* = 8 Hz, 2′,6′-H_2), 5.72 (q, 1, *J* = 5 Hz, CH), 4.38 (s, 1, OH), 2.68 [m, 6, $-CH_2N(CH_2)_2$], 1.43 (m, 4, CH_2CH_2), 0.83 (m, 3, CH_3); for **22**, 7.8 (m, 3), 7.5 (m, 3), 4.48 (s, 2 H); for **29**, 2.51 (s, 3, CH_3), 2.78 (s, 3, CH_3), 3.53 (s, 3, CH_3), 3.58 (s, 6, $2CH_3$), 6.03 (s, 1, CHO), 7.28–7.70 (m, 3) and 8.05–8.40 (m, 3, aromatic); for **30**, 2.52 (s, 3), 2.79 (s, 3) and 3.69 (s, 3, $3CH_3$), 7.50–7.80 (m, 3), 8.05–8.35 (m, 2), 8.63 (broad s, 1), 10.93 (s, 1); for **31**, 2.53 (s, 3, CH_3), 2.80 (s, 3, CH_3), 3.07–3.51 (m, 2, CH_2), 3.63 (s, 3, CH_3), 4.37 (m, 1, CH), 7.30–8.30 (m, 6, aromatic H). [r]Uv, nm ($\epsilon \times 10^{-3}$), for **15** (prepared like **14**), 232 (31.8), 265.5 (32.2), 290–340 (broad plateau, 8.7–9.3). [s]Were within ±0.4% of calculated values for C and H, and for [t]C, H, N; [u]C, H, Cl, N; [v]C, H, Br, N. [w]Crude but usable quality. Anal. calcd (found) C, 44.01 (44.78); H, 1.74 (1.74); Br, 17.22 (15.08); Cl, 30.56 (29.60); N, 3.02 (3.21). [x]Syntheses by J. Christenson and J. Riedmaier via Scheme I (ref 4). [y]Cf. ref 21.

$NaBH_4$ (15 g, 39.5 mmol), stirring (0.5 hr), basification to pH 11 (dilute NaOH), extraction with Et_2O, drying ($MgSO_4$), vacuum evaporation, solution in dry Et_2O, and addition of Et_2O–HCl gave **1** (0.5 g).

3-Methoxy-6,8-dimethyl-2-(*p*-chlorophenyl)-4-quinaldehyde Dimethyl Acetal (29). A solution of $MeOCH_2COPh$-*p*-Cl (4.3 g) and **27** (5.18 g; MeOH, 40 ml) was added rapidly to a stirred MeOH solution of 0.57 g of Na (30 ml). Refluxing (4.5 hr, precipitate appeared after 3.5 hr), cooling (−5°), filtration, and washing (MeOH, 0°) gave **29** (7.88 g, including recovery from filtrate).

3-Methoxy-6,8-dimethyl-2-(*p*-chlorophenyl)-4-quinaldehyde (30). A solution of **29** (5 g) in 5:1 dioxane–H_2O (60 ml) plus 1 ml of concentrated HCl was refluxed (35 min). Addition of H_2O (40 ml) and cooling (5°) gave **30** (4.27 g). **Epoxide 31** was made from **30** by methylenation[10] and converted into **amino alcohol 4** by $NHBu_2$ (3.5 hr, 145–150°, and 14 hr, 110°).

Toward a New Synthesis of 3-Substituted 2-Phenyl-4-quinolineamino Alcohols (Scheme III). The Schmidt reaction on α,β-dibromo-*cis*-chalcone (**32**) gave 3,4-dibromo-2-phenylquinoline (**33**).[20] From a quantity of **33** prepared by the Kaslow bromination procedures[21] **36** → **38** → **33** a small amount of tribromide **40** was isolated (5%) which was the predominant product of bromination by $POBr_3$ in DMF–toluene and was obtainable also from 6-bromo-2-phenylquinolone (**38** → **39** → **40**).

Reaction of 3,4-dibromo-2-phenylquinoline (33) with CuCN–DMF (reflux) gave a difficultly separable mixture which was shown by mass spectrum to be **mono- and 3,4-dinitriles 34** and **35** (ratio dependent on reaction time, 57/43 after 1 hr and 36/64 after 4 hr). Obviously the relatively inactive 3-Br in **33** is activated in **34** by the 4-CN. Use of highly polar DMF as solvent for $POBr_3$ brominations and for displacements of 4-Br by CN thus appears potentially useful, and there is the possibility for selective 4-metalation of **33** by BuLi and subsequent reaction with CO_2 or 2-pyridaldehyde for creation of the 4-amino alcohol chain. A start was made toward synthesis of the 3,4′,7-trichloro analog of **2** from *cis*-*p*-ClPhCCl=CClCOPh-*p*-Cl.[22]

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