

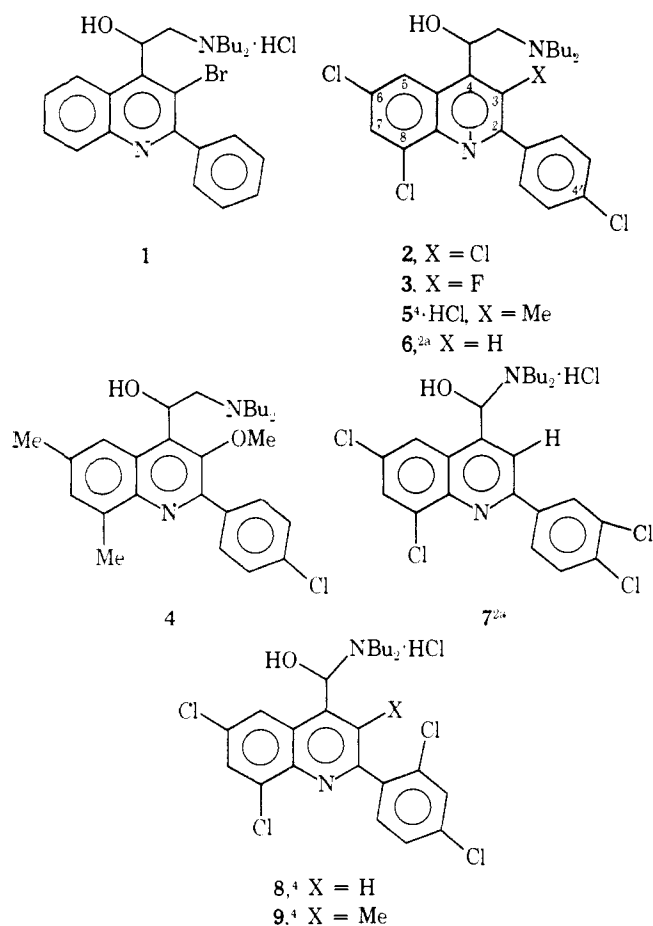
Antimalarials. 10. Substituted 3-Halo- and 3-Methoxy-2-aryl-4-quinoline(di-*n*-butylaminomethyl)methanols

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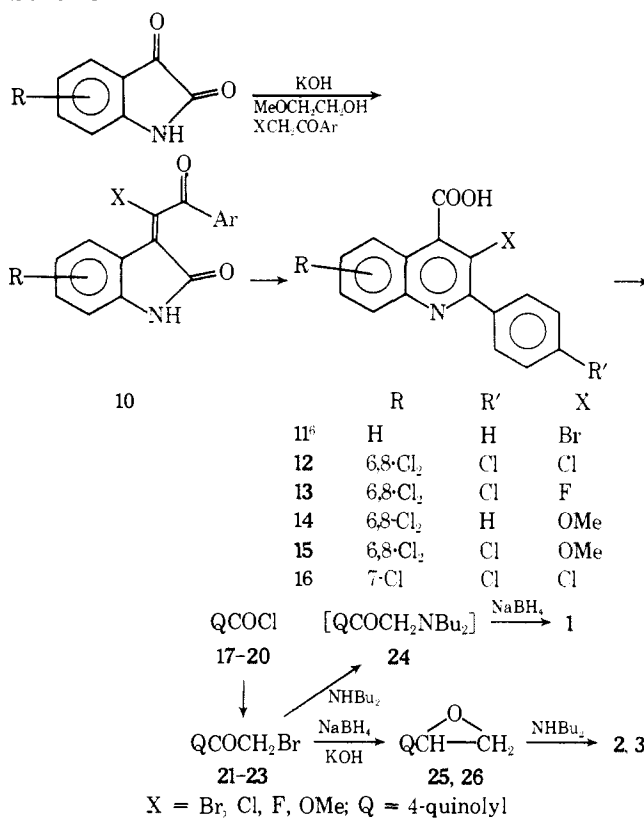
Four 2-aryl-4-quinoline(di-*n*-butylaminomethyl)methanols with Br, Cl, F, or OMe in position 3 were synthesized by modifications of standard reactions. The antimalarial activity decreased with increased size of the 3-substituent. The 3-F-4',6,8-Cl₃ compound was the most active (at 2.5 mg/kg) and was 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 > CH₃ > OCH₃, and is decreased by 3-Me and 2'-Cl which must interfere sterically with coplanarity and effectiveness of conjugation of the π systems³ (e.g., 5, 8, 9⁴). 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.



Chemistry. Attempts first to make 2-piperidyl analogs of 3-halo-2-aryl-4-quinolineamino alcohols by Boykin's procedure⁵ 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

Scheme I



ketone 21 with NHBu₂ and NaBH₄ reduction to 1, and NaBH₄-KOH reductions of bromo ketones 22 and 23 to epoxides 25 and 26 followed by condensations with NHBu₂ to 2 and 3.

Attempts to make intermediate cinchophens 12 and 13 from the isatin and the highly reactive 2-haloacetophenones by modified⁷ 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.

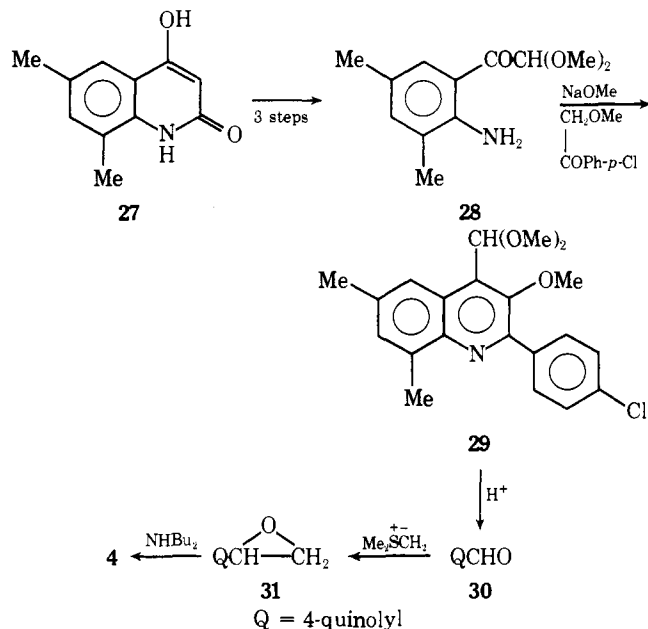
Diazomethylation of 3-methoxy-6,8-dichlorocinchophen acid chloride (20) followed by hydrobromination failed to give the desired bromomethyl ketone (loss of 3-OMe was shown by ir). A synthetic approach⁸ through the 4-hydroxycarbostyryl to 4-quinolaldehyde,⁹ Scheme II, was then successfully applied to make compound 4, starting from 6,8-dimethyl-4-hydroxycarbostyryl (27) which was chosen instead of the preferred 6,8-Cl₂ analog where reported yields were low.^{9c} This involved conversion of 27 into the 2-aminoxyloxy acetal 28, condensation with MeOCH₂COPh-*p*-Cl, hydrolysis of 29 to 4-quinolaldehyde 30, methylation¹⁰ to epoxide 31, and condensation with NHBu₂.

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

Compd	WR no.	Substituents			IMST (days), ^b C (cures), ^{c,d} dose, mg/kg						Photo-toxicity, ^e MED ^f (mice), mg/kg ip
		R	R'	X	10	20	40	80	160	320	
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 ^f	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	50
7 ^h	30090	6,8-Cl ₂	3,4-Cl ₂	H	15	3C	6C	8C	10C	10C	50
8 ^f	53188	6,8-Cl ₂	2,4-Cl ₂	H	1.0	3.5	9.1	2C	3C	4C	12.5
9 ^f	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

^aSee ref 11. ^bIMST = increase in mean survival time in days; compound considered active when IMST is at least twice that of controls (6 days). ^cC = number of cures (mice surviving 60 days) of test groups of five mice. ^dTest groups for 7 were ten mice. ^eReference 3. ^fMED = minimum effective dose. ^gReference 4. ^hReference 2a.

Scheme II



Pharmacology. Test results against *P. berghei* in mice (method of Rane¹¹) and phototoxicities³ 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.

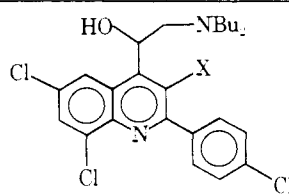
The results for the 6,8-dichloro-2-(*p*-chlorophenyl) and 2,3- and 2,4-dichlorophenyl compounds 2, 3, 5, and 6 and 7-9 show that as the bulk of the 3-substituent increases, H < F < Cl < Me, the antimalarial activities decrease in that order, 6 > 3 > 2 > 5 and 7 > 8 > 9, paralleling the Taft steric parameter E_s (Table II) which has been used by Hansch¹² 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 Craig¹³ reported on the antimalarial structure-activity relationships for a series of phenanthreneamino alcohols as determined by multiple parameter analysis and by additivity methods, and Craig¹⁴ 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-phenyl-quinoline 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-Cl₂ is a much better auxopharmacophoric combination than 6,8-Me₂.¹⁴ For example, comparison of ED₅₀ values for increase in mean survival times by 6,8-Cl₂ compound 6 with those of the 6,8-Me₂ analog 6a shows the former to be 3.7 times more potent, and the 2-*p*-chlorophenoxy counterpart of the 6,8-Cl₂ compound 6 is 5 times as active as its 6,8-Me₂ 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


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

Compd	X	E_s	π	σ_m	σ_p	MR	MW	Log 1/C		
								Obsd	Calcd	$\Delta \log 1/C$
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

^aValues calculated for 6,8-Cl₂ analog (3.7 × 4).

larial 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 $\pm 0.4\%$ of calculated values (Gailbraith Lab. Inc).

4- and 6-chloroisatins¹⁷ were prepared from isonitroso-3-chloroacetanilide by cyclizing (concentrated H₂SO₄, 80°) and separation by fractional precipitation by HCl from basic solution.

2-Methoxy-4'-chloroacetophenone;¹⁸ mp 65-66°; NMR (CDCl₃) δ 3.15 (s, 3), 4.69 (s, 2), 7.35-8.10 (m, 4).

New Modification of the Pfizinger Reaction. 3,4',6,8-Tetrachlorocinchophen (12) (13 Made Similarly). 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 (Me₂CO-*d*₆) δ 3.71 (s, 3, CH₃), 6.96 (broad s, concentration dependent, 1, COOH), 7.83 (m, 7, aromatic).

The 2-arylquinoline-4-carbonyl chlorides 17-20¹⁹ were made from 11-14 by excess SOCl₂ (1-1.5 g, 10 ml; reflux 2-3 hr), distilling, coevaporating with benzene to remove SOCl₂, solution of product in hot CH₂Cl₂, 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 Et₂O-CH₂N₂ (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 Et₂O solution (H₂O), drying (MgSO₄), evaporation, and slurring the residue (petroleum ether, bp 30-60°) gave 5.64 g (87%), mp 153-163° dec. In the case of 22, Et₂O-CH₂N₂ was added to 18 in CH₂Cl₂ (stirring, 0°). After solution in Me₂CO, evaporation, trituration with MeOH, and crystallization from Me₂CO, 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 NaBH₄ in 14.5 ml of 3% KOH-H₂O, 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 NHBu₂ was heated (17 hr, 132°). Vacuum evaporation (80°) removed NHBu₂, 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 NHBu₂ (1.3 g, 10 mmol) in Et₂O (standing 8 hr, dark, 30°), filtration [removing 6.2 g (94%) of NHBu₂-HBr], vacuum evaporation (70°), solution of the residue (EtOH, under N₂), addition of

Scheme III

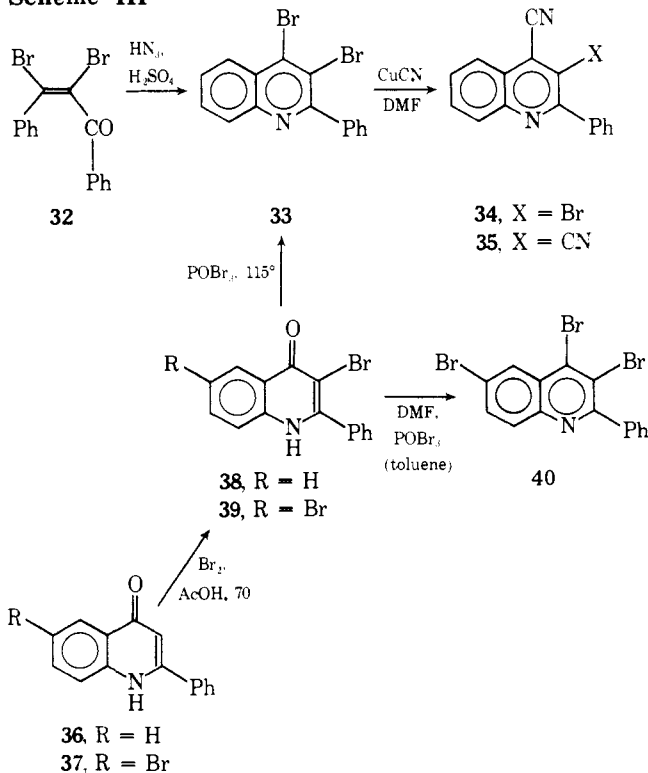


Table III. New Quinoline Derivatives

Compd	R	R'	X	4-R	Yield, % ^{a-o}	Mp, °C ^{p-r}	Analyses ^{s-w}
1	H	H	Br	CHOHCH ₂ NBu ₂	20 ^b	147 dec	C ₂₅ H ₃₁ BrNO • 2HCl ^f
2	6,8-Cl ₂	Cl	Cl	CHOHCH ₂ NBu ₂	96 ^c	139.5-141 ^{p,q}	C ₂₅ H ₂₈ Cl ₄ N ₂ O ^u
3	6,8-Cl ₂	Cl	F	CHOHCH ₂ NBu ₂	87 ^c	124-125.5	C ₂₃ H ₂₈ Cl ₃ FN ₂ O ^f
4	6,8-Me ₂	Cl	OMe	CHOHCH ₂ NBu ₂	59 ^d	96-97	C ₂₈ H ₃₇ ClN ₂ O ^{u,t}
5 • HCl	6,8-Cl ₂	Cl	Me	CH ₂ OHCH ₂ NBu ₂		187-189	C ₂₆ H ₃₂ Cl ₄ N ₂ O ^{u,x}
8 • HCl	6,8-Cl ₂	2',4'-Cl ₂	H	CH ₂ OHCH ₂ NBu ₂		193-193.5	C ₂₅ H ₂₁ Cl ₅ N ₂ O ^{u,x}
9 • HCl	6,8-Cl ₂	2',4'-Cl ₂	Me	CH ₂ OHCH ₂ NBu ₂		178-180	C ₂₆ H ₃₁ Cl ₅ N ₂ O ^{u,x}
12	6,8-Cl ₂	Cl	Cl	COOH	65 ^e	253 dec ^p	C ₁₈ H ₇ Cl ₄ NO ₂ ^u
13	6,8-Cl ₂	Cl	F	COOH	81 ^e	248-249	C ₁₆ H ₇ Cl ₃ FNO ₂ ^u
14	6,8-Cl ₂	H	OMe	COOH	73 ^f	217-219 dec	C ₁₆ H ₁₇ Cl ₄ NO ₂ ^u
15	6,8-Cl ₂	Cl	OMe	COOH	74 ^d	236-237 dec ^r	C ₁₇ H ₁₀ Cl ₃ NO ₃ ^t
16	7-Cl	Cl	Cl	COOH	52 ^{e,t}	272 dec ^p	C ₁₈ H ₈ Cl ₃ NO ₂ ^u
17	H	H	Br	COCl	49 ^h	148-149 ^{p,q}	
18	6,8-Cl ₂	Cl	Cl	COCl	86 ^k	148-150 ^p	C ₁₆ H ₁₆ Cl ₅ NO ^u
19	6,8-Cl ₂	Cl	F	COCl	50 ^{l,j}	168-169.5	C ₁₆ H ₆ Cl ₄ FNO ^t
20	6,8-Me ₂	H	OMe	COCl	89 ^h	155-157	C ₁₇ H ₁₀ Cl ₃ NO ₂ ^t
14	6,8-Cl ₂	H	OMe	CONH ₂	k	252-254 ^p	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂ ^t
amide							
12	6,8-Cl ₂	Cl	Cl	COOMe	87 ⁱ	207-207.5	C ₁₇ H ₉ Cl ₄ NO ₂ ^u
ester							
16	7-Cl	Cl	Cl	COOMe		200-201	C ₁₇ H ₁₀ Cl ₃ NO ₂ ^u
ester							
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 ₂ Br	60 ⁱ	95-96	C ₁₇ H ₁₁ Br ₂ CO ^v
22	6,8-Cl ₂	Cl	Cl	COCH ₂ Br	95 ^{e,m,n}	193-193.5	C ₁₇ H ₆ BrCl ₄ NO ^w
23	6,8-Cl ₂	Cl	F	COCH ₂ Br	64 ^{e,n,o}	178-180	C ₁₇ H ₈ BrCl ₃ FNO ^t
25	6,8-Cl ₂	Cl	Cl		83 ^c	219-219.5	C ₁₇ H ₉ Cl ₄ NO ^u
26	6,8-Cl ₂	Cl	F		46 ^{e,n,o}	178-179	C ₁₇ H ₉ Cl ₃ FNO ^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 ₉ N ₃ ^t
38 ^v	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 ₉ Br ₂ NO ^v
40	6-Br	H	Br	Br	90 ^t	194-195	C ₁₅ H ₈ Br ₃ N ^v

^aReasonably pure material unless otherwise specified; recrystallized from ^bMe₂CHOH-(Me₂CH)₂O; ^cAcOEt; ^dEt₂O; ^eEtOH; ^fEt₂O-hexane; ^gMe₂CO; ^hhexane; ⁱCH₂Cl₂-hexane; ^jvacuum sublimed [140° (0.15 mm)]; ^kCHCl₃-hexane; ^lcyclohexanone; ^mpetroleum ether (bp 65-100°); ⁿpartially purified; ^oMe₂CO-CH₂Cl₂. ^pIr (KBr) for 2, 2960, 2870, 1460, 1380 (CH₃), 2870, 2830, 1460 (CH₂), 1595, 1540, 1490, 1450 cm⁻¹ (aromatic); for 12, 1710, 1960, 2600, 3430 cm⁻¹; for 16 (from 12, CH₂N₂), 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, CH₂N₂), 1268 (COC), 1740 (C=O), 2860, 2970 cm⁻¹ (OMe); for 34 (from 20, NH₃), 1760 (C=O), 3180, 3375 cm⁻¹ (NH₂); for 36, 1640 cm⁻¹ (γ-quinolone). ^qNMR (CDCl₃) δ for 2, 8.89 (d, 1, J = 2 Hz, 5-H), 7.70 (d, 2 H, J = 8 Hz, 3',5'-H₂), 7.68 (d, 1, J = 2 Hz, 7-H), 7.46 (d, 2 H, J = 8 Hz, 2',6'-H₂), 5.72 (q, 1, J = 5 Hz, CH), 4.38 (s, 1, OH), 2.68 [m, 6, -CH₂N(CH₂)₂], 1.43 (m, 4, CH₂CH₂), 0.83 (m, 3, CH₃); for 22, 7.8 (m, 3), 7.5 (m, 3), 4.48 (s, 2 H); for 29, 2.51 (s, 3, CH₃), 2.78 (s, 3, CH₃), 3.53 (s, 3, CH₃), 3.58 (s, 6, 2CH₃), 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, 3CH₃), 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, CH₃), 2.80 (s, 3, CH₃), 3.07-3.51 (m, 2, CH₂), 3.63 (s, 3, CH₃), 4.37 (m, 1, CH), 7.30-8.30 (m, 6, aromatic H). ^rUv, nm (ε × 10⁻³), for 15 (prepared like 14), 232 (31.8), 265.5 (32.2), 290-340 (broad plateau, 8.7-9.3). ^sWere within ±0.4% of calculated values for C and H, and for ^tC, H, N; ^uC, H, Cl, N; ^vC, H, Br, N. ^wCrude 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). ^xSyntheses by J. Christenson and J. Riedmaier via Scheme I (ref 4). ^yCf. ref 21.

NaBH₄ (15 g, 39.5 mmol), stirring (0.5 hr), basification to pH 11 (dilute NaOH), extraction with Et₂O, drying (MgSO₄), vacuum evaporation, solution in dry Et₂O, and addition of Et₂O-HCl gave 1 (0.5 g).

3-Methoxy-6,8-dimethyl-2-(p-chlorophenyl)-4-quinolaldehyde Dimethyl Acetal (29). A solution of MeOCH₂COPh-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, precipi-

tate 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-quinolaldehyde (30). A solution of 29 (5 g) in 5:1 dioxane-H₂O (60 ml) plus 1 ml of concentrated HCl was refluxed (35 min). Addition of H₂O (40 ml) and cooling (5°) gave 30 (4.27 g). **Epoxide 31** was made from 30 by methylenation¹⁰ and converted into amino alcohol 4 by NHBu₂ (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 procedures²¹ 36 \rightarrow 38 \rightarrow 33 a small amount of tribromide 40 was isolated (5%) which was the predominant product of bromination by POBr₃ in DMF-toluene and was obtainable also from 6-bromo-2-phenylquinoline (38 \rightarrow 39 \rightarrow 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 POBr₃ 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 CO₂ 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*-CIPhCC=CCICOP-*p*-Cl.²²

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References and Notes

- (1) H. R. Munson, Jr., J. R. Shanklin, Jr., C. J. Ohnmacht, Jr., J. M. Sanders, A. R. Patel, C. R. Wetzel, F. C. Davis, R. E. Johnson, and R. E. Lutz, 21st Southeast Regional Meeting of the American Chemical Society, Richmond, Va., Nov 1969, Abstract 225.
- (2) (a) R. E. Lutz, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freek, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, Jr., J. M. Salsbury, N. H. Shearer, Jr., J. D. Smith, and J. W. Wilson, III, *J. Am. Chem. Soc.*, **68**, 1813 (1946); (b) D. C. Martin, J. D. Arnold, D. F. Clyde, M. Al Ibrahim, P. E. Carson, K. H. Rieckmann, and D. Willerson, Jr., *Antimicrob. Agents Chemother.*, **3**, 214 (1973); (c) D. F. Clyde, V. C. McCarthy, C. C. Rebert, and R. M. Miller, *ibid.*, **3**, 220 (1973); (d) C. J. Canfield, A. P. Hall, B. S. MacDonald, D. A. Newman, and J. A. Shaw, *ibid.*, **3**, 224 (1973).
- (3) (a) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968); (b) W. L. Fowles, *J. Invest. Dermatol.*, **32**, 223 (1959); (c) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
- (4) J. Christensen and J. Riedmaier, Aldrich Chemical Co., Milwaukee, Wis., U.S. Army Medical Research and Development Command, Contract DA-49-193-MD-2766, Second Annual Report, July 15, 1966–July 15, 1967, prepared by H. C. Koppel.
- (5) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968).
- (6) K. Feist and M. Kuklinski, *Arch. Pharm. (Weinheim, Ger.)*, **274**, 244 (1936).
- (7) (a) R. N. Dupois and H. G. Lindwall, *J. Am. Chem. Soc.*, **56**, 471, 2716 (1934); (b) H. G. Lindwall and J. S. MacLennan, *ibid.*, **54**, 4739 (1932); (c) H. R. Henze, J. W. Melton, and E. A. Forman, *ibid.*, **70**, 2622 (1948); (d) W. Dilthey and C. Thelen, *Ber.*, **58**, 1588 (1925).
- (8) R. E. Lutz and J. M. Sanders, *J. Med. Chem.*, in press (paper 11).
- (9) (a) E. Ziegler and K. Gelfert, *Monatsh. Chem.*, **90**, 822 (1959); (b) R. Salvador and Th. Kappe, *ibid.*, **93**, 1376 (1962); (c) R. Wolf and Th. Kappe, *ibid.*, **96**, 418 (1965); (d) Th. Kappe, *ibid.*, **96**, 889 (1965); (e) Th. Kappe and H. G. Foraita, *ibid.*, **97**, 409 (1966).
- (10) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866, 3782 (1962).
- (11) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
- (12) (a) C. Hansch, *Acc. Chem. Res.*, **2**, 232 (1969); (b) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969); (c) C. Hansch, *J. Org. Chem.*, **35**, 620 (1970).
- (13) P. N. Craig and C. Hansch, *J. Med. Chem.*, **16**, 661 (1973).
- (14) P. N. Craig, *J. Med. Chem.*, **15**, 144 (1972).
- (15) C. Hansch, A. Leo, S. H. Ungar, K. H. Kim, D. Nitaitani, and E. J. Lein, *J. Med. Chem.*, **16**, 1207 (1973).
- (16) C. B. Wetzel, J. R. Shanklin, Jr., and R. E. Lutz, *J. Med. Chem.*, **16**, 528 (1973).
- (17) A. E. Senear, H. Sargent, J. F. Mead, and J. B. Koepfli, *J. Am. Chem. Soc.*, **68**, 2692 (1946); (b) N. H. Leake, Ph.D. Dissertation, University of Virginia, 1946.
- (18) R. B. Moffett and R. L. Shriner, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 562.
- (19) J. Buechi, X. Perlia, and M. A. Preiswerk, *Pharm. Acta Helv.*, **41**, 164 (1966).
- (20) R. E. Pratt, W. J. Welstead, Jr., and R. E. Lutz, *J. Heterocycl. Chem.*, **7**, 1051 (1970).
- (21) (a) C. E. Kaslow and W. R. Lawton, *J. Am. Chem. Soc.*, **72**, 1723 (1950); (b) S. J. Nix, *Proc. Indiana Acad. Sci.*, **61**, 121 (1952) [*Chem. Abstr.*, **47**, 10533 (1953)].
- (22) T. N. Crowell, R. T. Kemp, R. E. Lutz, and A. A. Wall, *J. Am. Chem. Soc.*, **90**, 4638 (1968).