values. Nmr spectra were taken on all new compounds except compound 2 and were consistent with proposed structures.

7-Alkylmercapto-6-hydroxy-5,8-quinolinequinones. Four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones were prepared by treating 6-hydroxy-5,8-quinolinequinone in ethanol with the appropriate alkyl mercaptan in a manner similar to that previously described for the syntheses of some sulfur-containing benzoquinones by Snell and Weissberger.[7] Generally, the reaction mixtures were stirred at both room temperature and at 50–60° for several days. The crude product was generally purified by repeated fractional recrystallizations from ether–ethanol–chloroform. The synthesis of 7-*n*-dodecylmercapto-6-hydroxy-5,8-quinolinequinone, which is described below, is representative.

7-*n*-Dodecylmercapto-6-hydroxy-5,8-quinolinequinone. A mixture of 6-hydroxy-5,8-quinolinequinone (2 g) and *n*-dodecyl mercaptan (3.5 g) in ethanol (~50 ml) was stirred at about 50–60° for 3 days and then at room temperature for 3 days. After cooling in the refrigerator, the solid material was collected by filtration and repeatedly recrystallized from ether–ethanol (charcoal) to yield 650 mg of the purple crystalline product, mp 136–138° (with decomposition from 127°).

3-*n*-Dodecylmercapto-2-hydroxy-1,4-naphthoquinone. A mixture of 2-hydroxy-1,4-naphthoquinone (6 g) and *n*-dodecyl mercaptan (10.5 g) in ethanol was allowed to stir at room temperature 3 days and then was heated at about 50° for 1 week. The reaction mixture was cooled in the refrigerator, and the solid material was collected by filtration and repeatedly recrystallized from ethanol–ether–chloroform and ether–hexane to yield 800 mg of the purple product, mp 72–74°.

1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene. 1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene was synthesized by a procedure similar to that described for the preparation of a certain hydroquinone diacetate by Fieser and Gates.[8] A mixture of 3-*n*-dodecylmercapto-2-hydroxy-1,4-naphthoquinone (1.0 g), acetic anhydride (6.0 ml), zinc dust (1.3 g), and pyridine (0.5 ml) was allowed to stand at room temperature overnight (hand stirring initially). Water was added, and the mixture was extracted with ether. The ether extract, after being washed with water and dilute potassium carbonate solution and being dried over anhydrous potassium carbonate, was evaporated. Solvent (ethanol–ether) was added and the turbid mixture heated until clear. The crystalline triacetate was obtained from the cooled, seeded solution. 1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene (1.03 g), mp 67–69°, was obtained after recrystallization from ethanol–water (charcoal).

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3-Phenyl-5-quinolinemethanol Antimalarials†

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Special Skraup procedures have been developed for the synthesis of a series of new 3-phenyl-5-quinolinecarboxylic esters. These esters have been employed as starting materials for the elaboration of a series of α-dialkylaminomethyl-3-phenyl-5-quinolinemethanols *via* the corresponding acid chlorides, diazo ketones, bromo ketones, and epoxides. Alternate routes to the desired 3-phenyl-5-quinolinemethanols were also investigated. In the case of the reaction between the epoxide derived from 5-bromoacetyl-8-methyl-3-phenylquinoline with di-*n*-butylamine, both of the possible isomeric amino alcohols were isolated and characterized. Eight compounds (including intermediates) were tested for antimalarial activity against *Plasmodium berghei* in mice. α-Di-*n*-butylaminomethyl-3-(4-chlorophenyl)-8-methyl-5-quinolinemethanol dihydrobromide showed modest activity at doses of 160 mg/kg and higher.

The impressive activity of a number of 2-phenyl-4-quinolinemethanols against the malaria parasite in human and avian infections was discovered more than 20 years ago.[1-3] Pronounced photosensitization associated with the active compounds of this group has precluded extensive study or use in man. Recent research efforts in this area have led to the discovery of additional active compounds[4] and to the development of a practical and useful animal test for phototoxicity.[5] However, a clear-cut separation of the phototoxic liability and antimalarial activity has not been achieved with the 2-phenyl-4-quinolinemethanols, related heterocyclic analogs, or the positional isomers of the 2-phenylquinolinemethanols.

A small number of 5-quinolinemethanols have shown antimalarial activity in several species,[6-8] but the 2-aryl-5-quinolinemethanols have also produced phototoxic reactions at the effective dose levels.[8] Because of the antimalarial activity of the 5-quinolinemethanols and the concomitant phototoxicity of the 2-aryl analogs, we speculated that 3-aryl-5-quinolinemethanols, with no "blocking" group at the 2 position of the quinoline nucleus, might show antimalarial activity without phototoxicity. This paper describes the synthesis of a limited number of compounds to test this hypothesis.

Chemistry. In general, we chose to elaborate the 3-aryl-5-quinolinemethanols from the corresponding carboxylic acids, using procedures similar to those developed by Lutz and his coworkers[9] (see Scheme I). The absence of reports of 3-aryl-5-quinolinecarboxylic acids or esters in the literature necessitated the development of preparative methods for these starting materials.

3-Phenylquinoline has been prepared by Warren[10] using special Skraup conditions. Modification of this procedure, when applied to appropriately substituted anilines, proved to be an adequate preparative method for the 3-aryl-5-quinolinecarboxylic esters (**1-5**, *cf.* Table I). Synthesis of

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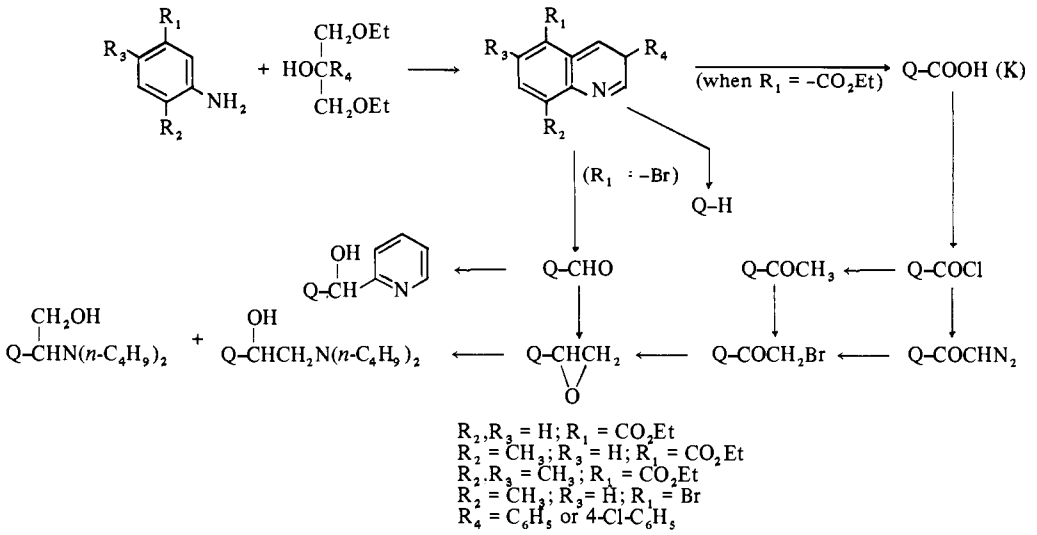
Scheme I



the 1,3-dialkoxy-2-arylpropan-2-ol precursors for the Skraup reaction was accomplished using Warren's procedure[10] which we found to be superior to the method described by Taeger and his coworkers.[11]

To achieve practical preparative yields of the 3-aryl-5-quinolinecarboxylic esters, mild Skraup conditions were developed. This was necessary to minimize both the polymerization of the α-arylacroleins formed *in situ* and the oxidative destruction of the 3-arylquinolines. By using a reaction medium of 85% phosphoric acid, arsenic acid as the oxidizing agent, and temperatures of 60–80° (N_2 atmosphere), appropriately substituted anilines were converted to the quinolinecarboxylic esters in 15–36% yield.

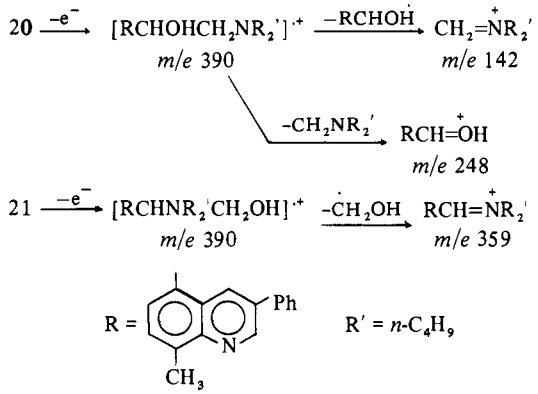
Alternative routes for the elaboration of the amino alcohols were investigated in several instances (see Scheme I). 5-Bromo-8-methyl-3-phenylquinoline (**26**) was converted[12] to the aldehyde **27** and this in turn to the epoxide **16**.[13] The 6,8-dimethyl-3-arylquinolinecarbonyl chlorides **12** and **13** were allowed to react with methylmagnesium bromide[14] to give in moderate yield (55–75%) the methyl ketones **24** and **25**. Although good preparative methods for the bromination[15] of these ketones were not developed, this would appear to be an attractive route to the amino alcohols in situations where steric hindrance is a factor.

With the 6,8-dimethylquinolines, steric hindrance required the use of forcing conditions for the saponification of the esters, conversion to the acid chlorides, and formation of the diazo ketones. Useful conversions to the diazo ketones were achieved only when large excesses of diazomethane were employed, at 25°, for several days. The resulting diazo ketones were badly contaminated with polymeric impurities, and satisfactory purification was not accomplished until the final step in the sequence.

Two products were isolated and characterized from the reaction of 5-(epoxyethyl)-8-methyl-3-phenylquinoline and di-*n*-butylamine. The desired α-aminomethylquinolinemethanol (**20**), resulting from attack on the sterically favored β-epoxide carbon, was obtained as the major product. The two isomeric amino alcohols were separated by thin-layer chromatography. The primary alcohol, 8-methyl-3-phenyl-5-(1-di-*n*-butylamino-2-hydroxyethyl)quinoline (**21**), had the higher R_f value on silica gel plates with ethyl acetate as the eluent. On alumina plates, however, the order was reversed, and the primary alcohol had the lower R_f. Both isomers could be obtained from a silica gel column, using chloroform as the eluent and a high sample-absorbant ratio (1:400). The minor product **21** was characterized and differentiated from the major product **20** using nmr and mass spectroscopic data.

The nmr interpretation was based on the fact that the deshielding effect of the hydroxy group on adjacent protons is of higher magnitude than the corresponding effect of a tertiary amine (see Experimental Section). The mass spectroscopic data showed ions resulting from the cleavage of the OC–CN bond. The spectrum of compound **20** showed characteristic peaks at *m/e* 142 and 248, while that of compound **21** had a characteristic peak at *m/e* 359 (see Scheme II). To the best of our knowledge, this is the first instance

Scheme II



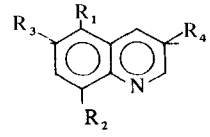
of the isolation and characterization of an α-aminoethanol derivative in the quinolineamino alcohol series.

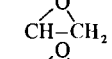
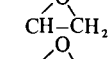
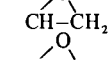
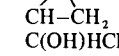
It was observed that 5-bromo-8-methyl-3-phenylquinoline (**26**) could be debrominated in excellent yield by hydrolysis of the corresponding lithium derivative. This procedure could be useful for the synthesis of a preferred quinoline isomer *via* the Skraup reaction.

Biological Activity. Compounds **6–8**, **20**, **22**, and **28** (see Table I), as well as the intermediate 1,3-diethoxy-2-phenylpropan-2-ol, were submitted for antimalarial testing against *Plasmodium berghei* in mice by Dr. Leo Rane‡ at the University of Miami. Insufficient quantities of compounds **21** and **23** were available for testing.

‡The test procedure has been described in ref 16. Test results were supplied by the Division of Medicinal Chemistry of the Walter Reed Army Institute of Research.

Table I



Compd no.	R_1	R_2	R_3	R_4	Formula	Yield, %	Mp, °C	Crystn solvent	Prepn[a]	Analyses[b]
1	CO_2Et[c]	H	H	C_6H_5	$C_{18}H_{15}NO_2$	19	110	n-C_7H_{16}	A	C, H, N
2	CO_2Et	CH_3	H	C_6H_5	$C_{19}H_{17}NO_2$	32	109–111	n-C_7H_{16}	A	C, H, N
3	CO_2Et	CH_3	H	4-Cl-C_6H_4	$C_{19}H_{16}ClNO_2 \cdot {}^1/_8C_7H_{16}$[d]	26	97–99	n-C_7H_{16}	A	C, H, N
4	CO_2Et	CH_3	CH_3	C_6H_5	$C_{20}H_{19}NO_2$	15	80–81.5	n-C_5H_{12}	A	C, H, N
5	CO_2Et	CH_3	CH_3	4-Cl-C_6H_4	$C_{20}H_{18}ClNO$	36	129–131	n-C_7H_{16}	A	C, H, N
6	COOH	CH_3	H	C_6H_5	$C_{17}H_{13}NO_2$		270–274	EtOH	B	C, H, N
7	COOH	CH_3	H	4-Cl-C_6H_4	$C_{17}H_{12}ClNO_2 \cdot 0.5EtOH$		280–282	EtOH	B	C,[i] H, N
8	COOH	CH_3	CH_3	C_6H_5	$C_{18}H_{15}NO_2$		302–305	EtOH–DMF	B	C,[j] H, N
9	COOH	CH_3	CH_3	4-Cl-C_6H_4	$C_{18}H_{14}ClNO_2$		312–318	EtOH–DMF	B	C, H, N
10	COCl	CH_3	H	C_6H_5	$C_{17}H_{12}ClNO$	86	127–128	Et_2O	C	C, H, N
11	COCl	CH_3	H	4-Cl-C_6H_4	$C_{17}H_{11}Cl_2NO$	87	177	CH_2Cl_2	C	C, H, N
12	COCl	CH_3	CH_3	C_6H_5	$C_{18}H_{14}ClNO$	73	122–124	i-Pr_2O	C	*e*
13	COCl	CH_3	CH_3	4-Cl-C_6H_4	$C_{18}H_{13}Cl_2NO$	88	159–161	i-Pr_2O	C	C, H, N
14	$COCH_2Br$	CH_3	H	C_6H_5	$C_{18}H_{14}BrNO \cdot HBr$	95	237–240	AcOH	E	C, H, N, Br
15	$COCH_2Br$	CH_3	H	4-Cl-C_6H_4	$C_{18}H_{13}BrClNO \cdot HBr$	91	220–224[f]	AcOH	E	C, H, N
16		CH_3	H	C_6H_5	$C_{18}H_{15}NO$	93	Oil		F, G	*e*
17		CH_3	H	4-Cl-C_6H_4	$C_{18}H_{14}ClNO$	81	119–120	MeOH	F	C, H, N
18		CH_3	CH_3	C_6H_5	$C_{19}H_{17}NO$	20	169–172	MeOH	F, H	*e*
19		CH_3	CH_3	4-Cl-C_6H_4	$C_{19}H_{16}ClNO$	70	153–161	C_6H_6	F	
20	$C(OH)HCH_2N(n\text{-}Bu)_2$	CH_3	H	C_6H_5	$C_{26}H_{34}N_2O \cdot 2HBr \cdot H_2O$	15	149–151	EtOH–Me_2CO	I	C, H, N
21	$N(n\text{-}Bu)_2$ $CHCH_2OH$	CH_3	H	C_6H_5	$C_{26}H_{34}N_2O \cdot 2HBr \cdot 0.5H_2O$	5		EtOH–Me_2CO	I	C, H
22	$C(OH)HCH_2N(n\text{-}Bu)_2$	CH_3	H	4-Cl-C_6H_4	$C_{26}H_{33}ClN_2O \cdot 2HBr$	15	175–177[g]	EtOH–Me_2CO	I	C, H, N
23	$C(OH)HCH_2N(n\text{-}Bu)_2$	CH_3	CH_3	4-Cl-C_6H_4	$C_{27}H_{35}ClN_2O \cdot 2HBr$	10	203–205.5	EtOH–Me_2CO	I	C, H, N
24	$COCH_3$	CH_3	CH_3	C_6H_5	$C_{19}H_{17}NO$	75	133.5–134.5	Cyclohexane	D	C, H, N
25	$COCH_3$	CH_3	CH_3	4-Cl-C_6H_4	$C_{19}H_{16}ClNO$	55	131–136	Cyclohexane	D	C, H, N
26	Br	CH_3	H	C_6H_5	$C_{16}H_{12}BrN \cdot HBr$	22	222–237	n-BuOH	*k*	C, H, N
27	CHO	CH_3	H	C_6H_5	$C_{17}H_{13}NO$	90	Oil		*k*	*h*
28	C(OH)H-Py	CH_3	H	C_6H_5	$C_{22}H_{18}N_2O \cdot 2HBr \cdot H_2O$	29	186–190	EtOH–Me_2CO	*k*	C, H
29	H	CH_3	H	C_6H_5	$C_{16}H_{13}N \cdot HBr$	90	237–238	$MeNO_2$	*k*	C, H, N

[a] The capital letters refer to the method of synthesis in the Experimental Section. [b] Analyses for the elements shown were within 0.4% of theoretical values. [c] The isomeric 7-carbethoxy-3-phenylquinoline, mp 108–109°, was isolated in 5% yield on an alumina (80–200 mesh) column. [d] The presence of heptane was confirmed by a strong peak (m/e 100$^+$) in the mass spectrum. [e] Elemental analysis not carried out, see Experimental Section for spectral data. [f] Free base had mp 94–96°. [g] Free base had mp 76–79° (MeOH). [h] Characterized as the phenylhydrazone, mp 154–156.5°. *Anal.* ($C_{23}H_{18}N_3$) C, H, N (see Experimental Section). [i] C: calcd, 67.40; found, 67.82. [j] C: calcd, 77.95; found, 77.49. [k] See Experimental Section.

The amino alcohols **20** and **22** showed some activity. Compound **20** produced an increase in survival time of 7.9 days over untreated controls at a dose of 640 mg/kg but did not give significant effects at lower doses. Compound **22** produced an increase in survival time of 8.0 days at 160 mg/kg and 10.5 days at 320 mg/kg. Significant activity was not seen with the other compounds tested. On the basis of these data, compound **22** seems to be slightly more active against *P. berghei* than 8-chloro-α-dibutylaminomethyl-2-phenyl-5-quinolinemethanol[8] but much less active than α-(dibutylaminomethyl)-2-phenyl-4′,6,8-trichloro-5-quinolinemethanol.[7] Both of these 2-phenyl derivatives were phototoxic at effective antimalarial doses. Unfortunately, phototoxicity data on compounds **20** and **22** are not available.

Compounds **8**, **20**, and **22**, when tested against *P. gallinaceum* infections in chicks by Dr. Rane,‡ were inactive in doses as high as 320 mg/kg sc.

Experimental Section §

Ethyl **5-Amino-2,4-dimethylbenzoate.** 2,4-Dimethyl-5-nitrobenzoic acid[17] (70 g, 0.36 mol) was esterified using a mixture of 260 ml of EtOH and 11 ml of concentrated H_2SO_4. Distillation [bp 102–135° (0.2 mm)] and crystallization from *n*-pentane gave 61 g (76%) of the desired nitro ester, mp 55–56°. A mixture of this ester (60 g, 0.3 mol), 20 g of Raney Ni, and 280 ml of EtOH was hydrogenated (55 psi, 25°) for 3 hr. After work-up through dilute aqueous H_2SO_4 extraction, the oily residue slowly crystallized, 48 g (83%), mp 30–32°. A small sample was converted to the HCl salt, mp 216–220° (*n*-BuOH). *Anal.* ($C_{11}H_{15}NO_2 \cdot HCl$) C, H, N.

Ethyl 3-amino-4-methylbenzoate, mp 47–49° (lit.[18] mp 48–50°), was prepared from 4-methyl-3-nitrobenzoic acid in a similar fashion. *Anal.* ($C_{10}H_{13}NO_1 \cdot HCl$) C, H, N.

1,3-Diethoxy-2-(4-chlorophenyl)propan-2-ol. To the Grignard reagent prepared from Mg turnings (24 g, 1.0 mol) and 4-bromochlorobenzene (191 g, 1.0 mol) in 600 ml of anhydrous Et_2O, under N_2, was added slowly with stirring and cooling a solution of 1,3-dichloropropan-2-one (137 g, 1.0 mol) in 600 ml of anhydrous Et_2O. After refluxing 1 hr, hydrolysis with aqueous NH_4Cl, and removal of the solvent, the crude 1,3-dichloro-2-(4-chlorophenyl)propan-2-ol was obtained as a brown oil: nmr ($CDCl_3$) δ 7.88 (s, 4 H), 3.87 (s, 4 H), 3.10 (s, br, exch with D_2O, 1 H). This crude material was refluxed for 4 hr with a solution of NaOEt (2 mol) in 500 ml of EtOH. After removal of the NaCl and EtOH, a C_6H_6 solution was washed with aqueous Na_2CO_3 and the crude product was fractionally distilled through a 12-in. Vigreux column to give 120 g (46%) of colorless liquid, bp 107° (0.27 mm). *Anal.* ($C_{13}H_{19}ClO_3$) C, H.

1,3-Diethoxy-2-phenylpropan-2-ol[10] was prepared in 50% yield in an analogous procedure, bp 75° (0.1 mm) [lit. bp 155° (21 mm)]. *Anal.* ($C_{13}H_{20}O_3$) H; C: calcd, 69.61; found, 69.18.

A. 5-Carbethoxy-8-methyl-3-phenylquinoline (2). To a warm (80°) mixture of ethyl 3-amino-4-methylbenzoate (43.7 g, 0.25 mol) and H_3AsO_4 (75.0 g, 0.53 mol) in 250 ml of 85% H_3PO_4, under N_2, was added with stirring over 6 hr 1,3-diethoxy-2-phenylpropan-2-ol (89.6 g, 0.4 mol). After an additional 1 hr, the mixture was poured onto cracked ice, made basic, and extracted with $CHCl_3$. The extracts were dried, the $CHCl_3$ was evaporated, and the residue was chromatographed over a silica gel (E. Merck AG, 0.05–0.20 mm) column, with CH_2Cl_2 as the eluent. The second component off the column was 5-carbethoxy-8-methyl-3-phenylquinoline: nmr ($CDCl_3$) δ 9.65 (d, J = 2.5 Hz, 1 H), 9.25 (d, J = 2.5 Hz, 1 H), 8.25 (d, J = 8 Hz, 1 H), 7.25–7.95 (m, 6 H), 4.49 (q, J = 7 Hz, 2 H), 2.88 (s, 3 H), 1.46 (t, J = 7 Hz, 3 H).

B. 8-Methyl-3-phenyl-5-quinolinecarboxylic Acid (6). A solution of 5-carbethoxy-8-methyl-3-phenylquinoline (22.5 g, 77 mmol) and KOH (4.3 g, 77 mmol) in 300 ml of 75% aqueous EtOH was refluxed 2 hr. The solvent was evaporated and the residue washed with $CHCl_3$. Potassium 8-methyl-3-phenyl-5-quinolinecarboxylate remained as a white solid, 17.0 g (77%), after drying over P_2O_5. An aqueous solution of a small portion of this salt was acidified (AcOH) and chilled, and the white crystalline acid filtered.

Saponification of the corresponding dimethylquinoline esters **4** and **5** required prolonged refluxing (4 days).

C. 8-Methyl-3-phenyl-5-quinolinecarbonyl Chloride (10). To a cold (10°), well-stirred solution of oxalyl chloride (10.7 g, 84 mmol) in 100 ml of anhydrous C_6H_6 was added portionwise potassium 8-methyl-3-phenyl-5-quinolinecarboxylate (10.1 g, 34 mmol). After 1 hr, the mixture was warmed to 25°, and after an additional 4 hr the solvent was evaporated *in vacuo*. The residue was taken up in 400 ml of C_6H_6 and washed with 150 ml of 10% aqueous Na_2CO_3 and 100 ml of H_2O. The now clear solution was dried and the C_6H_6 evaporated. 8-Methyl-3-phenyl-5-quinolinecarbonyl chloride remained as a yellow solid.

6,8-Dimethyl-3-phenyl-5-quinolinecarbonyl chloride (**12**) and 6,8-dimethyl-3-(4-chlorophenyl)-5-quinolinecarbonyl chloride (**13**) were prepared analogously, except the reaction was carried out at 55° for 2.5 hr.

D. 5-Acetyl-6,8-dimethyl-3-phenylquinoline (24).[14] To a stirred solution of 6,7-dimethyl-3-phenyl-5-quinolinecarbonyl chloride (2.0 g, 6.8 mmol) in 50 ml of anhydrous Et_2O, at 25°, was added dropwise a solution of MeMgBr (14 mmol) in 15 ml of Et_2O. After 1 hr, 25 ml of saturated aqueous NH_4Cl was added and the mixture extracted with Et_2O. The extracts were washed with H_2O and dried, and the Et_2O was evaporated to give 5-acetyl-6,8-dimethyl-3-phenylquinoline.

E. 5-Bromoacetyl-8-methyl-3-phenylquinoline Hydrobromide (14). To a cold (0°) solution of 8-methyl-3-phenyl-5-quinolinecarbonyl chloride (11.3 g, 0.04 mol) in a mixture of CH_2Cl_2 and 200 ml of Et_2O was added a solution of CH_2N_2[19] (0.10 mol) in 500 ml of Et_2O. After 2 hr at 0° a solution of gaseous HBr (17.0 g, 0.2 mol) in 150 ml of cold Et_2O was added. After an additional 1 hr, the pale yellow 5-bromoacetyl-8-methyl-3-phenylquinoline HBr was filtered.

To achieve reasonable conversions of the dimethylquinolinecarbonyl chlorides, **12** and **13**, to the diazo ketones, it was necessary to use a large excess (20-fold or more) of CH_2N_2 and long reaction times (24 hr or more) at 25°.

5-Bromo-8-methyl-3-phenylquinoline (26). To a warm (80°), well-stirred mixture of 2-amino-4-bromotoluene[20] (40 g, 0.22 mol) in 210 ml of 85% H_3PO_4 was added simultaneously over a 1-hr period 1,3-diethoxy-2-phenylpropan-2-ol (73 g, 0.33 mol) and H_3AsO_4 (61 g, 0.43 mol). After an additional 3.5 hr, the mixture was poured onto cracked ice, made basic (NH_4OH), and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), the solution was evaporated, and the black residue chromatographed over a silica gel column with CH_2Cl_2 as the eluent. The second component removed from the column was 5-bromo-8-methyl-3-phenylquinoline, which was crystallized from *n*-pentane, 14.0 g (22%), mp 148–153°. An analytical sample of the HBr salt was prepared with ethereal HBr.

3-Phenyl-8-methylquinoline (29). To a cold (−70°), well-stirred solution of *n*-BuLi (7.0 mmol) in 30 ml of anhydrous THF, under N_2, was added a cold solution of 5-bromo-3-phenyl-8-methylquinoline (1.0 g, 3.4 mmol) in 5 ml of anhydrous Et_2O. After 30 min, 5 ml of cold EtOH was added, followed by 10 ml of saturated aqueous NH_3Cl. The mixture was allowed to warm to 25° and was extracted with Et_2O. The extracts were washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated. Volatile impurities were removed by pumping in a vacuum (0.25 mm) overnight. Treatment with a solution of HBr in EtOH gave a 3-phenyl-8-methylquinoline hydrobromide.

5-Formyl-8-methyl-3-phenylquinoline (27).[12] To a cold (−70°) solution of *n*-BuLi (4 mmol) in a mixture of 10 ml of Et_2O and 10 ml of THF, under N_2, was added portionwise with stirring 5-bromo-8-methyl-3-phenylquinoline (0.6 g, 2 mmol). After 30 min a solution of DMF (1.5 g, 20.5 mmol) in 3 ml of THF was added. After an additional 15 min, 2 ml of cold EtOH was added, followed by 10 ml of saturated aqueous NH_4Cl. The mixture was warmed to 25° and extracted with Et_2O, the extracts were washed with H_2O and dried, and the solvent was evaporated. 5-Formyl-8-methyl-3-phenylquinoline remained as an oil.

A small sample of the aldehyde was converted to the phenylhydrazone derivative which was crystallized from MeOH.

8-Methyl-3-phenyl-α-(2-pyridyl)-5-quinolinemethanol Dihydrobromide (28). 2-Pyridyllithium was prepared as described by

§When several compounds were prepared by comparable procedures, only one representative example is included in this section. Reference should be made to Table I for supplementary information on each new compound. All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. All new compounds were characterized by nmr spectra obtained on a Varian Model T-60 spectrometer and ir spectra recorded on a Perkin-Elmer Model 257 spectrometer. Mass spectra were determined with a Model RMU-6E Hitachi Perkin-Elmer instrument.

Wibaut[21] from 2-bromopyridine (1.6 g, 10.1 mmol) and *n*-BuLi (14 mmol) in 25 ml of anhydrous Et_2O at −45°. To this cold red solution was added rapidly with stirring a solution of 5-formyl-8-methyl-3-phenylquinoline (2.5 g, 10 mmol) in 20 ml of Et_2O. After 30 min, 10 ml of EtOH was added, followed by 20 ml of saturated aqueous NH_4Cl. The Et_2O was separated and the aqueous phase extracted with Et_2O. The combined extracts were washed with H_2O and dried (Na_2SO_4), the solvent was evaporated, and the residue chromatographed over a silica gel column, using $CHCl_3$ as the eluent. The third component removed from the column was 8-methyl-3-phenyl-α-(2-pyridyl)-5-quinolinemethanol, 1.0 g (29%). This material was converted to the di-HBr salt.

A single attempt to selectively reduce the pyridyl ring of this compound (150 mg) by catalytic hydrogenation over PtO_2[4] (in EtOH with 2 drops of concentrated HCl) at 45 psi and 25°[5] failed. The nmr spectrum of the product after work-up was devoid of the characteristic doublets at 9.15 and 8.75 ppm, which indicated that reduction of the quinoline ring had also occurred.

F. 8-Methyl-3-(4-chlorophenyl)-5-quinolylethylene Oxide (17). A suspension of 5-bromoacetyl-8-methyl-3-(4-chlorophenyl)quinoline hydrobromide (11.5 g, 25 mmol) in 150 ml of 10% aqueous Na_2CO_3 was extracted with C_6H_6. The extracts were dried, and evaporation of the C_6H_6 gave 5-bromoacetyl-8-methyl-3-(4-chlorophenyl)quinoline, 8.8 g, mp 118–123°. A solution of this material in 500 ml of EtOH was treated with a solution of $NaBH_4$ (0.96 g, 25 mmol) in 100 ml of EtOH. After 3 hr at 25°, the solvent was evaporated; the residue was taken up in C_6H_6, washed with H_2O, and dried (Na_2SO_4). Evaporation of the C_6H_6 gave 8-methyl-3-(4-chlorophenyl)-5-quinolylethylene oxide as a yellow oil which slowly crystallized.

G. 8-Methyl-3-phenyl-5-quinolylethylene Oxide (16).[13] A 50% NaH dispersion (0.8 g) in mineral oil was washed free of the mineral oil with dry pentane. After carefully decanting the pentane from the NaH, a stream of dry N_2 was used to evaporate the last traces of solvent. To the NaH was added 7.2 g of DMSO, and the mixture was warmed to 75°. After 45 min (H_2 evolution had ceased) 8.0 ml of THF was added, and the mixture was cooled (−20°). A solution of trimethylsulfonium iodide (3.8 g) in 18 ml of DMSO was added over a 3-min period, followed by the rapid addition of a solution of 5-formyl-8-methyl-3-phenylquinoline (1.0 g, 4 mmol) in 10 ml of THF. The mixture was allowed to come to 25° and, after 1 hr, 10 ml of H_2O was added. The reaction mixture was extracted with Et_2O, the extracts were washed thoroughly with H_2O and dried (Na_2SO_4), and the solvent was evaporated. The residue was a yellow oil which, on the basis of nmr, ir, and tlc data, was identical with the corresponding product obtained by procedure F: nmr ($CDCl_3$) δ 9.18 (d, J = 2.4 Hz, 1 H), 8.60 (d, J = 2.4 Hz, 1 H), 7.20–7.87 (m, 7 H), 4.35–4.44 (m, 1 H), 3.30 (dd, J_{ax} = 5.8, J_{bx} = 4.4 Hz, 1 H), 2.76–2.96 (m, 1 H), 2.80 (s, 3 H).

H. 6,8-Dimethyl-3-phenyl-5-quinolylethylene Oxide (18). To a warm (100°) solution of 5-acetyl-6,8-dimethyl-3-phenylquinoline (1.0 g, 3.9 mmol) in 10 ml of AcOH was added a solution of $NaBrO_4$ (0.2 g, 1.3 mmol) in 2.64 g of 48% HBr.[16] After work-up and crystallization of the product from cyclohexane, the crude product weighed 0.87 g. Nmr data indicated that this material was a 4:1 mixture of the monobromoacetyl and the dibromoacetyl derivatives. Repeated recrystallization did not improve this ratio. Reduction of this crude material (0.5 g) with $NaBH_4$ (0.5 g), as described in procedure F, gave crude 6,7-dimethyl-3-phenyl-5-quinolylethylene oxide, 0.28 g, which was recrystallized from MeOH: mp 169–172°; nmr ($CDCl_3$) δ 9.33 (d, J = 2.5 Hz, 1 H), 9.00 (d, J = 2.5 Hz, 1 H), 7.10–7.84 (m, 6 H), 4.25 (m, 1 H), 3.30 (dd, J_{ax} = 5.4, J_{bx} = 4.0 Hz, 2 H), 2.64 (s, 3 H), 2.38 (s, 3 H).

I. α-(Di-*n*-butylaminomethyl)-8-methyl-3-phenyl-5-quinolinemethanol Dihydrobromide (20) and 5-(α-Di-*n*-butylamino-β-hydroxyethyl)-8-methyl-3-phenylquinoline Dihydrobromide (21). A mixture of 8-methyl-3-phenyl-5-quinolylethylene oxide (1.2 g, 4.7 mmol) and di-*n*-butylamine (1.22 g, 9.5 mmol) was heated in a sealed vial at 135° for 6 hr. Excess di-*n*-butylamine was removed by pumping the residue in a vacuum (0.05 mm) for 24 hr. The oily residue was chromatographed over a silica gel column (600 g, E. Merck, AG, 0.05–0.02 mm) with $CHCl_3$ as the eluent. The second component removed from the column was 5-(α-di-*n*-butylamino-β-hydroxyethyl)-8-methyl-3-phenylquinoline (100 mg). The di-HBr salt was prepared with the use of ethanolic HBr and crystallized from EtOH–Me_2CO as pale yellow needles: nmr (free base, $CDCl_3$) δ 9.25 (d, J = 2.4 Hz, 1 H), 8.78 (d, J = 2.4 Hz, 1 H), 7.37–7.96 (m, 7 H), 4.60–4.98 (m, 1 H), 4.44 (s, br, 1 H), 3.60–4.27 (m, 2 H), 2.84 (s, 3 H), 2.27–3.16 (m, 4 H), 0.60–1.90 (m, 14 H).

The third component removed from the column was α-(di-*n*-butylaminomethyl)-8-methyl-3-phenyl-5-quinolinemethanol, a pale yellow oil, 800 mg. It was similarly converted to the di-HBr salt and crystallized from EtOH–Me_2CO as pale yellow crystals: nmr (free base, $CDCl_3$) δ 9.25 (d, J = 2.5 Hz, 1 H), 8.68 (d, J = 2.5 Hz, 1 H), 7.22–7.96 (m, 7 H), 5.44 (dd, J_{ax} = 9.2, J_{bx} = 5.2 Hz, 1 H), 4.00 (s, br, 1 H), 2.86 (s, 3 H), 2.35–3.10 (m, 6 H), 0.63–1.90 (m, 14 H).

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