reaction was carried out and worked up as described for the preparation of Id to obtain 0.9 g (97%) of crude Ih, mp 168–172°. It was recrystd from petroleum ether (bp 60–110°) to recover 0.2 g (22%) of pure Ih, mp 181–182.5°, exhibiting a single spot on tlc (silica gel, C_6H_6, R_f 0.48). *Anal.* ($C_{17}H_{16}Br_2ClNO$): C, H, Br.

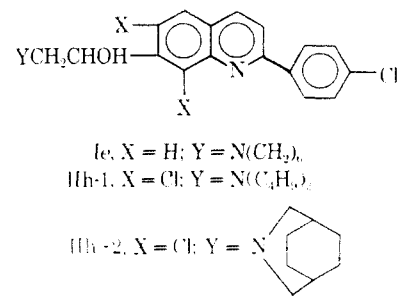
An alkaline oxidation with hypoiodite[6] cleaved the pure dibromo ketone Ih in 79% yield to 8-chloro-2-phenyl-5-quinolinecarboxylic acid (Ie) which did not depress the melting point of an authentic sample of the acid.

The monobromination of 0.026 mole of Ig was attempted with 0.009 mole of $KBrO_3$. The product obtained, after repeated recrystallization from petroleum ether (bp 60–110°), had mp 118–128.5°. Based on its Br content (27.22%) and tlc (silica gel, C_6H_6, R_f 0.35 and 0.45) it was a mixture of 64% of monobromide Ii and 36% of dibromide Ih.

8-Chloro-α-[(dibutylamino)methyl]-2-phenyl-5-quinolinemethanol Hydrochloride (IIe).—To the dry (KOH) Et_2O solution of CH_2N_2 obtained from 21.5 g of *N*-nitroso-*p*-toluenesulfonamide was added in small portions 6.06 g (0.02 mole) of powdered acyl chloride If over a period of 20 min at −5 to 0°. After 18 hr standing at 0°, there was added slowly to the reaction mixture a solution of 15 ml of 48% HBr and 15 ml of Et_2O and it was stirred for 2 hr at room temp. The two-phase reaction mixture was filtered, the residue was washed with H_2O and dried to give 4.66 g of the crude 5-(α-bromoacetyl)-8-chloro-2-phenylquinoline (Ii). An additional 2.2 g was obtained from the ethereal layer. The combined crops were recrystd from 95% EtOH to give 5.36 g (74%) of Ii, mp 139–140°, exhibiting a single spot on tlc (silica gel, C_6H_6, R_f 0.32). *Anal.* ($C_{17}H_{11}BrClNO$): C, H, N.

The crude monobromo ketone Ii (0.014 mole) was reduced to crude α-bromomethyl-8-chloro-2-phenyl-5-quinolinemethanol (IId) in 92% yield and the latter (0.013 mole) was treated with 0.05 mole of Bu_2NH as described for IIb. The reaction mixture was cooled and filtered and the filter cake was washed with anhyd Et_2O. The Et_2O filtrate was treated with 9 ml of *i*-PrOH–HCl (gas) (containing 0.028 mole of HCl) to remove the unreacted Bu_2NH. The crystalline $Bu_2NH \cdot HCl$ was filtered and washed with Et_2O. The filtrate was evapd to dryness *in vacuo*. The residual oil was dissolved in 13 ml of MeOH, cooled, treated with 3 ml of *i*-PrOH–HCl (gas) containing 0.008 mole of HCl, dild with 135 ml of Et_2O, and chilled to give 0.87 g of white crystals, mp 170–172°. The mother liquor was evapd to dryness and the residue was treated with Et_2O. On filtration, followed by washing with Et_2O, there was obtained another crop of 2.52 g of white crystals, mp 165–170°. The combined crops were recrystd from *i*-PrOH to recover 3.13 g (54%) of IIe, mp 171–172°. *Anal.* ($C_{25}H_{31}ClN_2O \cdot HCl$): C, H, N, Cl^-.

The synthesis of each, Ie, IIh-1, and IIh-2, is described fully in the Experimental Section, and the testing results are given in Table I.



Ie, X = H; Y = $N(CH_2)_4$
IIh-1, X = Cl; Y = $N(C_4H_9)_2$

TABLE I
ACTIVITIES OF
2-*p*-CHLOROPHENYL-7-QUINOLINEMETHANOLS[a]

Compd	Dose (mg/kg)	Mice mean survival time (days)	Relative activity[b]
None (control)		6.1	
Ie	160	6.3	
	320	6.5	0.1
	640	6.9	0.1
IIh-1[c]	20	6.6	
	40	11.6	12
	80	15.2	9.7
	160	22.0	9.0[d]
	320	Cure	
6,8-Dimethyl-4-(2-butylamino-1-hydroxyethyl)-2-(4-chlorophenyl)-quinoline(III)[e]	10	16.6	100

[a] Against *P. berghei*. [b] Relative activity = $100 \times \frac{\Delta MST}{11.5} \times \frac{10}{dose}$. See ref 1. [c] Phototoxic at 50 mg/kg. [d] The descending order of relative activity for IIh-1 suggests a slight toxic effect. [e] The 4-quinolinemethanol is used as a standard. The amino groups in Ie and IIh-1 differ, but only a fraction of the enhanced activity of IIh-1 can be attributed to this difference.

Two facts emerge from study of this table. (1) The 2-*p*-chlorophenyl-7-quinolinemethanol series is not as active as the corresponding 4-methanol series, but it still retains high phototoxicity. (2) More important, two Cl atoms flanking the basic side chain (in IIh-1) enhance activity considerably. Our interpretation is that the conformation of the 2-dibutylamino-1-hydroxyethyl side chain is altered to maximize the functions of the OH and aromatic groups in their therapeutic action. For instance in the intercalation theory[5] (binding of the side-chain amine to deoxyribonucleic acids with H bonding of the side-chain OH to the 2-CO of thymine in an orientation to allow entrance of a planar structure between base pairs of the DNA helix) the juxtapositions of the side-chain amino and OH groups to their binding sites in the DNA molecule may be altered by flanking halogen groups to improve intercalation of the aromatic ring. If true, the side chain flanked by halogen groups in other antimalarials may enhance activity further. Study of this possibility is under investigation.

Potential Antimalarials. V.[1,2] 2-*p*-Chlorophenyl-7-quinolinemethanols

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The high antimalarial activity but also very serious phototoxicity[4] of the 2-phenyl-4-quinolinemethanols suggested the preparation and testing of isomeric antimalarials with the side chain attached to other positions. This paper describes the synthesis of three such antimalarials with side chain in the 7 position of the quinoline ring.

(1) Paper IV: J. B. Wommack, Jr., and D. E. Pearson, *J. Med. Chem.*, **13**, 383 (1970).

(2) Contribution No. 823 to the Army Research Program on Malaria.

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Experimental Section[6]

2-(4-Chlorophenyl)-7-(2-[1-azacycloheptyl]-1-hydroxyethyl)-quinoline (Ie).[7] **7-Methylquinoline (Ia).**—A mixture (62%) of 5- and 7-methylquinolines was obtained by the Richter and Smith modification[8] of the Skraup reaction, treatment with Ac_2O, and steam distillation. After three partial freezing operations, the solid remaining was recrystallized from C_6H_{14} to yield 34.7 g (24%) of white plates, mp 37–39°, lit.[9] mp 39°.

2-(4-Chlorophenyl)-7-methylquinoline (Ib).—Under N_2 *p*-chlorobromobenzene (0.1 mole) in 500 ml of Et_2O was brought to reflux and 0.1 mole of 22% BuLi solution in C_6H_{14} added and the exchange allowed to take place for 10 min.[10] Ia (0.1 mole) was added as a solid followed by the immediate addition of 450 ml of C_6H_6. The mixture was refluxed for 20 min, 100 ml of EtOH and 150 ml of $C_6H_5NO_2$ were added, the volatile solvents removed by distillation, and the red $C_6H_5NO_2$ solution was refluxed for 20 min followed by steam distillation of the now green solution to remove $C_6H_5NO_2$. The residue was removed by filtration, washed with hot H_2O, and extracted with CCl_4 and the residue from the extract recrystallized from C_6H_{12} (decolorizing C) to give 15 g (64%) of white crystals, mp 141–142°; lit.[11] mp 143–144°.

2-(4-Chlorophenyl)-7-quinolinecarboxaldehyde (Ic, Sommelet Method).—Ib (0.04 mole), 150 ml of CCl_4, 0.1 g of I_2, and 30 ml of H_2O were refluxed and irradiated with a 150-W lamp while 0.044 mole of Br_2 in 70 ml of CCl_4 was added dropwise in 4 hr. The yellow precipitate (81% of which 72% was the α-bromomethyl compound by nmr analysis) was removed by filtration and washed with CCl_4. The crude product (10.7 g) in 160 ml of $CHCl_3$ was mixed with $(CH_2)_6N_4$ (0.14 mole) in 160 ml of $CHCl_3$. After 3 days, the quaternary salt (14 g) was filtered off and washed with $CHCl_3$. A solution of 0.1 mole of $(CH_2)_6N_4$, 100 ml of AcOH, 2 ml of concd HCl, and 30 ml of H_2O was refluxed while the quaternary salt (0.03 mole) was added portionwise in 6 hr. While hot, the solution was diluted with H_2O to cloudiness and cooled. The crystals were filtered, washed with cold H_2O–EtOH and hot H_2O, and recrystallized from EtOH to yield 2.8 g (26% from Me compound), mp 163–164°. *Anal.* ($C_{16}H_{10}ClNO$) C, H.

2-(4-Chlorophenyl)-7-epoxyethylquinoline (Id).—Under N_2 with magnetic stirring, DMSO (10.8 ml) and NaH (0.0194 mole) were heated at 65° for 45 min and cooled. At −10°, 10.8 ml of THF was added to the black solution and the mixture held there for 30 min and treated with Me_3SI (0.0194 mole) in 20.7 ml of DMSO within 1 min. Ic (0.00972 mole) in 20.7 ml of THF–DMSO was added in 2 min and the green solution stirred at −10° for 15 min and at 25° for 30 min. The mixture was poured over cracked ice and the precipitate filtered, dried, and recrystallized from EtOH (decolorizing C) to give 1.81 g, 66%, of light yellow plates, mp 139.5–141°. *Anal.* ($C_{17}H_{12}ClNO$) C, H.

Ie.—Id (0.0054 mole) and 17 g of azacycloheptane were heated at 115° for 14 hr and steam-distilled to remove amine. The brown, solid residue was recrystallized from aq EtOH (decolorizing C) to give 1.4 g, 68%, of beige tufts, mp 108.5–109.5°. *Anal.* ($C_{23}H_{25}ClN_2O$) C, H, N.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-dialkylamino-1-hydroxyethyl)quinoline (IIh-1 and -2).[12] **2,6-Dichloro-3-aminotoluene (IIb).**—This compound, mp 51–53°, lit.[13] mp 59–60°, was made in 48% overall yield from 2,6-dichlorotoluene, IIa.

6,8-Dichloro-7-methylquinoline (IIc).—The Skraup reaction[8] of IIb, 0.3 mole, gave a dark precipitate which was recrystallized first from H_2O–EtOH and then from C_6H_{14} to yield 32 g, 51%, of beige-colored crystals, mp 97.5–98.5°. *Anal.* ($C_{10}H_7Cl_2N$) Cl.

2-(*p*-Chlorophenyl-6,8-dichloro-7-methylquinoline (IId).—IId was made from 0.125 mole of IIc by the same method used for preparation of Ib. IId was obtained in 86% yield as beige needles, mp 134.5–136.5° from C_6H_{14}; analytical sample, mp 135.8–137.4°. *Anal.* ($C_{16}H_{10}Cl_3N$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-bromomethylquinoline (IIe).—IId (0.1 mole) in 1.3 l. of CCl_4 was refluxed and irradiated with a 150-W flood-lamp while 0.113 mole of *N*-bromosuccinimide was added portionwise and the final mixture refluxed 15 hr. The CCl_4 was evaporated, and the residue was washed thoroughly (H_2O), dried, and recrystallized from CCl_4 to give 34 g, 80%, of beige, powdery crystals, mp 177–180.5°; analytical sample, mp 180.2–181.2°. *Anal.* ($C_{16}H_9BrCl_3N$) C, H.

2-*p*-Chlorophenyl-6,8-dichloro-7-quinolinecarboxaldehyde (IIf).—IIe (0.08 mole) was treated with 0.08 mole each of NaOEt and Me_2CHNO_2 in EtOH according to the method of Hass and Bender[14] and gave, after recrystallization from EtOAc 16.3 g (60%) of pale yellow crystals, mp 199–201.5°; analytical sample, mp 200–201°. *Anal.* ($C_{16}H_{18}Cl_3NO$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-epoxyethylquinoline (IIg).—IIg was made in the same manner as Id from 0.05 mole of IIf. The residue from Et_2O extraction was chromatographed on silica gel (Baker's) using C_6H_{14}–C_6H_6 as an eluting solvent. Early fractions indicated by tlc that a pure substance was being eluted (R_f 0.34, 50% C_6H_6–C_6H_{14}) which recrystallized from MeCN gave 6.5 g, 38%, of pale yellow crystals, mp 159–161°; analytical sample, mp 162.1–16.24°. *Anal.* ($C_{17}H_{10}Cl_3NO$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-dibutylamino-1-hydroxyethyl)quinoline (IIh-1).—IIg (0.00856 mole) in 20 ml of Bu_2NH was heated and stirred at 115° for 19 hr and the excess amine removed by steam distillation. The residue was chromatographed on silica gel using C_6H_6–EtOAc as the developing solvent. When the eluted solute was pure (R_f 0 with C_6H_6; R_f 0.2–0.3 with C_6H_6–EtOAc), it was recovered and recrystallized from C_6H_{14} giving 2.1 g, 51%, of yellow crystals, mp 80–82.8°. *Anal.* ($C_{25}H_{29}Cl_3N_2O$) C, H, Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-[*N*-3-azabicyclo[3.2.2]-nonyl]-1-hydroxyethyl)quinoline (IIh-2).—IIg (0.0088 mole) and 3-azabicyclo[3.2.2]nonane[15] (0.0177 mole) in 20 ml of toluene were refluxed 24 hr and then steam distilled. The residue was chromatographed using silica gel and C_6H_6–EtOAc. A second chromatography was necessary using C_6H_6–20% EtOAc. The solute was recrystallized from C_6H_{14} giving 0.2 g of light yellow needles, mp 169–173°, R_f 0.46 (C_6H_6 and silica gel); not tested for activity because of small sample size. *Anal.* ($C_{25}H_{25}Cl_3N_2O$)C, H, Cl.

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(6) Analyses (by Galbraith Laboratories, Knoxville, Tenn.) are within 0.4% and recorded with the Editor. Melting points are uncorrected and were taken with A. H. Thomas Uni-Melt apparatus. Nmr spectra of new compounds are on file with the authors.

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Quinoxaline Studies. XVII.[1a] Potential Antimalarials. Some (*RS*)-α-(Dialkylaminomethyl)-6-chloro-2-quinoxalinemethanols[1b]

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Previously reported[2] quinoxalinemethanols, similar to antimalarial quinolinemethanols, were without antimalarial activity. Because a chloro substituent in-

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