of 0.8 days with no toxic deaths at 120 mg/kg and 5/5 toxic deaths at 240 mg/kg.

Experimental Section[13]

N-(3-Isoquinolyl)-3-chlorobutyramide (28).—A sample of 5 g (0.0345 mole) of 3-aminoisoquinoline[1] and 5.5 g (0.039 mole) of 3-chlorobutyryl chloride was heated at reflux temperature for 20 hr in 150 ml of dry C_6H_6. The cooled reaction mixture was diluted with 150 ml of $CHCl_3$ and washed with 200 ml of the following: 1.5 *M* Na_2CO_3, 0.1 *N* NaOH, H_2O, and saturated NaCl. The organic layer was filtered and dried ($MgSO_4$) in the presence of decolorizing charcoal. Stepwise concentration of the filtrate yielded three crops: 4.1 g, mp 141–142.5°; 1.3 g, mp 140.5–142°; and 0.55 g, mp 135–141° (total of 5.95 g, 69% yield) of **28** (Table I).

Similarly prepared from the appropriate 3-aminoisoquinoline and a chloroacyl chloride were **27**, **29–33** (Table I).

N-(3-Isoquinolyl)-3-diethylaminopropionamide (34).—A sample of 2.3 g (0.01 mole) of *N*-(3-isoquinolyl)-3-chloropropionamide (**27**) and 6 ml of $HNEt_2$ in 75 ml of $CHCl_3$ was allowed to reflux for 3 hr. The solution was concentrated to near dryness and was then treated with *ca.* 100 ml of Et_2O. The insoluble $Et_2NH \cdot HCl$ was removed by filtration. The filtrate was concentrated and dried at 60° under vacuum. The light brown sirupy residue (2.2 g) was dissolved in *ca.* 100 ml of EtOH. The solution was warmed and was treated with 3.5 g of concentrated $HClO_4$. Slow cooling caused crystallization to occur to give 3.45 g, mp 65–70°, of crude product which was further purified by recrystallization from 100 ml of EtOH–*n*-BuOH (1:1), 2.7 g, mp 125–128°, and then from 70 ml of EtOH to give 2.2 g of **34**, mp 128–129°. Absorption bands of spectra (ir, nmr) were as expected.

The free base was isolated by dissolving the perchlorate salt in water and neutralizing with Na_2CO_3. The residual oil, extracted from Et_2O, slowly crystallized when stored at −5° for several weeks, mp 27–28°.

Similarly prepared from the appropriate chloroalkylamides and α-dialkylamine were the **3-dialkylaminoamides of 3-aminoisoquinoline** shown in Table I (**34–41**).

N-[3-(1-Bromo-4-methylisoquinolyl)]-4-diethylaminobutyramide (42).—A sample of 5 g (0.021 mole) of 3-amino-1-bromo-4-methylisoquinoline (VIIb)[1] was dissolved in 200 ml of molecular sieve dried DMF, together with 4.25 g (0.0218 mole) of 4-diethylaminobutyric acid · HCl[6] and 4.5 g (0.0218 mole) of DCC. The mixture was stirred for 4 days at room temperature and was then poured into 1.5 l. of H_2O that was acidified with 10 ml of concentrated HCl. The precipitated dicyclohexylurea was removed by filtration. The filtrate was made alkaline by addition of 20 ml of 50% sodium hydroxide and the product was extracted into five 100-ml fractions of Et_2O. The combined Et_2O extracts were washed with H_2O and then dried over Na_2SO_4 in the presence of some decolorizing charcoal. The solution was filtered and the filtrate was concentrated to 100 ml and treated with 200 ml of low-boiling petroleum ether. The amide **42** precipitated as an off-white solid, 4.5 g (56%), mp 113.5–114.5°. A 2-g sample was recrystallized from a mixture of 100 ml of low-boiling petroleum ether, 20 ml of Et_2O, and 2 ml of ethanol, to give 1.2 g, mp 115–116°, of pure **42** (Table I).

Absorption bands of spectra (ir, nmr) were as expected.

N-(3-Isoquinolyl)-3-diethylaminopropylamine (44).—A sample of 4.8 g (0.0177 mole) of the amide **34** was dissolved in 60 ml of dry Et_2O and added dropwise under nitrogen at room temperature to a stirred slurry of 0.7 g (0.0184 mole) of LAH in 80 ml of dry Et_2O. Stirring was continued after complete addition. The total reaction time was 6 hr. About 2 ml of H_2O was added slowly and the resulting precipitate was removed by filtration. The filtrate, a clear yellow solution that rapidly turned green when exposed to air, was evaporated and the residue was distilled at 0.1 mm. Two fractions were collected, the first one distilling at 135–154° (0.8 ml), and the second as a yellow oil at 155–158° (2 ml) ($n^{23}D$ 1.5872). This compound decolorized when exposed to air.

Absorption bands of spectra (ir, nmr) were as expected.

N-[3-(1-Bromo-4-methylisoquinolyl)]-4-diethylaminobutylamine Dihydrobromide (52·2HBr).—A sample of 4.2 g (0.011 mole) of the amide **42** was dissolved in 150 ml of dry THF and stirred in the presence of 15 ml of dry THF that was *ca.* 1 *M* in diborane. After 15 hr 10 ml of acetone was added and the mixture was concentrated to near dryness. The residue was dissolved in 150 ml of *ca.* 2% HCl, made alkaline with excess NaOH, and extracted into Et_2O. The Et_2O extract was washed with H_2O and then saturated NaCl solution, and concentrated to near dryness. The residue was taken up in a small amount of EtOH and a white, fluffy precipitate was removed by filtration. The filtrate was concentrated and dried overnight over concentrated H_2SO_4 and at *ca.* 0.1 mm to give 3.4 g of a very viscous, deep yellow oil. This oil was redissolved in EtOH (10 ml) and treated with 30 ml of the same solvent that contained *ca.* 3.3 g of HBr. The mixture was concentrated to *ca.* 15 ml and a small amount (*ca.* 0.5 g of a precipitate, mp 238–244°) was removed by filtration and discarded. When the mother liquor was treated with Et_2O, 1.2 g of **52**·2HBr, mp 90–95°, resolidification, second mp 170–174°, was observed (Table II).

The absorption bands of the spectra (ir and nmr) were as expected.

1-{[4-(Diethylamino)-1-methylbutyl]amino}-3-fluoroisoquinoline (54).—A sample of 2.5 g (0.011 mole) of 1-bromo-3-fluoroisoquinoline (VIId)[1] was added to 3.5 g (0.022 mole) of 2-amino-5-diethylaminopentane and the mixture heated at 95° in an oil bath for ~20 hr. The mixture was then dispersed between aq Na_2CO_3 and Et_2O. The Et_2O layer was washed (H_2O) and extracted into 2% HCl. The acidic layer was washed once with Et_2O, then made alkaline with excess Na_2CO_3 and extracted into Et_2O. After removal of Et_2O the residue was distilled twice at 0.1 mm using a Kugelrohr. The compound distilled when the oven temperature had reached 230°. Distillate (1.3 g, 39%) of **54** was collected.

Absorption bands of spectra (ir and nmr) were as expected.

1,3-Bis{[2-(diethylamino)ethyl]amino}isoquinoline Trihydrochloride (51·3HCl).—A 1.5-g sample of 3-amino-1-bromoisoquinoline (VIIa)[1] was dissolved in 10 ml of *N,N*-diethylethylenediamine together with a catalytic amount of KI. The solution was stirred and heated to 130°. After the initial reaction subsided, the oil bath was heated to 145° and the reaction mixture was kept at this temperature for about 1 hr. The deep brown liquid was poured into ice–water and extracted (Et_2O). The ether was evaporated and the oily residue was dried at 40° (3 mm) (P_2O_5) to yield 1.8 g of brown oil. This oil was dissolved in Et_2O and an Et_2O solution of HCl was added. The Et_2O was decanted from the resulting solid, which was then dissolved in approximately 40 ml of EtOH. The hydrochloride was induced to crystallize and the resulting crystals were collected, washed with a small amount of EtOH–Et_2O 1:1, and dried at 40° *in vacuo*. The yellow microcrystalline compound (1.75 g, 56%, mp 191–195°) was recrystallized twice from EtOH–Et_2O, mp 198–200° (immersed at 198°) (Table II).

The structure of the compound was confirmed by elemental analysis, mass, nmr, and ir spectra. The molecular weight was determined by mass spectroscopy as 357 (free base, calculated 357.53).

(13) All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Antimalarial Agents. VI.[1] 5-Quinolinemethanols

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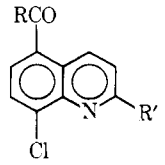
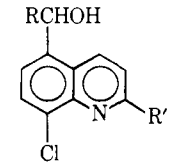
More than 200 4-quinolinemethanols, but only two of the 5 position isomers, have been screened

(1) (a) Part V, *J. Heterocycl. Chem.*, **6**, 959 (1969); (b) this study was supported in part by the U. S. Army Medical Research and Development Command. The compounds were tested by Dr. L. Rane of the University of Miami, Florida (except for those antimalarials indicated later) and Col. W. E. Rothe of Walter Reed Army Institute for Research (phototoxicity results are mentioned later); (c) analyses are indicated by symbols of the elements, since analytical results obtained for these elements were within ±0.4% of the theoretical values.

in the avian malaria test.[2] Recently, numerous new 4-quinolinemethanols[3a-e] were tested against *Plasmodium berghei* in mice. The considerable antiplasmodial activity found for many of them in the rodent test was accompanied by a undesirable phototoxicity.[3a,b,e,4a,b] In the hope that shifting of the methanol moiety from position 4 to position 5 would retain the antimalarial activity and eliminate the photosensitizing side action, we prepared and tested[1b] three new 5-quinolinemethanols (IIb, IIc, and IIe). The syntheses followed the general pattern established in the preparation of 4-quinolinemethanols:[5] Q-COOH $\rightarrow$ Q-COCl $\rightarrow$ Q-COCH$_3$(Q-COCHN$_2$) $\rightarrow$ Q-COCH$_2$Br $\rightarrow$ Q-CHOHCH$_2$NR$_2$. The 5-quinolinecarboxylic acids needed as starting materials were described recently.[1a]

The above listed reaction sequence was used without any difficulties for IIb and IIc. Isolation of pure acyl chloride (Ib) and pure bromohydrins IIa and IId was not necessary. Bromination of Ic to Id with





Ia, R = OH; R′ = H
b, R = Cl; R′ = H
c, R = CH$_3$; R′ = H
d, R = CH$_2$Br; R′ = H
e, R = OH; R′ = Ph
f, R = Cl; R′ = Ph
g, R = CH$_3$; R′ = Ph
h, R = CHBr$_2$; R′ = Ph
i, R = CH$_2$Br; R′ = Ph

IIa, R = CH$_2$Br; R′ = H
b, R = CH$_2$NBu$_2$·HCl; R′ = H
c, R = CH$_2$NHex$_2$·HCl; R′ = H
d, R = CH$_2$Br; R′ = Ph
e, R = CH$_2$NBu$_2$·HCl; R′ = Ph

KBrO$_3$–HBr proceeded smoothly. However, attempted monobromination of Ig by this method yielded a mixture of mono- and dibromo ketones Ii and Ih, respectively. Since the separation of Ii from this mixture did not appear promising, we obtained it *via* the reaction of If with CH$_2$N$_2$. The structure of the dibromo ketone Ih was established unequivocally by cleavage with hypoiodite[6] to Ie. Attempts to prepare Ic by the reaction of MeLi with Ia were not successful. It appears that this elegant method[7] is not applicable in all cases.[3d]

Compounds IIb and IIc were not phototoxic[4a] at 50 and 300 mg/kg, respectively, and were not active[8] against *P. berghei* at 160, 320, and 640 mg/kg; IIe was active at 320 and 640 mg/kg, but exhibited considerable photosensitization at 200 mg/kg. These results indicate that not only the 4-quinolinemethanols, but also the 5 position isomers exhibit the undesirable relationship of phototoxicity–antimalarial activity. The hydrochloride IIb killed 60, 40, and 20% of the test animals at 640, 320, and 160 mg/kg.

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(4) (a) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968); (b) I. G. Fels, *ibid.*, **11**, 887 (1968).

(5) See footnote 3 of ref 3a.

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Experimental Section

5-Acetyl-8-chloroquinoline (Ic).—A suspension of 33.2 g (0.16 mole) of 8-chloro-5-quinolinecarboxylic acid (Ia) in 107.0 g (0.9 mole) of freshly distd $SOCl_2$ was refluxed for 18 hr, and the excess of $SOCl_2$ was distd off under reduced pressure. The residue was crude 8-chloro-5-quinolinecarbonyl chloride (Ib).

The reaction mixture of 98.56 g (0.616 mole) of distd diethyl malonate and 14.78 g (0.616 mole) of NaH in 500 ml of C_6H_6 was refluxed for 2 hr and then stirred overnight at room temp. To this was added the powdered, crude Ib prepared above, the mixture was refluxed for 2 hr, cooled, and cautiously treated with 110 ml of 30% H_2SO_4. The C_6H_6 layer was washed with H_2O, dried (Na_2SO_4), and evapd to give a red oil. The latter was refluxed with 300 ml of 20% H_2SO_4, cooled, and extracted with Et_2O. The aq layer was filtered (Darco) and basified, and the solid obtained was recrystd from petroleum ether (bp 60–110°) to give 15.84 (48%) of Ic, mp 86–87.5°. *Anal.* ($C_{11}H_8ClNO$): C, H, N.

5-(α-Bromoacetyl)-8-chloroquinoline (Id).—To a stirred solution of 9.86 g (0.048 mole) of Ic in a mixture of 78 ml (0.69 mole) of 48% HBr and 500 ml of glacial AcOH was added gradually over a period of 20 min a solution of 3.0 g (0.018 mole) of $KBrO_3$ in a min amount of H_2O (40 ml). The reaction was heated to 75° over a period of 30 min and maintained at that temp for additional 30 min. It was poured on ice, adjusted to pH 5, and filtered. The solid was recrystd from petroleum ether (bp 60–110°) to give 7.8 g (57%) of the product: mp 126.5–128.5°. Another recrystallization from the same solvent gave an analytical sample, mp 129–130.5°. *Anal.* ($C_{11}H_7BrClNO$): C, H, Br, N.

8-Chloro-α-[(dibutylamino)methyl]-5-quinolinemethanol Hydrochloride (IIb).—A suspension of 5.12 g (0.18 mole) of Id (mp 126.5–128.5°) and 12.9 g (0.06 mole) of Al(*i*-OPr)$_3$ in 130 ml of anhyd *i*-PrOH was distd slowly at a rate of 3 g/hr. The distillate contained Me_2CO; after 3 hr the Me_2CO formation (90%) had ceased as determined by 2,4-dinitrophenylhydrazine. The solvent was distd off *in vacuo;* the residue was treated with 10% HCl and filtered. The solid was washed with H_2O and dried to provide 4.92 g (96%) of crude α-bromomethyl-8-chloro-5-quinolinemethanol (IIa), mp 85–89°. A mixture of 4.36 g (0.015 mole) of crude IIa and 8.22 g (0.063 mole) of Bu_2NH was heated for 3 hr at 75–80°. The reaction mixture was cooled, dild with 50 ml of Et_2O, filtered, and washed with Et_2O to give 2.8 g (89%) of $Bu_2NH \cdot HBr$. The ethereal filtrate was stripped off *in vacuo* to remove the solvent and excess of Bu_2NH. The residual oil was dissolved in *i*-PrOH, cooled, and treated with excess of *i*-PrOH–HCl (gas). The ppt was filtered, washed with Et_2O, and dissolved in H_2O. The aq solution was basified with $NaHCO_3$ and extracted with Et_2O. The ethereal solution was evapd to give the crude, oily free base. It was dissolved in MeOH treated with less than 1 equiv (0.013 mole of HCl) of *i*-PrOH–HCl (gas), dild with Et_2O to the cloud point, cooled in ice, and filtered. The crude, solid IIb was purified by treating its MeOH solution with Et_2O at 0–5°. There was obtained 1.77 g (35%) of pure IIb, mp 207–208°. *Anal.* ($C_{19}H_{27}ClN_2O \cdot HCl$): C, H, N, Cl^-.

8-Chloro-α-[(dihexylamino)methyl]-5-quinolinemethanol Hydrochloride (IIc).—A reasonably pure sample (mp 143–144°) was prepared in 79% yield by the method described for IIb. Steam distillation facilitated removal of the excess of $(Hex)_2NH$. Recrystallization from *i*-PrOH raised the melting point to 143.5–145°. *Anal.* ($C_{23}H_{31}ClN_2O \cdot HCl$): C, H, N, Cl^-.

8-Chloro-2-phenyl-5-quinolinecarbonyl chloride (If), mp 142–144°, was prepared in 67% yield by the method described for Ib. The crude product was recrystd from petroleum ether (bp 60–110°). *Anal.* ($C_{16}H_8Cl_2NO$): C, H, N, Cl.

5-Acetyl-8-chloro-2-phenylquinoline (Ig), mp 144.5–146°, was obtained in 66% yield from If by the method described for Ic. It was recrystd from petroleum ether (bp 60–110°). *Anal.* ($C_{17}H_{12}ClNO$): C, H, N.

8-Chloro-5-(α,α-dibromoacetyl)-2-phenylquinoline (Ih).—To a stirred solution of 0.72 g (0.026 mole) of Ig in 12.5 ml (0.11 mole) of 48% HBr and 20 ml of glacial AcOH was added gradually a solution of 0.312 g (0.019 mole) of $KBrO_3$ in 4 ml of H_2O. The

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.

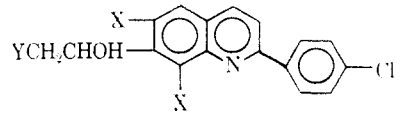
An alkaline oxidation with hypoiodite[6] cleaved the pure dibromo ketone Ih in 79% yield to 8-chloro-2-phenyl-5-quinolinecarboxylic acid (Ie) which did not depress the melting point of an authentic sample of the acid.

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.

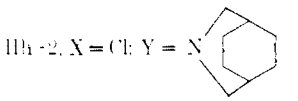
8-Chloro-α-[(dibutylamino)methyl]-2-phenyl-5-quinolinemethanol Hydrochloride (IIe).—To the dry (KOH) Et_2O solution of CH_2N_2 obtained from 21.5 g of *N*-nitroso-*p*-toluenesulfonamide was added in small portions 6.06 g (0.02 mole) of powdered acyl chloride If over a period of 20 min at −5 to 0°. After 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 = $N(C_4H_9)_2$



IIh-2, X = Cl; Y =

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.

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

(3) To whom correspondence should be sent.

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