To a solution of the foregoing ester (0.06 mole, 18.32 g) and ethyl 6-benzamidocaproate[4a] (0.061 mole, 16.06 g) in 50 ml of dry C_6H_6, $NaNH_2$ (0.075 mole, 2.93 g) was added. The mixture was heated at 90° with vigorous stirring for 24 hr. After cooling the mixture to 50°, 32 ml of concentrated H_2SO_4 in 50 ml of H_2O was added and refluxing was continued for 65 hr. The C_6H_6 was then distilled off azeotropically and the residue was made alkaline with 30% aqueous NaOH keeping the temperature below 40°. The mixture was then extracted with C_6H_6. After drying ($MgSO_4$) the solvent was removed under reduced pressure. The ir spectrum of the solid residue indicated that the N-benzoyl group was not cleaved. The material was therefore suspended again in a solution of 30 ml of concentrated H_2SO_4 in 50 ml of H_2O and the mixture was refluxed for 64 hr. After cooling it was made alkaline as before and extracted with C_6H_6. The dried C_6H_6 solution upon concentration *in vacuo* left an oil to which 23 g of 48% HBr was added. Upon standing for a short while a yellow precipitate was obtained and filtered; the yield of 6-[6-methyl-2-(*p*-tolyl)cinchoninyl]-*n*-amylamine dihydrobromide was 5.5 g (34% based on recovered acid).[15]

The aqueous alkaline phase was acidified with concentrated HCl and the resulting precipitate was filtered, washed with a little EtOH, and dried. The weight of recovered 6-methyl-2-(*p*-tolyl)-4-cinchoninic acid from the unreacted ethyl ester was 7.8 g.

The foregoing amine dihydrobromide (0.008 mole, 4 g) was dissolved in hot 18% HBr and treated rapidly with a solution of Br_2 (0.008 mole, 1.28 g) in an equal volume of 48% HBr. The crude product was filtered and dispersed in 40 ml of boiling 95% EtOH, and H_2O was added until a clear solution resulted. Cooling gave a light yellow precipitate. Concentration of the mother liquor yielded some additional product. The total yield of 6-bromo-6-[6-methyl-2-(*p*-tolyl)cinchoninyl]-*n*-amylamine dihydrobromide was 3.95 g (84%).

The foregoing product (1.5 g) was dissolved in 50 ml of 95% EtOH and 7 ml of 14% aqueous Na_2CO_3 was added. The mixture was shaken for 1 hr in a stoppered bottle and then hydrogenated over 20 mg of PtO_2 in a Parr hydrogenation apparatus. The reaction mixture was filtered and washed (EtOH, hot $CHCl_3$). The solvents were removed *in vacuo*. The residue was dissolved in hot $CHCl_3$ and filtered. Evaporation of the solvent left a brown residue. This was dissolved in absolute EtOH and the solution was saturated with dry HCl. After standing for a short while, Et_2O was added and the precipitate was filtered to yield 0.5 g of the hydrochloride. A small amount of this salt was converted into the free base **53**.

The ir spectra of the free base **53** and its hydrochloride salt were identical with those of the products obtained by catalytic reductions of the pyridyl ketone.

2-Aryl-4-quinolinecarboxylic Acids (Cinchoninic Acids) (I) (Table IV).—All of the substituted cinchophens required as starting material were synthesized by the Pfitzinger[16] condensation. In general, it was found that better yields were obtained when the mixtures of the appropriate isatins and substituted acetophenones in EtOH–KOH were refluxed for 30 hr; shorter periods of time gave poorer yields.

Acknowledgment.—The authors wish to thank Professor A. Burger for fruitful discussion before and during the course of this work.

(15) This intermediate and the ones which follow en route to **50** were used directly in the next synthetic step without characterization; *cf.* ref 9 and 14.

(16) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).

Fluorine-Containing 4-Quinolinemethanols as Antimalarials[1]

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Various fluorine-containing α-dialkylaminomethyl-2-phenyl-4-quinolinemethanol derivatives have been prepared for evaluation against *Plasmodium berghei* in mice. Preliminary biological data indicate the fluorine compounds to be more potent at comparable doses than the corresponding chloro derivatives. α-Di-*n*-butylaminomethyl-2-(4-chlorophenyl)-7-trifluoromethyl-4-quinolinemethanol when administered to mice in a single subcutaneous dose was curative at 40 mg/kg.

A high degree of antimalarial activity was discovered in the 4-quinolinemethanol series during the World War II program supported by the government. Reviews[2] of this work indicated that the most notable changes in activity in this series were caused by substituent variations in the aromatic rings. A considerable number of the chlorine-substituted α-dialkylaminomethyl-2-phenyl-4-quinolinemethanols showed pronounced antimalarial action.

In the past two decades pharmacological investigations have revealed that the replacement of chlorine and hydrogen in biologically active compounds by fluorine and fluorine-containing groups has provided in many cases highly potent fluorine-containing therapeutic agents.

We now report the synthesis and potent antimalarial activity of various fluorine-containing 4-quinolinemethanol derivatives. These compounds were prepared as part of a program to develop new and more-effective agents to combat drug-resistant malarial parasites.

Chemistry.—Our synthetic plan essentially paralleled those routes described previously for the preparation of 4-quinolinemethanols.[3,4] The general route to the fluorine-containing 4-quinolinemethanol derivatives commenced with the preparation of the appropriately substituted cinchophens (2-phenylcinchoninic acids). The latter (Table I) were obtained (a) from readily accessible anilines *via* the Sandmeyer isatin synthesis[5,6] and the Pfitzinger reaction[3,7,8] and (b) through the Doebner–Miller reaction[3,9,10] between the appropriate anilines, benzaldehydes, and pyruvic acid.

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract DA-49-193-MD-2950 and is Contribution No. 290 from the Army Research Program on Malaria.

(2) (a) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946; (b) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953.

(3) R. E. Lutz, *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(4) S. Winstein, *et al.*, *ibid.*, **68**, 1831 (1946).

(5) T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(6) R. C. Elderfield in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 208.

(7) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).

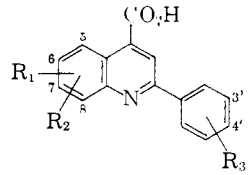
(8) For excellent reviews, see ref 6, Vol. 3, p 222; Vol. 4, p 47.

(9) O. Doebner, *Ann.*, **242**, 265 (1887).

(10) For a review, see ref 6, Vol. 4, p 25.

Table I

Fluorine-Containing Cinchophens

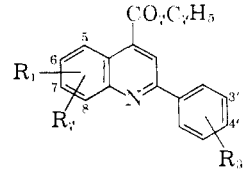


Compd	R_1	R_2	R_3	Prepn method[a]	Mp, °C dec	Recrystn solvent	Yield, %	Formula	Analyses
1	6-F	H	4'-Cl	P	247–248	EtOH	70	$C_{16}H_9ClFNO_2$	C, H, N
2	7-F	H	4'-Cl	P	227–228	MeOH	28	$C_{16}H_9ClFNO_2$	C, H, N
3	7-CF_3	H	4'-Cl	P	272–272.5	EtOH–H_2O	18	$C_{17}H_9ClF_3NO_2$	C, H, N
4	8-CF_3	H	4'-Cl	P, D[b]	264–265	MeOH	41[c]	$C_{17}H_9ClF_3NO_2$	C, H, N
5	6-Cl	8-Cl	3'-CF_3	P	243–244	MeOH	35	$C_{17}H_8Cl_2F_3NO_2$	C, H, N
6	6-Cl	8-Cl	4'-F	P	275–276	MeOH	10	$C_{16}H_8Cl_2FNO_2$	C, H, N
7	6-Cl	8-CF_3	4'-Cl	D	289–289.5	EtOH	22	$C_{17}H_8Cl_2F_3NO_2$	C, H, N

[a] Refers to the Pfitzinger reaction (P) and the Doebner–Miller synthesis (D). [b] Mixture melting point was not depressed and ir spectra of both products were identical. [c] Yield based on method D.

Table II

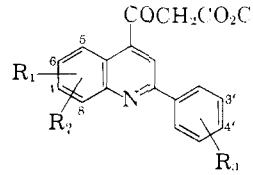
Fluorine-Containing Ethyl Cinchoninates



Compd	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
8	6-F	H	4'-Cl	131–132	EtOH	63	$C_{18}H_{13}ClFNO_2$	C, H, N
9	7-F	H	4'-Cl	109–110	EtOH	50	$C_{18}H_{13}ClFNO_2$	C, H, N
10	7-CF_3	H	4'-Cl	122–122.5	EtOH	80	$C_{19}H_{13}ClF_3NO_2$	C, H, N
11	8-CF_3	H	4'-Cl	150–151	MeOH–C_6H_6 (1:1)	87	$C_{19}H_{13}ClF_3NO_2$	C, H, N
12	6-Cl	8-Cl	3'-CF_3	126–127	EtOH	83	$C_{19}H_{12}Cl_2F_3NO_2$	C, H, N
13	6-Cl	8-Cl	4'-F	135–136	EtOH–C_6H_6 (2:1)	86	$C_{18}H_{12}Cl_2FNO_2$	C, H, N
14	6-Cl	8-CF_3	4'-Cl	167–168	C_6H_6–petr ether	80	$C_{19}H_{12}Cl_2F_3NO_2$	C, H, N

Table III

Fluorine-Containing Ethyl Cinchoninoylacetates



Compd	R_1	R_2	R_3	Mp, °C[a]	Yield, %	Formula	Analyses
15	8-CF_3	H	4'-Cl	119–120	51	$C_{21}H_{13}ClF_3NO_3$	C, H, N
16	6-Cl	8-Cl	3'-CF_3	129–130	28	$C_{21}H_{14}Cl_2F_3NO_3$	C, H, N
17	6-Cl	8-Cl	4'-F	97.5–98.5	17	$C_{20}H_{14}Cl_2FNO_3$	C, H, N

[a] Recrystallized from EtOH.

The conversion of the cinchophens to the corresponding α-bromomethyl ketone derivatives was carried out using methods A and B (see Tables II–VI). In method A, the synthesis proceeded through the following reaction sequence (Tables V and VI): (1) preparation of the cinchophen acid chlorides, (2) diazomethylation to the diazomethyl ketones, and (3) hydrobromination to the α-bromomethyl ketones.

The path (method B, Tables II–IV) from the cinchophens to the α-bromomethyl ketones involved (1) esterification of the cinchophens, (2) Claisen condensation between the cinchophen esters and ethyl acetate to the β-keto esters followed by ketone hydrolysis to the methyl ketones, and (3) bromination to the α-bromomethyl ketones.

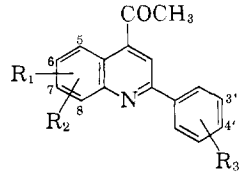
Finally, the general synthetic route continued from the α-bromomethyl ketones *via* aluminum isopropoxide reduction to the bromohydrins (Table VII). Condensation with the appropriate amines yielded the α-dialkylaminomethyl-4-quinolinemethanols (Table VIII).

Pharmacology.[11]—Five mice were infected with a

(11) The screening method for antimalarial acivity was developed by L. Rane, Malaria Screening Laboratory, University of Miami, Miami, Fla., and has been reported: T. S. Osdene, P. B. Russell, and L. Rane *J. Med. Chem.*, **10**, 431 (1967).

TABLE IV

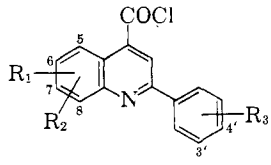
FLUORINE-CONTAINING 2-PHENYL-4-QUINOLYL METHYL KETONES



Compd	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
18	7-CF_3	H	4′-Cl	123.5–124	EtOH	54	$C_{18}H_{11}ClF_3NO$	C, H, N
19	8-CF_3	H	4′-Cl	178–179	Me_2CO–H_2O	80	$C_{18}H_{11}ClF_3NO$	C, H, N
20	6-Cl	8-Cl	3′-CF_3	145–146.5	EtOH	36	$C_{18}H_{10}Cl_2F_3NO$	C, H, N
21	6-Cl	8-Cl	4′-F	137–138	EtOH	12	$C_{17}H_{10}Cl_2FNO$	C, H, N
22	6-Cl	8-CF_3	4′-Cl	209–209.5	EtOAc	33	$C_{18}H_{10}Cl_2F_3NO$	C, H, N

TABLE V

FLUORINE-CONTAINING CINCHONINIC ACID CHLORIDES[a]



Compd	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %
23	6-F	H	4′-Cl	157–159	C_6H_6	86
24	7-F	H	4′-Cl	125–127	Ligroin	68
25	8-CF_3	H	4′-Cl	194–196	C_6H_6	73
26	6-Cl	8-Cl	3′-CF_3	136–138	Ligroin	90
27	6-Cl	8-Cl	4′-F	141–143	C_6H_6	67
28	6-Cl	8-CF_3	4′-Cl	195–196.5	C_6H_6	94

[a] Elemental analysis of these compounds was generally omitted. Ir spectra of the acid chlorides indicated the C=O absorption band at 5.7 μ, whereas the cinchoninic acids displayed the C=O peak at 5.9 μ.

lethal dose of *Plasmodium berghei* 3 days prior to administration of the chemical. Routinely, the chemical was administered subcutaneously in oil at each of three dose levels, namely at 40, 160, and 640 mg/kg. The mean survival time of infected control mice is 6.5 ± 0.5 days. Extension in survival time of the chemically treated mice is interpreted as evidence of antimalarial activity. The number of mice surviving (out of five) at 60 days post infection are considered cures.

Preliminary antimalarial test data are reported in Table IX. The results indicate that the fluorine-containing 4-quinolinemethanol derivatives possess potent antimalarial action and are curative in mice. Compound **45** was found to be significantly more active than the corresponding chloro derivative. None of the intermediates tested were active.

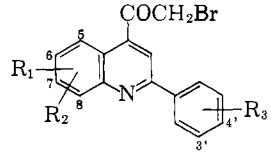
Photosensitization effects of 4-quinolinemethanol derivatives were described in an earlier review.[2a] Recently, the phototoxic potency of a number of quinolinemethanols, including compounds **45** and **48**, has been reported by Rothe and Jacobus.[12]

Experimental Section[13]

The object of this research was to prepare as quickly as possible the pure target compounds in sufficient quantity for antimalarial testing. Consequently, the experimental conditions described herein do not necessarily represent the optimum. Occasionally the isolation, extensive purification, or elemental analysis of an intermediate was omitted. Physical and analytical data are found in Tables I–VIII.

TABLE VI

FLUORINE-CONTAINING α-BROMOMETHYL 2-PHENYL-4-QUINOLYL KETONES



Compd	R_1	R_2	R_3	Prepn method[a]	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
29[b]	6-F	H	4′-Cl	A	245–246 dec	AcOH	85	$C_{17}H_{11}Br_2ClFNO$	C, H, N
30[b]	7-F	H	4′-Cl	A	239–241 dec	AcOH	55	$C_{17}H_{11}Br_2ClFNO$	C, H, N
31	7-CF_3	H	4′-Cl	B	169–171	EtOH	95	$C_{18}H_{10}BrClF_3NO$	C, H, N
32[c]	8-CF_3	H	4′-Cl	A, B	162–164	MeOH–H_2O	88[d]	$C_{18}H_{10}BrClF_3NO$	C, H, N
33[c]	6-Cl	8-Cl	3′-CF_3	A, B	168–169	EtOH	95[d]	$C_{18}H_9BrCl_2F_3NO$	C, H, N
34	6-Cl	8-Cl	4′-F	A	173–174	EtOH	89	$C_{17}H_9BrCl_2FNO$	C, H, N
35	6-Cl	8-CF_3	4′-Cl	A, B	195–196	EtOH	89[d]	$C_{18}H_9BrCl_2F_3NO$	H, N; C[e]

[a] Refers to methods A and B in the discussion. [b] Isolated and analyzed as the hydrobromide salt. [c] Prepared *via* methods A and B. Mixture melting point was not depressed and ir spectra of both products were identical. [d] Yield based on method A. [e] C: calcd, 46.68; found, 47.22.

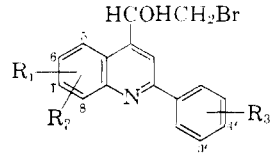
Materials.—3- and 4-Fluoroaniline, 4-trifluoromethylaniline, 4-chloro-2-trifluoromethylaniline, 4-chloro-3-nitrobenzotrifluoride, 3′-trifluoromethylacetophenone, and 4′-fluoroacetophenone were purchased from Pierce Chemical Co., Rockford, Ill. 2- and 3-trifluoromethylaniline were obtained from Maumee

(12) W. E. Rothe and D. J. Jacobus, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 11–14, 1967, p 37.

(13) Melting points were determined with an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Micro-analysis, Inc., Wilmington, Del. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table VII

Fluorine-Containing α-Bromomethyl-2-phenyl-4-quinolinemethanols[a]

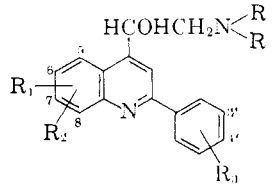


Compd	R_1	R_2	R_3	Mp, °C dec	Recrystn solvent	Yield, %
36	6-F	H	4′-Cl	262–264[b]	MeOH	69
37	7-F	H	4′-Cl	254–257[b]	[c]	95
38	7-CF_3	H	4′-Cl	138[d]	[c]	95
39[e]	8-CF_3	H	4′-Cl	143–144	MeOH–H_2O	99
40	6-Cl	8-Cl	3′-CF_3	126–128	[c]	92
41[e]	6-Cl	8-Cl	4′-F	132–133	EtOH	97
42[e]	6-Cl	8-CF_3	4′-Cl	141[d]	Ligroin	60

[a] Elemental analysis of these compounds was generally omitted. Ir spectra of the bromohydrins displayed the characteristic OH band at 2.9–3.05 μ and the absence of any C=O absorption at 5.9 μ. The latter is characteristic of the precursor α-bromomethyl ketones. [b] Hydrochloride salt. [c] Product was water washed and dried *in vacuo* over P_2O_5. [d] Resolidified soon after melting; the second melting points were as follows: **38**, 225–228°; **42**, 208–208.5°. This phenomenon of double melting points[3] probably exists for some of the other compounds under the proper conditions. However, this behavior was not studied in each case. [e] *Anal.* ($C_{18}H_{12}BrClF_3NO$) C, H, N. [f] *Anal.* ($C_{17}H_{11}BrCl_2FNO$) C, H, N. [g] *Anal.* ($C_{18}H_{11}BrCl_2F_3NO$) C, H, N.

Table VIII

Fluorine-Containing α-(Dialkylaminomethyl)-2-phenyl-4-quinolinemethanols[a]



Compd	R_1	R_2	R_3	R	Mp, °C dec	Recrystn solvent	Yield, %	Formula	Analyses
43	6-F	H	4′-Cl	C_4H_9	185–186	*i*-PrOH–petr ether	42	$C_{25}H_{31}Cl_2FN_2O$	C, H, N
44	7-F	H	4′-Cl	C_3H_9	179–180[b]	C_6H_6	10	$C_{25}H_{31}Cl_2FN_2O$	C, H, N
45	7-CF_3	H	4′-Cl	C_3H_9	203[b]	*i*-PrOH	43	$C_{26}H_{31}Cl_2F_3N_2O$	C, H, N
46	7-CF_3	H	4′-Cl	C_6H_{13}	195–196	*i*-PrOH	22	$C_{30}H_{39}Cl_2F_3N_2O$	C, H, N
47	8-CF_3	H	4′-Cl	C_4H_9	195–196	*i*-PrOH	55	$C_{26}H_{31}Cl_2F_3N_2O$	C, H, N
48	6-Cl	8-Cl	3′-CF_3	C_3H_9	185–186	*i*-PrOH	35	$C_{26}H_{30}Cl_3F_3N_2O$	C, H, N
49	6-Cl	8-Cl	3′-CF_3	C_6H_{13}	183–184	*i*-PrOH	37	$C_{30}H_{38}Cl_3F_3N_2O$	C, H, N
50	6-Cl	8-Cl	4′-F	C_3H_9	194–195	*i*-PrOH	58	$C_{25}H_{30}Cl_3FN_2O$	C, H, N
51	6-Cl	8-CF_3	4′-Cl	C_3H_9	217–218	*i*-PrOH	60	$C_{26}H_{30}Cl_3F_3N_2O$	C, H, N

[a] Isolated and analyzed as monohydrochloride salts. [b] Resolidified soon after melting; the second melting points were **44**, 225–243°; **45**, 234–237°. See ref 3 for a discussion of this phenomenon.

Chemical Co., Toledo, Ohio. The source of 4′-chloroacetophenone, di-*n*-butylamine, and di-*n*-hexylamine was Distillation Products Industries, Eastman Kodak Co., Rochester, N. Y. 5,7-Dichloroisatin was purchased from Aldrich Chemical Co., Milwaukee, Wis.

Isonitrosoacetanilides.—The method of Sandmeyer[5] was used essentially as described by Marvel and Hiers.[14] In some instances, AcOH was used as the reaction medium.

3-[15] and 4-fluoro-[16] and 2-, 3-, and 4-trifluoromethylisonitrosoacetanilides[17] were described earlier. 4-Chloro-2-trifluoromethylisonitrosoacetanilide (**52**) was obtained (16% yield) as white crystals (C_9H_6), mp 170–171.5°. *Anal.* ($C_9H_6ClF_3N_2O_2$) H, N; C: calcd, 40.54; found, 41.07.

Isatins.—5-[16] and 6-fluoro-[15] and 4-, 5-, and 7-trifluoromethylisatins[17] were obtained from the appropriate isonitrosoacetanilides and H_2SO_4. 6-Trifluoromethylisatin was prepared from 4-chloro-3-nitrobenzotrifluoride essentially as described by Sinet.[18]

Pfitzinger Synthesis of 2-Phenylcinchoninic Acids.—The appropriately substituted isatin (0.025 mole) and acetophenone derivative (0.028 mole) in EtOH (30 ml) containing 33% KOH (15 ml) were refluxed for 7–8 hr. EtOH was removed under reduced pressure and the residue was acidified with 10% HCl. Recrystallization of the precipitate afforded the corresponding fluorine-containing 2-phenylcinchoninic acids.

Doebner–Miller Synthesis of 2-Phenylcinchoninic Acids.—The following preparation of 6-chloro-8-trifluoromethylcinchoninic acid is a typical procedure. *p*-Chlorobenzaldehyde (178.5 g, 1.27 moles) was mixed at 20° with a solution of 2-amino-5-chlorobenzotrifluoride (249 g, 1.27 moles) in 500 ml of AcOH. The thick suspension was treated dropwise with H_2SO_4 (68 ml) at a rate that kept the internal temperature at 30–35°. Stirring was continued for an additional 15 min. Freshly distilled pyruvic acid (90 g, 1.01 moles) was added in 5 min at 20° and the mixture was heated gradually by mantle to 120° (internal temperature) *during 1 hr*. (At 87° a precipitate formed.) The cooled suspension was filtered and the precipitate, after being washed with cold AcOH, gave product, mp 289°.

Cinchoninic Esters.—The cinchoninic acids were heated with EtOH in the presence of H_2SO_4 for 1 hr. On cooling the ethyl esters precipitated.

2-Phenyl-4-quinolyl Methyl Ketones.—A suspension of the appropriate cinchoninic ester[19] (0.005 mole), anhydrous EtOAc (0.01 mole), and NaOEt (0.0073 mole) in predried C_6H_6 (1.5 ml)

(14) C. S. Marvel and G. S. Hiers, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p 327.

(15) P. W. Sadler, *J. Org. Chem.*, **21**, 169 (1956).

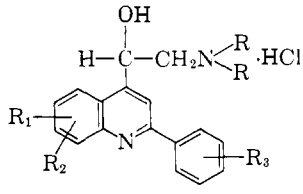
(16) V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.*, **23**, 1858 (1958).

(17) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951).

(18) L. Sinet, *J. Org. Chem.*, **28**, 3580 (1963).

TABLE IX

ANTIMALARIAL TEST DATA[a]



Compd	R_1	R_2	R_3	R	Dose level, mg/kg	Cures[b] (5 mice)
48	6-Cl	8-Cl	3′-CF_3	n-C_4H_9	40	3
					160	5
					640	5
49	6-Cl	8-Cl	3′-CF_3	n-C_6H_{13}	40	2.8[c]
					160	1
					640	5
45	7-CF_3	H	4′-Cl	n-C_4H_9	40	5
					160	5
					640	5
d	7-Cl	H	4′-Cl	n-C_4H_9	160	9.7[e]
					640	4[e]

[a] These preliminary test results were supplied by L. Rane, Malaria Screening Laboratory, University of Miami, Miami, Fla. [b] Cure is defined as a survival of 60 days or more post-infection. [c] Increase in mean survival time (MST) in days. MST of infected control mice is 6.5 ± 0.5 days. [d] Survey no. SN 13710, ref 2. [e] One toxic death.

was refluxed for 16 hr. The reaction mixture was poured into 5% NaOH (20 ml) and ice to precipitate the sodium salt of the corresponding β-keto ester. In a few cases, the β-keto ester was isolated by treating the sodium salt with warm AcOH. The Claisen reaction mixtures or the isolated β-keto esters were heated with 30–35% H_2SO_4 at reflux until CO_2 evolution ceased. After dilution with H_2O, the resulting precipitates on recrystallization provided the methyl ketones.

Bromination of 2-Phenyl-4-quinolyl Methyl Ketones.[4]—A solution of the methyl ketone (0.08 mole) in AcOH (655 ml) was slowly treated at room temperature with 129 ml (1.1 moles) of 48% HBr. After the addition of sodium bromate (4.5 g, 0.03 mole) in H_2O (47 ml) (dropwise during 20 min), the mixture was heated to 75° in 0.5 hr and at 75° for 0.5 hr. Dilution of the suspension with H_2O and recrystallization of the precipitate provided the α-bromomethyl ketones.

Cinchoninic Acid Chlorides.—$SOCl_2$ and the acids were heated at reflux for 3 hr. Excess reagent was removed under reduced pressure and the residue was slurried with C_6H_6. Recrystallization of the insoluble solid provided the acid chlorides.

α-Bromomethyl 2-Phenyl-4-quinolyl Ketones *via* Diazomethylation of the Cinchoninic Acid Chlorides.—The following synthesis of α-bromomethyl 6,8-dichloro-2-(3-trifluoromethylphenyl)-4-quinolyl ketone is a typical procedure. To a stirred mixture of 16.5 ml of 40% KOH and 55 ml of ether at 5° was added 7.5 g (0.054 mole dry wt) of moist[3] nitrosomethylurea[20] at such a rate (0.5 hr) that the reaction temperature did not exceed 5°. The ether layer containing CH_2N_2 was then decanted and dried over KOH pellets. To this well-stirred ethereal CH_2N_2 solution (0.037 mole) at −5° was added in 15 min the powdered cinchoninic acid chloride (5 g, 0.012 mole) and the reaction was kept at 0–4° overnight. A mixture of 48% HBr (6 ml) in ether (6 ml) was added to the ether suspension of diazomethyl ketone. After stirring for 4 hr, the reaction mixture was filtered and the solid was washed with H_2O. Recrystallization provided the α-bromomethyl ketone.

Aluminum Isopropoxide Reduction of α-Bromomethyl 4-Quinolyl Ketones.—A stirred suspension of the α-bromomethyl ketones (0.002 mole) and freshly prepared aluminum isopropoxide (0.007 mole) in 15 ml of anhydrous *i*-PrOH was slowly distilled under mild reflux until the distillate gave no further test for acetone with 2,4-dinitrophenylhydrazine (usually 1.5–2 hr). The solvent was removed under reduced pressure and the residue was treated with 10% HCl. The precipitated bromohydrins were washed with H_2O and dried. These compounds were used without further purification in the condensation with dialkylamines.

α-(Di-*n*-butylaminomethyl)-2-phenyl-4-quinolinemethanols.—The bromohydrins (0.002 mole) and di-*n*-butylamine (1.1 g, 0.008 mole) were heated at 75° for 12 hr. The reaction was cooled to room temperature, 21 ml of ether was added, and $Bu_2NH_2^+Br^-$ was filtered. The stirred filtrate was treated slowly with standardized ethereal HCl (0.0042 mole) and the precipitated $Bu_2NH_2^+Cl^-$ was removed. Further addition of an equivalent amount of ethereal HCl gave the α-(di-*n*-butylaminomethyl)-4-quinolinemethanol monohydrochlorides as almost-white salts which were then recrystallized.

The preparation of the di-*n*-hexylaminomethyl derivatives was carried out in a similar manner. Excess di-*n*-hexylamine was removed by steam distillation.

Ir spectra of α-dialkylaminomethyl-4-quinolinemethanol monohydrochloride salts displayed OH absorption at 3.05–3.10 μ and NH^+ absorption as a doublet at 3.85 and 3.94 μ.

Acknowledgment.—The technical assistance of Pauline Schwartz and Anthony Scotese is gratefully acknowledged.

(19) The attempted conversion of ethyl 6-fluoro-2-(4-chlorophenyl)-cinchoninate to the β-keto ester employing NaOEt in C_6H_6 resulted in displacement of the F atom and isolation of ethyl 6-ethoxy-2-(4-chlorophenyl)-cinchoninate (**53**). *Anal.* ($C_{20}H_{18}ClNO_3$) H, N; C: calcd, 67.51; found, 67.05.

(20) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 461.