A solution of aldehyde VI (1.2 g, 5 mmoles) in THF (15 ml) was then added dropwise at 20–30°, and the mixture was stirred and heated at 40–50° for 3 hr. It was decomposed with ice-cold saturated NH_4Cl and allowed to stand overnight. Ether and a little H_2O were added, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried ($MgSO_4$), the solvent was removed, and the residue was crystallized from petroleum ether, yielding 0.8 g of product.

6-(1-Hydroxy-2-nitroethyl)benzothiazole (VII).—A solution of 6-benzothiazolecarboxaldehyde (V) (3.25 g, 0.02 mole) and $MeNO_2$ (1.25 g, 0.02 mole) in dry Et_2O (75 ml) was added to a mixture of 4 ml of 5 *N* NaOMe in MeOH and ether (10 ml) over a period of 10 min. After being stirred at 28° for 1 hr, the mixture was treated with AcOH (3 ml) in ether (20 ml) and stirred for another 15 min, and NaOAc was filtered off and washed with ether. The residue from the ether solution was a pale yellow solid. It was washed (H_2O) and dried and weighed 3.85 g.

Antimalarials. IV.[1] A New Synthesis of α-(2-Pyridyl)- and α-(2-Piperidyl)-2-aryl-4-quinolinemethanols

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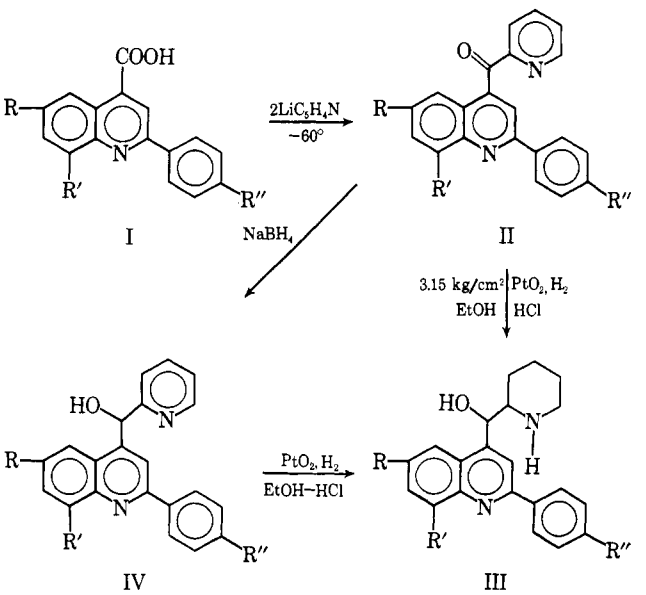
New convenient syntheses of α-(2-pyridyl)- and α-(2-piperidyl)-2-aryl-4-quinolinemethanols are reported. The key steps involve addition of pyridyllithium to quinoline-4-carboxylic acids and subsequent one-step selective catalytic 8 H hydrogenation of the ketopyridyl system to the α-piperidylmethanol. All of the α-piperidylmethanols were highly active against *Plasmodium berghei* in mice but were phototoxic, whereas the α-pyridyl analogs were considerably less phototoxic but were inactive.

This work is an extension of investigations carried out during the World War II antimalarial effort.[2] Earlier results had shown that 4-quinolylamino alcohols, particularly with a 2-aryl substituent as a deterrent to metabolic inactivation,[3] possessed considerable antiplasmodial activity against avian infections.[2,4,5]

α-Pyridyl- and α-Piperidylquinolinemethanols.—In a recent preliminary communication[1a] we have reported new syntheses for the title compounds. We now describe the details of the methods in full and report the antiplasmodial properties of these compounds.

The previous method for preparing α-piperidylquinolinemethanols was a tedious and cumbersome six-step synthesis starting from quinoline-4-carboxylic acids.[4] The new synthesis which we have developed is a convenient two-step process which also starts from quinoline-4-carboxylic acid (see Scheme I). The initial step involves conversion of the quinoline-4-carboxylic acid (I) by 2-pyridyllithium into the 2-pyridyl ketone II (Table I). The second step is the selective reduction of the 2-pyridyl and carbonyl groups of II by hydrogenation in acid solution over PtO_2 which produces the α-piperidylquinolinemethanols (III) (Table III). Recent reports of similar catalytic reductions include the selective reduction of the pyridine nucleus in 2-(2-pyridyl)-1,2-diarylalkanols[6]

SCHEME I



and reduction of the pyridine portion of a quinoline ring system.[7]

In the conversion II → III, the selectivity of reduction presumably arises from selective protonation of the α-pyridyl ring which enhances the susceptibility of that ring toward reduction. The presumption of preferential protonation of the α-pyridyl ring is based upon steric considerations. Indeed, the hydrobromides of many 2,8-disubstituted quinolines cannot be obtained, presumably because of this effect,[2] which demonstrates the sensitivity of protonation to steric effects by substituents adjacent to the ring nitrogen. The reduction of II probably proceeds stepwise, first by reduction of the carbonyl group which is in conjugation with the imino groups of the pyridyl and quinolyl rings, followed by preferential reduction of the pyridyl ring. In sup-

(1) (a) Part I: D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967). (b) Part III: A. Burger and S. N. Sawhney, *J. Med. Chem.*, **11**, 270 (1968). (c) Supported by U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2955, Contribution No. 311 to the Army Research Program on Malaria (Part I, No. 306), A. Burger and R. E. Lutz co-investigators.

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

(3) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p 655.

(4) A. D. Ainley and H. King, *Proc. Roy. Soc.* (London), **B125**, 60 (1938); (b) M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *J. Am. Chem. Soc.*, **68**, 2697 (1946); (c) R. F. Brown, *et al.*, *ibid.*, **68**, 2705 (1946).

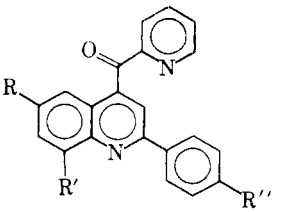
(5) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

(6) J. H. Burckhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. R. Dice, G. Rodney, and D. H. Kaump, *J. Med. Chem.*, **10**, 565 (1967).

(7) J. G. Cannon, S. A. Lazaris, and T. A. Wunderlich, *J. Heterocycl. Chem.*, **4**, 259 (1967).

Table I[a]

2-Pyridyl 2-Aryl-4-quinolyl Ketones (II)

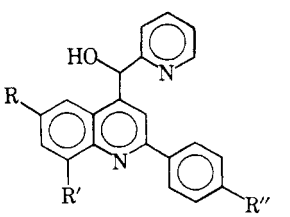


No.	R	R′	R″	Mp, °C	Yield, %	Formula	Analyses
1	CH_3	CH_3	H	143–145	76	$C_{23}H_{18}N_2O$	C, H
2	CH_3	CH_3	CH_3	144–145	81	$C_{24}H_{20}N_2O$	C, H
3	CH_3	CH_3	OCH_3	146–147	68	$C_{24}H_{20}N_2O_2$	C, H
4[b]	CH_3	CH_3	Cl	175–176	65	$C_{23}H_{17}ClN_2O$	C, H
5	CH_3	CH_3	F	140.5–142	62	$C_{23}H_{17}FN_2O$	C, H
6	H	CF_3	H	145–146.5	72	$C_{23}H_{15}F_3N_2O$	C,[c] H
7	H	CF_3	CH_3	162.5–163.5	74	$C_{24}H_{17}F_3N_2O$	C, H
8	H	CF_3	OCH_3	162–163	66	$C_{24}H_{17}F_3N_2O_2$	C, H
9	H	CF_3	Cl	192–193	85	$C_{23}H_{12}ClF_3N_2O$	C, H
10	H	CF_3	F	206–207	60	$C_{23}H_{12}F_4N_2O$	C, H
11	CH_3	H	H	140.5–142	45	$C_{22}H_{16}N_2O$	C, H
12	CH_3	H	CH_3	142–143	60	$C_{23}H_{18}N_2O$	C, H, N
13	CH_3	H	OCH_3	147–148	47	$C_{23}H_{18}N_2O_2$	C, H
14	CH_3	H	Cl	192.5–193	50	$C_{22}H_{15}ClN_2O$	C, H
15	CH_3	H	F	155–156.5	49	$C_{22}H_{15}FN_2O$	C, H, N
16	OCH_3	H	CH_3	166–167	45	$C_{23}H_{18}N_2O_2$	C, H
17	H	CH_3	H	130.5–132.5	84	$C_{22}H_{16}N_2O$	C, H
18	H	CH_3	CH_3	142.5–144	59	$C_{23}H_{18}N_2O$	C, H
19	H	CH_3	OCH_3	143–145	66	$C_{23}H_{18}N_2O_2$	C, H
20	H	CH_3	Cl	144–146	70	$C_{22}H_{15}ClN_2O$	C, H
21[d]	H	CH_3	F	141.5–142.5	75	$C_{22}H_{15}FN_2O$	...
22	F	H	CH_3	172–174	49	$C_{22}H_{15}FN_2O$	C, H

[a] Unless otherwise noted solvent of recrystallization was EtOH. [b] Recrystallization solvent MeCN. [c] C: calcd, 69.84; found, 69.40. [d] This compound was used directly without analysis.

Table II

α,2-Pyridyl-4-quinolinemethanols (IV)

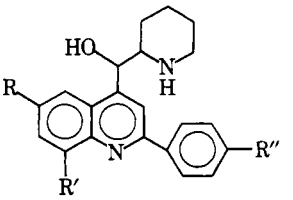


No.	R	R′	R″	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
23	CH_3	CH_3	H	163–164.5	80	MeCN–$CHCl_3$	$C_{23}H_{20}N_2O$	C, H, N
24	CH_3	CH_3	CH_3	193–194	70	EtOH	$C_{24}H_{22}N_2O$	C, H, N
25	CH_3	CH_3	OCH_3	185–187	90	EtOH	$C_{24}H_{22}N_2O_2$	C, H, N
26	CH_3	CH_3	Cl	167–169	87	EtOH	$C_{23}H_{19}ClN_2O$	C, H, N
27	CH_3	CH_3	F	173–175	87	EtOH	$C_{23}H_{19}FN_2O$	C, H, N
28	H	CF_3	H	193–194.5	93	MeCN	$C_{22}H_{15}F_3N_2O$	C, H, N
29	H	CF_3	CH_3	178–179.5	85	EtOH	$C_{23}H_{17}F_3N_2O$	C, H, N
30	H	CF_3	OCH_3	210–212	80	EtOAc	$C_{23}H_{17}F_3N_2O_2$	C, H, N
31	H	CF_3	Cl	214–216 dec	74	EtOH	$C_{22}H_{14}ClF_3N_2O$	C, H, N
32	H	CF_3	F	178–181	95	EtOH	$C_{22}H_{14}F_4N_2O$	C, H, N
33	CH_3	H	H	180–180.5	80	EtOH	$C_{22}H_{18}N_2O$	C, H, N
34	CH_3	H	CH_3	176–177.5	92	EtOH	$C_{23}H_{20}N_2O$	C, H, N
35	CH_3	H	OCH_3	191–192	95	EtOH	$C_{23}H_{20}N_2O_2$	C, H, N
36	CH_3	H	Cl	184–186	85	EtOH	$C_{22}H_{17}ClN_2O$	C, H, N
37	CH_3	H	F	176–178	70	EtOH	$C_{22}H_{17}FN_2O$	C, H, N
38	OCH_3	H	CH_3	178–180	80	EtOH	$C_{23}H_{20}N_2O_2$	C, H, N
39	H	CH_3	H	145–147	86	MeCN–$CHCl_3$	$C_{22}H_{18}N_2O$	C, H, N
40	H	CH_3	CH_3	174–175	92	EtOH	$C_{23}H_{20}N_2O$	C, H
41	H	CH_3	OCH_3	154–156	90	MeCN	$C_{23}H_{20}N_2O_2$	C, H
42	H	CH_3	Cl	174–175.5	83	MeCN	$C_{22}H_{17}ClN_2O$	C, H
43	H	CH_3	F	139–141[a]	95	EtOH	$C_{22}H_{17}FN_2O$	C, H

[a] Sinters at 128–130°.

TABLE III[a]

α,2-PIPERIDYL-4-QUINOLINEMETHANOLS (III)



No.	R	R′	R″	Mp, °C	Yield, %	Formula	Analyses	Antimalarial act.[b] Dose, mg/kg	Cures
44	CH_3	CH_3	CH_3	220–221	46	$C_{24}H_{28}N_2O$	C, H, N	160	1
45	CH_3	CH_3	OCH_3	200–201	43	$C_{24}H_{28}N_2O_2$	C, H, N	40	0[c]
								80	2[d]
46	CH_3	CH_3	Cl	212–214	19	$C_{23}H_{25}ClN_2O$	C, H, N	20	1
								40	3
47	CH_3	CH_3	F	175–177[e]	29	$C_{23}H_{25}FN_2O$	C, H, N	40	0[f]
								80	2
48	H	CF_3	H	197–198	46	$C_{22}H_{21}F_3N_2O$	C, H, N	20	2
49	H	CF_3	CH_3	195–197	75	$C_{23}H_{23}F_3N_2O$	C, H, N	20	0[g]
								40	2
50	H	CF_3	OCH_3	182–184	53	$C_{23}H_{23}F_3N_2O_2$	C, H, N	20	1
								40	3
51	H	CF_3	Cl	181–182	38	$C_{20}H_{20}ClF_3N_2O$	C, H, N	20	5
52	CH_3	H	H	179–181[h]	38	$C_{22}H_{24}N_2O$	C, H, N	640[i]	1
53	CH_3	H	CH_3	214–216[j]	56	$C_{23}H_{26}N_2O$	C, H, N	640	0[k]
54	CH_3	H	OCH_3	206–207	58	$C_{23}H_{26}N_2O_2$	C, H, N	160	0[l]
								320	2
55	CH_3	H	Cl	217–219	12	$C_{22}H_{23}ClN_2O$	H, N; C[m]		
56	H	CH_3	H	188–189[n]	31	$C_{22}H_{24}N_2O$	C, H, N	80	1
								160	3
57	H	CH_3	CH_3	175–175.5	32	$C_{23}H_{26}N_2O_2$	C, H, N	80	1[o]
								320	4
58	H	CH_3	Cl	169–171	23	$C_{22}H_{23}ClN_2O$	C, H	20	2
59	H	CH_3	F	182.5–184	26	$C_{22}H_{23}FN_2O$	C, H	40	2

[a] Recrystallization solvent MeCN. [b] Antimalarial test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research. Tests were carried out in groups of five mice infected with *Plasmodium berghei*. The drugs were injected in doses of 20, 40, 80, 160, 320, and 640 mg/kg. Unless shown all the animals were cured at higher doses up to the maximum of 640 mg/kg. Enhancement in survival time of treated animals is regarded as evidence of antimalarial activity. A compound is considered to be active if the mean survival time of the treated group is more than double the mean survival time of the control group (7.0 ± 0.5 days); it is said to be curative when the animal survives up to 60 days. [c] Active: increased survival time 7 days. [d] Two cures at 160 mg/kg. [e] Softens 140°. [f] Increased survival time 9.6 days. [g] Increased survival time 7.8 days. [h] Lit.[9] 182.5–182.9°. [i] Inactive below this dosage. [j] Softens 150°. [k] Increased survival time 9.6 days. [l] Increased survival time 9.2 days. [m] C: calcd, 72.02; found, 71.47. [n] Lit.[9] 187.8–188.3°. [o] One cure at 160 mg/kg.

port of the suggested steps are the following: (a) in a few cases the hydrogenation was interrupted before completion and the first-stage reduction product, the α-pyridyl alcohol, was isolated; and (b) reduction of the 2-pyridyl ring of the alcohol **29**[8] proceeded smoothly under the conditions which reduce the ketones II to III.

That the nucleus of the quinoline ring in the ketones II was unaffected by the catalytic reductions was demonstrated by spectral methods. Uv absorption characteristics of 2-arylquinolines were obtained for the reduction products III. The nmr spectra obtained from III were as expected for the type. In our previous report[1a] the spectral data and their interpretations for a typical example of III were presented.

The ultimate validation of the new synthetic scheme as an unambiguous route to compounds of type III rests in the identity of samples of **53** obtained by both the new method and by the older method.[4] Further support comes from the compounds **52** and **56** which were prepared by the new scheme and have physical properties which are in accord with those reported in the literature for these compounds synthesized by the older route.[9]

Two apparent exceptions have been observed; compound **15** seemingly undergoes reduction beyond the desired stage III[10] and **19** gave intractable resins. Thus, it is necessary to confirm the structure of each new compound obtained by this new method.

Reductions of the pyridyl ketones II by sodium borohydride produces in good yields the α-2-pyridylquinolinemethanols IV (Table II). The structure of the resulting compounds is based upon the method of synthesis and their spectral properties which are distinctive and corroborative (*cf.* ref 1a).

Biological Activity.—The compounds of types III and IV were tested for antimalarial activity against *Plasmodium berghei* in mice by the method of Rane.[11] All of the α-pyridylquinolinemethanols of type IV (Table II) were inactive in this test, but they showed phototoxicity. However, all of the α-piperidylquino-

(8) Arabic numbers used are for the compounds listed in the tables.

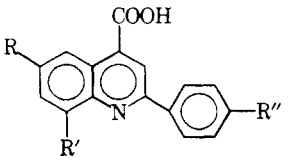
(9) E. R. Buchman and D. R. Howton, *J. Am. Chem. Soc.*, **68**, 2718 (1946).

(10) This requires further investigation.

(11) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

Table IV[a]

Substituted Cinchoninic Acids



I

No.	R	R′	R″	Mp, °C	Yield, %	Formula	Analyses
60	CH_3	H	CH_3	240–244 dec	90.9	$C_{18}H_{15}NO_2$	C, H
61	CH_3	H	OCH_3	237–238[b]	77.3	$C_{18}H_{15}NO_3$	C, H
62	CH_3	H	Cl	272–274[c]	85.1	$C_{17}H_{12}ClNO_2$	C, H
63	CH_3	H	F	225–228	92.4	$C_{17}H_{12}FNO_2$	C, H[d]
64[e]	CH_3	CH_3	CH_3	244–246	75.2	$C_{19}H_{17}NO_2$	C, H
65	CH_3	CH_3	OCH_3	250–252[f]	70.2	$C_{19}H_{17}NO_3$	C, H
66	CH_3	CH_3	F	246–251	70.7	$C_{18}H_{14}FNO_2$	C, H
67	H	CF_3	H	260–265 dec	88.3	$C_{17}H_{10}F_3NO_2$	C, H
68	H	CF_3	CH_3	268–271 dec	83.5	$C_{18}H_{12}F_3NO_2$	C, H
69	H	CF_3	OCH_3	238–241 dec	86.1	$C_{18}H_{12}F_3NO_3$	C, H
70	H	CF_3	Cl	265–275	94.4	$C_{17}H_9ClF_3NO_2$	C, H
71	H	CF_3	F	257–269	89.5	$C_{17}H_9F_4NO_2$	C, H
72	OCH_3	H	CH_3	242–245	75.0	$C_{18}H_{15}NO_3$	C, H
73	OCH_3	H	OCH_3	242–245	89.9	$C_{18}H_{15}NO_4$	C, H
74	OCH_3	H	F	223–230	59.4	$C_{17}H_{12}FNO_3$	C, H
75	F	H	CH_3	274–275	92.5	$C_{17}H_{12}FNO_2$	C, H
76	F	H	Cl	253–256	69.9	$C_{16}H_9ClFNO_2$	C, H
77	H	CH_3	CH_3	245–249	78.1	$C_{18}H_{15}NO_2$	C, H
78	H	CH_3	F	201–206	83.2	$C_{17}H_{12}FNO_2$	C, H

[a] Recrystallized from EtOH. [b] T. Kaku [*J. Pharm. Soc. Japan*, **545**, 577 (1927)] reported 230–231°. [c] N. P. Buu-Hoi, R. Royer, N. D. Xuong, and P. Jacquignon [*J. Org. Chem.*, **18**, 1209 (1953)]. [d] H: calcd, 4.30; found, 4.95. [e] A. H. Crosby, M.S. Thesis, University of Virginia, 1950, p 11. [f] Lit.[b] 239°.

linemethanols of type III were highly active but all consistently caused serious photosensitization in mice. The antimalarial test data for these compounds are shown in Table III. Of these α-piperidylquinolinemethanols only two have been tested previously.[5] The "quinine equivalents" of **52** ranged from 0.3 against *P. gallinaceum* in chicks to 10.0 against *P. cathemerium* in ducks, and that of **56** from 0.6 against *P. gallinaceum* in chicks to 8.0 against *P. lophurae* in ducks.

Experimental Section

Melting points were obtained on a Thomas–Hoover or a Fischer-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and Micro-Tech Laboratories, Inc. Satisfactory uv and ir spectra were recorded for each compound listed in the tables. Nmr spectra were obtained for all compounds of type IV which were soluble in $CDCl_3$ or DMSO-d_6; random nmr determinations were made on all the other types. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

2-Pyridyl Ketones (II). 2-Pyridyl 2-(*p*-Tolyl)-6-methyl-4-quinolyl Ketone (See Table I).—The pyridyllithium (from 18.0 g of 2-bromopyridine in 100 ml of Et_2O) was prepared essentially by the published method.[12,13] To the stirred solution of 2-pyridyllithium under N_2 and at −60° was added rapidly (1–2 min) finely ground 6-methyl-2-(*p*-tolyl)quinoline-4-carboxylic acid (10.0 g) *via* a powder funnel. The addition of acid was followed after 5 min of stirring by the addition of 100 ml of anhydrous Et_2O. The reaction mixture was allowed to stir for 3 hr at −60° under N_2, after which time the Dry Ice bath was removed and the solution was allowed to warm to 0–5°. At this temperature the reaction mixture was hydrolyzed cautiously by adding 100 ml of moist Et_2O to the stirred solution, followed by 100 ml of H_2O. The resulting heterogenous mixture was stirred for 2–3 min and the layers were separated. The Et_2O solution (normally dark red) was evaporated under reduced pressure and the resulting residue was taken up in hot EtOH and allowed to crystallize.

Piperidylquinolinemethanols (III). α-(2-Piperidyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol (See Table III).—2-Pyridyl 2-(*p*-tolyl)-6-methyl-4-quinolyl ketone (2 g) was dissolved in *ca.* 200 ml of hot absolute EtOH to which was added 2 ml of concentrated HCl (37–38%, sp gr 1.19). The EtOH solution was cooled and hydrogenated over 0.2 g of PtO_2 (Englehard) at 3.15 kg/cm². Absorption of H_2 stopped essentially in *ca.* 1 hr. The catalyst was removed by filtering over Celite and the EtOH solution was concentrated to *ca.* 30 ml by evaporation under reduced pressure and was poured into a stirred $NaHCO_3$ solution. The resulting aqueous suspension of the free base was extracted with Et_2O (*ca.* 300 ml). The Et_2O was evaporated and the residue taken up in MeCN (25–40 ml).

Frequently the crude product oils out and/or is quite impure, hence several (six–ten) recrystallizations are required to obtain analytical samples. In a few runs a small amount of MeCN-insoluble, high-melting fibrous material was obtained, which was removed by filtration.

Pyridylquinolinemethanols (IV). α-(2-Pyridyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol (See Table II).—To a stirred slurry of 2.0 g of the pyridyl ketone **18** in 50 ml of EtOH was added 0.2 g of $NaBH_4$. The mixture was stirred at room temperature for 1 hr and poured into 400 ml of H_2O, and the solid was filtered. Recrystallization was from EtOH.

Ethyl 6-Methyl-2-(*p*-tolyl)cinchoninate.—6-Methyl-2-(*p*-tolyl)-4-cinchoninic acid (0.08 mole, 24.18 g) was suspended in 450 ml of absolute EtOH and 20 ml of concentrated H_2SO_4 was added. The mixture was refluxed for 24 hr, cooled, and then poured onto ice–water and extracted with Et_2O. The Et_2O extract was washed (aqueous Na_2CO_3, H_2O) and after drying ($MgSO_4$) the Et_2O was removed under reduced pressure. The yield of product was 20 g, mp 74–76°. *Anal.* ($C_{20}H_{19}NO_2$) C, H, N.

α-(2-Piperidyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol.[9,14]—

(12) J. P. Wibaut, A. P. De Jonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, **70**, 1043 (1951).

(13) It is important that reactants and solvents are dry. The pyridyllithium solution should be prepared and maintained at a temperature at least below −45° (*cf.* ref 12).

(14) E. R. Buchman, H. Sargent, T. C. Myers, and D. R. Howton, *J. Am. Chem. Soc.*, **68**, 2710 (1946).

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.

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(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.

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(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.