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VIRGINIA UNIV CHARLOTTESVILLE DEPT OF CHEMISTRY
GUINOLINEMETHANOL ANTIMALARIALS. (U)
DEC 74 R E LUTZ, A BURGER

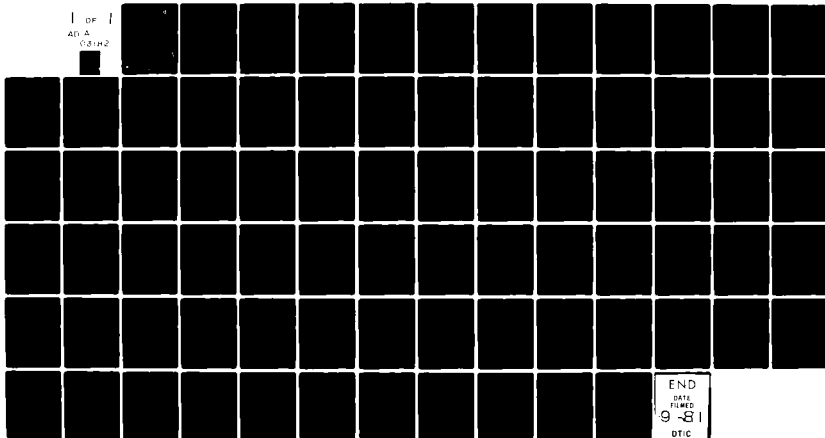
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6 QUINOLINEMETHANOL ANTIMALARIALS

9 FINAL REPORT

by

10 ROBERT E. LUTZ Alfred Burger

Professor of Organic Chemistry (Emeritus, 1970)

Principal Investigator

11 December 1974

For the 4-year and 5-month Extension, 5 May 1966 to October 1970

Including work directed by

259101

ALFRED PURGER

12 79

Professor of Organic Chemistry

Co-Principal Investigator for the First Year, 5 May 1966 to 4 May 1967

Supported by

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University of Virginia
Department of Chemistry, Charlottesville, Virginia 22901

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I. Personnel

Principal Investigator, 1966-present, Robert E. Lutz (Ph.D., Harvard), Professor of Chemistry, University of Virginia, Emeritus, 1970. (Principal Investigator during World War II at U.Va. on Synthesis of Antimalarials under a contract, recommended by the Committee on Medical Research, under the Office of Scientific Research and Development).

Co-Principal Investigator, 1966 only, Alfred Burger, (Ph.D., Vienna), Professor of Organic Chemistry, University of Virginia.

Postdoctoral Research Associates

1966-7 David W. Boykin, Jr. (Ph.D., U. Ala.) Professor, Georgia State University.

1966-9 A. R. Patel (Ph.D., California)

1966-7 S. N. Sawhney (Ph.D., Hull)

1966-7 Roger M. Pinder (Ph.D., Hull)

1967-8 David P. Clifford (Ph.D., East Anglica)

1969-70 Cyrus J. Ohnmacht (Ph.D., Lehigh Univ.)

1968-9 H. Randall Munson (Ph.D., Georgetown)

1969-70 James M. Sanders (Ph.D., Rice) (supported in smaller part by a National Science Foundation grant to REL)

Postgraduate Research Assistants

1967-8 Richard E. Johnson (B.S., Kent)

1967-8 Charles R. Wetzel (M.S., U.Va., 1968)

1968-9 Freddy Davis (B.S., Pikeville) (M.S., U.Va. 1969)

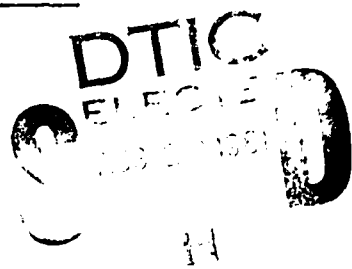
1968-70 James R. Shanklin (B.S., U.Va.) (Ph.D., U.Va., 1971) (supported in considerable part by NASA traineeship 1968-9 and A.H. Robins Co. research grant to REL)

II. Foreword and Introduction

This project began 5 May 1966 as part of the U.S. Army Program of Synthesis of Antimalarials to meet needs for drugs effective against new resistant strains of P. falciparum. For the first year it was under co-principal investigators, Robert E. Lutz and Alfred Burger; and it was continued under REL for another three years (to his retirement, summer 1970). The Chemistry Department then closed laboratory facilities for further work on unfinished last-minute problems. This Final Report was delayed in favor of attempts to complete the work elsewhere, and by decision of REL first to write the last five of the total of eleven papers which describe the results and which are incorporated herein. Papers 7-9 have since been published (1971, 1973); and it is expected that papers 10 and 11 will be published during 1975. Grateful Acknowledgment is made of the intelligence, perseverance, initiatives and hard work of the above named Postdoctoral and Postgraduate Research Associates and Assistants.

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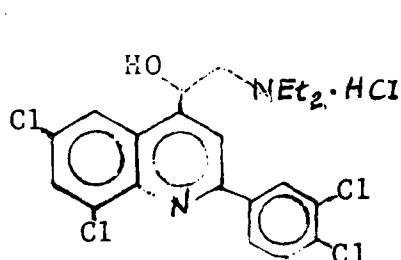


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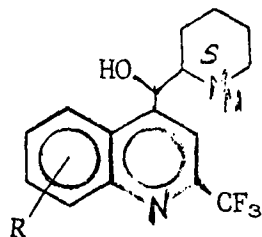
IV. Summary of Results

Seventy seven new aminoalcohols, chiefly of the 4-quinoline type, were synthesized, following older leads and in exploration of new ones (List, p. 70). The hope was to eliminate the phototoxicity then supposed to be associated with nuclear through-conjugation of the 2-arylquinoline ring system. However, the highly curative compound 1 made during World War II by the Virginia group, despite its phototoxicity in animals, was chosen by WRAIR for clinical study in man where it proved highly successful both as prophylactic and cure for several strains of P. falciparum, with phototoxicity inconsequential.

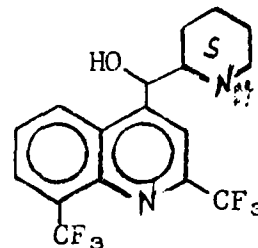
Part 1. Nineteen new 2-aryl-4-quinoline aminoalcohols, analogs of 1, proved highly active and curative against P. berghei, but they were phototoxic in animals. Attempted synthesis of 2-pentafluoro analogs was not completed (p. 16). Five new analogs without the 2-aryl were ineffective (p. 6).



1
Highly curative in animals and man; phototoxic in animals but not in man.



2
Moderately active; phototoxic in animals.

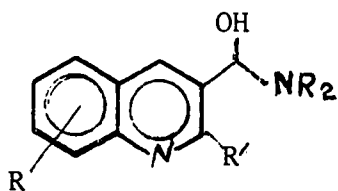


3
Highly curative and non-phototoxic, both in animals and man.

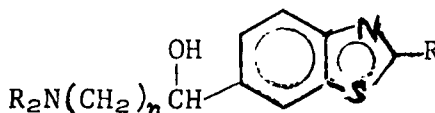
Part 2. Ten derivatives in which the 2-aryl was replaced by 2-CF₃ (2) showed moderate antimalarial activities but were phototoxic in animals (p. 17). Four bis-CF₃ analogs (of 3) were highly curative of P. berghei and non-phototoxic in animals; and clinical trials of the 2,8-bis-CF₃ compound 3 in man have proved highly successful (p. 20).

Part 3. Shifting the aminoalcohol chain from quinoline position-4 to 3 was ineffective in eight compounds (4) without a 2-aryl group (and also in six 2-aryl analogs made by the Monsanto Research Corp. group under P. F. Donovan and W. R. Smith) (p. 23).

Part 4. Twelve quinoline isosteres, 6-benzothiazole aminoalcohols 5, proved ineffective against P. berghei in mice (p. 30).

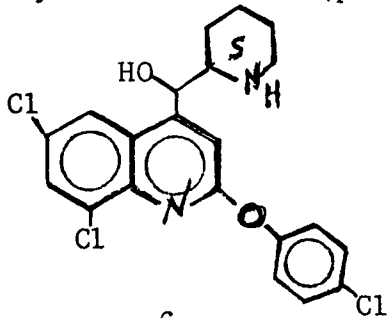


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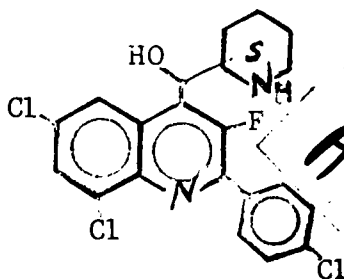


5
Inactive

Part 5. Twelve 4-quinoline aminoalcohols carrying 2-p-substituted-phenoxy (analogs of 5) were made, and also 2-(N-p-chloro-anilino) analogs, hoping that interruption of the 2-phenylquinoline conjugation by the heteroelement and conversion to a forked conjugated system would eliminate phototoxicity without impairment of anti-malarial activity. However, the five that were tested were phototoxic. The very high curativity of the 6,8-dichloro-2-(p-chlorophenoxy) compound (6) was comparable with that of 1, with high probability that (as with 1) the animal phototoxicity would not carry over into man. (p. 33).



6
Highly curative;
phototoxic in animals

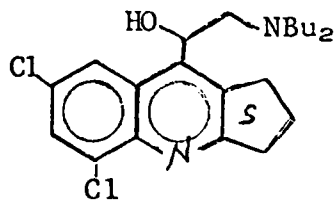


7
Highly curative;
phototoxic in animals

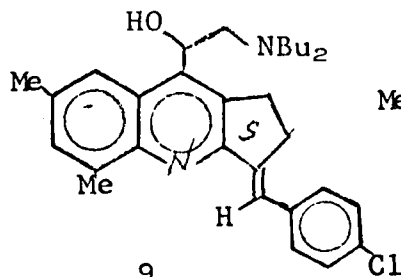
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Part 6. Four 2-aryl-quinoline aminoalcohols carrying Cl, Br, F, or O-Me in the 3-position were synthesised in the hope that steric interference with the nuclear planarity and through conjugation would lower phototoxicity without detriment to antimalarial curativity. Three of these with favorable 6,8,4'-trisubstitution showed high curativity toward P. berghei but were phototoxic. The most active compound was the 6,8,4'-trichloro-3-fluoro compound 7, and it appears very unlikely that its animal phtotoxicity would carry over into man and inhibit usefulness (p.37²). Earlier work begun under the Office of Ordinance Research offered a possible route to 3-substituted 2-aryl quinolines starting from suitably substituted cis-chalcones. With partial support from National Science Foundation grants to REL, and encouraged by possible usefulness here, this work was completed. (p. 50).

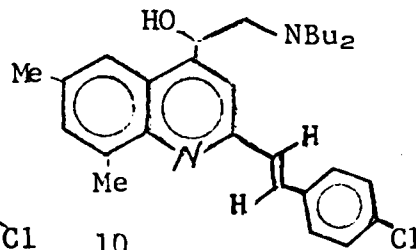
Part 7. The 6,8-dichloro-4-quinoline aminoalcohol with a 2,3-trimethylene fused ring, 8, proved to be moderately active and non-phototoxic in animals (p. 55). A unique 6,8-dimethyl analog of this, 9, the last compound made under the contract, is a 2-vinylog of 2-aryl-4-quinoline aminoalcohols, which carries a p-chlorostyryl group developed at the quinoline position-2 and extruding as a part of the rigid 2,3-tricarbon fused ring. This was highly curative in spite of the relatively poor auxopharmacophoric quality of the 6,8-dimethyls (as compared with 6,8-dichloro of the primary target analog, the synthesis of which was not completed^{7C}). It was non-phototoxic in animals and was chosen for clinical trials on man (a project now shelved) (p.57). A sample of the simpler 2-styryl analog 10 without the 2,3-tricarbon fused ring has since been made (1974) and submitted to WRAIR for test.



8
Moderately active;
phototoxic in
animals.



9
Highly curative;
non-phototoxic in
animals.



10

Part 1. 4-quinoline Aminoalcohols with and without 2-Aryl.

Communication to the Editor

Reprinted from the JOURNAL OF HETEROCYCLIC CHEMISTRY, 4, 459 (1967).

Department of Chemistry, University of Virginia

Pyridyl Ketones by Addition of Pyridyllithium to Carboxylic Acids.
A New Synthesis of α -(2-Piperidyl)-2-aryl-4-quinolinemethanols (I)

D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger

Antimalarials. I.

Sir:

Resurgence of the malaria problem led us to synthesize a number of the title compounds, a type which had previously been made by a cumbersome 6-step synthesis from the corresponding quinoline-4-carboxylic acids (2). We now report a new and more convenient 2-step synthesis by which we have made fifteen α -(2-piperidyl)-2-aryl-quinolinemethanols in the 6-methyl, 8-methyl, 6,8-dimethyl and 8-trifluoromethyl series (cf. III). Also, by a variant in the second step, we have made twenty α -(2-pyridyl) analogs of type IV which represent a new class of potential synthetic medicinals, but which appear to be inactive toward malaria (1b).

In the example illustrated below the first step involves conversion of 2-*p*-tolylquinoline-4-carboxylic acid (I) by 2-pyridyllithium into 2-pyridyl ketone II. This reaction represents the first pyridyl ketone synthesis by addition of α -pyridyllithium to a carboxylic acid. The second step in the synthesis is controlled reduction of II. Catalytic hydrogenation specifically reduces the carbonyl and pyridyl groups and gives α -piperidylquinolinemethanol III; whereas, sodium borohydride reduces only the carbonyl group of II and gives the α -(2-pyridyl)quinolinemethanol IV. These reactions should find wide application in the alkaloid and synthetic medicinal fields.

Addition of 2 moles of α -pyridyllithium (3) at -60° to acid I followed by hydrolysis gave pyridyl ketone II; 60%;

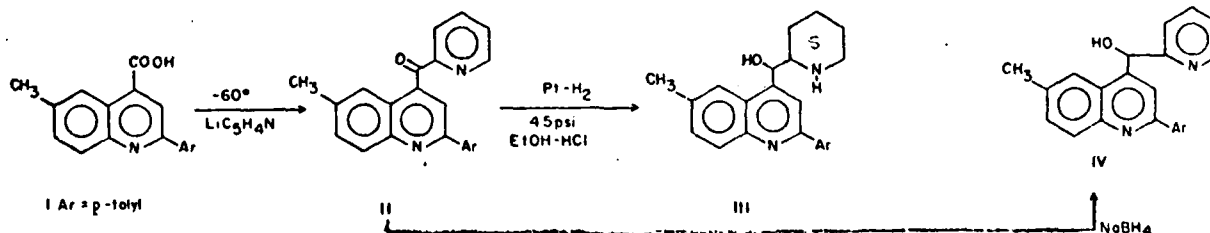
m.p. $142-143^\circ$ (4,5). The structure is supported by: ν max (KBr), 1670 cm^{-1} (C=O); λ max (EtOH), 268, 344 μ (2-arylquinoline type); nmr (deuteriochloroform), 1H signal at 1.3 τ characteristic of pyridine α -hydrogens.

Hydrogenation with platinum oxide of ketone II at 45 psi in ethanol containing 2 moles of hydrochloric acid, reduced the carbonyl and pyridyl groups, but not the quinoline nucleus. Only one of the two possible diastereoisomeric α -(2-piperidyl)quinolinemethanols III was isolated; 56%; m.p. $214-216^\circ$ (4); λ max (EtOH), 267, 330, 339 μ , ν max (KBr), ca. 3300 cm^{-1} ; $2550-2750\text{ cm}^{-1}$; nmr (deuteriochloroform), no signal at 1.3 τ , 1H doublet at 4.6 τ assignable to carbinol α -H, broad 3H and 6H multiplets at 6.5 and 8.4 τ , assigned to α -piperidyl and to β - and γ -piperidyl protons, respectively. The structure III was verified by infrared identity and mmp with a sample synthesized from I by the old route (2).

Reduction of only the carbonyl group of the 2-pyridyl ketone II by sodium borohydride afforded α -(2-pyridyl)quinolinemethanol IV; 90%; m.p. $176-177.5^\circ$ (4); ν max (KBr), 3200 cm^{-1} ; λ max (EtOH), 268, 329, 339 μ ; nmr (deuteriochloroform), 1.4 τ , 4.5 τ (1H signals).

REFERENCES

(1a) Supported by the Walter Reed Army Institute of Research, Contract No. DA-49-193-MD-2955. (b) Antimalarial testing is in progress.



(1a) Supported by the Walter Reed Army Institute of Research, Contract No. DA-49-193-MD-2955. (b) Antimalarial testing is in progress.

(2a) A. D. Ainly and H. King, *Proc. Roy. Soc. (London)*, 125B, 60 (1938). (b) M. M. Rapport, A. E. Seneor, J. F. Mead and J. B. Koepfli, *J. Am. Chem. Soc.*, 68, 2697 (1946). (c) R. F. Brown and 12 co-workers, *ibid.*, 68, 2705 (1946). (d) cf. α -Dialkylaminomethyl-2-aryl-4-quinolinemethanols; R. E. Lutz and 13 co-workers, *ibid.*, 68, 1813 (1946).

(3) J. P. Wibaut, A. P. DeJonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, 70, 1054 (1951).

(4) All new compounds gave correct elemental analyses.

(5) Addition of methyl lithium to I gives the corresponding methyl ketone (80%) [cf. C. Tegner, *Acta. Chem. Scand.*, 6, 782 (1952)] and bromination gave the α -bromo ketone. These reactions were substituted for the conversion of I to the acid chloride, the hazardous large scale diazomethylation, and hydrobromination, which were formerly used in the synthesis of α -dialkylaminomethyl-2-aryl-4-quinolinemethanols (2d).

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Charlottesville, Virginia 22901

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

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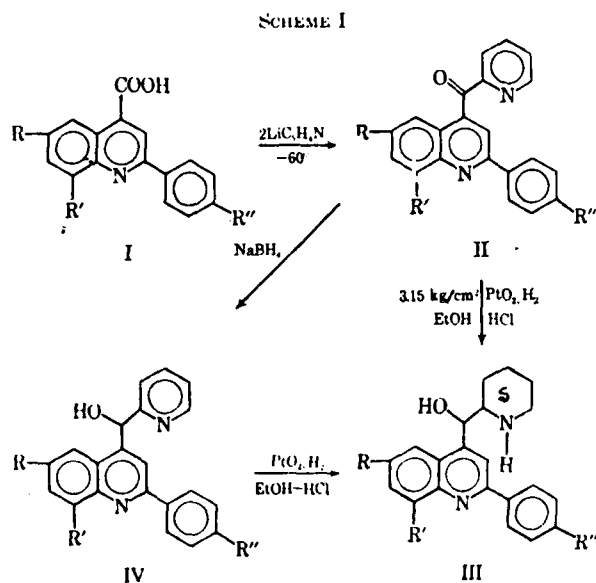
Received November 14, 1967

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 S II 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 antiparasmodial 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 antiparasmodial 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 PtO₂ 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-diarylanalogs⁶



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

In the conversion II \rightarrow 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. 309), A. Burger and R. E. Lutz co-investigators.

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

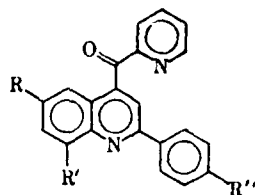
(3) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 655.

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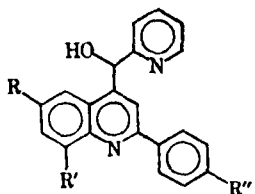
(6) J. H. Burckhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. R. Dice, G. Roduey, and D. H. Kauinp, *J. Med. Chem.*, **10**, 565 (1967).

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

TABLE I
 2-PYRIDYL-2-ARYL-1-QUINOLYL KETONES (II)


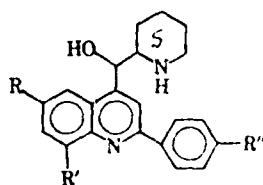
No.	R	R'	R''	Mp, °C	Yield, %	Formula	Analysis
1	CH ₃	CH ₃	H	143-145	76	C ₂₃ H ₁₆ N ₂ O	C, H
2	CH ₃	CH ₃	CH ₃	144-145	81	C ₂₄ H ₂₀ N ₂ O	C, H
3	CH ₃	CH ₃	OCH ₃	146-147	68	C ₂₄ H ₂₀ N ₂ O ₂	C, H
4 ^b	CH ₃	CH ₃	Cl	175-176	65	C ₂₃ H ₁₅ ClN ₂ O	C, H
5	CH ₃	CH ₃	F	140.5-142	62	C ₂₃ H ₁₅ FN ₂ O	C, H
6	H	CF ₃	H	145-146.5	72	C ₂₂ H ₁₃ F ₃ N ₂ O	C, H
7	H	CF ₃	CH ₃	162.5-163.5	74	C ₂₃ H ₁₅ F ₃ N ₂ O	C, H
8	H	CF ₃	OCH ₃	162-163	66	C ₂₃ H ₁₅ F ₃ N ₂ O ₂	C, H
9	H	CF ₃	Cl	192-193	85	C ₂₂ H ₁₂ ClF ₃ N ₂ O	C, H
10	H	CF ₃	F	206-207	60	C ₂₂ H ₁₁ F ₄ N ₂ O	C, H
11	CH ₃	H	H	140.5-142	45	C ₂₂ H ₁₆ N ₂ O	C, H
12	CH ₃	H	CH ₃	142-143	60	C ₂₃ H ₁₈ N ₂ O	C, H, N
13	CH ₃	H	OCH ₃	147-148	47	C ₂₃ H ₁₈ N ₂ O ₂	C, H
14	CH ₃	H	Cl	192.5-193	50	C ₂₂ H ₁₅ ClN ₂ O	C, H
15	CH ₃	H	F	155-156.5	49	C ₂₂ H ₁₅ FN ₂ O	C, H, N
16	OCH ₃	H	CH ₃	166-167	45	C ₂₃ H ₁₈ N ₂ O ₂	C, H
17	H	CH ₃	H	130.5-132.5	84	C ₂₂ H ₁₆ N ₂ O	C, H
18	H	CH ₃	CH ₃	142.5-144	59	C ₂₃ H ₁₈ N ₂ O	C, H
19	H	CH ₃	OCH ₃	143-145	66	C ₂₃ H ₁₈ N ₂ O ₂	C, H
20	H	CH ₃	Cl	144-146	70	C ₂₂ H ₁₅ ClN ₂ O	C, H
21 ^d	H	CH ₃	F	141.5-142.5	75	C ₂₂ H ₁₅ FN ₂ O	...
22	F	H	CH ₃	172-174	49	C ₂₂ H ₁₅ FN ₂ O	C, H

* 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-1-QUINOLINEMETHANOLS (IV)


No.	R	R'	R''	Mp, °C	Yield, %	Recryst solvent	Formula	Analysis
23	CH ₃	CH ₃	H	163-164.5	80	MeCN-CHCl ₃	C ₂₃ H ₁₆ N ₂ O	C, H, N
24	CH ₃	CH ₃	CH ₃	193-194	70	EtOH	C ₂₄ H ₂₀ N ₂ O	C, H, N
25	CH ₃	CH ₃	OCH ₃	185-187	90	EtOH	C ₂₄ H ₂₀ N ₂ O ₂	C, H, N
26	CH ₃	CH ₃	Cl	167-169	87	EtOH	C ₂₃ H ₁₅ ClN ₂ O	C, H, N
27	CH ₃	CH ₃	F	173-175	87	EtOH	C ₂₃ H ₁₅ FN ₂ O	C, H, N
28	H	CF ₃	H	193-194.5	93	MeCN	C ₂₂ H ₁₃ F ₃ N ₂ O	C, H, N
29	H	CF ₃	CH ₃	178-179.5	85	EtOH	C ₂₃ H ₁₅ F ₃ N ₂ O	C, H, N
30	H	CF ₃	OCH ₃	210-212	80	EtOAc	C ₂₃ H ₁₅ F ₃ N ₂ O ₂	C, H, N
31	H	CF ₃	Cl	214-216 dec	74	EtOH	C ₂₂ H ₁₂ ClF ₃ N ₂ O	C, H, N
32	H	CF ₃	F	178-181	95	EtOH	C ₂₂ H ₁₁ F ₄ N ₂ O	C, H, N
33	CH ₃	H	H	180-180.5	80	EtOH	C ₂₂ H ₁₆ N ₂ O	C, H, N
34	CH ₃	H	CH ₃	176-177.5	92	EtOH	C ₂₃ H ₁₈ N ₂ O	C, H, N
35	CH ₃	H	OCH ₃	191-192	95	EtOH	C ₂₃ H ₁₈ N ₂ O ₂	C, H, N
36	CH ₃	H	Cl	184-186	85	EtOH	C ₂₂ H ₁₅ ClN ₂ O	C, H, N
37	CH ₃	H	F	176-178	70	EtOH	C ₂₂ H ₁₅ FN ₂ O	C, H, N
38	OCH ₃	H	CH ₃	178-180	80	EtOH	C ₂₃ H ₁₈ N ₂ O ₂	C, H, N
39	H	CH ₃	H	145-147	86	MeCN-CHCl ₃	C ₂₂ H ₁₆ N ₂ O	C, H, N
40	H	CH ₃	CH ₃	174-175	92	EtOH	C ₂₃ H ₁₈ N ₂ O	C, H
41	H	CH ₃	OCH ₃	154-156	90	MeCN	C ₂₃ H ₁₈ N ₂ O ₂	C, H
42	H	CH ₃	Cl	174-175.5	83	MeCN	C ₂₂ H ₁₅ ClN ₂ O	C, H
43	H	CH ₃	F	139-141*	95	EtOH	C ₂₂ H ₁₅ FN ₂ O	C, H

Sinters at 128-130°.

TABLE III
 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 ₂₁ H ₂₃ N ₂ O	C, H, N	160	1
45	CH ₃	CH ₃	OCH ₃	200-201	43	C ₂₁ H ₂₃ N ₂ O ₂	C, H, N	40	0 ^c
								80	2 ^d
								20	1
46	CH ₃	CH ₃	Cl	212-214	19	C ₂₃ H ₂₃ ClN ₂ O	C, H, N	40	3
								20	1
47	CH ₃	CH ₃	F	175-177 ^e	29	C ₂₃ H ₂₃ FN ₂ O	C, H, N	40	0 ^f
								80	2
								20	2
48	H	CF ₃	H	197-198	46	C ₂₂ H ₂₁ F ₃ N ₂ O	C, H, N	20	2
49	H	CF ₃	CH ₃	195-197	75	C ₂₃ H ₂₃ F ₃ N ₂ O	C, H, N	20	0 ^g
								40	2
								20	1
50	H	CF ₃	OCH ₃	182-184	53	C ₂₃ H ₂₃ F ₃ N ₂ O ₂	C, H, N	20	1
								40	3
								20	5
51	H	CF ₃	Cl	181-182	38	C ₂₀ H ₂₀ ClF ₃ N ₂ O	C, H, N	20	5
52	CH ₃	H	H	179-181 ^h	38	C ₂₂ H ₂₄ N ₂ O	C, H, N	640 ⁱ	1
53	CH ₃	H	CH ₃	214-216 ^j	56	C ₂₃ H ₂₅ N ₂ O	C, H, N	640	0 ^k
54	CH	H	OCH ₃	206-207	58	C ₂₃ H ₂₆ N ₂ O ₂	C, H, N	160	0 ^l
								320	2
								20	2
55	CH ₃	H	Cl	217-219	12	C ₂₃ H ₂₃ ClN ₂ O	H, N; C ^m	80	1
56	H	CH ₃	H	188-189 ⁿ	31	C ₂₂ H ₂₄ N ₂ O	C, H, N	160	3
								80	1 ^o
								320	4
57	H	CH ₃	CH ₃	175-175.5	32	C ₂₃ H ₂₆ N ₂ O ₂	C, H, N	80	1 ^o
								320	4
								20	2
58	H	CH ₃	Cl	169-171	23	C ₂₂ H ₂₃ ClN ₂ O	C, H	20	2
59	H	CH ₃	F	182.5-184	26	C ₂₃ H ₂₃ FN ₂ O	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 29⁹ 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 III¹⁰ 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-pyridyl-quinolinemethanols 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).

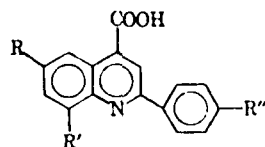
Biological Activity. The compounds of types III and IV were tested for antimalarial activity against *Plasmodium berghei* in mice by the method of Raje.¹¹ All of the α -pyridylquinolinemethanols of type IV (Table II) were inactive in this test, but they showed phototoxicity. However, all of the α -piperidylquino-

(9) E. R. Buckman and D. R. Houston, *J. Am. Chem. Soc.*, **68**, 2738 (1946).

(10) This requires further investigation.

(11) T. S. Osburn, P. B. Russell, and L. Raje, *J. Med. Chem.*, **10**, 43 (1967).

TABLE IV
SUBSTITUTED CINCHONINIC ACIDS



No.	R	R'	R''	Mp, °C	Yield, %	Formula	Analyses
60	CH ₃	H	CH ₃	240-244 dec	90.9	C ₁₉ H ₁₇ NO ₂	C, H
61	CH ₃	H	OCH ₃	237-238 ^b	77.3	C ₁₉ H ₁₇ NO ₂	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 ₂	C, H
66	CH ₃	CH ₃	F	246-251	70.7	C ₁₇ H ₁₂ FNO ₂	C, H
67	H	CF ₃	H	260-265 dec	88.3	C ₁₇ H ₁₂ F ₂ NO ₂	C, H
68	H	CF ₃	CH ₃	268-271 dec	83.5	C ₁₈ H ₁₂ F ₂ NO ₂	C, H
69	H	CF ₃	OCH ₃	238-241 dec	86.1	C ₁₈ H ₁₂ F ₂ NO ₂	C, H
70	H	CF ₃	Cl	265-275	94.4	C ₁₇ H ₁₂ ClF ₂ NO ₂	C, H
71	H	CF ₃	F	257-269	89.5	C ₁₇ H ₁₂ F ₃ NO ₂	C, H
72	OCH ₃	H	CH ₃	242-245	75.0	C ₁₉ H ₁₇ NO ₂	C, H
73	OCH ₃	H	OCH ₃	242-245	89.9	C ₁₉ H ₁₇ NO ₂	C, H
74	OCH ₃	H	F	223-230	59.4	C ₁₇ H ₁₂ FNO ₂	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 ₁₈ H ₁₂ ClFN ₂ O ₂	C, H
77	H	CH ₃	CH ₃	245-249	78.1	C ₁₉ H ₁₇ 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. Bun-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.⁶ 239°.

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 CDCl₃ 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 $\pm 0.4\%$ 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 Et₂O) was prepared essentially by the published method.^{12,13} To the stirred solution of 2-pyridyllithium under N₂ 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 Et₂O. The reaction mixture was allowed to stir for 3 hr at -60° under N₂, 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 Et₂O to the stirred solution, followed by 100 ml of H₂O. The resulting heterogenous mixture was stirred for 2-3 min and the layers were separated. The Et₂O 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 PtO₂ (Englehard) at 3.15 kg/cm². Absorption of H₂ 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 NaHCO₃ solution. The resulting aqueous suspension of the free base was extracted with Et₂O (ca. 300 ml). The Et₂O 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 NaBH₄. The mixture was stirred at room temperature for 1 hr and poured into 400 ml of H₂O, 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 H₂SO₄ was added. The mixture was refluxed for 24 hr, cooled, and then poured onto ice water and extracted with Et₂O. The Et₂O extract was washed (aqueous Na₂CO₃, H₂O) and after drying (MgSO₄) the Et₂O was removed under reduced pressure. The yield of product was 20 g, mp 74-76°. *Anal.* (C₂₀H₁₈NO₂) C, H, N.

α -(2-Piperidyl)-2-(p-tolyl)-6-methyl-4-quinolinemethanol.^{14,15}

(12) J. P. Wulout, A. P. De Jonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, **70**, 1013 (1951).

(13) It is important that reactants and solvents are dry. The pyridyllithium solution should be prepared and maintained at a temperature at least 5-10° below 0°.

(14) P. E. Bachmann, H. Sargent, T. C. Myers, and D. R. Peterson, *J. Am. Chem. Soc.*, **68**, 2230 (1946).

To a solution of the foregoing ester (0.06 mole, 18.32 g) and ethyl 6-benzamidocaproate* (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)cinchoninyll]-*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-cinchonic 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. Cool-

(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.

ing 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)cinchoninyll]-*n*-amylamine dihydrobromide was 3.35 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 PtO₂ 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, EtO 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 (Cinchonic Acids) (I) (Table IV).—All of the substituted cinchophens required as starting material were synthesized by the Pfitzinger¹⁶ 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.

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

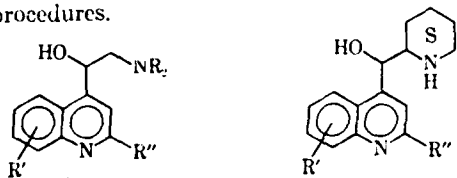
Antimalarials. 6. Some New α -Alkylaminomethyl-4-quinolinemethanols¹A. R. PATEL,² C. J. OHNMACHT,² D. P. CLIFFORD,² A. S. CROSBY,³ AND R. E. LUTZ^{4*}

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Received August 10, 1970

Nine new 4-quinoline amino alcohols were synthesized for antimalarial tests. Successful approaches for introducing the α -pyridyl group were addition of the 4-quinollythium to 2-pyridyl nitrile and to 2-pyridaldehyde. Selective hydrogenation of 8-trifluoromethyl-4-quinolyl 2-pyridyl ketone gave low yields of the quinoline α -pyridylmethanol and large yields of the tetrahydroquinoline. 7-Trifluoromethylquinoline-8-carboxylic acid added 2-pyridyllithium giving low yields of both the ketone and the α ,2-pyridyl ketone; the ester gave the pyridyl ketone in good yield but subsequent selective hydrogenation was unsuccessful.

A large number of 2-aryl-4-quinoline amino alcohols of types 1 and 2 ($R'' = \text{aryl}$)^{4,5} have proved to be active or curative against *Plasmodium berghei* in mice,⁶ but they were highly phototoxic, due possibly, it has been postulated,⁷ to enhancement of nuclear conjugation by the coplanar 2-aryl group. Substitution of CF_3 for the 2-aryl group produced only moderately active antimalarials and these were moderately phototoxic.⁸ This paper deals with syntheses and testing of 9 new analogs and investigation of some potentially useful procedures.

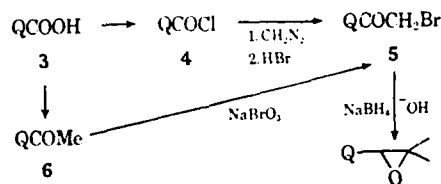


R	R'	R''	R'	R''
a Et	6,8-Me ₂	<i>p</i> -tolyl	a 6-F	<i>p</i> -tolyl
b Bu	6,8-Me ₂	<i>p</i> -tolyl	b 6-F	CF ₃
c Et	7-Cl	H	c 8-H	CF ₃
d Bu	7-CF ₃	H	d 8-CF ₃	H

 α -Dialkylaminomethyl-4-quinolinemethanols (1).—

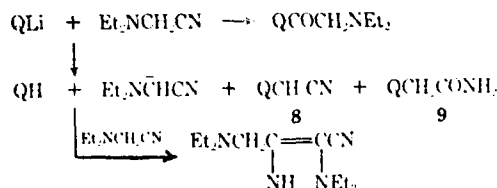
The recent and useful modification of the classical synthetic procedures⁴ involves the facile and high yield reaction of a dialkylamine with the ethylene oxide 7 which is made either from the appropriate aldehyde, if available,⁹ or from the bromo ketone 5 by NaBH_4 reduction and added base.^{9c,10} An alternative route to the bromo ketone 5, avoiding the use of CH_2N_2 ,⁴ was through the Me ketone 6 which was prepared by addition of MeLi to the acid 3. Bromination of 6 with

NaBrO_3 in HBr^{11} gave 5 in high yield, e.g., 2-*p*-tolyl-6,8-dimethyl-4-acetylquinoline (6a, 72% from 3) gave 5a in 88% yield (66% from 3 which is a better yield than *via* 4).³ The bromination of 6a directly in AcOH or by ammonium perbromide involved formation of considerable amounts of the dibromomethyl ketone as by-product.

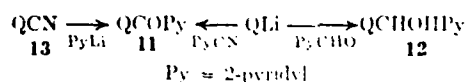


Q = substituted 4-quinolyl

Attempts toward a more direct introduction of the amino alcohol group into the quinoline through reaction of 2-trifluoromethyl-4-quinollythium⁸ with MeCN or with diethylaminoacetonitrile were unsuccessful (not surprisingly¹²). Neither the Me nor the diethylaminomethyl 4-quinolyl ketones were isolated. Evidently extensive ionization and dimerization of both nitriles had occurred, and in the case of diethylaminoacetonitrile, there occurred considerable displacement of the NEt_2 group by the 4-quinolyl anion, presumably giving 8 and 9. The structure of the one dimer characterized, namely 10, is based on anal. and ir and nmr spectra.



α -(2-Piperidyl)-4-quinolinemethanols (2).—Of particular interest as potentially useful methods are the following. The addition of 6-chloro- and 6-methyl-2-trifluoromethyl-4-quinollythiums at -70° to 2-cyanopyridine gave the known α -(2-pyridyl)-4-quinolyl ketones 11.⁸ The addition of 2-PyLi to 6,8-dimethyl-4-cyano-2-trifluoromethylquinoline also gave 11. Additions to 2-pyridaldehyde of 2-trifluoromethyl-4-quinollythium or its 6-Me derivative gave the corresponding known α -(2-pyridyl)-4-quinolinemethanols 12.³



Py = 2-pyridyl

(1) This work, largely done prior to summer 1968, was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-49-193-MD-2955. Contribution No. 838 of the Army Program on Malaria, R. E. Lutz, Responsible Investigator.

(2) Postdoctoral Research Associates.

(3) A. L. Crosby, M.S. Thesis, University of Virginia, Charlottesville, Va., 1950.

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

(5) (a) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 159 (1967); (b) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968); (c) C. J. Ohnmacht, F. Davis, and R. E. Lutz, *ibid.*, **14**, 17 (1971).

(6) T. S. Odene, P. B. Russell, and L. Itane, *ibid.*, **10**, 431 (1967). Tests were performed by Dr. Leo Rane, and results were provided through the Walter Reed Army Institute of Research.

(7) W. E. Ruthe and D. P. Jacobs, *ibid.*, **11**, 368 (1968).

(8) A. Burger and R. M. Funder, *ibid.*, **11**, 267 (1968).

(9) W. C. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *ibid.*, **11**, 1222 (1968).

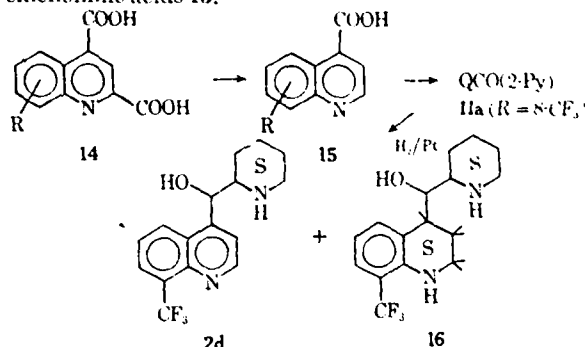
(10) E. R. Atkinson and A. J. Pattick, *ibid.*, **11**, 1223 (1968).

(11) J. W. G. *et al.*, *J. Amer. Chem. Soc.*, **68**, 1831 (1946).

(12) E. L. Ely and N. L. Johnson, *ibid.*, **75**, 1483 (1953).

4-Quinoline Amino Alcohols without a 2 Substituent (1c,d, 2d).—Three examples of these compounds were made to test the effectiveness of Cl and CF₃ groups in the 7 position and of the CF₃ in the 8 position. These, without the 2-aryl group, were not expected to be seriously phototoxic.

Syntheses started from the corresponding isatins which were prepared following published procedures.¹² Pfitzinger condensations of these with pyruvic acid to the quinoline-2,4-dicarboxylic acids 14¹⁴ and selective thermal decarboxylations in PhNO₂ or Ph₂O gave the cinchoninic acids 15.

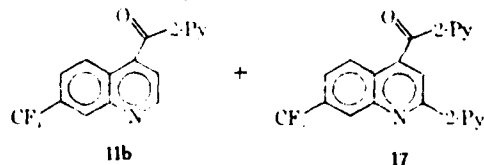


The 8-CF₃ acid 15 added 2-PyLi giving the pyridyl ketone 11a (76%). This, using Pt/H₂ under a variety of conditions, gave at best only 4% of the target α -(2-piperidyl)methanol 2d; the principal other product was the tetrahydroquinolyl analog 16 (46%). The unusually poor yield of 2d might be attributed to decreased selectivity of protonation of 11a at the pyridyl N because of the absence of the 2 substituent and/or the absence of the deterrent steric effects by 2 substituents on hydrogenation of the quinoline N ring.

An attempted preparation of 2d by the 6-step Ainy and King synthesis¹⁵ failed in the last stages.

Treatment of 7-trifluoromethylcinchoninic acid (15b) with 2-PyLi at -70° in 30% THF-Et₂O gave the desired 2-pyridyl ketone 11b but in only 16% yield. Also isolated in 12% yield was the diaddition product, α -pyridyl 2-(2-pyridyl)-7-trifluoromethyl-4-quinolyl ketone 17 which must have involved both addition of 2-PyLi at position 2 and oxidative aromatization of the resulting dihydroquinoline. These two compounds were characterized by anal. and nmr spectra.

Addition of 2-PyLi to the 7-trifluoromethylcinchoninic ester in Et₂O, unlike the addition to the acid 15b where THF was required for solubilizing the substrate, yielded the ketone 11b in 67% yield; and formation of 17 was not observed. Unfortunately in the several attempts to reduce the pyridyl ketone 11b by Pt/H₂, no pure piperidyl alcohol was isolated from the complex mixture of products.



(13) (a) S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.*, **148**, 181 (1958); (b) L. Sauer, *J. Org. Chem.*, **28**, 3780 (1963); **21**, 199 (1956).

(14) A. L. Smeat, H. Sargent, J. E. Mead, and J. B. Koepfle, *J. Amer. Chem. Soc.*, **68**, 2695 (1946).

(15) A. D. Ainy and H. King, *Proc. Roy. Soc. Ser. B*, **125**, 60 (1938).

Since the α -(2-piperidyl)-7-trifluoromethyl-4-quinolylmethanol corresponding to 17 was not obtained, the α -dibutylaminomethyl analog 1d was synthesized through the diazomethylation of the corresponding cinchoninic acid by standard procedures.^{16,19}

7-Chlorocinchoninic acid (15, R = 7-Cl) did not give the desired ketones upon treatment with MeLi or 2-PyLi. The α -diethylaminomethyl-7-chloro-4-quinolylmethanol was therefore synthesized by the classical procedure employed earlier for the dihexyl analog.¹⁶

2-Substituted- α -(2-piperidyl)-4-quinolinemethanols (2).—Three of these, the 6-fluoro-2-*p*-tolyl and 6-fluoro-2-trifluoromethyl derivatives 2a and 2b, and the 8-fluoro-2-trifluoromethyl compound 2c, were synthesized by known procedures.^{2,8} In each case, as in the many analogous syntheses in this series, only one of the two possible diastereoisomeric racemates was isolated, presumably formed predominantly by stereospecific hydrogenation.^{5c}

Biological Data.^c—The antimalarial activities of compounds 1 and 2, listed in Table I, were not outstanding. The most active, 1a and 1b, were partially curative at 640 mg/kg and active at 160 mg/kg. Only 1a effected low but significant increase in survival time at 40 mg/kg. The one tetrahydroquinoline, 16, was inactive.

TABLE I
ACTIVITIES^a AGAINST *P. berghei* IN MICE^b

Compound	640 mg/kg	160 mg/kg	40 mg/kg
1a	2C/29.1 ^c	6.8	0.8
1b	2C/27.2 ^c	16.7	2.9
1c	0.8	0.6	0.4
1d	8.5	0.1	0.1
2a	1.3	1.1	0.9
2b	9.1	3.5	0.7
2c	10.5	5.1	0.3
2d		5.9	0.5
16	0.5	0.3	0.3

^a Figures are average increases in survival time (days) of infected mice (5 per test group) beyond that of untreated controls. ^b See ref 6. ^c Two cures and an average increase in survival time of 3 mice.

Experimental Section¹⁷

2-Aryl-4-acetylquinolines (6).—In a typical example, 9.5 g (0.031 mole) of powdered 2-*p*-tolyl-6-methylcinchoninic acid followed by 200 ml of dry Et₂O was rapidly added to a vigorously stirred soln of 0.087 mole of MeLi (from 1.2 g of Li and 14 g of MeI) in 120 ml of anhyd Et₂O under N₂. After stirring for 2 add hr and hydrolysis and evapn of the ether layer, the residue was recrystd from abs EtOH: 8.1 g of 6b (86%).

α -Bromomethyl 2-Aryl-4-quinolyl Ketones (5a-d). A. — To a stirred refluxing soln of 2.75 g (0.01 mole) of 6b in 25 ml of glacial AcOH, was added over 15 min, a soln of 1.60 g (0.01 mole) of Br₂ in 15 ml of glacial AcOH, with continued refluxing for 10 min. Upon cooling and pouring onto ice, the resulting ppt was washed with NaHCO₃ soln, and recrystd from abs EtOH: 2.0 g (56%).

(16) (a) S. H. Leuke, Ph.D. Dissertation, University of Virginia, Charlottesville, Va., 1946, p 162; (b) R. E. Lutz, J. E. Colington, and S. H. Leuke, *J. Amer. Chem. Soc.*, **69**, 1260 (1947).

(17) Instruments used were: Thomas-Hoover apparatus for mp, uncorr. Anal. were correct ($\pm 0.4\%$): Gallorath Lab, Inc., and Swartzkopf Micro-analytical Lab. Vacuum sublimation of analytical samples was at 10-50° (the respective mp). Satisfactory spectra were obtained, for structural determination where required, and randomly in other cases: *ir*, Perkin-Elmer 337; *nmr*, Hitachi, P. E. R20; mass spectrograph, Hitachi, P-E, RMU 6F.

R. To a stirred slurry of 5.79 g (0.02 mole) of **6a** and 50 ml of glacial AcOH was added 1.01 g (0.0066 mole) of NaBrO, followed under heating at 100° by dropwise addition of 14 g of 48% HBr. The mixture was then poured onto ice-H₂O and the resulting ppt was recrystd from EtOH; 6.48 g (88%). The yield of **5b** by this method was 75%.

α-(Di-*n*-butylaminomethyl)-2-*p*-tolyl-6,8-dimethyl-4-quinolinemethanol-HCl (1b). A mixture of crude bromohydrin (11.1 g, 0.03 mole, obtained in 84% yield by Al(O-*i*-Pr)₃ reduction of the bromo ketone **5a**¹¹) and 19.5 g (0.015 mole) of *n*-Bu₂NH at 80-85° was stirred for 60 hr, cooled, and dild with dry Et₂O. After removing the pptd salt by filtration the soln was coned under reduced pressure and the unused *n*-Bu₂NH was then removed by vac distn. A soln of the residual viscous oil in a small amount of abs EtOH was cooled in ice and treated with ethereal HCl. The resulting ppt was recrystd from EtOH-Et₂O; 12.68 g (93%); **1a** was made similarly. Compd **1c** was prepared from the corresponding bromohydrin by the action of refluxing Et₃NH-benzene mixture (15 hr). An Et₂O soln of the base (obtained as above for **1b**) was treated with ethereal HCl, giving a hygroscopic brown dihydrochloride, which upon rapid recrystn from *i*-PrOH-Et₂O yielded 42% of analytically pure, hygroscopic monohydrochloride (**1c**), mp 135-138° dec.

Isatins.—The 6-Cl, 6-Br, 6-F, 6-CF₃, and 7-CF₃ isatins were prepd according to published procedures.¹² Mixtures of 4- and 6-substituted isatins were sep'd by the method of Sadler.¹⁰

Quinoline-2,4-dicarboxylic acids (14) were prepared from the corresponding isatins by the method of Senear, *et al.*¹⁴

Cinchonic acids (15) were obtained from the corresponding quinoline-2,4-dicarboxylic acids **14** by decarboxylation, in refluxing PhNO₂ for 1 hr, or in Ph₂O at 215° for 15 min.

α-(Bromomethyl)-7-Trifluoromethyl-4-quinolyl Ketone-HBr (5e).—A stirred soln of 12.1 g (0.05 mole) of **15b** in 60 ml of SOCl₂ was refluxed for 1.5 hr. The SOCl₂ was distd at 1 atm pressure and 100 ml of dry C₆H₆ was added and distd. A soln of the residue in 125 ml of dry Et₂O was filtered through glass wool, stored in a dropping funnel under a CaCl₂ drying tube, and added dropwise over 0.5 hr to a cooled, stirred soln of 6 g (0.14 mole) of Cl₂N₂ in 415 ml of Et₂O, a yellow ppt appearing toward the end. The mixture was stirred for 4 hr and then treated dropwise with 40 ml of 48% HBr. After 1 hr of additional stirring the tan solid **5c** was collected, washed with 30% AcOH-Et₂O, and oven-dried; 12.54 g (63%), yellow, mp 187-193° dec.

7-Trifluoromethyl-4-quinolyethylene Oxide (7a).—A soln of 9.36 g (0.021 mole) of **5c** in 75 ml of MeOH was treated with aq 5% NaHCO₃ until pH 7 was reached; it was then treated dropwise over 15 min with a soln of 1.5 g of NaBH₄ in 15 ml of H₂O to which had been added 4 ml of 2 *N* NaOH. After stirring for 1 hr, diluting with 125 ml of H₂O, and exg with petr ether (30-60°), the ext was dried (K₂CO₃) and evapd, giving 4.62 g (82%), wax product, mp 53-59°, recrystd from isoctane, 4.01 g (72%), mp 58-60°.

α-(Di-*n*-butylaminomethyl)-7-trifluoromethyl-4-quinolinemethanol Succinate (1d).—A stirred soln of **7a** (1.0 g, 0.0168 mole) and 20 ml of *n*-Bu₂NH was heated at 120° for 1.5 hr. After evapg excess *n*-Bu₂NH *in vacuo*, the residual oil was taken up in Et₂O; and the hydrochlorides were fractionally pptd by ethereal HCl. The first crop was crystn (*n*-Bu₂NH-HCl), but subsequent crops were gums from which Et₂O was decanted. Treatment of these with NaOH soln and extn with Et₂O, drying (MgSO₄), and re treating with ethereal HCl gave a tan oil which solidified upon cooling with Dry Ice-acetone; white, hygroscopic. Treatment of the salt with base and extn with Et₂O gave 3.51 g of tan oil (57%). A 125-ml Et₂O soln of this was treated with an equimolar amount (1.13 g) of succinic acid in 450 ml of Et₂O. Evapn to 400 ml and standing at 0° for several days gave 3.61 g (44%) of **1d** succinate, mp 96-97.5°; a second crop of 0.60 g (7%) was obtained ~~from~~ concn of the Et₂O soln to 100 ml (total yield 51%).

2-Pyridyl 1-Trifluoromethyl-4-quinolyl Ketone (1b). A.—Treatment of **15b** (9.67 g, 0.04 mole) with 2-PyLi (0.189 mole) in 30% THF-Et₂O at -70° and cryst the product from EtOH yielded 5.85 g of tan solid, mp 105-107°, which was then sublimed (overnight) at 110° (0.05 mm); 1.90 g (16%), colorless; mp 117-119°.

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

TABLE II

R	Reactant ^a	Products ^b
6-Cl	PyCN	QCOPy (43%)
6-Me	PyCN	QCOPy (76%)
H	PyCHO	QC(OH)OPy (43%)
6-Me	PyCHO	QC(OH)OPy (39%)
6-Me	PipCOOH	QH (23, 55%)
6,8-Me, 6-Cl	PipCOOH	None isolated
6-Me	MeCN ^c	QH (23, 61%)
6-OMe, 6,8-Cl	MeCN ^c	None isolated
6-Me	Et ₂ NCH ₂ CN ^d	QH (23, 30%); QCH ₂ CN (8a, 30%, mp 104°); ^d QCH ₂ CONH ₂ (9a, 20%, mp 200°); ^e 10 (25%) ^f
6-Cl	Et ₂ NCH ₂ CN ^d	QC(OH)CONH ₂ (9b, 50%) ^f

^a Q = Substituted 4-quinolyl; Py = 2-pyridyl; Pip = 2-piperidyl. ^b Reaction time 4 hr. ^c Worked up by column chromatography on silica gel, eluting successively with petr ether (30-60°), C₆H₆, CHCl₃, and Me₂CO. ^d Ir (Nujol) 2248 cm⁻¹ (C=N). ^e Anal. C₁₁H₁₁F₃N₂O, N; ir (Nujol) cm⁻¹, 3350, 3195 (NH₂), 1675 (C=O). ^f Bp 120° (3 mm); Anal. C₁₁H₁₁N₂O, C, H; N, calcd 25.00, found 24.43, ir (neat) 3480, 3360 (NH₂), 3970, 3940, 3830 (CH), 2175 (C≡N) and 1630 (C=C, C=N) cm⁻¹; nmr (CDCl₃) δ 0.97 (m, 12, CH₃), 2.48 (m, 8, CH₂), 3.26 (s, 2, NCH₂), and 5.26 (s, 2, NH₂). ^g Ir (KBr) 3350, 3165 (amide NH₂), 1680 cm⁻¹ (amide C=O).

B.—Ethyl 7-trifluoromethylcinchoninate (8.3 g, 0.031 mole), when treated in Et₂O as above with 0.137 mole of 2-PyLi, gave 6.25 g (67%) of **11b**, mp 111-114°. No **17** was found.

2-Pyridyl 2-(2-Pyridyl)-7-trifluoromethyl-4-quinolyl Ketone (17).—Recrystn from MeCN of the residue from the above sublimation of **11b** yielded 1.87 g of **17** (12%), mp 169°-171°.

α-(2-Piperidyl)-8-trifluoromethyl-4-quinolinemethanol-HCl (2d).—A mixture of 5.0 g (0.0165 mole) of **11a**, 1.2 ml of concd HCl, 0.25 g of PtO₂, and 125 ml of abs EtOH was hydrogenated at 2.8 kg/cm² for 1 hr; total H₂ absorbed, 0.059 mole. Filtering, evapn to 30 ml, pouring into dil NaOH, Et₂O extn, drying (MgSO₄), treatment with ethereal HCl, decantation from the gummy salt, dissolving in abs EtOH, and treatment with anhyd Et₂O until cloudy gave an oil-white ppt, which was filtered and air-dried; 0.80 g (14%), mp 165-172° dec; recrystd from *i*-PrOH-Et₂O; 0.22 g (4%); tan; mp 204-206° dec.

α-(2-Piperidyl)-8-trifluoromethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (16).—A mixture of 9.50 g (0.0315 mole) of **11a**, 5 ml of concd HCl, 0.95 g of PtO₂, and 200 ml of abs EtOH was hydrogenated as above, absorbing 0.15 mole. The base was recrystd from a small vol of MeCN; 0.60 g; colorless; mp 179-183°.

α-(2-Piperidyl)-6- and -8-fluoro-2-trifluoromethyl-4-quinolinemethanol-HCl (2b and 2c) were prepared by the previously reported reaction sequence⁹ the 4-quinolone → QBr → QC(OH) → QCOPy → 2b,c.

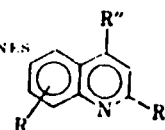
α-(2-Piperidyl)-6-fluoro-2-*p*-tolyl-4-quinolinemethanol (2a) was obtained (by published procedure⁹) from the corresponding 6-fluoro-2-*p*-tolyleinonic acid (prepared by the Pfitzinger reaction between 5-fluoroisatin and *p*-methylacetophenone).

Reactions of 2-Trifluoromethyl-4-quinolylithium Derivatives (Prepared as Previously Described).—The products were identified by comparison of mp and ir spectra with those of authentic samples.⁸ In a typical example, a slight excess of 2-cyanopyridine was added to a soln of 6-methyl-2-trifluoromethyl-4-quinolylithium in dry Et₂O under N₂ at -70°. After 2 hr the mixture was warmed to room temp and hydrolyzed (H₂O). The resulting α-(2-pyridyl) 6-methyl-2-trifluoromethyl-4-quinolyl ketone was recrystd from EtOH (30%) mp 155° (lit.⁸ mp 153°). The results of these experiments are shown in Table II.

As might have been expected the reaction between 4-quinolylithium and pipercolonic acid which has two active hydrogens and would form a diastem with two proximate negative charges, failed to give the piperidyl ketone; in the case of the 6-Me derivative the corresponding parent quinolone was obtained in 55% yield.

The reaction of 4-cyano-6,8-dimethyl-2-trifluoromethylquinoline (13^a) with 2-pyridyl in Et₂O at -70° for 4 hr under N₂ and purification by column chromatography on silica gel (CHCl₃) gave 50% of 2-pyridyl 6,8-dimethyl-2-trifluoromethyl-4-quinolyl ketone, mp 94° (lit.^a mp 98°).

TABLE III
4-FUNCTIONALIZED SUBSTITUTED QUINOLINES

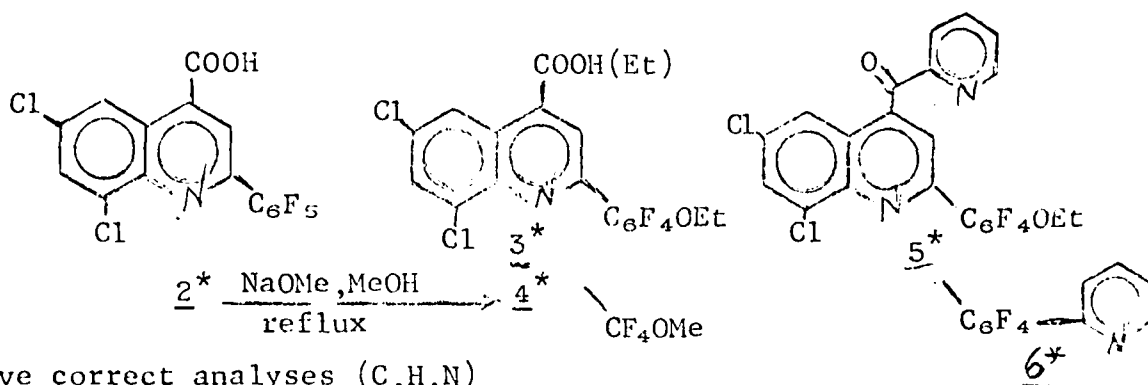
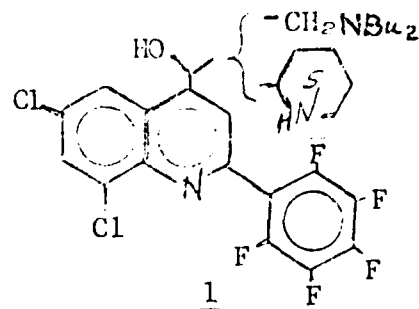


No. ^a	R	R' ^b	R'' ^c	Mp, °C ^{d-e-f}	Yield, %	Analysis ^{g-h}
23	6-Me	CF ₃	H	89		C ₁₁ H ₈ F ₃ N ₂ O
18a	6-F	CF ₃	OH	255-260	74	C ₁₀ H ₆ F ₃ NO
18b	8-F	CF ₃	OH	144-145	69	C ₁₀ H ₆ F ₃ NO
18c	6,8-F ₂	CF ₃	OH	164-165	63	C ₁₀ H ₄ F ₅ NO
19a	6-F	CF ₃	Br	93-95	78	C ₁₀ H ₆ BrF ₃ N
19b	8-F	CF ₃	Br	68-69	94	C ₁₀ H ₆ BrF ₃ N
19c	6,8-F ₂	CF ₃	Br	84-85	96	C ₁₀ H ₄ BrF ₅ N
14a	8-CF ₃	COOH	COOH	230-232 dec	92	C ₁₂ H ₈ F ₃ NO ₂
14b	7-CF ₃	COOH	COOH	235-237 dec	85	C ₁₂ H ₈ F ₃ NO ₂
14c	7-F	COOH	COOH	240-242 dec	91	C ₁₁ H ₈ FNO ₂
14d	7-Br	COOH	COOH		94	Not anal.
15a	8-CF ₃	H	COOH	232-235 dec ⁱ	85	C ₁₁ H ₈ F ₃ NO ₂
15b	7-CF ₃	H	COOH	283-286 dec ⁱ	91	C ₁₁ H ₈ F ₃ NO ₂
15c	7-F	H	COOH	289-290 dec ⁱ	35	C ₁₀ H ₆ FNO ₂
15d	7-Br	H	COOH	247-250 dec ⁱ	86	C ₁₀ H ₆ BrNO ₂
15e	6-F	PhMe	COOH	274-275	92	C ₁₇ H ₁₂ FNO ₂
20a	6-F	CF ₃	COOH	207-209	65	C ₁₁ H ₈ F ₃ NO ₂
20b	8-F	CF ₃	COOH	218-220	78	C ₁₁ H ₈ F ₃ NO ₂
25	7-CF ₃	H	COOEt	67-69 ⁱ	91	Not anal.
26	6,8-Me ₂	PhMe	COOMe	122-123	88	C ₂₀ H ₁₄ NO ₂
27	6,8-Me ₂	PhMe	COOEt	117-118	97	C ₂₁ H ₁₄ NO ₂
4a	6,8-Me ₂	PhMe	COCl	138-139 ⁱ	67	C ₁₉ H ₁₄ ClNO
6a	6,8-Me ₂	PhMe	COMe	123.5-124.5	72	C ₂₀ H ₁₄ NO
6b	6-Me	PhMe	COMe	117-118	86	C ₁₉ H ₁₃ NO
6c	6-Me	PhOMe	COMe	123-124	83	C ₁₉ H ₁₇ NO ₂
6d	6-Me	PhF	COMe	116-118	63	C ₁₈ H ₁₃ FNO
6e	6-Me	PhCl	COMe	133-134	85	C ₁₈ H ₁₃ ClNO
6f	6,8-Me ₂	PhOMe	COMe	101-102	81	C ₂₀ H ₁₄ NO ₂
24	6,8-Me ₂	PhCl	COEt	120-121	65	C ₂₀ H ₁₄ ClNO
28	6,8-Me ₂	PhMe	COCHN ₂	159-160	78	C ₂₀ H ₁₇ N ₂ O
5a ^v	6,8-Me ₂	PhMe	COCH ₂ Br	145-147	88	C ₂₀ H ₁₅ BrNO
5b	6-Me	PhMe	COCH ₂ Br	132-135	71	C ₁₉ H ₁₅ BrNO
5c	6-Me	PhOMe	COCH ₂ Br	106-108	75	C ₁₉ H ₁₅ BrNO ₂
5d	6-Me	PhF	COCH ₂ Br	134-136	72	C ₁₈ H ₁₃ BrFNO
5e	7-CF ₃	H	COCH ₂ Br	203-205 dec ⁱ	63	C ₁₂ H ₇ BrF ₃ NO·HBr ⁱ
7a	7-CF ₃	H	CH=CH ₂	60-62 ⁱ	72	C ₁₂ H ₈ F ₃ NO ^r
9a	6-Me	CF ₃	CH ₂ CONH ₂	200	20	C ₁₂ H ₁₁ ClF ₃ N ₂ O ^r
9b	6-Cl	CF ₃	CH ₂ CONH ₂	260-261	50	C ₁₂ H ₈ ClF ₃ N ₂ O ^r
21a	6-F	CF ₃	COPY	121-122	90	C ₁₀ H ₆ F ₃ N ₂ O
21b	8-F	CF ₃	COPY	130-132	62	C ₁₀ H ₆ F ₃ N ₂ O
21c	6-F	PhMe	COPY	172-174	49	C ₂₂ H ₁₅ FN ₂ O
11a	8-CF ₃	H	COPY	141-141.5	76	C ₁₀ H ₆ F ₃ N ₂ O
11b	7-CF ₃	H	COPY	118-119.5	16	C ₁₀ H ₆ F ₃ N ₂ O
17	7-CF ₃	Py	COPY	170-172 ^m	12	C ₂₁ H ₁₂ F ₃ N ₂ O
22a	6-F	CF ₃	CHOHPy	123-128	97	C ₁₀ H ₆ F ₃ N ₂ O
22b	8-CF ₃	H	CHOHPy	133-134	76	C ₁₀ H ₆ F ₃ N ₂ O
2a	6-F	PhMe	CHOHPip	165-168	33	C ₂₂ H ₁₇ FN ₂ O
2b	6-F	CF ₃	CHOHPip	256-258 dec	73	C ₁₀ H ₆ F ₃ N ₂ O·HCl
2c	8-F	CF ₃	CHOHPip	275-278 dec	62	C ₁₀ H ₆ F ₃ N ₂ O·HCl ^r
2d	8-CF ₃	H	CHOHPip	204-206 dec ⁿ	4	C ₁₀ H ₆ F ₃ N ₂ O·HCl ^r
10 ^a	8-CF ₃	H	CHOHPip	182-185 ⁿ	6-46	C ₁₀ H ₆ F ₃ N ₂ O ^r
1a	6,8-Me ₂	PhMe	CHOHN ₂ NEt ₂	217-219 dec ^r	92	C ₁₉ H ₁₄ N ₂ O·HCl ^r
1b(-HCl)	6,8-Me ₂	PhMe	CHOHCH ₂ NBu ₂ ·HCl	200-202 ^r	93	C ₁₉ H ₁₈ N ₂ O·HCl ^r
1b(base)			CHOHCH ₂ NBu ₂	78-79 ^r		C ₁₉ H ₁₈ N ₂ O
1c	7-Cl	H	CHOHCH ₂ NEt ₂	135-138 dec ⁿ	42	C ₁₉ H ₁₄ ClN ₂ O·HCl ^r
1d	7-CF ₃	H	CHOHCH ₂ NBu ₂ ·S ^r	96-97 ^r	51	C ₁₉ H ₁₂ F ₃ N ₂ O ^r

^a 16 is the 1,2,3,4-tetrahydroquinoline. ^b Ph = phenyl substituent para; Py = 2-pyridyl; Pip = 2-piperidyl. ^c 1d: S = succinic acid. ^d dec = melts with decomposition. ^e Decarboxylation solvent, PhO; ^f PhNO₂. ^g Recrystallization solvent, EtOH, unless otherwise specified as follows: ^h 2-methoxyethanol; ⁱ hexane; ^j AcOEt; ^k AcOH; ^l isooctane; ^m MeCN; ⁿ 7-PrOH-Et₂O; ^o EtOH-Et₂O; ^p MeCO-pentane. ^r Within ± 0.4%, and for C, H, except when otherwise specified: ^s for C, H, N; ^t for C, H, F; ^u for C, H, Br; ^v for N. ^w C: calcd 62.56, found 62.00. ^x C, H: calcd 49.91, 2.77, found 49.32, 2.08. ^y C: calcd, 52.68 found, 53.29. ^z A. L. Crosby, M. S. Thesis, University of Virginia, Charlottesville, Va., 1950.

Experiments Toward 6,8-Dichloro-2-perfluorophenyl-4-quinoline
Aminoalcohols of Type 1.

Synthetic efforts were frustrated by the facility of displacement of one F-atom and were discontinued. The yields of cinchophens 2 (and 3 by accompanying ethanolysis) were greatly improved by the modified Pfitzinger procedure. Reactions with 2-PyLi in Et₂O-THF or Et₂O gave 2-pyridyl ketone 5 and dipyridyl ketone 6.



Antimalarials. II.^{1a} α -(2-Piperidyl)- and
 α -(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols^{1b}

Journal of Medicinal Chemistry, 11, 267 (1968).

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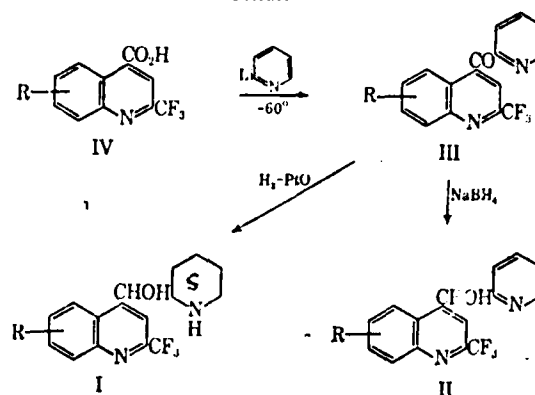
Received October 12, 1967

A series of α -(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols was synthesized in the hope that replacement of 2-aryl by 2-CF₃ would decrease the photosensitizing qualities of the 2-aryl analogs. All of the 2-trifluoromethyl derivatives carrying 6- or 8-CH₃, -CH₃O, or -Cl substituents increased the survival time of mice infected with *Plasmodium berghei*, but they retained photosensitizing properties, albeit less than the 2-aryl-substituted analogs.

A number of α -(2-piperidyl)-4-quinolinemethanols^{1a,2,3} have high antiplasmodial activity in avian infections.⁴ High activity is associated with a substituent in the 2 position of the quinoline nucleus, particularly phenyl, which will prevent oxidation at that position; the cinchona alkaloids and related compounds are rapidly biotransformed in man to the inactive carbostyryl derivatives.⁵ The most promising compound, 6,8-dichloro-2-phenyl- α -(2-piperidyl)-4-quinolinemethanol, was eighty times more active than quinine against *Plasmodium cathemerium* in the duck,⁴ but it produced severe photosensitivity and did not find clinical use in man.⁶ There is renewed interest in this type of antimalarial, both because it is firmly bound to host tissues and slowly released and therefore has repository properties, and because it has shown one of the highest recorded activities against *Plasmodium berghei* in mice.⁷ It has been theorized that phototoxicity arises because of the increased resonance conjugation from the 2-aryl group;⁷ a trifluoromethyl group in lieu of a 2-aryl group may modify this property and still prevent oxidation to the carbostyryl. We are therefore reporting the synthesis and antimalarial activity of a series of α -(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols (I) and of the corresponding α -(2-pyridyl) compounds (II) which represent a new type of analog.

The synthetic approach to amino alcohols of types I and II, starting from the corresponding quinoline-4-carboxylic acids (IV), is outlined in Scheme I and reduces the number of steps from six^{2,3} to two.^{1a} Addition of 2-lithiopyridine to the acids at -60° , followed

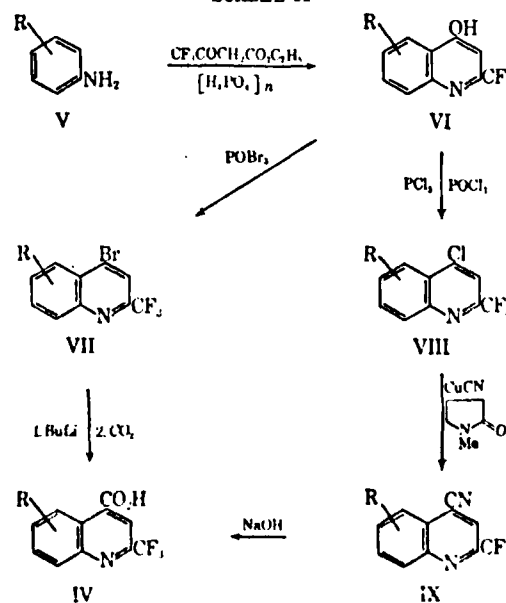
SCHEME I



by hydrolysis, gave the pyridyl ketones (III). Catalytic hydrogenation of III selectively reduced the carbonyl group and the pyridine nucleus without attacking the quinoline nucleus, giving the amino alcohols of type I, while reduction with sodium borohydride gave amino alcohols of type II.

The 2-trifluoromethylcinchoninic acids (IV) were prepared by the route outlined in Scheme II. Condensation of a substituted aniline (V) with ethyl 4,4,4-trifluoroacetoacetate⁸ in the presence of polyphosphoric

SCHEME II



(1) (a) Paper I: D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967). (b) This work was supported by the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2355, Contribution No. 297, A. Burger and R. E. Lutz co-responsible investigators.

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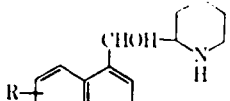
(5) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p.655.

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TABLE I
ANTIMALARIAL ACTIVITY OF
 α -(2-PIPERIDYL)-2-TRIFLUOROMETHYL-4-QUINOLINEMETHANOLS*



R	Dose, mg, kg (no. cured out of 5 mice)	Increase in mean survival time, days
6-OCH ₃	80 (1)	...
	160 (1)	...
	320 (2)	...
	640 (4)	...
6-CH ₃	160 (0)	7.1
	320 (0)	7.5
	640 (0)	8.5
8-CH ₃	160 (0)	7.3
	320 (1)	...
	640 (5)	...
6,8-(CH ₃) ₂	160 (0)	8.3
	320 (2)	...
	640 (3)	...
6-Cl	160 (0)	7.5
	320 (0)	8.7
	640 (1)	...

* Tests were carried out in mice infected with *P. berghei*.¹³ Test results were supplied by Walter Reed Army Institute of Research, Washington, D. C. Enhancement in survival time of treated animals is regarded as evidence of antimalarial activity. A compound is considered active if the mean survival time of the treated group is more than double the mean survival time (7.0 \pm 0.5 days) of the control group; it is said to be curative when the animal survives up to 9 days.

acid gave only the 4-quinolinols (VI). This reaction with ethyl acetoacetate itself gives a mixture of the 2- and 4-quinolinols, depending upon whether the amine reacts with the ester or the β -keto group.⁹ The electron-withdrawing power of the trifluoromethyl group apparently leads to exclusive reaction of the (now) electronegative β -keto group with the amine.¹⁰ The 4-quinolinols were brominated¹¹ or chlorinated¹⁰ with phosphorus oxybromide or oxychloride in excellent yields. The 4-bromoquinolines (VII) reacted readily with *n*-butyllithium at -35° , and treatment of the resulting lithioquinolines with dry CO₂ gave the required cinchoninic acids (IV). The 4-chloroquinolines (VIII) were converted to the corresponding nitriles by reaction with cuprous cyanide in *N*-methylpyrrolidone,¹² and the nitriles were then hydrolyzed to the cinchoninic acids.

Biological Data.—The antimalarial test¹³ data for the α -(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols are listed in Table I. These compounds possessed moderate antimalarial activity but were photosensitizing. The unsubstituted α -(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanol, however, was inactive. The corresponding α -(2-pyridyl) compounds were inactive, but did not cause photosensitization.

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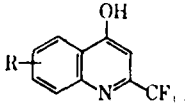
(13) F. S. Odene, P. B. Russell, and L. Itane, *J. Med. Chem.*, **10**, 431 (1967).

Experimental Section

Melting points were determined in a capillary melting point bath and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

In accordance with previous observations¹¹ regarding the properties of 2-trifluoromethylquinolines, the compounds described herein did not form salts due to the decreased basicity of the quinoline nitrogen atom. The 2-trifluoromethyl-4-quinolinols (Table II) and 2-trifluoromethyl-4-chloroquinolines (Table III) were prepared according to Dey and Joullic.¹⁰

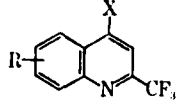
TABLE II
2-TRIFLUOROMETHYL-4-QUINOLINOLS



R	Yield, %	Mp, °C ^a	Formula ^b
6-Cl	70	274-275	C ₁₀ H ₆ ClF ₃ NO
8-Cl	55	134-135	C ₁₀ H ₆ ClF ₃ NO
6,8-Cl ₂	58	180-181	C ₁₀ H ₄ Cl ₂ F ₃ NO
6,8-(CH ₃) ₂	65	150-151	C ₁₂ H ₁₀ F ₃ NO

^a Recrystallized from EtOH. ^b All compounds were analyzed for C, H, N. Their ir spectra were as expected. ^c N: calcd, 5.32; found, 5.82.

TABLE III
2-TRIFLUOROMETHYLQUINOLINE DERIVATIVES



R	X	Yield, %	Mp, °C ^a	Formula ^b
H	Br	80	38-39	C ₁₀ H ₆ BrF ₃ N
H	CN	63	130-131	C ₁₀ H ₅ F ₃ N ₂ ^c
6-CH ₃	Br	91	70-71	C ₁₁ H ₇ BrF ₃ N
6,8-(CH ₃) ₂	Br	95	115-116	C ₁₂ H ₉ BrF ₃ N
6,8-(CH ₃) ₂	Cl	95	99-101	C ₁₂ H ₉ ClF ₃ N
6,8-(CH ₃) ₂	CN	76	126-127	C ₁₂ H ₇ F ₃ N ₂
8-CH ₃	CN	65	80-81	C ₁₂ H ₇ F ₃ N ₂
6-Cl	Br	90	119-120	C ₁₀ H ₄ BrClF ₃ N
6-Cl	Cl	92	103-104.5	C ₁₀ H ₄ Cl ₂ F ₃ N ^d
6-Cl	CN	51	142-143	C ₁₁ H ₄ ClF ₃ N ₂
8-Cl	Cl	84	58.5-59.5	C ₁₀ H ₄ Cl ₂ F ₃ N
8-Cl	CN	42	167-169	C ₁₁ H ₄ ClF ₃ N ₂
6,8-Cl ₂	Br	97	75-76	C ₁₀ H ₃ BrCl ₂ F ₃ N
6,8-Cl ₂	Cl	88	75-76	C ₁₀ H ₃ Cl ₃ F ₃ N
6-OCH ₃	Br	92	124-125	C ₁₁ H ₇ BrF ₃ NO

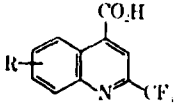
^a Recrystallized from EtOH. ^b All compounds were analyzed for C, H, N. Their ir spectra were as expected. ^c N: calcd, 12.61; found, 12.20. ^d C: calcd, 45.13; found, 45.56.

2-Trifluoromethyl-4-bromoquinolines (Table III).—In a typical preparation, a mixture of 2-trifluoromethyl-4-quinolinol (30 g, 0.14 mole) and POBr₂ (57 g, 0.2 mole) was stirred at 140° for 3 hr. The warm mixture was poured into ice-water (600 ml), and the solid material was filtered off and recrystallized from EtOH, yield 31 g.

2-Trifluoromethylcinchoninic Acids (Table IV). A. In a typical example, a solution of 4-bromo-2-trifluoromethylquinoline (55 g, 0.2 mole) in dry ether (600 ml) was added over 15 min to an Et₂O solution of *n*-BuLi (prepared from 3.5 g of Li wire and 35 g, 0.25 mole, of *n*-BuBr), stirred under N₂ at -35° for 20 min, and was then poured, with vigorous stirring, onto powdered solid CO₂. After removal of ether, the residue was dissolved in H₂O and the acid precipitated by careful acidification with AcOH. The collected solid was recrystallized from EtOAc, yield 31 g.

B.—The 4-chloroquinolines were converted to the 4-cinchoninonitriles (Table III) by the method of Newman and Boden.¹² In a typical hydrolysis, a mixture of 8-methyl-2-

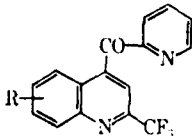
TABLE IV
2-TRIFLUOROMETHYLQUINOLINECARBOXYLIC ACIDS



R	Method	Yield, % ^a	Mp, °C ^b	Formula ^c
H	A, B	65, 51	196-197	C ₁₁ H ₈ F ₃ NO ₂
6-CH ₃	A	67	215-216	C ₁₂ H ₉ F ₃ NO ₂
8-CH ₃	B	51	199-200	C ₁₃ H ₉ F ₃ NO ₂
6,8-(CH ₃) ₂	A, B	62, 65	224-226	C ₁₃ H ₁₀ F ₃ NO ₂
6-Cl	A, B	72, 71	226-227	C ₁₁ H ₆ ClF ₃ NO ₂ ^d
8-Cl	B	18	210-212	C ₁₁ H ₆ ClF ₃ NO ₂ ^e
6-OCH ₃	A	63	238-239	C ₁₂ H ₈ F ₃ NO ₂

^a Yield from sequence B is based on the starting 4-chloroquinolines. ^b Recrystallized from EtOAc. ^c See footnote b, Table III. ^d C: calcd, 47.93; found, 47.36. ^e No N analysis.

TABLE V
2-TRIFLUOROMETHYL-4-PYRIDOYLQUINOLINES



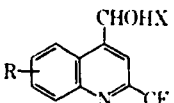
R	Yield, %	Mp, °C ^a	Formula	Analyses
H	63	130-132	C ₁₆ H ₉ F ₃ N ₂ O	C, H, N
6-CH ₃	60	125-126	C ₁₇ H ₁₁ F ₃ N ₂ O	C, H
8-CH ₃	64	98-99	C ₁₇ H ₁₁ F ₃ N ₂ O	C, H, N
6,8-(CH ₃) ₂	73	119-120	C ₁₈ H ₁₃ F ₃ N ₂ O	C, H
6-Cl	48	152-153	C ₁₆ H ₈ ClF ₃ N ₂ O	C, H
8-Cl	31	116-117	C ₁₆ H ₈ ClF ₃ N ₂ O	C, H
6,8-Cl ₂	34	138-139	C ₁₆ H ₇ Cl ₂ F ₃ N ₂ O	C, H, N
6-OCH ₃	67	132-133	C ₁₇ H ₁₁ F ₃ N ₂ O ₂	C, H, N

^a Recrystallized from EtOH.

trifluoromethylcinchoninonitrile (23.6 g, 0.1 mole) and a solution of NaOH (12 g, 0.3 mole) in H₂O (50 ml) and EtOH (120 ml) was stirred under reflux for 12 hr. The solution was evaporated to dryness, and the residue was dissolved in H₂O and filtered through Celite. The clear filtrate was acidified by dropwise addition of AcOH, and the white precipitate was collected and recrystallized from EtOAc, yield 20 g.

2-Pyridyl 4-Quinolyl Ketones (Table V).—To an ethereal solution of *n*-butyllithium (0.05 mole) at -60° was added rapidly 2-bromopyridine (8 g, 0.05 mole), and the brown mixture was stirred at -60° for 1 hr. Finely powdered 6-methoxy-2-trifluoromethylcinchoninic acid (5.4 g, 0.02 mole) was added all at once and the mixture was stirred at -60° for 2 hr. It was allowed to warm to room temperature and then hydrolyzed by addition of H₂O. The ether layer was dried (MgSO₄) and distilled

TABLE VI
2-TRIFLUOROMETHYLQUINOLINE-4-METHANOL DERIVATIVES



R	X ^a	Yield, %	Mp, °C	Recryst solvent	Formula ^b
H	Pip	50	254-255	EtOH	C ₁₁ H ₈ F ₃ N ₂ O · HCl
H	Pyr	80	115-116	MeOH	C ₁₁ H ₈ F ₃ N ₂ O
6-CH ₃	Pip	66	254-256	EtOH	C ₁₂ H ₉ F ₃ N ₂ O · HCl
6-CH ₃	Pyr	91	139-140	EtOH	C ₁₂ H ₉ F ₃ N ₂ O
8-CH ₃	Pip	60	284-286	EtOH	C ₁₃ H ₉ F ₃ N ₂ O · HCl
8-CH ₃	Pyr	100	120-122	MeOH-C ₆ H ₆	C ₁₃ H ₉ F ₃ N ₂ O
6,8-(CH ₃) ₂	Pip	55	279-280	EtOH	C ₁₃ H ₁₀ F ₃ N ₂ O · HCl
6,8-(CH ₃) ₂	Pyr	86	128-129	MeOH-C ₆ H ₆	C ₁₃ H ₁₀ F ₃ N ₂ O
6-Cl	Pip	45	265-266	EtOH	C ₁₁ H ₆ ClF ₃ N ₂ O · HCl
6-Cl	Pyr	89	149-150	EtOH-petr ether ^d	C ₁₁ H ₆ ClF ₃ N ₂ O
8-Cl	Pip	28	248-250	EtOH	C ₁₁ H ₆ ClF ₃ N ₂ O · HCl
8-Cl	Pyr	78	124-125	MeOH-C ₆ H ₆	C ₁₁ H ₆ ClF ₃ N ₂ O
6,8-Cl ₂	Pip	33	262-264	EtOH	C ₁₁ H ₅ Cl ₂ F ₃ N ₂ O · HCl
6,8-Cl ₂	Pyr	82	138-139	EtOH-petr ether ^d	C ₁₁ H ₅ Cl ₂ F ₃ N ₂ O
6-OCH ₃	Pip	52	241-242	EtOH	C ₁₂ H ₉ F ₃ N ₂ O ₂ · HCl
6-OCH ₃	Pyr	100	172-173	MeOH	C ₁₂ H ₉ F ₃ N ₂ O ₂

^a Pip = 2-piperidyl; Pyr = 2-pyridyl. ^b See footnote b, Table III. ^c N: calcd, 7.35; found, 7.80. ^d Bp 30-60°.

to give a yellow solid, which was recrystallized from EtOH as yellow needles, yield 4.7 g.

α-(2-Piperidyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—A solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (4 g) in EtOH (300 ml) containing 1 molar equiv of HCl was shaken with PtO₂ (200 mg) at 2.8 kg/cm² under H₂. The reduction was stopped when 4 equiv of H₂ had been absorbed; the catalyst was filtered off, and the residue was concentrated until crystallization began. Recrystallization from EtOH gave white needles, yield 2.2 g.

α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—NaBH₄ (0.26 g, 0.007 mole) was added portionwise to a stirred solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (2.2 g, 0.007 mole) in MeOH (200 ml), and the mixture was stirred at room temperature for 2 hr. MeOH was removed under reduced pressure and the residue was taken up in ether, washed (H₂O), and dried (MgSO₄). The ether was distilled, and the residue was recrystallized from MeOH, yield 2.3 g.

Acknowledgment.—This study has profited from frequent and helpful discussions with Professor R. E. Lutz and Drs. D. W. Boykin, Jr., and A. R. Patel of the University of Virginia.

Antimalarials. 7. Bis(trifluoromethyl)- α -(2-piperidyl)-4-quinolinemethanols¹

Journal of Medicinal Chemistry, 14, 926 (1971).

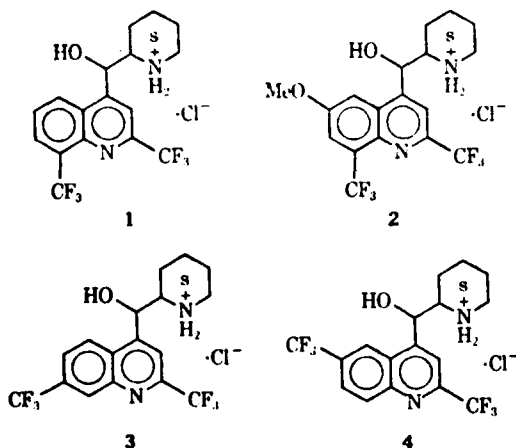
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Received April 12, 1971

The 2,6-, 2,7-, and 2,8-bis(trifluoromethyl)- α -(2-piperidyl)quinolinemethanols, and the 6-methoxy derivative of the latter, have been synthesized from the appropriate 4-quinolones, through the 4-bromoquinolones, CO₂ carboxylations of the 4-Li derivatives, additions of 2-PyrLi, and H₂/Pt reductions of the resulting pyridyl ketones. An attempt to obtain the 2,5-bis(trifluoromethyl) analog utilized the corresponding 4-quinolone formed as a by-product in the synthesis of the 2,7 isomer; addition of the 4-Li derivative to 2-pyridaldehyde gave the α -pyridylmethanol, but subsequent H₂/Pt reduction of this gave only the 4-dihydroquinolone- α -(2-piperidyl)methanol.

The α -(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols carrying OCH₃, CH₃, or Cl in positions 6 or 8 have consistently shown only moderate or slight antimalarial activities against *Plasmodium berghei* in mice, and they were also moderately phototoxic.^{3a} The synthesis of the 2,8-bis(trifluoromethyl) analog, **1**, begun before decision had been made to terminate work in this series, was nevertheless completed^{1c} for comparison with the 9-phenanthrene amino alcohols where 3,6-disubstitution of CF₃ groups had brought a very considerable increase in antimalarial activity.⁴ When this compd **1** proved to be curative at 20 mg/kg^{1d,5} and relatively nonphototoxic,^{1d,6} the synthesis of the 2,7 and 2,6 analogs **3** and **4** were undertaken to initiate evaluation of the pharmacological effects of different nuclear positions of 2 or more CF₃ groups with or without additional substituents.



Four target drugs **1-4** were synthesized each in 4 steps from the corresponding 4-quinolones **5a-5d** by adaptations of known procedures,^{3,7} as follows. Conversion by POBr₂ into the 4-bromoquinolones **6a-6d**

(1) (a) This work was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator. (b) Contribution No. 927 of the Army Research Program on Malaria. (c) Presented in part at the Southeast Regional American Chemical Society Meeting, Richmond, Va., Nov. 1969, Abstract 255. (d) Antimalarial test results were supplied by the Walter Reed Army Institute of Research.

(2) Postdoctoral Research Associates.

(3) (a) R. M. Parker and A. Burgess, *J. Med. Chem.*, **11**, 267 (1968); (b) A. R. Patel, C. J. Ohnmacht, D. P. Chatterjee, A. B. Crosby, and R. E. Lutz, *ibid.*, **14**, 198 (1971); (c) D. W. Boykin, A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

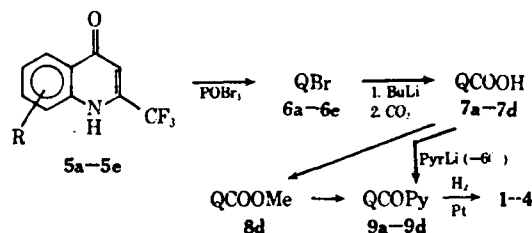
(4) E. A. Nudell, *et al.*, in preparation.

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

(6) W. E. Kothe and D. P. Jacobsen, *ibid.*, **11**, 366 (1968).

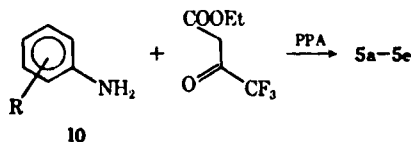
(7) A. S. Dey and M. M. Joudy, *J. Heterocycl. Chem.*, **2**, 113 (1965).

and CO₂ carboxylation of the 4-Li derivative gave cinchoninic acids **7a-7d**. Addition of 2-PyrLi gave the pyridyl ketones **9a-9d**, but only **9a,b** were obtained in good yields; **9d** was best obtained through the ester **8d**. Reductions with H₂/Pt gave good yields of **1** and **2**, but mediocre yields of **3** and **4**.



Q = substituted 4-quinolyl; Pyr = 2-pyridyl; a, R = 8-CF₃; b, R = 8-CF₃-6-OMe; c R = 7-CF₃; d, R = 6-CF₃; e, R = 5-CF₃.

The 4-quinolones **5a-5e** were obtained by PPA condensation of the appropriate trifluoromethylaniline (**10**) and ethyl 4,4,4-trifluoroacetoacetate in adaptation of previously described procedures.^{3a,7} However, 3-trifluoromethylaniline gave a mixture of 2,7- and 2,5-bis-

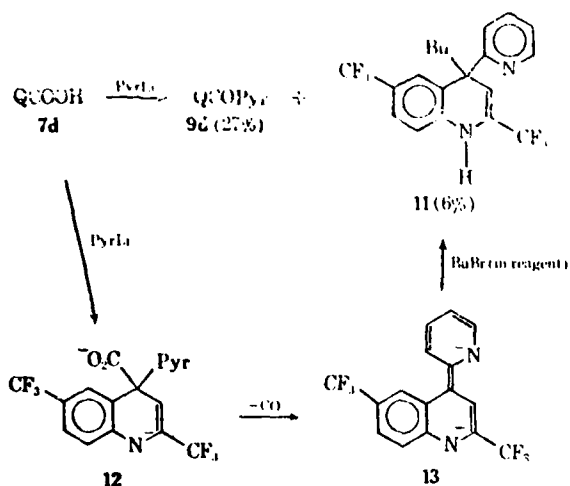


(trifluoromethyl)quinolones, **5c** and **5e**; this was best converted directly to a mixture of the 4-bromo derivatives, at which point it was separated into **6c** and **6e**.

The addition of 2-PyrLi to 2,6-bis(trifluoromethyl)cinchoninic acid (**7d**) gave, besides 27% of the pyridyl ketone **9d**, a 6% yield of a second product to which the structure **11** is assigned on the basis of anal. and ir, nmr, and mass spectra. The latter indicated formation of a fragment of relative intensity 100 corresponding to loss of Bu, and another of 32 corresponding to loss of Pyr.

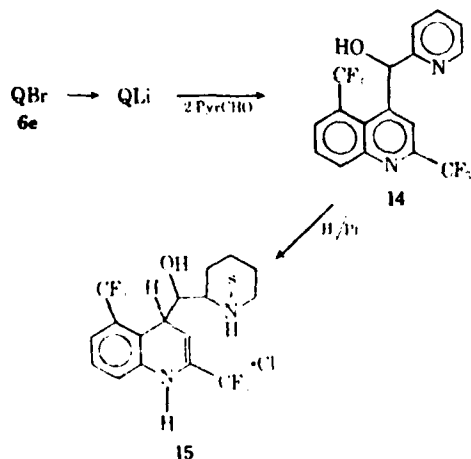
The formation of **11** is reasonably interpreted in terms of reversible Michael addition of 2-PyrLi to the Li carboxylate of **7d** to give dianion **12**, subsequent loss of CO₂ giving the new dianion **13**, followed by C-alkylation by BuBr present in the reagent to give the mono-anion of **11**. It may be significant that in the PyrLi reaction with ester **8d**, **11** was not detected as a product; and the pyridyl ketone **9d** was obtained in 55% yield.

In utilizing the limited amount of 2,5-bis(trifluoromethyl)-4-quinolone (**5e**), produced in the synthesis



of the isomers from 3-trifluoromethylaniline, it was feared that the PyrLi addition might be impeded by steric effects of the 5 substituent. Consequently this quinolone was converted through the 4-bromoquinoline **6e** to the Li derivative which was added successfully to 2-pyridaldehyde, giving the pyridyl alcohol **14** (37%) after tedious chromatographic work-up. Unfortunately, catalytic hydrogenation of this gave the dihydroquinoline which is presumed to be α -(2-piperidyl)-2,5-bis(trifluoromethyl)-1,4-dihydro-4-quinolinemethanol-HCl (**15**; nmr; 4 H, exchangeable by D₂O). Possibly this overreduction was facilitated by the appreciable release of steric strain in the quinoline 4,5-group nonbonded interaction which, conversely, would in some degree oppose the otherwise facile oxidation of the dihydroquinoline to the quinoline.

It is noteworthy that all of the reductions, of the four 2-pyridyl ketones **9a-9d** and also the 2-pyridylmethanol **14**, were in the main stereospecific, giving in each case as the isolated pure product one only of the theoretically possible diastereoisomers (racemates). It is hoped that the stereoisomer of **1** will be isolated in the large scale synthesis now under way,⁹ and that ir and nmr study will lead to configurational and conformational assignments, both here and, by analogy, in other cases where only one form has been obtained.



Biological Activities.¹⁴ Antimalarial tests^{14,5} (Table I) showed target compounds **1-4** to be curative against

(9) E. F. Hume, Acropet Solid Propulsion Co., work in progress.

TABLE I
ANTIMALARIAL ACTIVITIES* AGAINST
P. berghei IN MICE

Compd	Antimalarial act.				
	Dose, mg/kg				
	10	20	40	80	160
1 ^c	12.5 ^c	4 ^(*)	5 C		
2 ^d	11.5	1 C	2 C	5 C	
3	1.9	10.9	3 C	5 C	
4	0.7	7.7	14.3	2 C	5 C

* Expressed as increases in mean survival times, in days, and "numbers of cures" [C = cures], in 5 mice. A compd is considered to be active if the mean survival time of the treated group is more than double that of the control group (7.0 \pm 0.5 days); and it is said to be curative when the animal survives up to 6 days. ^c Also active at 120 mg/kg against *P. gallinacium* in chicks.^{14,5} ^d The corresponding 2-pyridyl ketone was inactive at 640 mg/kg. ^e See ref 1d and ref 5.

P. berghei in mice at 160 mg/kg or lower, and to compare very favorably with the 3,6-disubstituted 9-phenanthrene amino alcohols.⁴ Furthermore, the phototoxicities of these compds were relatively low.^{14,6} The most active of these, the 2,8-bis(trifluoromethyl) compd, **1**, which was curative at 20 mg/kg, has now been prepared on a large scale⁹ and is being evaluated further with promising results.

The one dihydroquinoline α -(2-piperidyl)methanol (**15**) with 2,5-bis(trifluoromethyl) groups obtained, proved to be inactive toward *P. berghei* in mice.^{14,5}

Because of the suspicion formerly held^{6,9} that there might be a relation between phototoxicity and uv absorptivities, these values have been assembled in Table II.

TABLE II
UV ABSORPTIVITIES OF AMINO ALCOHOLS 1-4 IN MeOH

Uv absorptivities		Uv absorptivities		Uv absorptivities		Uv absorptivities	
Compd		Compd		Compd		Compd	
nm	ϵ^*	nm	ϵ^*	nm	ϵ^*	nm	ϵ^*
222	46.7	236	52.5	226	46.0	225	42.1
283	6.6	284	5.8	281	5.4	279	5.8
304	4.0	294	5.3	304 ^b	3.0	309	3.2
318	3.1	326	7.4	318	1.6	322.5	3.1
		338	8.5				

* Shoulder.

Experimental Results¹⁰

5-Methoxy-2-nitrobenzotrifluoride, mp 30-32° (lit.,¹¹ mp 30°), was prepd in 80% yield by refluxing a soln of 5-chloro-2-nitrobenzotrifluoride in KOH-MeOH soln (4 hr).¹¹

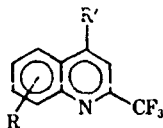
5-Methoxy-2-aminobenzotrifluoride (10b) was prepd by hydrogenation of the above nitro compd (3.25 g, 0.195 mole) with 10% Pd/C (0.15 g) in 200 ml of MeOH (5 hr). The yield of distd product was 33.2 g (89%), bp 97-98° (9 mm). The hydrochloride was recrystd from EtOH; mp 229-231° dec. Anal. (C₇H₇ClF₃NO)₂, C, H, N.

Quinolones 5a-5e, bromoquinolines 6a-6e, cinchoninic acids 7a-7d, pyridyl ketones 9a-9d, and 8-(2-pyridyl) methanols 1-4, and 15 were prepd by adaptations of previously described procedures.¹⁻⁷ Specific minor variations are listed in Table III and in the following paragraphs.

(9) E. R. Atkinson and A. J. Puttick **13**, 537 (1970), and refs cited.

(10) Satisfactory spectra were obtained, where required for structural determination and randomly in other cases. Instruments used were Thomas-Hoover apparatus for mp, ir, Perkin-Elmer 337, nmr, Hitachi PE-R 20, mass spectrograph, Hitachi PE-RM 6E. Microanalyses (Cagnoto Lab Inc) were correct within $\pm 0.4\%$.

(11) J. H. Brown, C. W. Suckling, and W. B. Whaley, *J. Chem. Soc.*, 875 (1939).

TABLE III
 2-TRIFLUOROMETHYL-4-QUINOLINE DERIVATIVES^a


Compd	R	R'	Mp, °C	% yield	Analysis ^b
5a ^{d,e}	8-CF ₃	OH	128-132	75 ^b	C ₁₁ H ₇ F ₆ N ₂ O ^g
5b ^{d,f}	6-OMe-8-CF ₃	OH	172-174	31	C ₁₂ H ₇ F ₆ N ₂ O ^g
5c ^{b,c}	7-CF ₃	OH	289-290	1	C ₁₁ H ₇ F ₆ N ₂ O ^g
5d ^{c,d}	6-CF ₃	OH	279-283	70	C ₁₁ H ₇ F ₆ N ₂ O ^g
5e ^{c,b}	5-CF ₃	OH	319-321 dec	1	C ₁₁ H ₇ F ₆ N ₂ O ^g
6a ^{b,d}	8-CF ₃	Br	62-64	95	C ₁₁ H ₆ BrF ₆ N ₂ O ^g
6b ^{b,d}	6-OMe-8-CF ₃	Br	164-166	91	C ₁₂ H ₆ BrF ₆ N ₂ O ^g
6c ^{b,d}	7-CF ₃	Br	106-108	67 ^m	C ₁₁ H ₆ BrF ₆ N ₂ O ^g
6d ^d	6-CF ₃	Br	73-75	77	C ₁₁ H ₆ BrF ₆ N ₂ O ^g
6e ^{d,g}	5-CF ₃	Br	49-51	18 ^m	C ₁₁ H ₆ BrF ₆ N ₂ O ^g
7a ^h	8-CF ₃	COOH	228-230.5	86	C ₁₂ H ₇ F ₆ N ₂ O ^g
7b ^{d,h}	6-OMe-8-CF ₃	COOH	246-248	57	C ₁₃ H ₇ F ₆ N ₂ O ^g
7c ^h	7-CF ₃	COOH	199-200.5	90	C ₁₂ H ₇ F ₆ N ₂ O ^g
7d ^h	6-CF ₃	COOH	216-218	87	C ₁₂ H ₇ F ₆ N ₂ O ^g
8d ^{d,i}	6-CF ₃	COOMe	130-131.5	100	C ₁₃ H ₇ F ₆ N ₂ O ^g
9a ^{b,d}	8-CF ₃	COPyr	128-129.5	61	C ₁₇ H ₁₀ F ₆ N ₂ O ^g
9b ^{b,d}	6-OMe-8-CF ₃	COPyr	164-165	90	C ₁₈ H ₁₀ F ₆ N ₂ O ^g
9c ^{b,d}	7-CF ₃	COPyr	124.5-125.5	27	C ₁₇ H ₉ F ₆ N ₂ O ^g
9d ^{b,e}	6-CF ₃	COPyr	138.5-140	13 ⁿ , 55 ^o	C ₁₇ H ₉ F ₆ N ₂ O ^g
14 ^{d,e}	5-CF ₃	CHOHPyr	107-109	37	C ₁₇ H ₁₀ F ₆ N ₂ O ^g
1 ^c	8-CF ₃	CHOHPip-HCl	259-260 dec	53	C ₁₇ H ₁₇ ClF ₆ N ₂ O ^g
2 ^b	6-OMe-8-CF ₃	CHOHPip-HCl	298-300 dec	86	C ₁₈ H ₁₉ ClF ₆ N ₂ O ^g
3 ^b	7-CF ₃	CHOHPip-HCl	244-245 dec	24	C ₁₇ H ₁₇ ClF ₆ N ₂ O ^g
4 ^c	6-CF ₃	CHOHPip-HCl	197-199 dec	22	C ₁₇ H ₁₇ ClF ₆ N ₂ O ^g
1,4-Dihydroquinolines					
15 ⁱ	5-CF ₃	H, CHOHPip-HCl	193 dec ^r	27	C ₁₇ H ₁₇ ClF ₆ N ₂ O ^g
11 ^b	6-CF ₃	Pyr, Bu	170-171	6	C ₂₀ H ₁₈ F ₆ N ₂ ^g

^a Pyr = 2-pyridyl; Pip = piperidyl. Recrystn solvent, or other purification methods are indicated: ^b EtOH, ^c MeCN, ^d Sublimed, ^e Hexane, ^f C₆H₆, ^g Column chromatog., ^h PhMe, ⁱ MeOH, ^j Me₂CO. ^k Yield of crude reaction product which was used directly in the next step. ^l Could not be fully sepd; total yield of mixt after crystn from EtOH, 70%. ^m Yield of pure material from a mixt of 5c and 5e. ⁿ Yield from the acid 7d. ^o Yield from the ester 8d. ^p Anal. were within $\pm 0.2\%$ for C, H, N or ^q for C, H. ^r n_D^{25} 227, 242, 354 (n_D^{25} 2.14, 6.0, 3.1).

6-Methoxy-2,8-bis(trifluoromethyl)-4-quinolone (5b) was purified by recrystn from C₆H₆ rather than the often less effective soln in base and pptn by acid.^{1,5}

2,5- and 2,7-Bis(trifluoromethyl)-4-bromoquinolines (6e,c.)
A mixture of 2,5- and 2,7-bis(trifluoromethyl)-4-quinolones (39.2 g, 0.14 mole; recrystd from EtOH), and POBr₂ (57 g, 0.2 mole), was stirred at 140° for 3 hr and poured into ice H₂O. The product was extd with CH₂Cl₂ and recrystd from EtOH, giving pure 6c (30.17 g, 63%), mp 104-106°. The residue obtd upon evapn of the EtOH liquors (15.13 g, 32%), was chromatogd on a 5-cm column of 1 kg of Woelm neutral alumina (activity no. 1). Eluting with hexane and 1, 2, 5, and 10% benzene-hexane gave 1.84 g of addnl 6e (total yield 67%), 8.79 g (18%) of 6e, mp 47-50°, and a small quantity of a mixt of these.

6-Methoxy-2,8-bis(trifluoromethyl)cinchoninic Acid (7b).
The required 4-Li derivative was prepd by addn of the very slightly Et₂O-sol 4-Br deriv 6b to a slight excess of BuLi in anhyd Et₂O and stirring for 2.5 hr. Pouring the reaction mixt onto dry powdered CO₂ gave 7b (57%), mp 246-248°. A decrease in the prepn time of the Li compd led to a decrease in the yield of 7b and a corresponding increase in recovered 6b.

Methyl 2,6-bis(trifluoromethyl)cinchoninate (8d) was prepd in quant yield by 45-min refluxing of a MeOH soln of crude acid chloride which had been prepd by the reaction of 7d with SOCl₂ (2 hr).

α -(2-Pyridyl)-2,6- and -2,7-bis(trifluoromethyl)-4-quinolyl ke-

tones (9c,d) were isolated by column chromatog (Florisil, CHCl₃ as eluent) and recrystd from EtOH. Concn of recrystn liquors from 9d yielded 11 (6%), pale yellow: ν (KBr) 3175 cm⁻¹ (NH); nmr (CDCl₃-DMSO-d₆): δ 9.00 (s, 1, NH), 8.60 (m, 1), 7.61 (m, 1), 7.12 (m, 5), 5.00 (s, 1, H-3), 2.2 (m, 2), 0.95 (m, 7); mass spec (70 eV) m/e (rel intensity) 400 (2), 381 (5), 343 (100), 322 (32), 303 (4), 273 (16), 78 (20).

α -(2-Pyridyl)-2,5-bis(trifluoromethyl)-4-quinolinemethanol (14). A soln of 6.4 g (0.06 mole) of 2-pyridaldehyde in 40 ml of anhyd Et₂O was added dropwise at -70° under N₂ to a stirred Et₂O soln (150 ml) of 2,5-bis(trifluoromethyl)-4-quinolylithium [from 7.93 g (0.023 mole) of 6e and 17.2 g (0.05 mole) of 2,2', BuLi in hexane soln], with stirring for an addnl 2 hr. After hydrolysis the Et₂O layer was evapd to dryness, and the residue was chromatogd on 400 g of Florisil (C₆H₆ as eluent). The crude oil obtd was recrystd from hexane, 3.64 g of 14 (tan), mp 95-103°. Sublimation at 70° (0.05 mm) returned 3.19 g (37%), mp 102-105°.

The Bis(trifluoromethyl)- α -(2-piperidyl)-4-quinolinemethanols (1 4) and the 5-Trifluoromethyl-1,4-dihydro Derivative (15).
The catalytic hydrogenations of 9a-9d and of 14 were carried out by published procedure in EtOH with PtO₂. After filtration through Celite, the EtOH was vacuum evapd. Crude 3 and 4 were initially purified by trituration of the residue with Et₂O and filtration.

Antimalarials. 5. α -Dibutylaminomethyl- and
 α -(2-Piperidyl)-3-quinolinemethanols¹

Journal of Medicinal Chemistry, 14, 17 (1971)

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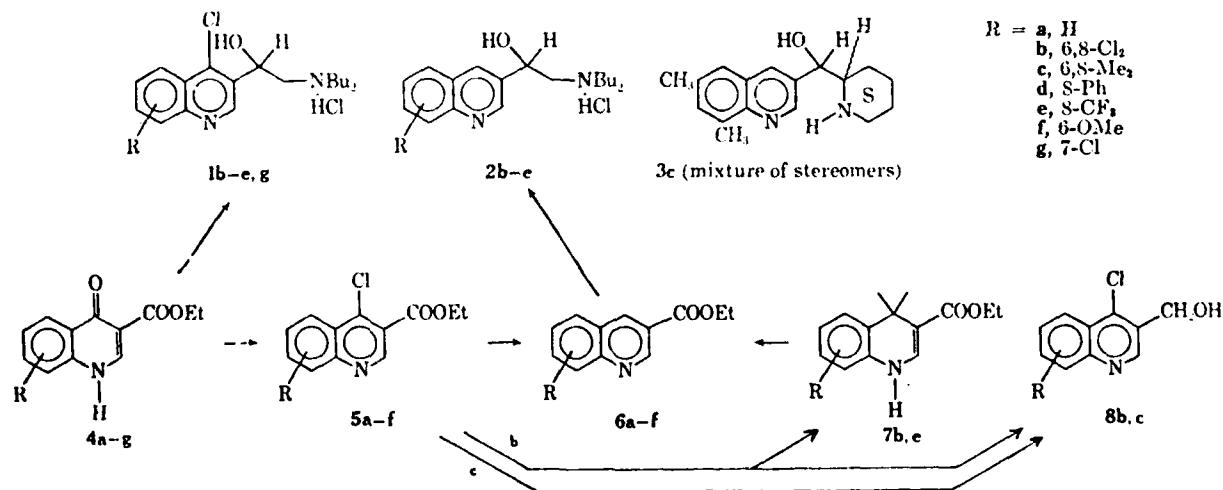
Received June 25, 1970

Eight α -dialkylaminomethyl-3-quinolinemethanols without 2 substituents were synthesized from 4-quinolone-3-carboxylic esters, by conversions into the 4-chloro esters and reductive 4-dechlorinations, and thence through the acids, diazomethyl ketones, and epoxides. Attempts to prepare α -(2-piperidyl) analogs involved complications due to nuclear additions of 2-pyridyllithium and nonselectivity in hydrogenations of the pyridyl ketones. One example, α -(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol, fortuitously, was produced by Pt-H₂ on 4-chloro-6,8-dimethyl-3-quinolyl 2-pyridyl ketone (a diastereoisomeric mixture). These 3-amino alcohols were inactive against *Plasmodium berghei* in mice.

In continuation of the search for improved antimalarials, eight new α -aminoalkyl-3-quinolinemethanols without 2 substituents,^{1b} 1-3, have been synthesized under the program of moving the amino alcohol group away from the 4 location in quinine and its many synthetic analogs. The hope was to find active drugs with a minimum of the phototoxicity so common to the 2-aryl-4-amino alcohols. As features of possible significance, these compounds lack the quasiconjugation of the amino alcohol group with the quinoline nuclear C=N=C system which is involved in the 4-quinoline amino alcohol series, and they have two rather than three nuclear carbons intervening between the quinoline N and the amino alcohol group.

obtainable by condensation of the appropriate aniline with ethoxymethylenemalonate ester.² Six 4-chloro esters 5a-f were made from these by the action of POCl₃.

Reductive 4-dechlorinations of 5 to 6 were accomplished by variations of previously reported hydrogenolyses, using Pd-C⁴ or Raney Ni⁵ as catalyst. In four cases, 5a, c, d, and f, the dechlorinations proceeded well using 10% Pd-C in glacial AcOH at 50°. However, 5e under these conditions gave low and nonreproducible yields of 6e along with an overreduction product, the 1,4-dihydroquinoline 7e; and when the Pd-C reduction was carried out in ethanolic KOH at 50° the dihydroquinoline 7e became the chief product (61%). This dihydro compound 7e in a second step underwent



The starting materials for these synthesis were the 4-quinolone-3-carboxylic esters 4a-g which were easily

S dehydrogenation in good yield to the desired 3-carboethoxyquinoline 6e.

Attempted Pd-C and Raney Ni 4-monodehalogenation of the 4,6,8-trichloro derivative 5b was unsuccessful. However, NaBH₄ reduction of 5b in cold 2-methoxyethanol gave the dihydro-4-dehalogenated ester 7b (39%) along with 4,6,8-trichloro-3-quinolinemethanol (8b), a result consistent with published observations.^{4,6}

* To whom correspondence should be addressed.

(1) (a) Supported by U. S. Army Medical Research and Development Command, Contract No. DA-19-193-MD-2955. (b) Contribution No. 855 to the Army Research Medical Program on Malaria, R. E. Lutz, Responsible Investigator. (c) Work reported at the Southern Regional American Chemical Society Meeting, Richmond, Va., Nov. 1969, abstract 20. (d) An independent and parallel program of synthesis of six α -dialkylaminomethyl 2-(6-chlorophenyl)-3-quinolinemethanols has been completed under Contract No. DADA-17-67-C-7053 with Monsanto Research Corp., Boston, Mass., P. F. Donovan and W. R. Smith. "Synthesis of Quinolone-methanol Antimalarial Drugs", Final Report, May 1969. Annual Progress Report, Feb. 1969. For comparison, and with permission of WRMB and the Monsanto Research Corp., the β -amino alcohols are listed in Table VII. Experimental details are to be found in the reports cited.

(2) (a) Post-doctoral Research Assistant; (b) M. S. Thesis, University of Virginia, 1969; (c) preliminary work toward starting materials was done by D. P. Clifford and A. R. Patel, Post-doctoral Research Assistants.

(3) (a) C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946). (b) J. H. Wilkinson, *J. Chem. Soc.*, 161 (1950). (c) W. Riegel, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1261 (1946).

(4) C. E. Kaslow and W. R. Clark, *J. Org. Chem.*, **18**, 55 (1953).

(5) (a) R. E. Lutz, G. Ashburn, and R. J. Rowlett, Jr., *J. Amer. Chem. Soc.*, **68**, 1422 (1946); (b) V. S. Day and M. M. Joshi, *J. Heterocycl. Chem.*, **2**, 113 (1964); (c) K. N. Campbell, *et al.*, *J. Org. Chem.*, **11**, 401 (1946).

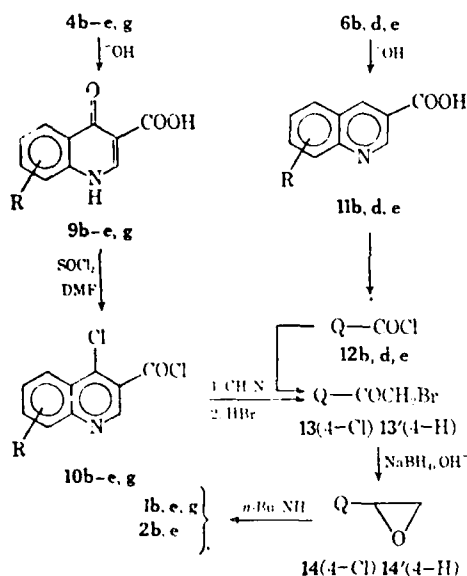
(6) (a) G. N. Walker and B. N. Weaver, *ibid.*, **28**, 181 (1963); (b) M. S. Brown and H. Rapoport, *ibid.*, **28**, 324 (1963).

Subsequent *S* dehydrogenation of **7b** gave the desired quinoline **6b** (92%).

Interestingly, NaBH₄ in 2-methoxyethanol did not dehalogenate 6,8-dimethyl-4-chloro-3-carbethoxyquinoline but instead brought about reduction of the 3-carbethoxy group to the methanol **8c** (53%).

α -Di-*n*-butylaminomethyl-3-quinolinemethanols.—

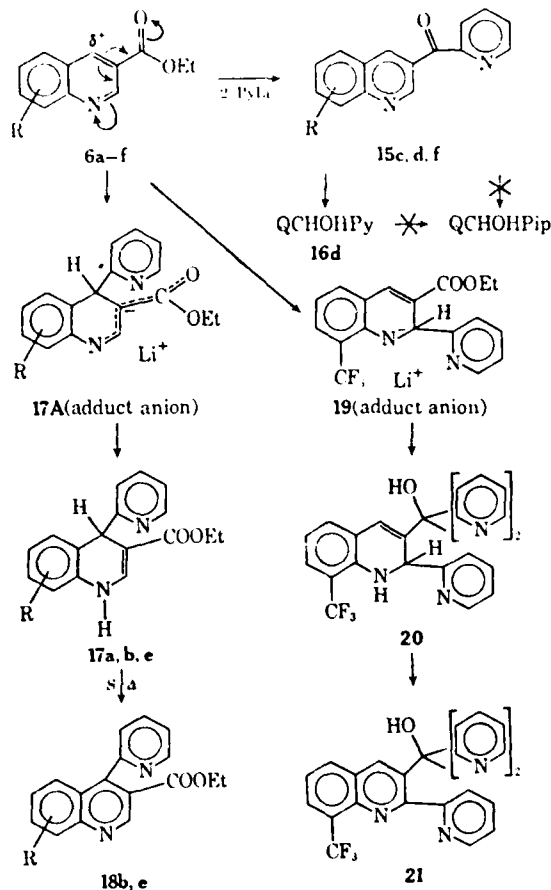
Seven of these, **1b-e**, **g**, and **2b-e**, were prepared by adaptations of the standard scheme.⁷ The 3-carbethoxy-4-quinolones and quinolines **4b-e**, **g** and **6b**, **d**, **e** were converted into the acids **9b-e**, **g** and **11b**, **d**, **e** and then by SOCl₂ into the acid chlorides **10b-e**, **g** and **12b**, **d**, **e**. DMF was required as catalyst in the latter reaction with the quinolones. Diazomethylations of the acid chlorides followed by hydrobromination without isolation of the diazoketones gave the bromo ketones **13** and **13'**. These were converted into the epoxides **14** and **14'** by NaBH₄ reduction and dehydrohalogenation of the resulting bromohydrins by accompanying or subsequently added base. Condensation of the epoxides with *n*-Bu₂NH gave the target amino alcohols **1b-e**, **g** and **2b**, **e**.



α -(2-Piperidyl)-3-quinolinemethanols (3).—The Boykin procedure for the preparation of α -(2-pyridyl)-3-quinolyl ketones from 3-quinolinecarboxylic acids, by addition of 2-pyridyllithium followed by selective catalytic reduction of the pyridyl ring,⁸ was not generally successful. Two of the acids without a substituent in the 4 position, **11d** and **11e**, gave only low yields of the desired 2-pyridyl ketones **15d** and **e**.

The addition of 2-pyridyllithium to 3-carboxylic esters was therefore investigated with interesting results of limited usefulness. To a significant extent addition occurred at the carbethoxy group of the 6,8-dimethyl, 8-phenyl, and 6-methoxy esters **6c**, **d**, **f**, giving 2-pyridyl ketones **15c**, **d**, **f** (15, 66, and 66%, respectively). On the other hand, the reactions with the parent ester and the 6,8-dichloro and 8-trifluoromethyl analogs, **6a**, **b**, **e**, gave the 4-(2-pyridyl)-1,4-dihydro-3-

carbethoxyquinolines **17a**, **b**, **e** in yields of 0.7, 18, and 20%, respectively. The structures **17** were assigned on the basis of elemental analyses, ir and nmr spectra, and *S* dehydrogenation of two of them (**17b**, **e**) to the 4-pyridyl-3-carbethoxyquinolines **18b**, **e**. The nmr spectra of the latter, **18b**, **e**, showed characteristic quinoline H-2



protons as sharp singlets at δ 9.58 and 9.46, respectively, which were assignable as such on the basis of the known chemical shifts of δ 9.36 \pm 0.02 for the H-2 protons of 4-phenyl-3-carbethoxyquinolines⁹ and the distinctive upfield chemical shifts for the H-4 protons of 2-substituted quinolines.¹⁰ Only in the reaction of **6e** was a second product isolated (11%), which appears to be the result of addition of pyridyllithium to the quinoline nucleus, and to which the structure **20**, α -bis(2-pyridyl)-2-(2-pyridyl)-1,2-dihydro-8-trifluoromethyl-3-quinolinemethanol, is tentatively assigned on the basis of elemental analysis, ir, nmr, and mass spectra, and *S* dehydrogenation to **21** where the nmr spectrum revealed a quinoline H-4 proton at δ 7.59 (see Experimental Section for comparison with nmr of **3c**) and no H-2 proton. In the above and presumably reversible Michael type addition of pyridyllithium to the crossconjugated system of **6** at the highly δ^+ C-4, the expected or necessary adduct anion **17A** would be considerably stabilized by resonance involving the ester CO and would resist further attack at the ester function. On the other hand ad-

(7) R. E. Lutz et al., *J. Amer. Chem. Soc.*, **60**, 1811 (1938).
 (8) (a) D. W. Boykin, Jr., V. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 129 (1967); (b) D. W. Boykin, Jr., V. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 253 (1968).

(9) N. D. Heindel, P. D. Kennwell, and C. J. Olinmacht, *J. Org. Chem.*, **34**, 1168 (1969).

(10) Japan Electron Optics Laboratory Co. Ltd., "JOEL High Resolution NMR Spectra," Sadler Research Laboratories, Inc., Philadelphia, Pa., 1967.

dition at C-2 would yield intermediate anion **19** in which the ester function is conjugatively free for further reaction. Literature analogies for these reactions are seen in the addition of $\text{PhCH}_2\text{MgBr}^{11}$ and BuLi^{12} to C-2 and C-4 of quinoline itself. The often low material balance in the PhLi additions is evident from Table I where

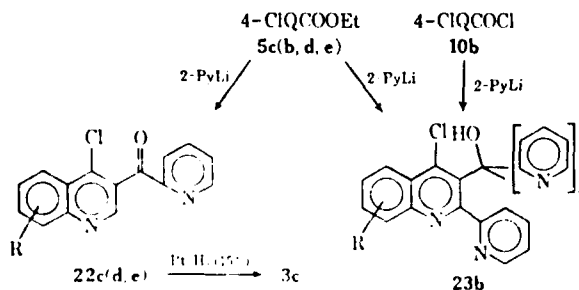
TABLE I
CHEMICAL SHIFTS OF H-2 AND H-4 OF SUBSTITUTED
3-CARBETHOXYQUINOLINES **6**

	R	Products (%)	H-2 δ	H-4 δ
6c	6,8-Me ₂	15c (15)	9.50	8.42
f	6-OCH ₃	15f (66)	9.38	8.73
b	6,8-Cl ₂	16b (18)	9.51	8.74
e	8-CF ₃	16e (20), 20 (11)	9.61	8.89
a	H	16a (0.8)	9.55	8.90
d	S-Ph	15d (66)	9.55	8.90

yields of products are compared with the H-2 and H-4 nmr chemical shifts which are a measure of substituent electronic effects on the two possible sites of initial nuclear attack. The seemingly anomalous behavior of the S-Ph analog **6d** in respect to prediction based solely on its H-4 nmr chemical shift might be explained in terms of steric hindrance at the quinoline N toward coordination with 2-pyridyllithium.¹³

Unfortunately attempts to hydrogenate selectively the 2-pyridyl nucleus of either pyridyl ketones **15c, d, f** or α -(2-pyridyl)-8-phenyl-3-quinolinemethanol (obtained through NaBH_4 reduction of **15d**) yielded dark mixtures which were shown by tlc to be multicomponent. These results are in contrast to the usually successful reductions of the pyridyl rings of the 2-aryl types⁷ where the 2 substituent appears to permit these selective reductions, probably by sterically decreasing the facility of reduction of the N-containing ring of the quinoline nucleus.

The successful and fortuitous synthesis of one example of the desired α -(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol (**3c**), stemmed from the work described below which was designed to obtain target analogs carrying Cl or some other heteroelemental group at position 4. This synthesis proceeded through the quinolone ester **4c** and the 4-chloro-(2-pyridyl) ketone **22c**. This ketone **22c** was unique in undergoing selective hydrogenation of the pyridyl nucleus with simultaneous reductive 4-dechlorination. This uniqueness possibly may be due to a combination of electronic stabilization by the electron-repelling Me groups and a steric effect of the 8-Me not unlike that of a 2-aryl group.

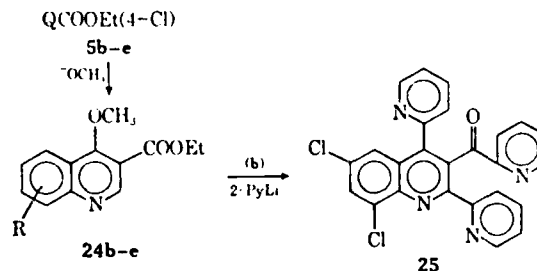


- (11) E. Bergmann and I. W. Rosenthal, *J. Prakt. Chem.*, **138**, 267 (1932).
 (12) K. Ziegler and H. Zeiser, *Justus Liebig's Ann. Chem.*, **485**, 174 (1931).
 (13) (a) A. Kaufmann, P. Daniliker and H. Burkhardt, *Ber.*, **46**, 2929 (1913); (b) J. R. Womack, T. G. Barbee, Jr., D. J. Tholness, M. A. McDonald and L. L. Pearson, *J. Heterocycl. Chem.*, **6**, 245 (1969).

The target amino alcohol **3c** was shown actually to be a mixture of difficultly separable diastereomers. This fact had not been revealed by tlc and became evident from the nmr spectrum of analytical samples which showed a pair of carbinol α -proton doublets of δ 4.76 ($J = 8$ Hz) and 4.85 ($J = 5$ Hz) in an integration ratio of 59:41 with total integration for one H^+ . Work on this problem has not been undertaken because of the lack of significant antimalarial activity of the mixture and low priority in the malaria program.

The 4-chloro-3-carbethoxyquinolines **5c, d, and e** reacted with 2-pyridyllithium giving the desired 4-chloro-3-quinolyl 2-pyridyl ketones **22c, d, and e** in 63, 27, and 63% yields, respectively. The 6,8-dichloro analog **5b**, however, gave the 2-pyridyl- α -di-(2-pyridyl)carbinol **23b** (43%; shown by ir (λ 1700 cm^{-1}) to contain a small amount of an unisolated pyridyl ketone). The corresponding acid chloride **10b** gave only the carbinol **23b** in 34% yield.

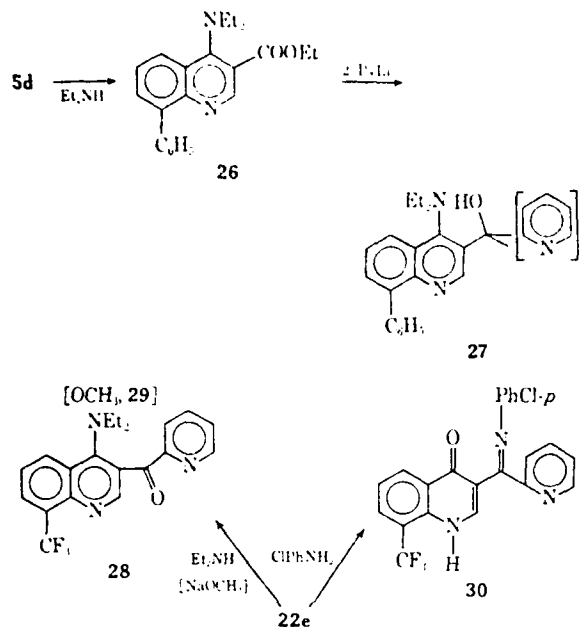
Approaches to the Synthesis of 4-Methoxy- and 4-Diethylamino-3-quinoline- α -aminomethanols.—4-Methoxy-3-quinolinecarboxylate esters **24b-e** were easily prepared by the action of NaOMe on the 4-chloro esters **5b-e**. A representative of these, **24b**, reacted with 2-pyridyllithium but gave a tripyridyl derivative, 2,4-di-(2-pyridyl)-3-quinolyl 2-pyridyl ketone (**25**, 44%) which evidently was contaminated with a small amount of unidentified material of molecular weight 440 (mass spectrum). The structure of **25** was established by elemental analysis and by ir, mass, and nmr spectra. It is of interest to compare the above reaction with that of PhCH_2MgBr at the 4 position of 2-methoxyquinoline (which did not at the same time displace the 2-MeO group),¹⁴ and to contrast it to the displacement of the EtO group of 2-ethoxyquinoline by BuLi .¹⁵



Displacement of the 4-Cl of the S-Ph ester **5d** by NET_2 gave the 4-diethylamino ester **26** which then upon reaction with 2 equiv of 2-pyridyllithium gave the dipyridyl carbinol **27**.

S-Trifluoromethyl-4-chloro-3-quinolyl 2-pyridyl ketone (**22e**) reacted with Et_2NH and with NaOMe to give the corresponding 4-diethylamino and 4-methoxy derivatives **28** and **29**. However, the desired α -piperidylmethanols were not obtained from these by catalytic reduction. One attempt to prepare a 4-*p*-chloroanilino derivative from the pyridyl ketone **22e** by reaction with *p*-chloroaniline and acidic work-up, involved hydrolysis of the 4-Cl and gave the 4-quinolone ketoanil **30** the structure of which is supported by analysis and nmr and ir spectra.

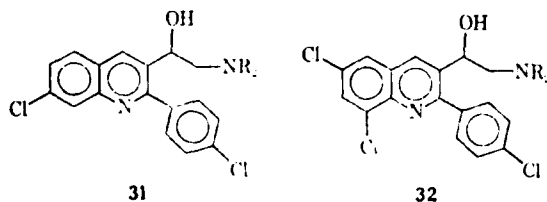
- (14) R. C. Fuson, H. L. Johnson, and E. Greishaber, *J. Org. Chem.*, **16**, 1529 (1951).
 (15) H. Gilman and J. A. Beel, *J. Amer. Chem. Soc.*, **73**, 774, 32 (1951).



Because of unpromising pharmacological tests on the compounds 1, 2, and 3, work on this series and on the several interesting unanswered chemical questions raised, has been suspended.

Biological Activity.—Antimalarial tests on compounds 1–3 were carried out on mice infected with *Plasmodium berghei* according to the method of Rane, *et al.*¹⁶ Defining a drug as active when the mean survival time (MST) of the treated group is more than double that of controls (7.0 ± 0.5 days), and “curative” upon survival up to 60 days, 1–3 exhibited no antimalarial activity at the highest recorded dose level. The increases in survival times at 640 mg/kg in fractions of a day were: 1b, 0.3; 1c, 0.1 (at 320 mg/kg); 1d, 0.4; 1e, 9.4; 1g, 0.5; 2b, 0.5; 2e, 0.3; and 3c, 1.0.

In contrast to the above, six α -dialkylaminomethyl-2-*p*-chlorophenyl-3-quinolinemethanols (31–32) synthesized by Donovan and Smith¹⁴ possessed low antimalarial activities. The most active of these was 32b which at 640 mg/kg increased the mean survival time 9.4 days.¹⁶ This compound was phototoxic as determined by the method of Rothe and Jacobus; the minimum effective phototoxic dose was below 200 mg/kg in mice administered ip.¹⁷ As a point of interest in this series, the 3-amino alcohol group must sterically interfere with the coplanarity and conjugation of the 2-aryl group with the quinoline nucleus, a conjugation with which the high phototoxicities in the 2-aryl-4-quinoline amino alcohols might possibly be associated.



(16) T. S. Osden, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data were supplied by the Walter Reed Army Institute of Research, Washington, D. C.

(17) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 360 (1968).

Experimental Section¹⁸

3-Carboethoxy- and 3-carboxy-4(1H)-quinolones (4 and 9) were prepared according to published procedures for the parent, 8-Ph,¹⁹ 6-MeO,¹⁹ and 7-Cl¹⁹ compounds. Ph₂O was employed as cyclization solvent in all preparations of 4.

Quinolinecarbonyl Chlorides (10, 12). A. 4,6,8-Trichloro-3-quinolinecarbonyl Chloride (10b).—DMF (2 ml) was added to a stirred refluxing slurry of 10 g (0.058 mole) of 9b and 50 ml of SOCl₂; refluxing was continued for 4 hr. Excess SOCl₂ was distilled at atm pressure and the last traces removed by codistillation with dry C₆H₆. Crystallization of the residue from pet ether (60–110°) gave 9.85 g (86%) of the yellow acid chloride 10b, mp 145–148°.

B.—12b and c were prepared as above but without DMF catalyst.

α -Bromomethyl-3-quinolyl ketones (13, 13') were prepared⁷ through but without isolation of the intermediate diazomethyl ketones.

3-Quinolylethylene Oxides (14, 14'). A. 4,6,8-Trichloro-3-quinolylethylene Oxide (14b).—To a stirred slurry of 6.9 g (0.02 mole) of bromoethyl 4,6,8-trichloroquinolyl ketone (13b) in 50 ml of MeOH was added dropwise, over 10 min, a soln of 1.0 g (0.026 mole) of NaBH₄, 3 ml of 2 N NaOH, and 10 ml of H₂O. The solid dissolved almost immediately and after 20 min a ppt formed. After an additional 1 hr of stirring the pale yellow product was collected and oven-dried: 4.4 g (82%); mp 131–133°.

B.—A modification of the above procedure was necessary for 14'b and e.

6,8-Dichloro-3-quinolylethylene Oxide (14'b).—A refluxing slurry of 8.74 g (0.0274 mole) of the bromomethyl ketone 13'b in 50 ml of MeOH was removed from the heat source and stirred while a soln of 2.0 g (0.053 mole) of NaBH₄ in 10 ml of H₂O was added dropwise over 10 min. Addition of 5 ml of 2 N NaOH to the stirred, clear yellow soln caused pptn of 14'b: 4.84 g (74%); pale yellow; mp 112–115°.

α -Di-*n*-butylaminomethyl-3-quinolinemethanols (1, 2). α -Di-*n*-butylaminomethyl-4,6,8-trichloro-3-quinolinemethanol (1b).—A stirred soln of 5.3 g (0.019 mole) of 14b and 35 ml of *n*-Bu₂NH was heated at 135° for 18 hr. After excess reagent was removed by vac distillation the orange residue was dissolved in dry Et₂O, and 1 was fractionally pptd by Et₂O-HCl (the last fractions tended to gum; total crude yield; 6.28 g (74%); recrystd from EtOH-Et₂O, 4.20 g (49%); mp 178–180° dec.

3-Carboethoxy-4-chloroquinolines (5) were prepared by the reaction of the 3-carboethoxyquinolones 4a–g with POCl₃ (3 moles, 3 hr, reflux); 5a and 5f¹⁹ had previously been prepared employing a POCl₃-PCl₅ mixture.

3-Carboethoxy-8-trifluoromethyl-1,4-dihydroquinoline (7e).—A mixture of 4.0 g (0.013 mole) of 5e, 0.84 g (0.015 mole) of KOH, 0.4 g of 10% Pd-C, and 25 ml of abs EtOH, was hydrogenated at 55° for 2.5 hr at 3.52 kg/cm². Filtration through Celite, concentration, and filtering gave 7e: 2.19 g (61%); mp 158–159°; nmr (CDCl₃) δ 7.17 (m, 4), 6.50 (m, 1), 4.25 (m, 2), 3.79 (s, 2), 1.36 (t, 3).

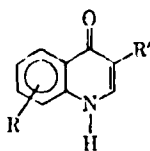
3-Carboethoxy-6,8-dichloro-1,4-dihydroquinoline (7b).—To a stirred, ice-cooled soln of 6.0 g (0.16 mole) of NaBH₄ in 125 ml of 2-methoxyethanol was added portionwise 19.1 g (0.063 mole) of 5b. The first addition caused temp rise to 60° and liberation of gas. The remainder of 5b was then added over 1 hr. The slurry was stirred for 3 hr and the resulting ppt (5b and 7b) was air-dried: 12.17 g (orange); mp 105–180°. Retreatment of this as above with 4 g of NaBH₄ in 125 ml of 2-methoxyethanol for 3 hr yielded 6.61 g (39%) of 7b (orange); mp 187.5–189.5°; anal. sample (EtOH), mp 196° dec; nmr (DMSO-*d*₆) δ 8.64 (m, 1), 7.19 (m, 3), 4.11 (q, 2), 3.67 (s, 2), 1.22 (t, 3). The mother liquors poured into H₂O gave 6.88 g (oven-dried), mp 130–160°. Extraction with refluxing pet ether (bp 60–110°) removed unreacted 5b; recrystd from EtOH, 2.1 g of 8b (13%); mp 193–198°.

3-Carboethoxyquinolines (6). Catalytic Dehalogenation. 3-Carboethoxy-8-phenylquinoline (6d).—The following improved

(18) Instruments: (a) Melting points were obtained on a Thomas-Hoover apparatus, uncorrected; (b) anal. were correct $\pm 0.4\%$; Gallorath Lab. Inc., and Swartzkopf Microanalytical Lab.; (c) sublimation of analytical samples was at 10–50° below the mp; (d) satisfactory spectra were obtained, for structural determination where required, and randomly in other cases; (e) ir, Perkin-Elmer 547; (f) nmr, Hitachi P-E R 20; (g) mass spectrograph, Hitachi P-E, RMU 6E.

(19) W. O. Kermack and N. Storey, *J. Chem. Soc.*, 1389 (1951).

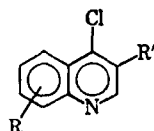
TABLE II
3-FUNCTIONALIZED-4-QUINOLINES



Compd	R	R'	Mp, °C ^a	% yield	Composition ^d
4b	6, 8-Cl ₂	COOEt	305-308 dec ^b	74	C ₁₂ H ₇ Cl ₂ NO ₂
9b	6, 8-Cl ₂	COOH	300 dec ^b	100	C ₁₀ H ₅ Cl ₂ NO ₂
4c	6, 8-Me ₂	COOEt	273-276 dec ^c	68	C ₁₄ H ₁₃ NO ₂
9c	6, 8-Me ₂	COOH	298-300 dec ^b	100	C ₁₂ H ₁₀ NO ₂
4e	8-CF ₃	COOEt	209-213 ^c	83	C ₁₂ H ₈ F ₃ NO ₂
9e	8-CF ₃	COOH	235 dec ^d	83	C ₁₁ H ₆ F ₃ NO ₂
30	8-CF ₃	C(2-Py)=NPhCl	199-200.5 ^e	92	C ₂₂ H ₁₃ ClF ₃ N ₃ O ^f

^a Dec, mp decomp. Recrystd from: ^b DMF; ^c EtOH. ^d Analytically pure from reaction mixture. ^e Analyzed within ±0.4% for C, H; ^f for C, H, Cl, N.

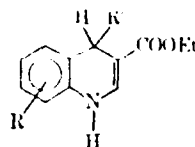
TABLE III
3-FUNCTIONALIZED-4-CHLOROQUINOLINES



Compd	R	R'	Mp, °C	% yield	Composition ^d
10b	6, 8-Cl ₂	COCl	145-147	90 ^{a,b}	C ₁₀ H ₂ Cl ₂ NO
10c	6, 8-Me ₂	COCl	103-105	38 ^{a,b}	C ₁₂ H ₂ Cl ₂ NO
10d	8-Ph	COCl	125-126.5	90 ^{a,b}	C ₁₆ H ₂ Cl ₂ NO ^m
10e	8-CF ₃	COCl	94-95.5	70 ^{a,b}	C ₁₁ H ₂ Cl ₂ F ₃ NO ^m
10g	7-Cl	COCl	137-139	38 ^{a,b}	C ₁₀ H ₂ Cl ₂ NO
13b	6, 8-Cl ₂	COCH ₂ Br	136-137.5	87 ^c	C ₁₁ H ₂ BrCl ₂ NO
13c	6, 8-Me ₂	COCH ₂ Br	76.5-78	58 ^c	C ₁₃ H ₁₁ BrClNO
13d	8-Ph	COCH ₂ Br	132-133 dec	98 ^d	C ₁₇ H ₁₁ BrClNO ^m
13e	8-CF ₃	COCH ₂ Br	98-99	79 ^c	(crude)
13g	7-Cl	COCH ₂ Br	104-106	83 ^a	C ₁₁ H ₂ BrCl ₂ NO
14b	6, 8-Cl ₂	CH-CH ₂ O	132.5-134	82 ^{a,b}	C ₁₁ H ₂ Cl ₂ NO
14c	6, 8-Me ₂	CH-CH ₂ O	95-96	91 ^a	C ₁₃ H ₁₂ ClNO ^f
14d	8-Ph	CH-CH ₂ O	140-141	83 ^{f,b}	C ₁₇ H ₁₂ ClNO ^f
14e	8-CF ₃	CH-CH ₂ O	82-83	52 ^a	C ₁₂ H ₂ ClF ₃ NO ^{a,m}
14g	7-Cl	CH-CH ₂ O	153.5-155	83 ^c	C ₁₁ H ₂ Cl ₂ NO
1b	6, 8-Cl ₂	CHOHCH ₂ NBu ₂	181-182 dec	74 ^e	C ₁₉ H ₂ Cl ₂ N ₂ O · HCl
1c	6, 8-Me ₂	CHOHCH ₂ NBu ₂	121-123 dec	66 ^e	C ₂₁ H ₁₁ ClN ₂ O · HCl
1d	8-Ph	CHOHCH ₂ NBu ₂	174 dec	90 ^e	C ₂₅ H ₁₁ ClN ₂ O · HCl
1e	8-CF ₃	CHOHCH ₂ NBu ₂	172 dec	56 ^e	C ₂₀ H ₂ ClF ₃ N ₂ O · HCl
1g	7-Cl	CHOHCH ₂ NBu ₂	168-170 dec	75 ^e	C ₁₉ H ₂ Cl ₂ N ₂ O · HCl
5b	6, 8-Cl ₂	COOEt	109-110	87 ^f	C ₁₂ H ₂ Cl ₂ NO ₂ ^m
5c	6, 8-Me ₂	COOEt	76-77.5	97 ^{f,a}	C ₁₄ H ₁₂ ClNO ₂ ^m
5d	8-Ph	COOEt	131-132.5	88 ^f	C ₁₈ H ₁₂ ClNO ₂ ^m
5e	8-CF ₃	COOEt	56-57	64 ^a	C ₁₃ H ₂ ClF ₃ NO ₂ ^m
22c	6, 8-Me ₂	COPY	148 dec	63 ^f	C ₁₆ H ₁₃ ClNO ₂
22d	8-Ph	COPY	102-103	27 ^c	C ₂₀ H ₁₃ ClN ₂ O
22e	8-CF ₃	COPY	155	63 ^f	C ₁₅ H ₂ ClF ₃ N ₂ O
8b	6, 8-Cl ₂	CH ₂ OH	196-198	13 ^c	C ₁₀ H ₂ Cl ₂ NO ^m
8c	6, 8-Me ₂	CH ₂ OH	166-169	53 ^f	C ₁₂ H ₁₂ ClNO ^m

Recrystd from: ^a Pet ether (bp 60-110°); ^b sublimed; ^c EtOH; ^d crude, EtOH washed; ^e MeOH; ^f hexane; ^g EtOH-Et₂O. ^a pet ether (bp 60-69°). ^b C: calcd 66.81, found 65.99. ^c C: calcd 72.47, found 71.00. ^d C: calcd 52.67, found 52.13. ^e Anal. for C, H, N; ^m for C, H only.

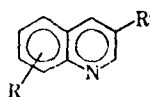
TABLE IV
1,4-DIHYDRO-3-QUINOLINE CARBOXYLATES



Compd	R	R'	Mp, °C	% yield	Composition ^f
7b	6, 8-Cl ₂	H	196 dec ^a	39	C ₁₂ H ₁₁ Cl ₂ NO ₂
7e	8-CF ₃	H	158-159 ^b	61	C ₁₃ H ₁₂ F ₃ NO ₂
17a	H	2-Py	199-201 ^{a,c}	0.7	C ₁₇ H ₁₆ N ₂ O ₂ ^d
17b	6, 8-Cl ₂	2-Py	221-222 dec ^d	18	C ₁₇ H ₁₁ Cl ₂ N ₂ O ₂
17e ^e	8-CF ₃	2-Py	175-176 ^a	20	C ₁₈ H ₁₅ F ₃ N ₂ O ₂ ^d

Recrystn solvent: ^a EtOH; ^b hexane; ^c sublimed; ^d 2-methoxyethanol. ^e Nmr (CDCl₃) δ 8.56 (d, 1), 7.32 (m, 8), 5.40 (s, 1), 4.10 (m, 2), 1.14 (t, 3). ^f Anal. ^g C, H, N; ^h C: calcd 72.83; found 73.47; ⁱ for C, H only.

TABLE V
3-FUNCTIONALIZED QUINOLINES



Compd	R	R'	Mp, °C	% yield	Composition ^m
6b	6, 8-Cl ₂	COOEt	131-133	96 ^a	C ₁₂ H ₇ Cl ₂ NO ₂
6c	6, 8-Me ₂	COOEt	80.5-81	51 ^b	C ₁₄ H ₁₃ NO ₂ ^a
6d	8-Ph	COOEt	106-107	54 ^c	C ₁₄ H ₁₃ NO ₂ ^a
6e	8-CF ₃	COOEt	88-89.5	73 ^c	C ₁₄ H ₁₀ F ₃ NO ₂ ^a
6f	6-OMe	COOEt	85-87	66 ^b	C ₁₄ H ₁₃ NO ₂ ^a
11b	6, 8-Cl ₂	COOH	300-301 dec	94 ^d	C ₁₀ H ₅ Cl ₂ NO ₂ ^a
11d	8-Ph	COOH	205-206	70 ^e	C ₁₄ H ₁₁ NO ₂ ^a
11e	8-CF ₃	COOH	208-209	78 ^c	C ₁₄ H ₈ F ₃ NO ₂ ^a
12b	6, 8-Cl ₂	COCl	170-172	92 ^{a,f}	C ₁₀ H ₄ Cl ₂ NO
12e	8-CF ₃	COCl	94-95	56 ^{f,g}	C ₁₁ H ₇ CF ₃ NO ^a
13'b	6, 8-Cl ₂	COCH ₂ Br	197-199 dec	81 ^a	C ₁₁ H ₄ BrCl ₂ NO
13'e	8-CF ₃	COCH ₂ Br	142-143	66 ^c	C ₁₂ H ₇ BrF ₃ NO
14'b	6, 8-Cl ₂	CH=CH ₂	118.5-120	74 ^e	C ₁₁ H ₇ Cl ₂ NO
14'e	8-CF ₃	CH=CH ₂	65-67	72 ^{f,g}	C ₁₁ H ₅ F ₃ NO
2b	6, 8-Cl ₂	CHOHCH ₂ NBn ₂	65-72 dec	38 ^f	C ₁₇ H ₂₀ Cl ₂ N ₂ O·HCl
2e	8-CF ₃	CHOHCH ₂ NBn ₂	90.5-92 dec	59 ^f	C ₂₀ H ₂₇ F ₃ N ₂ O·HCl
15c	6, 8-Me ₂	COPy	97.5-98	27 ^{a,h}	C ₁₅ H ₁₄ N ₂ O
15d	8-Ph	COPy	118-118.5	66 ^{e,k,l}	C ₂₁ H ₁₄ N ₂ O ^a
15e	8-CF ₃	COPy	99-99.5	58 ^{e,l}	C ₁₈ H ₁₃ F ₃ N ₂ O ^a
15f	6-OMe	COPy	129-131.5	66 ^c	C ₁₄ H ₁₁ N ₂ O ₂
3	6, 8-Me ₂	CHOHPip	143-148	15 ^a	C ₁₇ H ₂₂ N ₂ O
16d	8-Ph	CHOHPy	137.5-138	64 ^c	C ₂₁ H ₁₆ N ₂ O ^a

Recrystn from: ^a pet ether (60-100°), ^b (30-60°), ^c EtOH; ^d 2-methoxyethanol; ^e reaction product Et₂O washed; ^f sublimed; ^g hexane; ^h MeCN; ⁱ hygroscopic, not crystal; ^j EtOH-Et₂O; ^k prepared by the action of 2-PyLi on the 3-carboxylate ester; ^l by 2-PyLi on the 3-carboxylic acid (15d, 32%). ^m Anal. ⁿ for C, H, N; ^o for C, H only.

method of Kaslow and Clark was used to prepare 6a.⁴ A suspension of 4.0 g (0.013 mole) of 5d and 0.6 g of 10% Pd-C in 25 ml of glacial AcOH at 50° was hydrogenated (1 hr, 3.16 kg/cm²). Filtration through Celite, pouring into H₂O with stirring, collection of the ppt by filtration, and crystallization in hexane gave 1.92 g (54%) mp (96-107°).

Sulfur Dehydrogenation of a 1,4-Dihydroquinoline, 3-Carboxethoxy-6,8-dichloroquinoline (6b). An intimate mixture of 11.9 g (0.044 mole) of 7b and 5.15 g (0.097 mole) of S in a Wood's metal bath at 190° was heated at 250° for 15 min; reaction H₂S evolved vigorously. Cooling, extraction with 300 ml of refluxing pet ether (60-110°), filtering, concentrating to 120 ml, cooling, and recrystn of the yellow ppt from 250 ml of pet ether gave 11.43 g (96%) mp 152-151°.

4-Methoxy-3-carboxethoxyquinolines (21). 4-Methoxy-6,8-dichloro-3-carboxethoxyquinoline (21b). A soln of 17.5 g (0.058 mole) of 5b in 300 ml of MeOH was added to a soln of 0.17 mole of

NaOMe in 150 ml of MeOH. After 1-hr reflux the mixture was poured into 2 l. of H₂O giving 13.9 g (80%), oven-dried, mp 141-142.5°.

4-Diethylamino-8-phenyl-3-carboxethoxyquinoline (26). A soln of 6.2 g (0.02 mole) of 5d and 4.4 g (0.06 mole) of Et₃NH in 100 ml of EtOH was refluxed for 2 hr. Cooling in ice returned 2.25 g (37%) of 5d. Extraction of the residue from evapn of the filtrate with hexane, filtration to remove Et₃NH·HCl, and evapn to dryness gave 3.1 g of 26.

2-Pyridylithium Reactions. A. With Carboxylic Acids 11 d.e. 2-Pyridyl 8-Phenyl-3-quinolyl Ketone (15d). To a stirred soln of 2-pyridylithium^{26,29} (from 11 g of 2-bromopyridine in 150 ml of anhyd Et₂O at -70° under N₂) was added rapidly

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TABLE VI
3-FUNCTIONALIZED-4-SUBSTITUTED QUINOLINES

Compd ^a	R	R'	R''	Mp, °C	% yield ^b	Composition ^c
24b	6, 8-Cl ₂	OMe	COOEt	141.5-143	80% ^d	C ₁₇ H ₁₀ Cl ₂ N ₂ O ₂ ^f
24c	6, 8-Me ₂	OMe	COOEt	83.5-85	56% ^e	C ₁₇ H ₁₂ N ₂ O ₂ ^f
24d	8-Ph	OMe	COOEt	135.5-136	87%	C ₁₇ H ₁₂ N ₂ O ₂ ^f
24e	8-CF ₃	OMe	COOEt	79.5-80	70%	C ₁₇ H ₁₀ F ₃ N ₂ O ₂ ^f
18b	6, 8-Cl ₂	Py	COOEt	100-101.5	48%	C ₁₉ H ₁₂ Cl ₂ N ₂ O ₂ ^f
18e	8-CF ₃	Py	COOEt	64-66	15%	C ₁₈ H ₁₁ F ₃ N ₂ O ₂ ^f
26	8-Ph	NEt ₂	COOEt	72-74	72%	C ₂₂ H ₁₆ N ₂ O ₂ ^f
27 ^g	8-Ph	NEt ₂	C(OH)Py ₂	200-201	14%	C ₂₀ H ₁₄ N ₂ O
28	8-CF ₃	NEt ₂	COPy	130.5-131	60%	C ₂₀ H ₁₃ F ₃ N ₂ O
29	8-CF ₃	OMe	COPy	172.5-174	37% ^d	C ₁₇ H ₁₁ F ₃ N ₂ O ₂ ^f
23 ^h	6, 8-Cl ₂	Cl	C(OH)Py ₂ ⁱ	197-199	34% ^j	C ₂₁ H ₁₀ Cl ₃ N ₂ O

^a Py = 2-pyridyl. ^b Recryst from: ^c MeOH; ^d sublimed; ^e hexane; ^f EtOH. ^g Nmr (CDCl₃) δ 10.86 (s, 1), 8.87 (s, 1), 8.47 (d, 2), 7.51 (m, 14), 3.40 (m, 4), 1.05 (t, 6). ^h Also carries 2-(2-Py). ⁱ Prepared from acid chloride. ^j Prepared from ester, 47%^k. ^k Anal.^l for C, H, N; ^l for C, H only.

TABLE VII^a
α-DIALKYLAMINOMETHYL-2-(p-CHLOROPHENYL)-3-QUINOLINEMETHANOLS^b

Compd ^a	R	R'	Mp, °C	% yield	Composition ^c
31a	7-Cl	Et	113-115	72	C ₂₁ H ₂₂ Cl ₂ N ₂ O
31b	7-Cl	Bu	185-186.5	76	C ₂₃ H ₂₆ Cl ₂ N ₂ O · HCl
31c	7-Cl	Heptyl	171-172.5	62	C ₂₇ H ₃₄ Cl ₂ N ₂ O · HCl
32a	6, 8-Cl ₂	Et	133-134	83	C ₂₁ H ₁₈ Cl ₂ N ₂ O
32b	6, 8-Cl ₂	Bu	227.5-230	71	C ₂₃ H ₂₂ Cl ₂ N ₂ O · HCl
32c	6, 8-Cl ₂	Heptyl	162-164.5 ^b	73	C ₂₇ H ₃₀ Cl ₂ N ₂ O · HCl

^a Synthetic route: 6-Cl-isatin, *p*-Cl-propiofenone → Q-3-CH₂, 4-COOH → Q-3-CH₂ → Q-3-COOH → Q-3-COCl → Q-3-COCHN₂ → Q-COCl, Br → Q-CHOHCH₂Br → Q-CH(OH)-CH₂ → 31 and 32. ^b Solidifying and again melting at 177-178°. ^c Anal.^l C, H, Cl, N.

2.48 g (0.01 mole) of 11d. After 10 min 50 ml of anhyd THF (distd from CaH₂) was added, and stirring at -70° was continued for 3 hr. The mixture was allowed to warm to 40° and 100 ml of H₂O was added rapidly. After filtration to remove the insol pyridyl ketone (other such ketones are sol in Et₂O) the Et₂O layer was washed twice with H₂O and evapd under reduced pressure, giving additional 15d; recrystd from abs EtOH, 1.0 g (32%); mp 118-118.5°.

B. With Esters.—A THF soln of the ester was added to a two- to threefold excess of 2-pyridyllithium. Usually the product was isolated by evaporation of the Et₂O and crystallization of the residue from EtOH. In the prepn of 22d and 27, unreacted starting material crystallized first from EtOH. In a slightly different work-up, before further purification was carried out, unreacted starting ester was extracted from crude 15c and 17b with petroleum pentane (30-60°) and hexane, respectively.

8-Trifluoromethyl-4-(2-pyridyl)-1,4-dihydroquinoline (17c).—Reaction of ester 6e (3.4 g, 0.013 mole), work-up as above, and fractional crystallization from EtOH yielded two products: 20, 0.50 g (11%), mp 238.5-240°; ir (KBr disk), 3300 cm⁻¹ (C-OH; no CO band); [Anal. (C₁₇H₁₂F₃N₂O) H, N; C: calcd 67.82; found 66.87; mol, wt calcd and found 393 (mass spectroscopy);] and 17c, 0.88 g (20%), mp 175-176°; nmr (CDCl₃), δ 8.56 (d, 1), 7.32 (m, 8), 5.40 (s, 1), 4.10 (m, 2), 1.44 (t, 3). Compound 20 was dehydrogenated by S to yield a small amount of 21, identified on the basis of the nmr spectrum which exhibited a sharp singlet at δ 7.59 (H-1) and an aromatic multiplet (δ 6.58-8.58).

2-Pyridyl 2,4-Di(2-pyridyl)-6,8-dichloro-3-quinolyl Ketone (25). The 2-pyridyllithium reaction mixture was stirred for only 1 hr after addition of the ester 24b. Crystallization from EtOH gave 10% of starting ester 24b. Evaporation of the filtrate and column chromatography of the residue on Florisil (MeOH in C₆H₆ gradient elution) gave a red amorphous solid which contained trapped solvent (by nmr). Crystallization from acetone (upon slow evaporation) gave 25% of 25 (yellow, true yield

45%); mp 234-238°; recrystd from MeCN, mp 239-241°, mol wt, calcd and found 457 (mass spectroscopy). Anal. C₂₂H₁₄Cl₂N₄O: H, 1.8%; N, 18.6%; C, calcd, 65.66, found 66.28.

2-Pyridyl 4-Diethylamino-8-trifluoromethyl-3-quinolyl Ketone (28).—A soln of 1 g (2.96 mmoles) of 24e and 0.896 g (11.8 mmoles) of Et₂NH in 15 ml of EtOH was refluxed for 1 hr. Ice-bath cooling gave 0.67 g (60%) of crude 28.

2-Pyridyl 8-Trifluoromethyl-4(1*H*)-3-quinolonyl Ketone 4-Chlorophenylimine (30). A mixture of 2 g (5.95 mmoles) of 22d and 2.3 g (18 mmoles) of 4-chloroaniline in 75 ml of EtOH was refluxed for 1 hr. Concentrated HCl (1 ml) was added and refluxing continued for another hour. The mixture was cooled and quenched in ice H₂O containing excess KOH. Crystallization of the ppt from EtOH gave 2.34 g (92%); nmr (DMSO-*d*₆) δ 9.56 (s, 1), 8.79 (s, 1), 8.64 (d, 2), 8.25 (d, 1), 7.71 (m, 4), 6.81 (m, 4).

α-(2-Piperidyl)-6,8-dimethyl-3-quinolinemethanol (Stereoisomer Mixture 3c).—A slurry of 9.0 g of 22c (0.03 mole), 250 ml of abs EtOH, 6 ml of concd HCl, and 0.75 g of PtO₂ was hydrogenated at 3.15 kg cm⁻². After absorption of 5H₂, filtration through Celite, and concn to 30 ml, the soln was dil'd with H₂O and basified (NaOH). The Et₂O extract of the gummy ppt was washed with H₂O, dried (MgSO₄), and evapd. Treatment of the residual gum in 50 ml of Me₂CO with 75 ml of hexane and cooling gave 3.12 g (28%), mp 115-131°. Recrystallization from pet ether (60°-110°) and sublimation [150°(0.1 mm)] gave 1.23 g (15%), mp 143-148° (smets at 135°). An analytical sample was prepared by recrystn from MeCN; nmr (CDCl₃) δ 8.83 (d, 1, *J* = 2.5 Hz, H-2), 7.86 (q, 1, *J* = 2.5 Hz, nonequiv H-4 of diastereomers), 7.32 (s, 2), 1.85 (d, 0.41, *J* = 5 Hz), 4.56 (d, 0.59, *J* = 8 Hz), 4.21 (s, 2, NH, OH), 2.75 (s, 3), 2.46 (s, 3), 2.7 (m, 3), 1.45 (m, 6).

Antimalarials. III. Benzothiazole Amino Alcohols^{1a}

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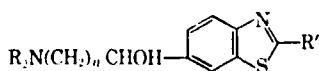
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Amino alcohols carrying a $\text{CHOH}(\text{CH}_2)_n\text{NR}_2$ chain in position 6 of a benzothiazole nucleus, unsubstituted or substituted by phenyl or trifluoromethyl in the 2 position, have been synthesized by standard methods and tested for activity against *Plasmodium berghei* in mice. Several of the amino alcohols showed weak antimalarial activity but only at toxic doses.

Bioisosteric substitution of benzothiazole for quinoline has been tried on three occasions,²⁻⁴ each time for derivatives containing the dialkylaminoalkylamino chain characteristic of the prototypes, pamaquine and chloroquine. Only one group of authors² reported lack of antimalarial activity for their compounds, while the others^{3,4} left biological behavior as unfinished business. In view of the renewed interest in amino alcohols incorporating some features of the quinine molecule⁵ we investigated amino alcohols derived from benzothiazole as an extension of our studies of quinoline analogs.

All of the amino alcohols described in this paper carry the functional side chain in position 6 (I), that is, *para* to the ring nitrogen. This simulates a relationship to the 4-substituted quinoline amino alcohols as far as the benzothiazole system permits. Apart from the otherwise unsubstituted derivatives (Ia), 2-phenyl-substituted derivatives (Ib) were also prepared because 2-phenyl substitution in the quinoline series had proved advantageous to antimalarial potency,⁶ perhaps due to inhibition of oxidative biotransformation. However, since the 2-phenyl-substituted quinoline amino alcohols cause photosensitization⁷ and this may be associated with their increased conjugation,⁸ 2-trifluoromethyl-substituted benzothiazole amino alcohols (Ic) were prepared to avoid this effect; in the quinoline series, 2- CF_3 substitution furnished amino alcohols with moderate antimalarial activity and less photosensitizing properties.⁹

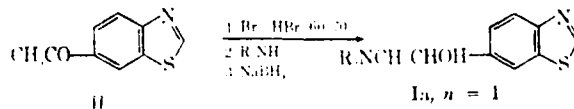


Ia, R' = H
 b, R' = C_6H_5
 c, R' = CF_3

$n = 1-3$; $\text{R}_2\text{N} =$ dialkylamino, piperidino

Chemistry.—For the synthesis of amino alcohols of type Ia ($n = 1$) *p*-aminoacetophenone was thiocyanated¹⁰ and then converted to 5-acetyl-2-amino-

benzenethiol¹¹ and this was cyclized with formic acid to 6-benzothiazolyl methyl ketone (II). Bromination of II was followed by treatment of the resulting bromo ketone with secondary amines and reduction of the amino ketones.

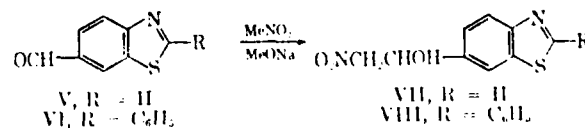


The 2-phenyl (Ib, $n = 1$) and 2-trifluoromethyl (Ic, $n = 1$) analogs were obtained essentially by similar routes, benzoyl chloride¹² and trifluoroacetic anhydride, respectively, being used in dimethylaniline solution in the ring closure instead of formic acid. The bromination of the 2-substituted 6-benzothiazolyl methyl ketones in acetic acid always led to mixtures of mono- and dibromo ketones from which the monobromo ketone could be separated by repeated crystallization.

6-[3-Dimethylamino- (and piperidino-) 1-hydroxypropyl]benzothiazoles (Ia-c, $n = 2$) were prepared by reduction of the corresponding Mannich bases.

The synthesis of one example of a 6-(4-dialkylamino-1-hydroxybutyl)-2-phenylbenzothiazole [Ib, $n = 3$; $\text{R}_2\text{N} = \text{N}(\text{CH}_2)_2$] was accomplished by reducing ethyl 2-phenyl-6-benzothiazolecarboxylate (III, $\text{R} = \text{C}_6\text{H}_5$) to 2-phenyl-6-benzothiazolemethanol (IV), oxidizing IV to 2-phenyl-6-benzothiazolealdehyde (V), and condensing this with γ -dimethylaminopropylmagnesium chloride (Scheme I).

The 2-unsubstituted aldehyde (V) was prepared by a similar sequence. Condensation of V and of VI with nitromethane yielded 1-(6-benzothiazolyl)-2-nitroethanol (VII) and its (2-phenyl-6-benzothiazolyl) derivative (VIII), respectively. Attempts to reduce these nitro alcohols to primary amino alcohols failed.



Biological Data. The twelve amino alcohols designated with Arabic numerals in Table I have been tested for activity against *Plasmodium berghei* in the mouse by the procedure of Rane, *et al.*¹³ Deaths occurring on days 2-5 after infection were attributed to drug action; infected control animals did not die before day 6. These compounds were highly toxic at 160-640 mg/kg. They exhibited negligible antimalarial action at lower doses, were not curative at 16-640 mg/kg, and increased survival time from 0.3-2.9 days

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(D) This work was supported by the U. S. Army Medical Research and Development Command, Contract DA-19-193-MD-2955, Contribution No. 298. (b) To whom inquiries should be directed. (c) On leave of absence from Kurukshetra University, Kurukshetra (Haryana), India.

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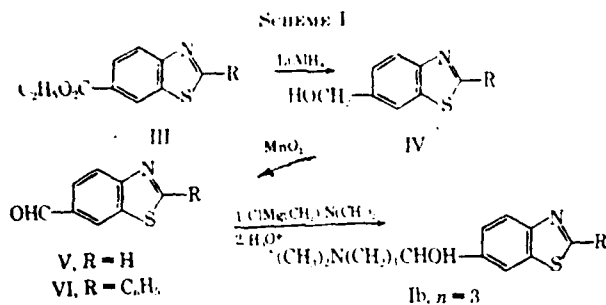
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only. Substitution by phenyl or trifluoromethyl at position 2 did not affect antimalarial behavior.¹⁴



Experimental Section

Melting points (taken in a heating bath) and boiling points are uncorrected. Ir spectra (KBr) were taken on a Perkin-Elmer Spectrocord and agreed with expected absorption bands. Where analyses in Table I are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.3\%$ of the theoretical values. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Yields, physical data, and solvents are listed in Table I.

6-Acetylbenzothiazole (II).—A stirred mixture of 4-amino-3-thioxyanacetophenone^{10,11} (48 g, 0.25 mole), $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (72 g), and H_2O (150 ml) was heated under reflux for 45 min, cooled, and filtered from some undissolved material. The filtrate was neutralized carefully with AcOH. The semisolid was extracted into ether, washed (H_2O), and dried (MgSO_4), and the residue from the ether solution was refluxed with 90% formic acid (64 g) and a spatula-full of Zn dust for 3 hr. The cooled dark mixture was stirred into H_2O (400 ml), and the yellow solid which separated was filtered off, washed (H_2O), dried, and crystallized (C_6H_6 -petroleum ether (bp 30–60°), then EtOH), yield 30.5 g.

6-Acetyl-2-phenylbenzothiazole.—4-Amino-3-mercaptobenzoic acid was converted to its hydrochloride with dry HCl in ether. The salt (30.5 g, 0.15 mole) was dissolved in dimethylaniline (210 ml) and the solution was treated slowly, with stirring and cooling, with 30 g (0.21 mole) of benzoyl chloride. After heating under reflux for 1 hr, the mixture was cooled, poured into 1300 ml of 3.9% HCl, and stirred for 2 hr. The solid ketone was filtered off, washed (H_2O), dried, and recrystallized from C_6H_6 yielding 28 g of pale yellow shiny flakes.

In a similar manner, 6-(2-trifluoromethylbenzothiazolyl) methyl ketone was prepared, using 0.29 mole of $(\text{F}_3\text{CCO})_2\text{O}$ /0.2 mole of starting aminothioli ketone. For additional data see Table I.

6-Bromoacetylbenzothiazole.—A solution of Br_2 (16 g, 0.1 mole) in 48% HBr (100 ml) was added dropwise to a hot stirred solution of ketone II (17.7 g, 0.1 mole) in 200 ml of 48% HBr over a period of 1 hr, the mixture being maintained at 60–65°. After additional stirring for 2 hr at 60–65° the mixture was cooled to 0° and the crystalline salt which separated was filtered off. This salt was stirred well with H_2O , filtered, washed (H_2O), dried, and crystallized from C_6H_6 as pale brown crystals, yield 19 g.

6-Bromoacetyl-2-phenylbenzothiazole.—A solution of 6-acetyl-2-phenylbenzothiazole (7.6 g, 0.03 mole) in AcOH (100 ml) was refluxed until clear. A solution of Br_2 (4.8 g, 0.03 mole) in AcOH (30 ml) was then added dropwise over 1 hr and refluxing was continued for another hour. A light yellow solid separated from the cooled solution. It was filtered off, washed (H_2O), dried, and recrystallized three times from C_6H_6 to separate the product from dibromoacetyl material; yield 4.5 g.

6-Dialkylamino- (or piperidino-) acetylbenzothiazoles.—The respective 6-bromoacetylbenzothiazoles were treated with a secondary amine in dry benzene or ether as specified in the footnotes to Table I. The precipitated amine hydrobromide was filtered off, and the filtrate was washed (H_2O), dried, and concentrated at reduced pressure. Solid amino ketones were purified by crystallization. Liquid products were reduced without purification.

(14) These test data were supplied by the Walter Reed Army Institute of Research, Washington, D. C.

6-[2-Dialkylamino- (or piperidino-) 1-hydroxyethyl]benzothiazoles (I, $n = 1$).—The appropriate amino-methyl ketone (0.02 mole) was dissolved or suspended in MeOH (50–75 ml) and a solution of NaBH_4 (0.01–0.015 mole) in H_2O (5 ml) and 2 N NaOH (1 ml) was added gradually with stirring at about 15°. After stirring the mixture for 3–5 hr at 25° about half of the solvent was removed, and the mixture was diluted with H_2O and allowed to stand overnight. Solid amino alcohols were collected, washed (H_2O), and recrystallized. Liquid products were extracted (Et₂O), dried, and converted to common salts. If these failed to crystallize, 1,1'-methylenebis(2-hydroxy-3-naphthoate) salts were prepared for testing purposes. Purates for characterization were usually prepared in ether.

Mannich Bases.—A solution of a 6-benzothiazolyl methyl ketone (0.05 mole), a secondary amine hydrochloride (0.055 mole), paraformaldehyde (0.08–0.12 mole), and 1–2 ml of ethereal HCl in 3-methylbutanol (50 ml) was refluxed. If the reaction required 12 hr, the paraformaldehyde was added in two to three portions. The β -amino ketone hydrochlorides either crystallized on cooling or could be precipitated with ether. The bases were liberated with aqueous Na_2CO_3 , purified, and reconverted to hydrochlorides in dry ether.

6-[3-Dimethylamino- (or piperidino-) 1-hydroxypropyl]benzothiazoles (I, $n = 2$).—The Mannich bases were obtained from their hydrochloride salts in MeOH–2 N NaOH and reduced with NaBH_4 as described for the preparation of I ($n = 1$) above.

6-Benzothiazolecarboxylic Acid (III, R = H) and Ethyl Ester.—A stirred mixture of ethyl 4-amino-3-thioxyanacetophenone¹⁰ (22.2 g, 0.1 mole), $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (29 g, 0.12 mole), and H_2O (60 ml) was refluxed for 45 min, cooled, and filtered from any undissolved material. The filtrate was neutralized with AcOH, and the precipitating semisolid aminothioliol was extracted (Et₂O), washed (H_2O), and dried (MgSO_4). Ether was removed under reduced pressure, and the residual aminothioliol was cyclized by refluxing with 25 g of 90% formic acid and a little Zn dust for 3 hr. The cooled reaction mixture was poured into cold water, the slowly solidifying material was filtered off and boiled with 5% NaHCO_3 , and the solid was again filtered off after cooling. It was dissolved in ether, dried (MgSO_4), and distilled. The ester had bp 122–125° (0.2 mm), yield 11.5 g.

The NaHCO_3 solution was acidified to furnish 3 g of the free acid.

Ethyl 2-Phenyl-6-benzothiazolecarboxylate (III, R = C_6H_5).—A crude mixture (11.7 g) of ethyl 4-amino-3-mercaptobenzoate and 4-amino-3-mercaptobenzoic acid hydrochlorides was dissolved in 75 ml of dimethylaniline and treated gradually, with cooling and stirring, with 10 g of benzoyl chloride. After refluxing for 90 min the mixture was cooled and poured into 400 ml of 9% HCl. A solid precipitated, was filtered off, and worked up as above.

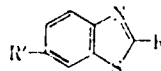
6-Benzothiazolemethanol (IV, R = H) and 2-phenyl-6-benzothiazolemethanol (IV, R = C_6H_5). were prepared by reduction of ethyl 6-benzothiazolecarboxylate and ethyl 2-phenyl-6-benzothiazolecarboxylate, respectively, with LiAlH_4 by the method of Zubarovskii and Khodot.¹⁵ Oxidation of these alcohols (0.05 mole) with active MnO_2 (80 g) in dry CHCl_3 (1 l.) at 27° for 24 hr, filtration from MnO and removal of the solvent gave 6-benzothiazolecarboxaldehyde (V) and 2-phenyl-6-benzothiazolecarboxaldehyde (VI), respectively.

6-(4-Dimethylamino-1-hydroxybutyl)-2-phenylbenzothiazole (Ib, $n = 3$; R = C_6H_5).—A solution of 1.5 g (0.012 mole) of γ -dimethylaminopropyl chloride in THF (2 ml) was added dropwise to a stirred mixture of Mg (0.3 g, 2 mg-atoms), dry THF (2 ml), and I_2 (one crystal) which had been activated with 0.1 ml of MeI. When the vigorous reaction had subsided the mixture was heated at 60° for 4 hr, another 0.2 g of γ -dimethylaminopropyl chloride was added, and heating was continued for 1 hr. 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.

(15) V. M. Zubarovskii and G. P. Khodot, *J. Gen. Chem. USSR*, 30 1268 (1960).

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.

TABLE I
DERIVATIVES OF BENZOTHIAZOLE^a



No.	R	R'	% yield	Solvent of crystals ^b	Mp, °C	Formula	Analyses
	H	COCH_3	69	$\text{PE-C}_6\text{H}_6$	94-95	$\text{C}_9\text{H}_7\text{NOS}$	C, H, N
	H	COCH_2Br	74	C_6H_6	133-135 ^c	$\text{C}_9\text{H}_6\text{BrNOS}$	C, H, Br
1	H	$\text{CHOHCH}_2\text{N}(\text{C}_2\text{H}_5)_2 \cdot 2\text{HBr}^d$ -Picrate	70	MeNO_2 MeCN	110-112 178-180	$\text{C}_{13}\text{H}_{16}\text{Br}_2\text{N}_2\text{O}_5\text{S}$ $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$	C, H, N C, H, N
2	H	$\text{CHOHCH}_2\text{N}(\text{C}_6\text{H}_5)_2^e$ -1,1'-Methylenebis(2-hydroxy-3-naphthoate) ^f -Picrate· HBr^g	69		128-130/ 153-154	$\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_8\text{S}$ $\text{C}_{22}\text{H}_{16}\text{BrN}_2\text{O}_8\text{S}$	C, H, N C, H, N
3	H	$\text{CHOHCH}_2\text{NC}_2\text{H}_5^h$	72	PE, EtOH	115-116	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{OS}$	C, H, N
	H	$\text{CO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2 \cdot \text{HCl}^i$	42	MeOH	210 dec.	$\text{C}_{12}\text{H}_{14}\text{ClN}_2\text{OS}$	C, H, N
	H	$\text{CO}(\text{CH}_2)_2\text{NC}_2\text{H}_5 \cdot \text{HCl}^{h,i}$	54	$\text{EtOH-H}_2\text{O}$	232-233	$\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{OS}$	C, H, N
4	H	$\text{CHOH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2 \cdot 2\text{HCl}^k$ -Picrate	53	EtOH MeCN	175-176 178-179	$\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{N}_2\text{OS}$ $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_5\text{S}$	N C, H, N
5	H	$\text{CHOH}(\text{CH}_2)_2\text{NC}_2\text{H}_5 \cdot 2\text{HCl}^{k,l}$ -Picrate	66	$\text{EtOH-Et}_2\text{O}$ MeCN	168-169 167-168	$\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{N}_2\text{OS}$ $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_5\text{S}$	C, H, N C, H, N
	C_6H_5	COCH_3	75	C_6H_6	191-192	$\text{C}_{13}\text{H}_{11}\text{NOS}$	C, H, N
	C_6H_5	COCH_2Br	45	C_6H_6	192-193	$\text{C}_{13}\text{H}_{10}\text{BrNOS}$	C, H, Br
	C_6H_5	$\text{COCH}_2\text{NC}_2\text{H}_5^m$	96	EtOH	123-125	$\text{C}_{20}\text{H}_{20}\text{N}_2\text{OS}$	C, H, N
	C_6H_5	$\text{COCH}_2\text{N}(\text{C}_2\text{H}_5)_2^m$ -Picrate	92				
6	C_6H_5	$\text{CHOHCH}_2\text{NC}_2\text{H}_5^h$	82	EtOAc	166 dec.	$\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_8\text{S}$	C, H, N
7	C_6H_5	$\text{CHOHCH}_2\text{N}(\text{C}_2\text{H}_5)_2$	71	Et_2O	84-86	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{OS}$	C, H, N
	C_6H_5	$\text{CO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2 \cdot \text{HCl}^n$	81	$\text{EtOH-H}_2\text{O}$	234	$\text{C}_{14}\text{H}_{17}\text{ClN}_2\text{OS}$	C, H, N
	C_6H_5	$\text{CO}(\text{CH}_2)_2\text{NC}_2\text{H}_5 \cdot \text{HCl}^{h,n}$	66	$\text{EtOH-H}_2\text{O}$	215	$\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{OS}$	C, H, N
8	C_6H_5	$\text{CHOH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$	81	PE	110-111	$\text{C}_{11}\text{H}_{13}\text{N}_2\text{OS}$	C, H, N
	C_6H_5	$\text{CHOH}(\text{CH}_2)_2\text{NC}_2\text{H}_5^h$	88	EtOH	149-150	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{OS}$	C, H, N
	C_6H_5	$\text{CHOH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$	50	PE	118-119	$\text{C}_{10}\text{H}_{12}\text{N}_2\text{OS}$	C, H, N
	CF_3	COCH_3	65	EtOH	104-105	$\text{C}_{10}\text{H}_6\text{F}_3\text{NOS}$	C, H, N
	CF_3	COCH_2Br^o	66	EtOH	113-114	$\text{C}_{11}\text{H}_6\text{BrF}_3\text{NOS}$	C, H, Br
	CF_3	$\text{CHOHCH}_2\text{N}(\text{C}_2\text{H}_5)_2^p$ -Picrate		EtOAc	164-165	$\text{C}_{20}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_8\text{S}$	C, H, N
9		-1,1'-Methylenebis(2-hydroxy-3-naphthoate) ^q	68			$\text{C}_{37}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_8\text{S} \cdot 2\text{H}_2\text{O}$	C, H, N
10	CF_3	$\text{CHOHCH}_2\text{NC}_2\text{H}_5 \cdot \text{HCl}^{h,p}$	74	EtOH	260-262	$\text{C}_{13}\text{H}_{14}\text{CF}_3\text{N}_2\text{OS}$	C, H, N
	CF_3	$\text{CO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2 \cdot \text{HCl}^r$	64	MeCN	180-181	$\text{C}_{12}\text{H}_{11}\text{CF}_3\text{N}_2\text{OS}$	C, H
	CF_3	$\text{CO}(\text{CH}_2)_2\text{NC}_2\text{H}_5 \cdot \text{HCl}^{h,r}$	57	MeCN	205-206	$\text{C}_{13}\text{H}_{14}\text{CF}_3\text{N}_2\text{OS}$	C, H
11	CF_3	$\text{CHOH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$	69	PE	104-105	$\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}_2\text{OS}$	C, H
12	CF_3	$\text{CHOH}(\text{CH}_2)_2\text{NC}_2\text{H}_5^h$	85	$\text{EtOH-H}_2\text{O}$	126-127	$\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_2\text{OS}$	C, H
	H	$\text{CO}_2\text{C}_2\text{H}_5$	55	PE	61-62	$\text{C}_{10}\text{H}_{11}\text{NO}_5\text{S}$	C, H
	H	CO_2H^s		EtOH	215-216		
	H	CHOH	74	C_6H_6	101-105	$\text{C}_9\text{H}_7\text{NOS}$	C, H
	H	CHO	78	$\text{Cyclohexane-C}_6\text{H}_6$	92-93	$\text{C}_9\text{H}_7\text{NOS}$	C, H, N
	H	$\text{CHOHCH}_2\text{NO}_2$	86	EtOH	130	$\text{C}_9\text{H}_9\text{N}_2\text{O}_5\text{S}$	C, H, N
	C_6H_5	CO_2H^s		AcOH	265	$\text{C}_{11}\text{H}_9\text{NO}_5\text{S}$	C, H
	C_6H_5	$\text{CO}_2\text{C}_2\text{H}_5$	55	EtOH	123	$\text{C}_{16}\text{H}_{15}\text{NO}_5\text{S}$	C, H
	C_6H_5	CHOH	91	C_6H_6	129-131	$\text{C}_{11}\text{H}_9\text{NOS}$	C, H
	C_6H_5	CHO	69	C_6H_6	160-162	$\text{C}_{11}\text{H}_9\text{NOS}$	C, H
	C_6H_5	$\text{CHOHCH}_2\text{NO}_2^t$	80	EtOH	180-181	$\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$	C, H, N

^a Compounds with Arabic numerals have been tested for antimalarial activity. ^b PE = petroleum ether (bp 50-60°). ^c Resolidified at 140° , decomposed at $230-240^\circ$. ^d The ketone, $\text{R} = \text{COCH}_2\text{NR}_2$, was prepared in C_6H_6 under N_2 at 27° for 3 hr. ^e Prepared by mixing equal or unequal amounts of the amine· HBr and the ammonium salt of the organic acid in H_2O , filtering, and drying (P_2O_5). ^f Double mp $128-130^\circ$, $240-250^\circ$ dec. ^g Prepared from the hydrobromide. ^h NC_2H_5 = piperidino. ⁱ Picrate from EtOAc , mp $163-164^\circ$, γ as not analyzed. ^j Mannich reaction time 1 hr, separated on cooling, light yellow solid, recrystallized after charcoal treatment. ^k Base was viscous liquid; dihydrochloride was prepared in dry Et_2O . ^l Prepared in C_6H_6 at 27° for 4 hr, then at 50° for 1 hr. ^m Decomposed on heating in solvents. ⁿ Reaction time 12 hr; separated on cooling. ^o Prepared from the ketone and Br_2 in AcOH at $60-70^\circ$. ^p From the bromo ketone in Et_2O at 27° for 24 hr. ^q Prepared from the crude base by the general procedure of J. H. Billman, D. G. Thomas, M. Hedrick, G. Schrottenboer, D. K. Barnes, J. Nemes, P. Trix, and E. Cleland, *J. Org. Chem.*, **11**, 77 (1946). ^r Reaction time 18 hr; separated on addition of Et_2O . ^s S. G. Fridman, *J. Gen. Chem. USSR*, **20**, 1191 (1950), gives mp 61° . ^t Lit. mp 245° . ^u Lit. mp 261° . ^v Prepared from aldehyde VI as described for the 2-substituted derivative, but using THF instead of Et_2O .

Antimalarials. 9. α -(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy and 2-(*p*-Chloroanilino) Groups^{†,1}

Journal of Medicinal Chemistry, 16, 528 (1973).

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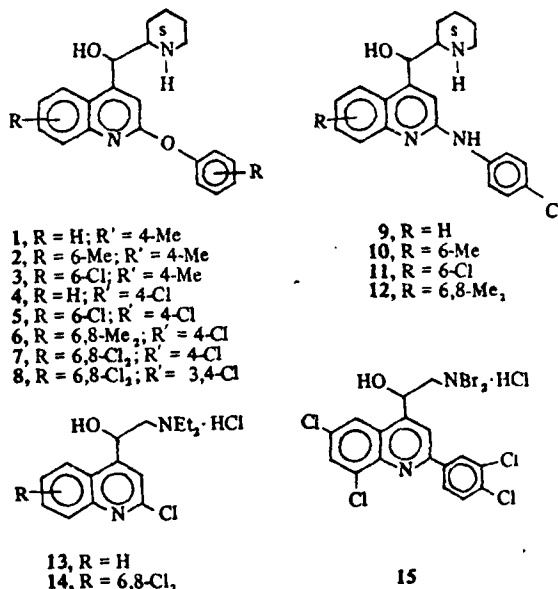
Twelve α -(2-piperidyl)-4-quinolinemethanols were synthesized from 2-chlorocinchoninic acids by additions of 2-PyLi, displacements of 2-Cl of the resulting 4-quinolyl 2-pyridyl ketones by aroxy or *p*-chloroanilino, and hydrogenations of the keto and pyridyl groups. Activities against *Plasmodium berghei* in mice were comparable with those of 2-aryl analogs. The 6,8-dichloro-2-(*p*-chlorophenoxy) compound was curative at 20 mg/kg but was phototoxic. 2-Chloro- α -diethylaminomethyl-4-quinolinemethanol, synthesized by a conventional route, was "inactive" against *P. berghei* but active against *Plasmodium gallinaceum* in birds

Syntheses of 12 α -(2-piperidyl)-4-quinolinemethanols (1-12) (and incidentally the 2-chlorodiethylamino alcohols 13 and 14) were undertaken with the following expectations: that the 2-aroxy and 2-(*p*-chloroanilino) would prevent oxidative biotransformations to less active carbostyrils,⁴ that these groups would lead to high activities against *Plasmodium berghei* in mice with firm binding of the molecules to the host tissues,⁵ and that phototoxicity, formerly thought to be associated with conjugation of aryl and the 2-quinoline nuclei⁶⁻⁸ in highly curative drugs such as 15,⁹ might be reduced by intervention between the aromatic nuclei of the heteroelement O or N which would destroy the direct conjugation although replacing it by forked conjugation.¹⁰

Chemistry. The α -(2-piperidyl)methanols 1-12 were synthesized from appropriate isatins through 2-hydroxy- and 2-chlorocinchoninic acids 16-20 (and ester 21).¹¹⁻¹⁴ Rather than displacing the 2-Cl at this stage,¹¹ the reactions outlined in Scheme I were used, namely, additions of 2-PyLi,¹⁵⁻¹⁹ then aroxy and anilino displacements of the active 2-Cl²⁰ of the 2-pyridyl ketones 22-26 (more difficult when an 8 substituent was present), and simultaneous Pt-H₂-AcOH¹⁷ hydrogenations of the keto and pyridyl groups of 27-38. Reduction of the *p*-methylthiophenoxy analog 40, however, was incomplete and stopped at the α -(2-pyridyl)methanol stage 43, presumably because of catalyst poisoning by sulfur of the substrate. The products 1-12 were isolated only in one of two possible racemic forms. Difficulties in and deviations from usual procedures are given in the Experimental Section.

In preliminary experiments toward making α -diethylaminomethyl-4-quinolinemethanols carrying 2-hetero substituents which might then be displaced,²⁰ 13 and 14 were synthesized by the standard sequence, Scheme II.^{9,21}

Biology. Results of tests against *P. berghei* in mice by the method of Rane²² are given in Table I. In activities, the α -(2-piperidyl)-2-aroxy- and 2-(*p*-chloroanilino)-4-quinolinemethanols 1-12 proved to be similar to 2-aryl analogs typified by 15.⁹ That chloro is a more effective auxopharmacophore than methyl is shown by marked and con-



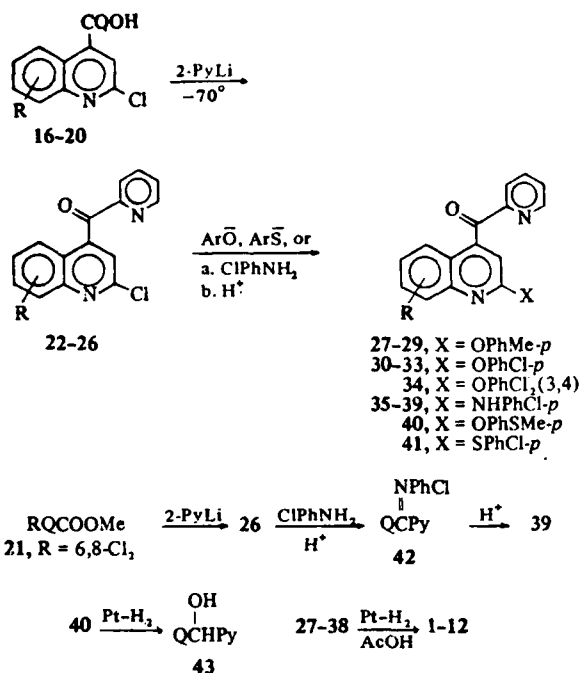
sistent activity differences between analogs, and *p*-chlorophenoxy appears to be slightly more effective than *p*-chloroanilino. The most active compound was the 6,8-dichloro-2-(*p*-chlorophenoxy) (7); it was "active" at 10 mg/kg, curative at 20 mg/kg, and somewhat more active than the α -dibutylaminomethyl-6,8-dichloro-2-(3,4-dichlorophenyl) analog 15. The combination of three aromatic chlorines plus the 2-aroxy oxygen in 7 has produced almost the same level of antimalarial activity as the combination of four aromatic chlorines in the α -dibutylaminomethyl 2-aryl analog 15.

Representatives of the more active of the compounds 1-12 proved to have high to moderate phototoxicities²³ comparable with those of 2-aryl and 2-aroxy analogs.^{7,8,10} It appears that intervention of the hetero elements, oxygen or nitrogen, between the 2-aryl and the quinoline nuclei (like the carbonyl group in 2-aroxy analogs¹⁰) has little or only moderate effect on both antimalarial activity and phototoxicity.

Experimental Section

Satisfactory spectra were obtained where required for structural determination. Instruments used were: for melting point, Thomas-Hoover apparatus; ir, Perkin-Elmer 337; nmr, Hitachi Perkin-Elmer R-20; and mass spectrum, Hitachi Perkin-Elmer RMU 6E. Microanalyses by Galbraith Lab., Inc., were correct within $\pm 0.4\%$ (see Table II for data).

[†]Contribution No. 1042 of the Army Research Program on Malaria. This work was supported in part by (a) the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. Da-48-193 MD-2955, R. E. Lutz, Responsible Investigator, with Postgraduate Research Assistantships to C. W. W. and J. R. S., 1968; (b) NASA Traineeship to J. R. S., 1968-1969; and (c) a fellowship to J. R. S. under A. H. Robins Co. research grant to R. E. L., University of Virginia, 1969-1970. Antimalarial and phototoxicity test results were supplied by Walter Reed Army Institute of Research (WRAIR).

Scheme I^a

^aQ = 4-quinolyl; R, see Table II.

2-Hydroxycinchoninic acid (75%) and derivatives, 6-Me (76%) and 7-Cl (30%), were prepared from the isatins through *N*-acetyl-isatin.^{11,12} The derivatives, 6-Cl (51%), 6,8-Me₂ (55%), 6,8-Cl₂ (89%), and 7-Cl (65%), were made from the isatin and malonic acid (AcOH, reflux 15-17 hr).¹⁴

2-Chlorocinchoninic acids¹² 16-20 were obtained (ca. 80%) by treatment of the 2-hydroxy acids¹³ with POCl₃ (reflux, 3 hr), hydrolysis by H₂O (3 hr; but for 17 and 20, by solution in dioxane containing excess 2 *N* NaOH), solution in NaHCO₃, and reprecipitation by acid.

Table I. Bioassay Data^{a,b}

1-12

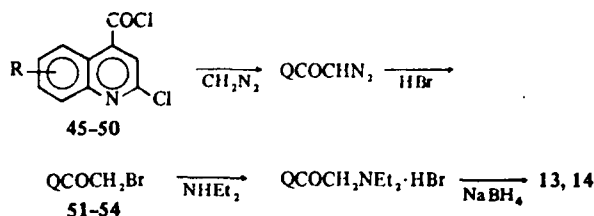
15

13

Compd	Rel no.	X	R	Antimalarial activities. ^a MST ^c (days), C (cures) ^{d,e}						Phototoxicity, ^b MED ^f Ip (oral), dose, mg/kg
				20	40	80	160	320	640	
1	932	OPhMe- <i>p</i>	H	0.4	0.4	0.6	0.8	0.8	1.0	
2	933	OPhMe- <i>p</i>	6-Me	0.4	0.4	0.6	0.6	2.6	7.8	
3	934	OPhMe- <i>p</i>	6-Cl	0.2	0.6	3.0	3.4	5.2	Toxic	
4	940	OPhCl- <i>p</i>	H	0.3	0.5	2.9	7.1	9.1	2C	
5	965	OPhCl- <i>p</i>	6-Cl	1.3	5.3	13.7	1C	4C	4C	75 (50)
6	945	OPhCl- <i>p</i>	6,8-Me ₂	0.5	5.5	12.5	13.9	2C	2C	
7	970	OPhCl- <i>p</i>	6,8-Cl ₂	2C	3C	5C	5C	5C	5C	(50)
8	973	OPhCl ₂ (3,4)	6,8-Cl ₂	13.9	3C	5C	5C	5C	5C	25 (25)
9	930	NHPhCl- <i>p</i>	H	0.6	0.6	1.0	7.8	10.0	1C	
10	931	NHPhCl- <i>p</i>	6-Me	0.6	0.6	0.8	1.8	11.2	4C	15
11	938	NHPhCl- <i>p</i>	6-Cl	0.3	0.5	1.7	6.1	2C	2C	
12	939	NHPhCl- <i>p</i>	6,8-Me ₂	0.3	0.3	1.7	3.7	6.9	2C	25
15 ^g	556	PhCl ₂ (3,4)	6,8-Cl ₂	3C ^e	6C	8C	10C	10C	10C ^e	25
13 ^h	935	Cl	H	0.4	1.0	1.2	3.2			

^aAgainst *P. berghei* in mice (see ref 22) ^bSee ref 23. ^cMean survival times in days; a compound is considered "active" when MST is doubled or more. ^dC = number of cures (mice surviving to 60 days) out of test groups of five mice. ^eFor 15 test groups were ten mice. ^fMED = minimum effective dose in milligrams per kilogram. ^g15 = WR 30090 (SN 15068), the 2-aryl-4-(CHO)CH₂-HCl analog, it is included for comparison. ^hThis is the *o*-CH₂NEt₂·HCl analog; it was active at 160 mg/kg against *P. gallinaceum* in birds.

Scheme II



Methyl 2,6,8-Trichlorocinchoninate (21).¹⁴ A solution of 10.8 g of 2-hydroxy-6,8-dichlorocinchoninic acid in 30 ml of SOCl₂, 9 ml of DMF, and 25 ml of C₆H₆ was refluxed (15 hr) and evaporated. Treatment of the residue with 5 l. of refluxing MeOH (10 min) gave 21 [ir (KBr) 1745 cm⁻¹ (C=O); nmr (CDCl₃) δ 4.10 (s, 3, OCH₃), 7.92 (d, 1, *J* = 3 Hz, 7-H), 8.05 (s, 1, 3-H), 8.78 (d, 1, *J* = 3 Hz, 5-H)].

2-Chloro-4-quinolyl 2-Pyridyl Ketones (22-25). To 51.5 g of 22% *n*-BuLi (in hexane, 0.177 mol), in 75 ml of Et₂O (distilled from dry-Na) (-60°, under N₂, stirring), was added 28.2 g (0.179 mol) of 2-BrPy (30 min) and then 11.6 g of 17 (0.048 mol) in 450 ml of THF (distilled from LiAlH₄) with stirring (4.5 hr). Warming to -35°, addition of 100 ml of H₂O, H₂O quenching, standing, filtering, washing, drying (110°), and chromatography (Al₂O₃, elution with C₆H₆ and CHCl₃) gave 24 [ir (KBr) 1680 cm⁻¹ (C=O)]. The use of Et₂O, Et₂O-THF, or THF-glyme as reaction solvent generally gave poorer yields (4% of 26).

2,6,8-Trichloro-4-quinolyl 2-Pyridyl Ketone (26). Portionwise addition of ester 21 to 2-PyLi in Et₂O (-78°) (charcoal treatment: CHCl₃, Celite) gave 26 [ir (KBr) 1680 cm⁻¹ (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 340 (18), 338 (54), 336 (55), 311 (36), 309 (100), 307 (100), 275 (74), 273 (100), 234 (9), 232 (32), 230 (32), 78 (78)]. A similar run in 1:1 Et₂O-THF (-60°) and chromatography (Al₂O₃, C₆H₆-CHCl) gave 4% of 26.

2-(*p*-Methylphenoxy)-, 2-(*p*-Methylthio)phenoxy-, and 2-(*p*-Chlorophenylthio)-4-quinolyl 2-Pyridyl Ketones (27, 40, 41). A solution of 2.6 g (9.2 mmol) of 22 and 3 g of NaOC₂H₄Me-*p* (23 mmol) in 35 ml of dioxane (distilled from CaH₂) was refluxed (15 hr); 27 was then precipitated by H₂O quenching. 40 and 41 were made like 27 (dioxane, reflux, ca. 22 hr). Under similar conditions 25 was recovered (90%), and in diglyme (reflux, 6 hr) the product was an intractable oil.

2-(*p*-Chlorophenoxy)-6-chloro and 6,8-Dimethyl-4-quinoyl 2-Pyridyl Ketones (31 and 32). Under the above conditions using NaOPhCl-*p* (reflux, 48 hr) 24 was recovered (80%). Use of DMSO or DMSO, as solvent (160 and 125°) gave intractable products. A solution of 1.36 g (4.5 mmol) of 25 and 4.5 g (30 mmol) of NaOPhCl-*p* in 32 g of molten *p*-chlorophenol was stirred at 95° (13 hr) and quenched in H₂O. The product, 32, was charcoaled (Et₂O) [ir (KBr) 1685 (C=O), 1232 cm⁻¹ (COC)]. Reaction of 24 under the above conditions was incomplete in 10 hr (tlc) but in 22 hr gave 31.

2-(*p*-Chloro- and 3,4-dichlorophenoxy)-6,8-dichloro-4-quinoyl 2-Pyridyl Ketones (33 and 34). To C₆H₆-washed NaH (0.069 mol, from 3 g of a 55% dispersion in mineral oil) in 200 ml of DMF (molecular sieve 4A, 48 hr) was added dropwise a solution of 22 g (0.17 mol) of *p*-chlorophenol (in 100 ml of DMF) and then 4 g (1.32 mmol) of 26. Heating (95°, 11 hr), H₂O quenching, and crystallization from Me₂CO (charcoal) gave 33 [ir (KBr) 1680 (C=O), 1235, 1215 cm⁻¹ (COC); mass spectrum (70 eV) *m/e* (rel intensity) 432 (15.6), 430 (43.8), 428 (43.8), 326 (26.5), 324 (79), 222 (79), 78 (100)]. Compound 34 was made similarly from 3,4-dichlorophenol.

2-(*p*-Chloroanilino)-4-quinoyl 2-Pyridyl Ketones (35-38). A 50-ml solution of 3.5 g (0.0118 mol) of 25 and 6 g of *p*-chloroaniline in absolute EtOH was refluxed (48 hr; 23 and 24 required only 6 hr). After adding 50 ml of H₂O and 25 ml of concentrated HCl, and again refluxing (1 hr), 38 was precipitated by H₂O-NaOH quenching [ir (KBr) 1720 cm⁻¹ (C=O)]. Without HCl the anil was obtained, mp 198-200° (not analyzed) [ir (KBr) 1630 cm⁻¹ (C=N)]. The 2,6-Cl₂ ketone 26 under these conditions failed to react with 2,4-dimethylaniline (24 hr).

2-(*p*-Chloroanilino)-6,8-dichloro-4-quinoyl 2-Pyridyl Ketone (39) and Its Anil (42). A solution of 5.9 g (17.6 mmol) of 26 and 5.1 g of *p*-chloroaniline·HCl in 100 ml of *p*-chloroaniline was stirred at 95° (under N₂, 8 hr). H₂O quenching gave 42. Solution in 1.8 l. of 1.5 M HCl in 60% EtOH and refluxing (2 hr) gave 39. In a separate experiment, anil 42 was washed with dilute NaOH [ir (KBr) 1685 cm⁻¹ (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 431 (36), 429 (98), 427 (100), 325 (20), 323 (59), 321 (59), 290 (8), 288 (27), 286 (34), 78 (61)]. It is evident that displacement of 2-Cl by an aniline is impeded by an 8-quinoline substituent and by *o*-Me in the aniline and that the reaction is autocatalyzed by HCl liberated.²⁴

2-Aroxy- and 2-(*p*-Chloroanilino)- α -(2-piperidyl)-4-quinoline-methanols (1-12). Hydrogenations of the 2-pyridyl ketones 27-39 were by Pt-H₂ (0.2 g of 84% PtO₂ per 3 g of substrate at 43 psi in 250 ml of AcOH), followed by filtration (Celite), and NaOH-H₂O quenching (directly or after vacuum evaporation of AcOH and solution in Me₂CO).

α -(2-Pyridyl)-2-[*p*-(methylthio)phenoxy]-4-quinolinemethanol (48) was made from 40 by Pt-H₂-AcOH (as above) [ir (KBr) 3100 cm⁻¹ (broad, OH); nmr (CDCl₃) δ 2.50 (s, 3, SCH₃), 4.40 (s, 1, OH), 6.42 (s, 1, CHOH)].

Attempted Synthesis of α -(2-Piperidyl)-6,8-dichloro-2-(*p*-chlorophenyl)-4-quinolinemethylamine (OCH(NH₂))Pip; for Comparison with 7 and 15). 6,8-Dichloro-2-(*p*-chlorophenyl)-4-quinoyl 2-Pyridyl Ketoxime, QC(2-Pip)=NOH (44). Reaction of 2-PyLi-Et₂O with the cinchoninic methyl ester (-78°, under N₂) and treatment of the resulting ketone (83%) with NH₂OH·HCl-pyridine in absolute EtOH (reflux 6 hr) gave 44 [ir (KBr) 3225 cm⁻¹ (OH), no C=O band]. Pt-H₂-AcOH reduction²⁵ gave an unpromising mixture (six compounds, tlc).

2-Chlorocinchoninyl Chlorides (45-50). For 45 and 48, see ref 13. For the others, a melt of 69 g (0.278 mol) of (e.g.) 20 and 112 g (0.535 mol) of PCl₅ was refluxed (5 hr), cooled, washed (Et₂O), and charcoaled (hot C₆H₆).

2-Chloro-4-quinoyl Bromomethyl Ketones (51-54). Addition of 49 (11.3 g, 0.05 mol) to 6 g (0.14 mol) of CH₃N₃ in 400 ml of alcohol-free Et₂O (4 hr), addition of 40 ml of 48% HBr (1 hr), extractions (Et₂O), drying (CaSO₄), and evaporation gave 53.

2-Chloro- α -diethylaminomethyl-4-quinolinemethanols (13, 14). To a solution of 2.84 g (0.01 mol) of (e.g.) 51 in 51 ml of Et₂O was added 2.82 g of Et₂NH (3 hr, 20°). After titration and vacuum evaporation, a solution of the oil in 50 ml of MeOH was treated with 0.35 g of NaBH₄²¹ and 4 ml of H₂O (stirring 3 hr). After quenching (1.5 l. of H₂O, standing 5 hr), vacuum evaporation of Et₂O extracts, solution of the residue in Et₂O, and drying (CaSO₄), 13·HCl was precipitated by dry HCl-Et₂O.

2-Chloro-4-cyanoquinolines (55-60).^{26,27} The 2-chlorocinchoninic acids (where attempts at direct KF exchange had failed) were converted to acid chlorides 45-50 and thence by C₆H₆-NH₃-H₂O (stirring) to crude amides (air-dried) which were then treated

(16 hr) with refluxing POCl₃-PCl₅ (rather than SOCl₂).

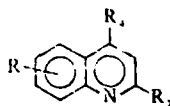
2-Hydroxy-4-acetylquinoline (61). Reaction of 2-chloro-4-cyanoquinoline (55) with MeLi (-60°, Et₂O, 3 hr) was incomplete. After recovery of 55 (38%) and hydrolysis of the EtOH filtrate, an equal volume of 18% HCl was added (reflux, 2 hr), giving 61.

2-Fluoro-4-cyanoquinolines²⁸ (62-66). With KF in DMSO (anhydrous, under N₂, 180°), 55-60 underwent selective displacement of 2-Cl by F. Attempted hydrolysis of CN of 62 (75%, H₂SO₄, 100°, 4 hr) gave 2-hydroxycinchoninic acid, whereas under these conditions 2-chloronitrile 55 was converted into 2-chlorocinchoninic acid (16).

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Table II. Quinoline Compounds^a

Compd	R	R ₁	R ₂	Crystn solvent ^{b-i}	Mp, °C	% yield	Formula	Analyses ^{m-p}
1	H	O _{Ph} Me- <i>p</i>	CHOHPip	EtOH	199-200	61	C ₂₂ H ₂₄ N ₂ O ₂	C, H, N
2	6-Me	O _{Ph} Me- <i>p</i>	CHOHPip	EtOH	167-169	38	C ₂₃ H ₂₆ N ₂ O ₂	C, H, N
3	6-Cl	O _{Ph} Me- <i>p</i>	CHOHPip	EtOH	180-181	46	C ₂₁ H ₁₉ ClN ₂ O ₂	C, H, N
4	H	O _{Ph} Cl- <i>p</i>	CHOHPip	EtOH	173-174	42	C ₂₁ H ₂₁ ClN ₂ O ₂	C, H, N
5	6-Cl	O _{Ph} Cl- <i>p</i>	CHOHPip	EtOH	183.5-185	40	C ₂₁ H ₂₀ Cl ₂ N ₂ O ₂	C, H, N
6	6,8-Me ₂	O _{Ph} Cl- <i>p</i>	CHOHPip	EtOH	171-172	52	C ₂₃ H ₂₅ ClN ₂ O ₂	C, H, N
7	6,8-Cl ₂	O _{Ph} Cl- <i>p</i>	CHOHPip	<i>h</i>	208-209 dec	42	C ₂₁ H ₁₉ Cl ₂ N ₂ O ₂	C, H, N
8	6,8-Cl ₂	O _{Ph} Cl ₂ (3,4)	CHOHPip	Me ₂ CO ^f	196-198 dec	51	C ₂₁ H ₁₈ Cl ₂ N ₂ O ₂	C, H, N, Cl
9	H	NHPhCl- <i>p</i>	CHOHPip	EtOH-H ₂ O ^f	183-185		C ₂₁ H ₂₂ ClN ₂ O	C, H, N
9·H ₂ O				EtOH-H ₂ O	131-133	87	C ₂₁ H ₂₂ ClN ₂ O·H ₂ O	C, H, N
10	6-Me	NHPhCl- <i>p</i>	CHOHPip	EtOH-H ₂ O ^f	117-119	89	C ₂₂ H ₂₄ ClN ₂ O	C, H, N
11	6-Cl	NHPhCl- <i>p</i>	CHOHPip	<i>j</i>	185-187		C ₂₁ H ₂₁ Cl ₂ N ₂ O	C, H
11·H ₂ O					115-117		C ₂₁ H ₂₁ Cl ₂ N ₂ O·H ₂ O	C, H, N
12	6,8-Me ₂	NHPhCl- <i>p</i>	CHOHPip	EtOH-H ₂ O ^f	228-229	63	C ₂₃ H ₂₆ ClN ₂ O	C, H
13	H	Cl	CHOHCH ₂ NEt ₂ ·HCl	EtOH-Et ₂ O	204-205	15	C ₁₃ H ₁₉ ClN ₂ O·HCl	C, H, N
14	6,8-Cl ₂	Cl	CHOHCH ₂ NEt ₂ ·HCl	<i>k</i>	96-99	40	C ₁₃ H ₁₇ Cl ₂ N ₂ O·HCl	C, H ⁿ
16	6-Me	Cl	COOH	<i>b</i>	195 dec		C ₁₁ H ₈ ClNO ₂	C, H
17	6-Cl	Cl	COOH	<i>b</i>	187 dec		C ₁₀ H ₇ Cl ₂ NO ₂	C, H
18	7-Cl	Cl	COOH	<i>b</i>	206 dec		C ₁₀ H ₇ Cl ₂ NO ₂	C, H
19	6,8-Me ₂	Cl	COOH	<i>b</i>	205 dec		C ₁₂ H ₁₀ ClNO ₂	C, H
20	6,8-Cl ₂	Cl	COOH	<i>b</i>	250-253 dec		C ₁₀ H ₇ Cl ₂ NO ₂	C, H
21	6,8-Cl ₂	Cl	COOMe	MeOH	167-169		C ₁₁ H ₈ Cl ₂ NO ₂	C, H
22	H	Cl	COPY	EtOH	149-150	69	C ₁₃ H ₉ ClN ₂ O	C, H, N
23	6-Me	Cl	COPY	EtOH	154.5-155.5	68	C ₁₄ H ₁₁ ClN ₂ O	C, H
24	6-Cl	Cl	COPY	<i>d</i>	203-204.5	54	C ₁₃ H ₉ Cl ₂ N ₂ O	C, H
25	6,8-Me ₂	Cl	COPY	EtOH	168-169	74	C ₁₅ H ₁₃ ClN ₂ O	C, H
26	6,8-Cl ₂	Cl	COPY	EtOH	212-214	68	C ₁₅ H ₁₁ Cl ₂ N ₂ O	C, H
27	H	O _{Ph} Me- <i>p</i>	COPY	EtOH	136-137.5	71	C ₂₂ H ₁₆ N ₂ O ₂	C, H
28	6-Me	O _{Ph} Me- <i>p</i>	COPY	EtOH	111-112.5	82	C ₂₃ H ₁₈ N ₂ O ₂	C, H
29	6-Cl	O _{Ph} Me- <i>p</i>	COPY	EtOH	87-89	35	C ₂₂ H ₁₇ ClN ₂ O ₂	C, H
30	H	O _{Ph} Cl- <i>p</i>	COPY	EtOH	151-153	40	C ₂₁ H ₁₇ ClN ₂ O ₂	C, H
31	6-Cl	O _{Ph} Cl- <i>p</i>	COPY	Me ₂ CO-CHCl ₃	163.5-165	71	C ₂₁ H ₁₇ Cl ₂ N ₂ O ₂	C, H, N, Cl
32	6,8-Me ₂	O _{Ph} Cl- <i>p</i>	COPY	EtOH	134-135	73	C ₂₃ H ₁₇ ClN ₂ O ₂	C, H, N
33	6,8-Cl ₂	O _{Ph} Cl- <i>p</i>	COPY	Me ₂ CO	207-208	80	C ₂₁ H ₁₇ Cl ₂ N ₂ O ₂	C, H, N
34	6,8-Cl ₂	O _{Ph} Cl ₂ (3,4)	COPY	EtOH ^g	222-223 dec	52	C ₂₁ H ₁₇ Cl ₂ N ₂ O ₂	C, H, N, Cl
35	H	NHPhCl- <i>p</i>	COPY	EtOH	182-184	83	C ₂₁ H ₁₉ ClN ₂ O	C, H
36	6-Me	NHPhCl- <i>p</i>	COPY	EtOH	180-182	56	C ₂₂ H ₂₀ ClN ₂ O	C, H
37	6-Cl	NHPhCl- <i>p</i>	COPY	EtOH	212-213	45	C ₂₁ H ₁₉ Cl ₂ N ₂ O	C, H
38	6,8-Me ₂	NHPhCl- <i>p</i>	COPY	EtOH	208-209.5	79	C ₂₃ H ₂₁ ClN ₂ O	C, H
39	6,8-Cl ₂	NHPhCl- <i>p</i>	COPY	EtOH ^g	236-237 dec	78	C ₂₁ H ₁₇ Cl ₂ N ₂ O	C, H, N
40	H	O _{Ph} SMe- <i>p</i>	COPY	Me ₂ CO	174.5-176	61	C ₂₂ H ₁₆ N ₂ O ₂ S	C, H, N
41	H	SPhCl- <i>p</i>	COPY		149.5-151		C ₂₁ H ₁₇ ClN ₂ OS	C, H ^o
42	6,8-Cl ₂	NHPhCl- <i>p</i>	C(Py)=NPhCl- <i>p</i>	CHCl ₃ -hexane	165-170 ^f		C ₂₇ H ₁₆ Cl ₂ N ₄	C, H, N
43	H	O _{Ph} SMe- <i>p</i>	CHOHPy		140-142	71	C ₂₂ H ₁₈ N ₂ O ₂ S	C, H, N
44	6,8-Cl ₂	PhCl- <i>p</i>	C(Pip)=NOH		264-265.5	58	C ₂₁ H ₁₇ Cl ₂ N ₂ O	C, H, N
45	H	Cl	COCl	C ₆ H ₆ ^c	95		C ₁₀ H ₇ Cl ₂ NO ₂	<i>q</i>
46	6-Me	Cl	COCl	C ₆ H ₆ ^c	125-126.5		C ₁₁ H ₉ Cl ₂ NO	C, H
47	6-Cl	Cl	COCl	C ₆ H ₆ ^c	128-129.5		C ₁₀ H ₇ Cl ₂ NO	C, H
48	7-Cl	Cl	COCl	C ₆ H ₆ ^c	106-107.5		C ₁₀ H ₇ Cl ₂ NO	C, H
49	6,8-Me ₂	Cl	COCl	C ₆ H ₆ ^c	94.5-96	49	C ₁₂ H ₉ Cl ₂ NO	C, H
50	6,8-Cl ₂	Cl	COCl	C ₆ H ₆ ^c	109-110	71	C ₁₀ H ₇ Cl ₂ NO	C, H
51	H	Cl	COCH ₂ Br	EtOH	101-102	86	C ₁₁ H ₉ BrClNO	C, H
52	6-Me	Cl	COCH ₂ Br	EtOH	97-98	80	C ₁₂ H ₁₁ BrClNO	C, H
53	6,8-Me ₂	Cl	COCH ₂ Br	EtOH	71-72.5	73	C ₁₄ H ₁₁ BrClNO	C, H
54	6,8-Cl ₂	Cl	COCH ₂ Br	EtOH	98-98	77	C ₁₁ H ₉ BrCl ₂ NO	C, H ^p
55	H	Cl	CN	EtOH	153-154	78	C ₁₀ H ₇ ClN ₂	C, H
56	6-Me	Cl	CN	EtOH	121-122	55	C ₁₁ H ₉ ClN ₂	C, H
57	6-Cl	Cl	CN	EtOH	178-179.5	63	C ₁₀ H ₇ Cl ₂ N ₂	C, H
58	7-Cl	Cl	CN	EtOH	145-147	47	C ₁₀ H ₇ Cl ₂ N ₂	C, H
59	6,8-Me ₂	Cl	CN	EtOH	153-154	64	C ₁₂ H ₉ ClN ₂	C, H
60	6,8-Cl ₂	Cl	CN	EtOH	174-175	78	C ₁₀ H ₇ Cl ₂ N ₂	C, H
61 ^r	H	OH	COMe	EtOH	199-200	60	C ₁₁ H ₉ NO ₂	C, H
62	H	F	CN	EtOH	141-141.5 ^c	67	C ₁₀ H ₇ FN ₂ ^c	C, H, N
63	6-Me	F	CN	EtOH	121-122 ^c	63	C ₁₁ H ₉ FN ₂ ^c	C, H, F
64	6-Cl	F	CN	EtOH	182-183.5 ^c	49	C ₁₀ H ₇ ClFN ₂ ^c	C, H, F
65	6,8-Me ₂	F	CN	EtOH	125-126 ^c	43	C ₁₂ H ₉ FN ₂ ^c	C, H, N
66	6,8-Cl ₂	F	CN	EtOH	155-156 ^c	54	C ₁₀ H ₇ Cl ₂ FN ₂ ^c	C, H, F

^aPy = 2-pyridyl; Pip = 2-piperidyl; Ph = phenyl. ^bPartial purification by solution in NaHCO₃ and precipitation by HCl, oven dried. ^cVacuum sublimed. ^dChromatography; Al₂O₃, C₆H₆-CHCl₃. ^eChromatography; Florisil, CHCl₃. ^fChromatography; Florisil, CHCl₃-hexane. ^gEtOH-CHCl₃. ^hMe₂CO-CH₂Cl₂ or CH₂Cl₂ (trapping of C₆H₆ or Me₂CO shown by nmr); dried at 100° (0.05 mm) (48 hr) or crystallized from CH₂Cl₂. ⁱCrystallization from Me₂CO rapidly gave polymorph A; crystallization slowly gave polymorph B with the same melting point and nmr (CDCl₃) but differing in the ir (KBr) fingerprint region, the ir (KBr) of A after solution in CHCl₃ and evaporation over KBr was identical with that of B (KBr). ^jVacuum dried (100°). ^kSample not recrystallized. ^lSolidified at 175°; remelted at 261.5-263°. ^mAnalyses were within 0.4% of theory except as follows. ⁿC calcd, 46.90, found, 47.40. ^oH calcd, 3.48, found, 3.85. ^pC calcd, 37.39, found, 35.15 (sample not recrystallized). ^qFound, 47.40, 47.40. ^rFound, 47.40.

Part 6. 3-Substituted-2-aryl-4-quinoline Aminoalcohols.

Antimalarials. 10. 3-Substituted α -Dialkylaminomethyl-2-aryl-4-quinolinemethanols.^{#1}

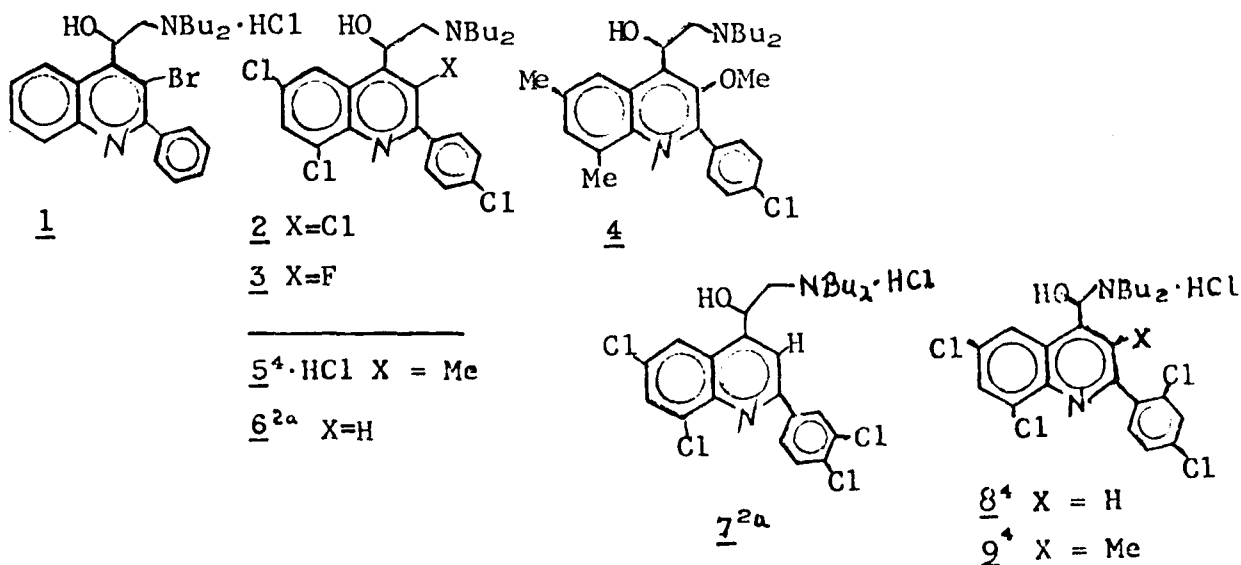
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Abstract 4',6,8-Trichloro-2-phenyl-4-quinoline aminoalcohols with a fourth group in the 3-position, Cl, F or OMe, were synthesized for antimalarial tests. A new modification of the Pfitzinger reaction was successful with α -haloacetophenones, utilizing methoxyethanol and trace amounts of KOH. The 3-halo aminoalcohols were made via diazomethylation of the acid chlorides; and the OMe derivative was made via the 4-quinolaldehyde and methylenation. The 3,4',6,8-Cl₄ and 3-F-4',6,8-Cl₃ compounds were curative against Plasmodium berghei in mice at 10-40 mg/kg; they were moderately phototoxic in animals.

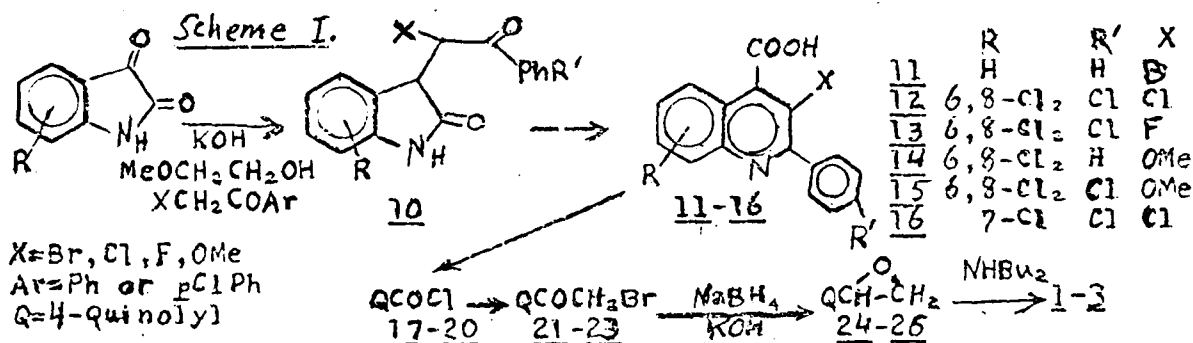
3-Halo and 3-methoxy 2-aryl-4-quinoline aminoalcohols 1-4 were synthesized for comparison with the highly curative antimalarial 7^{2a} to gain further information concerning earlier indications that phototoxicity in 2-aryl types paralleled electronegativities of 4'-substituents³, Cl > CH₃ > OCH₃, and is decreased by the combination of 3-Me and 2'-Cl which must sterically interfere with coplanarity and effectiveness of conjugation of the π -systems³ (eg 5,8,9⁴). This work when started was given impetus by the postulate that phototoxicity of a final drug might be anticipated from phototoxicity of the cinchophen from which it was made, and from the finding that 3-bromocinchophen (11) was not phototoxic. However, this factor per se now seems inconsequential in light of the effectiveness of 7^{2a} for treatment of acute malarial in clinical trials on man^{2b,c} where photosensitivity proved to be a minor consideration.



Chemistry

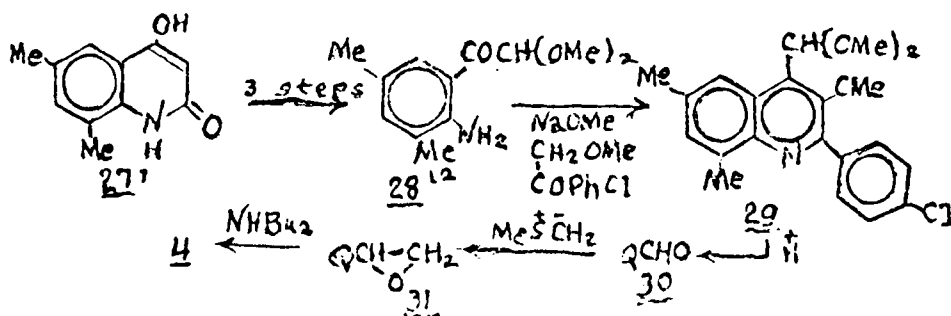
Attempted addition of 2-PyLi⁵ to 3-bromocinchophen (11^e) having failed, aminoalcohol 1 was synthesized by the classical route^{2a} outlined in Scheme I: diazomethylation of the acid chloride 17, hydrobromination of the diazoketone, NaBH₄-KOH reduction of bromoketone 21 to the epoxide 24, and condensation with NHBu₂.

Attempts to make intermediate cinchophens 12 and 13 from the isatin and the highly reactive 2-haloacetophenones by modified⁷ Pfitzinger procedure were unsuccessful, but 3-methoxycinchophens 14 and 15 were obtainable by this method^{7c,d} using the less reactive α-methoxyacetophenones. A new procedure was then developed for the reaction with α-haloacetophenones using methoxyethanol as solvent with smaller amounts of KOH, which gave 3-halocinchophens 11-13 in good yields. Since neither 12 nor its Me-ester reacted with 2-PyLi under the usual conditions⁵, the 3-halo cinchophens 12 and 13 were converted into aminoalcohols 2 and 3 by the classical route² as illustrated in Scheme I.



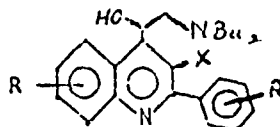
Diazomethylation of 3-methoxy-6,8-dichlorocinchophen acid chloride (20) and hydrobromination failed to give the desired bromomethyl ketone (loss of 3-OMe was shown by ir). A synthetic approach⁸ through the 4-hydroxycarbostyryl to 4-quinaldehyde⁹ was then successfully applied to make compound 4, as outlined in Scheme II, starting from 6,8-dimethyl-4-hydroxycarbostyryl (27), chosen instead of the preferred 6,8-Cl₂ analog where reported yields were low^{9c}. This involved conversion into the 2-amino glyoxal acetal 28, condensation with MeOCH₂COPhCl_p, hydrolysis of 29 to 4-quinaldehyde 30, methylenation¹⁰ to epoxide 31, and condensation with NHBu₂ to 4.

Scheme II.



Antimalarial Activities. Table I includes test results against *P. berghei* in mice (method of Rane¹¹) and phototoxicities³, on four new 3-substituted 4-quinoline aminocalcohols 1-4, and also on 5-9^{2,4} for comparisons. Of 1-4, the 3-fluoro derivative 3 was the most active (at 2.5 mg/kg) and curative at 10 mg/kg.

TABLE I.

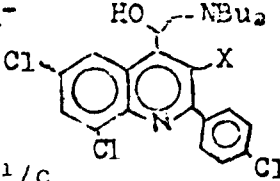
Antimalarial Activities Against *P. berghei* In Mice

Cpd.	WR No.	Substituents			IMST (days) ^b , C (cures) ^{c,d} Dose, mg/kg					Phototoxicity ^e MED ^f (mice) 320 Ip, mg/kg	
		R	R'	X	10	20	40	80	160		
<u>2</u>	140089	6,8-Cl ₂	4-Cl	Cl	6.4	8.2	10	30	30	50	50
<u>3</u>	149105	6,8-Cl ₂	4-Cl	F	10	20	30	50	50	50	100
<u>4</u>	157307	6,8-Me ₂	4-Cl	OMe	0.7	4.1	6.1	8.1	14.1	40	100
<u>5</u> ^g	42934	6,8-Cl ₂	4-Cl	Me	7.2	10.6	10	20	20	20	12.5
<u>6</u> ^h	29252	6,8-Cl ₂	4-Cl	H	20	30	40	50	50	50	25
<u>6A</u> ^h	28616	6,8-Me ₂	4-Cl	H	5.9	10.1	20	40	40	50	-
<u>7</u> ^h	30090	6,8-Cl ₂	3,4-Cl ₂	H	15	30	60	80	100	100	50
<u>8</u> ^g	53188	6,8-Cl ₂	2,4-Cl ₂	H	1.0	3.5	9.1	20	30	40	12.5
<u>9</u> ^g	63489	6,8-Cl ₂	2,4-Cl ₂	Me	0.3	1.3	1.7	7.1	10	20	100
<u>1</u>	121473	H	H	Br		0.1		0.1		0.3	Neg

^aSee ref. 11. ^bIMST=Increase in mean survival time in days; cpd. considered active when IMST is at least twice that of controls (6 days). ^cC=Number of cures (mice surviving 60 days) of test groups of five mice. ^dTest groups for 7 were ten mice. ^eRef. 3. ^fMED = Min. effective dose. ^gRef. 4. ^hRef. 2a.

The results for the 6,8-dichloro-2-(p-chlorophenyl) and dichlorophenyl compounds, 2,3,5,6 and 7,8,9, show that as the bulk of the 3-substituent increases (H < F < Cl < Me) the antimalarial activities decrease in that order, 6 > 3 > 2 > 5 and 7 > 8 > 9, paralleling the Taft steric parameter E_s (Table II) which has been used by Hansch¹² in quantitative multiparameter structure-activity correlations. The relationship can be seen at 10-20 mg/kg and is more pronounced at 40-80 mg/kg. Activity decreases as E_s becomes more negative. The same effect is observed for the isomeric 2-(dichlorophenyl) series 7-9 and 2 with regard to the ortho position in the 2-phenyl ring. A comparison of the activities of 2 and 8 shows that the 3 and 2'-positions are similar in effect for Cl as substituent. One explanation for this is that inhibition of coplanarity of the 2-phenyl and quinoline rings reduces antimalarial activity.

Table II. Structure-Activity Parameters for 3-X-2-Aryl-4-quinolinemethanols Against *P. berghei* in Mice.
$$\log 1/c = 0.661 (\pm 0.34)E_s - 3 + 0.824 (\pm 0.25)$$

$$\begin{matrix} n & r & s \\ 5 & 0.962 & 0.104 \end{matrix}$$


cpd	X	E_s	π	σ_m	σ_p	MR	MW	σ sd.	$\log 1/c$ calc.	$\Delta \log 1/c$
<u>6</u>	H	1.24	0	0	0	1.03	1	1.641	1.644	-0.003
<u>3</u>	F	0.78	0.10	0.34	0.06	0.92	19	1.462	1.340	0.122
<u>4</u> ^b	OMe	0.69	-0.33	0.12	-0.27	7.87	31	1.165 ^b	1.280	-0.115
<u>2</u>	Cl	0.27	0.59	0.37	0.23	6.03	35	0.955	1.003	-0.048
<u>5</u>	Me	0	0.68	-0.07	0.17	5.65	15	0.867	0.824	0.043

^aCalcd. using equation. ^bValues calcd. for 6,8-Cl₂ analog (3.7x6A).

Recently Hansch and Craig¹³ reported on the antimalarial structure-activity relationships for a series of phenanthrene amino-alcohols as determined by multiple parameter analysis and by additivity methods; and Craig¹⁴ reported on the Free-Wilson analysis of 2-phenylquinoline-4-aminoalcohols. It was concluded that both 1-octano-water partition coefficients (π) and electronic parameters (σ) could account for most of the biological variation for members of these series. For the quinoline series, the relative magnitude of these factors were separated according to functional group and position¹⁴. When the nature and position of all other substituents are held constant for the 3-X-phenylquinoline system, the steric effect of the 3-substituent for compounds 2-6 can be expressed by the equation in Table II using the method described by Hansch¹⁵. This is the best single parameter equation ($F_{1,3} = 37.2$, $F_{1,3\alpha 0.01} = 34.1$) for the limited set of compounds.

The methoxy derivative 4 which carries 6,8-dimethyl rather than the preferred 6,8-dichloro, has considerably lower antimalarial activity than expected for the steric effect of the methoxyl group alone. Obviously this is because 6,8-dichloro is a much better auxopharmacophoric combination than 6,8-dimethyl¹⁴. e.g. Comparison of ED₅₀ values for increase in mean survival times (*P. berghei* in mice) by the 6,8-dichloro compound 6 with those of the 6,8-dimethyl analog 6A, shows the former to be 3.7 times more potent. And the 2-p-chlorophenoxy analog of 6,8-dichloro compound 6 is 5 times as active as the 6,8-dimethyl analog¹⁵.

No relationship is obvious between planarity of the total π system and animal phototoxicities for any of the analogs except 5, 8 and 9 (cf. discussion by Rothe and Jacobs^{3a}). Recent results from clinical trials^{a,b-e} with 7 has cast considerable doubt on the correlatability of phototoxicity in animal models with that shown in man, as 7 was shown to be both prophylactic and effectively curative^{2d} for acute malaria caused by several strains of *P. falciparum* with no observed adverse side effects and phototoxicity a minor consideration¹¹.

Compound 7 and the new isomer 2 have equal phototoxicities in animals, but 2 has half the antimalarial activity of 7. The 3-fluoro compound 3, on the other hand, is considerably more active than 7 against *P. berghei* and half as phototoxic; it therefore appears to be a better candidate than was 7 for clinical trial in...

Experimental Section

4- and 6-Chloroisatins¹⁷ were prepared from isonitroso-3-chloro-acetanilide, cyclizing in concd H_2SO_4 (80°), and separating by fractional precipitation by H^+

2-Methoxy-4'-chloroacetophenone¹⁵. Mp $65-66^\circ$; nmr ($CDCl_3$) δ , 3.15 (s,3), 4.69 (s,2), 7.35-8.10 (m,4).

New Modification of the Pfitzinger Reaction. 3,4',6,8-Tetrachlorocinchophen (12) (13 made similarly).- To a suspension of 21.6 g (0.1 mol) of 5,7-dichloroisatin and 18.9 g (0.1 mol) of $\alpha,4'$ -dichloroacetophenone in 2-methoxyethanol (300 ml, stirred, 10 min) was added KOH (48 mg, stirring, 18 hr). Slow addition of concd HCl (250 ml) followed by EtOH (to suspend the precipitate), cooling (30°), basification (to pH 11, 10% NaOH), filtration, and acidification (to pH 3, 10% HCl), gave 12 (25.3 g, 65%), mp $245-250^\circ$ dec. Use of 2-propanol or DMF-EtOH mixture gave 12-25% of 12; and use of $MeOCH_2CH_2OH$ gave 55% (10% unreacted) and a very low yield of 14.

3-Methoxy-6,8-dichlorocinchophen (14) (cf. ref 7). Nmr (Me_2CO-d_3): δ 3.71 (s,3, CH_3), 6.96 (broad s, conc dependent, 1, $COOH$), 7.83 (m,7,aromatic).

The 2-Arylquinoline-4-carbonyl Chlorides 17-20¹⁶ were made from 11-14 by excess $SOCl_2$ (1-1.5 g/10 ml, reflux 2-3 hr), distilling and coevaporating with benzene to remove $SOCl_2$, solution of product in hot CH_2Cl_2 , filtration (Celite), evaporation and cooling.

3-Fluoro-6,8-dichloro-2-(4'-chlorophenyl)-4-quinolyl Bromomethyl Ketone (23) (21 and 22 were made similarly).- To stirred 350 ml of $Et_2O-CH_2N_2$ (0.7 mol) was added 5.6 g (0.014

mol) of 19 (18 hr), and then 20 ml of concd HBr (3 hr). Washing the Et₂O solution (H₂O), drying (MgSO₄), evaporation, and slurrying the residue (petroleum ether, 30-60°), gave 5.64 g (87%), mp 153-163° dec. [In the case of 22 Et₂O-CH₂N₂ was added to 18 in CH₂Cl₂ (stirring, 0°)]. After workup by solution in Me₂CO, evaporation, trituration with MeOH, and crystallization from Me₂CO, the product gave unsatisfactory analysis and was shown to contain at least one important minor compd (tlc, benzene-MeOH); however, spectra showed that the bulk of the mixture was 23, which in the next step gave 26.

3,6,8-Trichloro-2-(4'-chlorophenyl)-4-quinoline Ethylene Oxide (25) (26 and 31 were made similarly). To a soln of 22 (3 g, 6.46 mmol) in 50 ml of THF was added a soln of 1.25 g (3.30 mmol) of NaBH₄ in 14.5 ml of 3% KOH-H₂O, followed by addn of 40 ml of THF and 20 ml of EtOH to effect soln (stirred 1 hr); 25 (2.1 g) precipitated.

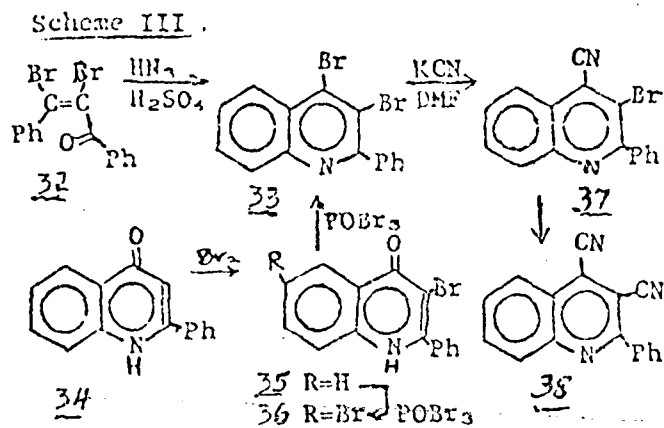
α-(Di-n-butylaminomethyl)-3,6,8-trichloro-2-(4'-chlorophenyl)-4-quinolinemethanol (2) (3 was made similarly). A mixture of 3.2 g (8.27 mmol) of 25 and 6 ml of NHBu₂ was heated (stirring, 17 hr, 132°), vac evaporated in vacuo to remove NHBu₂ (80°). Trituration with hexane and cooling gave 2 (4 g).

3-Bromo-α-(di-n-butylaminomethyl)-2-phenyl-4-quinolinemethanol·2 HCl (1). Solution of 21 (2 g, 5 mmol) and NHBu₂ (1.3 g, 10 mmol) in Et₂O (standing, dark, room temperature, 8 hr), filtration (removing 6.2 g (94%) of NHBu₂·HBr), vacuum evaporation (70°), solution of the residue (EtOH, under N₂), addition of NaBH₄ (15 g, 39.5 mmol), stirring (0.5 hr), basification (dil NaOH, to pH 11), extraction with Et₂O, drying (MgSO₄), vacuum evaporation, solution in dry Et₂O, and addition of Et₂O-HCl, gave 1 (0.5 g).

3-Methoxy-6,8-dimethyl-2-(4'-chlorophenyl)-4-quininaldehyde
Dimethyl Acetal (29). A soln of $\text{MeOCH}_2\text{COPhClp}$ (4.3 g) and 27 (5.18 g; MeOH, 40 ml), was added rapidly to a stirred MeOH solution of 0.57 g of Na (30 ml). Refluxing (4.5 hr, precipitate appeared after 3.5 hr), cooling (-5°), filtration, and washing (MeOH, 0°), gave 29 (7.88 g including recovery from filtrate).

3-Methoxy-6,8-dimethyl-2-(4'-chlorophenyl)-4-quininaldehyde (30). A solution of 29 (5 g) in 5:1 dioxane- H_2O (60 ml) plus 1 ml of conc HCl, was refluxed (35 min). Addition of H_2O (40 ml) and cooling (5°) gave 30 (4.27 g). Epoxide 31 was made from 30 by methylenation¹⁰ and converted into aminoalcohol 4 by NHBu_2 (3.5 hr, $145-150^\circ$ and 14 hr, 110°).

Toward a New Synthesis of 3-Substituted-2-phenyl-4-quinoline
Aminoalcohols (Scheme III). The Schmidt reaction on α,β -dibromo-cis-chalcone (32) gave 3,4-dibromo-2-phenylquinoline (33¹⁷). From a quantity of 33 prepared by the Kaslow bromination procedures, 34 \rightarrow 35 \rightarrow 33¹⁸, a small amount of tribromide 36 was isolated, which became the predominant product of bromination by POBr_3 in DMF. The reaction of 3,4-dibromo-2-phenylquinoline (33) with CuCN-DMF (reflux) gave a difficultly separable mixture which was shown by mass spectrum to be mono and 3,4-di-nitriles 37 and 38 in a ratio dependent on reaction time (57/43 after 1 hr and 36/64 after 4 hr). Obviously the 3-Br, relatively inactive in 33, is activated in 37 by the 4-CN. Use of highly polar DMF as solvent for POBr_3 brominations, and displacements of 4-Br by CN, thus appear to be potentially useful. There is the possibility for selective 4-metalation of 33 by BuLi and subsequent reaction with CO_2 or 2-pyridaldehyde, or reaction at the 4-CN of 37, for creation of the aminoalcohol chain. A start was made toward synthesis of the 3,4',7-trichloro analog of 2, from cis pClPhCCl=CClCOPhClp.¹⁹



Acknowledgment. Because only test data on 5, 8 and 9 have been published, chemical data by J. Riedmaier and J. Christensen are included here with their permission.⁴ We are grateful to Dr. S. W. Page (WRAIR) for providing the biological data, and to Mrs. E. Zacharias (A. H. Robins Co.) for programming assistance.

Footnotes and References

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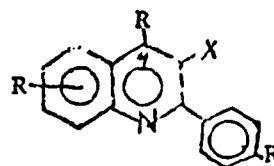
*To whom inquiries may be addressed (H. R. M., A. H. Robins Co., Richmond, Virginia 23220).

§ Satisfactory spectra were obtained. Instruments: mp, Thomas-Hoover Apparatus; ir, Perkins-Elmer 337, nmr, Hitachi Perkin-Elmer R-20; mass spectrum, Hitachi Perkin-Elmer RMU 6E. Microanalyses by Gailbraith Lab., Inc. were correct within $\pm 0.4\%$.

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Table II
Quinoline Compounds



Comp No.	Substituents			4-R	Yield ^{a-o} %	mp ^o C ^{p-r}	Analyses ^{s-w}
	R	R'	X				
<u>1</u>	H	H	Br	CHOHCH ₂ NBu ₂	20 ^b	147 dec	C ₂₅ H ₂₁ BrNO · 2HCl ^t
<u>2</u>	6,8-Cl ₂	Cl	Cl	CHOHCH ₂ NBu ₂	96 ^c	139.5-141 ^{p,q}	C ₂₅ H ₂₈ Cl ₄ N ₂ O ^u
<u>3</u>	6,8-Cl ₂	Cl	F	CHOHCH ₂ NBu ₂	87 ^c	124-125.5	C ₂₅ H ₂₈ Cl ₃ FN ₂ O ^t
<u>4</u>	6,8-Me ₂	Cl	OMe	CHOHCH ₂ NBu ₂	59 ^d	96-97	C ₂₈ H ₃₇ ClN ₂ O ₂ ^t
<u>12</u>	6,8-Cl ₂	Cl	Cl	COOH	65 ^e	253 dec ^p	C ₁₆ H ₇ Cl ₄ NO ₂ ^u
<u>13</u>	6,8-Cl ₂	Cl	F	COOH			C ₁₆ H ₇ Cl ₃ FNO ₂
<u>14</u>	6,8-Cl ₂	H	OMe	COOH	73 ^f	217-219 dec	C ₁₆ H ₇ Cl ₄ NO ₂ ^u
<u>15</u>	6,8-Cl ₂	Cl	OMe	COOH	74 ^d	236-237 dec ^r	C ₁₇ H ₁₀ Cl ₃ NO ₃ ^t
<u>16</u>	7-Cl	Cl	Cl	COOH	52 ^{e,g}	272 dec ^p	C ₁₆ H ₈ Cl ₃ NO ₂ ^u
<u>17</u>	H	H	Br	COCl	49 ^h	148-149 ^{p,q}	
<u>18</u>	6,8-Cl ₂	Cl	Cl	COCl	86 ^h	148-150 ^p	C ₁₆ H ₆ Cl ₅ NO ^u
<u>19</u>	6,8-Cl ₂	Cl	F	COCl	50 ^{i,j}	168-169.5	C ₁₆ H ₆ Cl ₄ FNO ^t
<u>20</u>	6,8-Me ₂	H	OMe	COCl	89 ^h	155-157	C ₁₇ H ₁₀ Cl ₃ NO ₂ ^t
<u>34</u>	6,8-Cl ₂	H	OMe	CONH ₂	- ^k	252-254 ^p	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₂ ^t
<u>32</u>	6,8-Cl ₂	Cl	Cl	COOMe	87 ⁱ	207-207.5	C ₁₇ H ₉ Cl ₄ NO ₂ ^u
<u>33</u>	7-Cl	Cl	Cl	COOMe	-	200-201	C ₁₇ H ₁₀ Cl ₃ NO ₂ ^u
<u>29</u>	6,8-Me ₂	Cl	OMe	CH(OMe) ₂	91 ^f	154-155 ^q	C ₂₁ H ₂₂ ClNO ₃ ^t
<u>30</u>	6,8-Me ₂	Cl	OMe	CHO	97 ^f	136-137 ^q	C ₁₉ H ₁₆ ClNO ₂ ^t
<u>21</u>	H	H	Br	COCH ₂ Br	60 ^l	95-96	C ₁₇ H ₁₁ Br ₂ CO ^v
<u>22</u>	6,8-Cl ₂	Cl	Cl	COCH ₂ Br	95 ^{g,m,n}	193-193.5	C ₁₇ H ₈ BrCl ₄ NO ^w
<u>23</u>	6,8-Cl ₂	Cl	F	COCH ₂ Br	64 ^{g,n,o}	178-180	C ₁₇ H ₈ BrCl ₃ FNO ^t
<u>25</u>	6,8-Cl ₂	Cl	Cl	CH $\begin{matrix} \diagup \text{O} \diagdown \\ \text{---} \end{matrix}$ CH ₂	83 ^c	219-219.5	C ₁₇ H ₉ Cl ₄ NO ^u
<u>26</u>	6,8-Cl ₂	Cl	F	CH $\begin{matrix} \diagup \text{O} \diagdown \\ \text{---} \end{matrix}$ CH ₂	46 ^{g,n,o}	178-179	C ₁₇ H ₉ Cl ₃ FNO ^t
<u>31</u>	6,8-Me ₂	Cl	OMe	CH $\begin{matrix} \diagup \text{O} \diagdown \\ \text{---} \end{matrix}$ CH ₂	90 ^{f,n}	101-103 ^q	- ^q
<u>5</u> ·HCl ⁴	6,8-Cl ₂	Cl	Me	CH ₂ OHCH ₂ NBu ₂		187-189	C ₂₆ H ₃₂ Cl ₄ N ₂ O ^{u,x}
<u>8</u> ·HCl ⁴	6,8-Cl ₂	2',4'-Cl ₂	H	"		193-193.5 ^o	C ₂₅ H ₂₁ Cl ₅ N ₂ O ^{u,x}
<u>9</u> ·HCl ⁴	6,8-Cl ₂	2',4'-Cl ₂	Me	"		178-180 ^o	C ₂₆ H ₃₁ Cl ₅ N ₂ O ^{u,x}

Footnotes to Table II

^aReasonably pure material unless otherwise specified: recrystallized from: ^bMe₂CHCH-(Me₂CH)₂O; ^cAcOEt; ^dEt₂O; ^eEtOH; ^fEt₂O-hexane; ^gMe₂CO; ^hhexane; ⁱCH₂Cl₂-hexane; ^jvac sublimed (140°/0.15 mm); ^kCHCl₃-hexane; ^lcyclohexanone; ^mpetroleum ether (65-100°); ⁿpartially purified; ^oMe₂CO-CH₂Cl₂; ^pIr (KBr), cm⁻¹: 2, 2960, 2870, 1460, 1380 (CH₃); 2870, 2830, 1460 (CH₂); 1595, 1540, 1490, 1450 (aromatic). 12, 1710, 1960, 2600, 3430. 16, (from 12, CH₂N₂), 3450, 2525, 1920, 1720. 17, 1760, 18, 1760 (COCl). 22, 1450, 1490, 1540, 1600, 1720, 1390, 2960. 25, 3025, 1240, 905, 828 (epoxide). 32, (from 18, CH₂N₂), 1268 (C-O-C), 1740 (C=O), 2860, 2970 (OMe), 34, (from 20, NH₃), 1760 (C=O), 3180, 3375 (NH₂), 36, 1640 (ν-quinolone). Nmr: (CDCl₃) δ: 2, 8.89 [d,1,J=2Hz; 5-H], 7.70 [d,2H,J=8Hz,3',5'-H₂], 7.63 [d,1,J=2Hz,7-H], 7.46 [d,2H,J=8Hz, 2',6'-H₂], 5.72 [q,1,J=5Hz,CH], 4.38 (s,1,OH), 2.68 [m,6,(-CH₂N(CH₂-)₂), 1.43 (m,4,CH₂CH₂), 0.83 (m,3,CH₃). 22, 7.8 (m,3), 7.5 (m,3), 4.48 (s,2H). 29: 2.51 (s,3,CH₃), 278 (s,3,CH₃), 3.53 (s,3,CH₃), 3.58 (s,6,2CH₃), 6.03 (s,1,CHO), 7.28-7.70 (m,3) and 8.05-8.40 (m,3 aromatic). 30: 2.52 (s,3), 2.79 (s,3) and 3.69 (s,3)(3CH₃), 7.50-7.80 (m,3), 8.05-8.35 (m,2), 8.63 (broad s,1), 10.93 (s,1). 31: 2.53 (s,3, CH₃), 2.80 (s,3,CH₃), 3.07-3.51 (m,2,CH₂) 3.63 (s,3,CH₃), 4.37 (m,1,CH), 7.30-8.30 (m,6,aromatic H). ^rUv, nm(×10⁻³): 15 (prepared like 14), 232 (31.8), 265.5 (32.2), 290-340 (broad plateau, 8.7-9-3). ^sWere within ±0.4% of calcd for C,H, and for: ^tC,H,N; ^uC,H,Cl,N; ^vC,H,Br,N; ^wcrude but usable quality; C,H,Br,Cl,N, calcd (found) C, 44.01 (44.78); H, 1.74 (1.74); Br, 17.22 (15.03); Cl, 30.56 (29.60); N, 3.02 (3.21). ^x Syntheses by J. Riedmaier and J. Christensen⁴ via Scheme I.

Antimalarials. 10. Munson, Johnson, Sanders, Ohnmacht, Lutz.

ANALYTICAL DATA	C Found (Calc.)	H Found (Calc.)	N Found (Calc.)	Cl Found (Calc.)	Br Found (Calc.)
Compound No.					
1	56.71 (56.93)	6.38 (6.12)	5.54 (5.31)		
2	58.50 (58.38)	5.52 (5.49)	5.71 (5.45)	27.39 (27.57)	
3	60.37 (60.31)	5.51 (5.67)	5.57 (5.63)		
4	71.85 (71.70)	8.04 (7.95)	5.76 (5.97)		
5 ⁴	58.50 (58.88)	6.02 (6.09)	5.30 (5.29)	Cl, 6.58 (6.70)	
8 ⁴	55.73 (55.29)	5.48 (5.53)	4.80 (4.96)	Cl, 6.06 (6.28)	
9 ⁴	54.69 (54.51)	5.12 (5.31)	5.28 (5.08)	Cl, 6.43 (6.44)	
12	49.96 (49.65)	1.64 (1.82)	3.46 (3.62)	36.85 (36.64)	
14	58.83 (58.64)	3.08 (3.19)	4.10 (4.03)		
16	54.29 (54.50)	2.10 (2.29)	3.82 (3.97)	30.32 (30.16)	
18	47.65 (47.39)	1.52 (1.49)	3.60 (3.45)	43.75 (43.72)	
19	49.22 (49.40)	1.58 (1.55)	3.55 (3.60)		
20	55.94 (55.70)	2.59 (2.75)	3.92 (3.82)		
21	50.43 (50.40)	2.82 (2.74)	3.41 (3.46)		39.34 (39.45)
22	44.76 (44.01)	1.74 (1.74)	3.21 (3.02)	29.60 (30.56)	15.08 (17.22)
23	45.66 (45.63)	1.87 (1.80)	3.19 (3.13)		
25	52.98 (53.03)	2.31 (2.36)	3.62 (3.64)	36.97 (36.38)	
26	45.66 (45.63)	1.87 (1.80)	3.19 (3.13)		
29	68.01 (67.83)	6.10 (5.96)	3.69 (3.77)		
30	70.00 (70.05)	5.05 (4.95)	4.17 (4.30)		
34	58.87 (58.81)	3.30 (3.49)	8.05 (8.07)		
32	50.76 (50.91)	2.03 (2.26)	3.28 (2.49)	35.69 (35.36)	
33	55.65 (55.69)	2.68 (2.75)	3.97 (3.82)	28.70 (29.01)	
36	59.87 (59.81)	3.28 (3.21)	4.90 (4.77)		26.86 (26.62)

Quinoline Syntheses

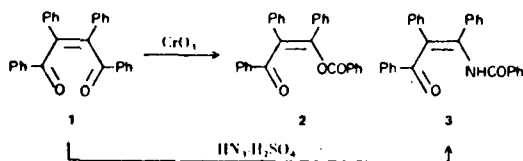
by Reaction of Hydrazoic Acid with α,β -Disubstituted *cis*-Chalcones (1)

Robert E. Pratt (2a, 3a, 4a), William J. Welstead, Jr. (2b, 3b, 4c) and Robert E. Lutz

Department of Chemistry, University of Virginia

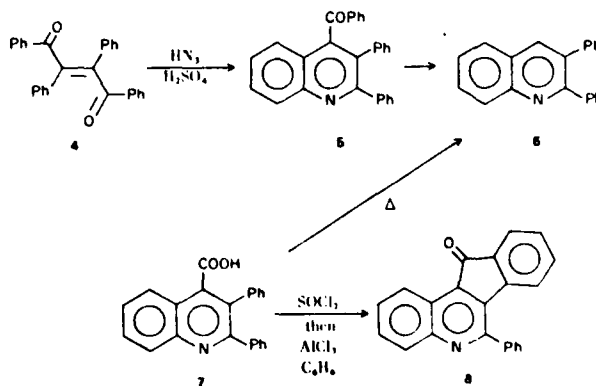
Hydrazoic-sulfuric acid mixture converted *cis*- α -phenyl- β -benzoylchalcone (*trans*-dibenzoylstilbene, **4**) into 2,3-diphenyl-4-benzoylquinoline (**5**) the structure of which was proved by debenzoylation to 2,3-diphenylquinoline. α,β -Diphenyl and *cis*- α,β -dibromochalcones similarly were converted respectively into 2,3,4-triphenylquinoline (**19**) and 2-phenyl-3,4-dibromoquinoline (**20**). The structure of **19** was shown by difference from the corresponding isoquinoline **21** (synthesized). Smith's mechanism for the analogous conversion of *o*-phenylbenzophenone into 9-phenylphenanthridine through the 9-fluorenone and the 9-hydroazide with loss of nitrogen and ring expansion, was supported by methyl label experiments using 2-(*p*-tolyl)benzophenone which gave a 53:47 mixture of 3- and 8-methyl-6-phenylphenanthridines. Applicability of the mechanism to the reactions with disubstituted *cis*-chalcones was shown by sulfuric acid conversions of two of these into indenol **22** and 2-bromo-3-phenylindenone (**24**), respectively. *trans*-Dibenzoylstilbene underwent resinification in sulfuric acid, giving the quinoline (**5**) only when hydrazoic acid was present.

This investigation stems from the study of 1,2-diaroyl mono and disubstituted ethylenes where *cis*-dicarbonyl group interactions seem to be responsible for certain of their reactions which proceed slowly or not at all with the *trans* isomers (**5**). For example, *cis*-dibenzoylstilbene (**1**) undergoes ready oxidative rearrangement with carbon-to-oxygen migration of the bulky vinyl moiety, giving the enol-benzoate **2**, whereas under similar conditions the *trans* isomer **4** is inert (**4c**, **5b**). Hydrazoic-sulfuric acid mixture also brings about oxidative rearrangement of **1** but with carbon-to-nitrogen migration of the vinyl moiety, giving the enamine benzoate **3** (**5b**, **6**, **7**).



For comparison, *trans*-dibenzoylstilbene (**4**) was also subjected to the conditions of the Schmidt reaction because, without the proximity of the carbonyl groups, slow reaction or none at all was expected. However, reaction did occur, rapidly, giving 2,3-diphenyl-4-benzoylquinoline (**5**), the structure of which was assigned on the basis of its properties and on first but incorrect ideas concerning the mechanism (9a below). This reaction had seemed to take place with retention of the *trans* config-

uration of **4** by attack of hydrazoic acid at a carbonyl group followed by cyclization involving the sterically adjacent phenyl group, an overall and typically facile *cis*-group interaction.

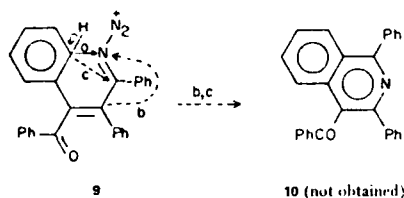


The structure of quinoline **5** was proved by base-induced hydrolytic debenzoylation to the known 2,3-diphenylquinoline (**6**) which was identified by comparison with a sample prepared by decarboxylation of 3-phenylcinchophen (**7**) (**8**).

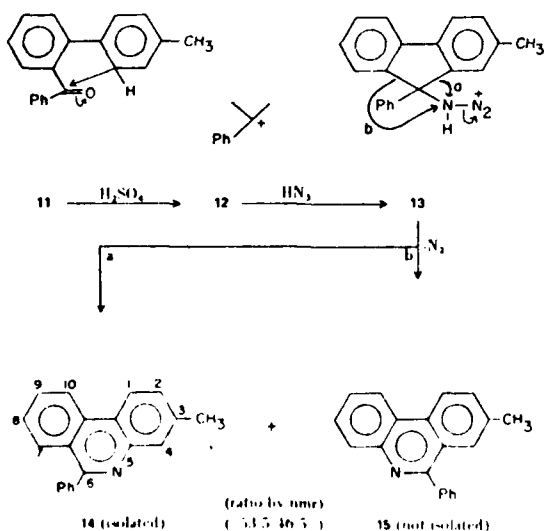
Attempts to synthesize quinoline **5** from **7** were unsuccessful because of the excessive steric hindrance at the β -carbonyl group. The methyl ester and the nitrile of **7** were unreactive toward phenyllithium. Attempted Grignard and Friedel-Crafts condensations of benzene with

the acid chloride of **7** caused intramolecular dehydrohalogenation to a new compound for which the tetracyclic fluorenone-type structure **8** is suggested on the basis of analysis and ultraviolet and infrared spectra.

Formation of the quinoline **5** by attack of hydrazoic acid at the sterically hindered carbonyl group seemed unlikely although subsequent ring closure **9a** with the proximate phenyl group, would then be possible, facilitated by the buttressing effects of nearby groups. Carbon-to-nitrogen migrations in **9** are excluded because phenyl group migration would have given an anilide, and because migration of the vinyl moiety followed by cyclization **9bc** would have led to isoquinoline **10** rather than to **5**. A mechanism involving hydrazoic acid β -attack on the chalcone system of **4** seemed unlikely, on steric grounds, and because it would not lead directly to quinoline **5**.



In an analogous reaction Smith (9) converted *o*-phenylbenzophenone, containing the *cis*- α - β -disubstituted chalcone system, to 6-phenylphenanthridine, first proposing a mechanism of type **9a** which requires the sterically unlikely initial attack at a carbonyl group, and which is excluded in the cases of the chalcones. He later (6) suggested a preferable mechanism which is without the steric objection and which would account both for his results and ours, namely: cyclodehydration to the 9-

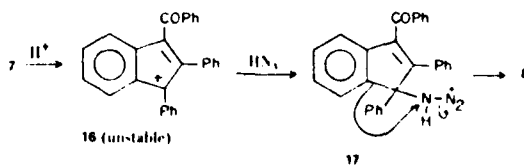


fluorenyl cation and the hydroazide, followed by ring expansion by migration of one arm of the fluorenyl system to nitrogen. This mechanism was put to test using the methyl labeled analog, *o*-tolylbenzophenone (**11**).

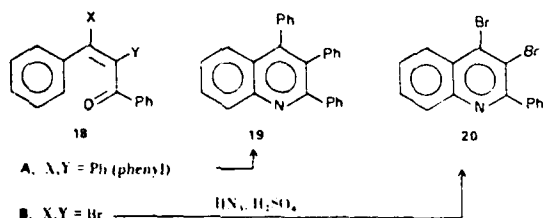
The synthesis of **11** was accomplished by a Diels-Alder condensation of butadiene and *trans*-*p'*-methylchalcone followed by sulfur dehydrogenation, a scheme successfully used in another series (10). The Schmidt reaction converted **11** into a mixture of 3- and 8-methyl-6-phenanthridines (**14** and **15**) from which pure 3-methyl isomer **14** was isolated by fractional crystallization and identified by mixture melting point and infrared comparison with a sample synthesized according to Ritchie (11). The 8-methyl isomer **15** was not isolated from the remaining constant-crystallizing mixture but its presence and concentration were shown by nmr analysis utilizing the 3-methyl peak (δ 2.56) of **14** and the second peak of the mixture at δ 2.46 which was assignable by difference to the 8-methyl group of the isomer **15**. The ratio of the isomers **14**:**15** of 53.5:46.5 was strikingly close to that reported for the hydrazoic acid conversion of 2-methyl-9-fluorenone to the mixture of the 3- and 8-methylphenanthridines (12).

Based on these results, the above Schmidt reaction is best formulated as **11** \rightarrow **12** \rightarrow **13** \rightarrow **14** + **15**. Operation of a mechanism of type **9a** would have led to **15** only; the first Smith mechanism (of type **9bc**, disproved for **4**) would have led to isomer **14** only; competition between mechanisms seems most unlikely.

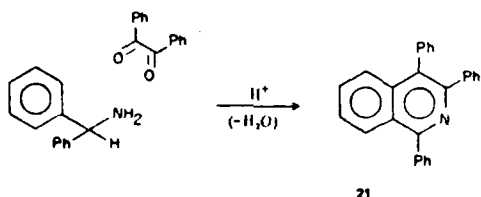
Convincing support for the assigned mechanism is the reaction of *o*-benzophenone with hydrogen bromide to give 9-bromo-9-phenylfluorene which is hydrolyzed to the fluorenone (**13**). In the case of the *trans*-dibenzoylstilbene **4**, concentrated sulfuric acid alone caused resinification; successful conversions to the quinoline **5** required constant presence of excess hydrazoic acid in the reaction mixture. This suggests that the indenyl cation **16** is formed first and is very reactive (it would be destabilized by the β -benzoyl group), but that it is converted through the hydroazide **17** to the quinoline **5**, rapidly, in successful competition with resinification. It is noteworthy that the bulky phenyl arm of the indenyl system of **17** migrates to nitrogen rather than the vinyl arm of the indenyl system or the phenyl group, as would be expected (cf. 6).



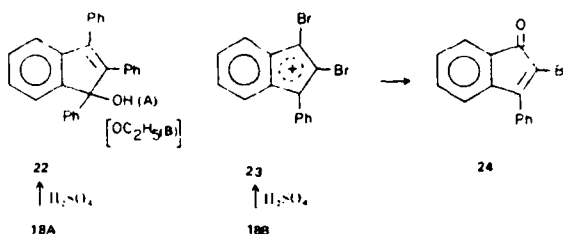
It appears that the essential requirement for a general reaction of the above type is the *cis*- α,β -disubstituted styrylketone system **18** where the *cis* configuration is persistent, where cyclization would be favored, and where an α -group (Y) would induce a hydroazide configuration favorable to migration of the vinyl moiety, with the β -group (X) offering complimentary buttressing effect. As we anticipated, Schmidt reaction conditions did indeed convert α,β -diphenylchalcone (**18A**) (**14**) into 2,3,4-triphenylquinoline (**19**). *cis*- α,β -Dibromochalcone (**18B**) (**15**) reacted similarly giving the known 3,4-dibromo-2-phenylquinoline (**20**) (**16**).



Attempts to prove the structure of 2,3,4-triphenylquinoline (**19**) synthetically by condensation of aniline and phenyldibenzoylmethane, failed. The isomer, 1,3,4-triphenylisoquinoline (**21**), was synthesized by condensing benzhydramine and benzil; it proved to be different from quinoline **19**, thereby supporting structure **19** by that difference.



That the mechanism of formation of **19** conformed to the general mechanism outlined above and involved formation of an indenyl cation analogous to, but more stable than, **16**, was shown by treatment of the *cis*-disubstituted ketones (**18A** and **18B**) with concentrated sulfuric acid alone. In the case of **18A**, water and ethanol quenches gave respectively triphenylindenol (**22A**) and its ethoxy analog (**22B**) (**17**) while the *cis*-dibromochalcone (**18B**) upon water quench gave 2-bromo-3-phenylindenone (**24**) (**18**).



The new quinoline synthesis promises to be useful although limited in applicability (**19**).

EXPERIMENTAL (20)

Preparation of β -Phenylchalcone (**14,2b**).

Pyrolysis of *cis*-1,2-dibenzoylstyrene (350° , 20 minutes, 100 mm.) gave β -phenylchalcone in 45% yield, m.p. 87.89° [lit. 92° (**21**)]. The Schmidt reaction, giving the anilide (**7a**), was repeated with identical results.

4-Benzoyl-2,3-diphenylquinoline (**5**).

A 75 ml. chloroform solution of 8 g. of *trans*-dibenzoylstilbene (**4**) (**22**) and 7 ml. of 1.38 *N* hydrazoic acid in chloroform (0.01 mole) was warmed to 40° . Under vigorous stirring 6 ml. of concentrated sulfuric acid was added dropwise over 30 minutes. Upon cessation of evolution of nitrogen, pouring into ice water, neutralizing with potassium hydroxide, and separation and evaporation of solvent, the residual oil was crystallized from absolute ethanol; 1.6 g. (53%); m.p. 130.132° (not hydrolyzed by hot sodium hydroxide or sulfuric acid); λ max: cm^{-1} 1655 ($\text{C}=\text{O}$); nm. (ϵ) 237.5 (46,100), shoulders at 252, 262 (41,000, 32,000).

Anal. Calcd. for $\text{C}_{28}\text{H}_{19}\text{NO}$: C, 87.25; H, 4.97; N, 3.63. Found: C, 87.07; H, 5.20; N, 4.12.

It forms an unstable hydrochloride with ether-hydrogen chloride, and a picrate from hot ethanol (m.p. 190.192°).

Action of Concentrated Sulfuric Acid-Chloroform Mixture on **4**.

Within one minute deep red color developed. Quenching in ice gave an oil which neither crystallized nor gave a crystalline product when submitted to the above Schmidt reaction conditions. Tetraphenylfuran failed to react with hydrochloric acid under the above conditions.

Debenzoylation of 4-Benzoyl-2,3-diphenylquinoline (**5**) to 2,3-Diphenylquinoline (**6**).

An intimate mixture of 2 g. of **5**, 5 g. of powdered potassium hydroxide and 1 ml. of water was heated until the water and an oil had distilled. The oil (**6**) was extracted by ether, washed with acid and then base, isolated by evaporation of solvent, and added to 20 ml. of saturated ethanolic picric acid (heated). The **6**-picrate separated and was recrystallized from ethanol [yellow, 1.4 g. (44%)]; m.p. 224.225° . Its ir spectrum was identical to that of a sample of m.p. 223.225° (**20a**) prepared from authentic 2,3-diphenylquinoline [m.p. 88.89° ; made by decarboxylation of **7** (**8**)].

Anal. Calcd. for $\text{C}_{27}\text{H}_{18}\text{N}_4\text{O}_7$: C, 63.53; H, 3.55. Found: C, 63.47; H, 3.59.

3-Phenylcinchophen (**7**) (**8**) and its Methyl Ester, Amide and Nitrile.

The acid **7** was prepared according to Pfitzinger (8) by condensation of isatin with desoxybenzoin in 73% ethanolic potassium hydroxide (20a); λ max: cm^{-1} 1755 (C=O); nm. (ϵ) 236, 330 (4,000, 8,270).

The methyl ester of **7** was made from the acid chloride of **7** by methanolic sodium methoxide (reflux, 1 hour); recrystallized from methanol; 5% m.p. 138-139°; λ max: cm^{-1} 1715 (C=O); nm. (ϵ) 237, 258, 332 (36,100, 25,700, 7,000). It did not react with phenyllithium in ether (toluene, reflux 3 hours).

Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{NO}_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.70; H, 5.02; N, 4.58.

The amide of **7** was prepared in a new way (95%) from **7**-acid chloride and concentrated ammonium hydroxide; m.p. 276-278° (23a); ν 1670 cm^{-1} (C=O), 3170, 3310 (NH).

The nitrile (of **7** (23b)) was prepared in a new way from the **7**-amide by phosphorus pentoxide in tetrachloroethane (reflux 2 hours); m.p. 154-155°; ν 2220 cm^{-1} (C≡N); λ (ethanol) 246, 345 nm. ϵ^{-3} 31.3, 6.95; no reaction with phenylmagnesium bromide (ether, reflux 12 hours) or with phenyllithium (toluene, reflux 3 hours).

3-Phenylcinchophen Acid Chloride.

A solution of 10 g. of **7** in 40 ml. of thionyl chloride was refluxed for 12 hours and evaporated. Benzene extraction of the residual oil, evaporation under reduced pressure and crystallizations of the residue from petroleum hexane-benzene mixture and from isooctane gave 7 g. of the acid chloride (60%); m.p. 140-142°; λ max: cm^{-1} 1780 (C=O).

Anal. Calcd. for $\text{C}_{22}\text{H}_{14}\text{ClNO}$: C, 76.85; H, 4.10. Found: C, 76.47; H, 3.91.

6-Phenyl-11-oxo-11H-indeno[1,2-c]quinoline (8).

To a mixture of 20 ml. of dry benzene and 0.8 g. of aluminum chloride was added dropwise a 10 ml. benzene solution of **7**-acid chloride. After stirring for one hour, hydrolysis of the red solution with ice-hydrochloric acid and crystallizations from absolute ethanol-benzene mixture and from glacial acetic acid gave orange crystals; 0.55 g. (62%); m.p. 259-261°; λ max: cm^{-1} 1730 (C=O); nm. (ϵ) 265 (47,000).

It was also obtained (8%) upon reaction of the acid chloride for 45 minutes with refluxing ethereal phenylmagnesium bromide (recovery of acid chloride 17%).

Anal. Calcd. for $\text{C}_{22}\text{H}_{13}\text{NO}$: C, 85.97; H, 4.26. Found: C, 85.71; H, 4.17.

Preparation of α,β -Diphenylchalcone (18A) (14,2b).

Pyrolysis of *cis*-dibenzoylstilbene (**1**) at 320° (20 minutes) and recrystallization from glacial acetic acid, gave **18A** in 78% yield, m.p. 152-153°; λ max: cm^{-1} 1660 (C=O).

Action of Concentrated Sulfuric Acid on α,β -Diphenylchalcone (18A).

While stirring, 5 ml. of concentrated sulfuric acid was added over 2 minutes to a solution of 12% of **18A** in 50 ml. of dry chloroform. The red solution after 5 minutes was quenched with ice. Evaporation of the washed and dried chloroform extracts and crystallization of the residual oil from hexane (requiring 2 days), gave 1,2,3-triphenylinden-1-ol (**22A**), m.p. 128.5-130.5° (20a) [lit. 129° (17)]. Another run with quenching in absolute ethanol gave 1,2,3-triphenylindene (**22B**); m.p. 172-173.5° (20a) [lit. 172° (17)].

2,3,4-Triphenylquinoline (19).

To a 75 ml. chloroform solution of 5 g. (0.12 mmoles) of **18A** and 18 ml. (15 mmoles) of 0.87 *N* hydrazoic acid in chloroform, was added dropwise with stirring (5°) 10 ml. of concentrated sulfuric acid (over 0.5 hours). After warming to room temperature, quenching in ice, and neutralization with aqueous sodium hydroxide, the chloroform solution was dried over sodium sulfate and evaporated. Recrystallization from absolute ethanol gave 1.75 g. (35%); m.p. 189-190°; λ max: nm (ϵ) 247, 298, 335 (47,600, 14,660, 12,480).

Anal. Calcd. for $\text{C}_{27}\text{H}_{19}\text{N}$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.68; H, 5.23; N, 4.38.

1,3,4-Triphenylisoquinoline (21).

A mixture of 5 g. of benzhydramine and 5.5 g. of benzoin was melted at 150° (10 minutes). Addition of 20 ml. of mineral oil, heating at 280° (20 minutes), cooling, and addition of 10 ml. of ether gave a solid which was crystallized from hexane; m.p. 208-209°.

Anal. Calcd. for $\text{C}_{27}\text{H}_{19}\text{N}$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.58; H, 5.89; N, 3.76.

Schmidt Reaction on *cis*- α,β -Dibromochalcone (18B).

To 10 ml. of chloroform, 0.5 g. (1.4 mmoles) of **18B** (15) and 1.5 ml. of 1.03 *N* hydrazoic acid in chloroform, was added dropwise with stirring, 1.5 ml. of concentrated sulfuric acid. After 2 hours, quenching in ice, neutralization, separation, and evaporation of the chloroform, gave a residue of 2-phenyl-3,4-dibromoquinoline (**20**) (0.2 g.) which was recrystallized from ethanol; 0.15 g. (30%); m.p. 148-149° (20a); identified by ir comparison with an authentic sample (16c).

Action of Concentrated Sulfuric Acid on *cis*- α,β -Dibromochalcone (18B).

A mixture of 4 g. of **18B** and 10 ml. of concentrated sulfuric acid in 100 ml. of chloroform at 40° was stirred for 10 minutes, quenched in ice, and neutralized. Evaporation of combined and dried chloroform extracts gave an oil which was placed on an alumina column by dry benzene and eluted with hexane-benzene mixtures; this gave small amounts of *cis* and *trans* **18B**, and then 1.5 g. of the yellow-orange 2-bromo-3-phenylinden-1-one (**24**), m.p. 111-113° [lit. 112-113° (18)]. This was identified by analysis (20a), mixture melting point and ir comparison with a sample synthesized from β,β -diphenylpropionic acid [m.p. 149-153° (18b,c)] through dehydration to 3-phenylinden-1-one [m.p. 73-76° (18d)], bromination to the dibromide [m.p. 120-123° (18a)], and pyridine dehydrobromination to **24** [m.p. 111-113° (18a)].

Synthesis of 3-Methyl-6-phenylphenanthridine (11).

2-Nitro-4-methyldiphenyl (b.p. 1,6 140-142°) (11) was reduced by treatment of a stirred mixture of 27 g. (0.127 mole), 250 ml. of 95% ethanol and palladium on charcoal (50°), with 15 ml. of hydrazine hydrate added dropwise over 30 minutes. Another 0.1 g. of catalyst was added with refluxing (1 hour). Filtration, washing with ethanol, and concentration to 50 ml. and addition of 50 ml. of hot water, gave an oil which was distilled; 23 g. (93%); b.p. 1,5 126-128° (cf. 11). Treatment of 20 g. (0.109 mole) of the oil in 15 ml. of pyridine and 23 g. of benzoyl chloride (100°, 20 hours), followed by 75 ml. of 5% sodium bicarbonate and extraction with 100 ml. of benzene and evaporation, gave 2-benzamido-4-methyldiphenyl; 21 g. (67%); m.p. 90-92° (cf. 11). Cyclization of 2 g. (7 mmoles) by 4 ml. of phosphoryl chloride (reflux, 8 hours), evaporation under reduced pressure, extraction with 25 ml. of benzene, evaporation, and crystallizations from

benzene gave 1.3 g. (96%) of **15**; m.p. 116-118° [analyzed (20a)] [picrate, m.p. 233-245° dec. (11)]; Nmr (carbon tetrachloride), δ 8.0 (m, 2H, aromatic) 2.56 (s, 3H, CH₃).

4-Benzoyl-5(4-tolyl)-cyclohexene

A mixture of 111 g. (0.5 mole) of 4-methylchalcone [m.p. 94-96° (cf. 24)], 120 ml. of absolute ethanol and 54 g. (0.5 mole) of butadiene, was heated in a steel reactor for 12 hours at 170°. Cooling gave 60 g. (37%); the product after recrystallization from *n*-hexane and ethanol had m.p. 83.5-85°; λ max: cm^{-1} 1678 (C=O).

Anal. Calcd. for C₂₀H₂₀O: C, 87.00; H, 7.24. Found: C, 86.94; H, 7.51.

2-(*p*-Tolyl)benzophenone (11)

A mixture of 27.6 g. (0.1 mole) of 4-benzoyl-5(*p*-tolyl)-cyclohexene and 0.4 g. (0.2 mole) of sulfur was heated for 1 hour at 200-230° and then for 2 hours at 260°. Distillation under reduced pressure and crystallization from hexane gave 4.1 g. (15%) of **11**, m.p. 77-79°; λ max: cm^{-1} 1671 (C=O).

Anal. Calcd. for C₂₀H₁₆O: C, 88.20; H, 5.92. Found: C, 88.41; H, 5.97.

The Schmidt Reaction on 11

This was carried out on 8 g. (0.0294 mole) in 80 ml. of stirred concentrated sulfuric acid at 50° by portionwise addition of 3 g. (0.046 mole) of sodium azide over 3 hours, stirring for an additional 12 hours, quenching in ice, filtration of the precipitate, solution of the precipitate in 200 ml. of ether, extraction with 50 ml. portions of 10% hydrochloric acid, and neutralization with 10% sodium hydroxide. The resulting orange oil (3 g.) was taken up in hexane, placed on a 60 g. florisil column, and eluted with 8:92 ether-benzene mixture which gave 2.8 g. of **14-15** mixture, m.p. 100-113°. Fractional crystallizations from hexane gave 9.0 g. of pure **14**, m.p. 116-118°; identified by correct analysis (20a), spectral comparison, and mixture m.p. with authentic **14** synthesized as above (11). The 1.9 g. of material from the combined filtrates from **14** was not resolved by further crystallizations and was a constant melting mixture, m.p. 97-106°; it showed gradual rise in melting point when mixed with increments of pure **14**, and gave correct C, H analysis for C₂₀H₁₅N. Its nmr spectrum showed a 12 proton aromatic multiplet resembling that of **15**, and two methyl singlets, one of δ 2.56 (**14**), and the other δ 2.46 which represents the one possible structural isomer, namely, 8-methyl-6-phenylphenanthrene (**15**) (not isolated pure). From the yield of pure **14** isolated, and the amounts of the two isomers in the mixtures obtained (estimated from the intensities of the respective nmr methyl peaks) the ratio of the isomers **14**:**15** was 53.5:46.5.

Acknowledgment.

Repetitions of the Schmidt reaction on **18B** and identification of **20** were carried out by Richard E. Johnson (16c,19).

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(1) Supported in part by: (a) a contract with the Office of Ordnance Research, U. S. Army. (b) Grants 25029, 5453 and

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(2) Fellowships: P. E. duPont (a) 1962-1963; (b) 1960-1961; (c) National Science Cooperative Fellowship 1963-1964.

(3) Present locations: (a) Union Oil Co., Research Center, Brea, California. (b) A. H. Robins Co., Richmond, Virginia.

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(20) Melting points are corrected. Instruments: Infrared: Perkin-Elmer 137 or 337, potassium bromide pellet. Ultraviolet: Perkin-Elmer 4000-A or Beckman DK-2, 5 x 10⁻⁵ M (ethanol). NMR: Varian A-60, deuteriochloroform (tetramethylsilane).

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Received April 15, 1970

Charlottesville, Virginia 22901

V. Part 7. A 2-Vinylog of 2-Aryl-4-quinoline
Aminoalcohols, Based on the 2,3-Trimethylene-
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Journal of Medicinal Chemistry, 14, 1126, (1971).

Antimalarials. 8¹.

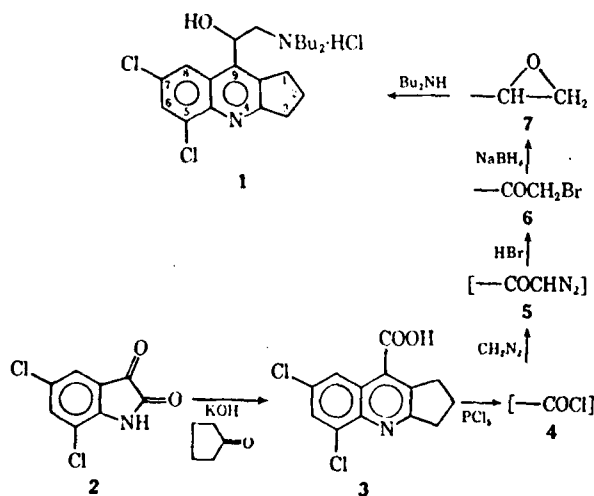
2,3-Trimethylene-4-quinoline Amino Alcohols.
5,7-Dichloro-2,3-dihydro-1H-cyclopenta[b]quino-
line-9-(α -di-*n*-butylaminomethyl)methanol

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The title compound (1) was synthesized to provide, for antimalarial testing, an example of a 4-quinoline amino alcohol in which position 2 was blocked by the CH₂ group of the rigid 2,3-trimethylene ring.³ It was hoped that this arrangement would prevent rapid bio-



degradation,⁴ and, through lack of conjugation of the type involved in the 2-aryl series, would minimize phototoxicity.⁵

The synthesis started from 5,7-dichloroisatin (2) and proceeded by the classical route,⁶ namely, Pfitzinger condensation with cyclopentanone to 6,8-dichloro-2,3-trimethylenecinchoninic acid (3),⁷ followed by diazomethylation of the acid chloride 4 to 5, hydrobromination to bromo ketone 6, reduction by NaBH₄-NaOH to the epoxide 7, and aminolysis with Bu₂NH.

Biological Activity.^{8,9} Target compound 1 proved to be only moderately active against *Plasmodium berghei* in mice, doubling survival time at a dosage of 320 mg/kg, and troubling it at 640 mg/kg.

Experimental Section⁸

6,8-Dichloro-2,3-trimethylenecinchoninic Acid (5,7-Dichloro-

2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic Acid) (3) (Cf. the Unchlorinated Acid⁷).—The purple slurry from addition of 21.6 g (0.1 mole) of 2 to 16.8 g (0.3 mole) of KOH in 125 ml of H₂O was added under stirring to 20 g (0.238 mole) of cyclopentanone in 150 ml of abs EtOH. After refluxing (25 hr) and evapn *in vacuo*, the residue was dissolved in 700 ml of H₂O. Acidification with AcOH gave 3; this was dissolved in KOH-H₂O, reprecipitated with AcOH, and washed successively with dil AcOH, H₂O, and cold EtOH: 23 g (81.6%); mp 272-274° dec. *Anal.* (C₁₇H₁₂Cl₂N₂O₂) C, H, N.¹⁰

3-Potassium Salt (8).—A hot soln of 5 g of KOH in 20 ml of abs EtOH was added with stirring to a suspension of 21.9 g of 3 in 150 ml of warm EtOH. Chilling, filtering, and washing with cold EtOH and with 250 ml of Et₂O gave 21.47 g: unchanged at 325°; ir (cm⁻¹) 2975, 2930, 1580 (C=O). *Anal.* (C₁₇H₁₁Cl₂KNO₂) C, H, N.

3-Methyl ester (9) was prepd by CH₃N₂-Et₂O on 3; crystd from EtOH-hexane: mp 177-178°; ir (cm⁻¹) 1720 (C=O); nmr (CDCl₃), δ 8.30 (1 H, doublet), 7.30 (1 H, d), 4.13 (3 H, s), 3.31 (4 H, triplet), 2.25 (2 H, quintuplet). *Anal.* (C₁₈H₁₄Cl₂N₂O₂) C, H, N.

3-Amide (10) was prepd from 4 by aq NH₃; crystd from Et₂O-hexane: mp 285-287° dec; ir (cm⁻¹) 3350, 3160, 1680. *Anal.* (C₁₇H₁₂Cl₂N₂O) C, H, N.

6,8-Dichloro-4-bromoacetyl-2,3-trimethylenequinoline (6).—A C₆H₆ soln of 3-acid chloride, 4,¹⁰ was prepared from 13.8 g of 3-HCl by reaction with PCl₅ (100°, 30 min) and extg with dry C₆H₆¹¹ (quenching of an aliquot in ice-NH₃ gave 10). This was added (below 10°, over 0.5 hr) to 5.61 g of dry CH₂N₂ in 700 ml of Et₂O (KBr pellets; H₂O present at this point readily converts 4 through 3 and CH₂N₂ to 9). After warming to room temp (2 hr) 48% HBr-H₂O was added (stirring, 40 min). The Et₂O layer was washed successively with 48% HBr, H₂O, and NaCl-H₂O, dried (MgSO₄), and evapd *in vacuo*. The residual oil in 700 ml of petr ether (bp 65-110°) was decolorized (charcoal, reflux) and successively coned and cooled giving 6: recrystd (hexane), mp 125-127° (still impure); ir (cm⁻¹) 3090, 3000, 2970, 2940, 1720; nmr (CDCl₃), 7.80 (1 H, d), 7.60 (1 H, d), 4.38 (2 H, s), 3.21 (4 H, overlapping triplets), 2.37 (2 H, quintuplet).

(1) (a) This work was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-49-193-MD-2955, R. E. Lutz, Responsible Investigator. (b) Contribution No. 934 of the Army Research Program on Malaria. (c) Presented in part at the Southeast Regional Meeting of the American Chemical Society, Richmond, Va., Nov 1969, Abstract 255. (d) Antimalarial test results were supplied by the Walter Reed Army Institute of Research.

(2) Postdoctoral Research Associates.

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6,8-Dichloro-4-epoxyethyl-2,3-trimethylenequinoline (7).—A soln of 1 g (0.026 mole) of NaBH₄ in 10 ml of H₂O and 7 ml of 2 N NaOH, was added dropwise over 10 min to a stirred suspension of 4.65 g (0.013 mole) of nearly pure 6 (above) in 50 ml of MeOH. Stirring for an addl 1.5 hr, cooling for 15 min, filtering, and washing with MeOH gave 3.42 g (94.5%) of 7 (mp 134–139°); recrystd from Et₂O-hexane, mp 144–145°; ir (cm⁻¹) 2960, 2980, 3100, none for C=O; nmr (CDCl₃), 8.02 (1 H, d), 7.71 (1 H, d), 4.26 (1 H, m), 3.10 (5 H, m), 2.17 (2 H, quintuplet). *Anal.* (C₁₄H₁₁Cl₂NO) C, H, N.

5,7-Dichloro-2,3-dihydro-1H-cyclopenta[b]quinoline-9-(α -di-n-butylaminomethyl)methanol·HCl (1).—A suspension of 3.6 g of 7 in 12 ml of Bu₂NH was stirred for 4.5 hr at 105–110°, monitoring disappearance of 7 (4 hr) by tlc (silica gel G, 1:1 Et₂O-hexane). After evapn *in vacuo* of Bu₂NH (60°) the oil (5.1 g), dissolved in 150 ml of Et₂O, was treated with increments of Et₂O·HCl, each sufficient to give 0.2–0.4 g of 1 (each fraction being washed with Et₂O). Fractions 1–4 contd decreasing amts of Bu₂NH·HCl; and 5–8 were largely 1 (2.65 g). Repeated recrystn from EtOH-Et₂O gave 0.5 g, light tan, mp 160–162° dec; ir (cm⁻¹) 3440, 3220 (OH), 2960, 2940, 2880 (CH), 2670, 2620, 2530 (NH). *Anal.* (C₂₂H₃₀Cl₂N₂O·HCl) C, H, N, Cl.

Incidental and Preliminary Experiments. Attempts to add 2-PyLi and MeLi to the 2,3-trimethylenecinchoninic acids were unsuccessful, presumably because of steric interference of the 3-CH₂ group and/or the activity of the 2-CH₂ hydrogens (*cf.* ref 12).

2,3-Trimethylenecinchoninic acid·HCl (11), pptd from Et₂O, mp 252–255° dec, was treated with PCl₅ (steam bath for 30 min, addn of C₆H₆, and reflux for 2 hr), giving a ppt presumed to be the acid chloride·HCl (12) (sublimed, 8%, mp 245° dec).

2,3-Trimethylenecinchoninamide (13) was prepd from 12 by treatment with H₂O-NH₃; crystd from EtOH, mp 276–277°;

ir (cm⁻¹) 3330 (s), 3140 (s) (NH₂), 1688 (C=O). *Anal.* (C₁₂H₁₄N₂O) C, H.

4-Bromoacetyl-2,3-trimethylenequinoline·HBr (14).—CH₂N₂-Et₂O with 3 g of 12 (overnight) gave orange cubes of diazo ketone. Treatment with 10 ml of 48% HBr-H₂O gave 14; crystd from EtOH; 2.1 g (70%); mp 208° dec; ir (cm⁻¹) 1730 (C=O), 2500 (NH). *Anal.* (C₁₄H₁₃Br₂NO) N.

Derivatives of 2,3-trimethylene-4-quinolones were made by the action of the appropriate aniline on ethyl cyclopentanone-2-carboxylate, cyclizing at 250°, and crystn from EtOH:^{12,13} **15**, (a) 6,8-Cl₂, 26%, mp 305–307° (b) cyclization by refluxing Ph₂O, recrystd, mp 314–315° (lit.¹² 313°) [*Anal.* (C₁₂H₉Cl₂NO) C, H, N]; **16**, 6,8-Me₂, 60%, mp 326–327° [*Anal.* (C₁₄H₁₃NO) N]; **17**, 6-Me, 39%, mp 319–322° [*Anal.* (C₁₃H₁₃NO) C, H]; **18**, 8-OMe, 26%, mp 212–213° [*Anal.* (C₁₃H₁₃NO₂) C, H, N]; **19**, 8-Cl, 21%, mp 269–270° [*Anal.* (C₁₂H₉ClNO) C, H, N]; **20**, 8-F, 15%, mp 292–293° [*Anal.* (C₁₂H₉FNO) C, H, N].

4-Bromo-2,3-trimethylenequinolones were prepd by treating the quinolone¹³ with POBr₃ at 120°; crystd from EtOH: **21** (parent compd), 50%, mp 72–73° [*Anal.* (C₁₂H₉BrN) C, H, N]; **22**, 6,8-Me₂, from **16**, 69%, mp 124–125° [*Anal.* (C₁₄H₁₄BrN) C, H].

4,6,8-Trichloro-2,3-trimethylenequinoline (23) was prepd by refluxing POCl₃ on **15**, crystd from EtOH, 80%, mp 160–162°. *Anal.* (C₁₂H₆Cl₃N) C, H, N.

Attempted preparation of 4-lithio-2,3-trimethylenequinolines from **21** and **22** by BuLi and addns to 2-pyridaldehyde were unsuccessful, presumably because of the activities of the 2-CH₂ groups.¹⁴

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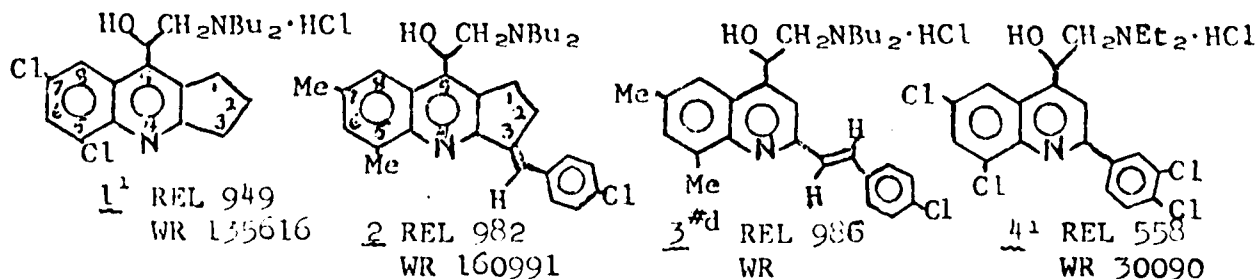
Antimalarials. 11.[#] Vinylogs of Substituted 2-Aryl-4-quinoline Aminoalcohols. 3-(p-Chlorobenzylidene)-5,7-dimethyl-1,2-dihydro-1H-cyclopenta[b]quinoline-9 and 2-p-Chlorostyryl-6,8-dimethyl-4-quinoline (α -Di-n-butylaminomethyl)methanols.

Manuscript. To be submitted to the Journal of Medicinal Chemistry. By J. M. Sanders⁵ and R. E. Lutz* (Supplements: by B. B. Corson, J. Pociask, H. Koppel and J. Riedmaier,⁹ and by R. G. Bass and R. R. Hirjibehdin¹¹).

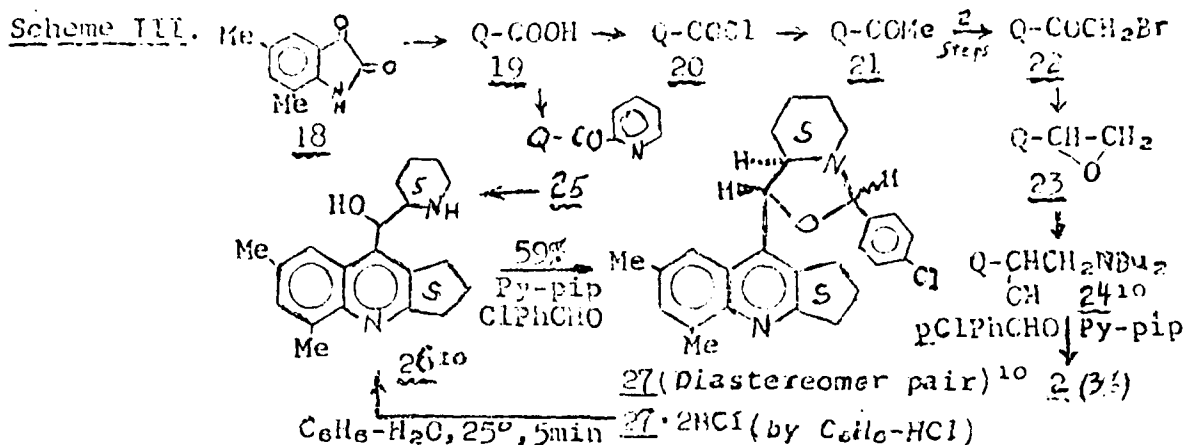
Department of Chemistry, University of Virginia, Charlottesville, Va.

Abstract. Syntheses were from 6,8-dimethyl-4-hydroxycarbostyryl by 3,3-dichlorination, dimethoxylation to the 3-ketal, hydrolysis to the glyoxal acetal, Pfitzinger condensation with cyclopentanone or acetone to the 2,3-trimethylene or 2-methylquinoline, condensation with 4-ClPhCHO at the 2-methylene or methyl group, hydrolysis to the 4-quininaldehyde, methylenation to the epoxide, and condensation with Bu₂NH. The first was curative against P. berghei in mice at 40 mg/kg.

Since 6,8-dichloro-2,3-trimethylene-4-quinoline-(α -di-n-butylaminomethyl)methanol (1)¹ was moderately active against P. berghei in mice and non-photoxic in animals, the p-chlorobenzylidene 6,8-dimethyl analog 2 and the parent 2-p-chlorostyryl-4-quinoline aminoalcohol 3 were synthesized for comparisons with the highly curative 2-aryl-4-quinolyl aminoalcohols of type 4². Compound 2 has a rigid tricyclic nucleus in which the quinoline moiety is conjugated through the 2-vinyl group with the p-ClPh in a presumably trans and relatively planar chalcone-like system where the 1,2-quinoline C=N replaces the chalcone C=O; and 3 has the simple trans-chalcone-like system planarized by resonance.



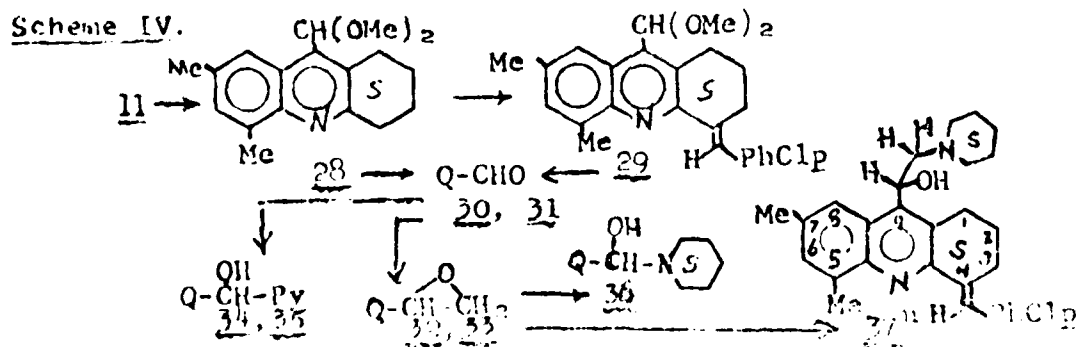
Chemistry. In an attempted synthesis of the 5,7,4'-trichloro analog of 2, p-ClPhCHO was condensed at the active CH₂ of the 2,3-trimethylene carboxylic ester (39→40), but the acid chloride on diazomethylation and hydrobromination^{2a} failed to give the bromoketone and exhausted supplies of intermediates. The Ziegler synthesis³ of 4-quininaldehydes was then utilized, starting from 2,4-Me₂PhNH₂ rather than the preferred 2,4-Cl₂PhNH₂ because of the reported much better yield of intermediate 2 (Scheme I). Condensation of ethyl malonate



Attempted synthesis of the 2-piperidyl analog of 2, via pyridylation of 19 to 25,^{6,7} hydrogenation to 26, and condensation with p-ClPhCHO, gave, instead of the desired aminoalcohol, an isomer which has now been shown to be the oxazolidine 27, the cyclic azaketal of the secondary amino alcohol 26.^{6,8,9} Possibly the azaketal group might serve protectively in forced condensations at the 2-methylene group, to be followed by the very facile acid-hydrolytic regeneration of the secondary aminoalcohol group.^{9c}

Proof of structure 27 rests on: (a) Total inactivity against P. berghei in mice in contrast to total curativity of 2 at 40 mg/kg^{#,5}. (b) Facility at 25° of hydrolytic cleavage^{8,9} of 27·2HCl to 26 and p-ClPhCHO. (c) Absence of N-H and O-H ir absorptivity at 3,400-3,500 cm⁻¹ (KBr or CHCl₃) (shown by 2). (d) Lack of chalcone type uv absorptivity above nm 350 (shown by 2). (e) Nmr spectra compatibility with 27 as a pair of diastereomers¹⁰ (unseen by tlc): δ , CDCl₃ (or C₆D₆), 5.70, 6.16, J₈, Hz 26(30), 1H-dd with all-equal peak intensities rather than the 1:2 peak-intensity ratios calculated for each of the doublets were they coupled (LACON III, least squares fit simulation). D₂O caused no D exchange required by O-H and D-H. (f) Chemical ionization mass spectrum (D. F. Hunt¹⁰): substituting D₂O for H₂O as reagent gas failed to increase the molecular weight of the abundant M+1 ion (M+H m/e 433, M+D m/e 434), thus excluding O-H and N-H (spectrum compatible).

Syntheses of 5,7-Dimethyl-4-(p-chlorobenzilidene-1,2,3,4-tetrahydroacridine-9-(α -N-piperidinomethanol)methanol (37), a 2,3-tetramethylenequinoline analog of 2, by Bass and Hirjibehdin¹¹, was accomplished via Scheme IV in spite of evident steric interference with reactions of groups at position-9 (paralleling Scheme I) (an antimalarial test sample has not yet been obtained).



Experimental.

Synthesis of 2 started with reaction of 2,4-dimethylaniline and diethyl malonate (1:6 mixture, 190° until evolution of EtOH ceased).^{c1a} Mixtures of 5 and 6 were obtained by pouring into MeOH (chilling), concentrating in vacuo (recovering diethyl malonate), and extraction of the residue (boiling Et₂O). Recrystallization (Et₂O-hexene) gave ethyl N-(2,4-dimethylphenyl)malonamate (5); mp 102-104°; characterized by ir (cm⁻¹), 3340, 3320, 1730, 1675; anal. by nmr (CDCl₃): δ 1.21 (t, 3, J = 7.5 Hz), 2.30 (s, 6), 3.49 (s, 2), 4.28 (q, 2, J = 7.5 Hz), 7.08 (m, 2), 7.81 (s, 1), 9.15 (s, broad, 1). Two successive treatments of 5-6 mixture with boiling 10% NaHCO₃ (6 hr), cooling and filtration, gave malonic acid bis-2,4-dimethylanilide (6); mp 126-164° (containing no 5, tlc, silica gel G, EtOH); characterized by mass spectrum, m/e 310 (M⁺), 163, 149, 148, 122, 121 (base peak), 120, 106, 77 (this should be convertible to 10 by AlCl₃).^{3c} Acidification of NaHCO₃ filtrates from 6 (HCl) precipitated N-(2,4-dimethylphenyl)malonic acid (7); recrystallized (EtOH) (75%), mp 158-159°; mass spectrum, m/e 297 (M⁺), 163, 122, 121 (base peak), 120, 106, 91, 77, 44. Anal. (C₁₁H₁₃NO₃) C (calcd 63.76, found 65.0), H, N.

Preparation of 6,8-dimethyl-4-hydroxycarbostyryl - (8) was by cyclization of 7 (PPA, 145°, 4 hr); recrystallized (DMF); mp 355° dec (lit^{3b} 360°).

3,3-Dichloro-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (9). — A relaxing solution of 8 (12:2:3 dioxane-H₂O-conc HCl) was treated dropwise with 600 ml of 30% H₂O₂ at a rate to maintain the exothermic reaction at 90-95°; 9 precipitated. After 30 min (80-85°), cooling and diluting (ice-H₂O), 9 was filtered, washed (H₂O) and dried (100°, 20 hr); yellow, mp 217-218° dec (lit^{3b} 215°); 61% from 7; recryst (THF-hexane), mp 222-223° dec; mass spectrum, m/e 257 (M⁺ base peak), 223, 189, 174, 158, 148, 130, 119, 104, 103, 92, 77. Anal. (C₁₁H₉Cl₂NO₂) C, H, N.

3,3-Dimethoxy-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (10). — Addition of a solution of 40 g of Na in MeOH (600 ml) to 9 (202 g in MeOH, 500 ml, exothermic reaction) refluxing (30 min), quenching (ice-5% HCl), filtration, and washing (H₂O), gave 10; recryst (MeOH, yellow), mp 206-208°; nmr (CDCl₃), δ 2.10 (s, 3), 2.22 (s, 3), 3.47 (s, 6), 5.32 (s, 1), 6.37 (s, 2), 7.08 (s, broad, 1), 7.72 (s, 1). Anal. (C₁₃H₁₅NO₄) C, H, N.

Diethoxy Analog of 10:— prepared from 9 by NaOEt; mp 191-192° dec. Anal. (C₁₃H₁₉NO₄) C, H, N.

2-Amino-3,5-dimethylphenylglyoxal Dimethylacetal (11). — A suspension of 11 in 1.15 l. of 6% aq NaOH was refluxed (1.25 hr), cooled (10°), saturated with NaCl,^{am} extracted portionwise with 1.6 l. of Et₂O, giving 11 (50% from dimethylaniline); bp 127-128°/0.23 mm. Nmr (CDCl₃), δ 2.10 (s, 3), 2.22 (s, 3), 3.47 (s, 6), 5.32 (s, 1), 6.27 (s, broad, 2), 7.78 (s, 1), 7.32 (s, 1). Anal. (C₁₃H₁₇NO₃) C, H, N.

5,7-Dimethyl-9-(dimethoxymethyl)-2,3-dihydro-1H-cyclopenta[b]quinoline (12). CF_3CO — A solution of Na (2.5 g, $EtOH$), 11 (29.3 g) and cyclopentanone (15 g) was refluxed (17 hr) and quenched (saturated NaCl). Et_2O extraction, evaporation, and crystallizations (hexane) gave 12 (25.1 g, 70%, yellow), mp 78-80°. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

3-(4-Chlorophenyl)-2-cyclopentenone (38) prepared (21%) like the phenyl analog³; sublimed (75°/0.3 mm), mp 96-98°; mass spectrum, m/e 192 (M^+), 157, 149, 136, 129 (base peak), 128, 127; nmr ($CDCl_3$); δ 2.60 (m, 2), 3.25 (m, 2), 6.59 (m, 1), 7.55 (m, 4). Anal. ($C_{11}H_9ClO$) C, H. Attempted condensation with 11 was unsuccessful.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta[b]quinoline-9-aldehyde (13). CF_3CO — A mixture of 12 (7.89 g), $pClPhCHO$ (4.26 g), dry NaOAc (2.51 g), Na_2CO_3 (10.6 g) and Ac_2O (300 ml), was refluxed (17 hr), cooled, and hydrolyzed (15% NaOH). The precipitate was washed (H_2O , Et_2O , 13-acetal, 9.76 g). A mixture of an aliquot (5.67 g), $CHCl_3$ (250 ml) and 5% HCl (50 ml) was stirred (1 hr) [1:4 H_2O -THF dissolves 12 and may be preferable.] Evapn of the $CHCl_3$ and Et_2O extracts gave 13 (5.45 g, 54% from 12), mp 233-235 dec; recrystallized (THF), mp 237-239° dec; mass spectrum, m/e 347 (M^+ , base peak), 346, 319, 318, 312. Anal. ($C_{22}H_{23}ClNO$) C, H, N.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta[b]quinoline-9-ethylene Oxide (14). CF_3CO — To a mixture of THF (100 ml) and N_2H (5.24 g of 54% mineral oil dispersion in DMSO, 100 ml, heated, 70°) was added THF (cooling to -5°), Me_3SI (25 g in DMSO, 175 ml, over 3-5 min, +5°), then THF (50 ml) and 13 [9 g suspended in THF (150 ml)] over 2-3 min (-5°). Stirring, 15 min at -5° and 1.25 hr at room temperature, quenching (H_2O and saturated NaCl), extraction (Et_2O , and 2:1 Et_2O -THF), and crystallization (Et_2O), gave 14 (4.57 g, 49%), mp. 203-206° dec, recrystallized (Et_2O), yellow, mp 205-207° dec; mass spectrum, 361 (M^+ , base peak), 345, 344, 343, 332, 318, 297, 296. Anal. ($C_{23}H_{20}ClNO$) C, H, N.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta[b]quinoline-9-(α -di-n-butylaminomethyl)methanol (2). — A suspension of 14 (3.32 g) in Bu_2NH (7.5 g) was heated (under N_2 , 145-150°, 9 hr, with disappearance of 14 monitored by tlc (silica gel G, Et_2O -hexane). Removal of excess Bu_2NH (55°/3 mm) and crystallization (Et_2O -THF) gave 3.63 g; recrystallized, yellow, mp 153-155° dec; uv ($EtOH$), nm ($\epsilon \times 10^{-3}$): 235 sh (1.79), 294 (28.3), 299 (29.8), 350 sh (17.5), 364 (25.2), 381 (25.2). Anal. ($C_{31}H_{39}ClN_2O$) C, H, N.

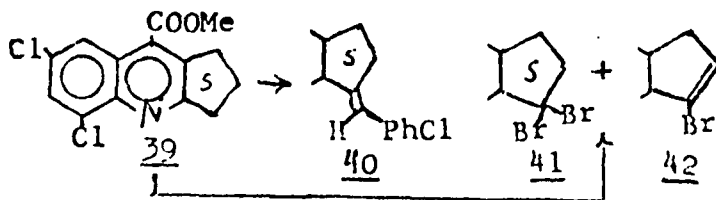
2,6,8-Trimethylquinoline-4-aldehyde Dimethyl Acetal 15^{cf3}. - A soln of 11³ (10.7 g) and Me₂CO (3 g) in abs EtOH (30 ml) was added rapidly to a 30 ml EtOH soln of Na (0.85 g). Refluxing (18 hr), quenching (aq NaCl), Et₂O extrn, vac evapn and chromatography (Florisil, 300 g, elution by hex and 9:1, 3:1 and 2:1 hex-Et₂O), gave 15, 11.29 g, (96%), tlc, single spot (silica gel-G, eluent 4:1 hex-Et₂O), bp 125-125.5°/0.33 mm, colorless; nmr (CDCl₃) δ 2.5 (3H, s), 2.8 (3H, s), 2.9 (3H, s), 3.38 (6H, s) 5.9 (1H, s), 7.44 (1H, broad s), 7.57 (1H, s), 7.86 (1H, broad s) Anal. (C₁₅H₁₉NO₂) C, H, N.

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-aldehyde (16).^{cf3} - A mixture of 15 (12.7g), p-ClPhCHO (7.9g), anhyd NaOAc (9.8g), anhyd Na₂CO₃ (14g), and Ac₂O (300ml), was refluxed (18 hr) and quenched (ice-H₂O-KOH-NaCl). 16-Acetal was isolated by repeated extrn (THF) and hydrolyzed (THF-H₂O-conc HCl, 300/150/25 ml, brief reflux). 16 was extrd (THF, Et₂O) and recryst (Et₂O-hex); 7.51g (50%); recryst, yellow, mp 167-169°; ir (KBr): 1700 cm⁻¹; nmr (CDCl₃), δ 2.50 (3H, s), 2.78 (3H, s), 7.12-7.65 (7H, m), 7.81 (1H, s), 8.47 (1H, broad s), 10.14 (1H, s). Anal. (C₂₀H₁₆ClNO) C, H, N.

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-ethylene Oxide (17).⁴ - Prepared like 14; recryst (Et₂O), yellow, mp 141-142°. Anal. (C₂₁H₁₈ClNO), C, H, N. Reaction with NHBu₂ (140-145°, 9 hr, under N₂) was shown to be incomplete (by H. R. Munson) by tlc; mass spectrum, m/e 464 (3), 142 (CH₂NHBu₂).

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-(α-di-n-butylaminomethyl) methanol·HCl (3). - To NaH (1.8g, Et₂O-Washed) in DMSO (10 ml, 70°, 1 hr), was added THF (50 ml), cooling to and maintaining below 0°. TMSI (8g in DMSO (50 ml) was added slowly, then 16 (2.3g in THF), stirring (25°, 3 hr). After pouring into H₂O, extrn (Et₂O), drying (Na₂SO₄), evapn, addn of NHBu₂ (10 ml) to the residue (17), and heating (160°, under N₂, 18 hr), and vac evapn of excess NHBu₂, the product was chromatographed (silica gel, EtOAc-C₆H₆). 3·HCl was pptd by Et₂O-HCl: 1.5g (40%), mp 125-130° (decomp, requires vac drying). Anal. C₂₉H₃₈Cl₂N₂O (C, H, N). Nmr, CI mass spectra: compatible.

Derivatives of 5,7-Dichloro-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic Methyl Ester 39-40¹ as intermediates for synthesis of antimalarials



3-(4-Chlorobenzylidene)5,7-dichloro-2,3-dihydrocyclopenta[b]quinoline-9-carboxylic Methyl Ester (40). - A mixture of 39 (29.6 g), 4-ClPhCHO (1.47 g), dry NaOAc (9 g) and Ac₂O (200 ml), was refluxed (18 hr) and quenched (ice-H₂O). Stirring (1.5 hr), basification (50% KOH),

washing the precipitate (H_2O , and Et_2O) and crystallization ($CHCl_3$), gave 39, 25 g (98%); recrystallized ($CHCl_3$), yellow needles, mp $280-283^\circ$ dec; mass spectrum, m/e 417 (M^+ , base peak), 416, 402, 382, 358, 322, 298, 251, 161, 149, 144, 143, 126, 125. Anal. ($C_{21}H_{14}Cl_3NO_2$) C, H, N. A similar condensation with the acid of 39 was unsuccessful. The acid of 40. A refluxing suspension of ester 40 (22 g) in 400 ml of THF (400 ml) to which was added 7.5 g of KOH (in 200 ml of H_2O), after 20 hr, was quenched (ice- H_2O); and acidification (concd HCl), gave 20.9 g (98%), recrystd (H_2O -THF), yellow, mp $297-300^\circ$ dec. Anal. ($C_{20}H_{12}Cl_3NO_2$) C, H, N.

Bromination of 39. A stirred suspension (12 g) and NaOAc (13.5 g) in AcOH (100 ml, $50-70^\circ$) was treated dropwise (3 hr) with Br_2 (13 g in 100 ml of AcOH), and (after 1 hr) was quenched (ice- H_2O), giving 10.5 g of 41-42 mixture (separated by chromatographing, fluorisil, elution with hexane and 9:1 hexane- C_6H_6).

3,3-Dibromo-5,7-dichloro-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic Methyl Ester (41); recrystallized (charcoal, Et_2O), mp $166-168^\circ$. Anal. ($C_{14}H_9Br_2Cl_2NO_2$) C, H, N.

3-Bromo-5,7-dichloro-1H-cyclopenta[b]quinoline-9-carboxylic Acid Methyl Ester (42); insoluble in Et_2O ; charcoaled (C_6H_6 , reflux); 0.29 g. recrystallized (C_6H_6), mp $165-170^\circ$. Anal. ($C_{14}H_8BrCl_2NO_2$) C, H, N.

New Compounds by B. B. Corson, J. Riedmaier, J. Pociask and H. Koppel, (mp) analyzed (C,H,N,Br,Cl within $\pm 0.4\%$)⁸ - 19, $C_{15}H_{15}NO_2$, 21 ($124-125^\circ$) $C_{16}H_{17}NO$, 22·HBr ($195-196^\circ$ dec.) $C_{16}H_{17}Br_2NO$, 23 ($140-141^\circ$) $C_{16}H_{17}NO$, 24 ($67.5-69^\circ$) $C_{24}H_{38}N_2O$, 25 ($192.5-193.5^\circ$) $C_{20}H_{18}N_2O$, 26 ($221-225^\circ$) $C_{20}H_{26}N_2O$, 27 from 26 by p-ClPhCHO, 26/1 ml Py/pip, $80-95^\circ$, 8 hr ($148-150^\circ$) $C_{27}H_{29}ClN_2O$; nmr ($CDCl_3$) δ 7.5-7.8 (m, 6H), 6.16, 5.70 (dd 1H, carbinol C-H, 2 diastereomers), 4.82 (bs, 1H), 2.78, 2.47 (s, 3H each, CH_3), 27·2HCl (dried, 1mm, 2 hr, 22°) $C_{27}H_{29}ClN_2O \cdot 2HCl$ (Cl, Cl). 2 from 24 by p-ClPhCHO, 50/2ml Py/pip, 100° ($149.5-153^\circ$). $C_{31}H_{39}ClN_2O$ (yield 3%, yellow) (anal, nmr compatible).

5,7-Dimethyl-4-(p-chlorobenzilidene-1,2,3,4-tetrahydroacridine-9-(α -N-piperidinomethyl)methanol (37), by R. G. Bass and R. R. Hirjibedin¹¹ (Scheme IV). New compounds (mp) analyzed (C,H,N ± 0.4). - 28 ($74-75^\circ$) $C_{18}H_{23}NO_2$. 29 ($110-111^\circ$, yellow) $C_{16}H_{17}NO$. 30 ($175-177^\circ$) $C_{23}H_{20}ClNO$. 31 ($93-95^\circ$) $C_{17}H_{19}NO$. 32 ($171-172^\circ$) $C_{24}H_{22}ClNO$. 34 ($198-200^\circ$) $C_{21}H_{22}N_2O$. 35 ($222-223^\circ$) $C_{28}H_{25}ClN_2O$. 36 ($158-160^\circ$) $C_{25}N_2Cl_2NO_2$. 37 (207°) $C_{23}H_{33}ClN_2O$. Ir, nmr and mass spectra were compatible with 28-37,¹¹ but 33 (mp $84-86^\circ$) did not analyze correctly.

Acknowledgements. A test sample of 2-(p-chlorostyryl) amino-alcohol 3 was prepared by D. A. Shamblee at Robins Co., Richmond, Va., working under S. J. Gillespie, Virginia Institute for Scientific Research, Richmond, Va. Work done independently is here reported (with permission^{9,11}) on: synthesis of 27 and a second synthesis of 2 by B. B. Corson, J. Riedmaier, J. Pociask and H. C. Koppel, Preparations Lab., Aldrich Chemical Co., Milwaukee, Wis.; and synthesis of 37 by R. G. Bass and R. R. Hirjibedin, Virginia

V. Part 7. Footnotes and References

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‡Postdoctoral Research Associate. *To whom inquiries may be directed.

*Instruments: Thomas-Hoover apparatus for mp; ir, Perkin-Elmer 337; nmr, Hitachi-P. E. R-20; mass spectrum, Hitachi P. E. RMU 6E. Microanal.: Gailbraith Lab., Inc., correct $\pm 0.4\%$.

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"Antimalarials. 11."		Analytical Data on new Compounds					
J. M. Sanders and R. E. Lutz		Calcd			Found		
Compd No.	formula	C	H	N	C	H	N
<u>2</u>	$C_{31}H_{39}ClN_2O$	75.82	8.00	5.70	75.64	8.14	5.64
<u>7</u>	$C_{11}H_{13}NO_3$	63.76	7.22 6.32	6.76	64.98	7.07 6.41	6.75
<u>9</u>	$C_{11}H_9Cl_2NO_2$	51.19	3.51	5.43	51.35	3.66	5.29
<u>10</u>	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.84	6.14	5.40
<u>10-diOEt analog</u>	$C_{15}H_{19}NO_4$	64.96	6.90	5.05	64.77	6.95	4.96
<u>11</u>	$C_{12}H_{17}NO_3$	64.55	7.68	6.27	64.28	7.70	6.02
<u>12</u>	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.50	7.92	5.17
<u>13</u>	$C_{22}H_{18}ClNO$	75.97	5.21	4.03	75.82	5.22	3.80
<u>14</u>	$C_{23}H_{20}ClNO$	76.34	5.57	3.87	76.28	5.60	3.65
<u>16</u>	$C_{21}H_{14}Cl_3NO_2$	60.24	3.37	3.34	60.24	3.26	3.28
<u>16-acid</u>	$C_{20}H_{12}Cl_3NO_2$	59.36	2.99	3.46	59.52	3.02	3.31
<u>17</u>	$C_{14}H_9Br_2Cl_2NO_2$	37.04	2.00	3.09	37.21	1.97	3.08
<u>18</u>	$C_{14}H_8BrCl_2NO_2$	45.08	2.16	3.76	45.13	2.15	3.78
<u>38</u>	$C_{11}H_9ClO$	68.58	4.71	---	68.37	4.87	---
<u>19</u>	$C_{15}H_{19}NO_2$	73.44	7.80	5.71	73.46	7.85	5.86
<u>20</u>	$C_{20}H_{18}ClNO$	74.65	5.01	4.35	74.63	5.22	4.17
<u>21</u>	$C_{21}H_{18}ClNO$	75.11	5.40	4.17	71.11	5.31	4.01
by Corson, Riedmaier, Pociask, Koppel, Compounds ¹⁰ of Scheme IV.							
<u>19</u>	$C_{15}H_{15}NO_2$			5.81			5.75
<u>21</u>	$C_{16}H_{17}NO$	80.3	7.16	5.85	80.38	7.13	5.89
<u>22</u>	$C_{16}H_{17}Br_2NO$	48.15	4.46	3.51	3.83	3.51	3.85
				(Br, 40.05)		39.68)	
<u>23</u>	$C_{16}H_{17}NO$	80.3	7.16	5.85	79.90	7.43	5.45
<u>24</u>	$C_{24}H_{36}N_2O$	78.21	9.85	7.60	78.29	9.86	7.63
<u>25</u>	$C_{20}H_{18}N_2O$	79.44	6.00	9.27	80.00	6.13	9.26
<u>26</u>	$C_{20}H_{20}N_2O$			9.03			8.86
<u>27</u>	$C_{27}H_{29}ClN_2O$	74.89	6.75	6.47	74.99	6.65	6.45
<u>27-2HCl</u>	$C_{27}H_{29}ClN_2O \cdot 2HCl$	Cl, Cl: 7		01, 14.02;		6.05, 14.7	
By Bass and Hirjibedin, Compounds ¹¹ of Scheme V.							
<u>28</u>	$C_{18}H_{23}NO_2$	75.77	8.12	4.91	75.93	8.17	4.99
<u>29</u>	$C_{16}H_{17}NO$	80.30	7.16	5.85	80.09	7.24	5.74
<u>30</u>	$C_{23}H_{20}ClNO$	76.34	5.57	3.87	76.07	5.61	3.71
<u>31</u>	$C_{17}H_{19}NO$	80.60	7.56	5.53	80.29	7.46	5.62
<u>32</u>	$C_{24}H_{22}ClNO$	76.69	5.90	3.73	76.53	5.95	3.62
<u>34</u>	$C_{21}H_{27}N_2O$	79.21	6.96	8.80	78.96	7.05	8.73
<u>35</u>	$C_{26}H_{25}ClN_2O$	76.26	5.71	6.35	76.23	5.79	6.36
<u>36</u>	$C_{25}H_{26}NClO_2$	75.61	6.42	3.43	73.34	6.35	3.32
<u>37</u>	$C_{25}H_{33}ClON_2$	75.55	7.21	6.08	75.45	7.20	5.85

VII. List of Publications On Work Under This Contract.

Antimalarials. Cf. Annual Reports by R. E. L., 1967, 1968, 1969.

1. Pyridyl Ketones by Addition of Pyridyllithium to Carboxylic Acids. A New Synthesis of
J. HETEROCYCLIC CHEMISTRY, 4, 459 (1967). α -(2-Piperidyl)-2-aryl-4-quinolinemethanols.
D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger.
2. α -(2-Piperidyl)- and α -(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols.
ROGER M. PINDER AND ALFRED BURGER. Journal of Medicinal Chemistry, 11, 267 (1968).
3. Benzothiazole Amino Alcohols. ALFRED BURGER^{1b} AND S. N. SAWHNEY.
Journal of Medicinal Chemistry, 11, 270 (1968).
4. New Synthesis of α -(2-Pyridyl)- and α -(2-Piperidyl)-2-aryl-4-quinolinemethanols
D. W. BOYKIN, JR., A. R. PATEL, AND R. E. LUTZ. Journal of Medicinal Chemistry, 11, 273 (1968).
5. α -Dibutylaminomethyl- and α -(2-Piperidyl)-3-quinolinemethanols.
CYRUS J. OHNMACHT, JR., FREDDY DAVIS, AND ROBERT E. LUTZ. J. Medicinal Chemistry, 14, 17 (1971).
6. Some New α -Alkylaminomethyl-4-quinolinemethanols J. Medicinal Chemistry, 1971, 14, 145.
A. R. PATEL, C. J. OHNMACHT, D. P. CLIFFORD, A. S. CROSBY, AND R. E. LUTZ.
7. Bis(trifluoromethyl)- α -(2-piperidyl)-4-quinolinemethanols.
Journal of Medicinal Chemistry, 14, 926 (1971). C. J. OHNMACHT, A. R. PATEL, AND R. E. LUTZ
8. 2,3-Trimethylene-4-quinoline Amino Alcohols. 5,7-Dichloro-2,3-dihydro-1H-
cyclopenta[b]quinoline-9-(α -di-n-butylaminomethyl)methanol.
J. M. SANDERS, D. P. CLIFFORD, AND R. E. LUTZ. Journal of Medicinal Chemistry, 14, 1126, (1971).
9. α -(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy and
Charles R. Wetzel, James R. Shanklin, Jr., and Robert E. Lutz. 2-(p-Chloroanilino) Groups.
Journal of Medicinal Chemistry, 16, 528 (1973).
10. 3-Substituted-2-aryl-4-quinoline Aminoalcohols.
H. R. Munson, Jr., R. E. Johnson, J. M. Sanders, C. J. Ohnmacht
and R. E. Lutz, Manuscript (p. 37), to be submitted to J. Med.
Chem.
11. Syntheses of 2-Vinylogs of Substituted 2-Aryl-4-quinoline Amino-
alcohols. 3-(4-Chlorobenzylidene)-5,7-dimethyl-1,2-dihydro-1H-
cyclopenta[b]quinoline-9-(α -di-n-butyl-aminomethyl)-methanol.
J. M. Sanders and R. E. Lutz, Manuscript (p. 54), to be
submitted to J. Med. Chem.
12. Quinoline Syntheses by Reaction of Hydrazoic Acid with α,β -Disubstituted cis-Chalcones.
JOURNAL OF HETEROCYCLIC CHEMISTRY 7, 1051 (1970).
Robert E. Pratt, William J. Welstead, Jr. and Robert E. Lutz.

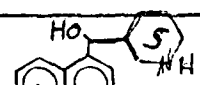
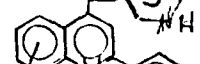
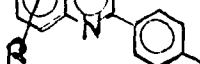



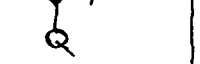



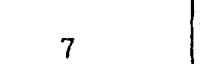

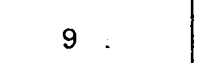


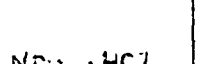
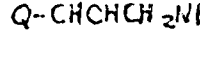
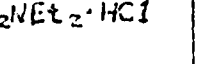


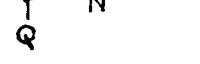
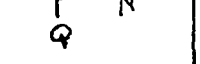
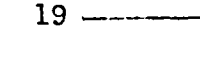
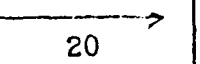
(This work was not financially supported by WRAIR, but was of interest and possibly applicable in V. Part 6.)

VII. List of Publications by R. E. Lutz on World War II
Research Under the Committee on Medical Research.
Aminoalcohols as Potential Antimalarials.

1. **Antimalarials. α -Alkyl and Dialkylaminomethyl-2-phenyl-4-quinolinemethanols**
BY ROBERT E. LUTZ, PHILIP S. BAILEY,^{2a} MARION T. CLARK,^{2b} JOHN F. CODINGTON,^{2c} ADOLPH J. DEINET,^{2d} JAMES A. FREEK, GRANT H. HARNEST,^{2e} NORMAN H. LEAKE,^{2f} TELLIS A. MARTIN, RUSSELL J. ROWLETT, JR.,^{2g} JASON M. SALSURY,^{2h} NEWTON H. SHEARER, JR.,²ⁱ J. DOYLE SMITH^{2j} AND JAMES W. WILSON, III^{2k}
American Chemical Society, 68, 1813 (1946)
2. **Antimalarials. 6- and 7-Chloro- α -(dialkylaminomethyl)-4-quinolinemethanols**
American Chemical Society, 69, 1260 (1947).
BY ROBERT E. LUTZ, JOHN F. CODINGTON^{2a} AND NORMAN H. LEAKE^{2b}
3. **ANTIMALARIALS. α -PHENYL- β -DIALKYLAMINO ALCOHOLS¹**
JOURNAL OF ORGANIC CHEMISTRY Vol. 12, No. 5, September, 1947
ROBERT E. LUTZ, RUFUS K. ALLISON,^{2a} GILBERT ASHBURN, PHILIP S. BAILEY,^{2b} MARION T. CLARK,^{2c} JOHN F. CODINGTON,^{2d} ADOLF J. DEINET,^{2e} JAMES A. FREEK, ROBERT H. JORDAN, NORMAN H. LEAKE,^{2f} TELLIS A. MARTIN, KENT C. NICODEMUS, RUSSELL J. ROWLETT, JR.,^{2g} NEWTON H. SHEARER, JR.,^{2h} J. DOYLE SMITH,²ⁱ AND JAMES W. WILSON, III^{2j}
4. **Antimalarials. 2,5-Diphenyl-3-furyl Amino Ketones and Alcohols**
American Chemical Society, 70, 1359 (1948).
BY ROBERT E. LUTZ AND RUSSELL J. ROWLETT, JR.²
5. **ANTIMALARIALS. ALIPHATIC AMINO KETONES AND ALCOHOLS**
JOURNAL OF ORGANIC CHEMISTRY Vol. 12, No. 6, November, 1947
ROBERT E. LUTZ AND JAMES W. WILSON, III²
6. **ANTIMALARIALS. SOME NEW LONG-CHAIN ALIPHATIC DI-(AMINO ALCOHOLS)**
JOURNAL OF ORGANIC CHEMISTRY Vol. 12, No. 6, November, 1947
JAMES W. WILSON, III,² ROBERT E. LUTZ, AND ROBERT H. JORDAN
7. **ANTIMALARIALS. SOME PIPERAZINE DERIVATIVES**
JOURNAL OF ORGANIC CHEMISTRY Vol. 11, No. 6, November, 1947
ROBERT E. LUTZ AND NEWTON H. SHEARER²
8. **Secondary and Tertiary Amino Ketones and Alcohols Derived from Desoxybenzoin and 1,2-Diphenylethanol.¹ Ring-Chain Tautomerism of the α -(β -Hydroxyethylamino) Ketones²**
Journal of the American Chemical Society, 70, 2015 (1948).
BY ROBERT E. LUTZ, JAMES A. FREEK^{2a} AND ROBERT S. MURPHEY^{2b}
9. **Substituted-Amino Ketones and Alcohols Related to 4,4'-Dichlorobenzoin**
American Chemical Society, 71, 478 (1949).
BY ROBERT E. LUTZ AND ROBERT S. MURPHEY²
10. **Ring-Chain Tautomerism of α -(Ethylethanolamino)-acetophenone**
Journal of the American Chemical Society, 71, 996 (1949).
BY ROBERT E. LUTZ AND ROBERT H. JORDAN²
11. **The Preparation of 4-Ethyl-2-methoxy-2-phenyl-morpholine**
Journal of the American Chemical Society, 72, 1409 (1950).
BY ROBERT H. JORDAN¹ AND ROBERT E. LUTZ
12. **Factors Interfering with the Oppenauer Oxidation of Amino Alcohols**
Journal of the American Chemical Society, 72, 1085 (1950).
BY ROBERT E. LUTZ, ROBERT H. JORDAN,^{2a} AND WILLIAM L. TRUETT^{2b,c}

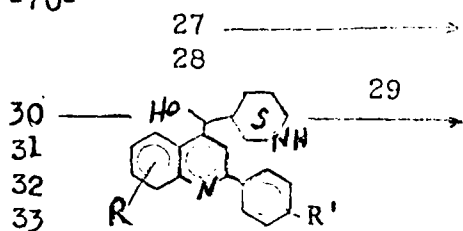
VIII. List of New Compounds[#] Submitted to WRAIR.

A. 76 New Aminoalcohols for Antimalarial test and some of their 2-pyridyl ketones and alcohols.

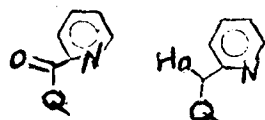
List No.	R	R'	REL No.	AB No.	WRAIR No.	Page No. (Refs p67)
1		H	869	746	7934	9 ⁴
2		H	854	719	7552B	↓
3		H	851	716	62175A	↓
4		H	819	674	54406	8 ⁴
5		H	820	675	54407	↓
6		H	865	742	73897	↓
7		H	853	718	62177	↓
8		H	866	743	73962	↓
9		H	852	717	62176	↓
10		H	867	744	73896	↓
11		H	850	715	62174	↓
12		Me	842	707	62189A	9 ⁴
13		Me	857	734	73871	↓
14		Me	844	709	62187	↓
15	Q-CHCHCH ₂ NBu ₂ ·HCl	Me	870	760	75261	15 ⁶
16	Q-CHCHCH ₂ NEt ₂ ·HCl	Me	871		79326	15 ⁶
17		Me	922			15 ⁶
18		Me	845	710	62186	9 ⁴
19		Me	807	662	54424	8 ⁴
20		Me	809	664	54426	↓
21		Me	856	733	73901	↓
22		Me	858	735	73899	↓
23		Me	817	672	54401	↓
24		Me	818	673	54405	↓
25		Me	821	676	54408	↓
26		Me	822	677	54409	↓

[#]For the first year of this project Dr. Alfred Burger and REL divided personnel and research supervision while Dr. Burger administered submission of samples from both groups to WRAIR under AB numbers (REL extended his personal file for his group using REL numbers). After REL became sole Principal Investigator, compounds were then submitted under REL numbers. Thus, where two numbers are given, it is for an REL compound which had been submitted during the first year to WRAIR and indexed there under AB numbers.

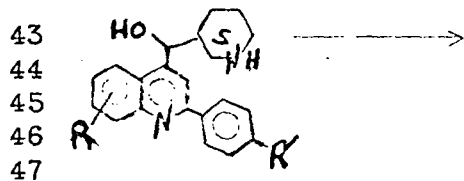
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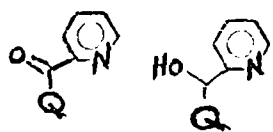
R	R'			
6-F	Me	892		45112
8-CF ₃	Me	831	686	54418
8-CF ₃	Me	832	687	54419
8-Me	Me	857	710	73891
8-Me	Cl	855	732	73892
6,8-Me ₂	Cl	868	745	73898
8-CF ₃	Cl	849	714	62182



34	6-Me	Cl	808	663	54425
35	6-Me	Cl	810	665	54427
36	8-Me	Cl	864	741	73895
37	6,8-Me ₂	Cl	829	684	54416
38	6,8-Me ₂	Cl	830	685	54417
39	8-CF ₃	Cl	827	682	54414
40	8-CF ₃	Cl	828	683	54415
41	8-CF ₃	F		688	54420
42	8-CF ₃	F		684	54421



43	8-Me	F	861	738	73893
44	6,8-Me ₂	F	848	713	62183
45	6-Me	OMe	843	708	62188
46	6,8-Me ₂	OMe	846	711	62185
47	8-CF ₃	OMe	847	712	62184



48	6-Me	F	813	668	54403
49	6-Me	F	814	669	54400
50	8-Me	F	862	739	73894
51	6,8-Me ₂	F	823	678	54401
52	6,8-Me ₂	F	824	679	54411
53	8-CF ₃	F	834	689	
54	8-CF ₃	F	833	688	
55	6-Me	OMe	815	670	54401
56	6-Me	OMe	816	671	54402
57	8-Me	OMe	860	737	73903
58	8-Me	OMe	859	736	73900
59	6,8-Me ₂	OMe	825	680	54412
60	6,8-Me ₂	OMe	826	681	54413
61	8-CF ₃	OMe	835	690	54422
62	8-CF ₃	OMe	836	691	54423

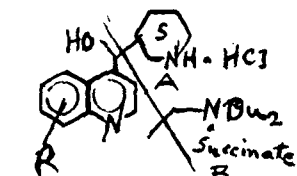
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8⁴9⁴8⁴9⁴8⁴

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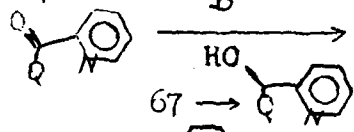
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A

R
7-CF₃
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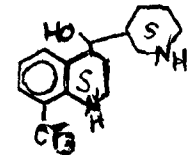


7-CF₃
8-CF₃
8-CF₃

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159960
113250
113252

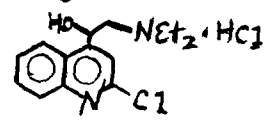
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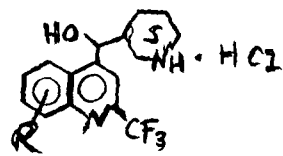
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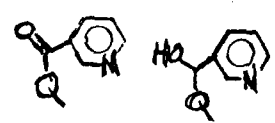
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6,8-Me₂
6-Cl
8-Cl
6F
6,8-Cl₂
8-F
6-OMe
6-CF₃
7-CF₃
8-CF₃
6-OMe,8-CF₃

725
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936
937
727
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969
956
974

69053
75435
73879
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75437

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60045
157309
155066
142490
159314



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8-Me
6,8-Me₂
6-Cl
6-F
6-F
6-OMe
6-OMe,8-CF₃

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728
730
747
906
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726
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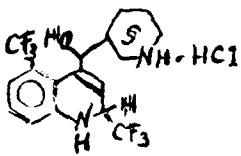
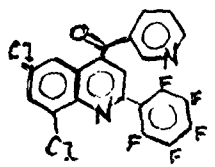
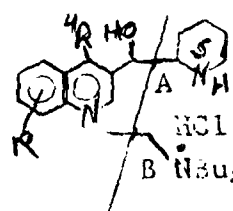
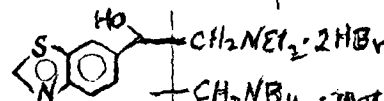
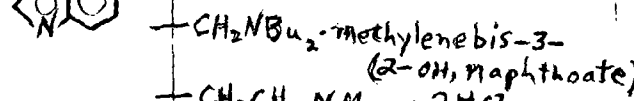
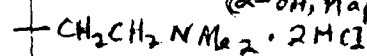

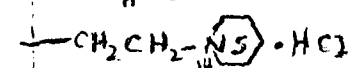
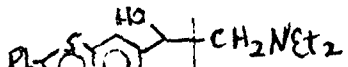
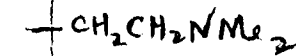
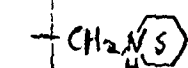
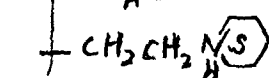
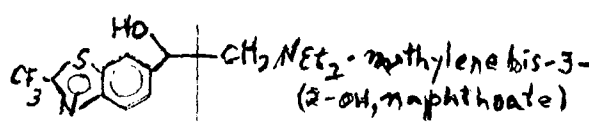
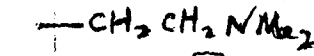
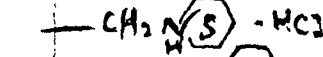
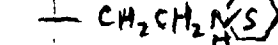
22⁷

19²

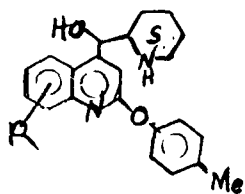
15⁶

19²

22⁷

93				975	159933	21 ⁷	
94				979	159935	16	
95		A	6,8-Me ₂	H	953	140090	23 ⁵
96		B	6,8-Me ₂	4-Cl	947	133090	
97		B	6,8-Cl ₂	H	954	142492	
98		B · 2HCl	7-Cl	4-Cl	948	134482	
99		B	8-CF ₃	H	955	142491	
100			8-CF ₃	4-Cl	951	136557	
101			6,8-Cl ₂	4-Cl	946	125432	
102			8-phenyl	4-Cl	950	136230	
103				721	62179	32 ³	
104				751	75252		
105				752	75253		
106				720	62178		
107				753	75254		
108				723	62181		
109				755	75256A		
110				722	62180		
111				754	75255		
112				756	75257		
113				758	75259		
114				757	75258		
115				759	75260		

116
117
118



R
H
6-Me
6-Cl

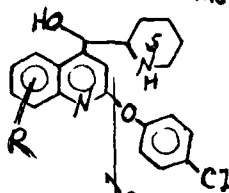
X

932
933
934

115726
115226
115224

36⁹

119
120
121
122



H
6,8-Me₂
6-Cl
6,8-Cl₂

940
945
965
970

121472
122950
148987
157308

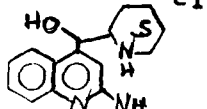
123

6,8-Cl₂

973

158284

124
125
126

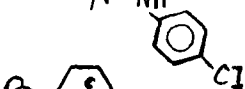


H
6-Me
6,8-Me₂

931
930
939

115225
115224
117110

127



6-Cl

938

117109

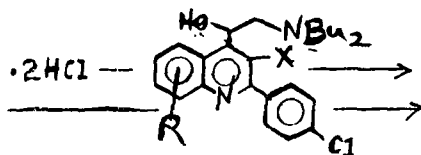


H
6-Me

928
929

115222
115223

130
131
132
133



H
6,8-Cl₂
6,8-Cl₂
6,8-Me₂

X
Br
Cl
F
OMe

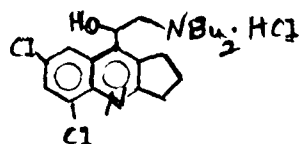
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952
966
971

121473
140089
149105
157307

42¹⁰

43¹⁰

134

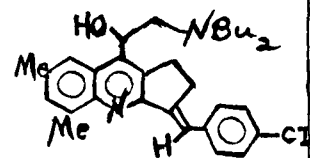


949

135616

56⁸

135

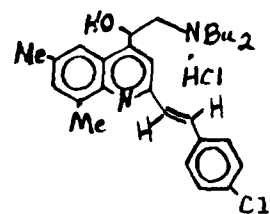


982

160991

61¹¹

136



986

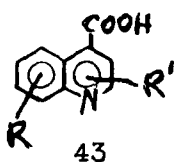
62

B. Supplemental List. Earlier-stage intermediates and incidental compounds

		R	R'				
1		6-Me	Me	841	696	54439	10 ⁴
	2 Q-COOEt	6-Me	Me	804	659	54432	↓
	3 Q-COMe	6-Me	Me	806	661	54434	↓
	4 Q-COCH ₂ Br	6-Me	Me	885		95105	↓
5	Q-COOH	8-Me	Me	881		95102	↓
6		6,8-Me ₂	Me	891		95111	↓
7		6-F	Me	886		95106	↓
8		6-OMe	Me	876		95097	↓
9		6-Me	Cl	800	655	54428	↓
	10 QCOOEt	6-Me	Cl	801	656	54429	↓
	11 QCOMe	6-Me	Cl	812	667	54436	↓
12	QCOOH	8-Me	Cl	883		15103	↓
13		6,8-Me ₂	Cl	838	693	50482B	↓
14		6-F	Cl	887		95107	10 ⁴
15		6-OMe	Cl	882		54353	↓
16		6-Me	F	874		95095	10 ⁴
	17 Q-COMe	6-Me	F	811	666	54435	↓
18	Q-COOH	8-Me	F	889		100925	↓
19		6,8-Me ₂	F	875		95096	↓
20		6-F	F	894		95114	↓
21		6-OMe	F	884		95104	10 ⁴
22		6-Me	OMe	802	657	54430	↓
	23 Q-COOEt	6-Me	OMe	803	658	54431	↓
	24 Q-COMe	6-Me	OMe	805	660	54433	15 ⁰
	25 Q-COCH ₂ Br	6-Me	OMe	890		95110	↓
26	Q-COOH	8-Me	OMe	888		95108	↓
27		6,8-Me ₂	OMe	837	692	54437	↓
	28 QCOMe	6,8-Me ₂	OMe	893		95113	↓
29	Q-COOH	6-OMe	OMe	879		95099	↓
30		8-CF ₃	H	880		95101	↓
31		8-CF ₃	Me	877		95098	↓
32		8-CF ₃	Cl	839	694	45852B	↓
33		8-CF ₃	F	840	695	54438	↓
34		8-CF ₃	OMe	878		95100	↓
35		R	X	R'			
36		H	Br	H	941	96685	38 ¹⁰
37		H	Cl	H	942	1474	↓
38		7-Cl	Cl	Cl	959	147046	↓
39		6,8-Cl ₂	Cl	Cl	958	147046	↓
40		6,8-Cl ₂	F	Cl	978	15961	↓
		H	NH ₂	H	873	95094	↓
41					983	160987	↓

-75-

42



44

45

46

47

48

49

50

50A

R⁶⁻⁸

R²⁻³

7-Br	H	913
7-Br	H	921
7-Cl	H	919
7-Cl	2-COOH	920
6,8-Cl ₂	Cl	927
7-F	H	918
7-CF ₃	H	916
7-CF ₃	2-COOH	915
8-CF ₃	H	917
8-CF ₃	2-COOH	914

109930
109929
061942
109221
115221
109933
109923
109922
109920

-75-

15⁸

↓

↓

51

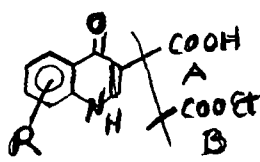
52

53

54

55

56



A	6,8-Cl ₂	963
B	6,8-Me ₂	962
B	6-OMe	964
B	8-CF ₃	960
B	8-CF ₃ (4-OH form?)	926
B	8-pher.yl	961

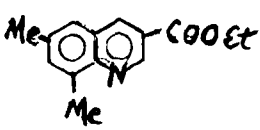
148986
50045
67704
85308
85308
148985

27⁵

↓

↓

57

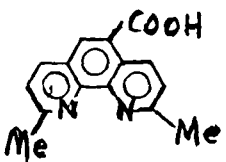


981

159935

27⁵

58

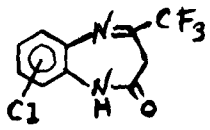


980

159934

59

60



mp 183-185°	968
mp 258-260°	967

153180
153179

IX. Distribution List

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- 19: (Continued)
- 2-Trifluoromethyl-4-quinolinemethanols
- Bis-trifluoromethyl-4-quinolinemethanols
- 2-aroxy-4-quinolinemethanols
- 2-(N-p-chloroanilino)-4-quinolinemethanols
- 2,3-Trimethylene-4-quinolinemethanols
- 1,2-Dihydro-1H-cyclopenta[b]quinoline-9-methanol
- 3-(4-Chlorobenzylidene)-1,2-etc.

Note: In the above, aminoalcohols may be substituted for "methanols".

20: (Continued)
of P. falciparum in man, with phototoxicity inconsequential.

(1) Nineteen new 2-aryl-4-quinoline aminoalcohols proved highly active and curative against P. berghei but were phototoxic in animals.

(2) Ten 2-CF₃ derivatives showed moderate antimalarial activities; and four 6,8-bis-CF₃ analogs were highly curative and non-phototoxic. The 2,8-bis-CF₃ compound proved highly successful in man.

(3) Shifting the aminoalcohol chain from quinoline position 4 to 3 was ineffective in eight compounds without a 2-aryl.

(4) Twelve 6-benzothiazole aminoalcohols proved ineffective.

(5) Twelve 4-quinoline aminoalcohols carrying 2-p-substituted-phenoxy or 2-(N-pCl-anilino), where nuclear through-conjugation is interrupted by the heteroelement, were curative but phototoxic in animals.

(6) Four 2-aryl-quinoline aminoalcohols carrying Cl, Br, F, or OMe in the 3-position (to sterically interfere with the nuclear planarity and through-conjugation), showed high curativity but were phototoxic.

(7) The 6,8-dichloro-4-quinoline aminoalcohol with a 2,3-trimethylene fused ring proved to be moderately active and non-phototoxic. The 6,8-Me₂ analog with pClPhCH= at the 2-CH₂ group, is a 2-vinylog of the 2-aryl-4-quinoline aminoalcohols, and it carries the p-chlorostyryl group at the quinoline position-2 and extruding as a part of the rigid 2,3-tricarbon fused ring. This was highly curative in spite of the relatively poor auxopharmacophoric quality of the 6,8-dimethyls. It was non-phototoxic in animals.

The supposed alpha-piperidyl analog (Corson, Aldrich Chem. Co.) made through a last step condensation of the secondary-amino alcohol with pClPhCHO, is now shown to be the oxazolidine.

ATE
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