Antimalarials. II. 8-Quinolinemethanols[1a,b]

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Received March 3, 1970

Sixteen new α-(dialkylaminomethyl)-8-quinolinemethanols have been synthesized for evaluation of their antimalarial activity. Desired substitution on the quinoline nucleus required development of two synthetic pathways to the key intermediates, the 8-quinolinecarboxaldehydes, which were converted through the oxiranes into the amino alcohols. 4-Me substituted compounds required preparation of 4-methyl-8-quinolinecarboxylic acids, esterification, reduction with LAH, and oxidation to the aldehyde. Intermediates without alkyl substitution were prepared by oxidation of 8-methylquinolines. Observations on reduction of 8-quinolinecarboxylates by LAH are described. Thirteen compounds were tested against *Plasmodium berghei* in mice. Three of them produced cures at 640 mg/kg. 6-Chloro-2-(4-chlorophenyl)-α-(dibutylaminomethyl)-8-quinolinemethanol hydrochloride (**3b**) was curative and not phototoxic.

Interest in quinolinemethanols as potential antimalarial agents has continued because this class of compounds has demonstrated significant activity against malarial infections in several species, including man.[2,3] The potent 2-phenyl-4-quinolinemethanols are phototoxic[4] and unsuitable for field use. Many molecular modifications[5] of the basic structure have been prepared in efforts to mitigate this side effect. This paper describes a major modification, that of moving the amino alcohol side chain to the 8 position of the quinoline nucleus.

The 8-quinolinemethanols have been studied[6] only cursorily, and early work uncovered no activity in them. Since nuclear substitution is required for activity in the parallel 4-quinolinemethanols, the unsubstituted compounds tested would not be expected to have antimalarial activity. The substituted 8-quinolinemethanols prepared by us are illustrated in Chart I.

Compounds in series **1**, **2**, and **3** were prepared from appropriately substituted 8-methylquinolines by SeO_2 oxidation to the 8-quinolinecarboxaldehydes, conversion of the aldehydes into oxiranes by the method of Corey, *et al.*,[7] and condensation of the oxiranes with dialkylamines (Scheme I).

Compounds in series **4**, **5**, **6**, and **7** were prepared from 4-methyl-8-quinolinecarboxylic acids by esterification, reduction of the esters with LAH, oxidation of the alcohols with pyridine–SO_3–DMSO,[8] conversion of the aldehydes to oxiranes, and condensation of the oxiranes with dialkylamines (Scheme II). This rather roundabout way was necessitated by failures of more direct routes.

Although it is reported that polyalkylquinolines can be selectively oxidized at the 8 position,[9] we failed to accomplish it with 5- or 6-chloro-4,8-dimethylquinolines. The method of Lutz, *et al.*,[10] for synthesizing the side chain of 4-quinolinemethanols failed when we were unable to prepare acid chlorides from 5- or 6-chloro-4-methyl-8-quinolinecarboxylic acids. This result was somewhat surprising in light of the successful preparation of 6-methoxy-8-quinolinecarboxylic acid chloride.[6a,b]

LAH reduction of methyl 5- and 6-chloro-4-methyl-8-quinolinecarboxylates by the usual procedure gave a mixture of products, including 1,2-dihydro-8-quinolinemethanols (Scheme III) identified by nmr. These dihydroquinolinemethanols could not be oxidized to quinolinemethanols with $PhNO_2$, $FeCl_3$, As_2O_5, or S. Treated with ceric ammonium nitrate[11] they yielded 1,2-dihydro-8-quinolinecarboxaldehydes. The procedure described in the Experimental Section gave excellent yields of 8-quinolinemethanols.

Introduction of ClC_6H_4 in the 2 position of the quinoline nucleus presented several problems.[12] A mixture of the desired 2-(4-chlorophenyl)-8-methylquinoline[13] and the 2-(4-chlorophenyl)-8-methyl-1,2,3,4-tetrahydroquinoline was obtained by 4-chlorophenylation by Gilman's method.[14] Apparently, the intermediate 1,2-dihydroquinoline disproportionated to give the quinoline and tetrahydroquinoline.

α-(Dialkylaminomethyl)-4-methyl-8-quinolinemethanols did not react with $4\text{-}ClC_6H_4Li$ even though sufficient reagent was used to react with the acidic protons of the $4\text{-}CH_3$ and -CHOH groups and to coordinate with the quinoline N.[15] Using the 4-methyl-8-quinolinemethanol *N*-oxides and a 4:1 mole ratio of LiAr

(1) (a) For the previous paper see J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *J. Med. Chem.*, **11**, 425 (1968); (b) the work described in this paper was performed under Contract DA-49-193-MD-2981 with the U. S. Army Medical Research and Development Command. This is Contribution No. 772 from the Army Research Program on Malaria. This paper was presented at the 21st Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., Nov 5–8, 1969; (c) To whom inquiries should be addressed.

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

(3) G. R. Coatney, "Survey of Antimalarial Agents," Public Health Service Monograph No. 9, Federal Security Agency, 1952; also known as Public Health Service Publication No. 193.

(4) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968).

(5) E. R. Atkinson and A. J. Puttick, *ibid.*, **11**, 1223 (1968).

(6) (a) K. N. Campbell, J. F. Kerwin, R. A. LaForge, and B. K. Campbell, *J. Amer. Chem. Soc.*, **68**, 1844 (1946); (b) A. McCoubrey and W. Webster, *J. Chem. Soc.*, **1948**, 97; (c) E. R. Buchman and H. Sargent, *J. Amer. Chem. Soc.*, **68**, 2720 (1946); (d) M. V. Rubstov, *J. Gen. Chem. USSR*, **9** 1493 (1939); *Chem. Abstr.*, **34**, 2850 (1940); (e) F. E. Kelsey, E. M. R. Geiling, F. K. Oldham, and E. H. Dearborn, *J. Pharmacol.*, **80**, 391 (1944); J. F. Mead and J. B. Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1352 (1956).

(8) J. R. Parikh and W. von E. Doering, *ibid.*, **89**, 5505 (1967).

(9) R. A. Glenn and J. R. Bailey, *ibid.*, **63**, 642 (1941).

(10) R. E. Lutz, *et al.*, *ibid.*, **68**, 1813 (1946).

(11) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).

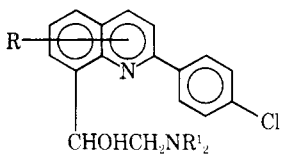
(12) Some attempts were made to prepare 2-phenyl-8-quinolinecarboxylic acids in the initial synthesis by the reaction of anthranilic acids with cinnamaldehyde without success.

(13) Proof of structure of the compound was obtained by nmr spectral studies. The spectrum showed no signal in the 8.7-ppm region, generally associated with the 2 proton. A doublet at 8.11 ppm, J = 8.25 cps, was assigned to the 4 proton in agreement with the usual $J_{3,4}$ = 8–10 cps for quinolines.

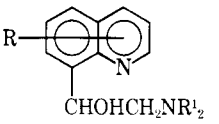
(14) H. Gilman, R. V. Christian, and S. M. Spatz, *J. Amer. Chem. Soc.*, **68**, 979 (1946).

(15) J. S. Wommack, T. G. Barbee, Jr., D. J. Thoeness, M. A. McDonald, and D. E. Pearson, *J. Heterocycl. Chem.*, **6**, 243 (1969).

CHART I



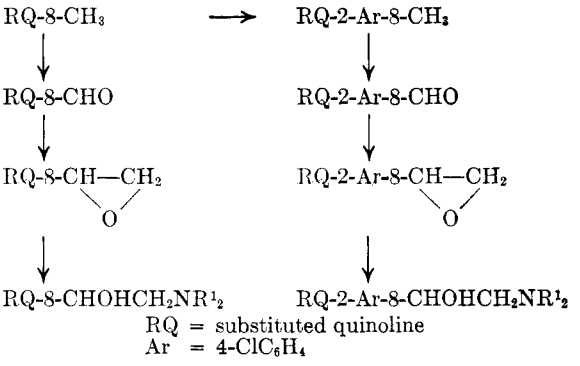
1, R = H
3, R = 6-Cl
5, R = 4-CH_3, 5-Cl
7, R = 4-CH_3, 6-Cl



2, R = 6-Cl
4, R = 4-CH_3, 5-Cl
6, R = 4-CH_3, 6-Cl

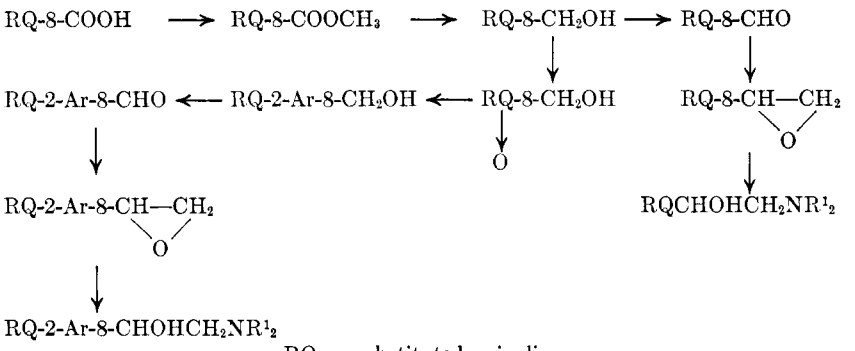
R^1 = **a**, C_2H_5
b, C_4H_9
c, C_7H_{15}

SCHEME I



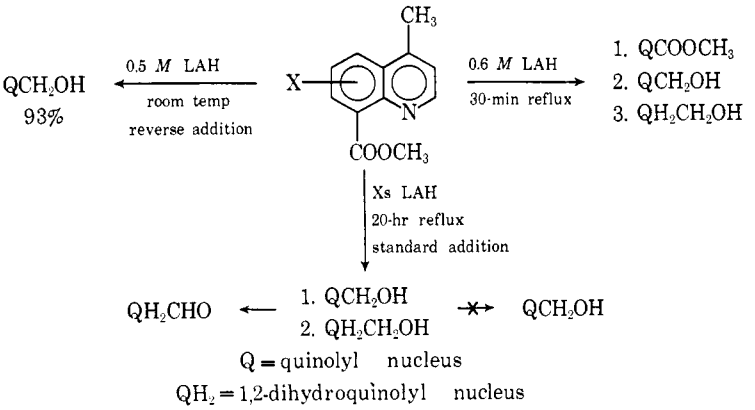
RQ = substituted quinoline
Ar = 4-ClC_6H_4

SCHEME II



RQ = substituted quinoline
Ar = 4-ClC_6H_4

SCHEME III



Q = quinolyl nucleus
QH_2 = 1,2-dihydroquinolyl nucleus

or Grignard reagent the 2-(4-chlorophenyl)-8-quinolinemethanols were obtained in moderate yields.

Biological Activity.—The 8-quinolinemethanols described herein have been tested for antimalarial activity against *Plasmodium berghei* in mice by Dr. Leo Rane[16] at the University of Miami. The results of these tests were furnished to us by Dr. D. P. Jacobus, Walter Reed Army Institute of Research. Antimalarial activity is summarized in Table I. The compounds, 6-chloro-2-(4-chlorophenyl)-α-(dibutylaminomethyl)-8-quinolinemethanol hydrochloride (**3b**), 6-chloro-2-(4-chlorophenyl)-α-(dibutylaminomethyl)-4-methyl-8-quinolinemethanol hydrochloride (**7b**), and 6-chloro-2-(4-chlorophenyl)-α-(diheptylaminomethyl)-4-methyl-8-quinolinemethanol hydrochloride (**7c**) produced cures at dosages of 640 mg/kg.

The pattern of antimalarial activity in the 8-quinolinemethanols largely paralleled that of the isomeric 4-quinolinemethanols. Those compounds which were unsubstituted at the quinoline 2 position were devoid of measurable activity. Introduction of 4-ClC_6H_4 at the 2 position without other nuclear substitution did not increase activity. When additional substitution *e.g.*, 6-Cl, was made, activity appeared. The activity of the best of the compounds tested was substantially lower than that of the corresponding 4-quinolinemethanol.

Two of the 8-quinolinemethanols were evaluated for phototoxicity in albino mice.[17] 6-Chloro-2-(4-chlorophenyl)-α-(dibutylaminomethyl)-quinolinemethanol·HCl (**3b**) was found to be nonphototoxic, but 6-chloro-2-(4-chlorophenyl)-4-methyl-α-(dibutylaminomethyl)-8-quinolinemethanol·HCl (**7b**) was reported as phototoxic. Although no supporting evidence for it

(16) Test procedure is described in T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

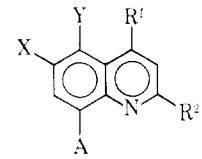
(17) W. E. Rothe, Walter Reed Army Institute of Research, private communication.

TABLE I
ANTIMALARIAL ACTIVITY OF α-(DIALKYLAMINOMETHYL)-8-QUINOLINEMETHANOLS

	Change in mean survival time[a] or no. of cures[b] — Dosage (mg/kg)					
No.	20	40	80	160	320	640
1b		0		0		0.2
2a		0.5		Toxic		Toxic
b		0.2		0.4		0.8
c		0.7		0.7		0.9
3a		0.3		1.7		6.1
b	0.3	0.7	1.7	5.7	11.7, 1 C	9.4, 3 C
c	0.3	1.1	1.5	4.5	8.1	9.3
5b	0.2	0.2	2.8	5.4	9.3	9.6
6a						<1
b						<1
c						<1
7b	1.1, 1.3	3.7	5.9	6.9, 7.3	12.5, 12.9	14.7, 1 C
c	0.5, 0.7	0.5, 0.9	2.3	5.1, 4.9	12.7, 12.9	13.7, 1 C

[a] Mean survival time of treated mice − the mean survival time of controls. [b] Number of treated mice in groups of 5 surviving to 30 days or more.

TABLE II
QUINOLINE DERIVATIVES



No.	X	Y	R¹	R²	A	Formula	Prepn[a]	Yield, %	Crystn solvent	Mp, °C	Analyses[b]
1	H	H	H	4-ClC$_6$H$_4$	COOH	$C_{16}H_{10}ClNO_2$		55	$CHCl_3$–petr ether	206–209	C, H, N
	H	H	H	4-ClC$_6$H$_4$	CHO	$C_{16}H_{10}ClNO$	F(1)	63.9	$CHCl_3$–petr ether	142–146	C, H, N
2	Cl	H	H	H	CH_3	$C_{10}H_8ClN$		51.8	Petr ether	60–63	c
	Cl	H	H	H	CH_2OH	$C_{10}H_8ClNO$	B,C	54.5	MeOH	151–153	C, H, N
	Cl	H	H	H	CHO	$C_{10}H_6ClNO$	F(1)	31.9	$CHCl_3$–EtOH	151–155	C, H, N
3	Cl	H	H	4-ClC$_6$H$_4$	CH_3	$C_{16}H_{11}Cl_2N$	D	20.2	Et_2O–MeOH	136.5–137.5	C, H, N
	Cl	H	H	4-ClC$_6$H$_4$	CHO	$C_{16}H_9Cl_2NO$	F(1)	88.0	$CHCl_3$–petr ether	195–196	C, H, N
4	H	Cl	CH_3	H	COOH	$C_{11}H_8ClNO_2$	A	61.8	Dioxane	203–206	C, H, N
	H	Cl	CH_3	H	$COOCH_3$	$C_{12}H_{10}ClNO_2$	B	100	Hexane	69–70	C, H, N
	H	Cl	CH_3	H	CH_2OH	$C_{11}H_{10}ClNO$	C	91	EtOH	126–128	C, H, N
	H	Cl	CH_3	H	CHO	$C_{11}H_8ClNO$	F(2)	67	Me_2CO	140–142	C, H, N
5	H	Cl	CH_3	4-ClC$_6$H$_4$	CH_2OH	$C_{17}H_{13}Cl_2NO$	E(2)	35	Me_2CO	166–167	C, H, N
	H	Cl	CH_3	4-ClC$_6$H$_4$	CHO	$C_{17}H_{11}Cl_2NO$	F(2)	82.4	$CHCl_3$	192–193	C, H, N
6	Cl	H	CH_3	H	COOH	$C_{11}H_8ClNO_2$	A	60.7	$CHCl_3$	232–233	C, H, N
	Cl	H	CH_3	H	$COOCH_3$	$C_{12}H_{10}ClNO_2$	B	100		83–87	
	Cl	H	CH_3	H	CH_2OH	$C_{11}H_{10}ClNO$	C	79.2	MeOH	142–143	C, H, N
	Cl	H	CH_3	H	CHO	$C_{11}H_8ClNO$	F(2)	70.7	Me_2CO	153.0–153.5	C, H, N
7	Cl	H	CH_3	4-ClC$_6$H$_4$	CH_2OH	$C_{17}H_{13}Cl_2NO$	E(1,2)	30.4	Me_2CO–EtOH	198–201	C, H, N
	Cl	H	CH_3	4-ClC$_6$H$_4$	CHO	$C_{17}H_{11}Cl_2NO$	F(2)	91.2	Me_2CO	242–245	N

[a] The capital letters refer to the descriptions in the Experimental Section. [b] Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of the theoretical values. [c] Previously prepared. See ref 18.

is available, an attractive hypothesis is that the presence of the 4-Me delayed the metabolism of the compound and allowed it to be retained in the tissues of the animal long enough for the phototoxic effect to appear.

Experimental Section

The general description of experimental procedures given in this section is supplemented by references to the appropriate table in which individual compounds are listed. All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

6-Chloro-8-methylquinoline.[18]—2-Amino-5-chlorotoluene (563 g, 3.98 moles), As_2O_5 (685 g, 2.98 moles), and anhyd glycerol (1468 g, 16 moles) were mixed and concd H_2SO_4 (453 ml, sp gr 1.84) was added, maintaining the temp below 130°. The temp was kept at 130–135° for 1 hr followed by refluxing for 24 hr. The mixture was diluted with ice–H_2O and made alkaline with NaOH solution. The oil which separated solidified sufficiently upon standing in a refrigerator overnight to be removed from the liquor by filtration. The wet solid was mixed with dilute NaOH solution and was steam distilled. The distillate was filtered and the waxy solid was pressed on a filter until it was free from a yellow oil,[19] yield 366.6 g (51.8%). The compound was crystallized from petr ether (30–60°), mp 60–63° (lit.[18] mp 65.5°).

A. 8-Quinolinecarboxylic Acids.[20]—The chloroanthranilic acid (1 mole) was suspended in 500 ml of MeOH and methyl vinyl ketone (1 mole) was added. The mixture was heated to reflux and after 30 min 120 ml of concd HCl was added slowly, followed by $FeCl_3 \cdot 6H_2O$ (500 g). Refluxing continued for 3 hr and MeOH was distilled. The residue was suspended in hot H_2O and was

(18) T. Mazonski, T. Mielecki and E. Sucharda, *Rocz. Chem.*, **16**, 519 (1936); *Chem. Abstr.*, **31**, 3921 (1937).

(19) This oil was tentatively identified as 6-chloro-8-methyl-1,2,3,4-tetrahydroquinoline by nmr.

(20) H. Araj, K. Saito and N. Murato, *Kogyo Kagaku Zasshi*, **63**, 319 (1960).

TABLE III

α-(DIALKYLAMINOMETHYL)-8-QUINOLINEMETHANOLS (A)

No.	X	Y	R^1	R^2	R^3	Formula[b]	Reaction temp, °C	Time	Yield, %	Crystn solvent	Mp, °C	Analyses[a]
1b	H	H	H	4-ClC_6H_4	C_4H_9	$C_{25}H_{32}ClN_2O \cdot HCl$	150–155	4	58.5	Me_2CO–Et_2O	174–176	C, H, N, Cl
2a	Cl	H	H	H	C_2H_5	$C_{15}H_{19}ClN_2O \cdot HCl$	100	48	75.5	EtOH–Et_2O	173	C, H, N
b	Cl	H	H	H	C_4H_9	$C_{19}H_{27}ClN_2O \cdot HCl$	150–153	40	90.0	MeOH	199–201	C, H, N, Cl
c	Cl	H	H	H	C_7H_{15}	$C_{25}H_{39}ClN_2O \cdot HCl$	150	24	66.5	EtOAc	160–162	C, H, N
3a	Cl	H	H	4-ClC_6H_4	C_2H_5	$C_{21}H_{22}Cl_2N_2O \cdot HCl$	100	72	57	EtOH	230–251 (vac)	C, H, N
b	Cl	H	H	4-ClC_6H_4	C_4H_9	$C_{25}H_{30}Cl_2N_2O \cdot HCl$	150–153	25	63	EtOH	214–216	C, H, N
c	Cl	H	H	4-ClC_6H_4	C_7H_{15}	$C_{31}H_{42}Cl_2N_2O \cdot HCl$	150	24	48	EtOH	154–156	C, H N,
4a	H	Cl	CH_3	H	C_2H_5	$C_{16}H_{21}ClN_2O \cdot HCl$	115	72	47.0	EtOH (abs)	220.5–221.5	C, H, N
b	H	Cl	CH_3	H	C_4H_9	$C_{20}H_{29}ClN_2O \cdot HCl$	165	12	62.8	Me_2CO	175.5–176.5	C, H, N, Cl
c	H	Cl	CH_3	H	C_7H_{15}	$C_{26}H_{41}ClN_2O \cdot HCl$	180	12	49.4	Me_2CO	135–136	C, H, N
5b	H	Cl	CH_3	4-ClC_6H_4	C_4H_9	$C_{26}H_{32}Cl_2N_2O \cdot HCl$	140–150	20	17.7	EtOH	245–247	C, H, N
6a	Cl	H	CH_3	H	C_2H_5	$C_{16}H_{21}ClN_2O \cdot HCl$	110	72	57.4	Me_2CO–EtOH	205–207	C, H, N
b	Cl	H	CH_3	H	C_4H_9	$C_{20}H_{29}ClN_2O \cdot HCl$	148–150	19	77.5	Me_2CO–EtOH	176–177	C, H, N
c	Cl	H	CH_3	H	C_7H_{15}	$C_{25}H_{41}ClN_2O \cdot HCl$	150	20	43.4	Me_2CO	160–162	C, H, N
7b	Cl	H	CH_3	4-ClC_6H_4	C_4H_9	$C_{26}H_{32}Cl_2N_2O \cdot HCl$	160–165	30	79.7	EtOH–H_2O	256–257 (vac)	C, H, N
c	Cl	H	CH_3	4-ClC_6H_4	C_7H_{15}	$C_{32}H_{44}Cl_2N_2O \cdot HCl$	170	40	59.5	EtOH–Me_2CO–H_2O	203–206	C, H, N

[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. [b] Structure is shown in text.

A

made alkaline with NaOH soln. The mixture was heated to boiling and filtered. The black residue was extracted with hot H_2O keeping the extracts basic until acidification of the extract did not give a precipitate. The extracts were pooled with the filtrate and heated to redissolve the precipitate. The hot solution was acidified with AcOH. The precipitated acid was separated by filtration and washed (Me_2CO).

B. Methyl 8-Quinolinecarboxylates.—The 8-quinolinecarboxylic acid was suspended in $CHCl_3$ and 2 moles of CH_2N_2 in Et_2O/mole of acid was added. The mixture was stirred overnight, filtered, and concd under vacuum. The residue was dissolved in Et_2O and filtered. The filtrate was charcoaled and evapd.

C. 8-Quinolinemethanols.—A clarified 0.5 *M* soln of LAH in Et_2O was added slowly with stirring to a soln of methyl 8-quinolinecarboxylate in Et_2O at room temp, and the reaction was followed by monitoring C=O in the ir spectrum. As soon as the CO band disappeared the addition of hydride solution was stopped and the mixture was stirred for 5 min at room temp. The complex was decomposed by twice the equiv of H_2O saturated with NH_4Cl. The mixture was stirred for 1 hr and filtered. The filtrate was evaporated.

8-Quinolinemethanol *N*-Oxides.—The 8-quinolinemethanol (1 mole) dissolved in $CHCl_3$ was heated to reflux. *m*-Chloroperbenzoic acid (2 moles) in $CHCl_3$ was added slowly. Total reflux time was 4–4.5 hr. (It is important neither greatly to reduce nor to exceed the total reflux time. Reduced reflux times resulted in recovery of a considerable amount of starting material, and excessive reflux times resulted in poor yields of highly contaminated product.) The $CHCl_3$ solution was cooled, extracted with 10% Na_2CO_3, and dried (Na_2SO_4). The $CHCl_3$ was removed and the *N*-oxide was washed with hot THF.

D. 2-(4-Chlorophenyl)-8-methylquinolines.—*n*-BuLi solution (1.1 moles; Foote Mineral) was diluted with Et_2O and cooled in an ice–salt mixture under N_2. 4-Bromochlorobenzene (1.2 moles) in Et_2O was added within 4–8 min, and the solution was stirred for 3–5 min. The 8-methylquinoline (1 mole) in Et_2O was added in 4 min, and the mixture was stirred for 15–20 min. It was poured into ice–H_2O and the Et_2O layer was separated. It was dried (Na_2SO_4) and the Et_2O was removed. The residue was distilled under reduced pressure and the distillate was crystallized from dioxane–H_2O. Fractional crystallization from MeOH–C_6H_6 separated the product from the 1,2,3,4-tetrahydroquinoline. [6-Chloro-2-(4-chlorophenyl)-8-methyl-1,2,3,4-tetrahydroquinoline, mp 120–122°, was isolated and identified by nmr. *Anal.* ($C_{16}H_{15}Cl_2N$) C, H, N.]

2-(4-Chlorophenyl)-8-quinolinecarboxylic Acid.—2-(4-Chlorophenyl)-8-methylquinoline (4.0 g, 15.8 mmoles) and 6 *N* H_2SO_4 (23 ml) were mixed at room temperature. $K_2Cr_2O_7$ (9.0 g) in concentrated H_2SO_4 (11.8 g) and H_2O (16.3 g) was added in 20 min. The mixture was stirred and heated for 22 hr. After cooling it was filtered and the collected solid washed with H_2O.

E. 2-(4-Chlorophenyl)-4-methyl-8-quinolinemethanols.—(1) A Grignard reagent from 4-bromochlorobenzene was prepared by the standard method and the *N*-oxide (0.25 mole/mole of Mg) was added as a slurry in Et_2O. The mixture was refluxed overnight and poured into a cold dilute NH_4Cl solution. The solid was separated. (2) *n*-BuLi (1 mole) soln in hexane was diluted with Et_2O and cooled to −50°. 4-Bromochlorobenzene (1.1 moles) in Et_2O was added, maintaining the temperature of the solution below −35°, and the solution was stirred for 15 min at −35°. The solution was forced by N_2 into a stirring solution of *N*-oxide (0.2 mole) in THF at room temperature. The mixture was stirred for 3 hr and poured into H_2O. The organic layer was separated and dried (Na_2SO_4). The solution was evaporated.

F. 8-Quinolinecarboxaldehydes.—(1) The 8-methylquinoline was ground with equimolar amounts of freshly prepared and sublimed SeO_2. The mixture was heated in an oil bath at 200° for 2–3 hr. After cooling the solid was extracted with boiling $CHCl_3$. The extract was filtered and washed with 10% Na_2CO_3 to remove

any acid by-product.[21] The $CHCl_3$ solution was dried ($NaSO_4$), charcoaled, and evaporated.

(2) The 8-quinolinemethanol (17.3 mmoles), Et_3N (17.5 g, 170 mmoles), and 30 ml of dry DMSO were mixed and heated to 70°. Pyridine–SO_3 (13 g, 83 mmoles) in 30 ml of DMSO was added slowly while stirring. The mixture was stirred at 70° for 2 hr. It was poured into H_2O, stirred for 15 min, and filtered. The precipitate was washed with H_2O.

8-(1,2-Epoxyethyl)quinolines (Oxiranes).—Henry's procedure[22] of addition of aldehyde to a four- to fivefold excess of dimethylsulfonium methylide gave unsatisfactory yields of impure products. The following procedure was uniformly successful.

Dimethylsulfonium methylide was prepared by Corey's method.[7] The stoichiometric amount of this ylid, immediately after preparation, was forced by N_2 into a solution of the 8-quinolinecarboxaldehyde in THF, and the mixture was stirred at room temperature for 1 hr. The THF was removed under reduced pressure at 50° and the remaining solution was diluted with H_2O. The precipitated oxirane was filtered and washed with H_2O.

α-(Dialkylaminomethyl)-8-quinolinemethanols.—The 8-quinolinemethanols listed in Table III were all prepared by the direct condensation of the corresponding oxirane with the appropriate secondary amine, using 4–5 moles of amine/mole of oxirane. The excess of amine was removed either by distilling under reduced pressure or by fractional pptn of the HCl salt. The Et_2O solution of amino alcohol was charcoaled and the amino alcohol was pptd as the HCl salt.

(21) The 2-(4-chlorophenyl)-8-methylquinolines gave good yields of the aldehydes with no formation of the corresponding carboxylic acids, but the 2-unsubstituted compounds readily overoxidized.

(22) W. G. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *J. Med. Chem.*, **11**, 1221 (1968).

Acknowledgments.—Nmr spectra were provided to us through the courtesy of Dr. William J. Welstead, Jr., A. H. Robins Company, Inc., Richmond, Va. Microanalysis were performed by Microanalysis, Inc., Wilmington, Del.

New Synthesis of Antimalarials Related to 2-Bromo-4,5-dimethoxy-*N*,*N*-bis(diethylaminoethyl)aniline. Terminal Nitrogen Modifications[1,2]

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Received January 12, 1970

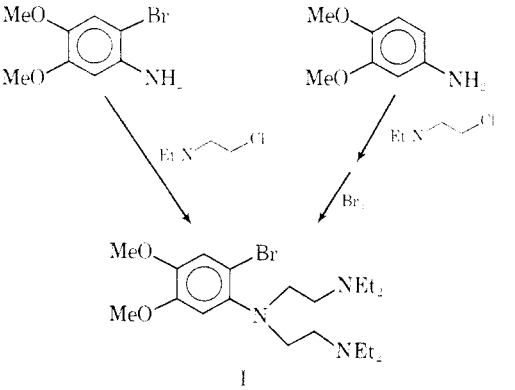
The antimalarial I can be synthesized in one step by a novel N-alkylation technique. The metalation of 2-bromo-4,5-dimethoxyaniline and subsequent reaction with various N mustards yielded modifications of I with the triamine terminating in small and medium sized rings. None of the reported modifications showed significant antimalarial activity.

The response of malaria-infected canaries[3] and Rhesus monkeys[4] toward treatment with I revived interest in a rather old class of antimalarials.[5] Anticipating that I in combination with an effective schizonticide might be of value in combating drug-resistant strains of *Plasmodium falciparum* structural variations of the basic side chain were synthesized for evaluation in antimalarial screens.

A basic side chain comprised of one or more amino nitrogens is a common structural feature of many classes of antimalarial drugs. It has been suggested that the distribution and absorption of a drug in the host is controlled by this ubiquitous basic side chain.[6a,b] As might be anticipated the requisite structural features of this side chain are quite specific. To illustrate, activity in the amino pyrocatechol dialkyl ether[7] antimalarials has only been observed when the triamine conforms to the structure shown in I. Russell[8] has described the structure of the basic side chain characteristic of other anitmalarials.

The structural limitations imposed on the two terminal nitrogens has received little attention. We have synthesized variations of I in which the basic side chain is terminated in small and medium sized rings. It seemed desirable to evaluate the influence on activity imposed by the rotational and conformational variations of this type of side chain termination.

Chemistry.—From the standpoint of simplicity and potential versatility the synthesis of I by the direct alkylation of 2-bromo-4,5-dimethoxyaniline would be desirable. This approach to I has been examined by us



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as well as others,[9] with little success. The difficulty arises from a combination of the rather drastic reaction

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DA-49-193-MD-2900. This is Contribution No. 652 from the Army Research Program on Malaria.

(2) For Part I of this series see E. L. Stogryn, *J. Med. Chem.*, **12**, 185 (1969).

(3) L. J. Bruce-Chwatt, *Trans. Roy. Soc. Trop. Med. Hyg.*, **59**, 105 (1965).

(4) L. H. Schmidt, R. N. Rossau, R. Fradkin, J. Woods, W. Schulemann, and L. Kratz, *Bull. W. H. O.*, **34**, 783 (1966).

(5) (a) W. Schulemann and W. Kropp, U. S. Patent 1,757,394, May 6, 1930; (b) R. Green, *Lancet*, **217**, 1137 (1929); (c) R. Green, *Bull. Inst. Med. Res. Fed. Malaya*, **28**, 29 (1929); (d) J. A. Sinton, *Indian J. Med. Res.*, **17**, 815 (1930).

(6) (a) O. Yu. Magidson, N. M. Delektorskaya, and I. M. Lipovich, *Arch. Pharm.*, **272**, 74 (1934); (b) O. Yu. Magidson and A. M. Grigorovskii, *Ber.*, **69B**, 396 (1936).

(7) F. Schoenhofer, "Chemotherapy," Office of Technical Services Report, P.B.-85033, 1948; FIAT, Review of German Science, 43.

(8) P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., Interscience, New York, N. Y., 1960, p 814.

(9) L. M. Werbel, E. F. Elslager, M. P. Hutt, and J. M. Vandenbelt, *J. Pharm. Sci.*, **56**, 1335 (1967).