

Antimalarials. II. 8-Quinolinemethanols^{1a,b}J. S. GILLESPIE, JR.,^{1c} SATYA PRAKASH ACHARYA, R. E. DAVIS, AND B. K. BARMAN*Virginia Institute for Scientific Research, Richmond, Virginia 23229**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 phototoxic⁴ and unsuitable for field use. Many molecular modifications⁵ 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 studied⁶ 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 SeO₂ 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-SO₃-DMSO,⁸ conversion of the aldehydes to oxiranes, and condensation of the oxiranes with dialkylamines (Scheme II). This rather round-

about 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 PhNO₂, FeCl₃, As₂O₅, or S. Treated with ceric ammonium nitrate¹¹ they yielded 1,2-dihydro-8-quinolinecarboxaldehydes. The procedure described in the Experimental Section gave excellent yields of 8-quinolinemethanols.

Introduction of ClC₆H₄ in the 2 position of the quinoline nucleus presented several problems.¹² A mixture of the desired 2-(4-chlorophenyl)-8-methylquinoline¹³ 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-ClC₆H₄Li even though sufficient reagent was used to react with the acidic protons of the 4-CH₃ 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.

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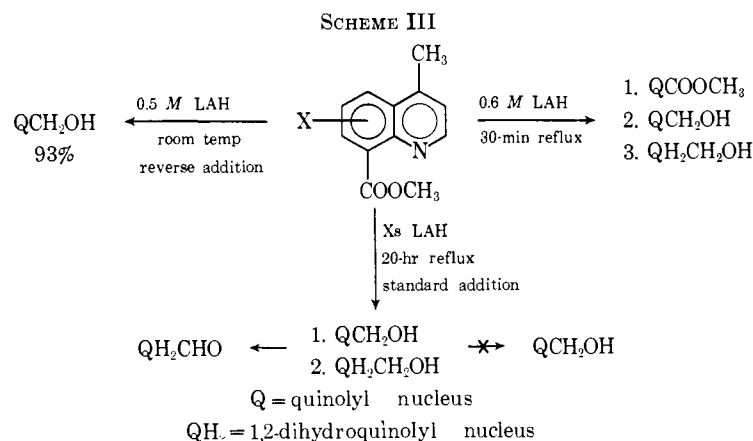
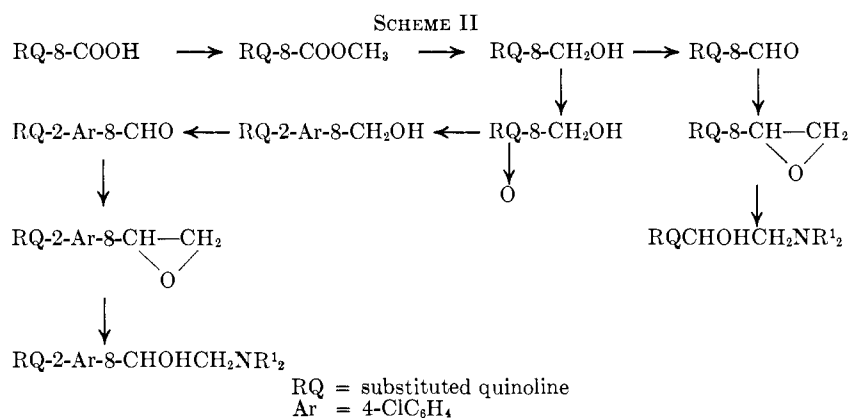
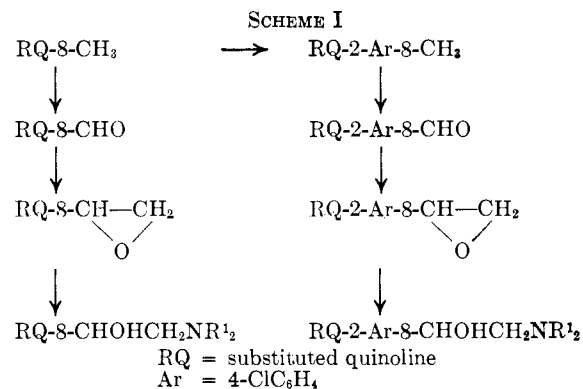
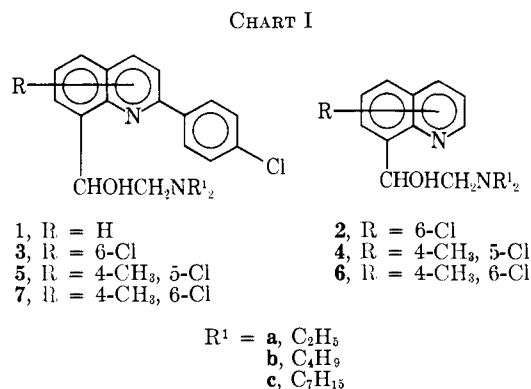
(11) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).

(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 $J_{4,8} = 8-10$ cps for quinolines.

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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 Rane¹⁶ 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-ClC₆H₄ 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

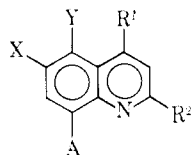
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TABLE I
 ANTIMALARIAL ACTIVITY OF α -[DIALKYLAMINOMETHYL]-8-QUINOLINEMETHANOLS

No.	Change in mean survival time ^a or no. of cures ^b					
	Dosage (mg/kg)					
	20	40	80	160	320	640
1b		0		4		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	R ¹	R ²	A	Formula	Prepn ^d	Yield, %	Crystn solvent	Mp, °C	Analyses ^b
1	H	H	H	4-ClC ₆ H ₄	COOH	C ₁₆ H ₁₀ ClNO ₂		57	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 ₈ ClN		51.8	Petr ether	60-63	c
	Cl	H	H	H	CH ₂ OH	C ₁₀ H ₈ ClNO	B, C	54.5	MeOH	151-153	C, H, N
3	Cl	H	H	H	CHO	C ₁₀ H ₈ ClNO	F(1)	31.9	CHCl ₃ -EtOH	151-155	C, H, N
	Cl	H	H	4-ClC ₆ H ₄	CH ₃	C ₁₆ H ₁₁ Cl ₂ N	D	20.2	Et ₂ O-MeOH	136.5-137.5	C, H, N
4	Cl	H	H	4-ClC ₆ H ₄	CHO	C ₁₆ H ₉ Cl ₂ NO	F(1)	88.0	CHCl ₃ -petr ether	195-196	C, H, N
	H	Cl	CH ₃	H	COOH	C ₁₇ H ₈ ClNO ₂	A	61.8	Dioxane	203-206	C, H, N
5	H	Cl	CH ₃	H	COOCH ₃	C ₁₇ H ₁₀ ClNO ₂	B	100	Hexane	69-70	C, H, N
	H	Cl	CH ₃	H	CH ₂ OH	C ₁₇ H ₁₀ ClNO	C	91	EtOH	126-128	C, H, N
	H	Cl	CH ₃	H	CHO	C ₁₇ H ₈ ClNO	F(2)	67	Me ₂ CO	140-142	C, H, N
	H	Cl	CH ₃	4-ClC ₆ H ₄	CH ₂ OH	C ₁₇ H ₁₃ Cl ₂ NO	E(2)	35	Me ₂ CO	166-167	C, H, N
6	Cl	H	CH ₃	4-ClC ₆ H ₄	CHO	C ₁₇ H ₁₁ Cl ₂ NO	F(2)	82.4	CHCl ₃	192-193	C, H, N
	Cl	H	CH ₃	H	COOH	C ₁₇ H ₈ ClNO ₂	A	60.7	CHCl ₃	232-233	C, H, N
	Cl	H	CH ₃	H	COOCH ₃	C ₁₇ H ₁₀ ClNO ₂	B	100		83-87	
	Cl	H	CH ₃	H	CH ₂ OH	C ₁₇ H ₁₀ ClNO	C	79.2	MeOH	142-143	C, H, N
7	Cl	H	CH ₃	H	CHO	C ₁₇ H ₈ ClNO	F(2)	70.7	Me ₂ CO	153.0-153.5	C, H, N
	Cl	H	CH ₃	4-ClC ₆ H ₄	CH ₂ OH	C ₁₇ H ₁₃ Cl ₂ NO	E(1,2)	30.4	Me ₂ CO-EtOH	198-201	C, H, N
	Cl	H	CH ₃	4-ClC ₆ H ₄	CHO	C ₁₇ H ₁₁ Cl ₂ NO	F(2)	91.2	Me ₂ CO	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), As₂O₅ (685 g, 2.98 moles), and anhyd glycerol (1468 g, 16 moles) were mixed and concd H₂SO₄ (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-H₂O 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 FeCl₃·6H₂O (500 g). Refluxing continued for 3 hr and MeOH was distilled. The residue was suspended in hot H₂O and was

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

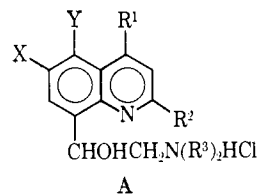
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TABLE III
 α -(DIALKYLAMINOMETHYL)-8-QUINOLINEMETHANOLS (A)

No.	X	Y	R ¹	R ²	R ³	Formula ^b	Reaction temp, °C	Time	Yield, %	Crystn solvent	Mp, °C	Analyses ^d
1b	H	H	H	4-ClC ₆ H ₄	C ₇ H ₉	C ₂₅ H ₃₁ ClN ₂ O·HCl	150-155	4	58.5	Me ₂ CO-Et ₂ O	174-176	C, H, N, Cl
2a	Cl	H	H	H	C ₂ H ₅	C ₁₃ H ₁₉ ClN ₂ O·HCl	100	48	75.5	EtOH-Et ₂ O	173	C, H, N
b	Cl	H	H	H	C ₃ H ₇	C ₁₉ H ₂₇ ClN ₂ O·HCl	150-153	40	90.0	MeOH	199-201	C, H, N, Cl
c	Cl	H	H	H	C ₇ H ₁₅	C ₂₅ H ₃₃ ClN ₂ O·HCl	150	24	66.5	EtOAc	160-162	C, H, N
3a	Cl	H	H	4-ClC ₆ H ₄	C ₂ H ₃	C ₂₁ H ₂₇ Cl ₂ N ₂ O·HCl	100	72	57	EtOH	250-251 (vac)	C, H, N
b	Cl	H	H	4-ClC ₆ H ₄	C ₃ H ₉	C ₂₅ H ₃₃ Cl ₂ N ₂ O·HCl	150-153	25	63	EtOH	214-216	C, H, N
c	Cl	H	H	4-ClC ₆ H ₄	C ₇ H ₁₅	C ₃₁ H ₄₂ Cl ₂ N ₂ O·HCl	150	24	48	EtOH	154-156	C, H, N
4a	H	Cl	CH ₃	H	C ₂ H ₅	C ₁₆ H ₂₁ ClN ₂ O·HCl	115	72	47.0	EtOH (abs)	220.5-221.5	C, H, N
b	H	Cl	CH ₃	H	C ₃ H ₇	C ₂₀ H ₂₉ ClN ₂ O·HCl	165	12	62.8	Me ₂ CO	175.5-176.5	C, H, N, Cl
c	H	Cl	CH ₃	H	C ₇ H ₁₅	C ₂₆ H ₄₁ ClN ₂ O·HCl	180	12	49.4	Me ₂ CO	135-136	C, H, N
5b	H	Cl	CH ₃	4-ClC ₆ H ₄	C ₃ H ₉	C ₂₆ H ₃₂ Cl ₂ N ₂ O·HCl	140-150	20	17.7	EtOH	245-247	C, H, N
6a	Cl	H	CH ₃	H	C ₂ H ₅	C ₁₆ H ₂₁ ClN ₂ O·HCl	110	72	57.4	Me ₂ CO-EtOH	205-207	C, H, N
b	Cl	H	CH ₃	H	C ₃ H ₇	C ₂₀ H ₂₉ ClN ₂ O·HCl	148-150	19	77.5	Me ₂ CO-EtOH	176-177	C, H, N
c	Cl	H	CH ₃	H	C ₇ H ₁₅	C ₂₆ H ₄₁ ClN ₂ O·HCl	150	20	43.4	Me ₂ CO	160-162	C, H, N
7b	Cl	H	CH ₃	4-ClC ₆ H ₄	C ₃ H ₉	C ₂₆ H ₃₂ Cl ₂ N ₂ O·HCl	160-165	30	79.7	EtOH-H ₂ O	256-257 (vac)	C, H, N
c	Cl	H	CH ₃	4-ClC ₆ H ₄	C ₇ H ₁₅	C ₃₂ H ₄₄ Cl ₂ N ₂ O·HCl	170	40	59.5	EtOH-Me ₂ CO-H ₂ O	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.



made alkaline with NaOH soln. The mixture was heated to boiling and filtered. The black residue was extracted with hot H₂O 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 (Me₂CO).

B. Methyl 8-Quinolinecarboxylates.—The 8-quinolinecarboxylic acid was suspended in CHCl₃ and 2 moles of CH₂N₂ in Et₂O/mole of acid was added. The mixture was stirred overnight, filtered, and concd under vacuum. The residue was dissolved in Et₂O and filtered. The filtrate was charcoaled and evapd.

C. 8-Quinolinemethanols.—A clarified 0.5 M soln of LAH in Et₂O was added slowly with stirring to a soln of methyl 8-quinolinecarboxylate in Et₂O 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 H₂O saturated with NH₄Cl. The mixture was stirred for 1 hr and filtered. The filtrate was evaporated.

8-Quinolinemethanol N-Oxides.—The 8-quinolinemethanol (1 mole) dissolved in CHCl₃ was heated to reflux. *m*-Chloroperbenzoic acid (2 moles) in CHCl₃ 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 CHCl₃ solution was cooled, extracted with 10% Na₂CO₃ and dried (Na₂SO₄). The CHCl₃ 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 Et₂O and cooled in an ice-salt mixture under N₂. 4-Bromochlorobenzene (1.2 moles) in Et₂O was added within 4-8 min, and the solution was stirred for 3-5 min. The 8-methylquinoline (1 mole) in Et₂O was added in 4 min, and the mixture was stirred for 15-20 min. It was poured into ice-H₂O and the Et₂O layer was separated. It was dried (Na₂SO₄) and the Et₂O was removed. The residue was distilled under reduced pressure and the distillate was crystallized from dioxane-H₂O. Fractional crystallization from MeOH-C₆H₆ 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.* (C₁₆H₁₅Cl₂N) C, H, N.]

2-(4-Chlorophenyl)-8-quinolinecarboxylic Acid.—2-(4-Chlorophenyl)-8-methylquinoline (4.0 g, 15.8 mmoles) and 6 N H₂SO₄ (23 ml) were mixed at room temperature. K₂Cr₂O₇ (9.0 g) in concentrated H₂SO₄ (11.8 g) and H₂O (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 H₂O.

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 Et₂O. The mixture was refluxed overnight and poured into a cold dilute NH₄Cl solution. The solid was separated. (2) *n*-BuLi (1 mole) soln in hexane was diluted with Et₂O and cooled to -50°. 4-Bromochlorobenzene (1.1 moles) in Et₂O 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 N₂ 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 H₂O. The organic layer was separated and dried (Na₂SO₄). The solution was evaporated.

F. 8-Quinolinecarboxaldehydes.—(1) The 8-methylquinoline was ground with equimolar amounts of freshly prepared and sublimed SeO₂. The mixture was heated in an oil bath at 200° for 2-3 hr. After cooling the solid was extracted with boiling CHCl₃. The extract was filtered and washed with 10% Na₂CO₃ to remove

any acid by-product.²¹ The CHCl_3 solution was dried (Na_2SO_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_2 (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 procedure²² 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-

(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).

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.

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}

EUGENE L. STOGRYN

Esso Research and Engineering Company, Linden, New Jersey 07036

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.

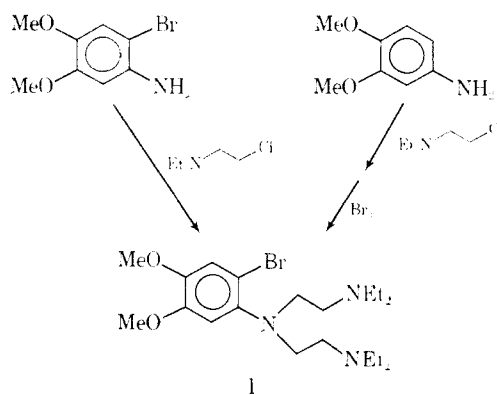
The response of malaria-infected canaries³ and Rhesus monkeys⁴ toward treatment with I revived interest in a rather old class of antimalarials.⁵ Anticipating that I in combination with an effective schizonticide might be of value in combating drug-resistant strains of *Plasmodium falciparum* structural 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 ether⁷ antimalarials has only been observed when the triamine conforms to the structure shown in I. Russell⁸ has

described the structure of the basic side chain characteristic of other antimalarials.

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



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).

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