In the case where a hydrazide·HCl was employed (*i.e.*, III), an equiv quantity of Et_3N was added to the condensing medium. Thus, a suspension of cyclopentylpropionic acid hydrazide·HCl (6.3 g, 33 mmol) and 2-hydroxy-1,4-napthoquinone (5.0 g, 29 mmol) in 80% HOAc (200 ml) containing Et_3N (3.3 g, 33 mmol) was stirred at 25° for 25 hr. The solvent was stripped *in vacuo* and the bright orange residue was freed from excess hydrazide and Et_3N·HCl using a wash solution of EtOH–H_2O–concd HCl (10:10:1). Additional successive washings with EtOH–H_2O (1:1), Me_2CO, and Et_2O gave a crude product (4.6 g) which afforded after two recrystallizations 2.73 g of III, mp 174–179°.

Critical Extraction Values (p*E*).—Extraction constants, p*E*, were determined using the standard procedures described as A and B by Fieser, *et al.*[4] Procedure B[4] was required only for IIf. Initial concentrations of naphthoquinone in Et_2O were in the order of 30–50 mg ± 0.01 mg/250 ml; which is approximately 0.4 that generally employed for the 2-hydroxy-3-alkyl-1,4-naphthoquinones.[4] This deviation from the standard procedure was necessary because of the lesser solubility of the lower molecular weight analogs of II. The concentration of naphthoquinone in the alkaline buffer was determined by measuring the absorbance at 535 mμ with a Model 2400 Beckman DU Spectrophotometer.

Antimalarials. II. Quinolinemethanols with Decreased Phototoxicity[1]

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Received November 29, 1969

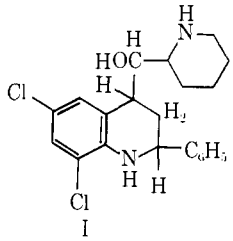
We have reported[2] that no significant decrease in phototoxicity was observed when the structures of certain 2-phenyl-4-quinolinemethanol antimalarials were modified by replacing chlorine by fluorine, or by changing the nature of the N-containing side chain.

We now report the results of a study of four additional structural modifications, three of which might be expected, on theoretical grounds, to cause a significant decrease in phototoxicity. The fourth modification involved the synthesis of a 2-phenyl-5-quinolinemethanol drug, a structure not reported previously.

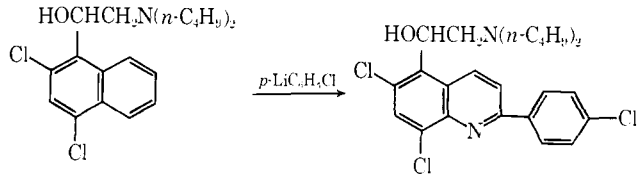
Chemistry.—The synthesis route to compounds containing iodine or free phenolic groups (Table I) was the same as that used previously.[2] Six novel oxides were prepared from the appropriate cinchoninic acids and the compounds in Table I were prepared by the reaction of these oxides with the appropriate amine. During the preparation of oxides having free phenolic groups it was necessary to protect the latter by acetylation at the cinchoninic acid stage; the protecting group was removed during the reduction of the bromomethyl ketone intermediate by $NaBH_4$.

6,8-Dichloro-2-phenyl-α-(2-piperidyl)-1,2,3,4-tetrahydro-4-quinolinemethanol (I) was prepared by catalytic reduction of the well-known antimalarial 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol.[3]

The 5-quinolinemethanol III was prepared by way of II so that the antimalarial activity and phototoxicity of II could be measured also. II was prepared by our standard route from 6,8-dichloroquinoline-5-carboxylic acid, which in turn was prepared from 5-amino-2,4-dichlorobenzoic acid by a Skraup reaction.



I



II III

Pharmacology.—Several major reviews of drug-induced phototoxicity[4–6] are available. It is apparent that phototoxic compounds fall into two classes, depending on whether the changes they evoke in tissues are oxygen-dependent or oxygen-independent. The best known oxygen-independent drugs are the furocoumarins (psoralens).[7] Recent work[8] shows that the phototoxic quinolinemethanol drugs are definitely oxygen-dependent. The photosensitizing furocoumarins are known to react with DNA in a photochemical reaction, which has been studied in detail;[9] no mechanism has yet been proposed for the photosensitizing action of the quinolinemethanols.

The possible role of long-lived triplet states in the phototoxic action of drugs[4] was the basis of our study of the iodine compounds **1–6**. It is known that molecules that contain atoms of large atomic number have a significantly decreased triplet state lifetime.[10] Examples of the effect of iodine as a "heavy atom" are available in which iodine functions in an intramolecular[11] and intermolecular[12] way.

The antimalarial activity of the iodine compounds (Table II) was equal or superior to that of analogous Cl and F compounds studied earlier. In the standard test of phototoxicity, in which the drug was administered ip, there was a significant decrease in phototoxicity (Table III) when iodine was at the 3′ or 4′ positions, but little or no decrease when iodine was at the 7 position. However, when any of these compounds was administered orally, the minimum effective phototoxic dose was 50 mg/kg or less. The high phototoxicity of the 4′,6-diiodo compound **6** seems anomalous.

The phenolic compounds **7–9** were prepared at a time when the differences in mechanism of phototoxic

(1) This work was performed under Contract DA-49-193-MD-2901 with the U.S. Army Medical Research and Development Command, Office of the Surgeon General. Contribution No. 735 of the Army Research Program on Malaria.

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

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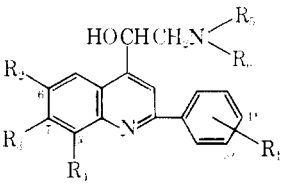
(12) H. Van Zwet, *Rec. Trav. Chim. Pays-Bas*, **87**, 1201 (1968).

TABLE I

α-(N-SUBSTITUTED AMINOMETHYL)-2-PHENYL-4-QUINOLINEMETHANOLS



Compd	R_1	R_2	R_3	R_4	R_5	R_6	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses[b]
1	3′-I	Cl	H	Cl	*n*-C_4H_9	*n*-C_4H_9	130–132	$EtOCH_2CH_2OH$	68	$C_{25}H_{29}Cl_2IN_2O$	C, H, Cl, I, N
2	3′-I	Cl	H	Cl	Piperidino		164–165	$EtOCH_2CH_2OH$	61	$C_{22}H_{21}Cl_2IN_2O$	C, H, Cl, I, N
3	4′-I	Cl	H	Cl	*n*-C_4H_9	*n*-C_4H_9	130	$EtOCH_2CH_2OH$	70	$C_{25}H_{29}Cl_2IN_2O$	C, H, Cl, I, N
4	4′-I	Cl	H	Cl	4-Phenyl-1-piperazinyl		207–210	$MeOCH_2CH_2OH$	75	$C_{27}H_{24}Cl_2IN_3O$	C, H, Cl, I, N
5	4′-Cl	H	I	H	*n*-C_4H_9	*n*-C_4H_9	77–78	Petr ether	43	$C_{25}H_{30}ClIN_2O$	C, H, Cl, I, N
6	4′-I	I	H	H	*n*-C_4H_9	*n*-C_4H_9	185–187		58	$C_{25}H_{30}I_2N_2O \cdot HCl$	N; C, H, Cl[c]
7	3′-OH	Cl	H	Cl	*n*-C_4H_9	*n*-C_4H_9	200–203		40	$C_{25}H_{30}Cl_2N_2O_2 \cdot HCl$	C, Cl, N; H[d]
8	4′-OH	Cl	H	Cl	*n*-C_4H_9	*n*-C_4H_9	165–168	*i*-PrOH–Et_2O	55	$C_{25}H_{30}Cl_2N_2O_2$	C, H, Cl, N
9	4′-OH	Cl	H	Cl	4-Methyl-1-piperazinyl		216–219	*i*-PrOH–H_2O	57	$C_{22}H_{23}Cl_2N_3O_2$	C, H, Cl, N

[a] Yields reported are those of recrystallized product. No attempt was made to improve reaction or work-up conditions. [b] Values for the elements indicated were within 0.4% of theoretical. [c] HCl salt was precipitated from Et_2O solution of base; C: calcd, 45.15; found, 45.69. H: calcd, 4.67; found, 4.08. Cl: calcd, 5.34; found, 4.81. [d] H: calcd, 6.32; found, 6.95. HCl salt was precipitated from Et_2O solution of base.

TABLE II

ANTIMALARIAL ACTIVITY[a]

	Increase in mean survival time, days; no. of cures (C)					
	Dosage, mg/kg					
Compd[b]	20	40	80	160	320	640
1	7.7 active	7.9 active	15.9 active	2C	2C	4C
2	0.5	3.7	5.7	8.1 active	11.3 active	13.5 active
3[c]	3C	3C	4C	5C	5C	5C
4	0.1	0.7	0.9	3.9	7.3 active	12.1 active
5[d]	13.3 active	2C	2C	2C	4C	4C
6[e]	2C	3C	5C	5C	5C	5C
7		0.9		0.9		1.3
8	0.3	0.5	0.5	1.1	1.1	1.3
9		0.3		0.3		0.5
I[f]	0.8	6.0	8.8 active	12.2 active	18.2 active	20.4 active
II	0.2		0.2		0.8	
III	1C	2C	2C	3C	5C	5C

[a] Test results were made available through the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D. C.; the procedures were described previously.[2] [b] Arabic numerals refer to compounds in Table I. [c] At 5 mg/kg, 7.1 (active), at 10 mg/kg, 10.3 (active). [d] Active in chick test at 120 mg/kg. [e] At 1.25 mg/kg, 0.3; at 5 mg/kg, 1.3; at 10 mg/kg, 6.3 (active); in mosquito test caused 50% oöcyst suppression at 0.1%. [f] In chick test gave 2 cures at 120 mg/kg; in mosquito test caused 100% sporozoite suppression at 0.1%.

action between the quinolinemethanols and the furocoumarins, described above, were not known. The complete suppression of phototoxicity by free phenolic functions in the furocoumarin series[7] suggested that a similar effect might be noted in the quinolinemethanol series. Compounds **7** and **8** had no significant phototoxicity; **9** was not studied because it, along with **7** and **8**, had no antimalarial activity. It is known[13] that the first isolable metabolic products of the closely related cinchophen are substances in which phenolic functions have appeared in the 4′, 6, and 8 positions. The inactivity of our compounds **7**–**9** shows that the antimalarial activity of the 2-phenyl-4-quinolinemethanols cannot be ascribed to their phenolic metabolite.

The tetrahydro compound I was prepared to determine the effect on phototoxicity of breaking the conjugation between the 2-phenyl substituent and the balance of the molecule and of removing the planarity of the system. In the case of phototoxic antimicrobials of the 2-phenylbenzothiazole series[14] it was observed that reduction of the thiazole ring caused a loss of both phototoxic and antifungal activities. In the case of I a significant decrease in antimalarial activity was observed although the compound was curative in the chick test. The decrease in phototoxicity that accompanied reduction of the pyridine ring was modest.[15] Unfortunately, the evaluation of the phototoxicity of I was complicated by an unusual toxicity to mice when ip administration was used. The uv spectra of all 2-phenyl-4-quinolinemethanol antimalarials known to us contain absorption maxima in the 320–360 nm region; the spectrum of I shows a weak maximum at 312 nm and the absorption in the 320–360 nm region is lower than that of unreduced analogs.

(13) Z. Sipal and A. Jindra, *Pharmazie*, **20**, 376 (1965).

(14) H. D. Cossey, J. Judd, and F. F. Stephens, *J. Chem. Soc.*, 954 (1965); we wish to thank Dr. J. P. Brown, Monsanto Chemicals Ltd., Ruabon, Wales, for calling this reference to our attention.

(15) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968). The minimum effective phototoxic dose of unreduced SN 10275 was 5 mg/kg.

TABLE III
THE PHOTOTOXICITY OF QUINOLINEMETHANOLS[a]

Compd[b]	Minimum effective phototoxic dose, mice mg/kg i.p.
1	300
	<50 (oral)
	>500 (sc)
2	<200
	50 (oral)
3	300
	<50 (oral)
5	50
6	25
	25 (oral)
7	400
	>400 (oral)
8	>300
	>300 (oral)
I	25[c]
III	25
	25 (oral)

[a] Tests were carried out by the procedure of W. E. Rothe and D. P. Jacobus [*J. Med. Chem.*, **11**, 366 (1968)] and were supplied by the Walter Reed Army Institute of Research, Washington, D.C.; confidence limits of these results are unknown. [b] Arabic numerals refer to compounds in Table I. Compounds **4**, **9**, and II were not tested because of their low antimalarial activity. [c] When administered by the ip route it was lethal at 50 mg/kg; compare with the high sc doses in Table II.

Substituted 2-Phenylcinchoninic Acids (Table IV).—Compound **12** was prepared by a Doebner–Miller reaction; the other compounds were prepared by a Pfitzinger reaction between the appropriate commercially available isatins and acetophenones. The experimental procedures used were similar to those described previously.[16,17]

3′-Acetoxy-6,8-dichloro-2-phenylcinchoninic Acid.—Ac_2O (87 ml) was added to a warm solution of 27.5 g (0.082 mol) of the acid **14** in 150 ml of pyridine, the mixture was stirred at 50° for 30 min, and then was stirred into 600 ml of cold H_2O. The suspension of almost colorless solid that formed was stirred for 15 hr at room temperature and then the solid was separated and washed with dilute HCl to remove adhering pyridine. After drying under vacuum at 60° for 48 hr there remained 30.3 g (98%), mp 274–276°. A portion for analysis had mp 278–281° ($EtOCH_2CH_2OH$). *Anal.* ($C_{18}H_{11}Cl_2NO_4$) C, H, Cl, N.

4′-Acetoxy-6,8-dichloro-2-phenylcinchoninic Acid.—The cinchoninic acid **15** was acetylated by the same procedure and gave a 96% yield of a yellow powder, mp 249–255°. A sample for analysis had mp 258–262° (*i*-PrOH). *Anal.* ($C_{18}H_{11}Cl_2NO_4$) C, H, Cl, N.

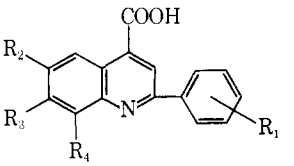
Bromomethyl 4-Quinolyl Ketones (Table V).—These were prepared from the cinchoninic acids **10–13** (and the acetyl derivatives of **14** and **15**) by way of intermediate acid chlorides and diazomethyl ketones. The procedures were quite similar to those described previously[16] but the following modifications were important.

In the conversion of the acetoxycinchoninic acids into their acid chlorides a mixture of $SOCl_2$ and AcCl (5:1) was used to prevent possible loss of acetyl function.

We found that for the decomposition of the diazomethyl ketones it was preferable to suspend them in C_6H_6, add excess ethereal HBr, and stir the suspension for several hours at room temperature. Compounds **18** and **19** were then separated as hydrobromide salts, while the remaining compounds were obtained as the free bases. To prevent possible loss of acetyl function the preparation of **20** and **21** included the use of 10% by volume of Ac_2O in the reaction mixture.

In early preparations of **21** we attempted to decompose the rather stable diazomethyl ketone precursor by the action of 48% HBr in refluxing AcOH. Elemental and spectroscopic analysis of the product showed that it contained 70–80% of the debrominated Me ketone along with 20–30% of **21**. We have reported previously[2] a similar result when the HOAc–HBr reagent was used with another diazomethyl ketone. We now believe that debromination occurred by the reaction, $RCOCH_2Br + HBr \rightarrow RCOCH_3 + Br_2$, for when a solution of authentic bromomethyl ketone in a mixture of 25 ml of AcOH and 2 ml of 48%

TABLE IV
SUBSTITUTED 2-PHENYLCINCHONINIC ACIDS



Compd	R_1	R_2	R_3	R_4	Mp, °C[a]	Recrystn solvent	Yield, %	Formula	Analyses
10	3′-I	Cl	H	Cl	270–272	EtOH	78	$C_{16}H_8Cl_2INO_2$	C, H, Cl, I, N
11	4′-I	Cl	H	Cl	286–289	EtOH	28[b]	$C_{16}H_8Cl_2INO_2$	C, H, Cl, I, N
12	4′-Cl	H	I	H	313–315	$EtOCH_2CH_2OH$	15[c]	$C_{16}H_9ClINO_2$	C, H, Cl, I, N
13	4′-I	I	H	H	311[d]	$EtOCH_2CH_2OH$	83	$C_{16}H_9I_2NO_2$	C, H, I, N
14	3′-OH	Cl	H	Cl	285 dec	EtOH–H_2O	67	$C_{16}H_9Cl_2NO_3$	C, H, Cl, N
15	4′-OH	Cl	H	Cl	295–296 dec	MeOH	68	$C_{16}H_9Cl_2NO_3 \cdot H_2O$	C, H, Cl, N

[a] Of analytical sample. [b] Low yield traced to inferior 4-iodoacetophenone used. [c] Principal product (50%) was 5-(4-chlorophenyl)-3-(3-iodoanilino)-1-(3-iodophenyl)-2(5H)pyrrolone, mp 195–196° (BuOH). *Anal.* ($C_{22}H_{15}ClI_2N_2O$) C, H, Cl, I, N. In earlier work [R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946)] this common type of by-product was known as a "pyrrolidinedione anil." The modified structure was assigned by W. L. Meyer and W. R. Vaughan [*J. Org. Chem.*, **22**, 98, 1554, 1560 (1957)]. [d] L. Musajo [*Gazz. Chim. Ital.*, **62**, 566 (1932)] reported mp 285–288°.

We were not surprised to find that the 5-quinolinemethanol II, having no substituent at the 2 position, had no antimalarial activity; the rapid metabolic destruction of such compounds is well known. The high antimalarial activity of III was unfortunately accompanied by a high phototoxicity. It is clear that neither type of activity requires an aminoalcohol side chain at the 4 position.

None of the intermediates involved in our work possessed significant antimalarial activity.

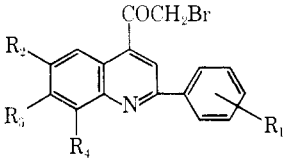
Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc. and by Dr. S. M. Nagy (Belmont, Mass.). Satisfactory uv and ir spectra were recorded for all compounds recorded in Table I.

(16) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).
(17) N. P. Buu-Hoi, M. Sy, and N. D. Xuong, *Bull. Soc. Chim. Fr.* 629 (1956).

TABLE V

SUBSTITUTED BROMOMETHYL 4-QUINOLYL KETONES

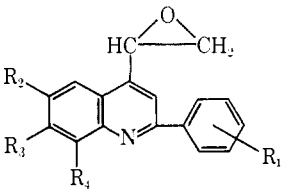


Compd	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses
16	3′-I	Cl	H	Cl	177–178	$EtOCH_2CH_2OH$	88	$C_{17}H_9BrCl_2INO$	C, H, N
17	4′-I	Cl	H	Cl	221–223	$EtOCH_2CH_2OH$	86	$C_{17}H_9BrCl_2INO$	C, H, N
18	4′-Cl	H	I	H	158–160	$EtOCH_2CH_2OH$–H_2O	50[b]	$C_{17}H_{10}BrClINO$	C, H, N
19	4′-I	I	H	H	258–263[c]		79		
20	3′-OAc	Cl	H	Cl	185–187	AcOH–Ac_2O	59	$C_{19}H_{12}BrCl_2NO_3$	H, N; C[d]
21	4′-OAc	Cl	H	Cl	208–210	AcOH	85	$C_{19}H_{12}BrCl_2NO_3$	C, H, Cl, N

[a] Overall, from cinchoninic acid. [b] The product was isolated in 81% yield as its HBr salt, mp 228–230° dec; recrystn from $EtOCH_2CH_2OH$–H_2O gave the free base. [c] HBr salt, not additionally characterized. [d] C: calcd, 50.33; found, 51.27.

TABLE VI

SUBSTITUTED 2-PHENYL-4-QUINOLYLETHYLENE OXIDES



Compd	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses
22	3′-I	Cl	H	Cl	203–204	$EtOCH_2CH_2OH$	66	$C_{17}H_{10}Cl_2INO$	C, H, Cl, I, N
23	4′-I	Cl	H	Cl	201–203	$EtOCH_2CH_2OH$	70	$C_{17}H_{10}Cl_2INO$	C, H, I, N; Cl[b]
24	4′-Cl	H	I	H	153–156	$EtOCH_2CH_2OH$	59	$C_{17}H_{11}ClINO$	C, H, Cl, I, N
25	4′-I	I	H	H	146–149 dec	*i*-PrOH	66	$C_{17}H_{11}I_2NO$	C, H, I, N
26	3′-OH	Cl	H	Cl	165–170	EtOH	69	$C_{17}H_{11}Cl_2NO_2$	C, H, Cl, N
27	4′-OH	Cl	H	Cl	228–231[c]	$EtOCH_2CH_2OH$–H_2O	70	$C_{17}H_{11}Cl_2NO_2$	C, H, Cl, N

[a] Yields of crude product were usually quantitative. [b] Cl: calcd, 16.06; found, 17.74. [c] When recrystallized from *i*-PrOH had mp 235–239°.

HBr was refluxed for 30 min the crude product isolated already contained 25% of Me ketone.

Substituted 2-Phenyl-4-quinolylethylene Oxides (Table VI).—All six compounds were prepared by the reduction of the bromomethyl ketones (5–20 g) (or their HBr salts) by $NaBH_4$ in MeOH or EtOH suspension, followed by an alkaline workup.[2]

α-(*N*-Substituted aminomethyl)-2-phenyl-4-quinolinemethanols (Table I).—The reactions of the oxides of Table VI with the appropriate amines were carried out by procedures described previously.[2]

6,8-Dichloro-2-phenyl-α-(2-piperidyl)-1,2,3,4-tetrahydro-4-quinolinemethanol Hydrochloride (I·HCl).—6,8-Dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol was prepared in the usual way from its HCl salt.[3,18] The base (1.94 g, 0.005 mol) in 50 ml of AcOH was reduced over 0.3 g of Adams' PtO_2 at 4.5 kg/cm² for 3.5 hr at room temperature at which time 0.01 mol of H_2 had been consumed. The isolated reduced base in Et_2O was converted into its hydrochloride by precipitation with ethereal HCl. The hydrochloride (1.6 g, 75%) shrank at about 147°, melted at 158–182°, and then decomposed slowly. The melting behavior, which we were unable to change by recrystallization, suggested that the substance was a mixture of stereoisomers. Tlc (SiO_2, MeOH–NH_3) showed that no unreduced material was present. *Anal.* ($C_{21}H_{24}Cl_2N_2O$·HCl) C, H, Cl, N.

Less satisfactory results were obtained when we attempted to reduce 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol in a mixture of AcOH and $(CH_2OH)_2$, or in a mixture of AcOH and HCl.

6,8-Dichloroquinoline-5-carboxylic Acid.—The preparation of this substance from 5-amino-2,4-dichlorobenzoic acid by a Skraup reaction was reasonable since both *m*-aminobenzoic acid[19,20] and 2,4-dichloroaniline[21,22] are known to undergo such a cyclization. Our procedure was based on that developed by Bradford[20] and used the technic of Manske.[23]

A warm fluid mixture of 5-amino-2,4-dichlorobenzoic acid[21] (4.53 g, 0.022 mol), 27.5 g of H_2SO_4, 7.5 ml of H_2O, and 5 g of glycerol was added during 10 min to a stirred mixture of 6 g (0.027 mol) of sodium *m*-nitrobenzenesulfonate and 0.5 g of $FeSO_4·7H_2O$ at 100°. The mixture was stirred for 30 min at 100° and then was heated cautiously to reflux temperature and held at reflux for 4 hr. The mixture was cooled, poured onto ice, made basic with strong aqueous NaOH, and diluted to 400 ml with H_2O. The solution was stirred at 60° with decolorizing carbon and acidified with HCl to give 4.1 g of crude product, which, after sublimation at 300° (1 mm), gave 3.3 g (62%) of a pale yellow acid, mp 270–275°. *Anal.* ($C_{10}H_5Cl_2NO_2$) C, H, Cl, N. The preparation was also carried out at 6 times the scale described and gave a comparable yield of sublimed product.

Bromomethyl 6,8-Dichloro-5-quinolyl Ketone Hydrobromide.—This substance was prepared from 6,8-dichloroquinoline-5-carboxylic acid by procedures similar to those used in the anal-

(18) The substance (SN 10275) was supplied by the Walter Reed Army Institute of Research; elemental analysis indicated that the composition of the sample lay between that of the anhydrous salt and the sesquihydrate described in the literature.[3]

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ogous transformations of the 4 series described above. The bromomethyl ketone hydrobromide was obtained in 61% yield, mp 244–249° dec. *Anal.* ($C_{11}H_6BrCl_2NO \cdot HBr$) C, H, Br, Cl, N.

6,8-Dichloro-5-quinolylethylene Oxide.—The bromomethyl ketone hydrobromide was reduced by $NaBH_4$ in MeOH suspension (as in the 4 series) to give the oxide (78%) which, after recrystallization from EtOH, had mp 146–147°. *Anal.* ($C_{11}H_7Cl_2NO$) C, H, Cl, N.

α-(Di-*n*-butylaminomethyl)-6,8-dichloro-5-quinolinemethanol Hydrochloride (II·HCl).—The oxide precursor and n-Bu_2NH reacted under the same conditions used in the 4 series to give an oil that was converted into the HCl salt by the action of ethereal HCl. The yield of product, mp 162–164°, was quantitative. *Anal.* ($C_{19}H_{26}Cl_2N_2O \cdot HCl$) C, H, Cl, N.

α-(Di-*n*-butylaminomethyl)-2-phenyl-4′,6,8-trichloro-5-quinolinemethanol Hydrochloride (III·HCl).—The 4-chlorophenylation reaction with II·HCl was carried out using a procedure similar to that described[19] for the phenylation of certain quinolinemethanols. 4-Chlorophenyllithium was prepared immediately before use by a literature procedure[25] and was used in a tenfold excess. The crude product was converted into the HCl salt by ethereal HCl and the salt was recrystallized from *i*-PrOH to give a 35% yield of a colorless powder, mp 258–260°. *Anal.* ($C_{25}H_{20}Cl_3N_2O \cdot HCl$) C, H, Cl, N.

Acknowledgment.—We wish to thank Dr. Francis J. Bullock, Professor Robert E. Lyle, and Dr. Richard E. Strube for their many helpful suggestions made during the course of this work.

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Antimalarials. Quinolinemethanol Derivatives

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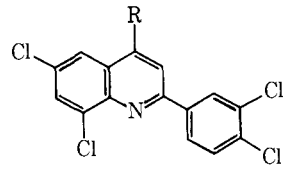
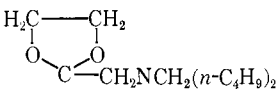
Received October 15, 1969

6,8-Dichloro-2-(3,4-dichlorophenyl)-4-(α-di-*n*-butylaminomethyl)quinolinemethanol (**1a**)[1] is a very active antimalarial compound among 4-quinolinemethanols,[2]



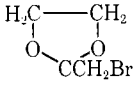
1a, R = $CHOHCH_2N(n\text{-}C_4H_9)_2$

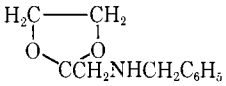
b, R = 

c, R = 

d, R = $COCH_2Br$

e, R = $CHOHCH_2NHCH_2C_6H_5 \cdot HCl$

f, R = 

g, R = 

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but is highly phototoxic, and therefore cannot be used for the treatment of malaria. Several approaches have been explored to prepare less phototoxic 4-quinolinemethanols[3] without reducing their antimalarial activity.

We started to make **1b** with a view that the modified environments at this carbon atom might decrease the phototoxicity.

By the reaction of **1d** with n-Bu_2NH, the desired di-*n*-butylaminoketone could not be obtained. When **1d** was converted into the dioxyethylene compound **1f**, it failed to react with di-*n*-butylamine even when heated in a sealed tube at 180° for 24 hr. Thus, the comparison of antimalarial activity between **1a** and **1b** could not be made. When **1c** was treated with benzylamine **1e** was obtained. The dioxyethylene bromo compound **1f** reacted with benzylamine smoothly to give the target compound **1g** which could be compared in its antimalarial activity and phototoxicity with **1e** to test the hypothesis we started with.

Biological Tests.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane according to the procedure already published.[4] **1e** showed activity at 40 mg/kg, cured 4 mice at 160 mg and all 5 mice at 320 mg with no toxic deaths. The dioxyethylene derivative **1g** was inactive even at a dose of 640 mg/kg. When tested for phototoxicity in mouse (ip), **1e** was approximately 9 times more phototoxic than **1g**.[5]

Experimental Section

6,8-Dichloro-2-(3,4-dichlorophenyl)-4-(α-benzylaminomethyl)-quinolinemethanol·HCl (1e) was prepared in 77.6% yield by the procedure of Lutz *et al.*[1] It was crystallized from MeOH–Et_2O, mp 250–254°. *Anal.* ($C_{24}H_{11}Cl_5N_2O$) C, H, Cl^-, N.

6,8-Dichloro-2-(3,4-dichlorophenyl)-4-(2-bromo-1,1-ethylenedioxyethyl)quinoline (1f) was prepared from **1d**[6] in 64.0% yield by the procedure of Takahashi and Tanabe.[7] It was crystallized several times from C_6H_6, mp 212–214°. *Anal.* ($C_{19}H_{12}BrCl_4NO_2$) C, H, Br, Cl, N.

6,8-Dichloro-2-(3,4-dichlorophenyl)-4-(2-benzylamino-1,1-ethylenedioxyethyl)quinoline (1g).—A mixture of **1f** (1.0 g), benzylamine (10 ml), ethoxyethanol (10 ml), and a crystal of I_2 was refluxed for 24 hr. Solvent and excess benzylamine were removed *in vacuo* and the residue was triturated with 10% NaOH and extracted (C_6H_6). The extract was dried (K_2CO_3), filtered, and concentrated to give 790 mg (67.0%) of crude product which, after two crystallizations from C_6H_6, melted at 159–161°. *Anal.* ($C_{26}H_{20}Cl_4N_2O_2$) C, H, N.

Acknowledgment.—This work was supported by U. S. Army Medical Research and Development Command under the Research Contract No. DA-49-193-MD-2869 and is Contribution No. 703 from the Army Research Program on Malaria.

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