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.* ($C_{25}H_{29}Cl_3N_2O \cdot HCl$) 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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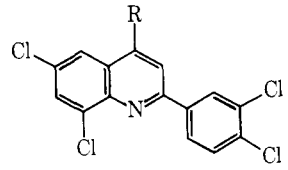
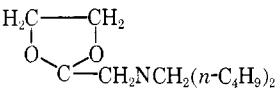
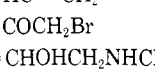
6,8-Dichloro-2-(3,4-dichlorophenyl)-4-(α-di-*n*-butylaminomethyl)quinolinemethanol (**1a**)[1] is a very active antimalarial compound among 4-quinolinemethanols,[2]



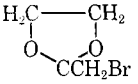
1a, R = $CHOHCH_2N(n\text{-}C_4H_9)_2$

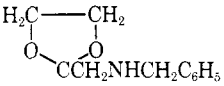
b, R = 

c, R = 

d, R = $COCH_2Br$

e, R = $CHOHCH_2NHCH_2C_6H_5 \cdot HCl$

f, R = 

g, R = 

(1) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1827 (1946).

(2) W. E. Roth and D. P. Jacobs, Paper No. 37, Division of Medicinal Chemistry, 154th Meeting of the American Chemical Society, September, 1967, Chicago, Ill.

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.

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(7) M. Takahashi and R. Tanabe, *Chem. Pharm. Bull.*, **15**, 793 (1967).