quinolone-2-carboxylate (**4b**) separated from the solvent phase (48%) and was purified by recrystallization from pyridine, mp 292–293°. The 5-chloro isomer (**4c**) was obtained in 15% yield by diluting the AcOH with H_2O. An analytical sample, mp 255–257°, was prepared by recrystallization from MeOH (charcoal).

Acknowledgment.—J. M. acknowledges predoctoral fellowship support from the Lehigh University Institute of Research and the National Defense Education Act Fellowship program.

Arylamino Alcohol Antimalarials. A New Method for Incorporating the Side Chain[1]

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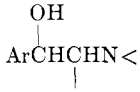
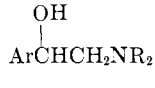
The arylamino alcohols (**1**) were one of the groups of antimalarial drugs most intensively studied during the World War II program.[2] Quinine, in which the aryl group is 4-quinolyl and the amino group is incorporated into a quinuclidine ring system, provided the inspiration for this series. This group is of special interest in



1

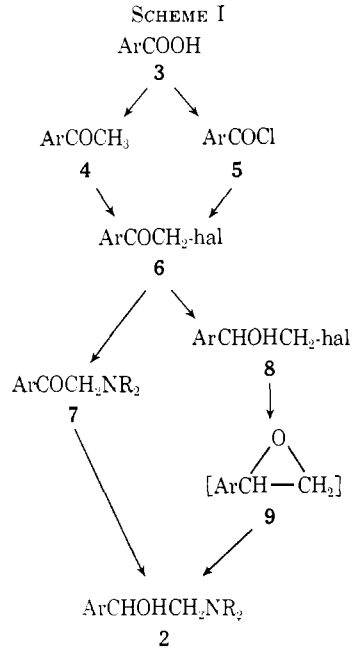


2

the current research program on new antimalarial agents[1] because quinine has proven to be the only curative agent for some strains of drug-resistant *Plasmodium falciparum*.[3] The massive amount of work devoted to this area revealed that significant antimalarial activity could be associated with a variety of aryl groups in addition to quinoline (*e.g.*, phenyl, naphthyl, phenanthryl).[2] It was also found that the simpler α-hydroxy-β-dialkylaminoethyl side chain (*e.g.*, **2**) was a satisfactory substitute for the complex side chain of quinine. As part of the Army Research Program on Malaria, we have been examining compounds of type **2** that contain novel heterocyclic aryl groups, and we had need of an efficient method for constructing the side chain on the aromatic nucleus. This note reports a new and general method for accomplishing this.

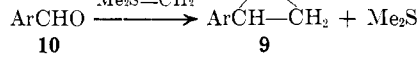
The established routes to compounds of type **2** are summarized in Scheme I. They typically proceed from an aromatic acid (**3**) or methyl ketone (**4**) through various intermediates to a halomethyl ketone (**6**). This ketone is then transformed into the final product (**2**) either *via* an amino ketone **7**[4] or *via* a halohydrin

SCHEME I



8.[5] In the latter case, an oxirane (epoxide) intermediate (**9**) is sometimes isolated.[5,6] The instability of amino ketones of type **7**,[7] especially when Ar is a nitrogen heterocycle, has generally made the halohydrin route somewhat preferable. In a few instances, neither route has been successful.[8] This was the case also when we attempted to apply these methods to a substrate where the aryl group was 6-benzo[*h*]quinolyl; therefore another method had to be sought.

Our attention was drawn to the well-documented[5,6] and facile transformation of intermediate oxirane **9** to the final product because of a recent report by Corey and Chaykovsky.[9] These authors found that such oxiranes are obtained in high yield upon treatment of aromatic aldehydes with dimethylsulfonium methylide (*i.e.*, **10** → **9**). When this reaction was applied to three



commercially available model aldehydes (A, B, and C of Table I) and the intermediate oxiranes were treated with diheptylamine without purification, good yields of the amino alcohols were obtained (Table I). The procedure was subsequently applied to a series of benzoquinoline and benzisoquinoline aldehydes with very similar results (D–H of Table I).

We have found it advantageous to employ a two- to sixfold excess of the ylide to ensure complete conversion of the aldehyde to the oxirane. This avoids the necessity of dealing with rigorously anhydrous solvents

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 416 from the Army Research Program on Malaria.

(2) (a) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953; (b) F. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946.

(3) *E.g.*, Y. A. Neva, *New Engl. J. Med.*, **277**, 1241 (1967), and references cited therein.

(4) *E.g.*, E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 1 (1946), and following papers.

(5) *E.g.*, (a) S. Winstein, T. L. Jacobs, R. B. Henderson, J. H. Robson, and B. F. Day, *ibid.*, **11**, 150 (1946); (b) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946); (c) R. C. Elderfield, M. Israel, J. H. Ross, and J. A. Waters, *J. Org. Chem.*, **26**, 2827 (1961).

(6) S. Winstein, T. L. Jacobs, R. B. Henderson, J. H. Robson, and B. F. Day, *ibid.*, **11**, 157 (1946).

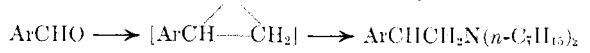
(7) (a) T. L. Jacobs, S. Winstein, J. Ralls, J. H. Robson, R. B. Henderson, R. Akawie, W. Florsheim, D. Seymour, and C. Seil, *ibid.*, **11**, 21 (1946); (b) K. N. Campbell and J. F. Kerwin, *J. Amer. Chem. Soc.*, **68**, 1837 (1946); (c) D. R. V. Golding and W. H. McNeely, *ibid.*, **68**, 1847 (1946).

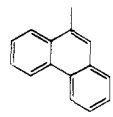
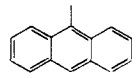
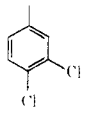
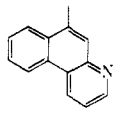
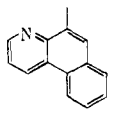
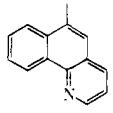
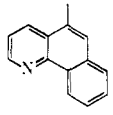
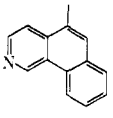
(8) *E.g.*, (a) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, *ibid.*, **68**, 1310 (1946); (b) K. N. Campbell, C. H. Helbing, and J. K. Kerwin, *ibid.*, **68**, 1840 (1946).

(9) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

TABLE I

ARYLAMINO ALCOHOLS FROM ARYLALDEHYDES



Reaction	Ar	ArCHO mp, °C	Product Yield, %[a]	Mp, °C	Formula	Analyses[b]
A		c	70	122.5–125	$C_{39}H_{48}NO \cdot HCl$[d]	
B		c	68	130–132	$C_{39}H_{32}NO \cdot HCl$	C, H, N, Cl
C		c	68	59–63	$C_{22}H_{37}Cl_2NO \cdot HCl$	C, H, N
D		172–177	49	227–229	$C_{29}H_{42}N_2O \cdot 2HCl$	C, H, N
E		157–158	71	185–187	$C_{29}H_{42}N_2O \cdot HCl \cdot 0.5H_2O$	C, H, N
F		129–130.5	65	198–206	$C_{29}H_{42}N_2O \cdot 2HCl$	C, H, N
G		124–126	60	182–186	$C_{29}H_{42}N_2O \cdot 2HCl$	C, H, N
H		162.5–163.5	27	220–230 dec	$C_{29}H_{42}N_2O \cdot 2HCl \cdot 0.5H_2O$	C, H, N

[a] Based on isolated, pure amino alcohol hydrochlorides. [b] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [c] Commercially available. [d] Known compound.[10]

and reagents as is necessary to observe the equimolar stoichiometry of the reaction.[9] No side reactions have been observed as a result of this practice and the oxiranes have appeared to be pure when examined by tlc. In one experiment in which insufficient ylide was employed, the resulting mixture of aldehyde and oxirane was resubmitted to the ylide reaction and converted completely to oxirane without difficulty. Oxirane intermediates were converted directly to amino alcohols without characterization.

The second step of the procedure, opening the epoxide with diheptylamine, proceeded at a reasonable rate at about 150° but not at 100°. The reaction was typically complete after 1–4 hr. A threefold excess of amine was arbitrarily employed, the excess being removed *in vacuo* at the conclusion of the reaction. The residual, nonvolatile amino alcohol products usually formed pure salts upon treatment with HCl.

In the case of benzisoquinoline H, dark by-products appeared during the epoxide opening step and it was necessary to chromatograph the crude product before forming the salt. Nmr spectroscopy was used to confirm the structures of most of the final products. From 4 to 15 mmoles of aldehyde was employed in the reactions described in Table I.

The known 9-phenanthrylamino alcohol (A of Table I) was also prepared from 9-acetylphenanthrene by the method of May and Mosettig.[10] The products obtained from the two synthetic methods were the same, according to a comparison of their melting points and infrared and nmr spectra.

The simplicity and reliability of the method, compared to the alternate procedures, has made it the method of choice in our laboratory. This procedure requires an aromatic aldehyde intermediate instead of a ketone, and many methods are available for their preparation, especially if the corresponding arylcarbinols are available.[11] In the case of the aldehyde precursors to D–H of Table I, carboxylic esters were reduced to carbinols with $LiAlH_4$, and these were subsequently oxidized to the aldehydes with DMSO–SO_3 reagent,[12] ceric ion,[13] or $Pb(OAc)_4$.[14] Because this over-all procedure was developed as part of an on-going project, detailed synthetic procedures for these benzoquinoline and benzisoquinoline aldehydes will not be

(10) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 10 (1946).
(11) J. Carnduff, *Quart. Rev.* (London), **20**, 169 (1966).
(12) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).
(13) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).
(14) R. E. Partch, *Tetrahedron Letters*, 3071 (1964).

reported until the work is complete and bioassay results are available.

Experimental Section[15]

General Procedure. Conversion of Arylaldehydes to Aryloxiranes.[16]—Into a round-bottom flask was introduced 50% NaH–oil dispersion in a molar amount four times that of the aldehyde to be used. Dry N_2 was passed through the flask during this and all subsequent operations. The oil was removed from the NaH by washing three times with pentane, the pentane being removed by pipet after each wash. Residual pentane was removed by evacuating the flask and refilling it with N_2. DMSO, about 12 times the weight of NaH–oil used, was added and the mixture was stirred at 70–75° until H_2 evolution ceased (*ca.* 0.5–0.75 hr). The solution of DMSO anion was stirred and chilled in an ice–salt bath, after adding a volume of THF equal to that of the DMSO. $Me_3S^+ \cdot I^-$ (molar amount equal to that of the NaH) in DMSO (1 g of salt/4–5 ml of DMSO) was added over *ca.* 3 min. The resulting solution of $Me_2S{=}CH_2$ was then treated over 1–2 min with a THF solution of the aldehyde. The cooling bath was removed and, after stirring for 0.5–1 hr, H_2O was added and the oxirane was isolated by extraction (Et_2O). At this point the Et_2O could be removed carefully to leave the oxirane in virtually quantitative yield. Usually, however, di-*n*-heptylamine (3 equiv/equiv of aldehyde) was added to the Et_2O extracts before boiling off the solvent, and the residue was taken directly to the next step of the sequence. In no instance was the oxirane characterized.

General Procedure. Amino Alcohols from Aryloxiranes—A mixture of the oxirane and 3 molar equiv of diheptylamine was heated in an oil bath under N_2 at 145–155° until tlc (silica gel F) indicated essentially complete disappearance of the oxirane (1-4 hr). The excess diheptylamine was removed from the reaction mixture in a sublimation apparatus at 70–150° (1–8 mm) while being stirred to prevent splattering. Where tlc indicated substantially one component, the residue of product, in Et_2O or absolute EtOH solution, was treated with **1** or 2 equiv (depending on the number of basic nitrogens in the molecule) of 18% HCl in EtOH. Slow dilution with additional Et_2O caused precipitation of the amino alcohol salts in pure condition. When tlc indicated that significant by-products were present, preliminary purification was effected by chromatography over alumina, using 30–60° petroleum ether–Et_2O for elution.

Heterocyclic Aldehydes.—Because heterocyclic aldehydes D–H were prepared as part of a larger synthetic effort, only an outline of their syntheses is given here. Preparative details and analytical data will be published later as part of the complete report.

Skraup reactions on 3-amino-1-naphthoic acid, 3-amino-2-naphthoic acid, and 4-amino-1-naphthonitrile provided benzo[*f*]quinoline-6-carboxylic acid,[17] benzo[*f*]quinoline-5-carboxylic acid,[18] and benzo[*h*]quinoline-6-carboxylic acid, respectively. Esters of these acids were reduced with $LiAlH_4$ and the resulting carbinols were oxidized to aldehydes D, E, and F, respectively. DMSO–SO_3 reagent[12] served as the oxidant that provided D and ceric ion[13] was used to provide E and F.

Aldehydes G and H were prepared from the corresponding esters by reduction to carbinols and subsequent oxidation of the alcohols with $Pb(OAc)_4$[14] and DMSO–SO_3, respectively.[12] The ester precursor to G, methyl benzo[*h*]quinoline-5-carboxylate, was obtained by photochemical ring closure of the methyl ester of β-phenyl-α-3-pyridylacrylic acid.[19] The ester precursor to H, methyl benz[*h*]isoquinoline-5-carboxylate, was obtained by a similar photoreaction employing methyl β-phenyl-α-4-pyridylacrylate.[20] The photolytic ring closures are analogous to a series reported by Loader and Timmons.[21]

(15) Melting points were obtained with a Mel-Temp appratus and are corrected. Microanalyses were performed by Miss Betty McCarthy of the Stanford Research Institute analytical laboratory. Nmr spectra were obtained on a Varian A60A instrument.

(16) This procedure is essentially that of Corey and Chaykovsky.[9]

(17) W. A. Jacobs and R. G. Gould, *J. Biol. Chem.*, **120**, 141 (1937).

(18) E. R. Barnum and C. S. Hamilton, *J. Amer. Chem. Soc.*, **64**, 540 (1942).

(19) A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 150 (1958).

(20) D. R. Bragg and D. G. Wibberly, *ibid.*, 5074 (1961).

(21) C. E. Loader and C. J. Timmons, *ibid.*, *C*, 1078 (1964).

Antimalarials. Analogs of Phototoxic 2-Phenyl-4-quinolinemethanols[1]

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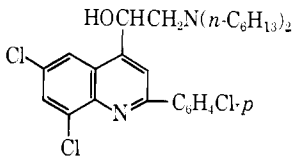
Received June, 3, 1968

The purpose of this work was to prepare analogs of the potent antimalarials I–III,[2] two of which were observed to cause the development of sensitivity to light and other toxic symptoms that interfered seriously with their clinical use. The new compounds (Table I) include those in which chlorine was replaced by fluorine[3] and those in which the nitrogen-containing side chain



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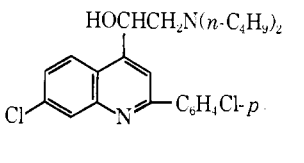
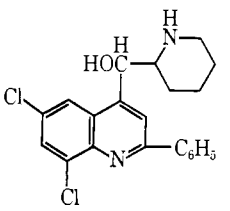


II



III

was derived from amines not studied previously. The pharmacology reported below indicates that, while some of these structural analogs continue to possess considerable antimalarial activity, the phototoxic side effect has not been overcome. Similar observations have been reported recently from other laboratories.[3–6]

It is now apparent that, if the phototoxic character is to be eliminated from the 2-phenyl-4-quinolinemethanol class, without at the same time decreasing the antimalarial potency, structural modifications of considerably greater sophistication must be examined; such studies are currently in progress in this and other laboratories participating in the Army Research Program on Malaria. Although some structure–activity data derived from phototoxicity studies have been reported[7] there exists a need for more fundamental data concerning the mechanism of development of phototoxic symptoms in laboratory animals and in man.

Chemistry.—The synthesis route to the compounds listed in Table I was quite similar to that described previously for the preparation of 2-phenyl-4-quinoline-

(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. 398 of the Army Research Program on Malaria.

(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946, pp 347, 357–358, 359.

(3) The pharmacological virtues of fluorine-containing drugs have been mentioned by A. J. Saggiomo, K. Kato, and T. Kaiya, *J. Med. Chem.*, **11**, 277 (1968).

(4) R. M. Pinder and A. Burger, *ibid.*, **11**, 267 (1968).

(5) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(6) J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *ibid.*, **11**, 425 (1968).

(7) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).