toluenesulfonamide hydrochloride (20.0 g, 90.0 mmoles), ethyl 6-amino-4-chloro-5-nitro-2-pyridinecarbamate (23.4 g, 89.0 mmoles), and Et_3N (25 ml) in 300 ml of MeOH was refluxed for 8 hr under N_2. The yellow solid which formed upon cooling was collected by filtration, triturated with boiling EtOH (200 ml), and dried (P_2O_5) at 100° for 8 hr; yield 29.5 g.

In the preparation of **1**·HCl the reaction was carried out in the absence of Et_3N.

Method B. Ethyl 5,6-Diamino-4-(*p*-chloroanilino)-2-pyridinecarbamate (6).—A suspension of **2** (5.0 g, 14.2 mmoles) in DMF (200 ml) was hydrogenated over RaNi catalyst (*ca.* 10 g) at an initial H_2 pressure of 3.68 kg/cm². After about 30 min the catalyst was removed by filtration under N_2. The colorless filtrate was poured into cold H_2O (1 l.) through which a vigorous stream of N_2 was bubbling. The precipitated white solid was collected by filtration under N_2 and dried *in vacuo* over P_2O_5; yield 3.8 g.

Method C. Ethyl 8-{[4-(Diethylamino)-1-methylbutyl]amino}-pyrido[2,3-*b*]pyrazine-6-carbamate (10).—A suspension of **1**·HCl (15.0 g, 35.8 mmoles) in EtOH (300 ml) was hydrogenated (Ra Ni) (*ca.* 10 g) at an initial H_2 pressure of 3.67 kg/cm². The catalyst was removed by filtration under N_2, and the nearly colorless filtrate was treated with a 40% aqueous solution of glyoxal (5.80 g, 39.4 mmoles). The resulting dark red solution was stirred under N_2 for 48 hr at room temperature. After evaporation of the solvent *in vacuo*, addition of H_2O (50 ml) and 10% NaOH (pH 8–9) caused separation of an orange oil, which was extracted with EtOAc (three 250-ml portions). Removal of the solvent left an oil, which did not solidify either as the free amine or as the corresponding HCl salt. A solution of the oil in $CHCl_3$ was poured onto a silica gel H column (150 g), which had been washed well with $CHCl_3$. The column was eluted successively with $CHCl_3$ and $CHCl_3$–MeOH (95:5). Evaporation of the 95:5 fraction and prolonged drying of the residue *in vacuo* yielded a brittle amber glass, which was shown to be homogeneous by tlc; yield 12.4 g.

Method D. 6-Amino-8-{[4-(diethylamino)-1-methylbutyl]-amino}-3-methylpyrido[2,3-*b*]pyrazine Dihydrochloride (13).—A solution of **12** (5.50 g, 14.2 mmoles) and KOH pellets (4.0 g, 71 mmoles) in absolute EtOH (100 ml) was refluxed under N_2 for 7 hr, then cooled to room temperature. The reaction mixture was acidified with 5.5 *M* ethanolic HCl (40 ml), and the precipitated KCl was removed by filtration. The dark brown filtrate was treated with charcoal, concentrated to *ca.* one-third volume *in vacuo*, and diluted (Et_2O, 200 ml). The semisolid which precipitated was separated by decantation and redissolved in warm EtOH (200 ml) containing 5.5 *M* ethanolic HCl (20 ml). Et_2O (500 ml) was added in small portions over a 2-day period until precipitation of the product appeared complete. The off-white solid was collected by filtration under N_2 and dried *in vacuo* over P_2O_5; yield 4.70 g.

Method E. Ethyl 8-{[(4-Diethylamino)-1-methylbutyl]-amino}-2,3-diphenylpyrido[2,3-*b*]pyrazine-6-carbamate Hydrochloride (14).—A solution of **1**·HCl (15.0 g, 35.8 mmoles) in MeOH (250 ml) was hydrogenated over RaNi at an initial pressure of 3.67 kg/cm². When the reduction was complete (3 hr), the catalyst was removed by filtration under N_2 and washed (MeOH). The combined filtrate and wash were treated with benzil (7.50 g, 35.8 mmoles); the resulting yellow solution was stirred under N_2 at room temperature for 24 hr, then at reflux temperature for 6 hr. The solvent was removed *in vacuo*, leaving a resinous mass which was purified by twice dissolving in MeOH and pouring into Et_2O. After the second precipitation the solid was collected by filtration, washed (Et_2O), and dried *in vacuo* over P_2O_5 at 110°; yield 15.7 g.

Method F. Ethyl 8-(*p*-Chloroanilino)-3-(*p*-chlorophenyl)-pyrido[2,3-*b*]pyrazine-6-carbamate (26).—To a solution of **6** (12.7 g, 39.5 mmoles) in DMF (20 ml) was added EtOH (200 ml) and *p*-chlorophenylglyoxal hydrate (7.8 g, 42.0 mmoles). The resulting bright orange solution was stirred on a 60° H_2O bath for 30 min under N_2. A yellow solid began to crystallize after about 10 min. After standing at room temperature for 2 hr, the solid was collected by filtration and dried *in vacuo* over P_2O_5; yield 17.2 g. This solid was recrystallized by dissolving in hot DMF, adding EtOH (800 ml), and cooling; yield 13.0 g.

Method G. 6-Amino-8-(*p*-chloroanilino)-2,3-bis(*p*-chlorophenyl)pyrido[2,3-*b*]pyrazine (29).—A suspension of **28** (16.8 g, 29.8 mmoles) and KOH pellets (8.40 g, 150 mmoles) in absolute EtOH (300 ml) was refluxed for 7 hr under N_2, then cooled to room temperature. The crystalline yellow solid was collected by filtration, washed with EtOH, and suspended in H_2O (400 ml) by vigorous stirring. Excess 6 *N* HCl (10 ml) was added, and stirring was continued until effervescence ceased. The mixture was readjusted to pH 8 with 10 *M* NaOH, and the yellow solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78°; yield 12.9 g.

Method H. α-[(6-Amino-2,3-diphenylpyrido[2,3-*b*]pyrazin-8-yl)amino]-*p*-toluenesulfonamide (35).—A solution of **3** (15.0 g, 36.6 mmoles) in DMF (250 ml) was hydrogenated over Ra Ni at an initial pressure of 3.67 kg/cm². When the reduction was complete, the catalyst was removed by filtration under N_2 and washed with DMF. Benzil (7.69 g, 36.6 mmoles) was added to the combined filtrate and wash, and the mixture was allowed to stand at room temperature overnight. Then the reaction mixture was heated under N_2 for 8 hr at 80° and 8 hr at reflux temperature on successive days. The reaction mixture was poured into 1 l. of H_2O, and the precipitated solid was collected by filtration and dried *in vacuo* over P_2O_5; yield 15.3 g. The product was extracted for 48 hr with MeOH in a Soxhlet apparatus. The yellow solid obtained from the cooled extract was dried *in vacuo* over P_2O_5 at 110°; yield 10.5 g.

Method I. Ethyl 8-{[*p*-(Diethylsulfamoyl)phenethyl]amino}-3-methylpyrido[2,3-*b*]pyrazine-6-carbamate (44).—A solution of **9** (20.9 g, 46.3 mmoles) in DMF (50 ml) was diluted with EtOH (350 ml) and a 30% solution of pyruvaldehyde (11.7 g, 48.6 mmoles). The red reaction mixture was stirred under N_2 for 48 hr; then the volatile matter was removed *in vacuo*, leaving a brown gummy residue. The gum was dissolved in a small volume of $CHCl_3$, and the solution was poured onto a silica gel H column (400 g) which had been washed with $CHCl_3$. The column was eluted first with $CHCl_3$, then with $CHCl_3$–MeOH (95:5). Evaporation of the solvent from the combined eluates gave 13.8 g (61%) of dark orange crystals. A contaminant, detected by thin layer chromatography, was present in the solid after four recrystallizations from EtOH and EtOH–H_2O. The solid was redissolved in $CHCl_3$ and added to another silica gel H column (200 g). Elution with $CHCl_3$ gave homogeneous yellow crystals upon evaporation of the $CHCl_3$. The combined fractions were recrystallized from hot EtOH; yield 12.2 g.

Acknowledgments.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical and Physical Chemistry Division of Southern Research Institute for the spectral and microanalytical determinations. Some of the analyses reported were performed by the Gailbraith Microanalytical Laboratories, Knoxville, Tenn.

Cyclization of Aniline–Acetylenedicarboxylate Adducts. A Modified Conrad–Limpach Method for the Synthesis of Potential Antimalarials[1]

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The interest in 4(1H)-quinolones has largely been directed toward their utility as intermediates in preparation of 4-aminoquinolines as antimalarial agents. In general such quinolones have been synthesized by thermal cyclization of the enamino esters obtained by condensation of anilines with ethoxymethylenemalonic ester (Gould–Jacobs reaction[2]) or β-keto esters

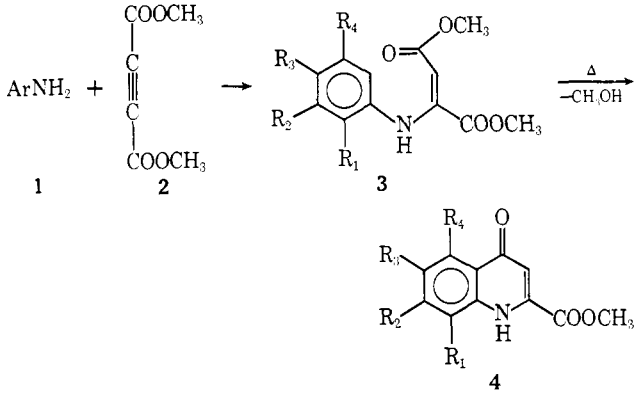
(1) This work has been supported by Contract No. DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command, and represents Contribution No. 469 from the Army Research Program on Malaria.

(2) R. Gould and W. Jacobs, *J. Amer. Chem. Soc.*, **61**, 2890 (1939).

(Conrad–Limpach reaction[3]). The intermediate enamino esters have seldom been isolated and characterized since in the majority of cases these were viscous oils more amenable to direct thermal cyclization and analysis as quinolone-2- (or 3-) carboxylates.[4]

Neither the intermediate adducts nor the 4(1H)-quinolonecarboxylates were evaluated in the antimalarial screening program during World War II. Several 4(1H)-quinolones,[5] however, did display modest activity against *Plasmodium cathemerium* in avian species.[6]

We wish to report an extension of our previous efforts in quinoline[7] and quinolone[8,9] synthesis which has produced several structurally defined enamino esters (**3**) and methyl 4(1H)-quinolone-2-carboxylates (**4**) which have been screened against *Plasmodium berghei* in mice. We have utilized the Michael condensation of substituted anilines (**1**) and dimethyl acetylenedicarboxylate (**2**) to make available dimethyl anilinofumarates (**3**). These adducts can be synthesized in high yield, as easily purified compounds possessing an isomeric homogeneity. Numerous workers have established that primary amines in a solvent possessing high proton mobility (such as MeOH) react with acetylenedicarboxylate to produce adducts in which the two ester moieties are transoid.[10,11] This geometry is that required for the thermal Conrad–Limpach closure to 4-(1H)-quinolones, and invariably excellent yields of the cyclized products result. The best evidence for the



existence of a single geometric enamine isomer and for the absence of any anil tautomer in equilibrium is that the nmr spectra of the adducts show only one vinyl proton resonance. It has been shown that when fumarate and maleate isomers are present in such systems, two different vinyl absorptions appear.[12,13] All of the adducts prepared in this work (see Table I) displayed a singlet in the vinyl resonance region at δ 5.49 ± 0.13 ppm integrating for one proton.

Although, as we have reported previously,[8] special conditions are necessary to ring close the adducts of **2** with *o*-nitroanilines, all other enamines (**3**) could be cyclized in the traditional medium, diphenyl ether. As would be expected the enamines derived from unsymmetrical anilines, *viz.*, **3b**, **3f**, **3h**, and **3i**, gave mixtures of isomeric quinolones. In the case of **3b** the isomeric quinolone carboxylates could be separated into their respective pure forms, *i.e.*, **4b** and **c**, on the basis of a differential solubility in AcOH (see Table II for yields and physical properties). Similarly, **3f** was ring closed to **4g** and **h** which were fractionally crystallized from MeOH. The cyclization of **3h** in diphenyl ether produced only a single isomer, **4l**. On the other hand, the two isomers formed on ring closure of **3i** could not be separated by fractional crystallization and the data reported in Table II for **4j** represent the unseparated combined isomers. Nmr analysis of the quinolones revealed that the mixture consisted of 77% methyl 6-methoxy-7-fluoro- and 23% methyl 5-fluoro-6-methoxy-4(1H)-quinolone-2-carboxylates.

Biological Activity.—The dimethyl anilinofumarates (**3**) and several of the 4(1H)-quinolone-2-carboxylates (**4a**, **d**, **f–h**, **j**, **l**) were screened for antimalarial activity against *P. berghei* in mice.[14] None of the compounds showed any significant increase in the mean survival time (normally 7.0 ± 0.5 days) of the infected rodents even at the highest dose level of 640 mg/kg. The anilinofumarate (**3f**) displayed the highest increase (1.2 days at 640 mg/kg) in mean survival time of all the compounds tested. The only toxic deaths recorded, *i.e.*, for rodents which survived less than the 7.0 ± 0.5 days observed with untreated control animals, resulted from administration of **3g**. With this compound at doses as low as 80 mg/kg all mice expired in less than 4 days.

Experimental Section[15]

Preparation of the Dimethyl Anilinofumarates (3).—All of the anilines required for preparation of the Michael adducts were commercially available materials with the exception of 2-benzamido-5-methoxyaniline,[16] of 3-fluoro-4-methoxyaniline,[17] and of 3-trifluoromethyl-4-methoxyaniline which was prepared in 97% yield by hydrogenation over PtO_2 of 0.23 mole of 2-methoxy-5-nitrobenzotrifluoride[18] in 200 ml of MeOH; mp 57–58°, lit.[19] 58–59°. Equimolar amounts (0.02 mol) of the aniline and of dimethyl acetylenedicarboxylate were mixed in 100 ml of an-

(3) R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., pp 33–35.

(4) Definition of an exact structure to the Conrad–Limpach intermediates is complicated by the expectation that these substances should exist in an anil–enamine equilibrium, each member of which could possess two geometric isomers. Both tautomeric possibilities have been diagramed in publications in this field; see for example ref 3, and A. R. Surrey and H. F. Hammer, *J. Amer. Chem. Soc.*, **68**, 113 (1946).

(5) In the earlier literature these are described as 4-hydroxyquinolines. Current experimental evidence supports the lactam structure as the predominant tautomer: A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 339 (1963).

(6) F. Y. Wiselogle, Ed., "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946, pp 1047–1053.

(7) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 1666 (1967).

(8) N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *ibid.*, **32**, 4155 (1967).

(9) E. C. Taylor and N. D. Heindel, *ibid.*, **32**, 3339 (1967).

(10) J. B. Henrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(11) E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6**, 423 (1967).

(12) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(13) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(14) Testing was carried out at the University of Miami under the sponsorship of the Walter Reed Army Institute of Research according to the standard screen described by T. S. Osdene, P. D. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(15) Nmr analyses were carried out on a Varian A60 nmr spectrometer and are calibrated against TMS. Combustion analyses were provided through the courtesy of Dr. Velmer B. Fish of these laboratories. Melting points were obtained on a Fisher-Johns block and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

(16) V. A. Izmail'skii and A. M. Simonov, *J. Gen. Chem. USSR*, **10**, 1580 (1940); *Chem. Abstr.*, **35**, 2870 (1941).

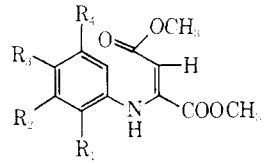
(17) J. English, J. F. Mead, and C. Niemann, *J. Amer. Chem. Soc.*, **62**, 350 (1940).

(18) Purchased from Pierce Chemical Co., Rockford, Ill.

(19) I. G. Farbenind, French Patent 745,293 (1933); *Chem. Abstr.*, **27**, 4414 (1933).

TABLE I

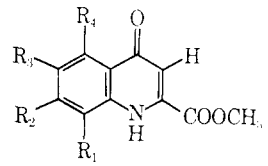
DIMETHYL ANILINOFUMARATES



Compd	R_1	R_2	R_3	R_4	Bp (mm) or mp, °C	% yield	Formula	Analyses
3a	Cl	H	H	H	69–70	81	$C_{12}H_{12}ClNO_4$	C, H, N
3b	H	Cl	H	H	135–136 (0.20)	76	$C_{12}H_{12}ClNO_4$	C, H, N
3c	Cl	H	H	CF_3	64–65	55	$C_{13}H_{11}F_3ClNO_4$	C, H, N
3d	H	Cl	H	Cl	87–88	77	$C_{12}H_{11}Cl_2NO_4$	C, H, N
3e	H	H	F	H	128–129 (0.30)	72	$C_{12}H_{12}FNO_4$	C, H, N
3f	H	Cl	OCH_3	H	104–105	66	$C_{13}H_{14}ClNO_5$	C, H, N
3g	PhCONH	H	H	OCH_3	161–162	79	$C_{20}H_{20}N_2O_6$	C, H, N
3h	H	CF_3	OCH_3	H	59.5–61	65	$C_{14}H_{14}F_3NO_5$	C, H, N
3i	H	F	OCH_3	H	55–56	54	$C_{13}H_{14}FNO_5$	N

TABLE II

METHYL 4(1H)-QUINOLONE-2-CARBOXYLATES



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Compd	R_1	R_2	R_3	R_4	Mp, °C	% yield	Formula	Analyses
4a	Cl	H	H	H	148–149	81	$C_{11}H_8ClNO_3$	C, H, N
4b	H	Cl	H	H	292–293	48[b]	$C_{11}H_8ClNO_3$	C, H, N
4c	H	H	H	Cl	255–257	15[b,a]	$C_{11}H_8ClNO_3$	C, H, N
4d	Cl	H	H	CF_3	126–127	68	$C_{12}H_7ClF_3NO_3$	C, H, N
4e	H	Cl	H	Cl	286–287	90	$C_{11}H_7Cl_2NO_3$	C, H, N
4f	H	H	F	H	252–254	73	$C_{11}H_8FNO_3$	C, H, N
4g	H	Cl	OCH_3	H	297–299	60[b]	$C_{12}H_{10}ClNO_4$	C, H, N
4h	H	H	OCH_3	Cl	246–248	25[b,a]	$C_{12}H_{10}ClNO_4$	C, H, N
4i[b]	PhCONH	H	H	OCH_3	250–252	30	$C_{19}H_{16}N_2O_5$	C, H, N
4j	H	F(OCH_3)	OCH_3	H(F)	277–278	74[c]	$C_{12}H_{10}FNO_4$	C, H, N
4k	H	H	SCH_3	H	264–267	57[d]	$C_{12}H_{11}NO_3S$	C, H, N
4l	H	CF_3	OCH_3	H	293–294	63	$C_{13}H_{10}F_3NO_4$	C, H, N

[a] Yields represent the purified separate quinolone isomers. Total yield of the combined forms is higher than sums of separated components due to losses in fractional crystallization. [b] Prepared by cyclization of **3g** in polyphosphoric acid by the method described in ref 8. [c] Yield represents the combined isomers. [d] The parent adduct of this quinolone (*i.e.*, **3**, $R_3 = SCH_3$) was a viscous oil which could not be distilled without inducing ring closure. Yield represented in this table is based on the parent amine, 4-aminothioanisole.

hydrous MeOH. The mixture was refluxed with stirring for 12 hr. The solution was then concentrated by evaporation of the MeOH under reduced pressure and allowed to cool to precipitate the product. Crystalline materials were purified to analytical purity by recrystallization from MeOH. The liquid adducts, **3b** and **3e**, were purified by distillation at reduced pressures. Yields and physical properties are reported in Table I.

Methyl 4(1H)-Quinolone-2-carboxylates (4).—The dried adducts (**3**) were added in small portions with vigorous stirring to 10–20 times their own weight of Ph_2O, which was maintained at 240–250°. In most cases the heterocyclic products began to precipitate almost immediately, but heating was continued for 10–15 min to ensure complete reaction. The reaction medium was diluted with petroleum ether (bp 60–110°); the quinolones were removed by filtration, washed well on the filter with petroleum ether, and recrystallized from MeOH. Analytical samples were prepared by sublimation at 0.05 mm. Specific exceptions to this general procedure are described below.

Separation of Isomeric Quinolonecarboxylates.—The cyclization of 100 g of **3f** according to the above procedure produced a mixture of quinolones which nmr analysis revealed to be a 4:1 ratio of **4g**:**4h**. When the crude isomeric mixture was refluxed with six successive 1-l. portions of MeOH, the more soluble **4h** isomer was extracted. By concentration of the alcohol 21.8 g (25%) of **4h**, mp 230–234°, was isolated. The analytical sample prepared by a sublimation and a second recrystallization from MeOH melted at 246–248°. The insoluble isomer, 53.0 g (60%), melted at 281–283°. An analytical sample was prepared by recrystallization from a large volume of MeOH and vacuum sublimation, mp 297–299°. The nmr spectrum in trifluoroacetic acid of **4h** revealed the C-7 and C-8 protons as a AB quartet (J = 9 cps) at δ 7.95 and 7.55. In the spectrum of **4g** the C-5 and C-8 protons appeared as sharp singlets at δ 7.47 and 7.92 ppm.

The ring closure of **3h** produced a single quinolone isomer in 63% yield. The aromatic portion of the nmr spectrum of this isomer revealed two noncoupled singlets at δ 8.14 and 8.64 ppm. This spectral pattern is consistent only with the 6-methoxy-7-trifluoromethyl isomer and excludes the 5-trifluoromethyl-6-methoxy isomer which would be expected to display the C-7–C-8 protons as an *ortho*-coupled AB quartet.

By cyclization of **3i** a quinolone mixture **4j** was obtained which consisted of 77% methyl 6-methoxy-7-fluoro- and 23% methyl 5-fluoro-6-methoxy-4(1H)-quinolone-2-carboxylates. Integration of the nmr signals for the two slightly different ester methoxyls at δ 4.35 and 4.15 ppm in the 6,7 and 5,6 isomers, respectively, could be utilized to quantitatively assay the mixture. The two quinolones could not be separated by fractional crystallization.

The crude quinolone mixture obtained by cyclization of 6.1 g of **3b** was digested in four times its weight of glacial AcOH and allowed to cool to room temperature. The 7-chloro-4(1H)-

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).

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

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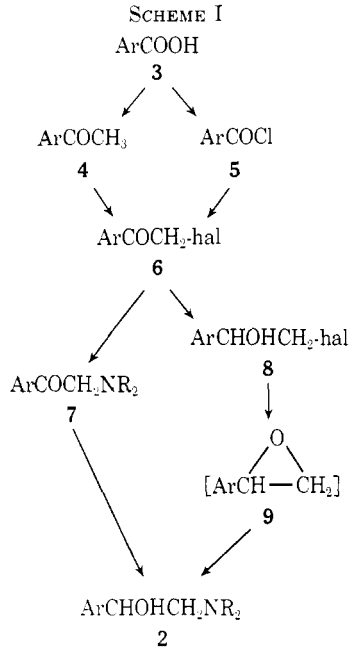
The arylamino alcohols (**1**) were one of the groups of antimalarial drugs most intensively studied during the World War II program.[2] Quinine, in which the aryl group is 4-quinolyl and the amino group is incorporated into a quinuclidine ring system, provided the inspiration for this series. This group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

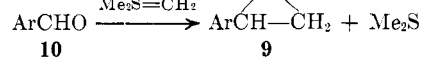
The established routes to compounds of type **2** are summarized in Scheme I. They typically proceed from an aromatic acid (**3**) or methyl ketone (**4**) through various intermediates to a halomethyl ketone (**6**). This ketone is then transformed into the final product (**2**) either *via* an amino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



10 **9**

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

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