Antimalarials. Substituted 2-Phenyl-4-quinolinemethanols[1a]

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Twenty-six new α-(alkylaminomethyl)-2-phenyl-4-quinolinemethanols have been synthesized for evaluation of their antimalarial activity. Nine new 2-phenylcinchoninic acids were prepared together with the several intermediates leading to the amino alcohols. An anomalous orientation effect of methoxy substitution in the anilines used in the Doebner reaction for the preparation of cinchoninic acids was noted. In the environment of the Doebner reaction the methoxy group became a *meta*-directing group rather than *ortho,para* directing. The position of the methoxy substitution in the 2-phenyl-4-quinolinemethanols prepared influenced the basicity of the quinoline nitrogen. The heterocyclic nitrogen in 2-(4-methoxyphenyl)- and 7-methoxy-2-phenyl-substituted 4-quinolinemethanols was seemingly equivalent in base strength to the aliphatic tertiary nitrogen in the amino alcohol side chain in contrast to similar compounds in which there was chloro substitution in these positions. Twenty of the compounds have been tested for antimalarial activity toward *Plasmodium berghei* in mice. Single doses of from 40 to 640 mg/kg prolonged the life of infected mice to at least 30 days, whereas the survival time of controls was 7.0 ± 0.5 days. The one dioctylamino derivative was inactive at a dose of 640 mg/kg. The diethylamino-1-methylbutylamino derivative was toxic at a dose of 40 mg/kg. The compounds were phototoxic to albino mice at dosage levels from 5 to 400 mg/kg.

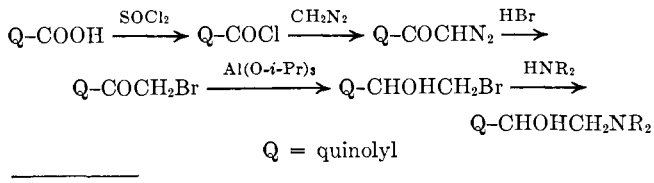
The α-(dialkylaminomethyl)-2-phenyl-4-quinolinemethanols have demonstrated significant activity against malarial infections in several species, including man.[2,3] These results provided an important lead to the development of new chemotherapeutic agents for the possible prophylaxis and cure of malaria caused by drug-resistant *Plasmodia*, a current military and medical problem.[4,5]

In previous studies of potential antimalarial agents six of the nine compounds with a therapeutic index[3] of over 100 were 2-(4-chlorophenyl)-4-quinolinemethanols. The seventh contained an additional chlorine atom in a 2-(3,4-dichlorophenyl) analog. The most active compound was 7-chloro-α-(dibutylaminomethyl)-6-methoxy-4-quinolinemethanol hydrochloride.[6] Other active 2-phenyl-4-quinolinemethanols contained either chloro or methoxy substituents in the 6 and 7 positions of the quinoline ring or in the 3 and 4 positions of the 2-phenyl group.

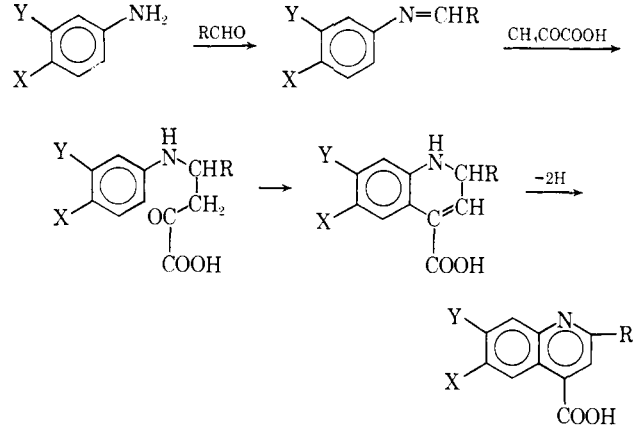
We have now prepared 26 4-quinolinemethanols from the ten possible 2-phenylcinchoninic acids substituted with two chloro and one methoxy, or one chloro and two methoxy, groups in the 6 and 7 positions of the quinoline ring and in the 3 and 4 positions of the 2-phenyl group. The general synthetic pathway was that of Lutz, *et al.*,[6] outlined in Scheme I. This sequence of reactions was used because in every case the intermediates could be prepared in adequate yield and purity. The newer procedure of Boykin, *et al.*,[7] in which the cinchoninic acid is converted to the methyl ketone with methyllithium,[8] was successful in only two of five cases which we attempted. Moderate yields of the methyl ketones were obtained from 7-chloro-2-(4-chlorophenyl)-6-methoxy- (I) and 7-chloro-6-methoxy-2-(4-methoxyphenyl)cinchoninic acids (VI). Unidentified products were obtained from 2-(3,4-dichlorophenyl)-6-methoxy- (III) and 6,7-dichloro-2-(4-methoxyphenyl)cinchoninic acids (IV). 7-Chloro-2-(3,4-dimethoxyphenyl)cinchoninic acid (X) was recovered in almost quantitative yield from attempted reaction with methyllithium.

The substituted cinchoninic acids were obtained by either the Doebner[9] or Pfitzinger[10] reactions. While attempting to prepare 6- and 7-methoxycinchophens by the Doebner reaction, we discovered an unexpected orientation effect of the methoxy group. The reaction pathway probably involves the formation of a benzalamine which reacts with pyruvic acid to form an α-keto acid. The latter cyclizes and is oxidized to the cinchophen, as shown in Scheme II.

SCHEME I



SCHEME II



(1) (a) The work described in this paper was performed under Contract No. DA-49-193-MD-2981 with the U. S. Army Medical Research and Development Command. This is contribution No. 319 from the Army Research Program on Malaria. (b) To whom inquires should be addressed.

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

(3) G. R. Coatney, Survey of Antimalarial Agents, Public Health Service Monograph No. 9, Federal Security Agency, 1952; also known as Public Health Service Publication No. 193.

(4) R. T. Cutting, *U. S. Med.*, 15 (Jan 1, 1967).

(5) W. D. Tigertt, paper presented at the 153rd National Meeting, American Chemical Society, Miami Beach, Fla., April 10–13, 1967.

(6) R. E. Lutz, *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(7) D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967).

(8) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(9) O. Doebner, *Ann. Chem.*, **242**, 265 (1887).

(10) W. Pfitzinger, *J. Prakt. Chem.*, **33**, 100 (1886); **38**, 582 (1888).

When Y = H and X is a *meta*-directing group, the Doebner reaction produces a moderate yield of a 6-substituted cinchophen. If X is an *ortho,para*-directing group, the ring closure to the cinchophen does not occur. Similarly, when X = H and Y is a *meta*-directing group, the ring closure does not occur. Thus, the reaction between 4-chloroaniline, 3,4-dimethoxybenzaldehyde, and pyruvic acid did not yield a cinchophen, but only a pyrrolidinonimine, while the reaction with 3-chloroaniline and the same reactants produced the expected[6] 7-chloro-2-(3,4-dimethoxyphenyl)cinchoninic acid (X). In contrast, the Doebner reaction between 4-anisidine, 3,4-dichlorobenzaldehyde, and pyruvic acid gave 2-(3,4-dichlorophenyl)-6-methoxycinchoninic acid (III), while the reaction under the same conditions with 3-anisidine produced no cinchophen but what appeared to be a benzalamine and a resinous material, probably from self-condensation of pyruvic acid.

In this connection it is interesting to note that 6,7-dichloro-2-(4-methoxyphenyl)cinchoninic acid (IV) could not be prepared by the Doebner reaction, but 2-(4-chlorophenyl)-6,7-dimethoxycinchoninic acid (VIII) was obtained in 49% yield by this method.

These results are contrary to the generally accepted theory of the orienting influence of the methoxy group, which in most reactions appears to be somewhat more *ortho,para* directing and activating than the chlorine atom attached to an aromatic ring. Indications are that the methoxy group is a stronger base than it is generally thought to be, at least in the environment of the Doebner reaction. A logical explanation is that the methoxy group becomes protonated and thus is an inactivating, *meta*-directing group.

In five series of compounds in which there was 4-methoxy substitution in the 2-phenyl ring or 7-methoxy substitution in the quinoline ring we noted certain effects which indicated that the methoxy group in these positions might be taking part in salt formation, as suggested above for the Doebner ring closure, or might increase the basicity of the quinoline nitrogen through conjugation. These compounds may be compared with two series in which there was 6-methoxy substitution. The structures are illustrated in Scheme III.

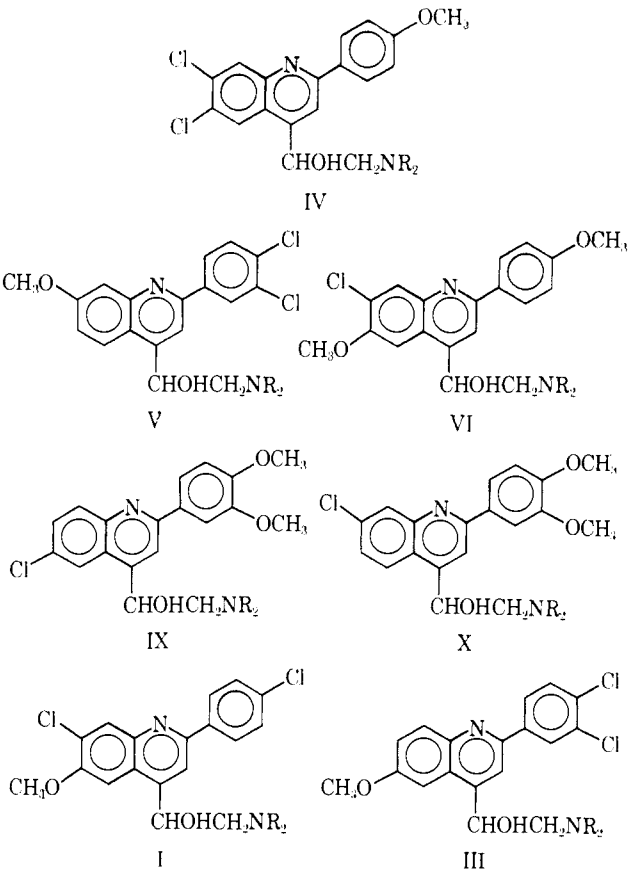
When the salts of IV–VI, IX, and X were precipitated with ethereal HCl from ether solutions of bases, the dihydrochlorides were obtained. Similar treatment of I and III resulted in the precipitation of the monohydrochlorides. The monohydrochloride of X (R = C_2H_5) was obtained by rapid addition of the stoichiometric amount of HCl to an ether solution of the base. When this salt was dissolved in a mixture of 2-butanone and ethanol, it disproportionated to the dihydrochloride and the free base. The monohydrochlorides of I and III were stable in alcoholic solution. The monohydrochloride of X (R = C_4H_9) was prepared in similar manner and was stable in 2-butanone solution, but not in alcoholic solution.

Biological Activity.—The 4-quinolinemethanols described herein have been tested for antimalarial activity[11] against *Plasmodium berghei* in mice by Dr. Leo Rane at the University of Miami. The results of the tests were furnished to us by Dr. David P. Jacobus, Walter Reed Army Institute of Research. Antimalarial activity is summarized in Table I. With the exception of 2-(3,4-dichlorophenyl)-α-(dioctylaminomethyl)-6-methoxy-4-quinolinemethanol hydrochloride (IIId) and 2-(3,4-dichlorophenyl)-α-(4-diethylamino-1-methylbutylaminomethyl)-6-methoxy-4-quinolinemethanol trihydrochloride (IIIf), the amino alcohols were active against *P. berghei*. Compound IIId, being a dioctyl derivative, was probably insufficiently absorbed by the test animals to show activity; IIIf was toxic at a dosage of 40 mg/kg and lethal at a dosage of 160 mg/kg. The 4-diethyl-1-methylbutylamino side chain, so effective in chloroquine and quinacrine, appears to give undesirable properties in this series of 4-quinolinemethanols, as was noted previously in 2-(4-chlorophenyl)-α-(4-diethylamino-1-methylbutylaminomethyl)-4-quinolinemethanol.[3]

Antimalarial activity in a given series of compounds varied with the size of the aminoalkyl group, an effect shown by the previously tested quinoline amino alcohols.[3] It is noteworthy that the most active compound, Ia, was a monoalkylamino derivative, a possible metabolic product of 7-chloro-α-(dibutylaminomethyl)-6-methoxy-4-quinolinemethanol. This result may point toward improvement in the activity of the 4-quinolinemethanols.

Several of the 4-quinolinemethanols were evaluated for phototoxicity in albino mice. Maximum tolerated doses ranged from 5 to 400 mg/kg. The results have been reported.[12]

SCHEME III



(11) Test procedure is described by T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

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

TABLE I

ANTIMALARIAL ACTIVITY OF α-(ALKYLAMINOMETHYL)-2-PHENYL-4-QUINOLINEMETHANOLS

	Change in mean survival time[a] or no. of cures (C)[b] — Dosage, mg/kg					
No.	20	40	80	160	320	640
Ia		2C		5C		5C
b	1.3	4.9	5.3	1C	2C	3C
IIIa	3.5	6.5	8.3	10.9, 1C	2C, 3C	3C, 4C
b	3.3	8.3	10.1	1C	4C	5C
c	0.3	2.1	3.1	2C, 4C	3C, 5C	5C
d		0		1.0		2.0
e	0.1	0.5	2.5	4.7	6.7	1C, 2C
f		(2)[c]		(5)[c]		(5)[c]
IVa	5.7	7.1, 8.1	1C	4C, 5C	5C	5C
b	0.2	3.0, 3.5	3.6	7.7, 1C	4C	4C
Va		1.8		1C		5C
b	2.3	4.3, 5.3	5.3	7.5	8.3	5C
VIa	0.7	2.9, 2.7	4.1	6.1	12.7, 1C	3C, 5C
b	1.3	7.1, 8.0, 2C	8.1	15.9, 16.4, 4C	3C, 5C	3C, 4C, 5C
c	2.9	5.8, 6.1	6.3	12.9, 13.4, 2C, 5C	13.9, 2C	3C, 4C, 5C
IXa		1.8		6.2		4C
b		5.8		2C		5C
c	0.2	0.2, 0.5	4.4	4.3, 1C	3C	4C
d	0.8	0.4, 0.8	1.6	3.4, 3.8	1C	3C, 4C
Xa		1.4		5.6		2C

[a] Mean survival time of treated mice − mean survival time of controls in days. [b] Number of treated mice in groups of five surviving to 30 days. [c] Toxic deaths.

Experimental Section

The general descriptions of experimental procedures given in this section should be supplemented by reference to the appropriate table in which the individual conditions of reactions are given. All melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected.

2-Phenylcinchoninic Acids.—Nine new 2-phenylcinchoninic acids (Table II) have been prepared, generally following the procedures of Lutz, *et al.*[6] The procedures are readily adapted to large laboratory-scale (3 mole) use. The choice between the Doebner and the Pfitzinger reactions was dictated by the substitution desired, as discussed above, and by the limited availability of the required substituted isatins.

A. Typical Preparation of a 2-Phenylcinchoninic Acid by the Doebner Reaction.—A solution of 136.0 g (1 mole) of 4-methoxybenzaldehyde in 400 ml of absolute EtOH was stirred and gently heated to reflux. To it was added 157.5 g (1 mole) of 3-chloro-4-methoxyaniline, and the solution was boiled for 15 min. Freshly distilled pyruvic acid (88.0 g, 1 mole) dissolved in 90 ml of absolute EtOH was added dropwise while stirring and heating continued. The yellow precipitate which formed before all the pyruvic acid had been added increased in amount with time. After 3.5 hr the mixture was cooled to room temperature and the precipitate was collected by filtration.

Two procedures were used to isolate and purify the cinchoninic acid. (1) The precipitate was washed on the filter with 95% EtOH until the washings were nearly colorless. After drying the solid was extracted with hot 10% Na_2CO_3 solution, and, in the cases (I and X) where a solid by-product was formed, the solution was filtered while hot and the residue was washed (hot H_2O) and extracted a second time with Na_2CO_3. The filtrate was acidified with AcOH, and the precipitated acid was collected by filtration, washed free of AcOH with H_2O, and dried. Prior to use the acid was digested with boiling 95% EtOH, in which it was only slightly soluble. (2) The precipitate was pressed as dry as possible on the filter and then digested with acetone. The acid obtained in this manner was of higher purity than that isolated by Na_2CO_3 extraction. Yields were comparable.

B. Preparation of 2-Phenylcinchoninic Acids by the Pfitzinger Reaction.—The procedure of Lutz, *et al.*,[6] was followed without modification.

2-Phenylcinchoninyl Chlorides.—The acid was suspended in a volume of $SOCl_2$ sufficient to dissolve it completely when the mixture was heated to boiling. In most cases this amounted to a volume of $SOCl_2$ equivalent to ten times the weight in grams of the acid. The $SOCl_2$ was distilled under reduced pressure; the acid chloride was triturated with C_6H_6, which was then removed by distillation under reduced pressure; the product was slurried in petroleum ether (bp 30–60°), collected by filtration, and stored in a vacuum desiccator until used. The crude preparations gave satisfactory results in the reaction with CH_2N_2.

Diazomethyl Ketones.—The powdered acid chloride was added slowly to a cold (−10 to −5°) well-stirred solution of CH_2N_2 in ether containing 4 moles of CH_2N_2/mole of acid chloride. The temperature of the reaction mixture was not allowed to rise above 5° during the addition. The mixture was stirred overnight and allowed to come to room temperature slowly. The solid was collected by filtration and washed well on the filter with ether.

Diazomethyl 2-(3,4-dichlorophenyl)-6-methoxy-4-quinolyl ketone (III) was prepared from a CH_2Cl_2 solution of CH_2N_2 according to the procedure of Lutz.[6]

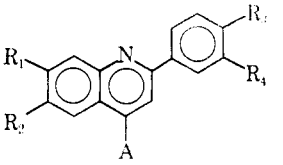
Bromomethyl Ketones. A. In EtOAc Solutions.—The diazomethyl ketone was dissolved in warm EtOAc, and the solution was filtered to remove a small quantity of an insoluble residue. To the solution kept warm enough to prevent crystallization of the diazo ketone 2.2 moles of HBr/mole of diazo ketone (as 30% HBr in HOAc diluted with an equal volume of EtOAc) was added dropwise while the solution was stirred mechanically. The reaction mixture from which the bromomethyl ketone hydrobromide had precipitated was cooled to room temperature, filtered, and washed (Et_2O). The product was obtained in excellent purity without further treatment.

B. In Ether Suspension.—The diazomethyl ketone was suspended in ether with good stirring while 2.2 moles of HBr/mole of diazomethyl ketone (as 48% HBr–Et_2O, 1:1) was added dropwise. There was gas evolution, and the color of the suspended solid changed. The mixture was stirred for 5 hr and filtered, and the product was washed free of acid with ether.

C. In CH_2Cl_2.—The mixture of the diazomethyl ketone in CH_2Cl_2, described in the preceding section, was treated with 30% HBr in HOAc diluted with an equal volume of ether. The bromomethyl ketone hydrobromide dissolved in the CH_2Cl_2. It crystallized when the solution was chilled to −5° and was col-

TABLE II[a]

2-PHENYLCINCHONINIC ACIDS AND DERIVATIVES

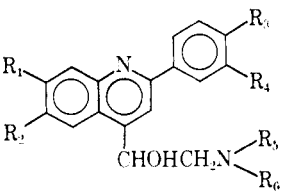


					A = COOH					
No.	R_1	R_2	R_3	R_4	Formula	Prepn[a]	Reaction time, hr	Yield, %	Mp, °C	Analyses[b]
I[e]	Cl	CH_3O	Cl	H	$C_{17}H_{11}Cl_2NO_3$	A(1)	16	22.9	284–286	
II	CH_3O	Cl	Cl	H	$C_{17}H_{11}Cl_2NO_3$	B	39.5	76.3	244	C, H, N
III	H	CH_3O	Cl	Cl	$C_{17}H_{11}Cl_2NO_3$	A(2)	18	30.2	264.0–264.5	C, H
IV	Cl	Cl	CH_3O	H	$C_{17}H_{11}Cl_2NO_3$	B	40	75.0	244–245	C, H, N
V	CH_3O	H	Cl	Cl	$C_{17}H_{11}Cl_2NO_3$	B	42.5	82.0	261–263	C, H
VI	Cl	CH_3O	CH_3O	H	$C_{18}H_{14}ClNO_4$	A(1, 2)	3.5	23.8	247–249	C, H, N
VII	CH_3O	Cl	CH_3O	H	$C_{18}H_{14}ClNO_4$	B	24	75.5	264–267	C, H, N
VIII[f]	CH_3O	CH_3O	Cl	H	$C_{18}H_{14}ClNO_4$	A(1)	3.5	49.0	286–287[d]	C, H, N
IX	H	Cl	CH_3O	CH_3O	$C_{18}H_{14}ClNO_4$	B	22	95.0	221–223	C, H
X	Cl	H	CH_3O	CH_3O	$C_{18}H_{14}ClNO_4$	A(2)	16	27.0	226–229	C, H, N

[a] The capital letters refer to the descriptions in the Experimental Section. [b] Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within 0.4% of the theoretical values. [c] With decomposition. [d] Many of the compounds had double melting points. The values given are for the first melting point. [e] Previously

TABLE III

α-(ALKYLAMINOMETHYL)-2-PHENYL-4-QUINOLINEMETHANOLS



No.	R_1	R_2	R_3	R_4	R_5	R_6	Formula[a]	Temp, °C	Time, hr	Yield, %	Crystn solvent	Mp, °C
Ia	Cl	CH_3O	Cl	H	C_4H_9	H	$C_{22}H_{28}Cl_2N_2O_3 \cdot HCl$	75	6	50.0	EtOH	226–227
b					C_6H_{13}	C_6H_{13}	$C_{30}H_{46}Cl_2N_2O_2 \cdot HCl$	85	16	89.4	EtOH	190–191
IIa	CH_3O	Cl	Cl	H	C_4H_9	C_4H_9	$C_{26}H_{32}Cl_2N_2O_2 \cdot HCl$	80	15	60.5	EtOH	195–195.5
b					C_6H_{13}	C_6H_{13}	$C_{30}H_{46}Cl_2N_2O_2 \cdot HCl$	80	15	59.0	EtOH	180–181
IIIa	H	CH_3O	Cl	Cl	C_2H_5	C_2H_5	$C_{22}H_{24}Cl_2N_2O_2 \cdot HCl$	80	41	92.0	EtOH	194–195
b					C_4H_9	C_4H_9	$C_{26}H_{32}Cl_2N_2O_2 \cdot HCl$	75	26.5	73.4	EtOH	195–196
c					C_6H_{13}	C_6H_{13}	$C_{30}H_{40}Cl_2N_2O_2 \cdot HCl$	90	66	63.5	EtOH	173–174
d					C_8H_{17}	C_8H_{17}	$C_{34}H_{48}Cl_2N_2O_2 \cdot HCl$	90	50.5	72.0	EtOH	161–162
e					$C_2H_4OC_2H_5$	$C_2H_4OC_2H_5$	$C_{26}H_{32}Cl_2N_2O_4 \cdot 2HCl$	80	18	59.0	EtOH	177–178
f					$CH(CH_3)(CH_2)_3CH(C_2H_5)_2N$	H	$C_{27}H_{36}Cl_2N_2O_2 \cdot 3HCl$	80	20	72.5	Me_2CO–H_2O	225–227
IVa	Cl	Cl	CH_3O	H	C_4H_9	C_4H_9	$C_{26}H_{32}Cl_2N_2O_2 \cdot HCl$	75	22	71.5	EtOH	188–189
b					C_6H_{13}	C_6H_{13}	$C_{30}H_{40}Cl_2N_2O_2 \cdot HCl$	90	21	44.0	EtOH	176–177
Va	CH_3O	H	Cl	Cl	C_4H_9	C_4H_9	$C_{26}H_{32}Cl_2N_2O_2 \cdot 2HCl$	80	16	58.2	Me_2CO–H_2O	125–128
b					C_6H_{13}	C_6H_{13}	$C_{30}H_{40}Cl_2N_2O_2 \cdot 2HCl$	90	16	18.3	EtOH	175–177
VIa	Cl	CH_3O	CH_3O	H	C_2H_5	C_2H_5	$C_{23}H_{27}ClN_2O_3$	80	27	81.5	EtOH	136–138
b					C_4H_9	C_4H_9	$C_{27}H_{36}ClN_2O_3$	75	26.5	82.6	EtOH	89–92
c					C_6H_{13}	C_6H_{13}	$C_{31}H_{43}ClN_2O_3$	75	73	53.0	EtOH	102–104
VIIa	CH_3O	Cl	CH_3O	H	C_4H_9	C_4H_9	$C_{27}H_{36}ClN_2O_3 \cdot HCl$	80	16	67.0	EtOH	184–186
b					C_6H_{13}	C_6H_{13}	$C_{31}H_{43}ClN_2O_3 \cdot HCl$	90	16	55.5	Butanone-naphtha	165–167
VIIIa	CH_3O	CH_3O	Cl	H	C_4H_9	C_4H_9	$C_{27}H_{36}ClN_2O_3 \cdot HCl$	80	16	81.0	EtOH	200–202
IXa	H	Cl	CH_3O	CH_3O	C_2H_5	C_2H_5	$C_{23}H_{27}ClN_2O_3 \cdot 2HCl$	80	19.5	58.4	EtOH–H_2O	195–197
b					C_4H_9	C_4H_9	$C_{27}H_{36}ClN_2O_3 \cdot HCl$	80	16	59.5	Me_2CO–H_2O	147–149
c					C_6H_{13}	C_6H_{13}	$C_{31}H_{43}ClN_2O_3 \cdot 2HCl$[b]	90	16	63.0	Me_2CO–H_2O	126–129
d					C_8H_{17}	C_8H_{17}	$C_{35}H_{51}ClN_2O_3 \cdot 2HCl$	90	21	78.5	EtOH–H_2O	132–134
Xa	Cl	H	CH_3O	CH_3O	C_2H_5	C_2H_5	$C_{23}H_{27}ClN_2O_3 \cdot 2HCl$	78	17	61.5	EtOH	160–161
b					C_4H_9	C_4H_9	$C_{27}H_{36}ClN_2O_3 \cdot HCl$	70	20	65.4	Butanone	161–163

[a] All compounds were analyzed for C, H, N. [b] C, H, N, O, Cl^- analyses. C: calcd, 62.05; found, 61.13. Cl^-: calcd, 11.82; found, 11.11.

lected and washed with Et_2O to free it from the solvent and acid.

α-(Bromomethyl)-2-phenyl-4-quinolinemethanols.—The bromomethyl ketone hydrobromides were reduced with Al(O-*i*-Pr)$_3$ in *i*-PrOH in the usual fashion,[13] using 1.1 moles of Al(O-*i*-Pr)$_3$/ mole of bromomethyl ketone. In one case (VIII) the salt did not react with the reagent. It was necessary to convert it to the free base which was easily reduced. The bromohydrins were digested with 95% EtOH prior to use.

α-(Alkylaminomethyl)-2-phenyl-4-quinolinemethanols.—The 4-quinolinemethanols listed in Table III were all made by the

(13) A. L. Wilds, *Org. Reactions*, **2**, 197 (1944).

A = COCl			A = $COCHN_2$	A = $COCH_2Br$			A = $CHOHCH_2Br$		
Reaction time, hr	Yield, %	Mp, °C	Mp,[c] °C	Prepn[a]	Yield, %	Mp, °C	Reaction time, hr	Yield, %	Mp,[d] °C
5.5	79.3	243–245	162–163	A	91.7	188–190[e]	4	100	216–218
3.5	85.6	172–173	162–165	A	95.0	216–217[e]	3.5	99.7	200
4	93.0		147.5–148.5	C	85.0	227–230	13.75	84.7	197–198
20	81.6	167–175	170–173	B	93.8	213–215	3	90.0	144–145
16.5	94.6	153–166	161–163	B	89.5	153–156[e]	4.5	92	108–115
3	93.0	215–218	155–157	B	94.5	222–224[e]	5	81.2	228–229
6	90.8	180–192	155–157	A	91.1	196–197[e]	6	83.8	190–192
5	74.7	187–195	160–161	A	85.0	231–232[e]	1	100	226–228
5	94.7	172–182	148–149	A	82.0	236–238	4	91	261–265
7.5	94.0	162–166	124–129	B	88.0	207–209[h]	14	97	126–127

prepared.[6] [f] Nmr spectra proved the 6,7 substitution. [g] Crystallized from DMF. All other acids crystallized from EtOH. [h] Crystallized from EtOAc.

direct condensation of the bromohydrin with the appropriate amine, using 6 moles of amine/mole of bromohydrin. The mixed hydrohalides of the amine precipitated on dilution of the reaction mixture with ether. The excess amine was removed by precipitation with standardized ethereal HCl except in the case of water-soluble amines where the amine was extracted from the ether solution with H_2O. The amino alcohols were then precipitated from the ether solution as hydrochlorides and purified by repeated crystallizations from suitable solvents.

Miscellaneous Starting Materials and By-Products.—The chemicals used for the syntheses described were commercial products with the following exceptions: 6-methoxyisatin,[14] 6-chloroisatin,[14,15] 5,6-dichloroisatin,[16] 3,4-dimethoxyacetophenone,[17] and 5-chloro-6-methoxyisatin. The synthesis of 5-chloro-6-methoxyisatin, a new compound, follows.

5-Chloro-6-methoxyisatin.—6-Methoxyisatin (83.7 g, 0.472 mole) was suspended in 1 l. of HOAc, and 127.4 g (0.944 mole) of SO_2Cl_2 and a small crystal of I_2 were added. The temperature of the mixture rose to 36°. After 0.5 hr, the mixture was heated to 50°, where it was held for 6.5 hr. The mixture cooled slowly to room temperature, and N_2 was passed through it for 0.5 hr to aid in removal of reaction gases. The mixture was then cooled in ice to 15°, and the orange solid was filtered off and washed free of HOAc with naphtha; yield 59.0 g (59.4%). The analytical sample crystallized from HOAc had mp 295–298°. *Anal.* ($C_9H_6ClNO_3$) C, H, N. The nmr spectrum proved the 5,6 substitution.

The by-product, **N-(3-chlorophenyl)veratrylamine,** was obtained in the synthesis of 7-chloro-2-(3,4-dimethoxyphenyl)-cinchoninic acid. Crystallized from HOAc it had mp 130–131°. *Anal.* ($C_{15}H_{16}ClNO_2$) C, H.

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