The method of increments is a fairly reliable approximation for these compounds. The over-all uncertainty of these estimates may exceed one cal./deg. mole, but the uncertainty of their differences probably is much less.

The method of increments, however, is not reliable for the other methyl derivatives in which steric effects are large and specific in character. A consideration of these steric effects indicates that the properties of *o*-methyl, α-methyl and *cis*-β-methylstyrene are about the same as those given for *p*-methylstyrene. This estimate is considered the best one possible at this time.

TABLE II

ESTIMATED THERMODYNAMIC PROPERTIES OF *p*-METHYLSTYRENE IN THE IDEAL GASEOUS STATE, CAL./DEG. MOLE

Estimates for the *o*-, *m*-, α- and *cis*-β-methylstyrenes are the same except that R ln 2 (1.4) should be added to the entropy and the $-(F^0 - H_0^0)T$ function of *m*-methylstyrene.

Temp., °K.	C_p^0	$(H^0 - H_0^0)/T$	$-(F^0 - H_0^0)/T$	S
298.16	34.7	20.3	71.4	91.7
300	34.9	20.3	71.5	91.9
400	44.8	25.2	78.1	103.3
500	53.5	30.0	84.2	114.3
600	60.7	34.6	90.1	124.7
700	66.8	38.8	95.8	134.5
800	71.8	42.6	101.2	143.7
900	76.1	46.1	106.4	152.5
1000	79.8	49.3	111.4	160.7
1100	82.9	52.2	116.3	168.4
1200	85.6	54.9	120.9	175.7
1300	87.9	57.3	125.4	182.7
1400	89.9	59.6	129.7	189.3
1500	91.6	61.6	133.9	195.5

TABLE III

ESTIMATED THERMODYNAMIC PROPERTIES OF *trans*-β-METHYLSTYRENE IN THE IDEAL GASEOUS STATE, CAL./DEG. MOLE

Temp., °K.	C_p^0	$(H^0 - H_0^0)/T$	$-(F^0 - H_0^0)/T$	S
298.16	34.9	19.9	71.0	90.9
300	35.1	20.0	71.1	91.1
400	45.2	25.1	77.6	102.6
500	54.0	30.0	83.7	113.7
600	61.2	34.6	89.6	124.2
700	67.2	38.9	95.3	134.1
800	72.2	42.7	100.7	143.4
900	76.4	46.2	105.9	152.2
1000	80.0	49.5	111.0	160.4
1100	83.1	52.4	115.8	168.2
1200	85.8	55.1	120.5	175.5
1300	88.1	57.5	125.0	182.5
1400	90.0	59.8	129.4	189.1
1500	91.7	61.8	133.5	195.4

Summary

Thermodynamic properties of styrene were calculated. Estimates were given for the properties of the various methyl styrenes.

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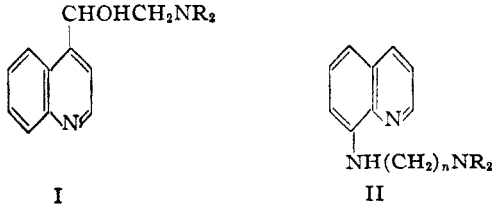
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

α-(Dialkylaminomethyl)-2-phenyl-4-quinolinemethanols with 8-Amino or Hydroxy Substituents[1]

BY RICHARD B. TURNER AND ARTHUR C. COPE

King and Work[2] have reported that the simple quinine analogs, α-(dialkylaminomethyl)-4-quinolinemethanols (I), are suppressive agents for certain forms of avian malaria. These compounds are less active and less toxic than 8-aminoquinolines of the Plasmochin type (II), which have a different mode of action on the malaria parasite.[3] In the search for superior antimalarial drugs sponsored by the Committee on Medical Research, it was considered of interest to investigate the properties of compounds containing both α-(dialkylaminomethyl)-4-quinolinemethanol and 8-amino groups. Earlier work had shown that a 2-phenyl substitutent greatly enhances antimalarial activity in 4-quinolinemethanols and diminishes it in 8-aminoquinolines.[3] Both series of drugs (I and II) include highly active compounds which do not contain the 6-methoxy group present in quinine and Plasmochin.[3]



I II

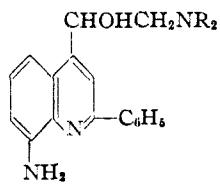
This paper reports the synthesis of 8-amino King–Work types, III, which contain a 2-phenyl substituent and are unsubstituted in the 6-position. The corresponding 8-hydroxy com-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Institute of Technology.

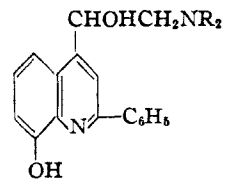
(2) King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942); see Kaufmann, *Ber.*, **46**, 1823 (1913); Rabe, Pasternack and Kindler, *ibid.*, **50**, 144 (1917).

(3) Pharmacological and clinical characteristics of the various classes of antimalarial drugs will be described in a forthcoming monograph by the Survey of Antimalarial Drugs.

pounds (IV) were prepared as intermediates in a projected synthesis of the 8-amino derivatives.



III a, R = ethyl
b, R = *n*-butyl
c, R = *n*-hexyl



IV a, R = ethyl
b, R = *n*-butyl
c, R = *n*-hexyl

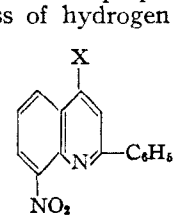
The plan originally devised for synthesis of the 8-amino compounds (III) utilized 8-hydroxy-2-phenylcinchoninic acid[4] as the starting material. The King–Work side chain was elaborated through the acid chloride, diazomethyl ketone, chloromethyl ketone and chlorohydrin, followed by condensation with a secondary amine to give IV.[5] The 8-amino or alkylamino group was then to be introduced in the 8-position through condensation with ammonia or a primary-tertiary diamine by the Bucherer reaction, which has been employed successfully with several 8-hydroxyquinoline derivatives.[6]

As the first step in this sequence, 8-hydroxy-2-phenylcinchoninic acid was acetylated with acetic anhydride in pyridine, and the 8-acetoxy acid so obtained was converted to the acid chloride by heating with thionyl chloride in benzene. After removal of the thionyl chloride, a benzene solution of the acid chloride was used in the next operation without isolation. Upon treatment with an ethereal solution of diazomethane which had been dried thoroughly with potassium hydroxide and sodium,[7] the crystalline diazomethyl ketone was obtained in a yield of 96%, based on 8-acetoxy-2-phenylcinchoninic acid. The conversion was unsatisfactory when the diazomethane solution was not carefully dried. This result probably was due to partial conversion of the phenolic acetate to the methyl ether by water and diazomethane.[8] The diazomethyl ketone was converted to the chloromethyl ketone in 87% yield by treatment with hydrogen chloride in a mixture of methylene chloride and ether. Reduction of the chloromethyl ketone to the chlorohydrin proceeded smoothly on treatment with aluminum isopropoxide in *i*-propyl alcohol, and after hydrolysis α-(chloromethyl) - 8 - hydroxy - 2 - phenyl - 4 - quinolinemethanol was obtained in 91% yield. Coupling of the chlorohydrin with diethylamine, di-*n*-butylamine and di-*n*-hexylamine proceeded with the formation of tarry by-products. Purification of the products was accomplished advantageously by crystallization of their monohydrochlorides, followed by conversion to the bases (IVa and b). The di-*n*-hexylamino base (IVc) failed to crystallize and was isolated as the monohydrochloride.

A number of attempts to apply the Bucherer reaction to IVb were unsuccessful, both with ammonia and with 4-diethylamino-1-methylbutylamine (noval diamine). Only unchanged IVb or decomposition products were isolated from each trial. In a model experiment, 8-hydroxy-2-phenylcinchoninic acid was converted to 8-amino-2-phenylcinchoninic acid (isolated as the ethyl ester)[9] through the Bucherer reaction. Success in this case and failure with IVb is believed to point to instability of the King–Work side chain under the conditions investigated for the Bucherer reaction.

A successful synthesis of III began with 8-nitro-2-phenylcinchoninic acid. This acid can be prepared by a modified Döbner reaction from *o*-nitroaniline, benzaldehyde and pyruvic acid, by a procedure recently developed by Buchman, McCloskey and Seneker.[9] As described by these authors, the acid is advantageously purified as the ethyl ester. Alkaline hydrolysis of the ester leads to a very dark product, but acid hydrolysis gives the pure acid in good yield. Application of the sequence of reactions outlined above (for the 8-acetoxy acid) to 8-nitro-2-phenylcinchoninic acid proceeded without difficulty and gave α-(chloromethyl) - 8 - nitro - 2 - phenyl - 4 - quinolinemethanol (Va) in an over-all yield of 78%. Pure samples of this chlorohydrin melted at 118–118.5° with effervescence followed by solidification and remelting at 158°. Reaction of the chlorohydrin with diethylamine, di-*n*-butylamine and di-*n*-hexylamine gave the α-(dialkylaminomethyl) - 8 - nitro - 2 - phenyl - 4 - quinolinemethanols. Hydrogenation of the 8-nitro compounds in alcohol solution in the presence of Adams platinum catalyst proceeded smoothly and yielded the 8-amino compounds, IIIa, b and c. Hydrogenations in acid solution gave poor yields of dark products. IIIa and b were isolated as the free bases, while IIIc failed to crystallize and was isolated as the dihydrochloride.

The chlorohydrin (Va), which is an intermediate in the preparation of III, readily undergoes loss of hydrogen chloride. The double melting



V

a, X = —CHOHCH$_2$Cl
b, X = —CH—CH$_2$ (O)
c, X = —COCH$_3$
d, X = —CH$_2$CHO

(4) Döbner and Fettback, *Ann.*, **281**, 1 (1894).

(5) This is the general method of synthesis employed by King and Work (ref. 2), as modified by Lutz, Winstein, Jacobs and others; Winstein, Jacobs, *et al.*, THIS JOURNAL, **68**, 1831 (1946); Lutz, *et al.*, *ibid.*, **68**, 1813 (1946). These investigators usually have employed the bromomethyl ketone and bromohydrin as intermediates.

(6) Woroshtzow and Kogan, *Ber.*, **65**, 142 (1932); Chelintzev and Dubinin, *J. Gen. Chem. U.S.S.R.*, **10**, 1395 (1940); Hartshorn and Baird, THIS JOURNAL, **68**, 1562 (1946).

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 165.

(8) Herzig and Tichatschek, *Ber.*, **39**, 268, 1557 (1906).

(9) Buchman, McCloskey and Seneker, to be published.

point noted above for this compound was found to be due to elimination of hydrogen chloride and transformation of Va into a new compound, $C_{17}H_{12}O_3N_2$, m. p. 157–157.5°. Structures considered possible for this compound included the epoxide Vb, the ketone Vc, and the aldehyde Vd which could be formed by rearrangement of the epoxide.

The compound gave a positive iodoform test and was not oxidized by potassium permanganate, results which exclude the aldehyde structure Vd. Reaction with dinitrophenylhydrazine gave a dinitrophenylhydrazone, while catalytic reduction proceeded with absorption of three molar equivalents of hydrogen and led to a product, m. p. 103–103.5°, which was identical with a compound obtained by catalytic reduction of chloromethyl (8-nitro-2-phenyl-4-quinolyl) ketone. This evidence establishes the methyl ketone structure Vc as most probable. The above conclusion was subsequently confirmed by an unequivocal synthesis of Vc in which 8-nitro-2-phenylcinchoninic acid was converted to the acid chloride and condensed with sodiomalonic ester. The resulting keto ester was not isolated, but on acid hydrolysis and decarboxylation yielded a ketone, m. p. 157–158°, which did not depress the melting point of a sample obtained by heating Va. The dinitrophenylhydrazones obtained from both samples were likewise shown to be identical.

The transformation of Va into Vc by heating may proceed by direct elimination of hydrogen chloride, or through the intermediate formation of the epoxide Vb. Evidence for the exact nature of the reaction is lacking. It is of interest in this connection that the rearrangement of phenylethylene oxide yields phenylacetaldehyde,[10] while Va is converted to the methyl ketone. These facts do not exclude a mechanism in which the epoxide is an intermediate, for this mode of rearrangement is similar to that of the epoxides of mesityl oxide and certain other α,β-unsaturated ketones which yield 1,2-diketones on heating.[11] Such a parallelism points to the analogy between Vb and the epoxide of a simple α,β-unsaturated ketone or a vinylog in which the epoxide ring is removed by the —CH=CH— grouping.

Compounds IIIa, b, c, and IVa, b, c, were tested for antimalarial activity in avian malaria, and proved to have a rather low order of activity.

TABLE I

AVIAN ANTIMALARIAL ACTIVITIES

Cpd.	Code no.	Quinine equiv. in Test D-1 (*lophurae* in the duck)
IIIa	MIT-42	Q < 1
IIIb	MIT-43	Q < 1
IIIc	MIT-44	Q 0.25
IVa	MIT-41	Q < 1
IVc	MIT-36	Q 2

(10) Breuer and Zinke, *Ber.*, **11**, 1402 (1878).

(11) Weitz and Scheffer, *ibid.*, **54**, 2344 (1921).

The activity of IVb will be reported in a forthcoming monograph prepared by the Survey of Antimalarial Drugs. Activities which were determined for the remaining compounds by Dr. E. K. Marshall, Jr., are listed in Table I.[12]

Experimental[13]

8-Hydroxy-2-phenylcinchoninic Acid.—This acid was prepared from *o*-aminophenol, benzaldehyde and pyruvic acid by the method of Döbner and Fettback[4] in yields of about 20%. An analytical sample was purified by crystallization from acetic acid and from dilute acetone and melted at 251–252°.

Anal. Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.5; H, 4.50; N, 5.29.

The ethyl ester was prepared as a derivative by refluxing the acid with ethanol and sulfuric acid. After recrystallization from ether–petroleum ether it melted at 87.5–88°.

Anal. Calcd. for $C_{18}H_{15}O_3N$: C, 73.71; H, 5.16; N, 4.78. Found: C, 73.66; H, 5.22; N, 5.04.

8-Acetoxy-2-phenylcinchoninic Acid.—A solution of 54.0 g. of 8-hydroxy-2-phenylcinchoninic acid in 150 ml. of acetic anhydride and 150 ml. of pyridine was allowed to stand at room temperature for forty-four hours. Most of the solvent was removed by concentration under reduced pressure, and the residue was treated with a large volume of ice water to decompose the remaining acetic anhydride. The crude product was separated by filtration, washed with water and crystallized from dilute dioxane; yield 54.7 g. (88%), m. p. 230–231° (dec.). An analytical sample was prepared by four recrystallizations from the same solvent; m. p. 231–231.5° (dec.).

Anal. Calcd. for $C_{18}H_{13}O_4N$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.2; H, 4.43; N, 4.75.

The methyl ester was prepared by treatment with diazomethane and recrystallized four times from methylene chloride–cyclohexane; m. p. 138–139°.

Anal. Calcd. for $C_{19}H_{15}O_4N$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.1; H, 4.62; N, 4.36.

Diazomethyl (8-Acetoxy-2-phenyl-4-quinolyl) Ketone.—A suspension of 77.0 g. (0.250 mole) of 8-acetoxy-2-phenylcinchoninic acid in 400 ml. of dry benzene and 60 ml. (an excess) of redistilled thionyl chloride was refluxed on the steam-bath for three hours, after which time solution was complete. The solvent was removed under reduced pressure, and the residue was concentrated four times, after adding dry benzene, to remove the last traces of thionyl chloride. The residual acid chloride was dissolved in 1500 ml. of dry benzene, cooled and added slowly with cooling in ice to 2330 ml. of an anhydrous ether solution[7] containing 0.56 mole (2.2 molar equivalents) of diazomethane. The solid product began to separate before the addition was completed. After standing overnight at 5° the benzene and ether were removed under reduced pressure and the residue was washed onto a filter with dry ether. The yield of the crude diazomethyl ketone, m. p. 163–165° (dec.) was 79.5 g. (96%). This material was used without further purification. An analytical sample was purified by four recrystallizations from methylene chloride–petroleum ether; m. p. 167–168° (dec.).

Anal. Calcd. for $C_{19}H_{13}O_3N_3$: C, 68.88; H, 3.95; N, 12.7. Found: C, 68.38; H, 4.03; N, 12.7.

Chloromethyl (8-Acetoxy-2-phenyl-4-quinolyl) Ketone.—The crude diazomethyl ketone described above (35.0 g., 0.105 mole) was dissolved in 1 liter of methylene chloride and 300 ml. of dry ether (added to increase solubility of hydrogen chloride in the reaction mixture). An excess of a saturated solution of hydrogen chloride in ether was added slowly with cooling. Nitrogen was evolved immediately,

(12) These results were obtained too late for inclusion in the monograph mentioned above and in footnote 3, and are cited in this paper at Dr. Marshall's suggestion.

(13) All melting points are corrected.

and the reaction was allowed to proceed at room temperature for four hours. Acetyl chloride (30 ml.) was then added to reacetylate any 8-hydroxy derivative which might have been formed from traces of water, and the mixture was allowed to stand overnight at room temperature. The solvent was removed under reduced pressure, and the residue was concentrated twice with dry benzene to remove any remaining acetyl chloride. The residue of the chloromethyl ketone was crystallized from chloroform–cyclohexane; yield 31 g. (87%), m. p. 187.5–188°. An analytical sample recrystallized four times from the same solvent melted at 188–188.5°.

Anal. Calcd. for $C_{19}H_{14}O_3NCl$: C, 67.16; H, 4.15; N, 4.12; Cl, 10.4. Found: C, 67.24; H, 4.18; N, 4.01; Cl, 10.6.

A small sample was converted to chloromethyl (8-hydroxy-2-phenyl-4-quinolyl) ketone by adding a few drops of acetyl chloride to a solution in equal parts of chloroform and ethanol.[14] The solution was allowed to stand overnight, and the product recrystallized several times from 95% ethanol; m. p. 138–139°.

Anal. Calcd. for $C_{17}H_{12}O_2NCl$: C, 68.56; H, 4.06; N, 4.70; Cl, 11.9. Found: C, 68.70; H, 4.20; N, 4.77; Cl, 11.9.

α-(Chloromethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol.—Chloromethyl (8-acetoxy-2-phenyl-4-quinolyl) ketone (15.0 g., 0.0442 mole) was suspended in 300 ml. of dry isopropyl alcohol, to which was added 66 ml. of 0.9 molar aluminum isopropoxide (1.34 molar equivalents) in *i*-propyl alcohol. The mixture was slowly distilled through a 38-cm. Vigreux column. About five minutes after distillation began the bright orange color of the supernatant liquid faded and the solid became light yellow and granular. Negative tests for acetone in the distillate were obtained after thirty minutes, and slow distillation was continued for a total period of one and one-half hours. Most of the solvent was removed under reduced pressure, and the residue was taken up in 300 ml. of water containing 20 ml. of concentrated hydrochloric acid. A small amount of alcohol was added, and the resulting clear yellow solution was refluxed for one and one-half hours to complete hydrolysis of the acetoxy group. The solution was made alkaline by adding dilute sodium bicarbonate solution, and the resulting suspension was extracted with chloroform until the extracts were colorless. The extracts were combined, washed with water and saturated sodium chloride solution, filtered through anhydrous sodium sulfate, and concentrated to a small volume. Cyclohexane was added to incipient turbidity, and on cooling the product separated as tan leaves; yield 12.0 g. (91%), m. p. 134.5–135.5°. An analytical sample was recrystallized from benzene; m. p. 138.5–139°.

Anal. Calcd. for $C_{17}H_{14}O_2NCl$: C, 68.11; H, 4.71; N, 4.67; Cl, 11.8. Found: C, 68.19; H, 4.76; N, 4.65; Cl, 11.9.

α-(Diethylaminomethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol (IVa, MIT-41).—A mixture of 3.20 g. of the above chlorohydrin and 25 ml. of diethylamine was sealed in a bomb tube and shaken in an electrically heated jacket at 110° overnight. The dark reaction mixture was diluted with ether and filtered to remove the diethylamine hydrochloride which separated. The filtrate was concentrated to dryness under reduced pressure and the residue was concentrated twice with benzene to remove any remaining diethylamine. The resulting dark oil was dissolved in methanol, acidified by addition of methanolic hydrogen chloride, and diluted with dry ether. The yellow solvated hydrochloride was treated with Darco (decolorizing charcoal), recrystallized from methanol–ether, and converted to the free base by shaking with ether and a dilute solution of sodium bicarbonate. The ether solution was washed with saturated sodium chloride solution, filtered through anhydrous sodium sulfate, concentrated to a small volume and diluted with petroleum ether. The product (1.60 g., 45%) separated as colorless prisms, m. p. 122–123°. An analytical sample purified by several recrystallizations from ether–petroleum ether and from methanol melted at 123–123.5°.

Anal. Calcd. for $C_{21}H_{24}O_2N_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.23; H, 7.39; N, 8.17.

α-(Di-*n*-butylaminomethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol (IVb, SN-15,214).—A mixture of 25.0 g. of α-(chloromethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol and 50 ml. of di-*n*-butylamine was heated for three and one-half hours in a loosely stoppered flask in an oil-bath maintained at 125–130°. Dibutylamine hydrochloride separated during the period of heating. The reaction mixture was cooled, diluted with ether, filtered to remove dibutylamine hydrochloride, and steam distilled until the odor of dibutylamine disappeared (about one hour). The dark oily residue was taken up in ether, washed and converted into the hydrochloride in the same manner as IVa. The hydrochloride separated as dark yellow crystals which became bright yellow after treatment with Darco and two recrystallizations from methanol–ether. The hydrochloride was converted to the base in the same manner as IVa. Crystallization from petroleum ether gave 16.0 g. (49%) of IVb, m. p. 80–81°. Several recrystallizations from petroleum ether gave an analytical sample as white prisms, m. p. 81.5–82.5°.

Anal. Calcd. for $C_{25}H_{32}O_2N_2$: C, 76.49; H, 8.22; N, 7.14. Found: C, 76.8; H, 8.30; N, 6.98.

A sample of the base IVb on treatment with an excess of methanolic hydrogen chloride gave the monohydrochloride, which crystallized from methanol–ether as a light yellow solvate of undetermined composition. The hydrochloride was purified by recrystallization from this solvent to constant melting point, determined after removal of the solvent of crystallization. After drying at 100° and 0.1 mm. for twenty-four hours the hydrochloride was white and melted at 169–170°.

Anal. Calcd. for $C_{25}H_{32}O_2N_2 \cdot HCl$: C, 69.99; H, 7.93; N, 6.53; Cl, 8.27. Found: C, 70.1; H, 7.90; N, 6.48; Cl, 8.37.

α-(Di-*n*-hexylaminomethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol Hydrochloride (IVc, MIT-36).—IVc was prepared by a procedure similar to the one described for IVb from 10.0 g. of α-(chloromethyl)-8-hydroxy-2-phenyl-4-quinolinemethanol and 30 ml. of di-*n*-hexylamine. In purification of the product, the excess dihexylamine was removed by steam distillation for three hours and IVc was isolated by crystallization from methanol–ether as a yellow solvated monohydrochloride. Drying at 100° and 0.1 mm. overnight gave 7.2 g. (44%) of a white monohydrochloride, m. p. 170–171° (dec.). Four recrystallizations from methanol–ether followed by drying at 100° and 0.1 mm. until the yellow solvate had changed completely to white IVc monohydrochloride gave an analytical sample of constant m. p., 172–173° (dec.).

Anal. Calcd. for $C_{29}H_{40}O_2N_2 \cdot HCl$: C, 71.80; H, 8.52; N, 5.78; Cl, 7.31. Found: C, 71.84; H, 8.45; N, 5.81; Cl, 7.38.

Ethyl 8-Amino-2-phenylcinchoninate.—A solution of 2.0 g. of 8-hydroxy-2-phenylcinchoninic acid in 24 g. of concentrated aqueous ammonia into which 5 g. of sulfur dioxide had been introduced was sealed in a bomb tube and shaken in an electrically heated jacket at 165° for twenty-four hours. The reaction mixture was diluted with water and neutralized with dilute hydrochloric acid. The crude product was collected on a filter, dried, and refluxed with 30 ml. of ethanol and 2 ml. of concentrated sulfuric acid for one hour. This solution was made alkaline with potassium carbonate, extracted with ether, and the ether solution was washed with sodium hydroxide to remove phenolic compounds. The ester was isolated by drying the ether solution over sodium sulfate, removing the solvent, and crystallizing the bright orange product from petroleum ether. The yield was 1.5 g. (68%), m. p. 68–69°. An analytical

(14) The use of acetyl chloride and alcohol for the generation of hydrogen chloride has been described by Freudenberg and Jakob, *Ber.*, **74B**, 1001 (1941). *trans*-Esterification in chloroform–ethanol was used because of the insolubility of the starting material.

sample was purified by three crystallizations from ether–petroleum ether; m. p. 69.5–70°.

Anal. Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.95; H, 5.52; N, 9.59. Found: C, 73.58; H, 5.60; N, 9.45.

After standing five months the ester had changed to a higher melting dimorphous form, m. p. 96–97°. Recrystallization from ether–petroleum ether gave the form with m. p. 69.5–70°, which had a mixed m. p. with the high melting dimorph of 96–97°. Recrystallization by seeding with the high melting form gave the high melting dimorph directly. This ester has been prepared by Buchman, McCloskey and Seneker[9] on a larger scale from ethyl 8-nitro-2-phenylcinchoninate. Properties of the ester prepared by the two routes are in good agreement.

Application of the Bucherer Reaction to IIIb.—IIIb (approximately 2 g.) was treated with ammonium hydroxide into which sulfur dioxide had been introduced and with 4-diethylamino-1-methylbutylamine (noval diamine) in the presence of sulfur dioxide under conditions employed by others with 8-hydroxyquinoline derivatives.[6] Under these conditions at 100–165° (usually in sealed tube reactions with shaking) and also in aqueous dioxane, phenol and alcohol (added to increase the solubility of IIIb) the only product isolated was recovered IIIb. Decomposition was more extensive and recovery of IIIb was poorer at the higher temperatures. In some instances the odor of dibutylamine was noted in the reaction mixtures, indicating partial cleavage of the side chain.

8-Nitro-2-phenylcinchoninic Acid.—This acid was prepared from ethyl 8-nitro-2-phenylcinchoninate, m. p. 140–142°, which was synthesized by the method of Buchman, McCloskey and Seneker.[9]

The ester (88.0 g.) was dissolved in a mixture of 500 ml. of glacial acetic acid, 100 ml. of water, and 200 ml. of concd. hydrochloric acid. The mixture was refluxed for sixteen hours, during which time some product separated. The remainder of the acid was precipitated by adding a large volume of water, and the product was crystallized from dioxane–water; yield 78.2 g. (97%), m. p. 275–276° (dec.). An analytical sample was prepared by five recrystallizations from the same solvent; m. p. 277.5–278° (dec.).

Anal. Calcd. for $C_{16}H_{10}O_4N_2$: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.26; H, 3.51; N, 9.66.

Diazomethyl (8-Nitro-2-phenyl-4-quinolyl) Ketone.—8-Nitro-2-phenylcinchoninic acid (57.0 g.) was converted to the acid chloride and diazoketone by the method described above for 8-acetoxy-2-phenylcinchoninic acid. Drying of the diazomethane solution with sodium was found to be unnecessary, and a solution containing 2.1 molar equivalents of diazomethane dried for three hours over potassium hydroxide was used in this case. After standing overnight at 5° the product was filtered and washed with ether; yield 53.0 g., m. p. 163–164° (dec.). An additional 6.4 g., m. p. 158–161° (dec.), was obtained by concentrating the mother liquor, making the total yield of crude product 59.4 g. (96%). An analytical sample was obtained by several crystallizations from methylene chloride–petroleum ether; m. p. 167–168° (dec.).

Anal. Calcd. for $C_{17}H_{10}O_3N_4$: C, 64.15; H, 3.17; N, 17.6. Found: C, 64.02; H, 3.21; N, 17.6.

Chloromethyl-(8-nitro-2-phenyl-4-quinolyl) Ketone.—A solution of 58.0 g. of the crude diazomethyl ketone described above in 1200 ml. of methylene chloride and 600 ml. of dry ether was cooled in ice, and a saturated solution of hydrogen chloride in dry ether was added until the mixture was acid to litmus. After standing overnight at room temperature the solvents were removed under diminished pressure. The residue was crystallized from chloroform after treatment with Darco, yielding 46.2 g. of the chloromethyl ketone, m. p. 184–186°. An additional 9.4 g., m. p. 183–185°, was obtained as a second crop, making the total yield of crude product 55.6 g. (94%). Four recrystallizations from benzene gave the analytical sample as yellow needles melting at 187–187.5°.

Anal. Calcd. for $C_{17}H_{11}O_3N_2Cl$: C, 62.49; H, 3.39; N, 8.58; Cl, 10.9. Found: C, 62.74; H, 3.53; N, 8.73; Cl, 10.7.

α-(Chloromethyl)-8-nitro-2-phenyl-4-quinolinemethanol.—A solution of 40.0 g. (0.123 mole) of the above chloromethyl ketone in 800 ml. of dry *i*-propyl alcohol was treated with 150 ml. of 0.9 molar aluminum *i*-propoxide (1.1 molar equivalents), and the mixture was distilled slowly through a 38-cm. Vigreux column for thirty minutes after negative tests for acetone were obtained on the distillate (total heating time one and one-half hours). After removing the remainder of the *i*-propyl alcohol under reduced pressure, the residue was taken up in cold chloroform and dilute hydrochloric acid. The layers were separated and the chloroform solution washed with water and dilute sodium bicarbonate solution. After drying over magnesium sulfate, the solution was concentrated under reduced pressure and diluted with petroleum ether. The yellow product weighed 30.5 g. and melted at 117–118° (dec.). By further dilution of the mother liquor with petroleum ether an additional 5.8 g. of the chlorohydrin was obtained, m. p. 117–119° (dec.), making the total crude yield 36.3 g. (90%). An analytical sample, purified by several recrystallizations from chloroform–petroleum ether, melted at 118–118.5° with loss of hydrogen chloride, solidified and remelted at 157–158°.

Anal. Calcd. for $C_{17}H_{13}O_3N_2Cl$: C, 62.11; H, 3.99; N, 8.52; Cl, 10.8. Found: C, 61.92; H, 4.17; N, 8.57; Cl, 10.8.

Methyl (8-Nitro-2-phenyl-4-quinolyl) Ketone (Vc).—In one preparation of the above chlorohydrin (Va) the chloroform solution was heated during concentration. Considerable hydrogen chloride was lost and the crude product was dark and melted at 140–150°. Sublimation of this material at a bath temperature of 190° and 0.8 mm. pressure gave yellow needles of Vc which were recrystallized from chloroform–petroleum ether; m. p. 157–157.5°.

Anal. Calcd. for $C_{17}H_{12}O_3N_2$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.81; H, 4.20; N, 9.67.

A mixed melting point with the product obtained by melting the chlorohydrin showed no depression. The compound gave the iodoform test and was not oxidized by potassium permanganate in acetone (negative tests for the aldehyde formula Vd). It did not react with hydrogen chloride in chloroform at room temperature or at the boiling point, or with diethylamine on heating for fifteen hours at 120° in a sealed tube (negative tests for the epoxide structure Vb). Some decomposition occurred in the latter reaction, and only the starting material could be isolated. The compound did give a 2,4-dinitrophenylhydrazone derivative, m. p. and mixed m. p. with a known sample described below 278–279° (dec.).

An authentic sample of Vc was prepared by adding the acid chloride obtained from 5 millimoles of 8-nitro-2-phenylcinchoninic acid to the enolate prepared from 5.4 millimoles of sodium and a 20% excess of ethyl malonate in xylene. The mixture was refluxed for two hours, filtered, and concentrated. The residue was hydrolyzed and decarboxylated by heating on the steam-bath for one hour with 24 ml. of sulfuric acid and 8 ml. of water. The product which separated on pouring the acid into a large volume of water was purified by washing with alkali and recrystallization from chloroform–petroleum ether; m. p. and mixed m. p. with the material described above which was obtained from Va, 157–158°.

The 2,4-dinitrophenylhydrazone, recrystallized from chloroform, melted at 278–279° (dec.).

Anal. Calcd. for $C_{23}H_{16}O_8N_6$: C, 58.47; H, 3.42; N, 17.8. Found: C, 58.46; H, 3.48; N, 17.8.

Methyl (8-Amino-2-phenyl-4-quinolyl) Ketone.—This compound was prepared as a derivative by hydrogenation of a small sample of Vc (prepared by heating Va) in ethyl acetate solution in the presence of palladinized charcoal. Three molar equivalents of hydrogen were absorbed and the product, recrystallized from ether–petroleum ether, melted at 103–103.5°.

Anal. Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.7. Found: C, 77.58; H, 5.61; N, 10.6.

A sample of the same compound was prepared by

hydrogenation of chloromethyl (8-nitro-2-phenyl-4-quinolyl) ketone. Four molar equivalents of hydrogen were absorbed under the same conditions, and the product was proved to be identical with the above sample by melting point and mixed melting point.

α-(Diethylaminomethyl)-8-nitro-2-phenyl-4-quinolinemethanol.—A mixture of 10.0 g. of α-(chloromethyl)-8-nitro-2-phenyl-4-quinolinemethanol and 80 ml. of diethylamine was heated at 110° in a sealed tube for eleven hours. The mixture was diluted with warm benzene and filtered to remove diethylamine hydrochloride, after which the filtrate was concentrated to dryness under reduced pressure. After taking to dryness twice with benzene under reduced pressure to remove any remaining diethylamine, two crystallizations from benzene following treatment with Darco gave 5.50 g. (49%) of a nearly white crystalline product, m. p. 166–167°. An analytical sample was prepared by four recrystallizations from benzene; m. p. 168.5–169.5°.

Anal. Calcd. for $C_{21}H_{23}O_3N_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.29; H, 6.55; N, 11.44.

α-(Diethylaminomethyl)-8-amino-2-phenyl-4-quinolinemethanol (IIIa, MIT-42).—The above nitro compound (4.10 g.) in 40 ml of methanol was hydrogenated in the presence of 0.3 g. of pre-reduced platinum oxide catalyst at room temperature. Ninety-three per cent. of the theoretical amount of hydrogen was absorbed in one hour. Ether was added to dissolve the part of the product which had separated. After filtration to remove the catalyst, the filtrate was concentrated, cooled, and the solid product collected on a filter. After recrystallization from ether–petroleum ether IVa was obtained as 3.00 g. of light yellow crystals, m. p. 122–124°. A second crop of 0.37 g., m. p. 121–123°, made the total crude yield 88%. An analytical sample was recrystallized four times from ether–petroleum ether; m. p. 129.5–130°.

Anal. Calcd. for $C_{21}H_{25}ON_3$: C, 75.19; H, 7.51; N, 12.5. Found: C, 75.20; H, 7.40; N, 12.5.

The base IVa was converted to the dihydrochloride by dissolving 2.0 g. in 20 ml. of 1.44 *N* methanolic hydrogen chloride. The salt which separated on dilution with ether was recrystallized from methanol–ether; yield 2.3 g., m. p. 202–203° (dec.). The analytical sample was recrystallized three times from methanol–ether; m. p. 203–204° (dec.).

Anal. Calcd. for $C_{21}H_{25}ON_3.2HCl$: C, 61.76; H, 6.67; N, 10.3; Cl, 17.4. Found: C, 61.50; H, 6.98; N, 10.2; Cl, 17.5.

α-(Di-*n*-butylaminomethyl)-8-nitro-2-phenyl-4-quinolinemethanol.—A mixture of 4.50 g. of α-(chloromethyl)-8-nitro-2-phenyl-4-quinolinemethanol and 30 ml. of di-*n*-butylamine was heated at 120° for six hours and the product was isolated by a procedure similar to the one described for IVb. The dried ether solution of the product from which dibutylamine had been removed was evaporated to dryness and the tarry residue which was obtained was triturated several times with hot petroleum ether (b. p. 58–86°). The light yellow extracts were combined and concentrated. The crude product so obtained (m. p. 103–105°) was recrystallized twice from methanol, yielding 2.52 g. (43%) of an almost white product, m. p. 109.5–111°. An analytical sample recrystallized five times from methanol melted at 112–112.5°.

Anal. Calcd. for $C_{25}H_{31}O_3N_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.23; H, 7.40; N, 9.97.

α-(Di-*n*-butylaminomethyl)-8-amino-2-phenyl-4-quinolinemethanol (IIIb, MIT-43).—IIIb was prepared in the same manner as IIIa by hydrogenation of 2.14 g. of the above nitro compound, which was complete in twenty minutes. The product was crystallized from petroleum ether as light yellow prisms in two crops, 1.70 g., m. p. 72–73.5°, and 0.14 g., m. p. 70–72°, corresponding to a total crude yield of 93%. An analytical sample was purified by four recrystallizations from petroleum ether; m. p. 74.5–75°.

Anal. Calcd. for $C_{25}H_{33}ON_3$: C, 76.69; H, 8.50; N, 10.7. Found: C, 77.03; H, 8.53; N, 10.7.

IIIb (2.0 g.) was converted to the dihydrochloride (in the same manner as IIIa), which was recrystallized to constant melting point from methanol–ether; yield 2.2 g. of a white product, m. p. 169–170° (dec.), with sintering beginning at 165°.

Anal. Calcd. for $C_{25}H_{33}ON_3.2HCl$: C, 64.64; H, 7.60; N, 9.05; Cl, 15.3. Found: C, 64.82; H, 7.72; N, 9.21; Cl, 15.4.

α-(Di-*n*-hexylaminomethyl)-8-nitro-2-phenyl-4-quinolinemethanol.—This compound was prepared by heating 10.0 g. of the chlorohydrin and 40 ml. of di-*n*-hexylamine in a bath at 130–135° for four and one-half hours, and purified in the same manner as the di-*n*-butylamino analog. Evaporation of the hot petroleum ether extracts of the crude product gave a red oil which was crystallized from methanol and methanol–water. The yield of a light tan product, m. p. 75–76°, was 2.24 g. (15%). An analytical sample after several recrystallizations from dilute methanol melted at 77–78°.

Anal. Calcd. for $C_{29}H_{39}O_3N_3$: C, 72.92; H, 8.23; N, 8.80. Found: C, 72.92; H, 8.41; N, 9.03.

α-(Di-*n*-hexylaminomethyl)-8-amino-2-phenyl-4-quinolinemethanol Dihydrochloride (IIIc, MIT-44).—The above nitro compound (2.00 g.) in 25 ml. of 95% ethanol was completely hydrogenated in ten minutes in the presence of 0.2 g. of pre-reduced platinum oxide catalyst. After removal of the catalyst by filtration the solvent was removed under reduced pressure and the residue was taken up in a small volume of methanol. Methanolic hydrogen chloride (12 ml. of a 1.44 *N* solution) was added, followed by addition of ether to incipient turbidity. The white dihydrochloride which separated was recrystallized from methanol–ether; yield 1.92 g. (88%), m. p. 179–180°. A sample which was recrystallized four times from methanol–ether melted at 180.5–181° (dec.).

Anal. Calcd. for $C_{29}H_{41}ON_3.2HCl$: C, 66.91; H, 8.33; N, 8.07; Cl, 13.6. Found: C, 66.87; H, 8.46; N, 8.24; Cl, 13.5.

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Summary

Synthetic methods are described by which three α - (dialkylaminomethyl) - 8 - amino - 2 - phenyl - 4-quinolinemethanols (formula III) and corresponding 8-hydroxy compounds (formula IV) were prepared for testing for antimalarial activity.

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