densed with 6-methoxy-8-aminoquinoline (Winthrop Chemical Company material further purified by one recrystallization from methanol) and with 5,6-dimethoxy-8-aminoquinoline,[12] according to Procedure B of Elderfield and co-workers.[13] Heating the reaction mixture after removal of the excess 8-aminoquinoline was dispensed with. The free bases, after two distillations under nitrogen, were converted to the oxalates.[13] In Table I are given the pertinent physical constants of the drugs. The numbers prefixed CN refer to numbers assigned to the drugs in this Laboratory. In Table II are given the elementary analyses of the oxalates and the homogeneity of the drug bases determined by the method of Craig,[14] using a chloroform citrate buffer system (*p*H 3.70) and a concentration of drug base of 0.5 mg. per ml.

The antimalarial activities also given in Table II are against *P. lophurae* in the duck.[15] The tests used, D-1 and G-5, are the standardized tests described elsewhere.[2] For comparison, data on Pamaquine are also included in Table II. Activities are expressed in terms of quinine as unity. Results of toxicity studies on the drugs will be reported elsewhere.

(12) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(13) Elderfield, *et al.*, *ibid.*, **68**, 1521 (1946).

(14) Craig, *et al*, *J. Biol. Chem.*, **161**, 321 (1945).

Summary

1. Syntheses of five derivatives of 8-aminoquinoline containing 5-alkylamino-1-methylpentylamino side chains have been described.

2. Antimalarial activities of the drugs against avian malaria are given.

(15) We are indebted to Drs. Arthur P. Richardson, of the Squibb Institute for Medical Research, and E. K. Marshall, Jr., of Johns Hopkins University, for permission to incorporate their screening test data in this paper.

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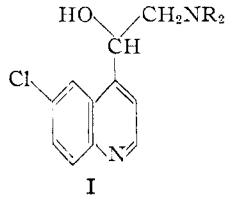
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. 6- and 7-Chloro-α-(dialkylaminomethyl)-4-quinolinemethanols[1]

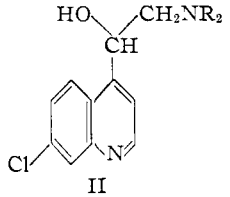
BY ROBERT E. LUTZ, JOHN F. CODINGTON[2a] AND NORMAN H. LEAKE[2b]

In an extension of the work on the quinoline 4-(β-*t*-amino alcohols)[3] three higher homologs of the 6-chloro-α-dialkylaminomethyl-4-quinolinemethanols (Ia,b,c) and the dioctylamino compound in the 7-chloroquinoline series (IIb) were synthesized for the purpose of antimalarial tests. This work was done in connection with the program of exploration of the activating effect of a chlorine atom at the various nuclear positions. The choice of homologs of relatively high molecular weight was made with the expectation of striking close to the highest antimalarial activity of which these particular series are capable.[4]



I

(a) R = hexyl
(b) R = octyl
(c) R = decyl
(d) NR_2 = morpholino



II

(a) R = hexyl
(b) R = octyl

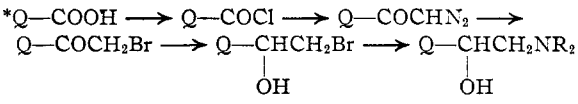
(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

(2) Present location: (a) National Institute of Health, Bethesda, Md.; (b) Rohm and Haas Co., Phila., Pa.

(3) (a) King and Work, *J. Chem. Soc.*, 1307 (1940); (b) the lower members of the 6-chloro series were made by Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946); for the α-(2-piperidyl)-methyl-4-quinolinemethanols see (c) Ainley and King, *Proc. Roy. Soc. (London)*, **125B**, 60 (1938); (d) Buchman, Sargent, Myers and Seneker, THIS JOURNAL, **68**, 2692 (1946); and (e) Senear, Sargent, Mead and Koepfli, *ibid.*, **68**, 2695 (1946).

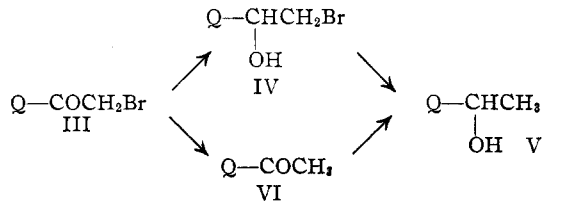
(4) *Cf.* (a) May and Mosettig, *J. Org. Chem.*, **11**, 1 (1946); Lutz, *et al.*, (b) THIS JOURNAL, **68**, 1813 (1946); (c) *J. Org. Chem.*, in press; (d) F. Y. Wiselogle, A Survey of "Antimalarial Drugs, 1941–1945." J. W. Edwards (1947).

The preparation of 6-chlorocinchoninic acid which was necessary in the making of the first of these series (I), followed the Halberkann[5] and Pfitzinger[5] procedures through 5-chloroisatin and 6-chloroquinoline-2,4-dicarboxylic acid; and the conversion of this to the amino alcohols was by way of the acid chloride through diazomethylation, hydrobromination, aluminum isopropoxide reduction and condensation with the appropriate amine, following the now well established procedures.[6]



* Q = 6-chloro-4-quinolyl-.

One point of particular interest in this synthesis was the ease of over-reduction of the bromoketone (III) to the secondary alcohol (V).



The elimination of the bromine in this reaction did not occur as the first step[7,8]; the bromohydrin (IV) is first formed in the reduction and can be isolated in good yield under identical reaction con-

(5) (a) Halberkann, *Ber.*, **54**, 3090 (1921); (b) *Cf.* Ref. 3e; (c) Pfitzinger, *J. prakt. Chem.*, **38**, 583 (1888).

(6) *Cf.* ref. 3 and 4; and especially see ref. 4b and references cited therein.

(7) *Cf.* Stevens, Allenby and DuBois, THIS JOURNAL, **62**, 1424 (1940).

(8) "Organic Reactions," Vol. II, Wiley and Sons, Inc., New York, N. Y., 1944, p. 193.

ditions upon a much shorter period of heating. That the over-reduction product was the secondary alcohol (V) and not the primary alcohol (Q—CH_2CH_2OH) was shown by its identity with the product of the unequivocal two-step conversion of the bromoketone by stannous chloride or palladium–catalyzed reduction to the acetylquinoline (VI) followed by aluminum isopropoxide reduction. Because of the inconclusiveness of mixture melting points, the identity of the several samples of this alcohol, in the form of the hydrochlorides, was established with certainty by the determination and comparison of their X-ray powder diffraction patterns.[9]

The course of the over-reduction of the bromoketone here is to be contrasted with the quite different results reported in the over-reduction of α-bromopropiophenone[7] which proceeds through the bromohydrin and the oxide to the alcohol, $C_6H_5CH_2CHOHCH_3$, and of α-naphthyl bromomethyl ketone[10] where the reaction appears to have given the primary rather than the secondary alcohol, namely, β-(α-naphthyl)-ethanol, $ArCH_2CH_2OH$.

The synthesis of the 7-chloroquinoline amino alcohol (IIb) was made in the same way as the 6-chloro compounds; the tendency toward over-reduction of the bromoketone in this series was still more pronounced.

The 6-chloroquinoline 4-(amino alcohols) have proved to be moderately active against avian malaria. As was expected the increase in size of the N-alkyl groups progressively raised the activity against lophurae in the duck[11]; the dibutylamino compound had been reported as inactive[3b,4d]; the dihexylamino compound (Ia) showed a quinine equivalent of 0.3, the dioctylamino (Ib), 0.6, and the didecylamino (Ic), 0.7.[12] The α-dioctylaminomethyl-7-chloro-4-quinolinemethanol (IIb) proved to be of even greater interest, with an antimalarial activity equal to that of quinine.[11]

Experimental[13,14]

4-Chloroisonitrosoacetanilide and 5-chloroisatin were prepared in 93 and 95% yields, respectively, by applying the "Organic Syntheses" procedures for isonitrosoacetanilide and for isatin itself.[15]

6-Chloroquinoline-2,4-dicarboxylic acid was made by an adaption of the method of Halberkann[5a] and of Senear, Sargent, Mead and Koepfli,[3e] and was prepared originally by Work.[16]

A suspension of 100 g. of 5-chloroisatin in 2.75 kg. of 30% potassium hydroxide was heated at 95° until the purple color disappeared. After cooling to 20°, treating with 172 ml. of 58% pyruvic acid and heating at 100° for three hours, the resulting brown semi-solid mass was dissolved in 5 liters of water and filtered from insoluble material. Acidification gave 108 g. (78%); m. p. 255–257° (Work,[16] 250°).

6-Chloroquinoline-4-carboxylic acid has been obtained by decarboxylating the 2,4-dicarboxylic acid in nitrobenzene.[3b,3e,16] The method proved only moderately successful because of extensive decomposition and difficulty in filtration. The use of Dowtherm (diphenyl–diphenyl ether) proved to be superior. A suspension of 108 g. of the dicarboxylic acid in 450 ml. of Dowtherm was heated with vigorous stirring at 205–210° for 1.3 hours (decarboxylation began at 195°); it was then cooled and filtered; the product was slurried with ether and again filtered; 79 g. (89%); m. p. 294–296° dec. (Work,[16] 302°). The over-all yield at this point, from *p*-chloroaniline, was 60.6%.

The **acid chloride hydrochloride** was made[17] by treating 32 g. of the acid with 160 ml. of thionyl chloride (mild reaction), refluxing for three hours (solution was complete in forty minutes) and distillation of the excess reagent under reduced pressure. The residual solid mass was broken up and washed with ether; yield 35.8 g. (88%); m. p. 170–178°. A sample of purified product sublimed at 184°.

The **ethyl ester**[3b] was made from the acid chloride hydrochloride by reaction with ethanol, treatment with decolorizing carbon (Darco) while still in solution, and then treatment of the isolated salt (m. p. 171–177°) with a weakly basic solution; recrystallization of the compound from 60% ethanol gave long white needles; m. p. 67–68° (Campbell and Kerwin,[3b] 68–69°).

6-Chloro-4-quinolyl Diazomethyl Ketone.—Using the King and Work method[3a] 35.8 g. of the acid chloride was added over a period of forty minutes to an ether solution of an excess of diazomethane (made from 110 g. of nitrosomethyl urea[6]). After standing for ten hours the red solution was filtered and used directly.

Bromomethyl 6-chloro-4-quinolyl ketone (III) hydrobromide[3b] was made from the above solution of the diazomethyl ketone (cooled to 0°) by addition of a mixture of 85 ml. of 48% hydrobromic acid (aqueous) and 85 ml. of dry ether (stirring) and, after one hour, filtering and washing the product thoroughly with absolute ether. The product was purified by digesting with concd. acetic acid for one hour, filtering and washing with ether; yield 34.4 g. (69% from the acid chloride); m. p. 209–215° dec. Recrystallization (including a treatment with Darco) gave the m. p. 224–227° (Campbell and Kerwin,[3b] 228–230°).

Anal. Calcd. for $C_{11}H_{17}BrClNO \cdot HBr$: N, 3.83. Found: N, 4.00.

The **hydrochloride** was made for comparison with the bromohydrin hydrochloride; this was needed because of the difficulties encountered in reduction and the necessity for identifying the products. It was made in ether and crystallized from absolute ethanol with Norit treatment; yellow crystals, m. p. 205–210° dec. (*in vacuo*).

α-Bromomethyl-6-chloro-4-quinolinemethanol (IV) Hydrochloride.—A mixture of 34.4 g. (0.094 mole) of the bromoketone hydrobromide and 373 ml. of 1.05 *N* aluminum isopropoxide was stirred mechanically, heated rapidly over five minutes to boiling, refluxed for twelve minutes, and then cooled. The solvent was evaporated under reduced pressure, the mixture temperature never being allowed to exceed 30°. The residue was hydrolyzed by 51 ml. of 7.8 *N* hydrochloric acid. Upon shaking for six hours, filtering, washing with absolute ether and recrystallizing from absolute ethanol, 21.3 g. of crude hydrochloride was obtained. Recrystallization (with Darco treatment) gave several crops totaling 16.9 g. (55.6%). Repeated recrystallizations from absolute ethanol brought the melting point to 254–260° dec. (*in vacuo*).

Anal. Calcd. for $C_{11}H_9BrClNO \cdot HCl$: N, 4.34. Found: N, 4.23.

(9) This identification was made by Mr. William White at the National Institute of Health.

(10) Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946).

(11) The D-1 tests; carried out at the Johns Hopkins School of Medicine under the direction of Dr. E. K. Marshall, Jr. (*cf.* ref. 4d).

(12) The G-5 test, carried out at the Squibb Institute for Medical Research under the direction of Dr. R. P. Richardson (*cf.* ref. 4d).

(13) The melting points reported herein are corrected.

(14) Microanalyses were by Mrs. Joyce B. Caliga.

(15) "Organic Syntheses," Coll. Vol. I, p. 327 [*cf.* Sandmeyer, *Helv. Chim. Acta*, **2**, 238 (1919)].

(16) Work, *J. Chem. Soc.*, 426 (1942).

(17) *Cf.* Späth and Spitzer, *Ber.*, **59**, 1487 (1926); *cf.* also ref. 6.

The **free base** was liberated by aqueous 10% sodium carbonate and crystallized from ethanol. It melted at 125.5–126°, became solid at 127° and melted again at 215–230°.

Anal. Calcd. for $C_{11}H_9BrClNO$: N, 4.89. Found: N, 4.88.

Over-reduction of the Bromomethyl Ketone by Aluminum Isopropoxide.—A mixture of 21 g. (0.057 mole) of the bromoketone hydrobromide and 179 ml. of 1 *N* aluminum isopropoxide was refluxed for two and one-half hours, evaporated under reduced pressure, and hydrolyzed by 65 ml. of 6 *N* hydrochloric acid (shaking for ten hours). The resulting oil resisted attempts to crystallize it; the base was liberated by means of sodium carbonate and the ether extract was dried, cooled to 0° and acidified (to congo) with ethereal hydrogen chloride. The resulting oil finally solidified on seeding; yield 14.5 g. Recrystallization from absolute ethanol gave 7.7 g. of yellow crystals; m. p. 191–194° (*in vacuo*).

Anal. Calcd. for $C_{11}H_{10}ClNO{\cdot}HCl$: N, 5.74. Found: N, 5.94.

These properties, and the analysis, correspond to those of 6-chloro-α-methyl-4-quinolinemethanol hydrochloride (V), and a mixture melting point with an authentic sample showed no depression. However, salt mixture melting points between this and the 7-chloro analog and other related compounds did not give significant depressions.

6-Chloro-α-methyl-4-quinolinemethanol (V) Hydrochloride by Reduction of the 4-Acetylquinoline.—Reduction of 1.5 g. of the bromoketone (III) with 1.9 g. of stannous chloride dihydrate in 14 ml. of 3.4 *N* hydrochloric acid at 100° for fifteen minutes gave a solid product which was filtered and washed; yield 1.45 g. The base, liberated by means of sodium carbonate and extracted by ether, was converted to the hydrochloride by ethereal hydrogen chloride; m. p. 184–190° dec. (not further characterized). This product (0.25 g.) was reduced by 3.5 ml. of 1.2 *N* aluminum isopropoxide (refluxed one and a quarter hours) and the product was isolated and purified as above; yield 0.09 g.; m. p. 190–193° (*in vacuo*). It showed no mixture melting point depression with the above sample made directly from the bromomethyl ketone by aluminum isopropoxide over-reduction.

Anal. Calcd. for $C_{11}H_{10}ClNO{\cdot}HCl$: N, 5.74. Found: N, 5.57.

4-Acetyl-6-chloroquinoline (VI) Hydrobromide.—Hydrogenation of 0.7 g. of the bromoketone (III) by means of palladium on Norit (10% palladium) in absolute ethanol at room temperature involved absorption of one molecule, and 0.4 g. of yellow needles was isolated; m. p. 248–258°.

Anal. Calcd. for $C_{11}H_8ClNO{\cdot}HBr$: C, 46.10; H, 3.17. Found: C, 46.21; H, 3.46.

Reduction of 0.1 g. of the hydrobromide (VI) by 10 ml. of 1.8 *N* aluminum isopropoxide (one and one-half hours) (the initial yellow color disappeared after fifteen minutes) gave an oil which produced a crystalline hydrochloride from ether. This was recrystallized from absolute ethanol; yellow needles; m. p. 183–184° dec.; 200–206° *in vacuo*.

Identification of the Samples of the Hydrochloride of V (made as described above from IV and VI).—Mixture melting points (which involved no depressions) were not reliable because of the indefinite nature of and decomposition at the melting point and because of the lack of mixture melting point depressions with other related compounds. The X-ray powder diffraction patterns of these samples were therefore determined[9] and their identity will be seen from the reproductions of the photographs (below). These X-ray patterns were obtained by Mr. William White at the National Institute of Health, using the powder wedge technique in a cylindrical camera with 7.16 cm. radius exposed to radiation from a copper anode X-ray tube with a nickel-foil filter giving essentially $Cu_{K\alpha}$ radiation.

6-Chloro-α-(N-morpholinomethyl)-4-quinolinemethanol (Id) dihydrochloride was made from the bromohydrin in order to test the method and materials (condensation in refluxing xylene for fifteen hours). The oily hydrochloride which precipitated from ether was recrystallized from absolute ethanol; m. p. 166–167°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2{\cdot}2HCl$: N, 7.66. Found: N, 7.76.

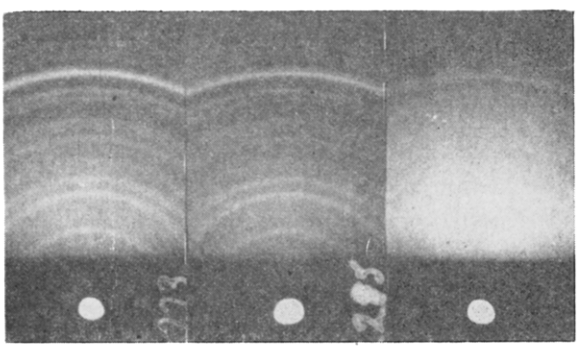
6-Chloro-α-(di-*n*-hexylaminomethyl)-4-quinolinemethanol (Ia) Dihydrochloride (SN[18]-11397).—Condensation of 14 g. (0.043 mole) of the bromohydrin hydrochloride with 40 g. (0.216 mole) of dihexylamine was carried out without solvent at 84° for eight hours (a shorter heating, one and one-half hours, gave a much poorer yield and product). Absolute ether precipitated 19.6 g. (about 93%) of dihexylamine salts. Fractional precipitation by addition of ethereal hydrogen chloride removed the excess dihexylamine; when an excess of acid had been added the product precipitated, but retained some dihexylamine hydrochloride. Conversion to the base and fractional reprecipitation removed the dihexylamine. The addition of excess ethereal hydrogen chloride gave the dihydrochloride which was purified by digesting with acetone and recrystallizing (with Darco treatment) from absolute ethanol; yield 11.5 g.; turns red suddenly at 140°, and melts at 195–201°.

Anal. Calcd. for $C_{35}H_{35}ClN_2O{\cdot}2HCl$: N, 6.04. Found: N, 6.28.

6-Chloro-α-(di-*n*-octylaminomethyl)-4-quinolinemethanol (Ib) Dihydrochloride (SN-10515).—The condensation was run under identically the above conditions with similar results, except that the separation of the excess secondary amine was effective in the first fractional precipitation. The product, however, crystallized much more slowly and required twelve hours at 0°. The crude product was washed by slurrying with acetone and filtering, and was crystallized from butanone; yield 10.6 g. (45%). Recrystallization (with Darco treatment), washing with acetone and digestion with ethyl acetate gave 7 g. of pure product; it melted partially at 127° (red), solidifying, and melted again at 180–186° dec.

Anal. Calcd. for $C_{27}H_{43}ClN_2O{\cdot}2HCl{\cdot}H_2O$: C, 60.27; H, 8.81; N, 5.21; Cl^-, 13.18. Found: C, 60.32; H, 8.62; N, 4.91; Cl^-, 13.25.

Drying *in vacuo* at 47° caused in about three hours the loss in weight corresponding to approximately one molecule of water; however, continued loss of weight upon further



Sample A Sample B Sample C

Fig. 1.—X-Ray powder diffraction patterns of three samples of 6-chloro-α-methyl-4-quinolinemethanol (V) hydrochloride: A, from over-reduction of IV; B, from III through VI by Pd-H_2 and aluminum isopropoxide reduction; C, from III through VI by $SnCl_2$ and aluminum isopropoxide reduction.

(18) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned are tabulated in the monograph.[4d]

heating under these conditions indicated the loss of some hydrogen chloride, and consequently no further attempt was made to obtain an analytically pure anhydrous form.

6-Chloro-α-(di-*n*-decylaminomethyl)-4-quinolinemethanol (Ic) Dihydrochloride (REL-604).[19]—Condensation of 5 g. of the bromohydrin hydrochloride with 23.9 g. of didecylamine was effected without solvent by heating in a boiling benzene bath for eighteen hours. The excess didecylamine was removed by fractional precipitation (*cf.* preceding experiment). The product (11.6 g.) was purified by solution in acetone, treatment with Darco and precipitation by addition of ether. Further purification was effected by repeated conversion to the free base, treatment of the ethereal solution with Darco and reprecipitation of the dihydrochloride with ethereal hydrogen chloride. The product was washed with ether and dried *in vacuo;* yield 2 g.; it darkened at 160° and melted at 181–184° dec.

Anal. Calcd. for $C_{31}H_{51}ClN_2O\cdot 2HCl\cdot H_2O$: C, 62.66; H, 9.33; N, 4.86; H_2O, 3.03. Found: C, 62.93; H, 9.18; N, 4.85; H_2O, 2.90. Dried *in vacuo* at room temperature: Calcd. for $C_{31}H_{51}ClN_2\cdot 2HCl$: C, 64.62; H, 9.27. Found: C, 64.36; H, 8.91.

3-Chloroisonitrosoacetanilide and the mixture of **4- and 6-chloroisatins** were prepared and the mixture of isatins was separated according to the directions of Senear, Sargent, Mead and Koepfli.[3e]

7-Chloroquinoline-2,4-dicarboxylic acid[3e] was obtained in 83% yield from 200 g. of 6-chloroisatin in the same manner as was the 6-chloro isomer; m. p. 286–288° [Senear, Sargent, Mead and Koepfli,[3e] 285–290°].

7-Chloroquinoline-4-carboxylic acid[3e] was obtained in 91% yield by decarboxylating the 2,4-dicarboxylic acid in Dowtherm. A suspension of 168 g. of the dicarboxylic acid was heated between 195–210° for ten minutes and then for five minutes longer at 210°. The product melted at 289–292° [Senear, Sargent, Mead and Koepfli,[3e] 290–291°].

The acid chloride hydrochloride was obtained in 94% yield from 46 g. of the acid by warming at about 80° with 100 ml. of thionyl chloride for three hours, addition of dry ether to the partially cooled solution and cooling. When heated rapidly it melted partially at 162–165°; with slower heating there was a gradual change in texture and melting occurred at 288–292°. It was not purified further.

7-Chloro-4-quinoline-carboxylic acid amide was prepared from the acid chloride by treatment with concentrated aqueous ammonia. When crystallized several times from absolute ethanol it melted at 239.5–240°.

Anal. Calcd. for $C_{10}H_7ClN_2O$: N, 13.56. Found: N, 13.10.

Bromomethyl 7-chloro-4-quinolyl ketone was prepared in the same manner as the corresponding 6-chloro isomer through the diazomethyl ketone which was not isolated. An 80% crude yield of the bromomethyl ketone hydrobromide was obtained which was purified by crystallizing from 87% formic acid; m. p. 242–243°. The free base was prepared by treating the hydrobromide with 10% sodium carbonate, extracting with ether and evaporating the ether solution. It was crystallized several times from absolute ethanol; m. p. 120° (dec.).

Anal. Calcd. for $C_{11}H_7BrClNO$: C, 46.43; H, 2.48. Found: C, 46.80; H, 2.41.

α-Bromomethyl-7-chloro-4-quinolinemethanol Hydrobromide.—It was necessary to regulate the conditions very carefully in the reduction of the bromomethyl ketone hydrobromide with aluminum isopropoxide in order to obtain adequate yields of this compound. The ketone was very sensitive toward the action of the reagent, aluminum isopropoxide, and if the reaction mixture was heated for longer than eight minutes, the yield of the bromohydrin was reduced considerably. For best results the ketone hydromide should be pure and very finely pulverized in order to facilitate solution; if it was not finely pulverized and if heating for longer than 8 min. was required in order to dissolve the hydrobromide, either negligible or very low yields were obtained. The following procedure was found to be the best of the numerous variations tried.

A hot suspension of 18 g. of finely pulverized bromomethyl ketone hydrobromide in 90 ml. of isopropanol was treated with 60 ml. of boiling 3 *N* aluminum isopropoxide and the mixture was refluxed for seven minutes while stirring. The resulting dark blue solution was quickly filtered and 1.3 g. of unchanged bromoketone hydrobromide was recovered. The filtrate was evaporated to dryness under reduced pressure with slight warming (30°). The residue was hydrolyzed with 40 ml. of glacial acetic acid and then treated with a slight excess of 30% hydrogen bromide in glacial acetic acid. Upon vigorously stirring for one and one-half hours, cooling, filtering, washing with acetic acid and drying, 11.6 g. (70%) of product was obtained. It was crystallized three times from glacial acetic acid; m. p. 153° dec.

Anal. Calcd. for $C_{11}H_9BrClNO\cdot HBr$: N, 3.81. Found: N, 3.83.

7-Chloro-α-(di-*n*-octylaminomethyl)-4-quinolinemethanol (IIb) dihydrochloride (SN-10519) was prepared in 92% yield in much the same manner as the 6-chlorodihexylamino isomer. The mixture of bromohydrin (17.5 g.) and dioctylamine (69 g.) was heated at 80° for eleven hours; the excess dioctylamine was separated from the product by fractional precipitation and the product, obtained as the dihydrochloride, was crystallized from butanone. It appeared to be unstable in hot solutions and purification had to be carried through rapidly. Its melting point behavior was as follows: it gradually softened from 85–107°, melted partially at 107–110°, resolidified at 130–135° and finally melted completely at 156–178° with decomposition.

Anal. Calcd. for $C_{27}H_{43}ClN_2O\cdot 2HCl\cdot H_2O$: C, 60.27; H, 8.81; N, 5.21; Cl^-, 13.18. Found: C, 60.40; H, 8.89; H, 5.03; Cl^-, 13.38.

7-Chloro-α-(di-*n*-hexylaminomethyl)-4-quinolinemethanol dihydrochloride (IIa) was prepared in 86% yield in the same manner as the 6-chlorodihexylamino isomer. The dihydrochloride was purified by repeated crystallizations from butanone after several Darco treatments and working rapidly in order to minimize deterioration in the hot solutions. It melted partially at 116–119°, and completely at 212–216°, with the evolution of gas.

Anal. Calcd. for $C_{23}H_{35}N_2ClO\cdot 2HCl$: N, 6.04. Found: N, 6.01.

(19) Code number of this Laboratory; this compound was made too late for inclusion in the Survey.

Summary

The syntheses of four new 6-chloro and two new 7-chloro-α-(dialkylaminomethyl)-4-quinolinemethanols have been accomplished from the corresponding chlorocinchoninic acids through the acid chlorides, diazomethyl ketones, bromomethyl ketones and bromohydrins.

The bromohydrins were easily over-reduced by the action of aluminum isopropoxide which was used in their preparation from the bromoketones. In one case the over-reduction product was isolated and identified as the secondary alcohol.

The new amino alcohols showed moderate activity against avian malaria.

CHARLOTTESVILLE, VIRGINIA RECEIVED JANUARY 17, 1947