of sodium, 200 ml. of toluene, 20.6 g. of alcohol, 40 g. of ethyl acetate and 72 g. of ethyl 6-chlorocinchoninate. The product was recrystallized from ligroin; yield, 65 g., 72%, m. p. 58–60°.

Anal. Calcd. for $C_{14}H_{12}NO_3Cl$: C, 60.6; H, 4.36; N, 5.05. Found: C, 60.9; H, 4.7; N, 5.0.

6-Chloro-4-acetylquinoline.—Six grams of the keto ester was heated with 100 ml. of 15% sulfuric acid until evolution of carbon dioxide ceased. There was obtained 3 g. of ketone as a white, crystalline solid, m. p. 101–103° after recrystallization from high-boiling ligroin.

Anal. Calcd. for $C_{11}H_8NOCl$: C, 64.24; H, 3.92; N, 6.81. Found: C, 64.42; H, 4.10; N, 6.65.

6-Chloro-4-bromoacetylquinoline.—Thirty-two grams of bromine was added dropwise with stirring to 56 g. of the keto ester in 150 ml. of chloroform. The solvent was removed under reduced pressure and 100 ml. of 24% hydrobromic acid was added to the residue. The red solution was warmed gradually to 100° and kept there for one hour. The product suddenly crystallized from the hot solution. 6-Chloro-4-bromoacetylquinoline hydrobromide was isolated in 60 g. (83%) yield as a yellow crystalline powder, m. p. 228–230° (dec.).

Anal. Calcd. for $C_{11}H_8NOBr_2Cl$: C, 36.13; H, 2.21; N, 3.83. Found: C, 36.8; H, 2.38; N, 3.69.

The free base melted at 100–103° and darkened in air.

6-Chloro-α-diethylaminomethyl-4-quinoline Methanol, SN-9209.—Eleven grams of the bromoketone hydrobromide was added to a cold (0°) solution of 11 g. of diethylamine in 75 ml. of anhydrous ether, in a nitrogen atmosphere, and the mixture was kept at 0° for four hours. The crude amino ketone was taken up in 100 ml. of methanol containing 4 ml. of concentrated hydrochloric acid and shaken with hydrogen in the presence of 70 mg. of platinum oxide. The calculated amount of hydrogen was absorbed in thirty minutes. The amino alcohol was isolated as the dihydrochloride dihydrate, m. p. 170–175°, in 32% yield.

Anal. Calcd. for $C_{15}H_{21}N_2OCl_3 \cdot 2H_2O$: C, 46.46; H, 6.50; N, 7.22. Found: C, 46.24; H, 6.5; N, 7.0.

6-Chloro-α-dibutylaminomethyl-4-quinoline Methanol, SN-10513.—This was prepared as described above using 10.3 g. of dibutylamine and 11 g. of the bromoketone hydrobromide. The amino alcohol dihydrochloride monohydrate, m. p. 152–155°, was isolated in 40% yield.

Anal. Calcd. for $C_{19}H_{29}N_2OCl_3 \cdot H_2O$: C, 53.59; H, 7.34; N, 6.58. Found: C, 54.1; H, 7.2; N, 6.4.

Summary

1. Several α-dialkylaminomethyl-4-quinoline methanols derived from cinchoninic acid, quininic acid and 6-chlorocinchoninic acid have been prepared.

2. The preparation of many quinoline derivatives used as intermediates has been described.

NOTRE DAME, INDIANA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. V. The Preparation of Some α-Dialkylaminomethyl-2-quinolinemethanols[1]

BY KENNETH N. CAMPBELL, CLARENCE H. HELBING[2] AND JAMES F. KERWIN[3]

In view of the fact that some α-dialkylaminomethyl-4-quinoline methanols show antimalarial activity[4] and that the 2- and 4-positions of the quinoline ring are very similar chemically, it was hoped that α-dialkylaminomethyl-2-quinoline methanols might also have antimalarial properties. As no compounds of this type are reported in the literature, we undertook the preparation of some of them. Compounds of the 2-quinoline methanol type with an α-2-piperidyl side chain have, however, been prepared during the general course of the Committee on Medical Research malaria program.[4a]

The original object of the present work was to prepare amino alcohols derived from quinaldic acid, 6-methoxyquinaldic acid and 7-chloroquinaldic acid. The syntheses of the 6-methoxy- and 7-chloro amino alcohols ran into unexpected difficulties, however, and the work was abandoned in favor of more promising compounds. Since several of the intermediates prepared in these series are new compounds, they are reported here.

Quinaldic acid was best prepared in large amounts from quinaldine by way of the α-tribromo derivative, by a modification of the method of Hammick.[5] This method was found to be much superior to oxidation of 2-styrylquinoline or to hydrolysis of 2-cyano-1-benzoyl-1,2-dihydroquinoline prepared by the Reissert reaction[6] on quinoline. Ethyl quinaldate condensed smoothly with ethyl acetate in the presence of sodium ethoxide to give good yields of the keto ester,[7] and the latter was hydrolyzed by dilute acid to 2-acetylquinoline. This ketone was best converted to 2-bromoacetylquinoline by bromination in aqueous hydrobromic acid; bromination in chloroform was less satisfactory. The bromo ketone reacted normally with secondary amines in anhydrous solvents, but it was necessary to exclude light and oxygen[7a] as otherwise the condensation products were tarry and could not be hydrogenated. Hydrogenation of the amino ketones over platinum gave the desired amino

(1) The work reported here was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame.

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(4) King and Work, *J. Chem. Soc.*, 1307 (1940).

(4a) Benson, Bergstrom, Norton and Seibert, THIS JOURNAL, **68**, in press (1946).

(5) Hammick, *J. Chem. Soc.*, **123**, 2883 (1923).

(6) Reissert, *Ber.*, **38**, 1610 (1905); Taylor, *J. Chem. Soc.*, 1110 (1929); Rupe, Paltzer and Engel, *Helv. chim. acta*, **20**, 211 (1937).

(7) Most of the 2- and 4-carbethoxyquinolines give surprisingly good yields in the Claisen condensation; see (a) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946); (b) Koelsch, *J. Org. Chem.*, **10**, 39 (1945).

alcohols, and the hydrogenolysis observed in the hydrogenation of some amino ketones[8] was not a major factor here.

The α-dialkylaminomethyl-2-quinoline methanols prepared in this work include the diethylamino, di-*n*-propylamino, di-isobutylamino, and butylethylamino compounds. These were oils which could not be distilled, and they were isolated and purified through the picrates or hydrochlorides. Since most of the hydrochlorides were hygroscopic, the compounds were submitted for testing as the 1-methylene-bis-(2-hydroxy-3-naphthoates).

6-Methoxyquinaldic acid was prepared from 6-methoxyquinaldine via the styryl derivative, and from 6-methoxyquinoline by the Reissert reaction; the former method gave the better results.[9] 6-Methoxy-2-acetylquinoline was obtained in good yield via the Claisen condensation, but all attempts to find a satisfactory method of converting it to the α-bromo ketone failed, as nuclear bromination occurred under most of the conditions tried.

The Doebner–Miller reaction between *m*-chloroaniline and 1,1,3-trimethoxybutane gave two isomeric quinaldines, which could be separated by a combination of fractional distillation and crystallization into a solid, m. p. 75°, and a liquid. The solid isomer was shown to be 7-chloroquinaldine, as the acid derived from it decarboxylated on heating to 7-chloroquinoline, whose identity was established by its melting point (29–30°) and by the melting point of its bichromate salt (172–174°).[10] The quinaldine, m. p. 78°, obtained by Bartow[11] from *m*-chloroaniline and paraldehyde is probably the 7-chloro isomer too.

In the 7-chloro series, the Claisen condensation gave but a poor yield of the keto ester, and 7-chloro-2-bromoacetylquinoline was best prepared from 7-chloroquinaldic acid through the diazo ketone. The bromoketone appeared to react normally with diethylamine, in that diethylamine hydrobromide was formed, but the condensation product could not be reduced to the amino alcohol. Catalytic hydrogenation led to the absorption of two moles of hydrogen with no break in the curve, and attempted reduction with aluminum isopropoxide gave only tars. Attention was then turned to 7-chloro-2-chloroacetylquinoline, which was easily prepared from the acid chloride by the diazomethane reaction. It was hoped to reduce the chloroketone to the chlorohydrin by Jacobs' procedure[12] and then treat the chlorohydrin with secondary amines. This approach failed, however, when it was found that aluminum isopropoxide reduction of the chloroketone led to loss of the aliphatic chlorine atom, with formation of α-(7-chloro-2-quinolyl)-ethanol.

(8) (a) King and Work, *J. Chem. Soc.*, 401 (1942); (b) Burger, THIS JOURNAL, **60**, 1533 (1938); Burger and Harnest, *ibid.*, **65**, 2382 (1943).

(9) After the work reported here was completed, an abstract of a paper by Rubtsov appeared (*J. Gen. Chem.*, (U. S. S. R.), **13**, 593 (1943); *C. A.*, **39**, 705 (1945)) in which many of these 6-methoxy compounds are described; in general his data are in good agreement with ours.

(10) Claus and Junghanns, *J. prakt. Chem.*, (2) **48**, 254 (1893); Fourneau, *et al.*, *Bull. soc. chim.*, (4) **47**, 749 (1930).

(11) Bartow, THIS JOURNAL, **26**, 703 (1904).

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

Experimental[13]

α-Tribromoquinaldine.—The procedure of Hammick[5] was adapted to a much larger scale. A solution of 246 ml. (4.8 moles) of bromine in 200 ml. of glacial acetic acid was added during twenty minutes to a mixture of 800 g. (9.75 moles) of anhydrous sodium acetate, 229 g. (1.6 moles) of quinaldine (E. K. Practical) and 2 liters of glacial acetic acid, kept at 70–75°. The mixture was then heated at 90–95° for one hour and allowed to stand overnight. The white solid was washed well with water, and after air-drying weighed 534 g. (79%); it melted at 129–130°. An additional 25–30 g. could be obtained by concentration of the filtrate, and the acetic acid could be recovered and used over again.

Quinaldic Acid.—A solution of 125 g. of tribromoquinaldine in 1100 ml. of 1:10 sulfuric acid was stirred at 115–125° (bath temperature) for ten hours. The cooled solution was adjusted to a *p*H of 3–4 with ammonium hydroxide, and extracted with six to eight 300-ml. portions of chloroform. Evaporation of the extracts (with recovery of the solvent) yielded 52–57 g. (90–98%) of quinaldic acid, m. p. 153–155°. This procedure is simpler and more satisfactory than isolating the quinaldic acid as the copper salt by Hammick's procedure.[5]

Ethyl Quinaldate.—The acid was esterified with absolute alcohol and sulfuric acid to give a 70–75% yield of ester, b. p. 131–136° (0.3 mm.), $n^{20}D$ 1.5973.

Ethyl Quinaldoylacetate.—Ethyl quinaldate and ethyl acetate were condensed in toluene solution in the presence of sodium ethoxide as described for the 4-isomer.[7a] The reaction mixture became very thick and a powerful stirrer was necessary. The yield of sodium salt was usually about 90%. This salt could be converted to the free keto ester by dilute acid in the cold, but usually it was hydrolyzed directly to the ketone. Ethyl quinaldoylacetate formed yellow crystals, m. p. 63–64° after recrystallization from high-boiling ligroin.

Anal. Calcd. for $C_{14}H_{13}NO_3$: N, 5.76. Found N, 5.90.

2-Acetylquinoline.—The sodium enolate (60.7 g.) was stirred and heated at 95–105° for seven hours with 1450 ml. of water containing 46 ml. of concentrated sulfuric acid. The solution was made alkaline and steam distilled to give 30.1 g. (76%) of 2-acetylquinoline, m. p. 43–45°. Recrystallization from aqueous alcohol raised the melting point to 47.5–48°. The phenylhydrazone melted at 152–153°. Kaufmann[14] who prepared the ketone from methylmagnesium iodide and 2-cyanoquinoline, reported the melting point of the ketone as 52° and of the phenylhydrazone as 154°.

Hydrogenation of 2-Acetylquinoline.—When the ketone was hydrogenated in aqueous or absolute alcohol over platinum oxide at room temperature, one mole of hydrogen was absorbed, and absorption then ceased. Methyl 2-quinolylcarbinol was isolated as a white solid, m. p. 81–82° after recrystallization from high-boiling ligroin. It was soluble in alcohol, ethyl acetate, hot benzene, hot dioxane and hot ligroin.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1; mol. wt., 173. Found: C, 76.2; H, 6.4; N, 8.2; mol. wt., 173.

When the hydrogenation was carried out in aqueous alcohol in the presence of a little hydrochloric acid, the main product was not the carbinol, but the pinacol. This was isolated as a white solid, m. p. 142.5–144°, which was

(13) Most of the carbon and hydrogen analyses, and some of the nitrogen analyses were carried out at Columbia University or Northwestern University.

(14) Kaufmann, Dandliker and Burkhart, *Ber.*, **46**, 2931 (1915).

much less soluble in the common solvents than the carbinol.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.7; H, 5.85; N, 8.14; mol. wt., 344. Found: C, 76.7; H, 6.2; N, 7.94; mol. wt. (cryoscopic in nitrobenzene), 360.

2-Bromoacetylquinoline.—A solution of 24.6 g. (0.154 mole) of bromine in 35 ml. of 40% hydrobromic acid was added in the course of ten minutes to a warm (63–67°) solution of 26.3 g. (0.154 mole) of 2-acetylquinoline in 60 ml. of 40% hydrobromic acid. The mixture was kept at 65° for one hour, and was then thoroughly chilled in an ice-bath until no more precipitate formed. The yield of bromoketone hydrobromide was 33 g. (85%), m. p. 214–216° (decomposition).

The free base, liberated by suspending the salt in distilled water and extracting with ether, was a cream-colored solid, m. p. 81–82°. It was soluble in most organic solvents, difficultly soluble in ligroin and darkened on standing.

Anal. Calcd. for $C_{11}H_8BrNO$: Br, 32.0; N, 5.6. Found: Br, 31.5; N, 5.4.

α-Diethylaminomethyl-2-quinoline Methanol, SN-8105.[15]—2-Bromoacetylquinoline hydrobromide (3.31 g., 0.01 mole) was added to a solution of 5 g. (0.07 mole) of diethylamine in 25 ml. of anhydrous ether, and the mixture was kept at 0° in an atmosphere of dry nitrogen for one and one-half hours. The diethylamine hydrobromide (2.6 g.) was removed, the filtrate evaporated at room temperature in a stream of nitrogen, and the residue taken up in 50 ml. of absolute alcohol. The alcohol solution was shaken with hydrogen in the presence of 0.06 g. of platinum oxide at room temperature and 3 atmospheres pressure until 0.01 mole was absorbed. The solution was evaporated and pumped at 5 mm. until no odor of diethylamine remained, and the oily residue was converted to the dipicrate (yield, 1.5 g.), which melted at 125–126° after recrystallization from absolute alcohol.

Anal. Calcd. for $C_{27}H_{26}N_8O_{15}$: C, 46.2; H, 3.73; N, 16.0. Found: C, 46.0; H, 4.0; N, 15.6.

The dihydrochloride, m. p. 109–110°, was very hygroscopic and the compound was submitted for testing as the 1-methylene-bis-(2-hydroxy-3-naphthoate), m. p. 285–290° (decomposition).

α-Di-*n*-propylaminomethyl-2-quinoline Methanol, SN-9795.—A solution of 5.6 g. of 2-bromoacetylquinoline (free base) in 60 ml. of dry benzene was added during twenty minutes to a solution of 7.0 g. of di-*n*-propylamine in 15 ml. of dry ether, and the mixture was kept under nitrogen at 0° for two and a half hours. The crude amino ketone was hydrogenated in aqueous alcohol over 0.06 g. of platinum oxide; the absorption of 0.02 mole of hydrogen required two hours. The amino alcohol was isolated as the hydrochloride, m. p. 110°, but as this was very hygroscopic, the 1-methylene-bis-(2-hydroxy-3-naphthoate), m. p. 216°, was prepared. The yield of salt was 5.8 g.

Anal. Calcd. for $C_{40}H_{40}N_2O_7 \cdot H_2O$: C, 70.8; H, 6.24; N, 4.13. Found: C, 70.9; H, 5.6; N, 4.0.

α-Di-isobutylaminomethyl-2-quinoline Methanol, SN-7998.—A mixture of 5.0 g. (0.02 mole) of the bromoketone, 6.0 g. (0.05 mole) of di-isobutylamine and 70 ml. of dry ether was kept in a nitrogen atmosphere at 26–30° for four hours. The crude amino ketone was hydrogenated in 100 ml. of 50% alcohol containing 4 ml. of concentrated hydrochloric acid and 0.06 g. of platinum oxide; 0.02 mole of hydrogen was absorbed in twenty minutes. The amino alcohol, freed from di-isobutylamine by pumping at 0.1 mm., was isolated as the hydrochloride, and this was converted into the 1-methylene-bis-(2-hydroxy-3-naphthoate), m. p. 250°; yield, 3.7 g.

Anal. Calcd. for $C_{42}H_{44}N_2O_7 \cdot 2H_2O$: C, 69.6; H, 6.7; N, 3.9. Found: C, 69.2; H, 6.2; N, 3.6.

(15) The numbers are those assigned by the Survey of Antimalarial Drugs to identify the drugs in their records. The antimalarial activities of these compounds will be tabulated in a forthcoming monograph.

α-Butylethylaminomethyl-2-quinoline Methanol, SN-7994.—This was prepared from the bromoketone (free base) and butylethylamine[16] in dry benzene, as described for the dipropyl compound. The amino alcohol was isolated as the hydrochloride, and submitted for testing as the 1-methylene-bis-(2-hydroxy-3-naphthoate), m. p. 220–225°.

Anal. Calcd. for $C_{40}H_{40}N_2O_7 \cdot 2H_2O$: C, 68.94; H, 6.4; N, 4.0. Found: C, 68.6; H, 6.1; N, 3.6.

6-Methoxyquinaldine.—The procedure developed by Campbell and Schaffner[17] for the preparation of 6-methoxylepidine was adapted to the preparation of the quinaldine. From 99.4 g. of *p*-anisidine hydrochloride and 30 g. of crotonaldehyde there was obtained 40 g. (45%) of 6-methoxyquinaldine, b. p. 145–146° (8 mm.), m. p. 58°. The melting point was raised to 65° by recrystallization from hexane. This is a considerably better yield of the quinaldine than that obtained by Cocker and Turner[18] from *p*-anisidine and acetaldehyde.

6-Methoxy-2-styrylquinoline.—A mixture of 25 g. (0.144 mole) of 6-methoxyquinaldine, 20 g. (0.18 mole) of benzaldehyde, and 1.5 g. of fused zinc chloride was heated at 150–160° for four hours. The cooled residue was powdered and shaken with sodium hydroxide solution to remove zinc salts, then thoroughly washed with water and dried. The crude material (obtained in 80–95% yield) was satisfactory for the next step. It could be purified by recrystallization from high-boiling ligroin, and then formed pale yellow crystals, m. p. 147–148°.

Anal. Calcd. for $C_{18}H_{15}NO$: N, 5.36. Found: N, 5.20.

6-Methoxyquinaldic Acid.—The styryl compound was oxidized with potassium permanganate in 50% pyridine by the procedure developed by Ainley and King[19] for quininic acid. The yield of acid of m. p. 179–180° was 85–95%. Recrystallization from water raised the melting point to 182°.

Anal. Calcd. for $C_{11}H_9NO_3 \cdot {}^1/_2H_2O$: N, 6.60; N.E., 212. Found: N, 6.4; N.E., 213.

6-Methoxyquinaldic acid hydrochloride melted at 217–218°.

Ethyl 6-Methoxyquinaldate.—The acid was esterified in 70–75% yield with ethyl alcohol and sulfuric acid. The ester was obtained as a crystalline colorless solid, m. p. 127.5–128° after recrystallization from alcohol.

Anal. Calcd. for $C_{13}H_{13}NO_3$: N, 6.06. Found: N, 6.12.

Ethyl 6-Methoxyquinaldoylacetate.—This was prepared as described earlier for the 4-isomer.[7a] The sodium enolate, freed from toluene by washing with ether, was added slowly to excess ice-cold hydrochloric acid, and the yellow solution adjusted to a *p*H of 6 with potassium carbonate. The keto ester so obtained weighed 11 g. (80%) and melted at 64–66°. It was used without purification.

Anal. Calcd. for $C_{15}H_{15}NO_4$: N, 5.13. Found: N, 5.0.

6-Methoxy-2-acetylquinoline.—A solution of 9 g. of the keto ester in 80 ml. of 20% sulfuric acid was heated at 90° for one hour, then cooled and made basic. The ketone, obtained in 6.5 g. yield (98%) melted at 97.5–98.5° after recrystallization from hexane.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.7; N, 6.93.

The ketone formed a hydrobromide salt, m. p. 189°, and a semicarbazone, which melted at 237–238° after recrystallization from alcohol.

Bromination of 6-Methoxy-2-acetylquinoline.—When the ketone was treated with one mole of bromine in 24% hydrobromic acid and the clear solution evaporated to

(16) Campbell, Sommers and Campbell, THIS JOURNAL, **66**, 82 (1944).

(17) Campbell and Schaffner, *ibid.*, **67**, 86 (1945).

(18) Cocker and Turner, *J. Chem. Soc.*, 143 (1941).

(19) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

dryness, the salt melted at 167–190°. The free base, m. p. 80–110°, was separated into unbrominated ketone and a small amount of bromoketone, m. p. 122°. This material gave nearly the correct bromine analysis for a monobromo derivative.

Anal. Calcd. for $C_{12}H_{10}NO_2Br$: Br, 28.5. Found: Br, 29.5.

The yield was too poor for the method to be feasible. Bromination of the keto ester in aqueous hydrobromic acid, followed by decarboxylation, gave similar results.

When the ketone was treated with one mole of bromine in chloroform solution, the product melted at 193°, and analyzed for a dibromide hydrobromide.

Anal. Calcd. for $C_{12}H_{10}NO_2Br_3$: Br, 54.3. Found: Br, 55.5.

The free base liberated from this salt melted at 144–146°, and did not react normally with diethylamine, giving only a small amount of diethylamine hydrobromide.

7-Chloroquinaldine.—*m*-Chloroaniline hydrochloride was treated with 1,1,3-trimethoxybutane[20] according to the general procedure of Campbell and Schaffner.[17] The crude product was a mixture of a solid and a liquid, which could be separated with difficulty by a combination of fractional distillation and recrystallization from high-boiling ligroin. 7-Chloroquinaldine, b. p. 87° (0.5 mm.), m. p. 74.5–76°, was finally isolated in about 30% yield. Bartow[11] reported 78° as the melting point of the compound obtained, in unstated yield, from paraldehyde and *m*-chloroaniline.

Anal. Calcd. for $C_{10}H_8NCl$: C, 67.6; H, 4.54; N, 7.89. Found: C, 67.8; H, 4.62; N, 7.75.

7-Chloro-2-styrylquinoline.—This was prepared as described above for the 6-methoxy compound. The styryl compound was obtained in 73% yield as yellow crystals, m. p. 125–127°, after recrystallization from high-boiling ligroin.

Anal. Calcd. for $C_{17}H_{12}NCl$: C, 76.85; H, 4.52; N, 5.27. Found: C, 76.3; H, 4.95; N, 5.49.

7-Chloroquinaldic Acid.—Powdered potassium permanganate (114 g.) was added in the course of one hour to a well-stirred solution of 96 g. of the styryl compound in 1500 ml. of acetone, kept at 0–10°. Stirring was continued for two hours longer, and the mixture was filtered. The filter cake, which contained practically all of the product, was extracted with four 400-ml. portions of boiling water. The cooled aqueous solution was acidified to a *p*H of 3, the precipitated acids collected, dried and stirred with three 100-ml. portions of ether to remove benzoic acid. The yield of product (m. p. 190°) suitable for the next step was 65 g. (87%). On recrystallization from water and alcohol, it melted sharply at 213° with decomposition.

Anal. Calcd. for $C_{10}H_6NO_2Cl$: Cl, 17.1; N. E., 207.6. Found: Cl, 17.0; N. E., 209.

7-Chloroquinoline.—When 4.2 g. of 7-chloroquinaldic acid was heated evolution of carbon dioxide began at 270° and was vigorous at 280–300°, and a yellowish distillate (3.0 g.) was obtained. This distillate solidified on cooling and after recrystallization from hexane melted at 29–30°. This material formed a dichromate salt which melted at 172–174° (decomposition). 7-Chloroquinoline melts at 32° and its dichromate at 172–178°, while 5-chloroquinoline melts at 45° and its dichromate at 120°.[10]

Ethyl 7-Chloroquinaldate.—This was prepared in 75–80% yield by esterification of the acid with alcohol–sulfuric acid. The ester had b. p. 155–157° (1 mm.), m. p. 72–74°.

Anal. Calcd. for $C_{12}H_{10}NO_2Cl$: N, 5.94; Cl, 14.97. Found: N, 6.20; Cl, 14.82.

7-Chloro-2-acetylquinoline.—Ethyl 7-chloroquinaldate was condensed with ethyl acetate in the presence of sodium ethoxide as described for the 6-methoxy compound, and the crude sodium salt was hydrolyzed directly with 15% sulfuric acid at 100°. The acid solution was made basic and steam-distilled to give a 27% yield of ketone, which was obtained as a white crystalline solid, m. p. 87–88.5°, soluble in alcohol, benzene and ether, difficultly soluble in ligroin. It formed a hydrobromide, m. p. 324°.

Anal. Calcd. for $C_{11}H_8NOCl$: N, 6.81; Cl, 17.24. Found: N, 6.98; Cl, 17.10.

A large amount of 7-chloroquinaldic acid was recovered from the steam-distillation residue. As attempts to improve the yield of ketone by this method failed, the procedure was abandoned in favor of the diazomethane reaction.

7-Chloro-2-bromoacetylquinoline.—A mixture of 15 g. (0.07 mole) of 7-chloroquinaldic acid and 75 ml. of purified thionyl chloride[21] was refluxed for two hours, and the excess thionyl chloride was removed at reduced pressure. The residue was added in portions with stirring to a cold solution of 0.3 mole of diazomethane in 400 ml. of ether, and the clear solution was allowed to stand at room temperature overnight. It was filtered from a small amount of insoluble residue, and an excess of a saturated ethereal solution of hydrogen bromide was added. The mixture on standing several hours deposited brownish-yellow crystals of the bromoketone hydrobromide. This was obtained in 17 g. (65%) yield, and melted at 215°. The free base was a light yellow crystalline solid, m. p. 117–118° after recrystallization from hexane.

Anal. Calcd. for $C_{11}H_7NOBrCl$: C, 46.4; H, 2.48. Found: C, 46.1; H, 2.51.

When the bromoketone hydrobromide and diethylamine were allowed to react in ether solution at 0°, practically the theoretical amount of diethylamine hydrobromide was precipitated in four hours. The ether solution was evaporated, and the residue taken up in isopropanol and treated with aluminum isopropoxide. Although this reaction was repeated several times, nothing but tarry material could be isolated from the reduction mixture. Attempts to reduce the amino ketone catalytically led to the rapid absorption of two moles of hydrogen, and no amino alcohol was obtained.

7-Chloro-2-chloroacetylquinoline.—The chloro ketone was prepared from 7-chloroquinaldic acid via the diazo ketone, as described above for the bromo compound. The yield of 7-chloro-2-chloroacetylquinoline hydrochloride, m. p. 127–129°, was 45%.

Anal. Calcd. for $C_{11}H_8NOCl_3$: Cl, 38.5. Found: Cl, 38.6.

The chloro ketone (free base, 6.0 g.) was added to a boiling solution of 25 g. of aluminum isopropoxide in 120 ml. of isopropanol, and the mixture was stirred and refluxed for ten minutes. The hot solution was then poured into ice and hydrochloric acid, and worked up in the usual way. The product (3 g.) was obtained as yellow crystals, m. p. 134–135°. Analysis showed it was not the desired chlorohydrin, but was probably methyl 7-chloro-2-quinolylcarbinol.

Anal. Calcd. for $C_{11}H_9NOCl_2$: Cl, 29.3. Calcd. for $C_{11}H_{10}NOCl$: Cl, 17.1. Found: Cl, 16.9.

Acknowledgment.—We wish to thank Mr. James M. Constantin for carrying out some of the experimental work in the 6-methoxy series, and Dr. Barbara K. Campbell for many helpful suggestions.

Summary

1. Several α-dialkylaminomethyl-2-quinoline methanols have been prepared.

2. The synthesis of 6-methoxy- and 7-chloroquinaldic acids and several of their derivatives have been described.

NOTRE DAME, INDIANA RECEIVED APRIL 5, 1946

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