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

Studies in the Quinoline Series. VII. The Preparation of Some α-Dialkylaminomethyl-8-quinoline Methanols[1]

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When King and Work[4] showed that some α-dialkylaminomethyl-4-quinoline methanols possessed antimalarial activity, it became of interest to learn whether similar activity would be possessed by isomers in which the side chain was attached to other positions in the quinoline nucleus. As a part of this program, we undertook the synthesis of some α-dialkylaminomethyl-8-quinoline methanols.

The original object of the work was to prepare amino alcohols derived from 8-quinoline carboxylic acid and 6-methoxy-8-quinoline carboxylic acid, but the preparation of the latter series ran into unexpected difficulties, and was abandoned in favor of more promising compounds.

The reactions used to prepare the amino carbinols were similar to those used earlier for the King–Work carbinols[4,5] and for the dialkylaminomethyl-2-quinoline methanols.[6] 8-Quinoline carboxylic acid was best prepared by the Skraup reaction on anthranilic acid; attempts to make it by oxidation of 8-methylquinoline gave very poor yields. The acid is not as easily esterified as are the 2- and 4-quinolinecarboxylic acids. Esterification with alcohol and sulfuric acid in the usual way gave but a low yield of ester, and it was necessary to go through the acid chloride to get satisfactory results. Like its 2- and 4-isomers,[5,6] ethyl 8-quinolinecarboxylate condensed smoothly with ethyl acetate in the presence of sodium ethoxide, and the keto ester was decarboxylated without isolation to 8-acetylquinoline.

In order to determine whether or not catalytic hydrogenation of the amino ketones would be feasible, the hydrogenation of 8-acetylquinoline was investigated. 2-Acetyl-[6] and 4-acetylquinolines can be hydrogenated over platinum to the corresponding carbinols, without any nuclear hydrogenation taking place. This is not true of the 8-isomer. In this case two equivalents of hydrogen were taken up without any break in the curve, and the product appeared to be a dihydroquinoline carbinol. It has been shown[7] that selective hydrogenation of a carbonyl group can be accomplished in some cases in the presence of ferrous sulfate. Hydrogenation of 8-acetylquinoline over platinum in the presence of ferrous sulfate, however, led to the absorption of three moles of hydrogen, with formation of a mixture of products. This ease of nuclear hydrogenation appears to be a general property of 8-substituted quinolines, for it was also found that 8-quinoline carboxylic acid took up two moles of hydrogen readily, to give 1,2,3,4-tetrahydro-8-quinolinecarboxylic acid, and ethyl 8-quinolinecarboxylate likewise formed a tetrahydro derivative easily.

8-Acetylquinoline was easily brominated to 8-bromoacetylquinoline, which reacted normally with secondary amines. The aminoketones were reduced to the amino alcohols with aluminum isopropoxide, in good yield.

6-Methoxy-8-aminoquinoline was used as the starting material for the preparation of the 6-methoxy - 8 - aminocarbinols. Strukov[8] prepared 6-methoxy-8-cyanoquinoline by a Sandmeyer reaction on the amine. In repeating this work, we found that the yields of nitrile were very erratic, and were unable to find the cause. Usually the yield of nitrile was 40–50%, but occasionally it would fall far below this figure, and a large amount of tar would be formed. In this connection it is of interest to note that Fieser and Hershberg[9] were unable to prepare 8-cyanoquinoline by a Sandmeyer reaction on the amine, as only tars were obtained. When 6-methoxy-8-cyanoquinoline was treated with methylmagnesium bromide, the corresponding ketone was formed, but in this case also, the yields were erratic and large amounts of tar were formed. All attempts to prepare 6-methoxy-8-bromoacetylquinoline by bromination of the ketone failed, as nuclear bromination, probably in the 5-position, occurred under all the conditions tried.

Since the desired bromoketone could not be prepared from 6-methoxy-8-acetylquinoline, it was hoped that it could be made from ethyl 6-methoxy - 8 - quinoloylacetate. 6-Methoxy-8-cyanoquinoline was found to be very resistant to hydrolysis. Bouveault's procedure,[10] using 90% sulfuric acid and sodium nitrite, could be used but isolation of the product was difficult. The acid was obtained in good yield, however, by heating the nitrile with potassium hydroxide in glycerol at 150–180°. The acid was found to be very resistant to esterification, and could not be esterified by alcohol and sulfuric acid, or by Newman's

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(4) King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942).

(5) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946).

(6) Campbell, Helbing and Kerwin, *ibid.*, **68**, 1840 (1946).

(7) Tuley and Adams, *ibid.*, **47**, 3061 (1925).

(8) Strukov, *Khim. Farm. Prom.*, No. 3, 13 (1934); *C. A.*, **29**, 1821 (1934).

(9) Fieser and Hershberg, THIS JOURNAL, **62**, 1644 (1940).

(10) Bouveault, *Bull. soc. chim.*, [3] **9**, 368 (1892); Sudborough, *J. Chem. Soc.*, **67**, 602 (1895).

procedure for hindered acids,[11] but could be esterified through the acid chloride. The ester condensed smoothly with ethyl acetate to give ethyl 6-methoxy-8-quinoloylacetate, but the hope that the greater reactivity of the methylene hydrogen atoms in the keto-ester would favor side chain bromination was not fulfilled, as bromination of the keto-ester, followed by acid cleavage, gave a polybromoketone.

In another attempt to prepare 6-methoxy-8-haloacetylquinolines, the acid chloride was treated with diazomethane and then with hydrogen halide, but only tars were obtained.

Experimental[12]

8-Quinolinecarboxylic Acid.—Of the many procedures tried for the preparation of this compound, the following gave the best results: A mixture of 102 g. (0.75 mole) of anthranilic acid, 75 g. (0.45 mole) of *o*-nitrobenzoic acid, 250 g. (2.7 mole) of anhydrous glycerol and 150 ml. of concentrated sulfuric acid was warmed gently until reaction began. After the initial vigorous reaction had subsided, the mixture was refluxed gently for seven hours, cooled and poured onto ice. The solution was adjusted to a *p*H of 3–4 with ammonium hydroxide, decanted from some tar, and extracted with five 150-ml. portions of chloroform. Evaporation of the solvent gave 68 g. (53%) of crude 8-quinolinecarboxylic acid, m. p. 179–182°, suitable for esterification. The acid could be purified by recrystallization from 95% alcohol, and then melted at 187–189°, in agreement with the literature value.[13]

In order to determine the ease of hydrogenation of a quinoline substituted in the 8-position, a 0.01-mole sample of the pure acid was hydrogenated at room temperature and 2 atmospheres pressure in ethanol, in the presence of 50 mg. of Adams catalyst; in one hour 0.02 mole of hydrogen was absorbed. The product was 1,2,3,4-tetrahydro-8-quinolinecarboxylic acid, m. p. 161–163°.[14]

Ethyl 8-Quinolinecarboxylate.—The following procedure gave much better results than esterification with alcohol and sulfuric acid. A mixture of 106 g. of the crude acid and 350 ml. of purified thionyl chloride[15] was refluxed for one hour, and the excess thionyl chloride removed under reduced pressure at 60°. The residue was refluxed for thirty minutes with 200 ml. of absolute alcohol, and the reaction mixture worked up in the usual way. There was obtained 101 g. (84%) of ester, b. p. 145–155° (0.5 mm.), m. p. 43–44°.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.51; N, 6.96. Found: C, 72.0; H, 5.56; N, 6.56.

The ester formed a picrate, m. p. 167–168°.

A 0.01-mole portion of the ester in ethanol was shaken with hydrogen in the presence of 50 mg. of Adams catalyst; in forty-five minutes 0.02 mole of hydrogen was absorbed.

8-Acetylquinoline.—Sodium ethoxide, prepared from 12.6 g. of sodium and 25.2 g. of ethanol, was suspended in 200 ml. of sodium-dried toluene, and treated with 85 g. (0.42 mole) of ethyl 8-quinolinecarboxylate and 48 g. (0.55 mole) of ethyl acetate. The mixture was stirred at 110° for eight hours; it was usually necessary to add more toluene to keep the mixture fluid enough for stirring. The sodium enolate so obtained was added to 600 ml. of 20% sulfuric acid and heated at 95° for three hours. The ketone was isolated in 38 g. (52%) yield, b. p. 114–116° (0.7 mm.), m. p. 42–43.5°. Howitz and Kopke[16] prepared this ketone by oxidation of the corresponding carbinol, and reported the melting point as 45°. The ketone 2,4-dinitrophenylhydrazone melted at 253°.

Hydrogenation of 8-Acetylquinoline.—When 0.02 mole of the ketone in 50 ml. of methanol was shaken with hydrogen at room temperature and 2 atmospheres pressure, in the presence of 50 mg. of Adams catalyst, 0.04 mole of hydrogen was taken up in one hour, and absorption then ceased. The product melted at 42–43.5°, and when mixed with the original ketone melted at room temperature. This compound formed a benzoate, m. p. 132–134°.

When the hydrogenation was carried out in the presence of a little ferrous ammonium sulfate, two molar equivalents of hydrogen were taken up rapidly (fifty minutes), and a third more slowly (four hours); the product was a mixture of an oil and a solid, m. p. 65–70°, and was not investigated farther.

8-Bromoacetylquinoline.—A solution of 22 g. of 8-acetylquinoline in 50 ml. of 40% hydrobromic acid was heated in a boiling water-bath and treated with 20 g. of bromine, added in the course of forty-five minutes. The clear yellow solution was evaporated to dryness under reduced pressure at 80°, and the residue was recrystallized from hot methanol; it formed yellow needles, m. p. 176–177°. The yield was 35 g. (82%).

Anal. Calcd. for $C_{11}H_9NOBr_2$: C, 39.9; H, 2.74; N, 4.2; Br, 48.3. Found: C, 40.6; H, 2.90; N, 3.8; Br, 48.0.

α-Diethylaminomethyl-8-quinoline Methanol, SN-9210.[17]—8-Bromoacetylquinoline hydrobromide (10 g., 0.03 mole) was added in the course of fifteen minutes to a solution of 8.7 g. (0.12 mole) of diethylamine in 50 ml. of anhydrous ether, at 0°, in a nitrogen atmosphere, and the reaction mixture was kept at 0° for four hours. The diethylamine hydrobromide was removed, the filtrate was evaporated, and the crude amino ketone, dissolved in 50 ml. of dry isopropanol, was added to 18 g. (0.09 mole) of aluminum isopropoxide in 50 ml. of isopropanol. The mixture was heated at 92° in a nitrogen atmosphere while acetone and isopropanol distilled out. At the end of three hours, no more acetone came over, and the mixture was poured into 100 ml. of 20% sodium hydroxide and extracted with ether. The dried ether solution was evaporated, the reddish oil was taken up in 300 ml. of benzene-hexane mixture (80% hexane by volume) and passed through a 20 × 1.5 cm. column packed with activated alumina (80 mesh). Some of the dark colored impurities remained on the column, while the amino alcohol was washed through with additional solvent. Evaporation of the solvent gave 3.7 g. (50%), of amino alcohol, m. p. 65–68°. Recrystallization from hexane raised the melting point to 68.5–70°.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.7; H, 8.2. Found: C, 73.7; H, 8.3.

Most of the amino alcohol salts were hygroscopic, had no satisfactory melting points, and became tarry in air, so the compound was submitted for testing as the free base.

α-Dibutylaminomethyl-8-quinoline Methanol, SN-10745.—The reaction between 8-bromoacetylquinoline hydrobromide (16.5 g., 0.05 mole) and di-*n*-butylamine (19.3 g., 0.15 mole) was carried out as described above. The amino ketone was reduced with 0.15 mole of aluminum isopropoxide, and reduction was complete in one and one-half hours. The reaction mixture was decomposed with 100 ml. of 25% sodium hydroxide, and the amino alcohol was extracted with ether. The product was obtained as a light reddish oil, b. p. 170–180° (0.4 mm.); it weighed 8.1 g. (54%). The dihydrochloride melted at 155°.

Anal. Calcd. for $C_{19}H_{30}N_2OCl_2$: C, 61.1; H, 8.1; Cl, 19.0. Found: C, 61.1; H, 7.4; Cl, 18.7.

The amino alcohol formed a benzoate hydrochloride which melted at 193–196°.

(11) Newman, THIS JOURNAL, **63**, 2431 (1941).

(12) Most of the carbon, hydrogen and nitrogen analyses reported here were carried out at Northwestern University.

(13) Schlosser and Skraup, *Monatsh.*, **2**, 530 (1881).

(14) Tafel, *Ber.*, **27**, 825 (1894).

(15) Fieser, "Experiments on Organic Chemistry," D. C. Heath and Co., New York, N. Y., 2nd ed., 1942, p. 381.

(16) Howitz and Kopke, *Ann.*, **396**, 38 (1913).

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

6-Methoxy-8-cyanoquinoline.—The procedure of Strukov[8] was investigated in some detail, and of the many modifications tried, the following gave the best results. Thirty-five grams of 6-methoxy-8-aminoquinoline was suspended in 73 g. of concentrated hydrochloric acid and 150 ml. of water, and the mixture warmed until solution was complete. The hot solution was cooled with constant stirring to −5°, and diazotized in the course of twenty to thirty minutes with a solution of 16 g. of sodium nitrite in 45 ml. of water. The red diazonium solution was added over a period of thirty minutes to a cold solution (0°) of 27 g. of cuprous cyanide and 59 g. of potassium cyanide in 100 ml. of water. The mixture was stirred at 0–10° for two hours, warmed gradually to 70° and stirred at 70° for three hours. The reddish precipitate was suspended in dilute sodium hydroxide solution and warmed at 80° for twenty minutes. The black solid was thoroughly dried *in vacuo* at about 50°, and was then refluxed for one hour each time with two 500-ml. portions of benzene. The benzene solutions were boiled with Norite and evaporated, to give 17–20 g. (46–54%) of nitrile, m. p. *ca.* 145°. The nitrile was best purified by vacuum distillation; it boiled at 158–161° (0.2 mm.), and formed pale yellow crystals, m. p. 149–151°.

6-Methoxy-8-acetylquinoline.—Methylmagnesium bromide, prepared from 5 g. of magnesium, 75 ml. of ether and excess methyl bromide, was diluted with 300 ml. of dry benzene and the solution was warmed to 55–60°. Solid 6-methoxy-8-cyanoquinoline (18 g.) was added in the course of one hour, and the mixture was stirred at 60° for fifteen hours. The reaction mixture was hydrolyzed with ice and hydrochloric acid, and the acid solution was allowed to stand for several hours at room temperature to hydrolyze the ketimine. The solution was then made basic with ammonia and extracted with ether. The yield of crude ketone, m. p. 75°, was 16 g. (79%). Recrystallization from hexane raised the melting point to 80°. The cream-colored solid was soluble in most organic solvents, difficultly soluble in ligroin.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.51; N, 6.96. Found: C, 71.3; H, 5.6; N, 7.1.

The ketone formed a hydrobromide, m. p. 215°, and a semicarbazone, m. p. 211–212°.

Bromination of 6-Methoxy-8-cyanoquinoline.—One molar equivalent of bromine was added dropwise to a solution of the ketone in 40% hydrobromic acid at 60°, and the mixture was heated at 60° for two hours. The precipitate was separated into two fractions by recrystallization from alcohol–ether. The more soluble fraction, m. p. 215°, was shown to be the hydrobromide of the original ketone. The less soluble fraction, m. p. 162°, analyzed for a dibromide hydrobromide:

Anal. Calcd. for $C_{12}H_{11}NO_2Br_2$: Br, 44.2. Calcd. for $C_{12}H_{10}NO_2Br_3$: Br, 54.5. Found: Br, 55.7.

Similar results were obtained when the bromination was carried out at 0°, or when 24% hydrobromic acid, ether or ethyl bromide was used as solvent.

6-Methoxy-8-quinolinecarboxylic Acid.—When the nitrile was treated with 90% sulfuric acid and sodium nitrite by Bouveault's procedure[10] the acid was obtained, but its isolation from the reaction mixture was very troublesome, and the following procedure, suggested by de Cuester's work[18] was preferred. A mixture of 25 g. of the crude nitrile, 46 g. of potassium hydroxide and 300 ml. of glycerol was stirred at 150–170° for nine hours. The cooled mixture was diluted with an equal volume of water, boiled with a little Norite and acidified to a *p*H of 5–6 with hydrochloric acid. The acid was collected, and the filtrate was extracted with chloroform to give a second crop of acid. The total yield of product of m. p. 188–192° was 21 g. (78%). If the acidification is carried too far, or is done too rapidly, a mixture of the acid and its hydrochloride precipitates, which melts about 230°. The acid can be purified by dissolving it in ammonia, treating with Norite and reacidifying, or by recrystallization from 95% alcohol; it then melts sharply at 195°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.0; H, 4.46; neut. equiv., 203. Found: C, 65.3; H, 4.6; neut. equiv., 202.

The acid hydrochloride formed beautiful gleaming crystals, m. p. 256° dec.

Ethyl 6-Methoxy-8-quinolinecarboxylate.—Six grams of pure, oven-dried acid, m. p. 195°, was refluxed with 20 ml. of purified thionyl chloride for two hours; the excess reagent was removed under reduced pressure at 60°, and the residue was refluxed for two hours with 25 ml. of absolute alcohol. The excess alcohol was removed by distillation, and the residue was treated with ice and ammonia. The crude ester was recrystallized from high-boiling ligroin to yield 5 g. (70%) of ester, m. p. 60–62°. The literature melting point is 62–63°, for the ester prepared by a Skraup reaction on methoxyanthranilic acid.[19]

Ethyl 6-Methoxy-8-quinoloylacetate.—Twelve grams of ethyl 6-methoxy-8-quinoline carboxylate and 6.6 g. of ethyl acetate were added to a suspension of sodium ethoxide (from 1.73 g. of sodium) in 50 ml. of toluene. The mixture was stirred at 100–110° for ten hours, cooled and the sodium enolate (12 g.) collected. The free keto-ester was an oil, so it was converted to the hydrobromide, m. p. 110°, in ether solution. The yield was 10.5 g. (57%). A portion of the keto-ester was boiled with 6 *N* hydrochloric acid to form 6-methoxy-8-acetylquinoline, m. p. 81°, identical with that obtained from the nitrile.

One molar equivalent of bromine vapor was drawn slowly through a solution of the keto-ester hydrobromide in 24% hydrobromic acid at room temperature, and the solution was then heated at 80–100° until no more carbon dioxide was evolved. The product proved to be a mixture of the ketone hydrobromide, m. p. 215°, and a polybromide hydrobromide, m. p. 160°.

Anal. Calcd. for $C_{12}H_{10}NO_2Br_3$: Br, 54.5. Found: Br, 57.1.

Similar results were obtained when the bromination was carried out in other solvents.

Summary

1. The preparation of α-diethylaminomethyl- and α-dibutylaminomethyl-8-quinoline methanols is described.

2. Methods are given for the preparation of several derivatives of 8-quinoline carboxylic acid and 6-methoxy-8-quinoline carboxylic acid.

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(18) de Cuester, *Natuur. Tijdschr.*, **14**, 3-6, 188 (1932); *C. A.*, **26**, 4324 (1932).

(19) British Patent 307,727; *Friedländer*, **16**, 2682.