these conditions has been demonstrated by studying electrophoretic mobility of human serum albumin soon after equilibration with acetate buffer and again after a period of some days at 4° when no alteration in the electrophoretic mobility of either component or in the ratio of the components was detected.[11]

The separation and characterization not only of the albumin but also of the various globulin components of normal and pathological sera[12] are being investigated further.

Summary

1. Although crystalline serum albumin has been demonstrated to consist of more than one chemical individual, it has been reported to migrate with uniform velocity both during ultracentrifugation and electrophoresis at neutral reactions.

2. At *p*H 4.0, where a fraction of horse serum albumin crystallizes as a sulfate, the protein exhibits two boundaries in the Tiselius electrophoresis apparatus, which migrate, respectively, with mobilities of 6.80 and 6.44 × 10^{-5} cm.²/volt-sec. in acetate buffers of *p*H 4.0 and Γ/2 0.02.

3. Human serum albumin also consists of at least two components, migrating with velocities of 7.25 and 5.95 × 10^{-5} cm.²/volt-sec., respectively, under the above conditions.

4. In normal sera, the faster moving component constitutes nearly two-thirds of the albumin, but in certain pathological conditions in man, both serum and urinary albumins show a greater diminution of the faster component, leaving the slower component preponderant.

BOSTON, MASS. RECEIVED AUGUST 11, 1939

(11) Several of the pathological specimens were made available through the kindness of Dr. Allan M. Butler of the Children's Hospital, Boston, Mass.

(12) Studies of this kind have been reported by Stenhagen, *Biochem. J.*, **32**, 714 (1938); Blix, *Z. exptl. Med.*, **105**, 595 (1939); MacInnes and Longsworth, *Science*, **89**, 438 (1939).

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Synthesis of Certain Substituted Quinolines and 5,6-Benzoquinolines

BY R. GORDON GOULD, JR., AND WALTER A. JACOBS

The synthesis of ergoline (I) and of several of its mono- and dimethyl derivatives by the sodium reduction of 3′-amino-5,6-benzoquinoline-7-carboxylic acid lactam and of the corresponding methyl derivatives already has been reported.[1] Although the yields were only about 5 to 10%, the method appeared to be of fairly general application to the alkyl derivatives. When, however, a free or esterified carboxyl group was present in the pyridine ring, the isolation of a crystalline ergoline derivative became extremely difficult. The preparation of ergoline-7-carboxylic acid in a yield of about 1% and in still somewhat impure condition already has been reported,[2] but all attempts to prepare the isomeric ergoline-8-carboxylic acid have given only amorphous products. This plan of attack on the problem of the synthesis of dihydrolysergic acid has therefore not been so promising as had been anticipated.

In the course of this work several new methods of synthesis of certain quinoline and benzoquinoline derivatives were developed, which are the subject of the present paper.

Conrad and Limpach[3] first prepared 4-hydroxyquinaldine (II) by condensation of aniline with acetoacetic ester at room temperature followed by cyclization at 250°, and Limpach[4] forty-four years later improved the yield from about 30 to 90–95% by the use of mineral oil as a diluent in the cyclization step.

This method of synthesis has now been found to be sufficiently general to be applicable not only to substituted anilines and β-naphthylamines, but also has been extended to the synthesis of 4-hydroxyquinoline-3-carboxylic acids (III) by the use of ethoxymethylenemalonic ester and of 4-hydroxyquinaldine-3-carboxylic acids (IV) by the use of acetylmalonic ester.

As examples, aniline condensed with ethoxymethylenemalonic ester to give anilidomethylenemalonic ester, as reported by Claisen.[5] Cyclization of the latter in mineral oil gave the previously known[6] 4-hydroxyquinoline-3-carboxylic acid (III).

$$C_6H_5NH_2 + C_2H_5OCH{=}C(COOR)_2 \longrightarrow C_6H_5NHCH{=}C(COOR)_2$$

(1) W. A. Jacobs and R. G. Gould, *J. Biol. Chem.*, **120**, 141 (1937).

(2) W. A. Jacobs and R. G. Gould, *ibid.*, **126**, 67 (1938).

(3) M. Conrad and L. Limpach, *Ber.*, **20**, 944 (1887).

(4) L. Limpach, *ibid.*, **64**, 969 (1931).

(5) L. Claisen, *Ann.*, **297**, 77 (1897).

(6) R. Camps, *Ber.*, **34**, 2714 (1901).

Aniline condensed with acetylmalonic ester and the resulting intermediate alkylidene derivative was cyclized in mineral oil. The resulting ester after saponification proved to be the previously known 4-hydroxyquinaldine-3-carboxylic acid[7] (IV).

$$C_6H_5NH_2 + CH_3COCH(COOR)_2 \longrightarrow C_6H_5NHC(CH_3)=C(COOR)_2$$

In the case of acetoacetic ester and of ethoxymethylenemalonic ester, the condensation to the intermediate alkylidene derivatives went smoothly and apparently in only one sense, with all of the amines used, but acetylmalonic ester was found to give poorer yields of the alkylidene derivatives because of competing side reactions. With aniline, a yield of about 30% of acetanilide and of about 70% of the normal anilidomethylmethylenemalonic ester was obtained.

The condensation of acetylmalonic ester with 3-aminonaphthostyril gave another type of abnormal product which was possibly the result of the condensation of an ester linkage rather than that of the carbonyl group, with the amino group, thus

$$(C_{11}H_6ON)NH_2 + CH_3COCH(COOR)_2 \longrightarrow (C_{11}H_6ON)NHCOCHCOCH_3 \quad (\text{COOR})$$

The alkylidene derivatives which resulted from the normal condensation of the three esters used with amines cyclized smoothly at 250°, and gave in each case the quinoline derivative. In the case of acetoacetic ester, this was a 4-hydroxyquinaldine or benzoquinaldine derivative, and in the cases of ethoxymethylenemalonic ester and acetylmalonic ester the products were derivatives of 4-hydroxyquinoline or benzoquinoline-3-carboxylic acids.

In addition to the examples already cited, the following new substances were prepared by the two steps of condensation, *viz.*, formation of the intermediate alkylidene derivative and subsequent cyclization to the quinoline or benzoquinoline. Acetoacetic ester and 3-amino-1-naphthoic acid (or its ester) gave **4-hydroxy-5,6-benzoquinaldine-7-carboxylic acid** (or its ester) (**V**). 3-Aminonaphthostyril and acetoacetic ester gave **3′ - amino - 4 - hydroxy - 5,6 - benzoquinaldine-7-carboxylic acid lactam** (**VI**).

Ethoxymethylenemalonic ester and 3-amino-1-naphthoic acid gave **4-hydroxy-5,6-benzoquinoline-3,7-dicarboxylic acid** (**VII**), and the same ester with 3-aminonaphthostyril gave **3′-amino-4 - hydroxy - 5,6 - benzoquinoline - 3,7 - dicarboxylic acid lactam** (**VIII**).

Since in the attempt to prepare **3′-amino-4-hydroxy - 5,6 - benzoquinaldine - 3,7 - dicarboxylic acid lactam** (**IX**) from 3-aminonaphthostyril and acetylmalonic ester the reaction proceeded abnormally, this substance was obtained instead by the following series of reactions. 4-Hydroxy - 5,6 - benzoquinaldine - 7 - carboxylic acid (V), when condensed with carbon tetrachloride and potassium hydroxide by the Reimer–Tiemann reaction, gave **4-hydroxy-5,6-benzoquinaldine-3,7-dicarboxylic acid** (**X**). This dibasic acid was characterized also as the **monomethyl ester,** the **dimethyl ester,** and as the **4-methoxy dimethyl ester.** Nitration of the hydroxy dibasic acid gave a mixture of mononitro derivatives which was directly reduced as such. After treatment of the reduction product with acid, 3′-amino-4-hydroxy-5,6-benzoquinaldine-3,7-dicarboxylic acid lactam (IX) was isolated as well as a simultaneously formed free amino derivative which did not lactamize. The latter was possibly **6′-amino-4-hydroxy-5,6-benzoquinaldine-3,7-dicarboxylic acid** (**XI**).

Several examples have been reported of the oxidation by selenium dioxide of the 2- or 4-methyl group in pyridine or quinoline derivatives to a carboxyl group[8] and of the 2-methyl group in 5,6 - benzoquinaldine - 7 - carboxylic acid.[2] The presence of a 4-hydroxy group appears to block this type of oxidation, however, since none of the 4-hydroxy-5,6-benzoquinaldine derivatives described above were oxidized by selenium dioxide under the conditions usually employed.

The 4-hydroxyl group similarly appeared to block the catalytic hydrogenation of the nitrogen ring of such substances to the tetrahydro derivatives. Ruzicka and Fornasir[9] reported that 4-hydroxypyridine could not be hydrogenated catalytically under ordinary conditions of temperature and pressure and our experience with 4-hydroxyquinoline and -benzoquinoline derivatives appears to confirm this. Also in the case of 3′ - amino - 4 - hydroxy - 5,6 - benzoquinoline-3,7-dicarboxylic acid lactam (VIII), reduction with amalgamated zinc and acetic acid appeared to stop at the dihydro stage, with the formation

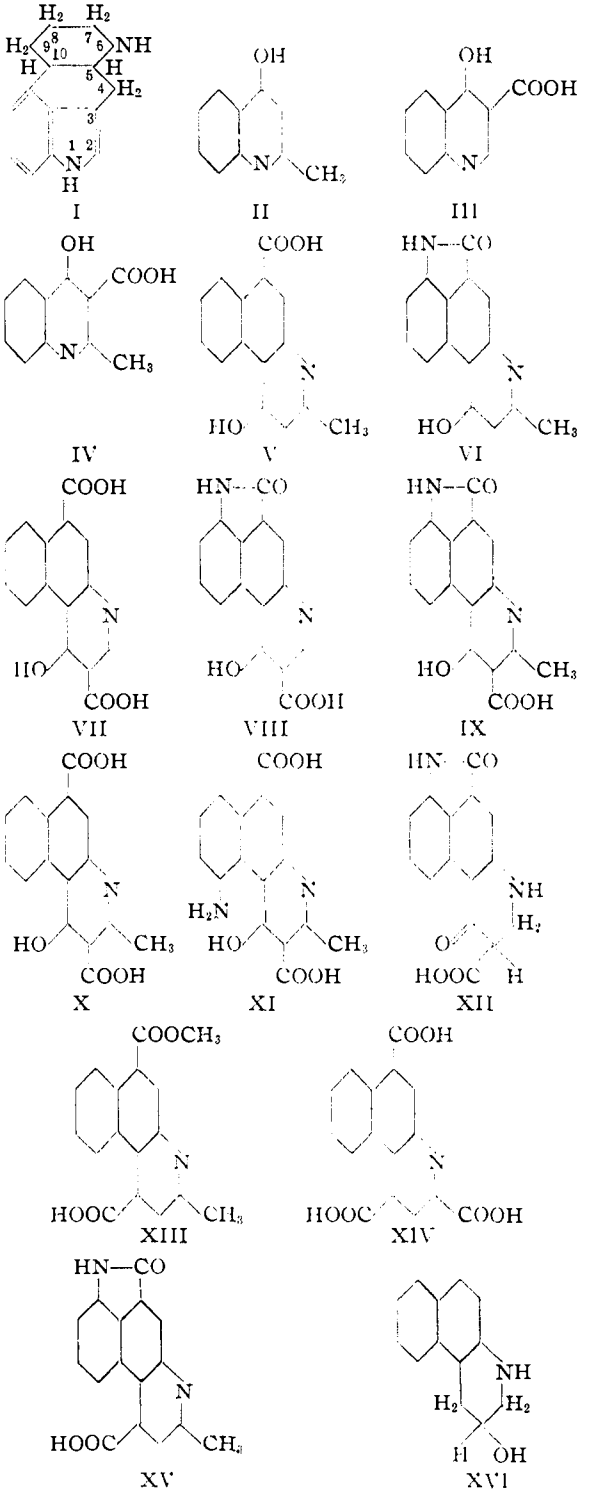
(7) M. Conrad and L. Limpach, *Ber.*, **21**, 1975 (1888).

(8) M. Henze, *Ber.*, **67**, 750 (1934); see also ref. 2.

(9) L. Ruzicka and V. Fornasir, *Helv. Chim. Acta*, **3**, 807 (1920).

of **3'-amino-4-keto-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (XII)**.

A few substituted 5,6-benzoquinoline-4-carboxylic acids were prepared by the application of the condensation of aromatic amines with pyruvic acid and aldehydes.[10] With formaldehyde, only complex dimolecular products were obtained, but with acetaldehyde the reaction went smoothly although the yields were poor. 3-Amino-1-naphthoic methyl ester gave **7-carbomethoxy-5,6-benzoquinaldine-4-carboxylic acid (XIII)** which after saponification and oxidation with selenium dioxide yielded **5,6-benzoquinoline-2,4,7-tricarboxylic acid (XIV)**. Attempts to prepare lactam derivatives from both the dibasic and tribasic acids by successive nitration and reduction were unsuccessful. Nitration in the 3' position was apparently not favored.



3-Aminonaphthostyril on condensation with pyruvic acid and acetaldehyde gave **3'-amino-5,6-benzoquinaldine-4,7-dicarboxylic acid lactam (XV)** in poor yield.

Finally, the method developed for the preparation of 3-hydroxy-1,2,3,4-tetrahydro-7,8-benzoquinoline derivatives by the condensation of epichlorohydrin with α-naphthylamine derivatives[11] was tried with several β-naphthylamine derivatives. It was found that β-naphthylamine gave **3-hydroxy-1,2,3,4-tetrahydro-5,6-benzoquinoline (XVI)**, but 3-aminonaphthostyril yielded an anomalous product, the nature of which has not been determined.

Experimental

For the preparation of alkylidene derivatives, except where otherwise stated, the condensations with acetoacetic ester and acetylmalonic ester were carried out at room temperature and with ethoxymethylenemalonic ester by heating on the steam-bath. In some cases methyl or ethyl alcohol was used as a solvent. The cyclizations of the alkylidene derivatives were carried out in 10–30 parts of mineral oil at 250–265°, in an atmosphere of dry nitrogen, and with good mechanical stirring. The substance was added in small portions and heating was continued for about fifteen minutes. After cooling, the mixture was treated with the appropriate solvent and the crystalline product was collected.

(3-Naphthyl-1-carboxylic Acid)-β-aminocrotonic Ethyl Ester.—Twenty grams of 3-amino-1-naphthoic acid and 20 g. of acetoacetic ester condensed readily in methyl alcoholic solution. After removal of the solvent *in vacuo* the crystalline product was collected with a cold ether–petroleum ether mixture. The yield was almost quantitative. For analysis it was recrystallized from ether and formed rosets of needles which melted at 157–158°.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.19; H, 5.73. Found: C, 68.08; H, 5.40.

(10) E. A. Robinson and M. T. Bogert, *J. Org. Chem.*, **1**, 65 (1936–1937).

(11) I. G. Farb. Akt. Ges., French Patent 799,322 (*Chem. Zentr.*, **107**, II, 2020 (1936); Swiss Patent 186,845 (*Chem. Zentr.*, **108**, I 4024 (1937)).

4 - Hydroxy - 5,6 - benzoquinaldine - 7 - carboxylic Acid (V).—Cyclization gave an almost quantitative yield of the benzoquinoline derivative. It was purified by recrystallization from 1% hydrochloric acid solution as the hydrochloride which separated as needles.

Anal. Calcd. for $C_{15}H_{11}O_3N \cdot HCl$: C, 62.16; H, 4.18. Found: C, 61.96; H, 4.40.

After liberation from the salt, the substance was obtained as a microcrystalline powder which did not melt below 360°.

Anal. Calcd. for $C_{15}H_{11}O_3N$: C, 71.10; H, 4.38. Found: C, 70.87, 71.34; H, 4.81, 4.50.

The Methyl Ester.—Treatment with boiling methyl alcohol and hydrogen chloride gave the ester, which after recrystallization melted at 295–296° with decomposition.

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.88; H, 4.91. Found: C, 71.74; H, 5.01.

The Ethyl Ester.—The ester was obtained with absolute alcohol and sulfuric acid and formed lustrous leaflets from alcohol, which melted at 295–297°.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.56; H, 5.38. Found: C, 72.78; H, 5.32.

N-(3-Naphthostyryl)-β-aminocrotonic Ethyl Ester.—Two and one-half grams of 3-aminonaphthostyril was refluxed with an excess of acetoacetic ester in alcohol solution for several hours. The condensation product was collected in a yield of 3.2 g. After recrystallization from alcohol, it melted at 180–182°.

Anal. Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.88; H, 5.44. Found: C, 68.65; H, 5.28.

4 - Hydroxy - 3' - amino - 5,6 - benzoquinaldine - 7 - carboxylic Acid Lactam (VI).—The above aminocrotonic ester was cyclized in mineral oil at 250° and the product was purified through the sparingly soluble hydrochloride which formed needles from dilute hydrochloric acid solution.

Anal. Calcd. for $C_{15}H_{11}O_2N_2Cl$: C, 62.81; H, 3.87. Found: C, 62.96; H, 3.51.

The free hydroxy lactam was insoluble in ammonia and very sparingly soluble in hot pyridine or dilute pyridine. It did not melt below 360°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2$: C, 71.97; H, 4.03. Found: C, 71.49; H, 4.41.

4-Hydroxyquinaldine-3-carboxylic Ethyl Ester.—Ten and one-tenth grams of acetylmalonic ester[12] and 4.7 g. of aniline were allowed to stand at room temperature for three days. Acetanilide separated and was collected in a yield corresponding to about 30% of the aniline used. The filtrate was cyclized in mineral oil, and the product collected with ether. After recrystallization from alcohol, the substance melted at 104–107°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.50; H, 5.67. Found: C, 66.97; H, 5.46.

4-Hydroxyquinaldine-3-carboxylic Acid (IV).—Saponification gave the free acid which melted at 245–247° with decomposition. Camps[6] gave 247–248° with decomposition.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.00; H, 4.47. Found: C, 65.20; H, 4.38.

(12) H. Lund, *Ber.*, **67**, 937 (1934).

α - Carbethoxyacetoacetyl - 3 - aminonaphthostyril.—One and eight-tenths grams of 3-aminonaphthostyril and 4 g. of acetylmalonic ester were allowed to stand at room temperature for several months. After recrystallization from alcohol, the substance melted at 268–270° with decomposition.

Anal. Calcd. for $C_{18}H_{16}O_5N_2$: C, 63.50; H, 4.71. Found: C, 63.19; H, 4.65.

4-Hydroxyquinoline-3-carboxylic Acid (III).—One gram of anilidomethylenemalonic ester[5] was cyclized in mineral oil and the crystalline product was collected in a yield of about 60%. Acidification of the aqueous alkaline solution gave long needles which melted at 267–268°. Camps[6] gave 266–267°.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.47; H, 3.72. Found: C, 63.60; H, 3.79.

N-(3 - Naphthyl - 1 - carbomethoxy) - β - amino - α - carbethoxyacrylic Ethyl Ester.—One gram of 3-amino-1-naphthoic methyl ester and 1.08 g. of ethoxymethylenemalonic ester[13] were heated for fifteen minutes at 100°. On cooling, a crystalline cake formed which was recrystallized from ether. It formed voluminous long needles melting at 89–90°.

Anal. Calcd. for $C_{20}H_{21}O_6N$: C, 64.66; H, 5.70. Found: C, 64.99; H, 5.62.

4 - Hydroxy - 5,6 - benzoquinoline - 3,7 - dicarboxylic Acid (VII).—One gram of the above alkylidene derivative at 250° gave 0.73 g. of cyclization product. This monomethyl ester was saponified by heating in dilute sodium hydroxide and the dibasic acid was recrystallized from sodium acetate solution as the beautifully crystalline monosodium salt. It was then isolated as the free acid which did not melt below 360°.

Anal. Calcd. for $C_{15}H_9O_5N$: C, 63.59; H, 3.22. Found: C, 63.91; H, 3.37.

N-(3 - Naphthostyryl) - β - amino - α - carbethoxyacrylic Ethyl Ester.—To 104.6 g. of 3-aminonaphthostyril dissolved in 185 cc. of boiling alcohol was added 6 g. of ethoxymethylenemalonic ester, and the solution was refluxed for one hour. The crystalline product was collected in about 75% yield. With material recovered from the mother liquor, the yield was almost the theoretical.

The substance formed light yellow needles from alcohol which melted at 231–232°.

Anal. Calcd. for $C_{19}H_{18}O_5N_2$: C, 64.38; H, 5.12. Found: C, 64.85; H, 5.10.

4 - Hydroxy - 3' - amino - 5,6 - benzoquinoline - 3,7 - dicarboxylic Acid Lactam (VIII).—Six and three-tenths grams of the above substance on cyclization gave an almost quantitative yield of the benzoquinoline derivative. Purification was effected by boiling in 5% sodium hydroxide solution for one hour in order to open the lactam group. After treatment with norite, the clear light yellow solution was made strongly acid to congo red with hydrochloric acid and brought to a boil. The lactam acid formed microscopic needles which did not melt below 360°.

It is soluble in dilute sodium bicarbonate on warming and in dilute piperidine. It forms a sparingly soluble sodium

(13) L. Claisen, *Ann.*, **297**, 76 (1897); H. L. Wheeler and C. O. Johns, *Am. Chem. J.*, **40**, 238 (1908).

salt in more concentrated alkaline solutions, and it is not appreciably soluble in the ordinary organic solvents.

Anal. Calcd. for $C_{15}H_8O_4N_2$: C, 64.27; H, 2.88; N, 10.00. Found: C, 64.01, 64.23; H, 3.09, 3.05; N, 10.20.

The free amino dibasic acid formed a dark red gelatinous precipitate.

3′ - Amino - 4 - hydroxy - 2,3 - dihydro - 5,6 - benzoquinoline-3,7-dicarboxylic Acid Lactam (XII).—The 3′-amino-4-hydroxy-5,6-benzoquinoline-3,7-dicarboxylic acid lactam was suspended in acetic acid and refluxed for about five hours with an excess of amalgamated zinc shot. The supernatant suspension was decanted from the excess zinc and was then collected. It was purified by reprecipitation from a dilute pyridine solution by addition of acetic acid, and did not melt below 350°.

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.81; H, 3.57. Found: C, 63.92; H, 3.84.

4 - Hydroxy - 5,6 - benzoquinaldine - 3,7 - dicarboxylic Acid (X).—To 11 g. of 4-hydroxy-5,6-benzoquinaldine-7-carboxylic acid (V) were added 60 cc. of 50% potassium hydroxide, 5 cc. of carbon tetrachloride, about 1 g. of copper powder, and a few cc. of alcohol, and the mixture was refluxed for twenty-four hours. It was then diluted with 5 volumes of water and filtered. The clear, dark-colored filtrate was made just acid to congo red by the addition of hydrochloric acid and then enough excess hydrochloric acid was added to bring the concentration to 1%. After bringing to a boil, the undissolved material was collected. It was again boiled in 200 cc. of 1% hydrochloric acid and collected hot. The insoluble material consisted of the dibasic acid. Unchanged monobasic acid was recovered from the combined filtrates. The yields of dibasic and recovered monobasic acids were respectively 3 g. and 6 g.

The dicarboxylic acid was purified by the following steps: extraction with hot alcohol (in which it is insoluble); recrystallization as the salt from sodium acetate solution; as the nitrate from nitric acid (1.4); and finally from dilute pyridine. It formed leaflets which did not melt below 360°.

Anal. Calcd. for $C_{16}H_{11}O_5N$: C, 64.63; H, 3.73. Found: C, 64.44, 64.57; H, 3.39, 3.74.

A **monomethyl ester** of undetermined identity was obtained by esterification with boiling methyl alcoholic hydrogen chloride. The hydrochloride crystallized from the boiling solution. The free ester, after recrystallization from aqueous pyridine, melted at 290–295°, with decomposition.

Anal. Calcd. for $C_{17}H_{13}O_5N$: C, 65.57; H, 4.21. Found: C, 65.56; H, 4.33.

The **dimethyl ester** was obtained from the dibasic acid in poor yield with methyl alcohol and sulfuric acid. When recrystallized from methyl alcohol it melted at 239–240°.

Anal. Calcd. for $C_{18}H_{15}O_5N$: C, 66.43; H, 4.65. Found: C, 66.72; H, 5.06.

4 - Methoxy - 5,6 - benzoquinaldine - 3,7 - dicarboxylic Dimethyl Ester.—This substance resulted from treatment of a methyl alcoholic suspension of the dibasic acid with diazomethane. It formed long colorless needles from ether or methyl alcohol, which melted at 142–144°.

Anal. Calcd. for $C_{19}H_{17}O_5N$: C, 67.23; H, 5.05. Found: C, 67.19; H, 5.17.

3′ - Nitro - 4 - hydroxy - 5,6 - benzoquinaldine - 3,7 - dicarboxylic Acid.—The preceding dicarboxylic acid was nitrated with fuming nitric acid (1.58). The material which separated on dilution was a mixture of isomeric mononitro derivatives, and was used directly for the following reduction without attempting a separation.

Anal. Calcd. for $C_{16}H_{10}O_7N_2$: C, 56.12; H, 2.95. Found: C, 55.63; H, 3.03.

3′ - Amino - 4 - hydroxy - 5,6 - benzoquinaldine - 3,7 - dicarboxylic Acid Lactam (IX).—The previously described method[1,2] with ferrous hydroxide was used for the reduction of the preceding substance. The crude product was collected after acidification to congo red and boiling for a short time. This material was found on analysis to consist approximately of 30% of the lactam of the 3′-amino derivative and 70% of an isomeric aminodicarboxylic acid, which did not lactamize. The mixture was separated by trituration with half saturated sodium bicarbonate solution at 60° which appeared to dissolve mainly the amino dicarboxylic acid. The lactam acid was purified by recrystallization as the sodium salt from sodium carbonate solution. After liberation from the salt, the lactam acid formed an orange-yellow microcrystalline powder, which did not melt below 360°.

Anal. Calcd. for $C_{16}H_{10}O_4N_2$: C, 65.28; H, 3.43; N, 9.53. Found: C, 65.39; H, 3.61; N, 9.70.

(?) - Amino - 4 - hydroxy - 5,6 - benzoquinaldine - 3,7-dicarboxylic Acid (XI).—The above sodium bicarbonate solution on acidification yielded the by-product which was obtained colorless after purification by repeated recrystallization as the hydrochloride from dilute hydrochloric acid. The free amino acid was obtained as a microcrystalline powder which did not melt below 360°.

Anal. Calcd. for $C_{16}H_{12}O_5N_2$: C, 61.51; H, 3.88. Found: C, 61.12; H, 4.22.

7 - Carbomethoxy - 5,6 - benzoquinaldine - 4 - carboxylic Acid (XIII).—Four grams of 3-amino-1-naphthoic methyl ester, 0.88 g. of pyruvic acid, and 0.88 g. of acetaldehyde were dissolved in 50 cc. of alcohol and the mixture was refluxed for four to five hours. A yield of 0.7 g. of the product crystallized on cooling; 0.2 g. more was obtained from the mother liquor.

The acid formed aggregates of fine white needles from a mixture of pyridine and alcohol, which melted at 265–266°, with decomposition.

Anal. Calcd. for $C_{17}H_{13}O_4N$: C, 69.13; H, 4.44. Found: C, 69.46; H, 4.56.

Saponification of the above monomethyl ester gave the **dibasic acid** as a colorless microcrystalline powder which melted at 298–299°, with decomposition.

Anal. Calcd. for $C_{16}H_{11}O_4N$: C, 68.30; H, 3.95. Found: C, 68.08; H, 3.82.

7 - Carbomethoxy - 5,6 - benzoquinoline - 2,4 - dicarboxylic Acid.—The previous monomethyl ester was oxidized with excess selenium dioxide in pyridine solution. The resulting product was recrystallized from a mixture of pyridine and methyl alcohol from which it separated as diamond-shaped prisms. It melted at 199–200° with decomposition and contained pyridine of crystallization which was not removed by heating to 100° *in vacuo*.

Anal. Calcd. for $C_{17}H_{11}O_6N \cdot C_5H_5N$: C, 65.32; H, 3.99. Found: C, 65.22; H, 4.01.

Saponification of the above oxidation product yielded **5,6-benzoquinoline-2,4,7-tricarboxylic acid (XIV)**, which melted at 285–286° with decomposition.

Anal. Calcd. for $C_{16}H_9O_6N$: C, 61.72; H, 2.92. Found: C, 61.81; H, 3.19.

3′ - Amino - 5,6 - benzoquinaldine - 4,7 - dicarboxylic Acid Lactam (XV).—Three and sixty-eight hundredths grams of 3-aminonaphthostyril, 0.88 g. of acetaldehyde, and 0.88 g. of pyruvic acid dissolved in 200 cc. of alcohol were refluxed for four hours. After concentration a yellow crystalline precipitate was obtained, which was purified from non-acidic material and was finally obtained in a yield of 0.5 g. It melted at 340–342° with decomposition.

Anal. Calcd. for $C_{16}H_{10}O_3N_2$: C, 69.04; H, 3.62. Found: C, 69.04; H, 3.40.

3-Hydroxy-1,2,3,4-tetrahydro-5,6-benzoquinoline (XVI).—β-Naphthylamine was condensed with an equimolecular amount of epichlorohydrin by the method recently developed for α-naphthylamine derivatives,[11] and the resulting product was purified as the hydrochloride, from dilute hydrochloric acid.

Anal. Calcd. for $C_{13}H_{14}ONCl$: C, 66.22; H, 5.99. Found: C, 66.41; H, 5.95.

The free base after recrystallization melted at 82–83°.

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.35; H, 6.58. Found: C, 78.65; H, 6.95.

Summary

1. A convenient method of synthesis of certain 4-hydroxyquinoline and 4-hydroxy-5,6-benzoquinoline derivatives has been found in the condensation of aniline and β-naphthylamine derivatives with acetylmalonic ester or ethoxymethylenemalonic ester followed by cyclization at 250°.

2. The method of Conrad and Limpach for the synthesis of 4-hydroxyquinaldine from acetoacetic ester and aniline has been extended to include certain substituted β-naphthylamines.

3. The introduction of a carboxyl group in position 3 of 4-hydroxy-5,6-benzoquinaldine-7-carboxylic acid was accomplished by means of the Reimer–Tiemann reaction.

4. Epichlorohydrin on condensation with β-naphthylamine gave 3-hydroxy-1,2,3,4-tetrahydro-5,6-benzoquinoline.

NEW YORK, N. Y. RECEIVED JUNE 28, 1939

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Cleavage of Quaternary Ammonium Salts by Sodium Sulfide. II

BY H. R. SNYDER AND J. C. SPECK

In an earlier communication[1] it was shown that benzyldimethylphenylammonium chloride (I) is cleaved readily by aqueous sodium sulfide to yield benzyl sulfide and dimethylaniline. A number of other salts containing sulfur in its lower valences were also found to be effective cleaving agents. The reaction is of the same type as that observed in the splitting of thiamin[2] (vitamin B_1) with sodium bisulfite, in which a group similar to benzyl is detached from a quaternary nitrogen atom.

$$2[C_6H_5CH_2N(CH_3)_2C_6H_5]^+Cl^- + Na_2S \longrightarrow (C_6H_5CH_2)_2S + 2C_6H_5N(CH_3)_2 + 2NaCl$$

It now has been found that the groups other than benzyl attached to the nitrogen atom play an important part in the cleavage. For instance, benzyltrimethylammonium chloride was completely unaffected under conditions which brought about rapid decomposition of benzyldimethylphenylammonium chloride. That this difference is not due merely to the weight of the phenyl group was shown by the fact that benzylcyclohexyldiethylammonium chloride also resisted the action of aqueous sodium sulfide. Phenyltrimethylammonium iodide, and tetra-*n*-butylammonium iodide also failed to undergo cleavage. Even the presence of two benzyl groups on the nitrogen atom does not produce an activation similar to that in benzyldimethylphenylammonium chloride, since dibenzyldiethylammonium iodide was only very slightly cleaved. Benzylpyridinium chloride, on the other hand, underwent rapid scission to pyridine and benzyl sulfide. It appears, therefore, that the linkage between an alkyl group and the nitrogen atom of a quaternary salt is labilized when the nitrogen is attached to or is part of an aromatic system.

It might be predicted that the allyl group would display a mobility similar to that of

(1) For the first paper in this series see Snyder and Speck, THIS JOURNAL, **61**, 668 (1939).

(2) Williams, Waterman, Keresztesy and Buchman, *ibid.*, **57**, 536 (1935).