50 cc. of 90% acetic acid. After standing for fifteen minutes, water was added and the organic material was extracted with ether. The ethereal solution was washed well with water and dilute hydrochloric acid and then with dilute potassium hydroxide. The alkaline solution was acidified and extracted with ether. The ether solution was concentrated and pentane was added. This produced 2.4 g. of crystalline acid, m. p. 207–211°. Coprostane-3,4-dicarboxylic acid crystallized from methanol as large transparent rods, m. p. 217°. It gave a 15–20° depression in melting point with dihydro-Diels acid of m. p. 251°, and also with coprostane-2,3-dicarboxylic acid, m. p. 247°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.8; H, 10.7.

The dimethyl ester was prepared with diazomethane in the usual way. It crystallized from methanol as large white flakes, m. p. 74°.

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.3; H, 10.7. Found: C, 75.6; H, 11.0.

Summary

Pregnanetriol-3,4,20(α) was oxidized to the 3,4-dicarboxylic acid of pregnanone-20, which was different from the dicarboxylic acid of pregnanone-20 formed by direct oxidation of pregnanedione. The latter acid must therefore be a 2,3-derivative.

Coprostanediol-3,4 was oxidized to a coprostane-dicarboxylic acid. This acid was different from the dicarboxylic acid obtained by direct oxidation of coprostanone.

The greater part of the oxidative fission of 3-substituted derivatives of the coprostane configuration (except those of the bile acid series) takes place at the 2,3-bond rather than at the 3,4-bond as has been generally assumed.

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[CONTRIBUTION FROM THE NICHOLS CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

The Preparation of Some Py-Amino Quinolines and Derivatives

BY R. R. RENSHAW[1] AND H. L. FRIEDMAN[2]

This paper describes the preparation of several py-amino quinolines and some of their derivatives. The amines were needed for a study of their coupling reactions with benzene diazonium chloride.[3] The 2-aminoquinoline was readily prepared by the sodamide reaction.[4]

Reduction of 3-nitroquinoline[5] gave the 3-aminoquinoline in small over-all yields. For better yields, Wibaut's[6] method was modified by preparing 3-bromoquinoline from quinoline, bromine and sulfur,[7] followed by conversion to the amine with concentrated ammonia and copper sulfate catalyst.[8]

Since it was found that 3-aminoquinoline forms the 4-azo derivative in the coupling reaction with benzenediazonium chloride,[3] an attempt was made to prepare the unknown 4-nitroquinoline. Anhydrous 3-acetylaminoquinoline was nitrated in concentrated sulfuric acid and the acetyl group removed by hydrolysis. A red nitro-amine was formed. An attempt to remove the amino group by diazotization and boiling in alcohol yielded only a nitro-ethoxy derivative. Attempted reduction to the known 3,4-diaminoquinoline[9] failed; the compound could not be reduced. It is tentatively postulated that 4-nitro-3-aminoquinoline was obtained, although the authors have never seen a quinoline compound with a nitro group in the 4 position recorded in the literature.

The 4-aminoquinoline and the 2,4-diaminoquinoline were prepared from the same material, the 2,4-quinoline-dicarboxylic acid.[9] Decarboxylation of the acid in boiling nitrobenzene gave excellent yields of cinchoninic acid which was converted through the acid chloride,[10] methyl ester,[11] and amide[12] to the amine[13] in an over-all yield of 68%. Similarly, it was found that starting with the 2,4-quinolinedicarboxylic acid, the 2,4-diaminoquinoline could be obtained by the same series of reactions in an over-all yield of 50%. The only method of preparation of the

(1) This paper is being published, following the death of Professor Renshaw, by his collaborator.

(2) Present address: Pyridium Corporation, Yonkers, New York.

(3) Renshaw, Friedman and Gajewski, THIS JOURNAL, **61**, 3322 (1939).

(4) Chichibabin, *et al.*, *J. Russ. Phys.-Chem. Soc.*, **46**, 1232 (1914); **50**, 554 (1918); *Ber.*, **58**, 803 (1925).

(5) Bargellini and Settimi, *Gass. chim. ital.*, **53**, 601 (1923).

(6) Jansen and Wibaut, *Rec. trav. chim.*, **56**, 709 (1937).

(7) Edinger, *J. prakt. Chem.*, **54**, 358 (1896).

(8) Maier-Bode, *Ber.*, **69**, 1536 (1936). Preparation of 3-aminopyridine from 3-bromopyridine.

(9) Pfitzinger, in Houben-Weyl, "Methoden," Vol. IV, 1924, p. 559.

(10) Spaeth and Spitzer, *Ber.*, **59**, 1484 (1926).

(11) Meyer, *Monatsh.*, **22**, 115 (1901).

(12) Wenzel, *ibid.*, **15**, 456 (1894).

(13) Wenzel, *ibid.*, **15**, 457 (1894).

diamine recorded previously in the literature is the reaction of the 2,4-quinolinedisulfonic acid with concentrated ammonia and zinc chloride.[14]

It was found that the 2-carbethoxy group in the 2,4-diethyl ester could be converted readily into the carboxamide group without the 4-carbethoxy group being appreciably affected. Hofmann degradation of the resulting compound gave the hitherto unknown 2-aminocinchoninic acid.[15] The structure was proved by decarboxylation to 2-aminoquinoline and by diazotization to the known 2-hydroxycinchoninic acid.[16]

Experimental Part[17]

3-Aminoquinoline.—*o*-Aminobenzaldehyde[18] and metazonic acid[19] on standing in a weakly acidic solution gave a 22% yield of 3-nitroquinoline,[20] m. p. 129–130°. Ether extraction of the neutral mother liquor gave an approximately equal weight of the oxime of the aldehyde, m. p. 137–37.5°.[21] Reduction of the nitro compound with stannous chloride in concentrated hydrochloric acid,[5] addition of excess sodium hydroxide, and extraction with ether gave a 97% yield of the 3-amine, m. p. 82–83°; acetyl derivative, m. p. 171–172° (anhydrous), 127–128° (hydrate).

Bromination of quinoline with sulfur and bromine according to Edinger[7] gave 3-bromoquinoline in 50% yield, b. p. (24 mm.) 158–162°. Heating with concentrated ammonium hydroxide and copper sulfate catalyst[8] in a rocking autoclave (twelve hours at 160°) and extraction with ether gave the 3-aminoquinoline in 73% yield.

3-Acetylamino-4(?)-nitroquinoline.—Attempted nitration of the acetylamine in glacial acetic acid precipitated the nitrate of the acetylamine, m. p. 195.5° (with decomp. to gas).

3-Acetylaminoquinoline (2 g.) was dissolved in concentrated sulfuric acid (15 cc.), cooled, fuming nitric acid added (1.5 g.), and the solution allowed to stand for one hour at room temperature. The solution was then poured on cracked ice, made basic, and the precipitate crystallized from much water; small golden yellow needles, m. p. 205–206°.

Anal. Calcd. for $C_{11}H_9N_3O_3$: N, 18.2. Found: N, 18.0.

3-Amino-4(?)-nitroquinoline.—The acetylamino-nitroquinoline was hydrolyzed by boiling in 95% alcohol with potassium hydroxide for fifteen minutes. The red solution was then poured into water, boiled to remove the alcohol, cooled, the precipitate filtered and crystallized from water; small lustrous red needles, m. p. 189–189.5°.

Anal. Calcd. for $C_9H_7N_3O_2$: N, 22.2. Found: N, 21.8.

Attempted reduction in hydrochloric acid with stannous chloride failed. The red color did not disappear after heating for one hour. The solution was made basic and extracted with ether. The ether showed a marked blue fluorescence but no diamine was obtained on evaporation. Reductions were also attempted with stannous chloride and hydrogen chloride in alcohol, with iron powder and acetic acid in water, and with zinc dust in alcoholic sodium hydroxide. No color change was found in any case nor could any product resembling a diamine be obtained.

3-Ethoxy-4(?)-nitroquinoline.—Dry sodium nitrite (90 mg.) was added to the nitroaminoquinoline (200 mg.) in cold concentrated sulfuric acid (5 cc.). The solution was allowed to warm to room temperature and stand for fifteen minutes, then poured into 30 cc. of absolute alcohol and boiled. Most of the alcohol was distilled off and a small amount of water added. On further boiling a solid steam distilled and was crystallized from water, approximately 40 mg. of long, slightly tan crystals, m. p. 113–114°. Evaporation of the alcoholic distillate at room temperature left no residue. Ether extraction of the clear liquid remaining in the distilling flask yielded only a little unreacted nitro-aminoquinoline.

Anal. Calcd. for $C_9H_6N_2O_2$ (nitroquinoline): N, 16.1. For $C_{11}H_{10}N_2O_3$ (nitro-ethoxyquinoline): N, 12.8. Found: N, 12.5.

4-Aminoquinoline.—Finely powdered dry quinoline 2,4-dicarboxylic acid (25 g.) was boiled on a hot-plate with nitrobenzene (100 cc.). Decarboxylation was complete in about ten minutes accompanied by solution. On cooling, the cinchoninic acid crystallized out and was recrystallized from water, yield 90%.

The cinchoninic acid (1 part) was boiled with thionyl chloride[10] (3 parts) for ten minutes and the thionyl chloride removed *in vacuo*. The acid chloride–hydrochloride formed gave with methyl alcohol the methyl ester,[9] b. p. (4 mm.) 136–140°, in 83% yield. The ester (10 g.) with ammoniacal methanol (50 cc. saturated with ammonia at 10°) gave the amide[12] in quantitative amount (twelve hours at 50°), rectangular plates, m. p. 179–181°. Hofmann degradation[13] gave the amine in 90% yield, m. p. 69° (hydrate), 154–156° (anhydr.); acetyl derivative, 177–178°.

2,4-Dicarbomethoxyquinoline and 2,4-Dicarbethoxyquinoline.—Quinoline-2,4-dicarboxylic acid (1 part) was refluxed for eight to ten hours on the water-bath with thionyl chloride (10 parts), at which time complete solution was effected. The thionyl chloride was distilled off *in vacuo* and feathery golden-yellow crystals of the dicarbonyl chloride remained. The chloride may be crystallized from ligroin or petroleum ether but this is not necessary for production of the esters.[22]

The dicarbonyl chloride was dissolved in absolute methanol (or ethanol), boiled with bone-black, filtered, water added to turbidity and the solution cooled. The esters formed white needle crystals; dimethyl ester, m. p. 130–131°; diethyl ester, m. p. 74–75.5°; very insoluble in water, soluble in concentrated sulfuric acid (yellow).

Anal. (Dimethyl ester) Calcd. for $C_{13}H_{11}NO_4$: N, 5.71. Found: N, 5.83, 5.60. (Diethyl ester) Calcd. for $C_{15}H_{15}NO_4$: N, 5.13. Found: N, 5.08, 5.18.

(14) German Patent 615,184; *Chem. Abs.*, **29**, 6249 (1935).

(15) This compound has since been prepared by the action of sodamide on cinchoninic acid; Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(16) Beilstein, "Handbuch," Vol. 22, p. 233.

(17) All melting points are corrected.

(18) Bamberger, *Ber.*, **34**, 1330 (1901).

(19) Meister, *ibid.*, **40**, 2441 (1907).

(20) German Patent 335,197, *Jahresber. der Chem. Tech.*, **67**, 68 (1921).

(21) Beilstein, Vol. 14, p. 24.

(22) Compare French Patent 806,640 noted after completion of this work.

Quinoline-2,4-dicarboxanilide.—The dicarbonyl chloride was dissolved in an excess of hot aniline. The dianilide crystallized out on cooling. The compound when recrystallized from aniline or nitrobenzene formed small bluish-white needles; very insoluble in hot water, slightly soluble in hot alcohol, m. p. 285–286°. The crystals turn red in cold concentrated sulfuric acid and go into solution (orange) on warming.

Anal. Calcd. for $C_{23}H_{17}N_3O_2$: N, 11.44. Found: N, 11.42, 11.41.

2,4-Dicarbamylquinoline.—The dimethyl ester (10 g.) was heated with ammoniacal methanol (100 cc.) at 85° for twenty hours. The amide, formed in quantitative yield, crystallized from water or alcohol as small white needles, m. p. 277.5–279.5°; soluble in concentrated sulfuric acid (yellow).

Anal. Calcd. for $C_{11}H_9N_3O_2$: N, 19.53. Found: N, 19.33, 19.02.

2,4-Diaminoquinoline.—Fifteen grams of the diamide was added to 725 cc. of a solution containing 50 g. of potassium hydroxide and 23 g. of bromine. The amide dissolved readily in the cold. The solution was heated on the water-bath for one hour, the small amount of dark brown precipitate filtered off, and the solution bone-blacked, filtered and cooled. The diamine slowly crystallized from the solution. More product was obtained by concentrating the solution. The diamine was recrystallized from water (tendency for supersaturation) as lustrous white needles, m. p. 197–198.5°,[23] yield, 85%. The picrate, crystallized from much hot water, melted at approximately 283° (decomp.).

Anal. Calcd. for $C_9H_9N_3$: N, 26.41. Found: N, 26.51. Calcd. for $C_{15}H_{12}N_6O_7$ (monopicrate): N, 21.64. Found: N, 21.84.

(23) The m. p. in German Patent 615,184 is given as 188–190°; the analysis reported was N, 25.3.

2-Carbamylethyl Cinchoninate.—On heating 2,4-dicarbethoxyquinoline with ammoniacal methanol at 50°, the mono amide was formed in 86% yield; slightly soluble in hot alcohol, very insoluble in water, m. p. 226–227.5° (melts to a tan liquid with a green fluorescence).

Anal. Calcd. for $C_{13}H_{13}N_2O_3$: N, 11.41. Found: N, 11.59, 11.56.

2-Aminocinchoninic Acid.—Five grams of 2-carbamylethyl cinchoninate was heated on the steam-bath for one hour with 250 cc. of water containing 10 g. of potassium hydroxide and 4.75 g. of bromine. Solution (red) was effected on warming. The solution, after being cooled, was diluted to dissolve the potassium salt and made weakly acidic with hydrochloric acid. The yellow precipitate of 2-aminocinchoninic acid was crystallized from much water as lustrous tan crystals, m. p. 362° (dec.); soluble in concentrated sulfuric acid (red), concentrated hydrochloric acid (red), and dilute sodium hydroxide; insoluble in alcohol and benzene.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.9; neut. equiv., 188. Found: N, 14.3; neut. equiv., 187.

Diazotization in concentrated sulfuric acid with dry sodium nitrite and pouring into water gave the known 2-hydroxycinchoninic acid,[16] m. p. 342°. Fusion with soda-lime gave 2-aminoquinoline, white plates from water, m. p. 125–127°.

Summary

Improved preparations of 3- and 4-aminoquinoline, and a new method of preparation of 2,4-diaminoquinoline and of 2-aminocinchoninic acid are described. The attempted preparation of 4-nitroquinoline from 3-aminoquinoline is discussed.

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Coupling Reactions of Aminoquinolines with Benzenediazonium Chloride. A Study of Orientation in the Quinoline Ring

BY R. R. RENSHAW,[1] H. L. FRIEDMAN[2] AND F. J. GAJEWSKI[3]

Knorr[4] and Marckwald[5] pointed out that the chemical properties of naphthalene and quinoline are best explained by accepting the static bond structure proposed by Erlenmeyer, while the chemical properties of benzene are better explained on the basis of Kekulé's concept of shifting double bonds. More recently Pauling[6] has arrived at the same conclusion from quantum mechanical studies, and Le Fèvre and Le Fèvre,[7] from dipole studies of quinoline, favor the Erlenmeyer structure.

There are several good recent surveys of the naphthalene problem,[8] but quinoline has been given only brief discussions.[7,9] Therefore, a comprehensive study of the coupling reactions of the aminoquinolines was undertaken to char-

(1) This paper is being published, following the death of Professor Renshaw, by his collaborators.

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(3) Present address: General Aniline Works, Inc., Grasselli, N. J.

(4) Knorr, *Ann.*, **279**, 212 (1894).

(5) Marckwald, *Ann.*, **274**, 334 (1893); **279**, 14 (1894).

(6) Pauling in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., Chap. 22, p. 1876.

(7) Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1470 (1935).

(8) Fieser in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., Chap. 2, p. 81; Fieser, THIS JOURNAL, **57**, 1459 (1935); *Ann. Repts. Chem. Soc.*, 281 ff. (1936).

(9) Mills and Smith, *J. Chem. Soc.*, 2724 (1922).