[Contribution from the Department of Chemistry of the University of Kansas]

The Preparation of Quinolinic and Cinchomeronic Acids by Ozone Oxidation

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In an attempt to develop a convenient synthesis for quinolinic and cinchomeronic acids, a study was made of the ozone oxidation of quinoline, 8-hydroxyquinoline and isoquinoline. Mainly out of theoretical interest, the investigation was later extended to include 6-aminoquinoline, 6-nitroquinoline, 6-fluoroquinoline, and 6-fluoro-8-aminoquinoline.

The manufacture of pyridine carboxylic acids by the action of ozone on pyridine derivatives has been claimed previously,[1] but details concerning the ozonolysis, isolation, and characterization procedures are lacking. Quinolinic acid has been prepared by the oxidation of quinoline with hydrogen peroxide in the presence of copper sulfate and sulfuric acid,[2] of quinoline and quinoline derivatives carrying substituents in the benzene ring with alkaline permanganate[3] and of 8-hydroxyquinoline with fuming nitric acid,[4] as well as by the electrolytic oxidation of quinoline.[5] Cinchomeronic acid is commonly obtained by oxidation of isoquinoline with alkaline permanganate[6] and of quinine hydrochloride with nitric acid.[7]

Our studies have shown that with quinoline, one mole of ozone was readily fixed, whereupon further addition of ozone to form a diozonide was considerably slower.[8] In all cases, the addition compound formed was usually stable, resisting decomposition, even under drastic conditions, by the reagents commonly employed for decomposing ozonides. Only when 30% hydrogen peroxide[9] or concentrated nitric acid was used, could traces of the desired product, quinolinic acid, be obtained. Upon strong heating, samples of the addition compound liberated ozone and quinoline.

Quinoline derivatives bearing one or more substituents in the benzene ring added ozone less rapidly than quinoline itself, particularly if the substituents were electron-withdrawing in nature. All gave quinolinic acid as the only identifiable product, in poor yield if the substituents were electron-withdrawing, in good yield if they were electron-releasing. Ozone oxidation of 8-hydroxyquinoline, for example, consistently gave 90–95% yields of quinolinic acid, whereas the yields with 6-nitroquinoline for corresponding ozonization times were less than 6%. In the cases of those compounds which gave only low yields of acid, almost half of the starting material could be recovered by steam distillation of the ozonized reaction mixture. These results substantiate the observation that the pyridine ring in quinoline is much more resistant to oxidation than the benzene ring. Because it gave a clean, facile reaction, hydrogen peroxide in acid solution was utilized in the decomposition of the substituted quinoline ozonides.[10] Decomposition, in every case, could be accomplished merely by treatment with hot water, but the reaction was slower and the yields of acid somewhat lower.

Ozone added relatively slowly to isoquinoline forming diozonides. The diozonide formed by the attack of ozone on the benzene nucleus was reactive in comparison with the unsubstituted quinoline diozonide, decomposing directly in solution to yield cinchomeronic acid, if small amounts of water were present. Treatment of the remaining ozonated solution with 30% hydrogen peroxide[11] yielded phthalic acid and small amounts of cinchomeronic acid, indicating that, in marked contrast to its action on quinoline, ozone attacked both the benzene and pyridine rings. Cinchomeronic and phthalic acids prepared in this manner were obtained together in yields of 45 and 50%, respectively.

Experimental Details

Ozonizer.—The source of ozone was a Type T-12 ozonator purchased from Ozone Processes, Inc., Philadelphia, Pa., designed for operation on a 115-volt, 60 cycle a. c. current. At an oxygen rate of 20 liters per hour, the weight concentration of ozone produced was 9–10%.

Ozonization of 8-Hydroxyquinoline.—A solution of 72.5 g. (0.5 mole) of 8-hydroxyquinoline in 400 ml. of glacial acetic acid was subjected to a stream of 9–10% ozonized oxygen at 20 l. per hour, for forty-eight hours at room temperature. During the early stages of the ozonization the solution turned dark brown and the temperature rose to 35°. After twenty-four hours, the solution turned a light yellow color and the temperature dropped to that of the room. Then 110 g. of 30% hydrogen peroxide[12] was added cautiously to the ozonated solution. The resulting solution was refluxed for two hours and then concentrated almost to dryness. The yellow

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[1] British Patent 17,003, January 26 (1914).

[2] Stiks and Bulgach, *Ber.*, **65B**, 11 (1932).

[3] Hoogewerff and Van Dorp, *Ann.*, **204**, 84 (1880); Kirpal, *Monatsh.*, **22**, 361 (1901); Guha and Maller, *Current Sci. (India)*, **13**, 206 (1944).

[4] Sucharda, *Ber.*, **58**, 1727 (1925).

[5] Kulka, This Journal, **68**, 2472 (1946).

[6] Hoogewerff and Van Dorp, *Rec. trav. chim.*, **4**, 285 (1885).

[7] Kirpal, *Monatsh.*, **23**, 239 (1902).

[8] Ozonized oxygen of known ozone concentration was employed, and ozone absorption was followed by systematic titration of the effluent gases. The curve obtained by plotting time *vs.* ozone concentration flattened when ozone was no longer absorbed by the reacting solution. The fact that no quinoline could be obtained upon distillation of the reaction product in basic solution indicated that all of the quinoline had been converted to the ozonide.

[9] Henne and Hill, This Journal, **65**, 752 (1943).

[10] Only starting material and tarry oxidation products could be isolated after similar treatment of any of the substituted quinolines themselves.

[11] Similar treatment of isoquinoline yielded, in addition to starting material, only tarry oxidation products from which no pure compound could be isolated.

[12] When decomposition of the ozonide was effected by use of water, rather than of hydrogen peroxide, the yields were slightly over 70%. The ozonized solution was concentrated under vacuum to one-fifth its original volume, an equal volume of water added, and the mixture refluxed for four hours.

solid obtained was recrystallized from hot water yielding 76 g. (92%) of quinolinic acid, which decomposed at 190.0–191.2° into a black solid (nicotinic acid), which remelted at 229.2–230.4°. The melting point was not depressed when the product was mixed with an authentic sample of quinolinic acid. If small amounts of water were present some quinolinic acid precipitated during the ozonization.

Ozonization of Quinoline.—The ozonization was conducted as described above. The solvent was removed under vacuum and the resulting product refluxed in turn with water, concentrated sodium hydroxide solution, concentrated hydrochloric acid, glacial acetic acid and zinc, stannous chloride and hydrochloric acid, 30% hydrogen peroxide and concentrated nitric acid. Traces of quinolinic acid were isolated only in the last two cases as well as upon low pressure catalytic hydrogenation with 5% palladium on charcoal and subsequent treatment with 30% hydrogen peroxide. The addition compound, upon steam distillation in a basic solution, did not produce any unreacted quinoline. Attempts to distill the compound under low pressures failed, the majority of the material forming a tar, while, to a lesser extent, quinoline and ozone were regenerated. The ozone was detected by the formation of a sodium hydroxide ozonate,[13] which results from the action of ozone on solid sodium hydroxide and which liberates oxygen when placed in an acid solution.

Ozonization of Isoquinoline.—A solution of 20.0 g. (0.155 mole) of isoquinoline in 200 ml. of glacial acetic acid was ozonized as previously described. Best results were obtained if a small amount of water was added to the solvent; cinchomeronic acid (11.4 g., 44.5%), m. p. 259–260°, then precipitated from solution during the ozonization. The solid material was separated by filtration and the filtrate refluxed with 35 g. of 30% hydrogen peroxide for two hours. Evaporation to dryness (or continuous ether extraction) of the resulting solution yielded 12.8 g. (49.5%) of phthalic acid, melting at 204–205°, and small amounts of cinchomeronic acid. The yield of cinchomeronic acid was lowered to 10% when the ozonization time was reduced to twelve hours.

Ozonization of Other Quinolines.—6-Amino-, 6-fluoro-8-amino-, 6-fluoro- and 6-nitroquinoline yielded 65, 44, 15 and 6%, respectively, of quinolinic acid when ozonized as previously described. Tarry oxidation products were also formed and, in the last two cases, almost half of the quinolines were recovered unchanged.

Summary

1. Preparation of quinolinic acid in 90–95% yield and of cinchomeronic acid in 45% yield by ozone oxidation of 8-hydroxyquinoline and isoquinoline, respectively, is described.

2. Studies on the oxidation by ozone of quinoline, 6-aminoquinoline, 6-fluoroquinoline, 6-nitroquinoline, and 6-fluoro-8-aminoquinoline are also reported.

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[13] A study of sodium hydroxide ozonates is being conducted in this Laboratory by Mr. Thomas Whaley.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

The Chemical Effects Accompanying Hydrogen Bonding. II. Alkylation of the Oximes of 2-Hydroxy-5-methylbenzophenone

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The chemical effects of hydrogen bonding were examined in a study of the acyl derivatives of the oximes of 2-hydroxy-5-methylbenzophenone where it was shown that the isomeric bonded (I) and non-bonded (II) oximes behaved similarly on acylation, but that their acyl derivatives showed striking differences in behavior.[2] We have examined the alkylation of these same oximes and find that the differences in behavior show up in the alkylation reaction rather than in the chemistry of the alkylation products.

The generalization in the chemical literature which describes the alkylation of ketoximes in alkaline solution with alkyl halides or dimethyl sulfate is that mixtures of O- and N-alkyl derivatives are formed.[3] The generalization is not applicable to the alkylation of the oximes I and II. The bonded oxime I in normal sodium methoxide solution with methyl iodide (ratios of oxime, alkyl halide, base = 1, 1.5, 1) furnishes the O-methyl ether III in 77–83% yield.[4] None of the N-methyl ether V is obtained. The non-bonded oxime II under the same conditions furnishes the N-methyl ether VI in 83–90% yield. None of the isomeric O-methyl ether IV is obtained. The course of the alkylation is completely controlled by the presence or absence of bonding and it seems reasonable to suggest that the bonding operates by freezing the configuration shown in I and thus preventing the rear-ward approach to the nitrogen atom which would lead to the N-ether V. A scale model of the oxime I shows this clearly. A similar model of the isomeric oxime shows that the oximino group cannot be accommodated to the atomic dimensions involved in IIa and that some rotation about the bond between the substituted phenyl group and the carbon atom of the C=N group is necessary to accommodate the oximino group. In arrangements such as II in which this rotation has taken place the nitrogen atom is relatively accessible to rear-ward approach.

In the alkylation of the non-bonded oxime II, variations in the ratio of oxime to base and to alkylating agent as well as variations in the concentration of the base were without effect. The only product obtained was the N-ether VI. In the alkylation of the bonded oxime I, by con-

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[1] Present address: Sterling-Winthrop Research Institute, Rensselaer, New York.

[2] Blatt, THIS JOURNAL, **60**, 205 (1938).

[3] Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, Vol. 3, p. 1035.

[4] The evidence for the configuration and structure of the alkylation products is to be found in the experimental section.