[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

A New Synthesis of 5-Benzyl-8-hydroxyquinoline and the Antiseptic Activity of its Sulfate

BY L. MCMASTER AND WALTER M. BRUNER

In an attempt to prepare 5-benzyl-8-hydroxyquinoline we found that the method of Karst[1] gave a very poor yield. An improved method was found in a modified Skraup synthesis, starting with *o*-amino-*p*-benzylphenol, a compound not previously described. Satisfactory yields of both compounds were obtained.

A study of the action of 5-benzyl-8-hydroxyquinoline sulfate on *B. coli* has revealed that it is superior to 8-hydroxyquinoline sulfate, being at least equally toxic against *B. coli* and much less irritating to mucous membranes.

Experimental

***o*-Amino-*p*-benzylphenol.**—To 20 g. of *o*-nitro-*p*-benzylphenol prepared by the method of Rennie[2] was added 40 g. of powdered iron. The mixture was agitated with 50 cc. of distilled water and 200 cc. of hydrochloric acid of sp. gr. 1.2 at 100° for seven hours. It was then filtered while still hot and the residue washed with 50 cc. of hot distilled water. The filtrate was rendered strongly alkaline with sodium hydroxide to precipitate the iron hydroxide, which was filtered off. The filtrate was carefully neutralized with dilute hydrochloric acid, which precipitated the *o*-amino-*p*-benzylphenol as a white powder which darkened on exposure to air; yield 13.3 g. (81%).

This product melts at 133° and is soluble in dilute alkali and dilute acid. It diazotizes and gives a reddish-brown dye with an alkaline solution of β-naphthol. The hydrochloride may be precipitated out of a dilute acid solution by means of concentrated hydrochloric acid. Bromine adds to it very readily. The hydrochloride consists of glistening plates which gradually melt with darkening at about 200°.

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.3; H, 6.6. Found (micro): C, 77.8; H, 6.5.

5-Benzyl-8-hydroxyquinoline.—A mixture of 15 g. of *o*-amino-*p*-benzylphenol, 9.8 g. of *o*-nitro-*p*-benzylphenol, 37.5 g. of dry glycerol, 22.5 cc. of 80% acetic acid and 15 cc. of concentrated sulfuric acid was allowed to boil very slowly for sixteen hours, after which it was steam distilled for four to five hours until the distillate became clear, colorless and nearly odorless. About 2 g. of decolorizing charcoal was kept in the mixture during the steam distillation. The residue in the flask was filtered off and the filtrate cooled with ice overnight. The sulfate of 5-benzyl-8-hydroxyquinoline separated as a golden-yellow resin. The free base, obtained by careful neutralization of the product with dilute ammonia water, was converted into the hydrochloride by crystallization from 10% hydrochloric acid. It consisted of fine yellow needles; m. p. 244°; yield 18.6 g. (86%).

The free base crystallized from an alcohol–water solution melted at 111°. It is soluble in warm dilute acid and to a somewhat less extent in warm dilute alkali. Bromine adds to it very slowly.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.57. Found: C, 81.8; H, 5.44.

Bacteriological Tests.—For the purpose of making these tests, the 5-benzyl-8-hydroxyquinoline sulfate was prepared by the method used by Ostermann[3] for preparing 8-hydroxyquinoline sulfate. Yellow rosets of needles of m. p. 216–217° were obtained. Owing to the fact that the benzyl derivative is somewhat less soluble in water than 8-hydroxyquinoline sulfate, it was necessary in making the bacteriological tests to dissolve it in sufficient alcohol equivalent to 1% of the total volume of aqueous solution. Klarmann, Gates and Shternov[4] have shown that this small amount of alcohol does not invalidate bacteriological tests.

Two hundred cc. of a standard lactose broth was inoculated with feces and incubated at 37° for twenty-four hours. Ten cc. of each of the solutions of the concentrations given in Table I was introduced into flasks containing 1 cc. of the inoculated broth in 100 cc. of distilled water. After one hour 10 cc. of this mixture was placed in each of four fermentation tubes containing 20 cc. of the lactose broth. This was repeated in duplicate using 1 cc. and 0.1 cc. of the inoculated solutions. These samples were incubated at 37° for twenty-four hours. The cases where gas formation was observed are marked + in Table I. We desire to thank Mr. Dan O'Gorman of the St. Louis Water Works for making these tests.

TABLE I

Antiseptic solution		Gas formation (cc. of antiseptic solution used)							
		10	10	10	10	1	1	0.1	0.1
Blank		+	+	+	+	+	+	+	+
Phenol	1:100	+	+	+	+	+	+	+	+
8-Hydroxy-	1:100							+	+
quinoline	1:500					+	+	+	+
sulfate	1:1000					+	+	+	+
	1:10,000	+	+	+	+	+	+	+	+
5-Benzyl-8-	1:100							+	+
hydroxy-	1:500					+	+	+	+
quinoline	1:1000					+	+	+	+
sulfate	1:10,000	+	+	+	+	+	+	+	+

Since the absence of gas formation in the fermentation tubes shows effective antiseptic activity, these results prove that the 5-benzyl derivative of 8-hydroxyquinoline sulfate is considerably more germicidal toward *B. coli* than phenol and at least as effective as 8-hydroxyquinoline sulfate.

In order to compare the irritation produced by 5-benzyl-

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[1] Karst, "Dissertation," University of Kiel, 1933, p. 26.

[2] Rennie, *J. Chem. Soc.*, **41**, 223 (1882).

[3] Ostermann, United States Patent 906,918, Dec. 15, 1908.

[4] Klarmann, Gates and Shternov, THIS JOURNAL, **54**, 3318 (1932).

8-hydroxyquinoline sulfate and 8-hydroxyquinoline sulfate a small amount of each of the solid substances was placed on the tongue. In the case of the first compound only a mild tingling sensation but no irritation was noted after twenty minutes. The 8-hydroxyquinoline sulfate proved to be so irritating that it had to be washed from the tongue within two minutes.

Summary

1. *o*-Amino-*p*-benzylphenol has been synthesized.

2. 5-Benzyl-8-hydroxyquinoline was prepared by a modified Skraup reaction. Bacteriological tests with the sulfate of 5-benzyl-8-hydroxyquinoline proved it to be as effective toward *B. coli* as 8-hydroxyquinoline sulfate and considerably more so than phenol. It is, moreover, considerably less irritating to mucous membrane than either of these substances.

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

The Mobility of the Hydrogen Ion Constituent in Aqueous Mixtures of Hydrogen Chloride and Calcium Chloride at 25°

BY L. G. LONGSWORTH[1]

Introduction

The extension of the interionic attraction theory to the conductance of ternary ion mixtures has been made by Bennewitz, Wagner and Küchler[2] and Onsager and Fuoss.[3] The theory indicates that, in an aqueous mixture of hydrogen chloride and calcium chloride, for example, at constant ionic strength, the conductance of the common ion constituent, chloride, deviates but little from the simple additive rule. In such a mixture, however, the mobility of the fast hydrogen ion constituent is less in the presence of the slow calcium ion than in a solution of pure hydrogen chloride at the same ionic strength while the mobility of the calcium ion is greater than in a solution of pure calcium chloride. Moreover the absolute decrease in the mobility of the fast ion is greater than the corresponding increase in that of the slow ion, so that the total conductance of the mixture is less than the value computed on the basis of additivity.

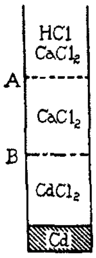

Fig. 1.

The experimental results which are reported in this paper show that the mobility of the hydrogen ion constituent in mixtures of hydrogen chloride and calcium chloride at a constant total concentration of 0.1 *N* decreases continuously with increasing calcium concentration, and has a value in a pure calcium chloride solution that is 6% less than in a hydrochloric acid solution of the same ionic strength. Since the mathematical approximations which were made in the development of the theory become rather serious at the concentration at which the measurements were made, the theory can predict only the magnitude of the effect. The experimental results, however, afford an interesting qualitative confirmation of the theory.

The mobility of the hydrogen ion constituent in the mixtures was determined from a combination of conductance and transference measurements, the moving boundary method having been used for the latter. A comprehensive review of this method has been published by MacInnes and Longsworth.[4] In the application of this method to the cation constituents of the mixtures two boundaries are developed simultaneously, as is shown in Fig. 1, and move at different rates. The displacement of the leading boundary A measures directly the transference number of the hydrogen ion constituent in the mixture, while the motion of the second boundary B yields information concerning the concentration of a solution of pure calcium chloride that has been separated, by electrolysis, from the mixture originally placed in the graduated tube of the moving boundary cell. Although the data are not reported in this paper, the observed displacements of this second boundary deviated by less than 0.5%, on the average, from values that were computed with the aid of the theory developed by MacInnes and Longsworth[5] for the concentration changes on electrolysis in ternary ion mixtures.

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[1] The experimental part of this work was completed while the author held a National Research Council Fellowship in Chemistry.

[2] Bennewitz, Wagner and Küchler, *Physik. Z.*, **30**, 623 (1929).

[3] Onsager and Fuoss, *J. Phys. Chem.*, **36**, 2689 (1932).

[4] MacInnes and Longsworth, *Chem. Rev.*, **11**, 171 (1932).

[5] See Ref. 4, p. 214.