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SOLUBILITY AND HYDROGEN-ION CONCENTRATION OF QUININE SALTS.*

PART II. A NEW SERIES OF DOUBLE QUININE SALTS.

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In view of the evidence in a previous paper (1) and with the hope of preparing a series of more soluble and less acid quinine salts, attempts were made to prepare double salts by adding weakly dissociated organic acids to the quinoline nitrogen of quinine hydrochloride. A review of the literature brought to light seventy-nine quinine salts excluding those prepared for the purpose of separating optical isomers. It is hoped that this investigation and the new salts here recorded will subtract from rather than add to the present confusion. The only quinine salts reported thus far which have a weak acid on the quinoline nitrogen have been quinine diformate (2) which is soluble approximately 4%, and quinine disalicylosalicylate (3) which is insoluble. For the double salts discussed here, the first acid, as in quinine.HCl.CH_3COOH, will refer to the acid on the quinuclidine nitrogen, and the second acid will refer to that on the quinoline nitrogen. The difficulties involved in adding a weak acid to the quinoline nitrogen were studied in detail using acetic acid. A summary of the methods used and of the degrees of success is as follows:

Method 1.—Direct Solution. 2.0 Gm. of quinine hydrochloride would not dissolve in an equivalent of normal acetic acid. The acetic acid caused no increase in solubility and the hydrochloride was obtained pure by evaporation and drying.

Method 2.—Precipitation of Quinine.HCl.$^1/_2H_2SO_4$ with Barium Acetate. This was first tried in a concentrated solution and using equivalents of acetic acid and barium hydroxide. The results of several attempts were variable due to the formation of temporary concentrated colloidal solutions peptized by acetate ion. Attempts at crystallization always produced a mixture of quinine acetate and quinine hydrochloride. Crystallization of quinine.HCl.CH_3COOH was also a failure when an equivalent of barium acetate was added to a dilute solution of a quinine.HCl.$^1/_2H_2SO_4$. Addition of a large excess of potassium acetate and acetic acid to the crystallizing mixture caused precipitation of pure quinine acetate.

Method 3.—Crystallization from Alcohol. By the same method but using absolute alcohol instead of water, quinine hydrochloride was the only product that could be crystallized. When the same procedure was performed in 50% alcohol, a large precipitate of quinine acetate was obtained. The substance still in solution was crystallized five times from water and dried at room temperature. Analysis was as follows: 77.18% quinine, 8.64% HCl, 14.40% CH_3COOH, $^1/_2$ mol H_2O. This conforms to quinine.HCl.CH_3COOH. Solubility 10.7 Gm. per 100 cc. Per cent yield = 1.35.

Method 4.—Formation in Alcohol and Extraction with Ether. To a mixture of 6.00 Gm. of quinine.HCl and one equivalent of acetic acid in 5 cc. of absolute alcohol was added a large ex-

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cess of anhydrous ether. A large precipitate formed which was quinine hydrochloride. The ether was decanted and repeatedly evaporated until free from acetic acid and then extracted with water. From the water there was crystallized 0.37 Gm. of product assaying quinine.HCl.CH_3-COOH. Per cent quinine = 77.2. Per cent HCl + CH_3COOH = 22.93. Melting point: when heated rapidly the salt decomposed between 119° and 122° C.

Method 5.—Formation in Ether. Crystallization of equivalents of quinine.HCl and CH_3-COOH from ether was not successful.

Method 6.—Preparation in Solution by Barium Acetate Method. Accurately standardized equivalents of quinine.HCl.$^1/_2H_2SO_4$ and barium acetate were mixed slowly in dilute solution, the precipitate being centrifuged down after each addition. The solution was separated and concentrated to the saturation point. The following properties were determined: Solubility at 25° C. = 10.81 Gm. per 100 cc. p_H = 3.87. $[\alpha]_D^{25}$ = levo 165°. This product was apparently stable for two days and then precipitation occurred. When equilibrium was reached (after 8 days), the concentration was 3.16% as free quinine, and the p_H had decreased to 2.36. The precipitate was a mixture of quinine.HCl and quinine.CH_3COOH. A second preparation by the same method gave the following properties: Solubility = 10.84%, p_H = 3.87. Stable for 24 hours.

In order to compare properties, quinine.CH_3COOH.HCl was prepared. It would not crystallize from a hydrochloric acid solution of quinine.CH_3COOH, so quinine.CH_3COOH was dissolved in two equivalents of H_2SO_4 and precipitated with an equivalent of barium chloride. Crystallization was best from a 45:20 alcohol-ether mixture. A comparison of the properties of these two salts furnishes proof of their configuration.

Quinine.HCl.CH_3COOH.		Quinine.CH_3COOH.HCl.	
% quinine	= 77.20	% quinine	= 77.16
% acid	= 22.89	% acid	= 22.94
Solubility	= 10.84 Gm. per 100 cc.	Solubility	= 72.40 Gm. per 100 cc.
p_H of 10.84% soln.	= 3.87	p_H of 10.84% soln.	= 2.09
Unstable in solution.		Stable in solution.	

Quinine diacetate was prepared in solution by the same general method. The product was stable in a saturated solution of 2.15%. p_H = 4.60. Crystallization from water was successful but difficult.

Quinine.HCl.Propionate was prepared in solution by the same general method, that is, by precipitating the sulfate with an exact equivalent of barium propionate and evaporating to the saturation point. The analysis was quinine 7.82 Gm. per 100 cc., and total acid 2.68 Gm. per 100 cc. Properties at 20° C. were: Solubility = 10.47 Gm. per 100 cc.; p_H of saturated solution = 4.76; $[\alpha]_D^{20}$ = levo 137° at p_H 4.76. The p_H of these saturated solutions was determined with a glass electrode and 0.1 normal salt bridge. A pure product could not be obtained by crystallization from water.

Quinine.HCl.Valerate was prepared in solution by the same method. The analysis of the solution was quinine 8.32 Gm. per 100 cc., and total acid 3.56 Gm. per 100 cc. Properties at 20° C. were: Solubility = 11.87 Gm. per 100 cc.; p_H of saturated solution = 4.10; $[\alpha]_D^{20}$ = levo 131°. Crystallization from water was unsuccessful.

Quinine.HCl.Lactate was prepared in solution by the same method. The analysis of the saturated solution was quinine 82.66 Gm. per 100 cc., and total acid 32.74 Gm. per 100 cc. Properties at 20° C. were: Solubility = 114.9 Gm. per 100 cc.; p_H of saturated solution = 4.13; $[\alpha]_D^{20}$ = levo 153°. The product was

crystallized pure from water by maintaining a solution slightly below saturation at 5° C. for two weeks. Crystallization from ether-alcohol mixtures was unsuccessful.

SUMMARY.

The following new quinine salts were prepared with the weak acids added to the weak nitrogen: quinine.HCl.acetate, quinine diacetate, quinine.HCl.propionate, quinine.HCl.valerate and quinine.HCl.lactate. The latter is soluble 115 Gm. per 100 cc. of solution with a p_H of 4.13.

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THE RANDOM SAMPLING ERROR AS A POSSIBLE ANSWER TO THE APPARENT VARIATIONS IN ANTISEPTIC TEST DATA.[1]

BY ARTHUR R. CADE.[2]

Lack of uniformity in the results of duplicate antiseptic tests, as obtained either by the same worker on different days using supposedly identical cultures and techniques, or by different workers using the same procedures, has brought about recently a somewhat extended discussion as to the cause for these differences in findings. Variation in the day-to-day resistance of the test organism has been suggested as the most probable cause, in a recent series of papers published by members of the AMERICAN PHARMACEUTICAL ASSOCIATION Committee who have investigated antiseptic testing procedures. As a result of this work by Gathercoal and his co-workers (1) there has been established and incorporated into the latest National Formulary a standard of resistance for the test organism *Staphylococcus aureus*, which appears to be slightly inferior to the standard set by the Food and Drug Administration of the United States Department of Agriculture (2). The specifications of the latter state that the test organism must live in 1–80 phenol for 5 minutes, and must be killed by the same concentration in 10 minutes, at 37° C. At the same time, the organism should live in 1–90 phenol solution for 10 minutes at 37° C. The National Formulary standard states that the organism must be killed in the 1–80 phenol solution in 10 minutes, but live in the 1–90 strength for 10 minutes at 37° C. Thus, the difference is that the National Formulary does not require that the organism remain alive in 1–80 phenol for 5 minutes, at 37° C., which requirement the F. D. A. insists upon. The National Formulary specifications have been so drawn up, it is claimed, because experience has taught that it is difficult to get an organism which will retain this resistance with any degree of

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[1] The experiments reported in this paper form the basis for a thesis presented by Arthur R. Cade in partial fulfilment of the requirements for the degree of Doctor of Philosophy, at the University of Minnesota, December 1933.

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