SCIENTIFIC SECTION

SOLUBILITY AND HYDROGEN-ION CONCENTRATION OF QUININE SALTS.*

PART I. EFFECT OF THE QUINOLINE AND QUINUCLIDINE NITROGENS.

FREDERICK F. JOHNSON.[1,2]

This work was undertaken with the hope of obtaining more fundamental information concerning the dissociation of free acid from an alkaloidal salt. The principles shown and verified in this paper will be used in an attempt to prepare a series of more soluble and less acid quinine salts.

Since there were no data in the literature concerning the change in acidity of quinine dihydrochloride during sterilization and storage, it was decided to observe these changes while the work was in progress. Solutions were prepared of strengths equivalent to those commonly used for injection purposes, namely, 3.25%, 10%, 25% and 50%. The p_H was determined before and after sterilization in soft glass ampuls for 30 minutes at 15 lbs. The p_H values were determined with quinhydrone —0.1 normal calomel electrodes, precipitation occurring when a saturated salt bridge was used. These ampuls were then stored in the dark at room temperature.

Strength.	p_H.	p_H after Sterilization.	p_H—36 Days' Storage.	p_H—2 Years' Storage.
3.25%	2.59	2.61	2.62	2.66
10.0 %	2.14	2.14	2.16	2.22
25.0 %	1.68	1.67	1.71	1.84
50.0 %	1.26	1.26	1.29	1.44

From this data it is clear that the reaction remains constant during sterilization in soft glass, but becomes less acid during prolonged storage. No precipitation occurred.

The data concerning the production of acidity in quinine salts should be preceded by a review of the very meager literature on this subject. The most acceptable measurements of the dissociation constants of quinine are those of Kolthoff (1). The results at 15° C. were: $K_1 = 1.1 \times 10^{-6}$ and $K_2 = 2.0 \times 10^{-10}$. Kolthoff also determined the K of quinoline to be 3.2×10^{-10}. Dietzel and Söllner (2) assumed the dissociation of acid from the nitrogens to be due to an ionization of the nitrogens, the increasing ionization of the nitrogens being due to an increased hydrogen-ion concentration and proportional to the increase in optical rotation. Arnall (3) approached this dissociation from a different standpoint, measuring the amount of HCl produced by hydrolysis of the monohydrochloride by the acceleration of the rate of inversion of a sucrose solution. The value obtained for quinoline hydrochloride was twenty times greater than the corresponding value for quinine hydrochloride.

There is no relation between the dissociation of the alkaloid and the hydrogen-ion concentration of its salts. By calculation from the dissociation constants,

* Scientific Section, A. PH. A., New York meeting, 1937.

[1] Assistant State Chemist, Seattle, Washington.

[2] Univ. of Washington, College of Pharmacy, Dept. of Pharmaceutical Chemistry.

$[OH_1^-]$ should be 26 times greater than $[OH_2^-]$. However, $[H^+]$ of B.2HCl is 2800 times greater than of B.HCl. Also no proportion exists between the difference in dissociation constants of the alkaloid and the difference in acidity of the two salts. Further measurements indicated that this discrepancy decreases somewhat as concentration decreases.

It was then attempted to formulate the degree of dissociation of the alkaloidal salt. This cannot be obtained accurately unless the $[OH^-]$ produced by the dissociation of the hydrolyzed base is considered. Mayeda (4) previously had derived the following expression:

$\gamma_b = \dfrac{K_w}{K_w + K_b.10^{-p_H}}$ where γ_b = the degree of hydrolysis of an alkaloid after being freed by dissociation of the salt. That is, (1) $\gamma_b = \dfrac{[BOH]}{[C]}$. In his derivation, Mayeda assumed complete dissociation of the salt.

Considering the assumption too great for this purpose, the derivation was repeated while considering the dissociation represented by $BA \rightleftarrows [B^+] + [A^-]$. This derivation has been omitted to conserve space as it is similar in many respects to the formulation of Mayeda (4). The final expression obtained is

$$\gamma_b = \frac{K_w.10^{-p_H}}{C(K_w + K_b.10^{-p_H})} \tag{2}$$

This equation represents the degree of hydrolysis of an alkaloid as a function of hydrogen-ion concentration and the total salt concentration. γ_b does not vary inversely with C because the hydrogen-ion concentration increases with C.

With an expression available for γ_b, the degree of liberation of free acid from an alkaloidal salt can be obtained from the hydrogen-ion concentration even in weakly acid solutions. Consider the dissociation of an alkaloidal salt.

$$BA \rightleftarrows [B^+] + [A^-]$$

Let γ_a = the degree of dissociation into free acid.

$$\gamma_a = \frac{[A^-]}{[C]}$$

Assuming complete dissociation of the liberated acid, and accounting for the hydroxyl-ion concentration produced by the hydrolyzed base,

$$[A^-] = [H^+] + \frac{K_b[BOH]}{[B^+]}$$

Equating [BOH] and $[B^+]$ in terms of γ_b,

$$[A^-] = [H^+] + \frac{K_b[C]\gamma_b}{[C](1 - \gamma_b) - [C] + [H^+]}$$

Substituting the value of γ_b from Equation 2 and simplifying gives

$$[A^-] = [H^+] + \frac{K_bK_w}{2K_w + K_b.10^{-p_H}}$$

$$\text{from which } T_a = \frac{10^{-p_H} + \dfrac{K_bK_w}{2K_w + K_b.10^{-p_H}}}{C} \tag{3}$$

In order to calculate the degree of dissociation (γ_a) of the alkaloidal salt quinine hydrochloride as a function of the concentration, it was necessary to determine the p_H values used in Equation 3, especially at low concentrations. When the p_H was plotted against concentration of quinine hydrochloride, a very distorted curve was obtained due to the effect of the atmospheric CO_2 as concentration decreased. Pure water of p_H 6.90 was prepared and the concentration: p_H curve was repeated using this water.

The method was as follows. Definite weights of anhydrous quinine hydrochloride were placed in weighed 700-cc. tin containers, each provided with a two-holed rubber stopper admitting either a 10-cc. or a 100-cc. pipette and a tube branching into two $Ba(OH)_2$ traps, one through which air could be removed and one through which air could be entered. Water was distilled four times; before the fourth distillation the water was alkalinized with KOH, the tin receiver was connected through the pipette with the condenser and the entire apparatus was evacuated through the $Ba(OH)_2$ trap. Solutions were removed and placed in color comparison tubes by being sucked into the evacuated pipette and forced with CO_2-free air into the evacuated comparison tubes containing the proper amounts of bromothymol blue. The two solutions of lowest concentration were prepared from the 0.001 molar solution by sucking the solution into an evacuated pipette and making up the volume by distillation as before. The p_H of the three solutions of greatest concentration could not be determined colorimetrically as slight precipitation of the dye occurred. The CO_2 effect being negligible at this concentration, the p_H values were determined with a quinhydrone electrode using a tenth-normal instead of a saturated salt bridge.

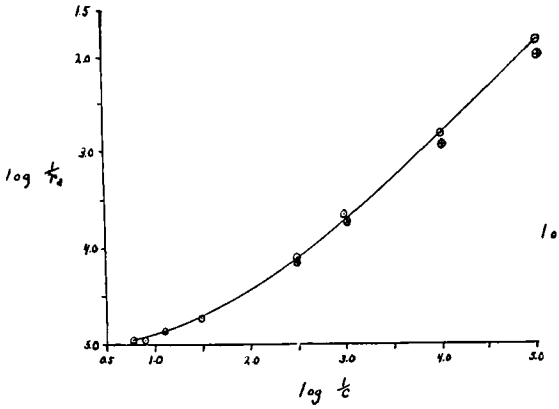

Fig. 1. — Concentration and γ_a of Quinine. HCl
● represents values obtained by disregarding hydrolysis of base.

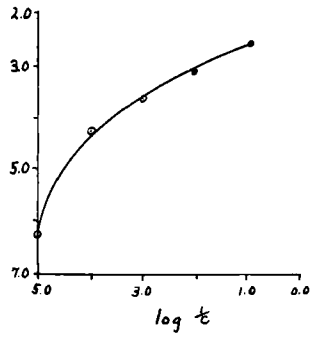

Fig 2

TABLE I.

Log $\frac{1}{C}$.	p_H.	Log $\frac{1}{\gamma_a}$.
0.79	5.77	4.98
0.85	5.82	4.98
0.90	5.87	4.97
1.10	6.00	4.89
1.50	6.23	4.71
2.00	6.45	4.43
2.50	6.62	4.09
3.00	6.74	3.68
4.00	6.90	2.80
5.00	6.95	1.83

In Table I are shown the p_H values as determined and the values for γ_a as calculated and compared with the concentrations. The function is plotted in Fig. 1 and shows the following to be true: (*a*) The degree of dissociation is independent of the concentration in ordinary dilutions. (*b*) The degree of dissociation increases sharply below a concentration of about 0.08 molar and becomes inversely proportional to the concentration. (*c*) The hydrolysis and dissociation of the alkaloid has a negligible effect on the apparent dissociation of the salt.

The difference in p_H between the two hydrochlorides of quinine is plotted in Fig. 2 as a function of concentration.

Dietzel and Söllner (2) assumed that the first equivalent of acid adds to the quinuclidine nitrogen of quinine because of the proximity of the hydroxyl group. A comparison of γ_b and γ_a of the nitrogens of quinine and the nitrogen of quinoline should definitely verify this assumption. For this purpose quinoline was carefully purified in the form of the sulfate and then converted to the hydrochloride and free base for subsequent measurements. The dissociation constant was determined on the free base in water of p_H 6.84 with a glass electrode. At 20° C., $p_H = 8.87$. $K_b = \frac{[OH^-]^2}{C} = 3.3 \times 10^{-10}$ agreeing with the second dissociation constant of quinine which is 3.3×10^{-10} at 15° C.

p_H 0.1 molar quinoline.HCl at 20° C. = 2.91
p_H 0.1 molar quinine.2HCl at 20° C. = 2.82
p_H 0.1 molar quinine.HCl at 20° C. = 5.87

From these the values for γ were calculated.

Quinine.HCl	$\gamma_b = 10^{-6.45}$	for quinuclidine nitrogen
Quinine.2HCl	$\gamma_b = 10^{-3.63}$	for quinoline nitrogen
Quinoline.HCL	$\gamma_b = 10^{-3.62}$	
Quinine.HCl	$\gamma_a = 10^{-4.93}$	for quinuclidine nitrogen
Quinine.2HCl	$\gamma_a = 10^{-1.82}$	for quinoline nitrogen
Quinoline.HCl	$\gamma_a = 10^{-1.91}$	

It is evident that K_1 is due to the quinuclidine hydrolysis and K_2 to the quinoline hydrolysis. The first equivalent of acid adds to the quinuclidine nitrogen and the second to the quinoline nitrogen. The infallibility of this was further verified by comparing values of γ for the quinine formates, acetates and lactates.

SUMMARY.

1. The reaction of quinine dihydrochloride remains constant during sterilization but becomes considerably less acid without precipitation during storage for two years in soft glass ampuls.

2. Expressions were derived for (*a*) the degree of hydrolysis of an alkaloid after being freed by dissociation of a salt, (*b*) the degree of dissociation of an alkaloidal salt into free acid.

3. The statement was verified that in quinine the first equivalent of acid adds to the quinuclidine nitrogen and the second equivalent adds to the quinoline nitrogen. The latter is responsible for the large solubility and large acidity.

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SOLUBILITY AND HYDROGEN-ION CONCENTRATION OF QUININE SALTS.*

PART II. A NEW SERIES OF DOUBLE QUININE SALTS.

FREDERICK F. JOHNSON.[1,2]

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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* Scientific Section, A. PH. A., New York meeting, 1937.

[1] Assistant State Chemist, Seattle, Washington.

[2] University of Washington, College of Pharmacy, Dept. of Pharmaceutical Chemistry.