THE ELECTROMETRIC TITRATION OF ALKALOIDS: APPLICATION OF THE QUINHYDRONE ELECTRODE TO ALKALOIDAL TITRATIONS.*

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INTRODUCTION.

Einar Biilmann and others[1] have shown that by means of quinhydrone, which is a combination of one molecule of hydroquinone and one molecule of quinone, an electrode may be prepared which in many cases can be used as a very good hydrogen electrode. Such an electrode gives a hydrogen pressure which is exceedingly feeble, but in the case of a dilute electrolyte, constant and well-defined at a given temperature. The hydrogen pressure results from the transformation of dissolved hydroquinone to dissolved quinone and hydrogen, and *vice versa*. The chemical reaction involved is:

$$\underset{\text{quinone}}{C_6H_4O_2} + H_2 \rightleftarrows \underset{\text{hydroquinone}}{C_6H_4O_2H_2}$$

According to the law of mass action,

$$[H_2] = k \cdot \frac{[C_6H_4OH]}{[C_6H_4O_2]}$$

i. e., at a particular temperature the hydrogen concentration in the quinone-hydroquinone electrode is exclusively dependent on the ratio between the concentration of hydroquinone and quinone.

Biilmann determined the E. M. F. of such an electrode by measurement of a series of cells of the type

$$\text{Pt/quinhydrone, } a\text{-}nH + /\text{-}anH + H_2 \text{ 1 atm./pt.}$$

where *a-nH* represents an *a*-normal, dilute acid electrolyte, whose molar concentration does not exceed 0.1; this was found to be 0.7044–18°, 0.699–25°. The platinum immersed in the quinhydrone solution is positive to the platinum of the hydrogen electrode.

In the quinhydrone electrode, one does not use a mixture of hydroquinone and quinone, but the compound quinhydrone, which in aqueous solution dissociates almost completely into equal molecules of its components.

Quinhydrone is easily prepared according to the directions of Biilmann. To a solution of 25 Gms. of hydroquinone in 100 cc. of water (may need warming) one adds 300 cc. of a warm solution (about 65°) of 100 Gms. ferriammonium sulphate. The quinhydrone comes down in very find needles. Cool the mixture in ice, filter with suction, and wash three or four times with cold water. A yield of about 15 Gms. is obtained.

PURPOSE OF INVESTIGATION.

A great number of indicators have been comparatively recently placed at the disposal of the analyst as a result of the work of Soerensen, Clark and others.

* The expenses of this investigation have been supported in part by a grant from the Research Fund of the AMERICAN PHARMACEUTICAL ASSOCIATION.

[1] "Trans. of the Faraday Society," 19 (1924), No. 57, 676.

During the past three years, workers in this laboratory have been endeavoring to select from these, that particular indicator best suited for use in the acidimetric determination of each of the alkaloids.[1,2,3]

The only rational method for such selections would seem to be actual electrometric measurements of the p_H value of solutions of the alkaloidal salts, and a subsequent choice of the indicator upon this basis.

A natural development of this work was the application of electrometric titrations to the alkaloidal determination of residues in actual crude drug assays. All electrometric determinations had been made with the hydrogen electrode *versus* a ($N/1$ KCl) calomel electrode.

It was found that in these electrometric titrations, equilibrium was not rapidly obtained, thereby consuming much time between readings. This time element also increased the danger of reduction of the alkaloid by the hydrogen in the presence of the platinum black electrode. Biilmann's work[4] suggested the use of quinhydrone. We found that the quinhydrone electrode can be quickly prepared and that equilibrium is obtained in a very short time. The danger of reduction is greatly lessened.

We accordingly have determined the p_H value of solutions of morphine, atropine and strychnine salts, using the quinhydrone electrode and have also attempted to apply it to actual electrometric titrations of these alkaloids. The following formula was used in all p_H determinations:

$$p_H = \frac{4148 - \text{E. M. F.}}{0.0577} \text{ at } 25°$$

EXPERIMENTAL DATA.

The p_H values were first determined of solutions of 0.4740 Gm. of morphine sulphate dissolved in 30 cc. and 240 cc. respectively of boiled distilled water, plus a pinch of quinhydrone. The measured potential difference, by which the p_H value was obtained was made by connecting a quinhydrone electrode through a saturated KCl salt bridge to a standard mercury calomel $N/1$ KCl combination, the calomel electrode being negative to the quinhydrone electrode. The p_H value was next determined on 0.4740 Gm. of morphine sulphate in the presence of 0.05325 Gm. of anhydrous sodium sulphate, again using 30 cc. and 240 cc. respectively of boiled distilled water plus a pinch of quinhydrone. The effect was also tried on 0.438 Gm. of sodium chloride with the same dilutions of morphine sulphate. Approximately the amounts of morphine sulphate and the salts were used which one would find at the end-point in a routine titration of the alkaloidal residue from an opium sample. In the U. S. P. assay, 20 cc. of $N/10$ H_2SO_4 are used, which represents an excess in titrating 4 Gms. of opium. In using 0.4740 Gm. of morphine (0.35645 Gm. of anhydrous morphine) 12.5 cc. of $N/10$ H_2SO_4 are taken up, an excess of 7.5 of $N/10$ H_2SO_4 remains to be neutralized with $N/10$ NaOH.

At the neutral point then, there would be in the titrating flask, providing the sample of opium contained 0.35645 Gm. of anhydrous morphine, the following:

[1] JOUR. A. PH. A., 11 (1922), No. 12.
[2] *J. Am. Chem. Soc.*, 44 (1922), No. 10.
[3] JOUR. A. PH. A., 12 (1923), No. 10.
[4] "Trans. of the Faraday Society," 19 (1924), No. 57, 676.

0.4740 Gm. of morphine sulphate, 0.05325 Gm. of sodium sulphate, or if $N/10$ HCl were used, 0.438 Gm. of sodium chloride, in place of the sodium sulphate.

The object of the determination of the p_H value in the presence of salts was to note the effect, if any, of these salts which are normally formed in the indirect titration of alkaloidal residues in the assay of opium.

A number of determinations were made, the results as indicated below being typical. Recrystallized morphine sulphate and boiled distilled water were used in each experiment.

TABLE I.

Morphine sulphate Gm.	Sodium sulphate Gm.	Sodium chloride.	Amount of solvent.	p_H values.
0.4740	0.05325	.....	30 cc.	5.287
0.4740	0.05325	.....	240 cc.	5.748
0.4740	.....	0.0435	30 cc.	5.27
0.4740	.....	0.0435	240 cc.	5.69
0.4740	.....	.....	30 cc.	5.26
0.4740	.....	.....	240 cc.	5.64

The influence of salt upon the p_H seemingly is negligible. The effect of increasing amounts of sodium sulphate added to a definite volume of $N/20$ morphine sulphate containing small amount of quinhydrone was determined. A normal KCl calomel electrode was used as the other cell.

TABLE II.

$N/20$ morphine sulphate.	Quinhydrone *versus* calomel.	p_H values.	Sodium sulphate Gm.
.....	.....	4.66	0
.....	.....	4.70	0.001
.....	.....	4.78	0.005
.....	.....	4.82	0.008
.....	.....	4.87	0.015
.....	.....	4.92	0.025
.....	.....	5.01	0.040
.....	.....	5.1	1.

It has been found that with increased concentration of salts the potential decreases. This is due, perhaps to the influence of the salts on the solubility of hydroquinone and quinone which it decreases, but not in the same degree. The quinhydrone electrode in a solution rich in salt is more negative than that of a quinhydrone in a solution with lower salt concentration. It must be noted here that the p_H change is not great, and also that but 30 cc. of solution was used whereas in an actual titration 250 cc. of solution was used.

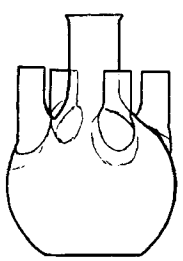

Fig. 1.—Titrating flask.

In carrying out alkaloidal titrations with the quinhydrone electrode we used a 500-cc. round bottom flask (Fig. 1) having four openings in the top, one for each of the following: stirring rod, blank platinum foil, burette containing the $N/10$ sodium hydroxide and the comparison electrode side arm. In this round bottom flask were placed a known amount of anhydrous morphine, a calculated amount of $N/10$ sulphuric acid, and a pinch of quinhydrone and this mixture diluted to 250 cc.

Our comparison electrode (Fig. 2) contains a solution of morphine sulphate, sodium sulphate and a small amount of quinhydrone of the same strength that theoretically will be present at the neutral point in the titrating flask (Fig. 1). This cell necessarily also has a blank platinum foil with attachments for connecting the comparison cell to the potentiometer, then to galvanometer and back to the titrating flask, thereby completing the circuit for our titrating experiments. The solution in the comparison cell was prepared as indicated because at the neutral point (zero reading on galvanometer) after adding sufficient $N/10$ NaOH, the solution which we are titrating should be identical with the solution in comparator (no potential difference) and from the amount of $N/10$ sodium hydroxide added to our titrating flask, the amount of morphine present in the solution can be determined in the usual way. It is not necessary in the experiment to use a potentiometer unless one wishes to show results by plotting the changes in E. M. F. against the amounts of standard alkali added. Equally as accurate results can be obtained more rapidly by attaching both comparator and round bottom flask to galvanometer through electrodes, bridging the two cells by placing the tip of the comparator cell in the solution in the titration flask (Fig. 3) and adding $N/10$ NaOH until a zero reading is obtained on galvanometer (no deflection). This is the neutral point indicating that both solutions are alike. A number of determinations were made. We give the results of three which are typical of the majority.

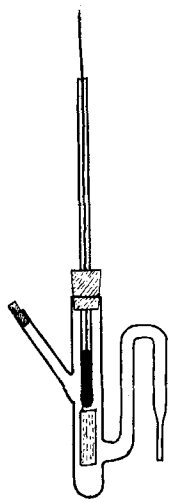

Fig. 2.—Comparison electrode.

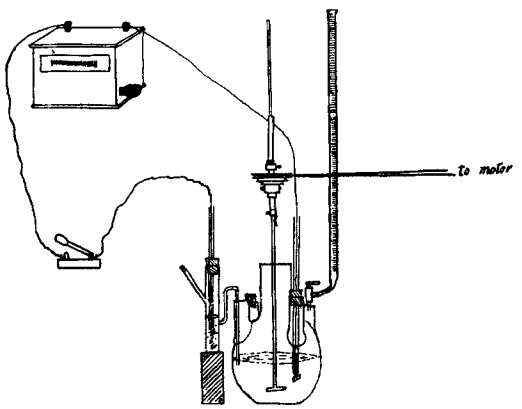

Fig. 3.—Titration flask.

CONTENTS OF TITRATION FLASK AT BEGINNING OF TITRATION.

Morphine, anhydrous	0.1723 Gm.
Sulphuric acid $N/10$	10 cc.
Quinhydrone	minute amount
Water, boiled distilled q. s.	250 cc.

CONTENTS OF COMPARISON FLASK.

Morphine Sulphate	1.2291 Gm.
Sodium Sulphate, anhydrous	0.284 Gm.
Quinhydrone	minute amount
Water, boiled distilled q. s.	250 cc.

$N/10$ NaOH added to titrating flask, to zero galvanometer reading or neutral point.

RESULTS.

TABLE III.

	Gm. anhydrous morphine. Present.	Found.
Sample 1	0.1723	0.1729
Sample 2	0.2010	0.1970
Sample 3	0.1715	0.16944

Using methyl red as an indicator, No. 3 result gave 0.17145 Gm. morphine present. We were unable to obtain an end-point with brom phenol blue.

We determined the p_H value of $N/100$ strychnine sulphate, also $N/200$ strychnine sulphate, using as a comparison a $N/1$ potassium chloride calomel cell, each solution containing quinhydrone.

TABLE IV.

		p_H.
$N/100$ Strychnine Sulphate	Q/cal.	4.887
$N/200$ Strychnine Sulphate	Q/cal.	5.380

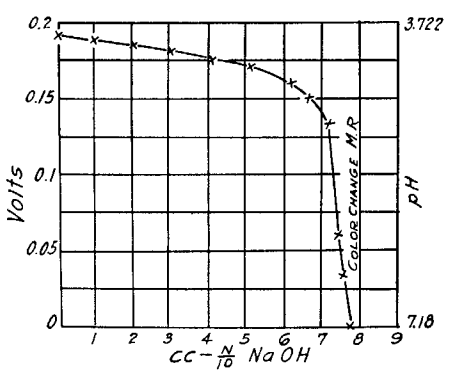

Fig. 4.

A definite amount of strychnine, recrystallized and dried to constant weight was treated with an excess of $N/10$ sulphuric acid and titrated with $N/10$ sodium hydroxide. The set up used in the morphine determination was employed, the end-point being the zero reading on the galvanometer. As a check, we used methyl red for our colorimetric determination. The strychnine titrating curve in Fig. 4 shows the relation of voltage to cc. of $N/10$ NaOH added. The p_H values at beginning and at the end of titration are also indicated.

VALUES.

Strychnine.

Present	0.4177 Gm.
Found	0.4161 Gm.

The p_H values of solutions of atropine sulphate were determined using the quinhydrone electrode *versus* the calomel electrode.

TABLE V.

COMMERCIAL SAMPLE—BOILED DISTILLED WATER.

Sample.	Strength.	Voltage.	p_H values.
No. 1	1%	0.07565	5.877
No. 2	1%	0.0752	5.885
No. 3	1%	0.0907	5.61

TABLE VI.

ATROPINE SULPHATE RECRYSTALLIZED THREE TIMES.

Sample.	Strength.	Voltage.	p_H values.
No. 1	1%	0.1727	4.19
No. 2	1%	0.1811	4.03

Titrations of atropine were also carried out using the same set up as in the morphine determination.

TABLE VII.

Sample.	Present.	Found.
No. 1	0.1446	0.14517
No. 2	0.1446	0.14259
No. 3	0.1446	0.1424

DISCUSSION OF RESULTS.

In the majority of cases, results were obtained which were slightly lower than the theoretical values. In the determinations where methyl red was also added to the solution, the end-point as indicated by the color change invariably was reached before the electrometric end-point, the colorimetric results consequently being higher and nearer the theoretical values. Although the alkaloids used in all of the titration experiments had been recrystallized several times, and then dried to constant weight at temperatures insuring the absence of decomposition, it is not possible to say that these samples were 100% pure. Since the purity of an alkaloid is ordinarily determined by acidimetric titration, the accuracy of which is questionable, we have no absolute criterion for the purity of our samples. It is therefore, not permissible to assume that the results obtained by the use of the quinhydrone electrode, are either more or less nearly correct values than those obtained colorimetrically. The results obtained with the quinhydrone electrode are reproducible, however, and it remains for further investigation to discover whether the electrometric or the colorimetric method of titration gives the more nearly correct result.

SUMMARY.

The application of the quinhydrone electrode to the titration of alkaloids has been described.

It has been shown that electrometric titrations carried out with the quinhydrone electrode, using a comparator electrode set up, give results which are consistent, but invariably slightly lower than those given by the calorimetric method.

ACKNOWLEDGMENTS.

The completion of the experimental work in this paper was made possible by a grant from the Research Fund of the AMERICAN PHARMACEUTICAL ASSOCIATION.

We wish to thank Mr. J. Lester Hayman of this department for the drawings in this paper.

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THE USE OF THE POTENTIOMETER IN THE QUANTITATIVE ANALYSIS OF ALKALOIDAL SOLUTIONS.*

BY JOHN C. KRANTZ, JR.

INTRODUCTION.

There is no instrument which, in recent years, has helped the scientist in the study of chemical phenomena more than the potentiometer. The pharmacist has not been slow to recognize the possibilities of the use of this instrument in solving many of the pharmaceutical problems which have confronted the manufacturer, retailer and drug analyst. Thus Masucci and Moffat[1] have very comprehensively shown how easily the actual acidity of medicinal solutions may be determined by this instrument in conjunction with the other apparatus necessary for its proper use. Smith and Giesy[2] have employed the potentiometer in the determination of the alkalinity of Magma Magnesiæ. McGill[3] and his associates have begun a pioneer phase of research in employing electrical instruments to evaluate the alkaloidal value of crude drugs.

In this work McGill has determined the voltage end-point for several alkaloidal residues and consequently he has been able to employ the potentiometer as an indicator in the residual titration of the excess of acid. After carefully reviewing this important investigation, it occurred to the writer that, based upon definite physical chemical principles, a method of analysis might be devised, in which the potentiometer would not only replace a chemical indicator but, at the same time, take the place of the alkali solution.

THEORETICAL CONSIDERATIONS.

McGill pointed out, in his experiments with Cinchona residues, that the concentration of the alkaloidal salts has very little effect upon the hydrogen-ion concentration of the solution. This fact was verified by the author as can be observed from the results tabulated in this paper. Based upon this fact—if the molarity of the alkaloidal salt solution does not influence the p_H of the solution, a definite excess of acid added to variable amounts of alkaloidal salts and made up to a definite volume, at which the ionization of the acid is practically complete, will yield solutions with a p_H which is a function of the excess of acid present. The

* Scientific Section A. PH. A., Buffalo meeting, 1924.

[1] JOUR. A. PH. A., 12, 609 (1923).

[2] *Ibid.*, 12, 955 (1923).

[3] *Ibid.*, 11, 1003 (1922).