TABLE II.—COMPARISON OF THE PERCENTAGES OF TOTAL ALKALOIDS INDICATED AS BEING PRESENT BY THE VOLUMETRIC AND GRAVIMETRIC METHODS.

Sample.	Percentage of total alkaloids. Volumetric method.	Gravimetric method.
Datura stramonium	1.825	1.90
Datura tatula	1.279	1.33
Datura stramonium inermis	1.247	1.36

It will be noted that the results from the gravimetric method substantiate those obtained by the usual volumetric assay methods, the slightly higher results being due to the presence of some impurities in the mixed alkaloids obtained.

So far as the writer is aware, the literature records nothing comparable to the results obtained in this experiment, which were so unexpected that they invited further and more comprehensive study. It was planned to duplicate the work the next summer at the Drug Garden at Arlington, Va., on a much larger scale but unfortunately the entire patch of Daturas became infected with the Mosaic disease and the experiment was abandoned for the season. Since that time the writer has had no opportunity to take up the work again and very likely will not do so in the future. For this reason these results are presented here in the hope that others who are engaged in problems on drug plant culture may find an opportunity to repeat this experiment. It should prove interesting to work with the following questions in mind:

(1) Does the removal of flowering buds always result in the development of larger leaves and greater percentages of alkaloids?

(2) Is it by preventing flowering or preventing the seed from maturing that the typical effect is obtained?

(3) Has the extent of the leaf development any relation to the formation of the excessive quantities of alkaloids?

(4) Is the great increase in alkaloids confined to the leaves or is it equally true of the stems and roots?

(5) What is the effect of similar treatment on the other plants containing mydriatic alkaloids?

(6) Is it a seasonal or geographic characteristic?

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THE TITRATION OF CERTAIN ALKALOIDS.*

BY NORMAN EVERS.[1]

In examining the literature of analytical chemistry in the light of modern development of the theory of titrations one is struck by the haphazard way in which indicators are recommended for titrations. Most frequently indicators appear to have been chosen on account of the sharpness of the end-point rather than on account of suitability on the theoretical grounds for the titration in question. Further,

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[1] Analytical and Research Laboratories of Messrs. Allen & Hanbury's Ltd.

the indicators used are chiefly confined to methyl orange, phenolphthalein, litmus, and cochineal, no one of which, with the exception of phenolphthalein, can be regarded as a good indicator when compared with the new and brilliant indicators which are now available. Probably the chief reason why these new indicators are not in more common use is the absence of any data as to the titrations to which they are applicable.

THEORETICAL CONSIDERATIONS.

In a theoretically perfect titration of a weak base, such as morphine, we should run in standard hydrochloric acid until we had in our solution nothing but pure morphine hydrochloride. The means by which we determine when the morphine is in the state of hydrochloride is by adding an indicator. Now all indicators change in color over a definite range of hydrogen ion concentration—that is to say, the change of color of an indicator is brought about by hydrogen ions, and what we are actually doing when we bring a solution to the neutral point of methyl orange, say, is to bring it to a definite hydrogen ion concentration. Therefore, if we add methyl orange to our morphine titration and bring the solution to the neutral point we are bringing the solution to a hydrogen ion concentration of about [1] $P_H = 4$, or, if we use cochineal, to about $P_H = 6$. Now if the hydrogen ion concentration of a solution of morphine hydrochloride of the strength used in the titration is $P_H = 4$, methyl orange will give a correct result; if $P_H = 6$, cochineal will give a correct result; but they cannot *both* give a correct result. It is necessary, therefore, in order to find the best indicator for use in any given titration, to determine the hydrogen ion concentration of a solution of the end product of the titration of the same strength as that produced in the titration. Then if we can find an indicator which has its color change at this hydrogen ion concentration, that indicator (other things being equal) should be the best for use in that titration.

TITRATION OF MORPHINE.

The British Pharmacopoeia recommends methyl orange for the titration of morphine; the United States Pharmacopoeia advises cochineal. In Allen's "Commercial Organic Analysis," Vol. V., p. 376, we find: "Morphine forms salts which are perfectly neutral in reaction to litmus and methyl orange, and hence it may be titrated with accuracy by the aid of standard hydrochloric acid and either of these indicators."

Experiments were therefore carried out in order to find the hydrogen ion concentration of pure morphine hydrochloride in 1% solution, which is about the strength most frequently employed in a titration.

Pure morphine was prepared from ordinary pure morphine hydrochloride by twice crystallizing from a dilute slightly alkaline solution saturated with ether. The crystals were dried and rendered anhydrous by heating at 115°.

A solution of exactly $\frac{N}{10}$ hydrochloric acid was prepared, standardized to phenolphthalein against $\frac{N}{10}$ sodium hydroxide (free from carbonate), which

[1] P_H is the logarithm of the reciprocal of the hydrogen ion concentration in terms of normal, *i. e.*, if $P_H = 1$ the hydrogen ion concentration is $\frac{N}{10}$; if $P_H = 2$, $\frac{N}{100}$, etc. The lower the value of P_H the more acid is the solution and *vice versa*. At the point of absolute neutrality $P_H = 7$.

had been standardized against pure potassium hydrogen phthalate. In one experiment 0.817 Gm. anhydrous morphine was dissolved in 28.65 Cc. $\frac{N}{10}$ hydrochloric acid, and made up to 107.5 Cc. with neutral distilled water (giving a 1 per cent solution of morphine hydrochloride). The hydrogen ion concentration of this solution was determined by the colorimetric method, and found to be PH = 3.65.

The mean of several experiments gave the PH of a 1% solution of morphine hydrochloride as 3.65. Now, this figure is within the range of the color change of methyl orange, but is on the acid side of the neutral tint, that is to say, a 1% solution of morphine hydrochloride will give a decidedly pink color with methyl orange. In order to titrate morphine to methyl orange, therefore, we must finish up with a decidedly pink color. As the usual procedure in morphine titrations is to add excess of acid and titrate back with alkali, it is much more likely that the end-point taken will be on the yellow side rather than pink, and the result will be low. But methyl orange is not the best indicator for morphine titrations. If we use brom-phenol blue, an indicator which is yellow in acid solutions and blue in alkaline solutions, we find that a hydrogen ion concentration of PH = 3.65 corresponds to the first appearance of a distinct blue color when we are passing from acid to alkaline. If, therefore, we dissolve morphine in excess of standard acid and titrate back with standard alkali to brom-phenol blue until a distinct blue color appears we get a more accurate result.

With cochineal, which has a range of hydrogen ion concentration of PH = 5 to 7, it is obvious that an accurate result cannot be obtained. The results of three titrations with the three indicators may be of interest. In each case the standard solutions were standardized to the indicators used. Methyl orange was taken to its neutral orange tint:

Indicator.	Percent morphine found.
Brom-phenol blue	100.0
Methyl orange	99.5
Cochineal	98.8

It may be noted that the statement frequently seen in the textbooks that a solution of morphine hydrochloride is neutral to litmus is unfounded. Pure morphine hydrochloride should be acid to litmus. Two commercial samples of morphine hydrochloride in 1 percent solution had a PH = 4.83 and 4.50, respectively, showing a slight excess of morphine over hydrochloric acid present. A sample of morphine crystals when titrated to the above end-point gave 101.4 percent morphine (hydrated), showing them to be slightly effloresced.

THE TITRATION OF QUININE.

Allen's "Commercial Organic Analysis," Vol. V, p. 514, states that "Quinine is a strong base, completely neutralizing acids and forming crystallizable salts having a slight alkaline indication to litmus. Quinine also forms a series of acid salts which are neutral to methyl orange."

Squire's "Companion" states that "Quinine hydrochloride is neutral, or at the most but faintly alkaline, in reaction towards litmus paper. It is usually recommended in the textbooks to titrate quinine salts to phenolphthalein. In this way the whole of the quinine is precipitated in the course of the titration, and the end-point is not very satisfactory.

A sample of carefully purified quinine free from other cinchona alkaloids was dehydrated by heating to 120°.

0.6744 Gm. anhydrous quinine was dissolved in 41.60 Cc. $\frac{N}{10}$ hydrochloric acid, thus forming quinine acid hydrochloride, and diluted to 1%. The PH of this solution was then determined and found as a mean of three experiments to be 3.40.

Quinine acid hydrochloride should therefore in 1% solution be neutral to brom-phenol blue, with which it should give a pale greenish yellow color. Methyl orange would be decidedly pink at this PH.

0.7144 Gm. anhydrous quinine was dissolved in 22.03 Cc. $\frac{N}{10}$ hydrochloric acid and diluted to 1 percent, forming the neutral hydrochloride. The PH of this solution was as a mean 5.15.

A solution of this PH is neutral to methyl red, with which it gives an orange color. It will be seen from the above results that we can most accurately titrate a solution of quinine hydrochloride or sulphate by adding standard acid until a pale greenish yellow color corresponding to PH = 3.4 is obtained. A commercial sample of quinine hydrochloride titrated in this way gave 99.97 percent. In the same way quinine acid hydrochloride or sulphate may be titrated with standard alkali until an orange color corresponding to a PH of about 5.15 is obtained with methyl red solution. A sample of quinine acid hydrochloride titrated in this way gave 97.3 percent. The end-points are not quite so sharp with quinine as with morphine, but with a little practice quite reliable results can be obtained. This method of titration may be applied to ammoniated tincture of quinine for the combined determination of quinine and ammonia in the following manner: 25 Cc. of the tincture are run into 50 Cc. $\frac{N}{2}$ hydrochloric acid, brom-phenol blue is added, and the liquid titrated back with $\frac{N}{2}$ alkali until a pale greenish yellow color is obtained. Let a = No. of Cc. $\frac{N}{2}$ alkali used. Methyl red is then added to the solution and the titration continued with $\frac{N}{10}$ alkali until the pink color of the methyl red disappears and only the blue color of the brom-phenol blue remains.

Let b = No. of Cc. $\frac{N}{10}$ alkali used.

W/v quinine sulphate B. P. $= b \times 0.1763$

$$\text{W/v ammonia} = 50 - \left(a + \frac{b}{5}\right) \times 0.034.$$

Commercial samples of quinine salts tested in 1% solution gave the following values for PH:

	PH.
Quinine hydrochloride	6.2
Quinine acid hydrochloride	3.7
Quinine acid sulphate	3.6

THE TITRATION OF ATROPINE.

The B. P. and U. S. P. employ cochineal for the titration of the alkaloids obtained from belladonna.

Squire's "Companion" (nineteenth edition) states that "atropine may be readily determined by titration, using cochineal or iodeosin as an indicator." Atropine sulphate is stated to be neutral to litmus paper.

Allen's "Commercial Organic Analysis," Vol. V, page 296, states that commercial atropine sulphate is often faintly alkaline, and keeps better when so made.

In order to determine the PH of a 1% solution of atropine hydrochloride, a known weight of pure atropine was dissolved in the theoretical volume of $\frac{N}{10}$ hydrochloric acid and made up to 1 percent strength. The PH of the solution was found to be 3.75.

This corresponds to a distinct blue color with brom-phenol blue, and is reasonably close to the end-point of the morphine titration given above. It is again evident the cochineal is an unsuitable indicator for this titration, and that brom-phenol blue should be used, finishing with a distinct blue color.

A commercial sample of atropine sulphate had in 1% solution PH = 5.9, showing that it contained an excess of atropine over the sulphuric acid.

SUMMARY.

On theoretical grounds and as the result of practical experiments it has been shown that the indicators ordinarily employed for the titration of the alkaloids, morphine, quinine, and atropine, are not the most suitable for the titrations.

From measurement of the hydrogen ion concentration of the solutions of the pure hydrochlorides it was found that brom-phenol blue is a better indicator to use for morphine, atropine, and the neutral salts of quinine. For the acid salts of quinine, methyl red is the most suitable indicator.

THE STRUCTURAL RELATIONS AMONG OPIUM, BERBERIS, CORYDALIS, AND HYDRASTIS ALKALOIDS.

BY INGO W. D. HACKH.*

This paper has a twofold purpose: first, to discuss some striking relations in structure of a number of important alkaloids which enables a systematic classification; second, to point the way to synthetic preparation of these alkaloids.

The rapid rise and success of synthetic organic chemistry has come mainly by an application of the structure theory, for once the structure is established, it remains only a matter of time until some synthetic method for the preparation of the compound is discovered. The painstaking investigations of a number of workers have established, with some certainty, the structure of many alkaloids, a number of which contain the isoquinoline nucleus. The structure formulas of the more important isoquinoline alkaloids are shown on the following page. All these structure formulas are taken from one of the larger reference books, yet they illustrate the random method of the present system of notation. Thus the formulas for hydrastine and narcotine are printed completely—showing every atom; the other six structure formulas are incomplete in varying degrees through absence of symbols or double bonds. It is small wonder that this inconsistent way of representing the structures of organic compounds clouds the understanding and bewilders the student while it remains forever a mystery to the layman. Small progress can be made if the notation is not precise and complete. On looking over these same structure formulas, there appears to be no relationship among these alkaloids, even though the reader's knowledge supplies all the missing double bonds and symbols. The isoquinoline group, when hunted for, is found in each case, either standing on its head or inclined at various angles. With the use of

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