INDICATORS FOR THE TITRATION OF ALKALOIDS

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TABLE of CONTENTS

IN attempting to assay alkaloids, either in the crude alkaloidal drugs or in pharmaceutical preparations, by means of volumetric chemical analysis, one meets with many difficulties, not the least of which is the choice of a suitable indicator for determining the end of the reaction. This is evidenced in part by the changes in indicators directed to be used in the various editions of the pharmacopoeias. For example, the United States Pharmacopoeia of 1900 directs that, if the solution of alkaloid to be titrated still retains some color, iodeosin should be used; but if the solution is colorless it is safe to use hematoxylin or cochineal. In the editions of 1910 and 1920 the pharmacopoeia allows the operator the option of using cochineal or methyl red for all titrations, stating that these indicators are interchangeable and that either may be used at the discretion of the operator.

This statement would lead one to suppose that cochineal and methyl red cover the same range of alkalinity or acidity and that the points at which stable salts are formed with all alkaloids lie within this range. This supposition, however, is far from true, since the two indicators have not the same range and there are certain alkaloids the hydrogen ion concentration of whose salts lies wholly outside the range of either indicator. The two indicators mentioned, used to supplement each other, might serve for all alkaloidal titrations but they should not be used interchangeably.

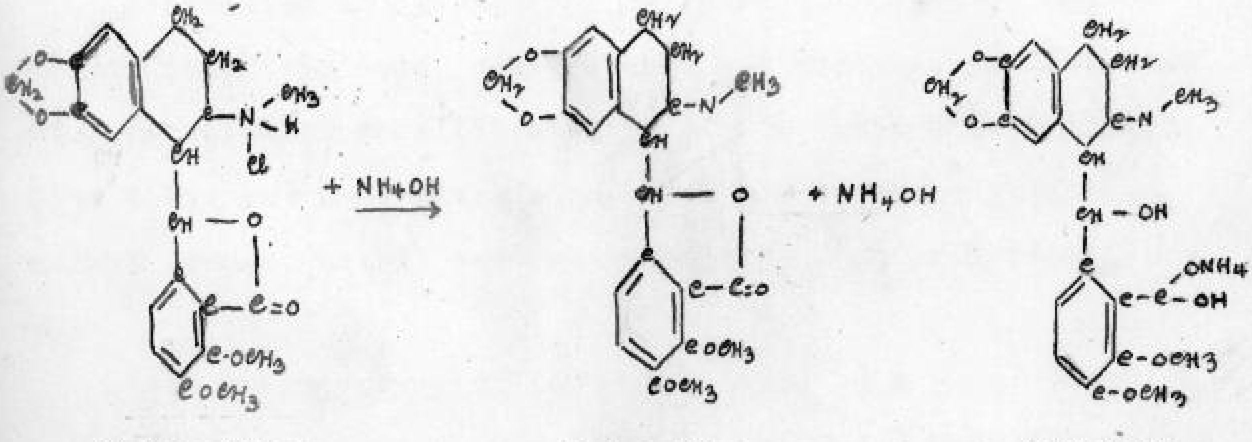
In a theoretically perfect titration of a weak base, such as an alkaloid, a standard solution of an acid should be run into a solution of the alkaloid until nothing is present in solution but the pure salt of the alkaloid with the acid being used. This point is to be determined by the change in color of the indicator. Now all indicators change in color over a definite range of hydrogen ion concentration, and what we are actually doing when we bring a solution to the neutral point with any indicator is to bring it to a definite hydrogen ion concentration corresponding to that of the color change of the indicator. For example, the range of hydrogen ion concentration covering the changes of color with methyl red is pH 4.2 - 6.3, therefore in order to reach the point of neutrality with that indicator the solution must be brought to that hydrogen ion concentration; and an alkaloid in connection with which methyl red is used as an indicator should form a stable salt the hydrogen ion concentration of which corresponds to a pH value of 4.2 - 6.3.

In the same way the range of hydrogen ion concentration covering the change in color with cochineal is pH 5 - 7, overlapping that of methyl red, but by no means coinciding with it.

The ranges of pH value of these two indicators supplementing each other cover the pH values given for most alkaloidal salts. Probably if solutions of pure alkaloids were used and titrations were made with standard acid until the formation of salts occurred, one or the other of these indicators would give a fairly accurate value in every case, methyl red for those having the lower and cochineal for those having the higher pH values. This, however, is not the way titration is carried out in actual practice. The alkaloid or alkaloidal salt is dissolved in an excess of acid and the solution is titrated back to the point of neutrality with standard alkali. The result taken will therefore be, undoubtedly, on the alkaline rather than the acid side of the indicator's range and the results will be low with methyl red if the pH value lies much below pH 5 or low with cochineal if much below pH 6.

EXPERIMENTAL

The writer became interested in the subject of indicators for alkaloidal titrations in connection with an assay of hydrastis. Hydrastine, the alkaloid for which hydrastis is valued, is ordinarily determined gravimetrically because it does not form stable salts with acids, the alkaloid itself containing a lactone grouping which breaks down when the excess of acid is removed, forming an acid which will form salts with alkalies.



Hydrastine Hydrochloride

Hydrastine Alkaloid

Ammonium Salt

Therefore, as is shown in the above formulas, it is possible to have two kinds of salts of hydrastine, those in which the alkaloid acts as a base and forms salts with acids, and those in which it acts as an acid and forms salts with bases. Because of its dual nature, both acidic and basic, hydrastine may be regarded as both a very weak base and a very weak acid, the basic properties somewhat predominating. Both kinds of salts might be expected to be very unstable, and a state of equilibrium between the two would be the end-point of a titration of the alkaloid.

The writer was told that if he could find an indicator which would show this equilibrium under conditions of acid concentration indicating the true quantity of alkaloid present, namely one molecule of acid for one molecule of the base, he would be able to make a successful titration of hydrastine. Whether or not this would serve for the assay of hydrastis, on account of the presence of other alkaloids, would be an entirely different matter.

A solution of hydrastine, .5 grams in 200 cc of tenth-normal sulphuric acid, was prepared and portions of 10cc each of this solution were titrated back with tenth-normal alkali. Five different indicators were used, namely phenolphthalein, methyl orange, methyl red, methyl violet, and brom-cresol purple.

With PHENOLPHTHALEIN (pH 8.3 - 10.0) 10.3 cc of tenth-normal NaOH produced a white precipitate, with no color change, while 10.5 cc of alkali produced the red color, obscured by a still heavier white precipitate. Phenolphthalein, therefore does not show its alkaline color before the alkali reacts with all of the acid and frees the alkaloid, its pH range being entirely too high and its sensibility to alkalies entirely too weak.

More satisfactory results were obtained with METHYL ORANGE, (pH 3.1 - 4.4), 9.7 cc of tenth-normal NaOH being required to titrate the excess acid in 10 cc of the solution. The alkaloid therefore combined with .853 cc of tenth-normal acid, each cc of tenth-normal acid corresponding to .03833 grams of hydrastine. The alkaloidal content thus computed would be .0335 grams as against .025 grams actually present in 10 cc of the solution, an error of .0085 grams or 34 per cent.

Using METHYL RED as indicator, with a pH value of 4.2 to 6.3, there was found to be 9.24 cc of excess acid, leaving .76 cc combined with alkaloid. This gave .0299 grams of hydrastine, as against the .025 grams actually present, an error of .004 grams or 16 per cent. The pH range of hydrastine salts in 1 per cent solution has been reported to be 4.45. The pH value of methyl red indicator being 4.2 acid to 4.4 alkaline, the quite accurate results obtained are not surprising.

METHYL VIOLET, having a pH range of 1.0 acid to 3.2 alkaline, gave poor results. The excess of acid required 7.4 cc of tenth-normal alkali for neutralization, indicating .114 grams of hydrastine against .025 grams actually present and an error of 360per cent. The extreme sensibility of methyl violet toward alkalies makes it undesirable as an indicator for alkaloids, even in the titration of hydrastine, where a a sensitive alkaline indicator is in order. This emphasizes the fact that the first step in the choice of an indicator for a particular alkaloid must be an attempt to approximate the pH ranges of alkaloid and indicator.

BROM-CRESOL PURPLE, with a pH range of 5.2 yellow acid to 6.8 purple alkaline, gave by far the best results, although this would not be expected judging from the reported pH value of hydrastine (4.45). But the peculiar structure and reactions of this alkaloid may explain this discrepancy. Two titrations were carried out with brom-cresol purple with the following results::

The sodium hydroxide required to neutralize the excess acid in 10 cc of the solution was 9.6 cc of tenth-normal solution, indicating .665 cc of standard tenth-normal acid combined with alkaloid. Four drops of the indicator were used, producing a bright yellow in the acid solution. Alkali was then added, drop by drop, until an instantaneous change from bright yellow to grayish yellow was produced. This is a neutral shade for the indicator. The change in color is sudden and sharp, and is brought about by one drop of tenth-normal alkali. The first titration showed .02617 grams of alkaloid to be present, and the second, .02617 grams. The average of these is .02542 grams, as against .025 grams actually present. This comparatively small error of 1 per cent might suggest brom-cresol purple as a fair indicator in the titration of hydrastine.

Reactions With Other Alkaloids.

After obtaining the foregoing results with hydrastine, it was decided to try the same indicators with other alkaloids. The salts of Quinine, Morphine, and Strychnine were accordingly chosen.

To make an accurate titration of any alkaloid with a given indicator, a sample solution of the alkaloidal salt should be tested with the indicator and saved as a blank for the actual titration. If Tincture of Opium is known to contain approximately 1 per cent Morphine, then a 1 per cent aqueous solution of morphine sulphate (if sulphuric acid is used) should be tested with a few drops of the indicator and the color recorded. A few experiments of this sort showed a considerable variation in the reactions of 1 per cent solutions of different alkaloidal salts toward the five indicators mentioned above. The results of these experiments showed that the hydrogen ion concentration of a 1 per cent solution of morphine sulphate, for instance, is greater than that of a solution of Strychnine Sulphate of the same alkaloidal strength, and also, that a 1 per cent solution of Morphine Sulphate, while registring a nearly neutral, but slightly alkaline shade with methyl orange, is distinctly acid toward methyl red.

The details of these experiments follow -

Accurate 1 per cent solutions of pure Morphine Sulphate, Strychnine Sulphate, Quinine Sulphate, and Quinine Bisulphate were prepared. 10 cc portions of these solutions were tested separately for their reactions toward each of the indicators.

Then to 5 cc samples a measured quantity of standard tenth-normal acid was added, and the latter titrated back to the original color and to the neutral color of the indicator with stnadard fiftieth normal alkali. The results are noteworthy.

METHYL ORANGE.

Using 10 cc of each alkaloidal solution, and 4 drops of Methyl Orange in each, we have the following variations in color:

Quinine Bisulphate	orange (acid)
Quinine Sulphate	yellow (alkaline)
Morphine Sulphate	orange-yellow (nearly neutral, slightly alkaline)
Strychnine Sulphate	yellow (alkaline)

Titration of solutions:

Quinine Bisulphate.

To 5 cc of the orange-colored solutions, representing .05 grams of alkaloidal salt, 5 cc of tenth-normal sulphuric acid were added, and this titrated back with fiftieth-normal NaOH.

24.8 cc NaOH N/50 produced the original orange-acid color.

26.0 cc " " " a neutral color.

27.4 cc " " " an alkaline color.

Note. Four more drops of methyl orange were added at intervals during the titration to allow for fading from dilution, permitting a comparison with the original orange-colored sample.

Quinine Bisulphate, computed from titration to neutral point: .04578 grams, as against .05 grams actually present. Error: 8.4 per cent., low.

Quinine Sulphate.

Same procedure, using 5 cc of yellow solution and 5 cc of standard acid.

18.3 cc NaOH N/50 produced a neutral shade.

19.8 cc " " " a distinctly alkaline shade.

21.9 cc " " " the original bright yellow alkaline shade.

Quinine Sulphate computed from titration to neutral point: .15 grams, as against .05 grams actually present. Error: 20 per cent.

Morphine Sulphate.

Same procedure, using 5 cc of orange-yellow solution and 5 cc of standard acid.

23.4 cc NaOH N/50 produced a neutral color.

23.9 cc " " " a more alkaline color.

24.0 cc " " " the original slightly alkaline color.

Morphine Sulphate computed from titration to neutral point: .0591 grams as against .05 grams actually present. Error: 18 per cent, high.

Strychnine Sulphate.

Same procedure, using 5 cc of yellow solution and 5 cc of standard acid.

23.4 cc NaOH N/50 produced a neutral color.

23.6 cc " " " a distinctly alkaline color.

25.0 cc " " " the original alkaline shade.

Strychnine Sulphate computed from titration to neutral point: .0745 grams as against .05 grams actually present. Error: 49 per cent, high.

From the above results we may conclude that methyl orange is not a good indicator for any of the alkaloidal salts used, the smallest error, that with Quinine Bisulphate, being 8.4 per cent.

METHYL RED.

10 cc portions of each alkaloidal solution were used, as before, with 2 drops of the indicator in each:

Quinine Bisulphate	lavender red (distinctly acid)
Quinine Sulphate	bright yellow (distinctly alkaline)
Morphine Sulphate	lavender red (distinctly acid)
Strychnine Sulphate	deep red (distinctly acid, very slightly less so than Morphine)

Titration of solutions:

Quinine Bisulphate.

5 cc standard tenth-normal sulphuric acid added to 5 cc of the lavender red solution and this titrated back with fiftieth-normal NaOH as before.

25 cc NaOH N/50 produced no change in the lavender red color.

28.5 cc NaOH N/50 produced a plain red color.

29.3 cc " " " an orange-yellow neutral shade.

29.6 cc " " " a yellow alkaline shade.

Quinine Bisulphate computed from titration to neutral point: .0321 grams as against .05 grams actually present. Error: 35 per cent low.

Quinine Sulphate.

5 cc tenth-normal acid added to 5 cc of bright yellow solution.

23.2 cc NaOH N/50 produced the first change in shade from distinct acid (lavender red) to slightly acid (red).

23.9 cc NaOH N/50 gave to the solution an orange-red shade, but leaving it still slightly acid.

24.0 cc NaOH N/50 produced the neutral point, an orange yellow.

24.2 cc NaOH N/50 produced a yellow alkaline shade.

24.4 cc " " " the original bright yellow distinctly alkaline shade.

Quinine Sulphate computed from titration to neutral point:: .06 grams as against the .05 grams actually present. Error:: 20 per cent high.

Note. It might be added here in connection with Quinine Sulphate that the solution was kept at a temperature of 60 to 80 degrees centigrade throughout the work to keep the salt dissolved.

Morphine Sulphate.

The addition of 5 cc of tenth-normal acid to 5 cc of the lavender red solution deepened this shade somewhat but otherwise produced no change, thus demonstrating the salt's high degree of acidity toward methyl red.

24.2 cc NaOH N/50 reproduced the original lavender red shade.

24.3 cc NaOH N/50 produced a sudden change to orange red.

24.5 cc " " " a neutral orange yellow.

24.6 cc " " " a yellow alkaline shade.

24.8 cc " " " apronounced bright yellow alkaline shade.

Morphine Sulphate computed from titration to neutral point:: .05285 grams as against the .05 grams actually present. Error: 5.7 per cent high.

Strychnine Sulphate.

5 cc of tenth-normal acid added to 5 cc of the deep red colored solution changed it to the characteristic lavender-red acid shade.

24.1 cc standard N/50 alkali produced the original deep red shade.

24.2 cc standard alkali produced an orange-red shade.

24.3 cc " " " an orange-yellow neutral shade.

24.4 cc " " " a yellow alkaline shade.

24.5 cc " " " a bright yellow alkaline shade.

Strychnine Sulphate computed from titration to end-point: .0572 grams as against the .05 grams actually present. Error: 14 per cent high.

From these results we observe that while methyl red, the indicator specified by the pharmacopoeia for alkaloidal titrations, is, on the whole, rather better than methyl orange, it is far from satisfactory for any of the salts used except Morphine Sulphate, and here the error is greater than 5 per cent.

PHENOLPHTHALEIN.

Again 10 cc of each solution was used, with 2 drops of indicator in each.

Quinine Bisulphate	colorless (acid)
Quineine Sulphate	colorless (acid)
Morphine Sulphate	colorless (acid)
Strychnine Sulphate	colorless (acid)

The titration of any alkaloid with phenolphthalein as indicator is entirely impracticable, since the extreme sensibility of this indicator toward acids runs the titration far past the correct end-point.

BROM-CRESOL PURPLE.

Using 10 cc of each solution and 2 drops of indicator in each.

Quinine Bisulphate	greenish-yellow (acid)
Quinine Sulphate	greenish-blue (neutral, slightly alkaline)
Morphine Sulphate	greenish-yellow, identical with quinine bisulphate (acid)
Strychnine Sulphate	greenish-yellow with an added shade of green (very slightly less acid than morphine)

Titration of solutions.

Quinine Bisulphate.

5 cc tenth-normal acid added to 5 cc of greenish yellow solution produced no change in shade; 1 per cent solution is distinctly acid.

29.8 cc ~~tenth~~ fiftieth-normal alkali added a greenish tinge.

30.1 cc " " produced a greenish-blue neutral shade.

30.2 cc produced a distinct blue, still neutral.

30.4 cc " a purple against a dark background, alkaline.

Quinine Bisulphate computed from neutral point: .02889 grams as against .05 grams actually present. Error: 42 per cent low.

Note. In titrating with Brom-cresol Purple, the colors should be read against a white background and also while held to the light. The alkaline purple shade appears blue when the solution is held to the light, but slight changes in shade can best be detected by this method.

Quinine Sulphate.

5 cc N/10 acid added to 5 cc of the greenish-yellow, neutral solution changed the color to bright yellow, acid.

21.6 cc fiftieth-normal alkali produced the first slight evidence of change in shade.

Change is very gradual up to 24.3 cc, where the original neutral, slightly alkaline shade is reached. (greenish-blue).

24.6 cc fiftieth-normal alkali produced and orchid color against a white background.

3 more drops of alkali (24.7) produced a distinct purple, alkaline shade.

Quinine Sulphate computed from titration to neutral point: .06 grams as against the .05 grams actually present. Error: 20 per cent.

This result is identical with the methyl red titration.

Morphine Sulphate.

5 cc N/10 acid produced no change in 5 cc of the original bright yellow acid solution.

24.2 cc fiftieth-normal alkali produced the first evidence of change in shade, a neutral bluish-green when held toward light.

24.4 cc (3 more drops) produced an orchid shade against a white background, while an additional 3 drops (24.6 cc) produced the purple, alkaline shade.

Morphine Sulphate computed from titration to bluish-green neutral point: .04544 grams as against the .05 grams actually present. Error: 9.1 per cent.

This titration indicates that Morphine Sulphate is quite acid to brom-cresol purple.

Strychnine Sulphate.

5 cc N/10 acid added to 5 cc of the greenish-yellow solution produced no noticeable change in the acid shade.

24.2 cc fiftieth normal alkali produced the first indication of change in shade to a bluish-green when held to the light.

24.3 cc standard alkali produced a typical neutral shade.

24.5 cc produced an orchid shade against a white background.

24.7 cc produced a purple (alkaline) shade.

Strychnine Sulphate computed from titration to neutral point: .0607 grams, as against .05 grams actually present. Error: 21 per cent high.

From the above results we conclude that brom-cresol purple is not as good an indicator for alkaloids as is methyl red, though the results of the two with quinine sulphate are the same.

METHYL VIOLET

Using 10 cc of alkaloidal solution with 2 drops of indicator in each.

Quinine Bisulphate	purple,(slightly alkaline)
Quinine Sulphate	purple, shade darker than bisulphate (alkaline)
Morphine Sulphate	dark purple (alkaline)
Strychnine Sulphate	dark purple, same shade as morphine (alkaline)

Titration of solutions.

Quinine Bisulphate.

5 cc of N/10 acid added to 5 cc of solution produced a

change from the alkaline purple to medium blue (acid).

18.5 cc fiftieth normal alkali produced a neutral, bluish-purple shade.

19.2 cc standard alkali produced the original purple shade (slightly alkaline).

Further addition of alkali produced a darkening of the purple (distinct alkaline).

Quinine Bisulphate computed from titration to neutral point: .077 grams as against .05 grams actually present. Error: 5 per cent.

Quinine Sulphate.

5 cc tenth-normal acid added to 5 cc of purple solution produced the blue, acid shade.

14.0 cc fiftieth normal alkali produced the first change in shade from blue to neutral (bluish-purple)

14.5 cc standard alkali produced the original purple alkaline shade.

Quinine Sulphate computed from titration to neutral point:: .259 grams as against .05 grams actually present. Error: 410 per cent high.

Morphine Sulphate.

5 cc tenth-normal acid added to 5 cc of the dark purple solution.

15 cc fiftieth normal alkali produced the first change in shade to neutral.

16.2 cc standard alkali produced the violet-purple alkaline shade.

20.9 cc alkali produced the original dark purple, strongly alkaline shade.

Morphine Sulphate from titration to neutral point: .107 grams as against .05 grams actually present. Error: 110 per cent high.

Strychnine Sulphate.

5 cc tenth-normal acid added to 5 cc of the dark purple solution.

13.7 cc fiftieth normal alkali produced the first change in shade to dark bluish-purple - neutral.

20.0 cc standard alkali produced a vidlet-purple - alkaline.

22.1 cc alkali produced the original dark purple alkaline shade.

Strychnine Sulphate computed from titration to neutral point: .223 grams as against .05 grams actually present. Error: 340 per cent high.

OBSERVATIONS

From these experiments it becomes evident that phenolphthalein and methyl violet are to be eliminated entirely as indicators in the titration of alkaloids, the former having too high a pH range and the latter too low. Brom-cresol purple runs close to methyl red in many cases, and under certain circumstances its use as an indicator in alkaloidal titration is to be recommended. Methyl orange in quinine bisulphate titration is of possible value, the per cent of error being small (8.4 per cent). With the other alkaloids it is deserving of little consideration, however.

An interesting fact of considerable importance is to be

noted

noted in the methyl red titration of morphine. It will be seen that 24.5 cc of fiftieth-normal alkali produced a neutral shade of methyl red (orange-yellow). A computation from this point showed .05285 grams of morphine sulphate, against .05 grams actually present in the solution, representing a difference of .00285 grams, and an error of 5.7 per cent. The addition of 2 more drops of fiftieth normal alkali produced a distinctly alkaline, pale yellow shade. But a computation from this point (24.6 cc), shows .0522 grams of salt, and an error of only 4.5 per cent. Judging from this, it might be advisable to titrate morphine sulphate to the first indication of alkalinity in the methyl red color range. But the fact that Morphine Sulphate is acid to methyl red in 1 per cent solution should bring the neutral shade beyond the point of neutralization of excess acid and give a low estimate. Since the opposite of this took place in the titration, it can only be explained by an error in the strength of the N/50 alkali solution, this solution not having been accurately checked at the time. Time did not admit of further checking of these results, but the fact remains that the methyl red titration of mprphine sulphate is by no means perfect, and that considerable work may yet be done in effecting a better quantitative determination of this highly important alkaloid.

Moreover, from these observations it becomes apparent that a more thorough investigation of the detailed color reactions of various probable alkaloid indicators is both interesting and advisable. Accuracy is the goal, just as it is in volumetric analysis over the gravimetric method. But it seems that the only part of the volumetric method which has not been perfected for accuracy is a fine distinction of the various color changes in the acid-alkali reactions of the indicators. Of this the pharmacopoeias make no mention, though it becomes inevitable that a large percentage of arror may occur from the fact the the proper end-point for alkaloid and indicator is not known before titration is begun.

TABLE of ALKALOIDS, THEIR AVERAGE pH VALUES, and the MORE COMMON CORRESPONDING INDICATORS.

Alkaloid	pH	pH for Ind.	Indicator
Aconitine	5.04	4.2 - 5.8	Methyl Red
Arecoline	4.81	3.8 - 5.8	Methyl Red
Atropine	5.56	3.8 - 7.2	Methyl red Propyl red Brom-cresol purple
Brucine	4.85	3.9 - 6.0	Methyl red
Cephaeline	4.81	4.2 - 5.4	Methyl red
Cinchonine	6.02	5.5 - 6.5	Brom-cresol purple
Cinchonidine	5.90	5.4 - 6.4	Brom-cresol purple
Cocaine	5.20	4.0 - 6.5	Methyl red
Codeine	4.86	3.6 - 6.3	Methyl red
Cotarnine	5.97	4.9 - 7.0	Brom-cresol purple
Delcosine	4.42	3.6 - 5.2	Brom-phenol blue
Diacetyl Morphine	4.89	4.2 - 5.7	Methyl red
Emetine	4.90	4.2 - 5.6	Methyl red
Ethyl Hydrocupreine	6.63	5.6 - 7.0	Brom-cresol purple
Ethyl Morphine	4.99	4.2 - 5.8	Methyl red
Homatropine	5.74	3.9 - 7.6	Methyl red Propyl red Brom-cresol purple
Hydrastine	4.45	3.8 - 5.0	No end-point
Hyoscine	4.83	3.6 - 5.6	Brom-phenol blue
Hyoscyamine	5.83	3.8 - 7.6	Methyl red Propyl red Brom-cresol purple
Morphine	4.78	4.0 - 5.0	Methyl red
Narceine	Salt is completely dissociated		
Narcotine	4.43	3.9 - 4.9	Brom-phenol blue
Nicotine	5.26	4.4 - 6.1	Methyl red
Papaverine	4.23	3.8 - 4.5	Indistinct
Physostigmine	4.85	3.8 - 6.0	Methyl red
Pilocarpine	4.31	3.6 - 5.0	Brom-phenol blue
Quinine	6.12	5.5 - 6.5	Brom-cresol purple
Quinidine	6.10	5.5 - 6.5	Brom-cresol purple
Sparteine	Salt is dissociated		
Strychnine	4.81	3.8 - 6.0	Methyl red
Thebaine	5.08	4.0 - 6.2	Methyl red
Yohimbine	4.72	4.0 - 5.3	Methyl red

Note. The heading "pH for Ind." does not mean the exact pH value of the indicator, but the range within which the pH of the alkaloid comes. The indicators named have pH ranges approximating these.

LIST of PROBABLE INDICATORS for HYDRASTINE

pH value of Hydrastine: 4.45
pH range for Indicator: 3.8 to 5.0

Indicator	pH range
a-naphthylamino-azo-benzene	3.7 - 5.0
a-naphthylamino-azo-p-benzene sulfonic acid	3.5 - 5.7
Brom-phenol blue (yellow to blue)	3.0 - 4.6
2-3-dinitro-phenol (colorless to yellow	3.9 - 5.9
O-carboxybenzene azo-diphenylamine	3.0 - 4.6
p-benzene sulfonic acid-azo-a-naphthylamine	3.5 - 5.7
Benzene-azo-a-naphthylamine (pink to yellow)	3.7 - 5.0
p-toluene-azo-a-naphthylamine (pink to yellow)	3.7 - 5.0
diphenyl-diazo-binaphthionic acid (blue to red) (Congo Red)	3.0 - 5.0
Trisulphonate of ethyl roasaniline (Red Violet)	3.6 - 6.0
Resorcin-phthalein (light yellow to fluorescent) (Uranin or Fluorescein)	3.6 - 5.6
Tetrachlorophenol sulfonphthalein	3.0 - 4.6
Phenacetolin (yellow to red)	3.0 - 6.0

Note. Some of the above indicators are not easily available, but all have been tried and successfully used in titrations other than alkaloidal.

LIST of AVAILABLE INDICATORS with their pH VALUES.

From Clark-

"The Determination of Hydrogen Ions"

(a) Some of Sorensen's Selected Indicators.

Methyl Violet 6B extra (517)	.1 to 3.2
Diphenylamino-azobenzene (688) sulfonic acid	1.2 to 2.1
Dimethyl-anilino-azo-benzene (32)	2.9 to 4.0
Methyl orange, Helianthine (38)	3.1 to 4.4
Para-nitro-phenol	5.0 to 7.0
Neutral red (670)	6.8 to 8.0
Phenolphthalein	8.3 to 10.0
Thymolphthalein	9.3 to 10.5

(b) Some of Clark & Lubs' Indicators Possibly Available.

Thymolsulfonphthalein (acid range, red to yellow) (Thymol blue)	1.2 to 2.8
Tetra-bromo-phenol sulfonphthalein (yellow to blue) (Bromphenol blue)	3.0 to 4.6
Ortho-carboxy-benzene-azo-dimethyl aniline (Methyl red)	4.4 to 6.0
Dibromo-ortho-cresol sulfonphthalein (Brom-cresol purple)	5.2 to 6.8
Dibromo thymol sulfonphthalein (Brom-thymol blue)	6.0 to 7.6
Phenolsulfonphthalein (yellow to red) (Phenol red)	6.8 to 8.4
Ortho-cresol sulfonphthalein (yellow to red) (Cresol red)	7.2 to 8.8
Thymosulfonphthalein (neutral range) (Thymol blue)	8.0 to 9.6
Ortho-cresol phthalein (colorless to red) (Cresol-phthalein)	8.2 to 9.8

(c) Nitro Compounds.

Picric acid (2-4-6-trinitro phenol)	0.0 to 1.3
2-6-dinitro-phenol (B) colorless to yellow	1.7 to 4.4
2-4-dinitrophenol (a) colorless to yellow	2.0 to 4.7
2-5-dinitro-hydroquinone (coloress to various colors)	3.0 to 9.0
1-3-5-trinitro-benzene (coloress to orange)	11.5 to 14.0
2-4-6- trinitro-toluene (TNT) (pink to orange)	11.5 to 14.0

(d) Many Mono-azo Compounds listed in Clark, p. 85 Table 9.

(e) Triphenylmethane Compounds.

Crystal violet (516) (hexamethyl para-rosaniline) (green to blue)	0.0 to 2.0

Malachite green (495) (tetra-methyl-di-p-amino triphenyl-carbonol) (yellow to green)	0.0 - 2.0
(blue to fading)	11.5 - 14.
Iodine green (heptamethyl rosaniline) (yellow to blue)	0.0 - 2.6
Ethyl violet (hexa-ethyl pararosaniline) (yellow to blue)	0.0 - 3.6
Methyl violet 6B extra (517) (mixture of benzyl-tetra and penta-methyl-p-rosaniline and hexamethyl-p-rosaniline)	0.1 - 3.2
Fuchsin (512) base (mixture of rosaniline and p-rosaniline) (purple to fading)	0.1 - 3.2
Red violet 5 RS (525) (trisulfonate of ethyl-rosaniline) (pink to colorless)	3.6 - 6.0

BIBLIOGRAPHY

Brubaker, -- 1920

Vegetable Indicators.

Journal of the American Chemical Society through Druggist's Circular, 64, p. 141.

Twenty-five vegetable pigments can be used as indicators.

Coloring matter of Rosa Gallica is deep red with alkalies with a green fluorescence, and pink with acids.

Coloring matter of Rosa rugosa is green in alkalies, red in acids, and colorless in neutral solutions. Coloring matter of Lathyrus latifolius, perennial pea, is the same with acids and alkalies as is rose pigment. Also Iris Versicolor pigment. Method of extraction with sea-sand and alcohol is given.

Evers, N. 1921

Indicators in Titration of Alkaloids.

Chemist and Druggist, 94, p. 834; (Yr. Book of the American Pharmaceutical Association, 10, p. 496).

Discussed in terms of hydrogen-ion concentrations. Methyl orange (pH 4), brom-phenol blue (pH 4), and Morphine, as 1% HCl solution, (pH 3.65). Methyl orange may be because a definite shade is agreed upon, but brom-phenol blue is the best indicator for morphine.

Quinine acid HCl, pH: 3.64. Quinine neutral HCl, pH: 5.15. Use methyl orange here with a distinct color specification.

Atropine 1% HCl, pH: 3.75. Use brom-phenol blue

Using brom-phenol blue, 100% morphine was found in 1% solution. Using methyl orange, 99.5%. Using Cochineal, 98.8%.

The object was to first find the correct pH value of a certain strength of pure alkaloidal salt, and choose an indicator corresponding to this pH value, where the color change was evident, much in the same way that the writer worked with these 1% solutions.

Dott, D. B. 1922

Melting Points of Hydrastine and its Hydrochloride.

Pharmaceutical Journal (4) 55, p. 607. (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference, 1923, p. 11).

Melting point of Hydrastine:: 132 degrees.
No loss of weight when exposed in water bath. Melts and becomes colored at 130 - 135 degrees, but no perceptible loss of weight. Melting point raised when converted into salt and ammonium hydroxide added to its solution. In this case, some of the precipitated hydrastine was crystallized from alcohol and melted at 145 degrees.
Melting point of Hydrastine Hydrochloride: 116 degrees or less.
Dried at 100 degrees, it melts at 168 degrees.

McGill, W. J. 1922

Use of the Newer Indicators in the Titration of Alkaloids.

Journal of the American Chemical Society, 44, p. 2156; (Yr. Book of the American Pharmaceutical Association, 11, p. 415).

Brom-cresol purple gives better results than methyl red in the titration of Cinchona alkaloids, also in titrating atropine. Methyl red gives better results than brom-cresol purple with strychnine. Brom-phenol blue is better than bfom-cresol purple for morphine.

--------, ---- 1922

Suitable Indicators for the Titration of Cinchona Alkaloids.

Pharm. Weekbl., 59, p. 369; (Yr. Book of the American Pharmaceutical Association, 11, p. 415).

Hematoxylin is not a good indicator for Cinchona alkaloids. Quinine Hydrochloride is alkaline against methyl red and acid against neutral red. By applying the two indicators successively, satisfactory results are obtained.

Ionescu, A.
Spirescu, E. 1923

New Volumetric Method for the Determination of Alkaloids.

Bulletin Soc. Chim., Rumania, 5, p. 74. (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference). 1924, p. 2

The method depends in principle on precipitation by the Mayer-Valzer mercury reagent, solution of the precipitate in sulphuric acid and nitric acid, and titration of mercury ions with NaCl by the method of Votocek and Kaspareck. Full details are given in Year Book with the results obtained, which were very accurate.

Baggesgaard, ---
Rasmussen, H.
Schou, S. A. 1925

Alkaloidal Titrations.

Z. Elektrochem, 31, p. 189, through Chem. Abstr., 19, p. 2388. (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference, 1925, p. 41).

Strychnine, brucine, morphine, codeine, and atropine are best titrated with methyl red, cinchonine with the same indicator with a pH of about 5.8. Quinine, being a mono-acid base, is determined with p-nitro-phenol as indicator. Narcotine was titrated with methyl orange having a pH of about 4.5. Hydrastine is difficult of exact titration, but fairly good results are obtained with methyl red, pH about 4.8.

Kolthoff, I. M. 1925

Brom-phenol Blue as Indicator in Alkaloidal Titrations.

Pharm. Weekblad., 62, p. 478 through Chem. Abstr., 19, p. 2105. (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference, 1925, p. 42).

When alkaloids are dissolved in an excess of dilute acid and titrated back with alkali, methyl red is a satisfactory indicator. In the presence of alkcohol, alkaloids such as cocaine, pilocarpine and morphine give a sharp end-point with brom-phenol blue.

Dott, D. B. 1926

Iodeosin as Indicator in Alkaloidal Estimations.

Pharmaceutical Journal and Pharmacist, 116, p. 357; (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference, 1926, p. 40.).

Iodeosin is not recommended here in the titration of strychnine, and mixed alkaloids of Nux Vomica. Used in attenuated solution, 1 : 10,000 or less, its use for alkaloidal titration is uncertain, and the end-point is very indefinite.

Thiel, A. 1926

Substitute for Methyl Orange With Sharp End-point.

Tech.-Ind. Scheiz. Chem. Ztg., p. 24, through Chem. Abstr. (20), p. 2296. (Yr. Book of Pharmaceutical Conference and Transactions (British), 1926, p. 319.

Bromphenol blue can be substituted advantageously for methyl orange. To prepare the indicator solution, add hydrochloric acid tenth-normal to the 1% solution in alcohol until a wine-red color is obtained. Use 15 drops for 150 cc of titration liquid. To produce the normal shade, add the same amount of indicator to 150 cc of water saturated with carbon dioxide in a beaker of the same size and shape as that used for the titration.

Wales, H. 1926

The Choice of Indicators for Alkaloidal Titrations.

Pharmaceutical Journal and Pharmacist, 116, p. 604; (Yr. Book of Pharmacy and Transactions of the British Pharmaceutical Conference, 1926, p. 39).

The pH values of a number of alkaloidal salts have been found. Table given with most suitable indicators.

Approved
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