THE PREPARATION, PROPERTIES, AND USES OF SILICO-DUODECITUNGSTIC ACID.*

II. THE USE OF THE ACID AS A VOLUMETRIC REAGENT FOR ALKALOIDS.†

BY EDWARD OSCAR NORTH‡ WITH GEORGE D. BEAL.

HISTORICAL.

In a preceding paper (1) the authors have described the method of preparation of silicoduodecitungstic acid by a simple and convenient method which yields a product of very definite and stable character. This acid, as prepared by the authors, was found to have the composition $4H_2O.SiO_2.12WO_3.5H_2O$. The composition of the normal potassium and ammonium salts was determined, as well as the composition of the salts formed by this acid with alkaloids in hydrochloric acid solution. For the sake of convenience, the acid will be referred to in this article as silicotungstic acid.

Goddefroy (2) was the first to call attention to the insolubility of alkaloidal silicotungstates. Bertrand later (3) published the results of a series of investigations, claiming that the work of Goddefroy was unknown to him at the time the work was begun, and alone (4) and with Javillier (5) he studied in detail the properties of salts of this type applying the acid in the quantitative precipitation of nicotine. Javillier (6) continued the study on the salts of coniine, atropine, sparteine, antipyrine, and pyramidone.

The first direct gravimetric method was described by Chapin (7), in which nicotine was precipitated from tobacco extracts and the precipitate ignited, the anhydride of the acid being weighed. Ferenz and David (8) used the acid for the qualitative detection of alkaloids; Rasmusson (9) determined atropine gravimetrically, applying a correction for the solubility of the atropine salt. Taigner (10), working with atropine, cocaine, and strychnine, found that all of their salts had the same general type formula, which has been confirmed by the authors for all of the monacid tertiary bases studied. Heiduschka and Wolff (11) have studied the proper conditions for the formation of the alkaloidal salts and Sindlinger and Mach have described a method for the determination of pyridine and nicotine in mixtures.

The authors, in their previous paper (*loc. cit.*), have shown that for the monacid tertiary bases, the salts have the type formula $4Alkaloid, 2H_2O.SiO_2.12WO_3$, and for the diacid tertiary bases, the type formula $2Alkaloid, 2H_2O.SiO_2.12WO_3$. They have also shown that towards methyl orange and methyl red the acid, in its neutralizing power towards inorganic bases, is tetrabasic.

EDITOR'S NOTE.—For Part I see October JOURNAL. pp. 889–898.

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THEORETICAL AND EXPERIMENTAL.

The usual methods for the quantitative determination of alkaloids in vegetable drugs or their preparations involve the separation of the alkaloid by the so-called "shaking-out process." In this procedure, advantage is taken of the solubility of the alkaloidal salts in water and of the free bases in the organic solvents which are immiscible with water. Following the purification of the alkaloid, it is determined quantitatively by evaporation of the immiscible solvent solution, when the residue is weighed, titrated alkalimetrically, or titrated with a standard solution of one of the alkaloidal precipitants such as potassium-mercuric iodide or iodine-potassium iodide.

Beal and Lewis (13) and Beal and Hamilton (14) have reviewed the literature of the "shaking-out" process, calling attention to the sources of error therein and have established optimum conditions for these extractions. In this connection attention was called to the fact that the number of extractions required for complete removal of alkaloid from either the aqueous or organic solvent phase of a system could not be calculated directly from the simple coefficient of distribution which would assume the absence of acid salts or hydrates of a base. They have also cited the experience of other investigators, together with their own, in which the difficulty of avoiding decomposition of the alkaloidal residue during the final removal of the solvent, especially chloroform, is shown.

In the alkalimetric determination of alkaloids, difficulty is experienced in the selection of a suitable indicator, since the alkaloids are not only weak bases but vary widely in their degree of basicity. McGill (15) and others have recently met with some success in the application of the hydrogen electrode and other methods of electrometric titration to these determinations.

Gordin (16) has precipitated various alkaloids from a solution containing a known volume of standard hydrochloric acid by means of a neutral reagent such as iodine-potassium iodide or potassium-mercuric iodide, finding that an equivalent quantity of acid is carried down by the precipitate. He, therefore, titrated acidimetrically the excess of the standard acid in the filtrate from this precipitate. This method was further studied by Kippenberger (17). Heikel (18) precipitated various alkaloids with a standard solution of potassium-mercuric iodide, determining the excess of reagent in the filtrate by titration with potassium cyanide and silver nitrate.

There are at least two objections to these last methods. The methods have, in the first place, the usual disadvantages attendant upon quantitative filtration and back titration. It is also an established fact that the greater number of alkaloidal precipitates of this character begin to decompose after a short time, with the accompanying liberation of iodine.

The contribution of the authors of this paper to the gravimetric determination of alkaloids has been in the way of standardizing the method of preparing silicotungstic acid and determining in some additional salts the constancy of their composition. They have attempted to devise a rapid volumetric method for general application in the determination of alkaloids which would as far as possible be independent of the degree of ionization of the base and upon which moderate variations in hydrogen-ion concentration would be without effect. The manner of formation of the alkaloidal silicotungstates suggested the possibility of a volumetric precipitation method.

Heiduschka and Wolff (*loc. cit.*) added an excess of a standard solution of silicotungstic acid to the alcoholic solution of the alkaloid, filtered off the precipitate so formed and determined the excess of the acid by titration with alkali. The majority of the alkaloidal silicotungstates are best precipitated from a rather strongly acid solution. The authors have therefore made a search for an indicator which will show the presence of an excess of silicotungstic acid in a solution.

Because of the fact that derivatives of tungstic acid may be reduced with the formation of lower oxides of tungsten having a blue color, attempts were at first made to use as an indicator a strong reducing agent such as titanous chloride or colorless ammonium sulphide. The solution of titanous chloride showed some promise. It cannot be used as an inside indicator since it will reduce even the precipitated silicotungstate. There is also some difficulty in the preservation of the reagent. As an outside indicator the results are fairly satisfactory, the end-point, a blue color, being rather faint. The ammonium sulphide could not be used with the acid solution in which precipitation took place.

The leuco bases of some blue or green dyestuffs, such as reduced malachite green and methylene blue, were next tried, with the idea that the color of the redeveloped dye would reinforce the color of the tungsten blue. Again only moderate success was met with, the endpoint being rather faint and the solutions of the leuco bases being very unstable in the presence of atmospheric oxygen.

When malachite green is dissolved in hydrochloric acid of moderate concentration, the solution instead of being bluish green in color has a tone which is a shade of reddish or brownish orange. The characteristic color of the dye is restored upon dilution with a large amount of water, but one drop of 0.01 molar silicotungstic acid in 200 cc. of 0.6 normal hydrochloric acid will at once restore the color of the indicator when one drop of each solution is placed on a porcelain test plate and the drops mixed. The best range of acidity for the proper behavior of the indicator lies between 0.25 and 1.5 normal hydrochloric acid.

Preparation of the Indicator.—Two grams of malachite green was dissolved in 300 cc. of 6 *N* hydrochloric acid.

Standardization of Silicotungstic Acid.—The molecular weight of the acid is 3006.—An approximately 0.01 molar solution was prepared by dissolving 30 grams of the acid in enough water to make 1000 cc. of solution. A known amount of pure cinchonine was dissolved in 200 cc. of 0.6 normal hydrochloric acid and the solution titrated with silicotungstic acid. After allowing the precipitate to settle, a drop of the *clear* supernatant liquid was removed to a spot plate by means of a glass tube having an internal diameter of 3 mm. A drop of the indicator solution was then added to this by means of a platinum wire loop of 1.5 to 2 mm. diameter, and the two drops mixed. While the alkaloid was present in solution the color of the mixed drops was deep yellow. With silicotungstic acid in excess the color was bluish green.

An endpoint with methyl red is obtained when four hydrogens of the acid have been neutralized. The acid solution was also standardized by titration with standard sodium hydroxide, using methyl red as the indicator.

The solution of the acid may also be standardized by evaporating a definite volume to dryness, igniting the residue and weighing the silicotungstic anhydride formed.

Volumetric Assay of Cinchona Bark.—The method used for the extraction of the mixed alkaloids was that proposed by Scoville (19) for the Tenth Revision of the United States Pharmacopœia. Five grams of powdered cinchona bark were placed in a 250-cc. flask with 15 cc. of water and 5 cc. of hydrochloric acid. After mixing, the contents were digested for 2 hours on the steam-bath, then cooled and 200 cc. of a mixture of 3 volumes of ether and 1 volume of chloroform added, and after thorough shaking 10 cc. of ammonia water. The mixture was then shaken frequently

during a period of 12 hours. After the drug had settled, 160 cc. of clear supernatant liquid were decanted into a separatory funnel and repeatedly shaken out with 2 normal sulphuric acid. The combined acid extracts were made alkaline with ammonia and shaken out with chloroform to complete extraction. The chloroform extract was drawn off through a small filter into a beaker and the chloroform evaporated on the steam-bath, expelling the last traces by means of alcohol.

Instead of weighing the alkaloidal residue it was softened with alcohol and dissolved in a measured volume of 0.1 normal sulphuric acid, and the excess of acid determined by titration with 0.02 normal sodium hydroxide solution, using methyl red as indicator.

Following the alkalimetric titration the solution was diluted to a volume of 200 cc. and 20 cc. of 6 normal hydrochloric acid added. The solution was then titrated with approximately 0.01 molar silicotungstic acid, using the same procedure as in standardizing against cinchonine, with malachite green hydrochloride as the indicator. In both the alkalimetric and silicotungstic acid titrations the value 309 was used as the average molecular weight of the mixed anhydrous alkaloids. The principal alkaloids of cinchona contain two atoms of tertiary nitrogen, but the basicity of one of these is so slight that in the ordinary alkalimetric titrations the alkaloids are regarded as monobasic. Silicotungstic acid, however, reacts with both nitrogen atoms of these alkaloids.

TABLE I.

RESULTS OF THE ASSAY OF CINCHONA BARK.

No.		H_2SO_4 titration, Per cent.	Titration with $4H_2O.SiO_2.12WO_3$, Per cent.
1		5.70	5.85
2		5.67	5.73
3		5.92	5.60
4		5.67	5.47
5		5.62	5.50
6		5.76	5.68
	Ave.	5.72	5.64

Volumetric Determination of Cinchona Alkaloids without Purification.—Obviously the original ether-chloroform extract of cinchona bark is unsuitable for the direct gravimetric determination of total alkaloids because of the presence of non-alkaloidal extractives and ammonia. The presence of this ammonia also makes it impossible to extract the mixed alkaloids by shaking out with measured volumes of standard acid, afterwards determining the excess of acid by titration. However, ammonium salts do not precipitate our reagent in acid solution and the ether-chloroform extraction followed by a shaking-out with sulphuric acid should give a protein-free solution. It, therefore, seemed possible to save much time and obviate a source of error by making a direct titration with silicotungstic acid in the sulfuric acid solution obtained as a result of the first series of shakings.

Accordingly in a new series of assays two 80-cc. portions of the ether-chloroform extract were withdrawn. One portion was treated according to the full U. S. P. method, the mixed alkaloids being weighed, titrated with sulphuric acid and silicotungstic acid. The other portion was extracted with 2 normal sulphuric acid, the combined extracts diluted with water to 200 cc. and 10 cc. of 12 normal hydrochloric acid added. This solution was then titrated with silicotungstic acid in the usual manner.

The volume of silicotungstic acid solution used in these titrations averages about 19 cc. The volume of standard sulphuric acid actually consumed is only about 4 cc. In spite of the fact that the excess of sulphuric acid is determined by titration

TABLE II.

No.	Gravimetric.	H_2SO_4 titration.	Titration with $4H_2O.SiO_2.12WO_3$.	Titration with $4H_2O.SiO_2.12WO_3$ without purification.
1	5.69	5.85	5.90	5.90
2	6.19	5.87	5.85	5.90
3	6.37	6.00	5.95	5.99
4	5.83	5.71	5.68	5.84
5	5.91	5.95	5.84	5.89
6	5.99	5.70	5.68	5.92
Ave.	6.00	5.84	5.82	5.91

with a much weaker alkali, there is a potential source of error in the measurement of the sulfuric acid which is greater than the possible error in the endpoint with the silicotungstic acid.

Various chemists have pointed out a possible source of error in both gravimetric and alkalimetric determinations of alkaloids due to the presence of ammonium salts in water solution dissolved in the immiscible solvent. On evaporation to dryness there is a possibility that the alkaloid, as a non-volatile base, will expel ammonia, forming an alkaloidal salt. White spots have frequently been observed in such residues which upon examination have proved to be the alkaloidal salt, as chloride or sulfate, entirely free from the ammonium radical. This will naturally give high results in the gravimetric assay, and, being neutral, will give low results in the alkalimetric titration.

The reaction with silicotungstic acid is independent of the presence of an acid forming a soluble salt, and such a form of contamination will not interfere in the proposed method of determination.

*Assay of Fluidextract of Cinchona.**—These preparations were assayed according to the Scoville modification previously mentioned. Five cc. of the fluidextract were mixed with 5 grams of purified sawdust in a 250-cc. flask and carefully dried on the steam-bath. This residue was then digested with hydrochloric acid and extracted in the same manner as cinchona bark. The chloroform residue was weighed, and titrated with sulphuric acid and sodium hydroxide, and the sulphuric acid extract titrated with silicotungstic acid as above.

TABLE III.

ASSAY OF FLUIDEXTRACT OF CINCHONA.

	Gravimetric Gms. per 100 cc.	H_2SO_4 titration Gms. per 100 cc.	Titration with $4H_2O.SiO_2.12WO_3$ Gms. per 100 cc.
Red cinchona	3.41	3.26	3.36
	3.29	3.32	3.39
Cinchona U. S. P.	3.34	3.21	3.36
	3.39	3.35	3.33

Assay of Nux Vomica.—This was assayed by the method of the U. S. P. IX, weighing the chloroform residue before the alkalimetric titration and titrating these solutions with silicotungstic acid after adding hydrochloric acid to the neutral solution. The sulphuric acid extract was also titrated as in the assay of cinchona.

* Samples of percolates of cinchona and of red cinchona were furnished by Parke, Davis and Company through the courtesy of Mr. F. O. Taylor.

TABLE IV.

ASSAY OF NUX VOMICA.

No.	Gravimetric.	H_2SO_4 titration.	Titration with $4H_2O.SiO_2.12WO_3$.	Titration with $4H_2O.SiO_2.12WO_3$ without purification.
1	3.08	2.49	3.06	. . .
2	2.64	2.09	2.75	....
3	2.54	1.85	2.41	....
4	2.62	2.38	2.88	....
5	....	....	....	3.56
6	....	....	....	3.52
7	....	....	....	3.34
8	....	....	....	3.40

Since the titrations with silicotungstic acid gave values which were very much higher than those by the alkalimetric method, the silicotungstic acid which had been standardized against cinchonine was titrated against pure strychnine and brucine.

TABLE V.

Wt. alkaloid.	Amt. by H_2SO_4 titration.	Amt. by $4H_2O.SiO_2.12WO_3$ titration.	Per cent recovery by $4H_2O.SiO_2.12WO_3$.
0.1017 Gm. cinchonine	.....	0.1018	100.0
0.2109 Gm. strychnine	0.2080	0.2492	118.1
0.2066 Gm. strychnine	0.2042	0.2430	117.5
0.2073 Gm. brucine	.....	0.2766	133.4
0.2054 Gm. brucine	.....	0.2715	132.2
0.2065 Gm. brucine	0.2070	.....	.....
0.2090 Gm. brucine	0.2100	.....	.....

The apparent result in the brucine titration was 32.8% too high and for strychnine 17.8% too high. The average for both was 25.3%. With this correction the average value in the assay of the drug became 2.74%, a very fair agreement with the gravimetric assay.

Assay of Belladonna Leaves.—Belladonna leaves in No. 60 powder were extracted according to the method of the U. S. P. IX, and the final chloroformic residue weighed and titrated with sulphuric acid and sodium hydroxide, using methyl red as indicator. Other portions of the drug were analyzed by titrating the sulphuric acid solution with silicotungstic acid before the final purification as in the assay of cinchona bark. Because of the solubility of atropine silicotungstate in dilute acids (9), the sulphuric acid extract was titrated without dilution with water, and a correction of 0.0048 Gm. of atropine per 100 cc. of solution was made.

TABLE VI.

ASSAY OF BELLADONNA ROOT.

No.	Gravimetric.	H_2SO_4 titration.	Titration with $4H_2O.SiO_2.12WO_3$ without purification.
1	0.410	0.431	.....
2	0.415	0.428	.....
3	.....	.....	0.420
4	.....	.....	0.440
5	.....	.....	0.445
6	.....	.....	0.445

Assay of Stramonium Leaves.—Stramonium leaves were assayed in the same manner as the belladonna leaves above, determining the total alkaloids volumetrically by the U. S. P. process and also by titration with silicotungstic acid without the final purification. The same correction was applied as in the assay of belladonna leaves.

TABLE VII.

ASSAY OF STRAMONIUM LEAVES.

No.	H_2SO_4 titration, Per cent.	Titration with $4H_2O.SiO_2.12WO_3$ without final purification. Per cent.
1	.....	0.456
2	.....	0.466
3	0.440	.....
4	0.446	.....

Assay of Hydrastis Root.—Hydrastis root was assayed gravimetrically according to the method of the U. S. P. IX, and by silicotungstic acid without the final purification.

TABLE VIII.

ASSAY OF HYDRASTIS ROOT.

No.	U. S. P. Gravimetric, Per cent.	Titration with $4H_2O.SiO_2.12WO_3$ without final purification. Per cent.
1	3.44	....
2	3.52	....
3	....	3.09
4	....	3.15
5	....	3.32
6	....	3.29

Realizing the possibility of error due to the solubility of the alkaloidal silicotungstates, Nos. 5 and 6 were titrated by adding the silicotungstic acid in excess, allowing the precipitate to stand for thirty minutes, then filtering and washing with 1% hydrochloric acid. The excess of silicotungstic acid in the filtrate was titrated with a standard solution of cinchonine hydrochloride.

A Source of Error in the Method of Assay by Aliquot Parts.—In practically all of the alkaloidal assays of the U. S. P. IX, the alkaloids are extracted in the free

TABLE IX.

LOSS BY EVAPORATION OF PROLLIUS SOLUTION IN CINCHONA ASSAYS.

No.	Weight of flask and solution, before.	Weight of flask and solution, after.	Loss.
1	324.5	324.0	0.5
2	331.5	331.0	0.5
3	319.0	318.5	0.5
4	305.1	304.7	0.4
5	320.8	320.8	0.0
6	312.7	312.4	0.3
7	325.4	323.8	1.6
8	305.1	304.7	0.4
9	325.0	324.5	0.5
10	310.0	310.0	0.0
11	326.5	324.8	1.7
12	317.0	317.0	0.0
13	311.0	311.0	0.0
14	316.0	315.0	1.0
15	305.5	304.5	1.0
16	318.0	315.0	3.0
		Ave.	0.7 Gm.

state by macerating with some modification of Prollius mixture. Following this maceration, the drug is agglutinated, if necessary, by the addition of a small

amount of water and a definite volume of the non-aqueous solution decanted. The final calculation is based upon the supposed relationship of this volume of solution to the volume of liquid with which the drug was originally macerated. Unless perfectly stoppered vessels are used for the maceration, there is inevitably some loss of solvent during maceration, an effect which is oftentimes intensified by shaking. For this reason we have made it our practice to weigh the extraction flask at the beginning of the maceration and just before the removal of the aliquot, making up to the original weight if necessary by adding more of the non-aqueous solvent. We are of the opinion that the Pharmacopœia should contain a cautionary statement regarding this loss. The foregoing table contains the weights obtained in a series of extractions of cinchona, the macerations being made in Erlenmeyer flasks having well-fitting ground glass stoppers.

SUMMARY.

1. Aqueous solutions of silicotungstic acid restore the green color to an orange-colored solution of malachite green in hydrochloric acid.

2. Using the hydrochloric acid solution of malachite green as an outside indicator, it has been found possible to titrate alkaloidal salts with standard solutions of silicotungstic acid in the presence of free hydrochloric or sulphuric acid.

3. The results so obtained by slightly modifying the U. S. P. assay processes compare favorably with those obtained by the official method.

4. It has been found possible to materially shorten the official methods by titrating the first sulphuric acid extract with silicotungstic acid.

5. Attention is called to the possibility of losses of solvent in the initial extraction of the drug in the official assay processes.

6. A further study is being made of the possibilities of this reagent in the volumetric determination of alkaloids.

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ABSTRACT OF DISCUSSION.

J. P. Snyder emphasized the importance of the paper. It seemed to him that the method might be utilized for the determination of alkaloids in tablets; he said there was not at present an

ideal process, and hoped that Dr. Beal's method may prove to be well adapted, for example, in the determination of morphine in tablets.

Mr. L. E. Warren said if future results show up as satisfactory as indicated, this will prove the most important contribution to alkaloidal science since the discovery of Lloyd's reagent. He asked whether the reagent was adaptable to the recovery of alkaloids from plant extracts on a large scale.

To the first question, Dr. Beal replied he thought by a modification of the method it would prove satisfactory in the morphine determination; the results in belladonna by this method checked within two or three hundreths of one per cent.

In reply to the other question, Dr. Beal thought the method was applicable; he had separated pure strychnine in toxicological work.

TOXICITY OF QUININE-ASPIRIN MIXTURE.*

BY E. A. RUDDIMAN AND C. F. LANWERMEYER.

From time to time articles have appeared in pharmaceutical and medical journals relative to the toxicity of mixtures of quinine salts with organic acids. Professor Biddle (*Journal Am. Chem. Soc.*, XXXIV, 500, 1912) states that salts of cinchonine and quinine in solution with hydrochloric or sulphuric acid change more slowly at 36° C. than at 98° to 102° C. and the change at the latter temperature is very slight in 48 hours. With acetic or propionic acid the change is much more rapid, particularly if heated. Much of his work was done with the product formed by heating quinine with acetic acid. He was chiefly concerned in isolating and identifying quinotoxin and cinchotoxin. He bases his statements about toxicity on Hildebrandt's work.

Hildebrandt (*Arch. Exp. Path. and Pharmacol.*, 59, 127, 1908) produced his cinchotoxin by the action of acetic acid on cinchonine. This he administered to white mice. He says that 0.5 cc. of a 0.3 per cent. solution given to mice weighing 13 grams will produce severe cramps from which they recover, but die in a few days. This dose is equivalent to 0.00011 Gm. per gram body weight. Later on he says that the toxic dose is 0.00015 per gram body weight. The article does not state whether the weight of substance given is pure cinchotoxin or the product resulting from heating cinchonine with acetic acid. According to this worker quinotoxin is not as toxic as cinchotoxin.

Still earlier, in 1895, Miller and Rhode (*Ber. der Deutsche Chem. Ges.* XXVIII, 1058) worked with these products and named them cinchotoxin and quinotoxin, claiming that they are extraordinarily poisonous and the alkaloids lose their antipyretic effect.

Doctor Reid Hunt (*Arch. Inıernat. de Pharmacol.*, XII, 105, 1904) gave to a cat weighing 800 grams, by subcutaneous injection, 5 cc. of a 0.3 per cent. solution of cinchotoxin which caused severe cramps and death in a few minutes. The same sized dose of cinchonine produced only vomiting and recovery followed.

The work here recorded was not for the purpose of determining the presence of quinotoxin, but for the purpose of determining whether the mixture of quinine and aspirin, after standing sufficiently long to mass and become brown-red, is any more toxic than the mixture when first made. The results obtained are not conclusive, but on the whole are fairly satisfactory as far as they go.

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