3. Hydrochloric acid, used in proper proportions, imparts stability to the preparation, reducing precipitation and holding the alkaloids in solution. This property is further aided by glycerin or sugars.

4. Lactic acid is inferior to hydrochloric acid in extracting cinchona.

5. Hot extraction is of no advantage for cinchona, and may be of disadvantage through the formation of phlobaphenes.

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THE QUANTITATIVE DETERMINATION OF SPARTEINE IN TABLETS.*

BY PAUL W. JEWEL.†

This investigation was carried out with a view to developing a method for the quantitative determination of sparteine which would be rapid and simple and which could be depended upon to give accurate results.

This alkaloid was discovered in 1851 by Stenhouse,[1] who isolated it from *Spartium scoparium* Linné and later from the common Scotch Broom, *Cytisus scoparius* (Linné), Link, which now forms the chief source of supply. The alkaloid occurs in all parts of the plant and the amount present varies from 0.23% to 0.68%, being richest in March and poorest in August just after flowering.

Physical Properties.—Sparteine is a colorless oily liquid with a heavy odor recalling aniline, turning brown on exposure to air, especially if heated; readily soluble in alcohol, chloroform and ether, slightly soluble in water, and insoluble in benzine. Its density is greater than water, its specific gravity being 1.0196 at 20° C. It is laevo-rotatory. Its specific rotation in alcohol is variously given as —16.42°[2] and —14.6°.[3] The sulphate of the U. S. P. shows a rotation of — 22.12° in water.[2] The refractive index of the pure alkaloid is 1.5291 in sodium light at 20° C.[2] The boiling points given by various authors are: 328° C.,[3] 288° C.,[6] 311° C.,[7] 326° C.[8] Under 18 mm. pressure it boils at 188° C., and at 754 mm. in hydrogen it boils at 325° C.[2] It is slightly volatile at 100° C., if the heat is applied for a considerable length of time as is shown by an experiment described later in this paper. H. W. Jones[4] states that in the quantitative determination heat must be avoided, but gives no reason for this observation.

Chemical Properties.—Sparteine has the formula $C_{15}H_{26}N_2$, mol. wt. 234.30, and the sulphate of the U. S. P. is $C_{15}H_{26}N_2H_2SO_4.5H_2O$, mol. wt. 422.39. A number of attempts have been made to determine the structure of this alkaloid, perhaps the most comprehensive of which is that by Moureau and Valeur;[11] but so far its structure has not been established. It is readily oxidized, giving a great variety of oxidation products, none of which have, however, thrown much light on the structure of the alkaloid. The brown color observed when sparteine is heated in air is probably due to a partial oxidation. According to the British Pharmaceutical Codex, sparteine absorbs oxygen under the influence of air and light, becoming yellowish to dark brown and thicker.

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* Read before Scientific Section, A. Ph. A., Cleveland meeting, 1922.

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It is strongly alkaline and forms well-defined salts. It is monoacidic to phenolphthalein and litmus, but diacidic to methyl orange.[2]

The free alkaloid is precipitated from solutions of its salts by ammonia, sodium carbonate and sodium bicarbonate, and is soluble in an excess of these alkalis. With sodium or potassium hydroxide the alkaloid separates and collects on the sides of the flask in oily drops.

Qualitative Tests.—The one distinctive test of the U. S. P. IX was tried and gave excellent results, large, green, well-formed crystals of sparteine tetra-iodide appearing in a very few minutes. To about 0.10 Gm. of sparteine sulphate add 25 cc of ether and a few drops of ammonia water. Shake. Add an ethereal solution of iodine 1:50 until the resulting mixture is orange or brownish red upon shaking. Characteristic greenish brown crystals form in the presence of sparteine.

Jorissen's[9] test also gives excellent results: To a solution of the alkaloid in ether add a small amount of sulfur; mix by shaking and pass in hydrogen sulphide. A bulky, red precipitate is formed if sparteine is present. Coniine gives an orange and atropine a yellow precipitate under these conditions.

The following test reported by E. H. Grant[10] was tried but found to be less characteristic than the preceding ones:

To the alkaloid add a few drops of bromine water and evaporate to dryness. While still hot, invert over a dish of ammonia; a pink color is developed if sparteine is present. Caffeine gives a purple color under these conditions which can be distinguished from that given by sparteine only by comparison of the two. From their physiological action, it is hardly likely that sparteine and caffeine would be found in the same preparation, and it would seem that this test should only be used as a confirmation test for sparteine after other tests have given positive results.

Sparteine gives a picrate, crystallizing in needles from hot alcohol, which has a melting point of 208° C.[2]

QUANTITATIVE DETERMINATION.

Gravimetric Methods.—The following method, which, with slight variations, is used for most of the commoner alkaloids, was used and found to be entirely satisfactory both as regards accuracy and speed and ease of operation.

Dissolve a sufficient number of tablets or such a weight of the substance as will yield about 0.25 Gm. of pure alkaloid in water, with the aid of a small amount of dilute sulphuric acid if necessary. Make the solution alkaline to litmus with ammonia and shake out with three portions of chloroform, using 30, 20 and 10 cc, respectively. Combine the chloroform washings and extract with dilute sulphuric acid, using three portions of 30, 20 and 10 cc, respectively. Combine the acid portions, make alkaline with ammonia and reëxtract with chloroform as above, filter the chloroform through a paper previously moistened with chloroform, remove the chloroform by means of the steam-bath, allowing the current of air flowing through the hood to play over the surface of the evaporating liquid, which may be done by adjusting the windows of the hood to the level of the beaker. Use 2 cc of ether to aid in removing the last traces of chloroform. Remove the dish from the steam as soon as the ether and chloroform are completely removed, so that the heating may not be unnecessarily prolonged; cool and weigh. Multiply the weight of sparteine alkaloid obtained by the factor 1.8028 to get the amount of sparteine sulphate U. S. P. present in the original sample.

The residue thus obtained should be a clear, nearly colorless, oily liquid, with no trace of crystalline or other solid material present.

A number of hypodermic tablets of sparteine sulphate from reputable manufacturers were analyzed by this method, with the following results:

Size, gr.	Declared, Gm.	Found, Gm.	Variation, per cent.
1/30	0.0021	0.0021	None
1/10	0.0065	0.0064	−1.5
1/30	0.0021	0.0022	+2.3
1/30	0.0021	0.0020	−6.1
1/2	0.0324	0.0343	+5.7

It must be borne in mind that this method cannot be used if other interfering alkaloids are present; but, since sparteine is nearly always found alone and not in mixtures, as the pure salt, or in tablets containing only sparteine sulphate, its application may be regarded as practically universal.

Allowing the air to blow over the evaporating liquid hastens the evaporation and saves time, but the results are not altered if this is not done unless the alkaloid is allowed to stand on the steam-bath for a considerable length of time after the chloroform is gone. An electric fan may be substituted for the air current of the hoods for this.

It has been suggested that the volatility of sparteine could be taken advantage of in separating it from other non-volatile alkaloids. However, sparteine is not appreciably volatile except at high temperatures, and, unless kept in an atmosphere of hydrogen, decomposes rapidly due to oxidation. Separation could be effected on a commercial scale by steam distillation, but this could hardly be used for analytical work.

Objection has been made to methods[4] of this type, where heat is applied to the alkaloid, on account of the fact that, since sparteine is a volatile liquid alkaloid, appreciable amounts would be lost by volatilization if heated. To determine whether or not this objection is valid, the following experiment was carried out:

A sample of sparteine was prepared from sparteine sulphate U. S. P. by shaking out with chloroform, the solvent evaporated, the residue accurately weighed, dissolved in 60 cc of chloroform, and the chloroform removed as stated in the determination given above, using 2 cc of ether to remove the last traces. The resulting residue was again accurately weighed. The loss was not weighable. This residue was then heated for successive intervals, with results as follows:

One hour on steam-bath—loss of 3.1%.

One-half hour more in an electric oven at 100° C.—an additional loss of 1%.

Seven hours more in an electric oven at 100° C.—an additional loss of 2.5%.

From this it would appear that sparteine is slightly volatile at 100° C.; but, if the chloroform is removed as described in the determination above, and the heating discontinued as soon as the ether and chloroform are completely removed, no weighable amount will be lost.

Volumetric Methods.—When it is desirable to check the accuracy of a gravimetric determination of most of the common alkaloids, or when it is difficult to obtain the alkaloid in a sufficiently pure form to weigh, it is often possible to titrate the residue from the gravimetric determinations with standard acid and alkali and from the amount of acid consumed by the alkaloid calculate the amount of

alkaloid present. An attempt was accordingly made to titrate the residues from the gravimetric determinations of sparteine with a view to checking their accuracy.

The results thus obtained were not as expected. No end-point could be obtained and even an excess of alkali did not give a distinct yellow color. Probably the reason for this is that the color of the residue from the gravimetric determination is light brown, as is also the acid solution, and that this color obscures the end-point. No practical means of avoiding the formation of this color could be found and, therefore, this method was discarded as being of no value. If phenolphthalein is used as an indicator in place of methyl red the end-point is distinct enough but the results are in every case too low, 90% of the amount of alkaloid present being the greatest amount which could be recovered in this way.

A method reported by P. Lemaire[5] was tried and found to be of no value for the determination of sparteine.

Sparteine picrate is quite soluble in water and, therefore, the results obtained are far from accurate. This error can be reduced somewhat if the amount of solution used is kept as small as possible, but on account of the fact that even a saturated solution of picric acid is very dilute, the smallest amount of solution it is possible to use still leaves the error too large for even ordinary routine work.

It is a well-known fact that sparteine sulphate can be titrated direct with standard alkali, if no interfering substances are present. Sparteine is monoacidic to phenolphthalein and litmus, and, therefore, in using either of these indicators, the end-point will appear when exactly one-half of the sulphuric acid present is neutralized. One cc of sodium hydroxide then is equivalent to 0.0084478 Gm. of sparteine sulphate U. S. P. To methyl orange sparteine is diacidic, and the factor therefore will be 0.0042239. No reference could be found in the literature to the reaction of sparteine toward methyl red, and since this indicator has several advantages over methyl orange or phenolphthalein and is preferred by the writer for practically all alkaloids, an experiment was made to determine its reaction toward this alkaloid. A sample of pure sparteine sulphate U. S. P. was weighed, dissolved in distilled water, methyl red indicator added, and titrated with standard $N/50$ sodium hydroxide. It was found that one cc of $N/50$ sodium hydroxide was the equivalent of 0.0084478 Gm. of sparteine sulphate U. S. P. and the alkaloid is, therefore, monoacidic to methyl red.

Phenolphthalein may be used in place of methyl red; it appears to be fully as accurate, and the end-point is very distinct.

This method is very accurate when no interfering substances are present, but can hardly be depended upon for mixtures or tablets, the constituents of which are not definitely known. In practically all cases the results obtained by this method will be found to be accurate, as sparteine sulphate nearly always is found alone and interfering substances are usually absent.

The end-points are very sharp and distinct if the indicators used are of good quality. No trouble has been experienced by the writer in this respect with phenolphthalein or methyl orange, but one sample of methyl red was met which could not be made to dissolve completely in alcohol and which gave a very indistinct color change, no amount of alkali serving to give it a yellow color. However, the methyl red indicator used in these experiments was entirely satisfactory in every way.

Since methyl red changes from red in acid to yellow in alkali without any intermediate tint, it is much to be preferred to methyl orange. In the presence of carbonates the change is not so marked, the color "sliding" from red through brown to yellow. However, standard solutions free from carbonates can quite easily be prepared and the additional trouble is well repaid in the excellent results obtained. It is an exceptionally delicate indicator especially for alkaloids, and the end-point occurs when the solution is practically neutral. The hydrogen-ion concentration of the solution, at the point where the color of methyl red changes, is 10^{-8}, and the hydroxyl-ion concentration 10^{-6}, that of distilled water being 10^{-7} in each case.[12]

The following method, which has been used successfully for apomorphine, and which was said to be a method for the determination of apomorphine and sparteine, was tried. Several analysts have attempted to use this method and all report that a distinct end-point is difficult to obtain and that the results were inaccurate. The method follows:

Dissolve the tablets in water; make alkaline with sodium bicarbonate, and shake out with three 30-cc portions of ether. Wash the ether three times with 5 cc of water, separating carefully. Add an excess of $N/50$ acid, shake well, and draw off the acid solution. Wash the ether three times with water and combine the aqueous solutions. Add methyl red indicator and titrate at once.

No trouble was had with the end-point obtained, but the results were far from being accurate. Only a small amount of the sparteine present was indicated by the titration. Upon evaporation of the ether a considerable amount of alkaloid was found to be present, indicating that the prescribed treatment with acid does not quantitatively remove the alkaloid from the ether. A modification of this method was tried out to determine whether or not a longer contact of the acid with the ether solution of the alkaloid would result in a quantitative recovery of the alkaloid. Carried out as above the recovery is about 2%. After shaking intermittently for one hour the recovery was 5.5%, and after shaking for two hours was 6.1%. This would seem to indicate that almost no amount of shaking would ever remove all of the alkaloid from the ether solution. It would therefore seem that this method should be discarded as being of no value for the determination of sparteine.

SUMMARY.

Sparteine is only slightly volatile at 100° C., the loss being only 3.1% after an hour's heating at this temperature, 1.0% more after half an hour, and at the end of seven hours' continual heat 2.5% additional. The use of a small amount of heat does not affect the accuracy of the gravimetric determination, and the alkaloid is not lost through volatilization in the vapors of chloroform. This is further substantiated by the fact that the quantitative determination of pure sparteine sulphate showed a recovery of 99.3–99.5%.

The U. S. P. and Jorrissen qualitative tests are very distinctive and considered to be preferable to that of E. H. Grant.

Sparteine sulphate U. S. P. is monoacidic to methyl red and to phenolphthalein and may be titrated direct with $N/50$ sodium hydroxide, using these indicators, phenolphthalein being preferable to methyl red.

The picric acid method of P. Lemaire was found to be unsuitable for the quantitative determination of sparteine because of the solubility of sparteine picrate in water.

It was found to be impossible to titrate the alkaloid after extraction with chloroform, as methyl red indicator does not give a sharp end-point. This is apparently due to the brown color of the alkaloid and to partial oxidation. If phenolphthalein is used the end-point is fairly distinct but the results are in every case about 10% low.

Another method which consists of shaking the alkaloid out from ether solution with standard acid was found to be impractical because of the difficulty of quantitatively recovering the alkaloid in this way. The method as given recovers about 2.0% of the alkaloid present, two hours' shaking at frequent intervals recovering only 6.1%.

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SOLUTION OF CHLORINATED SODA.*

BY E. F. KELLEY AND JOHN C. KRANTZ, JR.

The well-known Dakin's Solution and the present official Solution of Chlorinated Soda have been the source of extensive research work among the members of the Pharmacopœia Revision Committee. The fact that Labarraque's Solution is seldom used and the increasing demand for Dakin's Solution makes this a question of great importance.

The chief objection to Labarraque's Solution is its strong alkalinity, on account of which it cannot be used as an irrigating solution in antiseptiology. The recent formula submitted by Samuel L. Hilton proposed the use of a mixture of sodium bicarbonate and carbonate to precipitate the lime salt and thus if any alkali salts are carried into the finished product, the acid carbonate ion, furnished by the acid salt, neutralizes the hydroxyl ion, formed by the hydrolysis of the normal carbonate. Dakin's Solution is best suited for clinical purposes when its hydrogen-ion concentration has a value of (—10); roughly this degree of alkalinity may be observed when the solution is not colored by solid phenolphthalein but is alkaline to an alcoholic solution of the indicator. The solution prepared by Mr. Hilton's formula meets the above neutrality requirement, but has one objection inasmuch as it is prone to become pink on standing.

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* Read before Scientific Section, A. Ph. A., Cleveland meeting, 1922.