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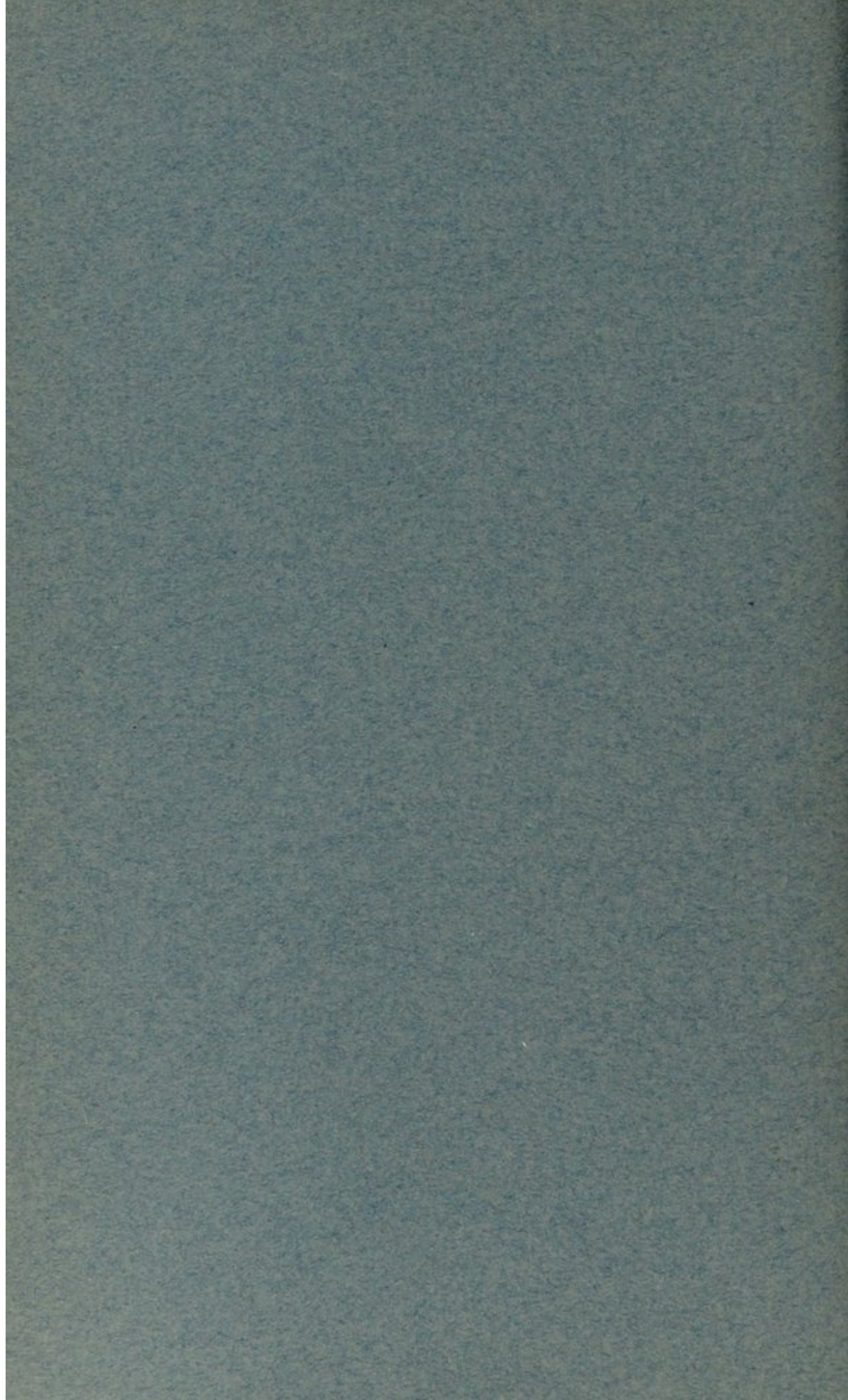
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THE TESTS FOR PURITY
OF
QUININE SALTS

BY
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THE TESTS FOR PURITY OF QUININE SALTS.*

BY

FRANK TUTIN, F.C.S.

The tests adopted by the various national pharmacopœias for ascertaining the freedom of quinine salts from an undue proportion of other cinchona alkaloids may be divided into two general classes. One of these is represented by the so-called ammonia test, which is based on a method originally proposed by Kerner,† and is now adopted by most of the pharmacopœias. The other class is represented by the method of the British Pharmacopœia, and involves separate tests for cinchonidine and cinchonine, quinidine, and cupreine.

The respective merits of these two general methods have been critically considered from time to time by various investigators. Nevertheless, it has recently been brought to the author's notice that there are several conditions affecting the accuracy of the ammonia test, and this fact has suggested its further investigation. A number of important observations have thus been made whereby it has been rendered evident that the ammonia test has a much more limited application than has generally been supposed.

I. Quinine Sulphate.

The test originally proposed by Kerner for the detection in quinine sulphate of other cinchona alkaloids, and which is referred to in this communication as the "ammonia test," depends upon the fact that, whilst quinine sulphate is less soluble in water than the corresponding salts of the other alkaloids with which it is usually associated, quinine itself, when freshly precipitated, is much more soluble in ammonia than the bases yielded by the latter salts. For the purpose of this test, an aqueous solution of the salt, saturated at 15°, is prepared, and the amount of 10 per cent. aqueous ammonia which will, at 15°, yield a clear liquid when mixed with 5 C.c. of the former solution is then determined. This is considered to afford some indication of the amount of cinchona alkaloids other than quinine in the sample of salt tested. The method of procedure differs somewhat in the various

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† *Arch. d. Pharm.* 1881, [3], 16, 186.

pharmacopœias which have adopted this test, and there is also an appreciable difference in the respective standards of purity. Thus, the United States Pharmacopœia, in its list of additions and corrections, states that not more than 7 C.c. of ammonia should be required, the French Pharmacopœia places the minimum at 5 C.c., and the Dutch Pharmacopœia at 4.5 C.c., whilst the German Pharmacopœia is the most stringent of all, since it limits the amount of ammonia to 4 C.c. The most important difference in the method of conducting this test, as described by the various Pharmacopœias, is in the preparation of the saturated solution of the quinine salt. Thus, the French Pharmacopœia states that one gramme of the hydrated quinine sulphate should be dissolved by boiling with 30 C.c. of water, after which the liquid must be cooled to 15° and then maintained at this temperature, with shaking, during half an hour. The German Pharmacopœia (fourth edition), on the other hand, requires 2 grammes of the salt, dried at $40-45^{\circ}$, to be digested with 20 C.c. of water for thirty minutes at $60-65^{\circ}$, after which the mixture is cooled to 15° , and then maintained at this temperature, with shaking, during two hours.

In this investigation the influence of variations in the length of time during which the mixture is maintained at 15° was first ascertained. A sample of quinine sulphate was taken which was free from impurities other than the so-called associate alkaloids, and, when tested according to the French method, required 5.0—5.1 C.c. of ammonia to yield a clear solution. A number of portions of this salt were then tested according to the instructions of the French Pharmacopœia, but with the exception that the time during which the mixture was kept at 15° was varied in each experiment. The results were as follows:—

Time of Digestion at 15° .	Amount of Ammonia Required.
Twenty minutes.....	6.2 C.c.
Twenty-five minutes.....	5.3 C.c.
Thirty minutes ..	5.0 C.c.
One hour	5.0 C.c.
Two hours.....	5.0 C.c.
Four hours	5.1 C.c.

It is seen from these results that it is unnecessary to keep the mixture at 15° longer than thirty minutes, the time allowed by the French Pharmacopœia.

It was subsequently ascertained that variations of the intervals between the operations of shaking, while the mixture is being digested at 15° , had no effect on the result. Experiment also showed that the result of the test, when conducted according to the French method, was, within fairly wide limits, independent of the amount of quinine employed. Thus, the result obtained when using 0.3 gramme of quinine sulphate for the test hardly differed beyond the limit of experimental error from that obtained when 1 gramme was employed. The French Pharmacopœia states that, after the salt

has been dissolved by boiling with 30 C.c. of water, the mixture should be cooled to 15° , but there is no requirement regarding the rate or manner of this initial cooling. On investigation it was found that any considerable variation of this factor had an appreciable effect on the result. Thus, if the hot solution were allowed to cool slowly to 15° , without agitation until it had reached this temperature, the mixture then being kept at 15° for thirty minutes, as directed, it was found that the amount of ammonia required to yield a clear solution was greater by about 0.3 C.c. than when the mixture had been quickly cooled, whilst shaking or stirring. This difference in the result is owing to the fact that, by slow cooling, larger crystals are formed, and the time required for the solution to attain equilibrium is then greater than the thirty minutes allowed. When conducting the test according to the French method it is, therefore, necessary to shake or stir the mixture during the initial cooling. As previously stated, a diversity of opinion exists as to whether, when conducting the ammonia test, it is better completely to dissolve the quinine sulphate, as required by the French Pharmacopœia, or to digest it at $60-65^{\circ}$ with an amount of water insufficient to effect its solution. With a view to settling this point, several samples of quinine sulphate were tested according to the method of both the French and German Pharmacopœias.

Sample.	Result by French Method.	Result by German Method.
A	4.4 C.c.	4.4 C.c.
B	4.5 C.c.	4.5 C.c.
C	5.0 C.c.	4.8 C.c.
D	5.6 C.c.	5.2 C.c.
E	5.9 C.c.	5.4 C.c.

Sample (A) was a pure quinine sulphate, which will be referred to later, whilst sample (B) was supplied by a well-known German firm, and was stated to meet the requirements of the German Pharmacopœia. It will be observed that only in these two cases were identical results obtained by both methods, and that the other samples, which were impure, all yielded higher results by the French than by the German method.

The French Pharmacopœia test is, therefore, to be preferred to that of the German Pharmacopœia, not only because it is far more expeditious, but also on account of being more sensitive, and requiring less material for its execution. The methods described by the Dutch and United States Pharmacopœias and by the British Pharmaceutical Codex respectively do not differ essentially from the German.

Having ascertained the best way of applying the ammonia test, the question of the standards adopted by the various pharmacopœias was next considered. For this purpose it was necessary to ascertain what results would be obtained on applying the ammonia test to absolutely pure quinine sulphate, and to mixtures of the latter with known proportions of the

pure sulphates of other cinchona alkaloids. With this object in view, a quantity (130 grammes) of a sample of quinine sulphate, which when tested according to the French method required 5.0—5.1 C.c. of ammonia, was recrystallised five times from a large volume of water. The material before recrystallisation was in the form of light crystals, and had a slight alkaline reaction to litmus. The recrystallised product was much more compact, but the behaviour to litmus remained unchanged. When tested according to the French method it required 4.6 C.c. of ammonia. The combined mother liquors were concentrated, when two successive crops of crystals were obtained. On testing these it was found that the first required 6.3 C.c. of ammonia, and the second 14.0 C.c.; the final mother liquors, after cooling to 15° for one hour and removing the crystals which separated, required 22 C.c. It is evident, therefore, that by the recrystallisation of the sulphate a very considerable concentration of the impurity had been effected in the mother liquor. This impurity was found to be hydroquinine sulphate, as the corresponding base was easily isolated after removing the quinine by oxidation. The statement which occurs in the literature to the effect that quinine cannot be separated from hydroquinine by the crystallisation of its normal sulphate is, therefore, not correct.

The recrystallised quinine sulphate was then converted into the acid sulphate, and the latter twice recrystallised from water. The recrystallised material was subsequently reconverted into the normal salt, and the latter recrystallised, first from slightly acid solution, and afterwards from water. The material thus obtained required 4.4 C.c. of ammonia when tested according to the French method, or only 0.2 C.c. less than before conversion into the acid sulphate. The quinine obtained from this purified salt was then converted into the *d-camphorsulphonate*, a salt of quinine which has not previously been described. This new salt was found to crystallise well, in needles, from either water, dilute alcohol, or ethyl acetate. It melted at 191°. The entire amount of the camphorsulphonate was crystallised twice from water, after which the base was isolated and again converted into the normal sulphate, the latter being crystallised twice, as before. It was then found that no further purification had been effected, the salt, when tested according to the French method, still requiring 4.4 C.c. of ammonia. Nevertheless, further efforts at purification were made. The purified base was converted into the *d-bromocamphorsulphonate* (melting and decomposing at 260°), and this new salt, which crystallises with great facility, but is practically insoluble in cold water, was twice recrystallised from dilute alcohol. The base was then isolated, converted into the normal sulphate, and the latter twice recrystallised as before described. The salt thus obtained amounted to only 23 grammes, whereas 130 grammes of the initial material had been used. It still

required 4.4 C.c. of ammonia when tested according to the French Pharmacopœia, and the same result was obtained by following the procedure described by either the German, the United States, or the Dutch Pharmacopœia. This fact is in itself evidence of the purity of the preparation, since it is obvious that the composition of a solution of a pure salt, saturated at any given temperature, is invariable, and cannot be affected by differences in the mode of procedure by which it is obtained. The pure salt was in the form known as "heavy" crystals, and possessed a slight but distinct alkaline reaction to litmus paper.

As the above process of purification was most drastic, but, nevertheless, failed to effect any further change, it can only be concluded that the quinine sulphate which, when tested, requires 4.4 C.c. of ammonia to yield a clear solution, is pure and absolutely free from other cinchona alkaloids. It thus appears that the standard adopted by the German Pharmacopœia (4 C.c. of ammonia) is incapable of being met by a pure quinine sulphate, but, as will be seen from the facts given later, it can be met by a slightly impure salt.*

The behaviour of mixtures of pure quinine sulphate with known percentages of the carefully purified sulphates of certain other cinchona alkaloids was then investigated. The hydroquinine sulphate used for this purpose was obtained from a commercial sample of the corresponding base, after purifying the latter by means of several crystallisations successively of its *d-camphorsulphonate* and *d-bromocamphorsulphonate*. These two salts have not previously been prepared; they crystallise similarly to the corresponding salts of quinine, and melt respectively at 217-218° and 266°.

Name of Salt.	Proportion Added.	Amount of Ammonia Required.
Cinchonidine sulphate	5 per cent.	 5.6 C.c.
Cinchonidine sulphate	2 per cent.	 5.1 C.c.
Hydroquinine sulphate	5 per cent.	 6.0 C.c.
Hydroquinine sulphate	2 per cent.	 5.2 C.c.
Cinchonine sulphate	5 per cent.	 8.0 C.c.
Quinidine sulphate	5 per cent.	 14.0 C.c.

The clear, ammoniacal liquids obtained from the mixtures containing respectively cinchonidine and hydroquinine deposited nothing on standing, but those containing cinchonine or quinidine soon commenced to deposit the respective base in a crystalline condition.

The two impurities most frequently met with in commercial quinine sulphate are cinchonidine and hydroquinine, but the presence of small quantities of these alkaloids cannot be considered as very objectionable. Indeed, so far as our present knowledge goes concerning hydroquinine there is no evidence that it is less valuable than quinine. It would,

* It was found, for example, that pure quinine sulphate to which but 0.1 per cent. of anhydrous sodium sulphate had been added would answer the requirement of the German Pharmacopœia as regards the ammonia test.

therefore, appear that the standards of the French and Dutch Pharmacopœias are unduly stringent. A reasonable degree of purity would be ensured by the provision that quinine sulphate, when tested according to the method of the French Pharmacopœia, should require not more than 6 C.c. of ammonia.

The next point investigated was the effect of basicity of the quinine sulphate on the result of the ammonia test. For this purpose the French test was applied to samples of pure quinine sulphate to which varying amounts of acid or alkali had been added before dissolving the salt in the water. The results obtained were as follows:—

Name of Reagent.	Amount Added.	Volume of Ammonia Required.
Normal sulphuric acid	2 drops	 7.4 C.c.
Decinormal sulphuric acid	5 drops	 5.5 C.c.
Normal ammonia ..	2 drops	 6.7 C.c.
Decinormal ammonia	5 drops	 5.4 C.c.

It is thus seen that the addition of either acid or alkali to pure quinine sulphate increases the amount of ammonia required when applying the test. The pure salt is, however, itself alkaline to litmus paper, although only slightly so, and this alkalinity is not completely neutralised by the addition of 5 drops of N/10 sulphuric acid to 1 gramme of the hydrated salt. The statement in the German and United States Pharmacopœias to the effect that quinine sulphate is neutral to litmus paper is, therefore, incorrect. The latter pharmacopœia, however, has recently modified its requirement in this respect, and now states that the salt in question should be "neutral or slightly alkaline." In this connection it may be noted that a neutral sample of quinine sulphate would require considerably more ammonia when tested than would the pure, slightly alkaline salt. A curious point regarding the alkaline reaction of quinine sulphate solutions is that this property becomes much more marked when heat is applied, and again diminishes on cooling. It is possible, moreover, by the careful addition of acid to a solution of the salt to prepare a liquid which will be alkaline when hot and acid when cold. On account of these facts it has been found impossible by the present author accurately to titrate quinine, as it is only by chance that that degree of alkalinity exactly corresponding to the complete formation of the normal sulphate can be attained, particularly as the requisite alkalinity depends upon the temperature of the solution during titration.

The effect of crystallising quinine sulphate from slightly acid or alkaline solutions was next investigated. It was found that when crystallised from an acid solution, collected and washed, quinine sulphate was still alkaline to litmus. The result of applying the ammonia test to the recrystallised product was but little higher than before this treatment, 4.6 C.c. instead of 4.4 C.c. of ammonia being required. The result of crystallising pure quinine sulphate from an alkaline solution

was, however, entirely different. Two grammes of pure quinine sulphate were dissolved in 100 C.c. of boiling water, and 6 drops of N/1 ammonia added. On allowing the solution to cool, the salt separated in an extremely bulky and light condition; it was collected and washed, and was then found to be distinctly more alkaline to litmus than was the original preparation. The ammonia test was applied according to the French method, when it was found that 6.4 C.c. of alkali was required. That is to say, that we have here a salt which is free from "associate alkaloids," but requires 2 C.c. of ammonia in excess of that necessary for the pure salt. Kerner's ammonia test is, therefore, not merely a test for the presence in quinine sulphate of other cinchona alkaloids, but is also a test for the basicity of the salt. A salt which is really pure, but only somewhat basic, might, therefore, be rejected as impure. It might be argued that this contingency could be guarded against by means of the litmus paper test, but this is only practicable to a limited extent, for, as shown above, pure quinine sulphate is itself alkaline, and it is only salts which are considerably basic which show a very noticeable increase in alkalinity. As it has been ascertained that samples of quinine sulphate which are somewhat basic commonly occur in commerce, it follows that the only way in which the ammonia test can with certainty be made to indicate the amount of alkaloids other than quinine present in a given sample of salt is by conducting successive tests, the first being made in the usual manner, and the subsequent ones with the addition of gradually increasing quantities of N/10 sulphuric acid. The test which requires the least amount of ammonia must then be taken as a criterion of the purity of the sample. The following experiments, conducted with a commercial sample of quinine sulphate, will serve as an example. The test was applied according to the French method:—

Amount of N/10 Acid Added.	Volume of Ammonia Required.
Nil.	8.0 C.c.
2 drops	7.4 C.c.
5 drops	6.7 C.c.
7 drops	6.5 C.c.
10 drops	6.9 C.c.
12 drops	7.3 C.c.

It is obvious that the result obtained when 7 drops of the acid had been added is the one which affords a true indication of the purity of the salt.

Finally, some tests for cinchonidine were made in the manner directed by the British Pharmacopœia, using quinine sulphate containing known proportions of the former alkaloid. It was then found that if less than about 7 per cent. of cinchonidine were present this alkaloid escaped detection. The test was then repeated, but with the use of "Æther Purificatus" instead of "Æther," when it was found possible to detect as little as 3 per cent. of cinchonidine.

II.—Quinine Bisulphate.

The method given by the United States, Dutch, and French Pharmacopœias and the British Pharmaceutical Codex for testing quinine bisulphate for the presence of other cinchona alkaloids may briefly be stated as follows:—A weighed quantity of the salt is dissolved in water and converted into the normal sulphate by careful neutralisation with an alkali. The remainder of the test is then conducted according to the method given in the case of the latter salt.

By this mode of procedure a molecular proportion of inorganic sulphate is formed, and the test is necessarily conducted in the presence of the latter. It was therefore sought to ascertain whether the presence of inorganic sulphate had any effect on the result of the test. Portions of pure quinine sulphate were therefore tested according to the French method, but with the addition of a small quantity of various inorganic sulphates. The results were as follows:—

Name of Salt.	Amount Added.	Volume of Ammonia Required.
Ammonium sulphate..	One molecular proportion..	0.5 C.c.
Ammonium sulphate..	One per cent.	3.0 C.c.
Sodium sulphate.....	One molecular proportion..	0.4-0.5 C.c.
Potassium sulphate ..	One molecular proportion..	0.4 C.c.

It is thus seen that the presence of inorganic sulphate has a very profound effect on the result of the ammonia test. The method given by the authorities previously mentioned for testing quinine bisulphate for the presence of other cinchona alkaloids is therefore absolutely devoid of value.

It was thought at first that this difficulty might be surmounted, and a satisfactory method of applying the ammonia test to quinine bisulphate devised, by separating the base from a weighed quantity of the salt and converting it quantitatively into the normal sulphate by titration with sulphuric acid. Unfortunately, however, as previously observed, it was found impossible to titrate the quinine with sufficient accuracy to render the results of the test reliable.

III.—Quinine Hydrochloride.

The method by which the ammonia test is applied to quinine hydrochloride depends on the conversion of the haloid salt into the sulphate by the addition of sodium or potassium sulphate. The amount of inorganic sulphate recommended to be added by the different pharmacopœias is in each case very appreciably in excess of the quantity theoretically required for the conversion of the quinine hydrochloride into sulphate. The test is therefore conducted in the presence of inorganic sulphate, in addition to the quantity of inorganic chloride formed. It has been shown above, however, that the presence of inorganic sulphate invalidates the result of the test. Experiments were therefore made with the addition of exactly the theoretical quantity of inorganic sulphate to the quinine hydrochloride. It was then found that the presence of the inorganic chloride formed had a very marked effect on

the result of the test, but of a nature opposite to that produced by the sulphates. Thus when a sample of pure quinine sulphate was tested according to the French method, but with the addition of two molecular proportions of either sodium or potassium chloride, 8.5—8.6 C.c. of ammonia were required, instead of 4.4 C.c. Mixtures of quinine sulphate with the respective sulphates of cinchonidine and hydroquinine were tested in the presence of two molecular proportions of inorganic chloride. It was then found that the presence of the latter rendered the test much less delicate, for the addition of 5 per cent. of hydroquinine sulphate only caused an increase of about 0.4 C.c. in the amount of ammonia required, whereas had the inorganic chloride been absent it would have caused an increase of 1.6 C.c. Unfortunately, this decreased sensitiveness of the test still persists when both inorganic sulphate and chloride are present in such proportions that the effect of one neutralises that of the other. Thus, 1 gramme of pure quinine sulphate was tested according to the French method, but with the addition of one molecular proportion of potassium sulphate and two of sodium chloride. It then required 4.4 C.c. of ammonia; that is, the same amount that would have been used had the inorganic salts been absent. The experiment was then repeated, but with the use of a quinine sulphate mixture containing 5 per cent. of hydroquinine sulphate, when 4.9 C.c. of ammonia were required, whereas, as previously shown, 6.0 C.c. would have been required had the inorganic salts been absent.

Results precisely similar to the above were obtained when bromides were substituted for chlorides.

The conclusion arrived at is, therefore, that the ammonia test cannot be satisfactorily adapted to estimate the purity of the haloid salts of quinine.

Optical Rotation of Quinine Salts.

The new edition of the French Pharmacopœia gives values for the optical rotation of the various quinine salts, and this factor certainly affords a good means of detecting the presence of cinchonidine or quinidine in commercial quinine salts. The present author, however, is unable to confirm the correctness of these values as given by the French Pharmacopœia. This work states that a 1 per cent. solution of anhydrous quinine sulphate in dilute sulphuric acid should have $[\alpha]_D -243.5^\circ$ at 15° , whilst it was found that the pure salt, when examined as directed by the French Pharmacopœia, yields a lower result, namely $[\alpha]_D -235.0^\circ$. In contradistinction to this, the rotation of quinine hydrochloride has been ascertained by the present author to be higher than the value given by the French Pharmacopœia for this salt—namely, $[\alpha]_D -155.8^\circ$ instead of $[\alpha]_D -147.8^\circ$. The values now obtained for the rotations of the sulphate and hydrochloride respectively are, however, in harmony with each other, for if the rotation of the latter salt be determined in presence of an excess of sulphuric acid, and the result calculated for

an amount of normal sulphate equivalent to the quantity of hydrochloride taken, the figure $[\alpha]_D - 234.8^\circ$ is obtained. This figure is practically identical with that directly observed for the normal sulphate—viz., $[\alpha]_D - 235.0^\circ$. The value found by the present author for the hepta-hydrated bisulphate of quinine is $[\alpha]_D - 159.1^\circ$, and this figure also differs from the corresponding value given by the French Pharmacopœia—namely, 204.8° . If, however, the former value be recalculated for an equivalent amount of anhydrous normal sulphate, the figure $[\alpha]_D - 234.2^\circ$ is obtained, which is in practical agreement with that given by the latter salt when dissolved in dilute sulphuric acid. On the other hand, if a similar recalculation be made with the figures given by the French Pharmacopœia the value $[\alpha]_D - 300.9^\circ$ is obtained, whereas this work states that the anhydrous normal sulphate, when dissolved in dilute sulphuric acid, has $[\alpha]_D - 243.5^\circ$.

The respective specific rotations given by the French Pharmacopœia for the sulphate, acid sulphate, and hydrochloride of quinine are therefore not in harmony with one another. Moreover, since the discrepancies are so great, it must be concluded that at least some of the figures given are erroneous.

Summary and Conclusions.

The results of the foregoing experiments may be summarised as follows:—

The method for applying the ammonia test to quinine sulphate, as described by the French Pharmacopœia, is to be preferred to that given by other Pharmacopœias.

The minimum amount of 10 per cent. ammonia which will yield a clear solution at 15° with 5 C.c. of a solution of pure quinine sulphate, saturated at 15° , is 4.4 C.c. It is therefore impossible to meet the requirements of the German Pharmacopœia—namely, that not more than 4.0 C.c. of ammonia should be needed for this purpose. It would appear, furthermore, that the standards of the French and Dutch Pharmacopœias, especially that of the latter, are more stringent than is desirable. A minimum of 6.0 C.c. of ammonia, when conducting the test according to the French method, would seem a reasonable requirement.

The ammonia test, however, is not only a test for the presence in quinine sulphate of other cinchona alkaloids, inasmuch as basicity of the salt has precisely the same effect as impurity. Commercial salts of quinine, which are frequently somewhat basic, may therefore appear to be far less pure than is actually the case, unless a laborious method of correction for this factor is adopted.

Owing to the profound influence exerted by the presence of small amounts of inorganic salts on the results obtained by the ammonia test, the latter is valueless as a means of ascertaining the purity of any salt of quinine other than the normal sulphate.

Since the usefulness of the ammonia test is so limited, the test for cinchonine and cinchonidine prescribed by the present British Pharmacopœia is much to be preferred, as it is applicable to any quinine salt. This test, however, is rendered more delicate by the use of "Æther Purificatus" instead of "Æther." The ammonia test, on the other hand, is the only means of detecting hydroquinine without having recourse to the actual isolation of this alkaloid. It yet remains to be shown, however, whether there is anything to be gained by requiring quinine sulphate to be free from the small amounts of hydroquinine sulphate with which it is liable to be associated.

It may finally be noted that the results given throughout this paper were not obtained by isolated determinations, but that in each case they were amply confirmed.

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