Section on Scientific Papers

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THE PREPARATION, QUALITY AND TESTING OF QUININE TANNATE.

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Quinine is one of the very few specifics known to medicine. It is probably more used than any other single remedy. Because of the extremely bitter taste of its soluble salts its administration, especially to children, is a perplexing problem. Many attempts have been made to overcome this difficulty but few of them are without objections. The administration of the alkaloid in capsules or coated tablets is fairly satisfactory but most children and some adults cannot be induced to swallow these. Suspension of the alkaloid or some of its sparingly soluble compounds in flavored syrup has met with moderate success. Besides the alkaloid itself the most common combinations which are administered in this way are the sulphate, salicylate, tannate and certain esters.

Quinine tannate has been known in medicine for a very long time and the literature concerning it, although chiefly of pharmaceutical interest, is extensive. It is employed chiefly because it exhibits the quinine in an extremely insoluble form, one part of the salt requiring several thousand parts of cold water for solution. The salt is official in the Austrian, Danish, Dutch, German, Hungarian, Russian, Spanish and Swiss Pharmacopœias. Numerous methods have been proposed for the preparation of quinine tannate. In most of them quinine sulphate is employed as the starting point. This is dissolved in very dilute sulphuric acid and the solution precipitated with a solution of tannic acid containing a small amount of alkali, usually sodium bicarbonate or ammonia. In other methods the acetate or the hydrochloride of the alkaloid is employed and in some the precipitation is made in a hydro-alcoholic menstruum. The precipitate is then freed from soluble impurities more or less completely by washing.

Since the literature of quinine tannate is so voluminous and since it deals for the most part with unimportant modifications of processes for making the salt, no attempt is here made to review any except a few of the more important papers.

Between the years 1875 and 1885 Rozsnay,[1] a Hungarian pharmacist, perfected a process for preparing quinine tannate which produces a salt of great purity. For a time the method remained a secret but later the details became known and the process has now been incorporated in several of the pharmacopœias. By the process which Rozsnay introduced the salt is prepared in the usual way, washed with a small quantity of water and is then melted in hot water. By this process the small individual particles coalesce and the substance is thereby rendered less

[1] Pharm. Zentralhalle, 16, 106 (1875).
New Remedies, 12, 274 (1883).

bitter. On pouring off the supernatant liquid the quinine tannate is left as a resin-like mass which soon solidifies and may then be powdered and dried.

A process for preparing quinine tannate which was quite popular a quarter of a century ago deserves mention.[2] Quinine was first prepared by precipitation from the solution of the sulphate of the alkaloid with solution of sodium carbonate. The precipitate was washed and dissolved in alcohol. The alcoholic solution was then poured slowly into an aqueous solution of tannic acid. The precipitate after washing and drying was light in color and practically tasteless. Because of its expensiveness, owing to the alcohol used, and because of the low alkaloidal content of the finished product (about 20 per cent.) the method is no longer used.

The therapeutic efficiency of quinine tannate has been questioned. Many years ago, Hager[3] reported that from the results of experiments upon his own person and upon others he had concluded that this salt has only about one-tenth of the value of quinine sulphate. His conclusions, however, cannot be considered authoritative since he states that nine-tenths of the alkaloid may be recovered from the urine and feces. He evidently assumes that the alkaloid eliminated by the urine is inert, a conclusion which, in the light of present knowledge, is not justified.

Some years after Hager's report was published Field[4] experimented with the solubility of quinine tannate in gastric juice. He prepared artificial gastric juice and also collected the natural secretion from a healthy dog. He attempted to dissolve the quinine tannate in these solutions but found that the salt was practically insoluble. From the results of his experiments, which also included the administration of the drug to the human subject, the author concluded that quinine tannate is practically inert as a medicinal substance. It would appear that this conclusion, so far as it is based upon the solubility of the salt in gastric juice, is untenable because the salt is prepared by precipitation from a slightly acid solution and it could not, therefore, be expected to dissolve appreciably in gastric juice. Field pointed out that even if the salt were absorbed in the stomach of the patient, the ingestion of such large proportions of tannic acid might be very undesirable.

On the other hand Zeig[5] contends that the salt is active. He states that if a grain of the salt be dissolved in an ounce of very dilute hydrochloric acid at a temperature of 140° F. (60° C.) the solution will possess a taste as bitter as that of a control using an equivalent amount of quinine sulphate.

Christian[6] working in Koch's clinic has studied the efficiency of some of the difficultly soluble quinine salts and esters. He administered known quantities of the alkaloidal combination, collected the urine of the patients and extracted the alkaloid therefrom, the percentage of alkaloid excreted being considered as the

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[2]Pharm. Zentralhalle, 23, 550 (1882).
Am. Druggist, 16, 68 (1887).
[3]Pharm. Zentralhalle, 13, 247 (1872).
[4]Phys. Surg., 5, 353 (1883).
Proc. Am. Pharm. Assn., 21, 379 (1873).
Pharm. Rec., 4, 5 (1884).
Proc. Am. Pharm. Assn., 32, 308 (1884).
[5]West. Druggist, 15, 361 (1893); from Proc. Cal. Pharm. Assn. (1892).
Proc. Am. Pharm. Assn., 42, 651 (1894).
[6]Deutsch. Med. Woch., 29, 216 (1903).

efficiency criterion. While a number of experiments were carried out with such compounds as euquinine and saloquinine only two tests with quinine tannate were recorded. From one of these 13.18 per cent. of the alkaloid given was recovered and from the other 23.79 per cent.

From the conflicting results of these inadequate and for the most part unscientific experiments, it can be seen that the question of the therapeutic efficiency of the salt is still an open one. It is to be hoped that the value of quinine tannate will be determined by scientific experimentation.

But few reports of examinations of commercial quinine tannate have appeared. In 1879 Jobst[7] examined several specimens of the preparation, the method of manufacture of which was unknown to him, and at the same time several factory specimens of known origin were studied. The examination revealed great variations in composition, not only in respect to the content of water and total alkaloid, but also in the *kind* of alkaloid, as several of the commercial specimens contained mixtures of the cinchona alkaloids. His findings are tabulated below:

Method of Manufacture	Water (Loss at 120°) Per Cent.	Quinine, Per Cent.	Quinidine, Per Cent.	Cinchonidine Per Cent.	Cinchonine Per Cent.
Known	7.2	31.37			
Known	9.7	22.72			
Known	10.7	10.00			
Known	11.4	7.40			
Unknown	9.1	4.46	11.97	7.33	
Unknown	9.8	4.93	2.43	13.10	3.35
Unknown	10.2	6.23	Trace	20.80	Trace

He assigns the formula, $C_{20}H_{24}O_2N_2.2C_{14}H_{10}O_9+4H_2O$, as the most probable one for the salt having the highest quinine content, viz., 31.37 per cent. The total alkaloidal content was determined by mixing with freshly slacked lime, drying and extracting the pulverized mass with chloroform. As the author's methods for the quantitative separation of the several alkaloids are not given, no estimate of the accuracy of the recorded results can be made. Water was determined by drying at 120°. From the results of his experiments he concluded that tannic acid is capable of forming very variable compounds with quinine according to the proportion and manner in which it is employed in the manufacture of the combination. To obtain products of even an approximately constant composition definite quantities of tannic acid and of quinine must always be employed.

In 1889 Neumann[8] examined four commercial specimens of quinine tannate while testing a method which he had worked out for the assay of the product. The quinine content varied between 13.9 per cent. and 28.8 per cent., three of the specimens assaying more than 25 per cent. of the alkaloid. These results, however, could not be considered as authoritative as controls indicated that the method gave values about 3 per cent. too high.

In 1892 Zeig[9] stated that he had found the alkaloidal content of commercial

[7] Arch. Pharm., 212, 331 (1878).
Proc. Am. Pharm. Assn., 26, 578 (1878).

[8] Zeit. anal. Chemie, 28, 663 (1889).
Proc. Am. Pharm. Assn., 38, 673 (1890).

[9] West. Druggist, 15, 361 (1893); from Proc. Cal. Pharm Assn. (1892).
Proc. Am. Pharm. Assn., 42, 651 (1894).

specimens of quinine tannate to vary between 10 and 25 per cent. but he gave no information concerning the number of specimens examined nor of the names of the brands studied.

Quinine tannate having been considered by the Council on Pharmacy and Chemistry of the American Medical Association, the association laboratory took up the examination of the several brands of the product on the American market. At the same time specimens of the salt were prepared by various methods and these were included in the examination. Tentative academic standards for the substance were prepared and submitted for criticism to several manufacturers of pharmaceutical chemicals whom it was thought might be interested.

LABORATORY SPECIMENS.

The method of manufacture first employed was that of the Swiss Pharmacopoeia. Briefly the method is as follows:

Nine parts of quinine sulphate are dissolved in a mixture consisting of 16 parts diluted sulphuric acid and 300 parts of water. Twenty-one parts of tannic acid and 3.5 parts of sodium bicarbonate are dissolved in 300 parts of water without the application of heat. This solution is poured with constant stirring into the solution of quinine sulphate. The resultant precipitate is washed with water until the washings, after acidification with nitric acid, cease to give a turbidity with barium nitrate solution.

In preparing the salt by this method it was found impracticable to follow the directions concerning the washing to completion, as the precipitate was of such bulk that the sulphate could not be completely removed. Although the standard of the Swiss Pharmacopoeia requires that the salt shall contain from 30 to 35 per cent. quinine, the laboratory specimen prepared as above contained but about 25.8 per cent. alkaloid. Quinine was determined by suspending the salt in weak ammonia water, shaking the mixture with successive portions of chloroform until extraction was complete, evaporating the solvent, drying the residue at 100°, and weighing the alkaloid.* Water was determined by drying at 100° C. This specimen lost 7.6 per cent. of its weight on drying. In the appended table of analytical results it is designated as "No. 1."

A leading manufacturer of quinine salts, having criticised the Swiss method of manufacture (the method included in the tentative academic standards which were submitted to the manufacturers) in respect to the proportions of the several ingredients used, a specimen was prepared in the laboratory by the Swiss method but using the quantities suggested by this manufacturer, which were as follows:

Quinine sulphate	8.4 parts
Diluted sulphuric acid	15.0 "
Tannic acid	15.0 "
Sodium bicarbonate	3.0 "

The manufacturer stated that these proportions would yield a product corresponding very nearly to the formula, $C_{20}H_{24}O_2N_2(HC_{14}H_9O_2)+4H_2O$, and containing 31.16 per cent. anhydrous quinine, 61.91 per cent. tannic acid and 6.93 per cent. water. The laboratory specimen prepared according to the manufacturer's suggestion contained 31.3 per cent. alkaloid and lost 9.0 per cent. of its weight on drying. This specimen is designated as "No. 2" in the table of analytical results.

Quinine tannate was prepared by the method of the Hungarian Pharmacopoeia,

*This method is described in greater detail in the tentative description for Quinine Tannate given elsewhere in this paper.

aliquot parts of the prescribed quantities being used. The following is the method as used:

Ten parts of quinine sulphate are dissolved in 150 parts of distilled water by the aid of the smallest necessary quantity of diluted sulphuric acid. Twenty parts of tannic acid are dissolved in 140 parts of water and the filtered solution poured with constant stirring into the solution of quinine sulphate. A mixture of 5 parts of tannic acid, 80 parts of water and 5 parts of ammonia water is filtered and poured slowly and with constant stirring into the quinine-tannin mixture prepared as above described. The resultant precipitate is collected on a filter and washed with 80 parts of water. The mass is then gently expressed and warmed with 40 parts water until it melts to a resin-like mass. It is then dried and pulverized.

Although the Hungarian Pharmacopoeia requires that the salt shall contain from 30 to 32 per cent. anhydrous quinine the laboratory specimen prepared as above described contained but about 25 per cent. alkaloid. In drying the specimen lost about 10 per cent. of its weight. (In the table of analytical results this specimen is designated as "No. 3.")

The salt was then prepared by the method of the Hungarian Pharmacopoeia except that the quantities of the several ingredients used were modified to conform to the proportions employed in the preparation of "No. 2." Ammonia water was used as the precipitant. The following quantities were used:

Solution 1—Quinine sulphate	8.4	gm.
Diluted sulphuric acid	15.5	c.c.
Water	150.0	c.c.
Solution 2—Tannic acid	10	gm.
Water	70	c.c.
Solution 3—Tannic acid	3	gm.
Ammonia water	5	c.c.
Water	50	c.c.

This laboratory specimen prepared as above contained 28.7 per cent. alkaloid and lost 10.0 per cent. of its weight on drying. The specimen is designated as "No. 4" in the table of analytical results.

Another specimen was prepared exactly like "No. 4" except that sodium bicarbonate was used as the precipitant instead of ammonia water, 3 gm. being used. This specimen contained 33.3 per cent. alkaloid and lost 7.2 per cent. of its weight on drying. It is designated as "No. 5" in the table of analytical results.

Quinine tannate was prepared by the method official in the German Pharmacopœia. Essentially this is the Rozsnay method, official in the Hungarian Pharmacopoeia, but it has been modified in one important particular. It is directed that after the salt has been dried in a warm place, it is to be dried at 100° C. The preparation of a specimen by this method was begun and completed through the stage of drying at 30° to 40° C. The air-dried specimen was then divided into two equal portions and one of them was dried at 100° C. as directed. The two sub-divisions were then compared. The air-dried specimen was a drab colored, moderately bulky powder which did not adhere to the surfaces of glass or paper. It contained 25.8 per cent. quinine and the loss on drying at 100° C. amounted to 9.8 per cent. The portion which had been dried at 100° C. was somewhat darker in color than the other, was slightly less bulky, and adhered to glass and paper in a troublesome way. It contained 27.8 per cent. of quinine. These specimens are respectively designated in the table of analytical results as "No. 6" and "No. 6-a." The German Pharmacopoeia requires that the salt shall contain at least 30 per cent. of quinine.

Another specimen was prepared by the following method:

Ten gm. of quinine sulphate are dissolved in a mixture of 15 c.c. of diluted sulphuric acid and 300 c.c. of water. Twelve gm. tannic acid are dissolved in 100 c.c. water and the filtered solution poured slowly and with constant stirring into the solution of quinine sulphate. Six gm. tannic acid are then dissolved in 50 c.c. water and 2 gm. sodium bicarbonate dissolved in the solution. This solution is filtered and the filtrate poured slowly and with constant stirring into the quinine-tannin mixture prepared as above described. The precipitated quinine tannate is allowed to stand for 24 hours. It is then poured onto a muslin filter, washed with 100 c.c. water and expressed with moderate pressure. The expressed mass is then transferred to a porcelain dish, 100 c.c. water added and the mixture heated on the water bath until the quinine tannate melts to a resin-like mass. The supernatant liquid is poured off, the mass dried in the air, and pulverized.

This specimen contained 29.3 per cent. alkaloid and lost 7.9 per cent. of its weight on drying. It is designated as "No. 7" in the tabulated analytical results.

As it seemed probable that the amount of sodium bicarbonate was too small to obtain a salt containing the maximum amount of alkaloid, the experiment was repeated with some variations. Three gm. sodium bicarbonate were employed instead of two and the amounts of solvent in some cases were changed. The details of the variations may be seen by consulting Table I. This process yielded 22.2 gm. of the salt (from 10 gm. quinine sulphate), and the specimen ("No. 8" in table II) contained 29.1 per cent. alkaloid and the loss on drying amounted to 7.3 per cent.

In the hope of obtaining a salt with a higher alkaloidal content another specimen was prepared by the same method as was used in "No. 8" except that 4 gm. sodium bicarbonate were used as the precipitant. The quantities of the several ingredients used may be seen by consulting Table I. This specimen was very dark colored and otherwise objectionable in appearance. The yield was less than that obtained by some of the other methods and the product was less bulky. It contained 34.2 per cent. of quinine and lost 8.1 per cent. of its weight on drying. This specimen is designated as "No. 9" in Table II.

Another specimen was prepared by a method which is very similar to that used in the preparation of "No. 8," the quantities of the several ingredients used being given in Table I. This specimen contained 33.7 per cent. alkaloid and lost 7.7 per cent. of its weight on drying. It is designated as "No. 10" in Table II.

A general idea of the variations in the processes used in the preparation of the several specimens may be gained by a study of Table I. In this table the composition is given of the several "solutions" used in the manufacture of each specimen. It is to be understood, of course, that precipitation is brought about by mixing the several solutions.

From the results of the experimental work it is concluded that it is easily possible to obtain quinine tannate containing over 30 per cent. of anhydrous quinine, but that this desideratum is not attainable if the substance be prepared by any of the methods now official in the pharmacopoeias. Sodium bicarbonate is more satisfactory as a precipitant than ammonia water, but it is essential that an excess of the alkali be avoided. While the observations and experiments are too few to warrant a positive conclusion, it appears that if ammonia water be used as the precipitant, the yield of the finished product will be larger than is the case when sodium bicarbonate is employed. The quinine content, however, is

proportionately smaller. The observation of Jobst that in order to obtain products of even an approximately constant composition it is necessary to employ definite proportions of tannic acid and of quinine has been confirmed by our experiments.

TABLE I

Solution		1	2	3	4	5
1	Quinine sulphate.....	9	8.4	10 gm.	8.4 gm.	8.4 gm.
	Diluted sulphuric acid.	16	15.0	q. s.	15.5 cc.	15 cc.
	Water	300	300	150	150 cc.	150 cc.
2	Tannic acid			20 gm.	10 gm.	10 gm.
	Water			140 cc.	70 cc.	70 cc.
3	Tannic acid	21	15			3 gm.
	Sodium bicarbonate....	3.5	3			3 gm.
	Water	300	300			50 cc.
4	Tannic acid			5 gm.	3 gm.	
	Ammonia water			5 cc.	5 cc.	
	Water			80 cc.	50 cc.	
5	Sodium bicarbonate....					
	Water					
6	Tannic acid					
	Water					

Solution		6—6a	7	8	9	10
1	Quinine sulphate.....	4 gm.	10 gm.	10 gm.	10 gm.	10 gm.
	Diluted sulphuric acid.	q. s.	15 cc.	15 cc.	15 cc.	15 cc.
	Water	120 cc.	300 cc.	150 cc.	150 cc.	150 cc.
2	Tannic acid	8 gm.	12 gm.	12 gm.	12 gm.	12 gm.
	Water	50 cc.	100 cc.	100 cc.	75 cc.	75 cc.
3	Tannic acid		6 gm.			
	Sodium bicarbonate....		2 gm.			
	Water		50 cc.			
4	Tannic acid	2 gm.				
	Ammonia water	2 cc.				
	Water	32 cc.				
5	Sodium bicarbonate....			3 gm.	4 gm.	3 gm.
	Water			40 cc.	50 cc.	50 cc.
6	Tannic acid			3 gm.	3 gm.	3 gm.
	Water			25 cc.	50 cc.	50 cc.

COMMERCIAL SPECIMENS.

Four specimens of quinine tannate bearing the labels of as many manufacturers were purchased and examined with particular reference to the alkaloidal content and to the loss on drying at 100° C. These specimens are designated as Nos. "11," "12," "13" and "14." Specimen "No. 11" contained 29.3 per cent. anhydrous quinine and the loss on drying the specimen amounted to 7.9 per cent. of the original weight. Specimen "No. 12" contained 29.5 per cent, of quinine and the loss on drying amounted to 6.5 per cent. Specimen "No. 13" contained about 33.4 per cent. of alkaloid and the loss on drying amounted to 8.0 per cent. Specimen "No. 14" contained about 34.0 per cent. total alkaloid and the loss on drying amounted to 9.0 per cent. This specimen contained a considerable quantity of uncombined alkaloid to which reference will again be made.

The amount soluble in anhydrous ether under specified conditions was determined, not only in the specimens purchased, but also in those prepared in the laboratory. Tests for chloride and sulphate were also carried out and an attempt was made to obtain some idea of the relative bitterness of the several specimens examined.

Ether-Soluble. Preliminary tests indicated that one of the specimens contained considerable amounts of uncombined alkaloid. Accordingly the amount soluble in dry ether was determined as follows:

Two gm. quinine tannate were placed in a beaker, 25 c.c. anhydrous ether poured upon it and the mixture stirred with a glass rod. After allowing the suspended salt to settle the supernatant liquid was poured through a dry filter into a tared flask. The insoluble residue was similarly treated twice more with 25 c.c. portions of dry ether and the filter finally washed with 10 c.c. of the solvent. The united filtrates were distilled, the residue dried at 100° C. and weighed. As quinine tannate is slightly soluble in anhydrous ether a weighable residue may always be expected.

When tested by the above described method, the several specimens, with a single exception, gave residues varying not far from 0.1 per cent. to 0.3 per cent. One specimen ("No. 19") contained about 9 per cent. ether-soluble matter, which latter appeared for the most part to consist of free-alkaloid.

Chloride and sulphate. One gm. of quinine tannate was thoroughly shaken with 100 c.c. of water and the mixture allowed to settle. The supernatant liquid was poured through a filter, the filtrate acidified with diluted nitric acid and the usual tests for chloride and sulphate applied. With one exception each specimen contained appreciable amounts of sulphate and traces of chloride. In this one exception sulphate was absent, but considerable amounts of chloride were present, thus indicating the probable source from which the salt had been prepared.

Bitterness. One gm. of the salt was shaken with 100 c.c. of water and filtered. The filtrates from several specimens were then compared by tasting. While none of the filtrates were free from bitterness in general, the relative bitterness was found to coincide with the relative turbidity found in the tests for chloride or sulphate. Specimen "No. 14," which contained a large amount of free alkaloid, was much more bitter than any of the others, although it is described upon the label as "Neutral-Tasteless."

The results found from the several specimens examined are tabulated below:

Number or brand	Anhydrous quinine	Water (Loss at 100°)	Ether-soluble	Sulphate
1	25.75	7.64	0.17	Very marked turbidity
2	31.33	9.01	0.08	Very marked turbidity
3	25.02	9.96	0.10	Faint turbidity
4	28.70	9.96	0.05	Marked turbidity
5	33.31	7.20	0.11	Faint turbidity
6	25.85	9.78	0.08	Faint turbidity
6-a	27.82		0.09	Faint turbidity
7	29.33	7.94	0.09	Faint turbidity
8	29.12	7.35	0.12	Faint turbidity
9	34.25	8.12	0.09	Faint turbidity
10	33.72	7.74	0.08	Faint turbidity
11	29.30	7.88	0.10	Distinct turbidity
12	29.51	6.50	0.19	Absent
13	33.36	8.05	0.36	Distinct turbidity
14	33.97	9.06	9.02	Very faint opalescence

Number or brand	Chloride	Taste of filtrate	Yield (in gm.) calculated from 10 gm. quinine sulphate	Remarks
1	Noticeable opalescence	Noticeably bitter		
2	Very faint opalescence	Noticeably bitter		
3	Very faint opalescence	Slightly bitter	31	
4	Very faint opalescence	Slightly bitter		
5	Very faint opalescence	Slightly bitter		
6	Very faint opalescence	Slightly bitter	28.8	
6-a	Very faint opalescence	Slightly bitter	26.0	Adheres to glass and paper
7	Very faint opalescence	Slightly bitter		
8	Very faint opalescence	Slightly bitter	23.2	Dark color
9	Very faint opalescence	Slightly bitter	20.0	
10	Very faint opalescence	Slightly bitter	20.6	
11	Noticeable opalescence	Noticeably bitter		
12	Very marked opalescence	Noticeably bitter		Evidently prepared from quinine hydrochloride
13	Noticeable opalescence	Noticeably bitter		
14	Very faint opalescence	Very bitter		

From the results of the examination it is seen that commercial quinine tannate varies somewhat in composition. Doubtless this is due to slight differences in the manufacturing methods of the various makers. However, with the exception of specimen "No. 14," which bears evidence of careless manufacture, the several makes of quinine tannate on the American market may, on the whole, be regarded as of sufficiently uniform composition for practical purposes.

Based upon the provisional academic standards as first prepared but modified as found necessary by the results of the experimental work, and by the suggestions offered by those to whom the provisional description was submitted for criticism, tentative standards for quinine tannate have been prepared. Our thanks are due to those manufacturers who have made suggestions and criticisms in the preparation of these provisional standards for quinine tannate. The description and standards suggested are as follows:

QUININE TANNATE.—Quininæ Tannas. Quinine tannate is the tannate of the alkaloid, quinine, containing from 30 to 35 per cent. of quinine.

Quinine tannate may be prepared as follows:

Ten gm. of quinine sulphate are dissolved in a mixture of 15 c.c. of diluted sulphuric acid and 150 c.c. of water. Twelve gm. tannic acid are dissolved in 75 c.c. water and the filtered solution poured slowly and with constant stirring into the solution of quinine sulphate. Three

gm. tannic acid are then dissolved in 50 c.c. water and 3 gm. sodium bicarbonate dissolved in 50 c.c. water. These solutions are filtered, the filtrates mixed, and the mixture poured slowly and with constant stirring into the quinine-tannin mixture prepared as above described. The precipitated quinine tannate is allowed to stand for 24 hours. It is then poured onto a muslin filter, washed with 100 c.c. water and expressed with moderate pressure. The expressed mass is then transferred to a porcelain dish, 50 c.c. water added and the mixture heated on the water bath until the quinine tannate melts to a resin-like mass. The supernatant liquid is poured off, the mass cooled, dried in the air and pulverized.

Quinine tannate is an amorphous, pale lemon-yellow to yellowish-white, odorless powder without taste, or at most slightly bitter, and with scarcely any astringency. It is slightly soluble in water, ether and chloroform, but somewhat more soluble in alcohol. The aqueous and alcoholic solutions are colored bluish-black by ferric chloride test solution. Quinine tannate melts on heating in a glass tube to a purplish, tar-like material.

If 1.0 gm. of quinine tannate be shaken with a mixture of 50 c.c. of water and 1 c.c. nitric acid and the mixture filtered, a portion of the filtrate should not become more than slightly opalescent after the addition of 1 c.c. of silver nitrate test solution; nor should there by any darkening after the addition of 1 c.c. of hydrogen sulphide test solution; nor should a portion be rendered turbid immediately by barium chloride test solution.

If from 0.5 gm. to 1.0 gm. of quinine tannate be mixed with 25 c.c. water and an excess of ammonia water, the mixture extracted with three successive portions of 20 c.c. each of chloroform, the total solvent washed with water and evaporated, the weight of residue obtained after drying at 100° C. should correspond to from 30 to 35 per cent. of anhydrous quinine. If this residue be dissolved in 30 c.c. of water by the aid of a few drops of diluted hydrochloric acid and 1 c.c. of the solution be mixed with 20 c.c. of water and two or three drops of bromine test solution, the mixture should assume a green coloration on the addition of ammonia water.

If 0.2 gm. quinine tannate be ignited no weighable residue should be obtained.

If from 0.5 gm. to 1.0 gm. quinine tannate be dried at 100° C. to constant weight the loss should not correspond to more than 10 per cent. of the weight of substance taken.

If 2.0 gm. of quinine tannate be shaken with three successive portions of 25 c.c. each of anhydrous ether, the solvent poured through a filter, the filter washed with 10 c.c. of the solvent, the several filtrates united, evaporated and the residue dried to constant weight at 100° C., the weight of the residue should not exceed 0.005 gm. (limit of *uncombined alkaloid*).

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Pharm. Zentralhalle, 13, 247; from Neu. Jahrber. Pharm. (1872).
Proc. Am. Pharm. Assn., 21, 379 (1873).
Recommends the therapeutic use of the tannate of quinine instead of the sulphate. Notes that the dose of the tannate must be larger than that of the sulphate.

1872 Hager.
Pharm. Zentralhalle, 13, 247.
Proc. Am. Pharm. Assn., 21, 379 (1873).
Concludes that quinine tannate has only 1-10 of the therapeutic value of the sulphate. Reports finding about 9-10 of the alkaloid in the urine and feces.

1872 Klever.
Chem. Zentr., 43, 434; from Pharm. Ztschr. Russ. (1872).
States that 100 gm. glycerol dissolve 0.25 gm. quinine tannate.

1874 Regnault.
Pharm. Zentralhalle, 16, 41; from Repert. Pharm. (1874).
Proc. Am. Pharm. Assn., 23, 214 (1875).
A method of manufacture is described in which quinine acetate is used as the starting point.

1875 Rozsnay.
Pharm. Zentralhalle, 16, 106.
Proc. Am. Pharm. Assn., 23, 414 (1875).
Quinine sulphate is dissolved in boiling water and precipitation brought about by the addition of tannate of ammonia.

1877 Haaxman.
Jour. pharm. chim., [4], 25, 420.
Describes a process for the manufacture of quinine tannate.

1877 Pharmaceutical Society of Paris.
Pharm. Jour. Tr., [3], 8, 86.
Proc. Am. Pharm. Assn., 26, 577 (1878).
Method for preparing tasteless quinine tannate.

1877 Stocker.
Jour. pharm. chim., [4], 26, 418.
Describes a method of preparation. Product contains about 22 per cent. alkaloid.

1878 Jobst.
Arch. Pharm., 212, 331.
Proc. Am. Pharm. Assn., 26, 578 (1878).
Report of an examination of several specimens of commercial quinine tannate.

1878 Dwars.
Jahresber. Forschr. Pharm., etc., 38, 472; from Ned. Tijdschr (1878).

1878 Berwick.
Am. Jour. Pharm., 50, 259; from Pharm. Ztg. (1878).
Proc. Am. Pharm. Assn., 26, 578 (1878).
Process for manufacturing quinine tannate.

1882 Dukla.
Pharm. Jour. Tr., [3], 13, 444; from Pharm. Ztg. (1882).
Process for manufacture of the salt by the alcohol solvent method.

1882 Anonymous.
New Remedies, 11, 173.
Proc. Am. Pharm. Assn., 30, 414 (1882).
Review of a process of manufacture which employs acetate of ammonia. Product contains 19 to 21 per cent. of quinine.

1882 Fiebert
Pharm. Zentralhalle, 23, 550; from Zeit. cest. Ap. Ver. (1882).
Proc. Am. Pharm. Assn., 31, 273 (1883).
Process of manufacture by the alcohol solvent method.

1883 Rosznay.
Proc. Am. Pharm. Assn., 32, 308; from Gy. Rund. (1883).
New Rem., 12, 274 (1883).
A method of assay. Substance is mixed with calcium and sodium hydroxides, dried, and the mass extracted with chloroform.

1883 Rother.
Am. Jour. Pharm., 55, 172.
Maintains that the compounds of quinine and tannic acid are not true salts but are analogous to the alcoholates. Suggests that they be called "tannolates." Theoretical composition discussed.

1883 Weiss.
Proc. Am. Pharm. Assn., 32, 84 (1884); from Pharm. Ztg. (1883).
Describes a method for preparing a finely divided quinine tannate in a syrup.

1883 Field.
Phys. Surg, 5, 353.
Pharm. Rec., 4, 5 (1884).
Proc. Am. Pharm. Assn., 32, 308 (1884).
Experiments with the solubility of quinine tannate in gastric juice.

1885 Schwarz.
Pharm. Zentralhalle, 26, 471; from Pharm. Ztg. (1885).
Proc. Am. Pharm. Assn., 34, 605 (1886).
Apparently the first to employ sodium bicarbonate as a precipitant in the manufacture of quinine tannate. Produced a specimen containing 33.3 per cent. of quinine.

1885 Peltz.
Pharm. Ztschr. Russ., 24, 80.
Proc. Am. Pharm. Assn., 33, 303 (1885).
Recommends the use of quinine hydrochloride in place of the sulphate in the manufacture of quinine tannate.

1889 Neumann.
Zeit. anal. Chemie, 28, 663.
Proc. Am. Pharm. Assn., 38, 673 (1890).
Describes a process for the alkaloidal assay of quinine tannate. Controls indicate that the method gives values about 3 per cent. too high. Examined several commercial specimens, the alkaloidal content of which (as found) ranged from 13.9 per cent. to 28.8 per cent.

1891 De Vrij.
Ned. Tijdschr., 3, 113.
Proc. Am. Pharm. Assn., 40, 744 (1892).
A method of preparation is described.

1892. Zeig.
West. Druggist, 15, 361 (1893); from Proc. Cal. Pharm. Assn. (1892).
Proc. Am. Pharm. Assn., 42, 651 (1894).
States that commercial quinine tannate contains from 10 per cent. to 25 per cent. alkaloid. Believes that the salt is sufficiently soluble in gastric juice to be therapeutically active.

1893 Drake.
Proc. Am. Pharm. Assn., 42, 675 (1894); from Proc. Mass. Pharm. Assn. (1893).
Describes a process of manufacture in which no alkali is employed.

1894 De Vrij.
Pharm. Zentralhalle, 35, 155.
Proc. Am. Pharm. Assn., 42, 1108 (1894).
Describes a process for preparing the salt.

1898 Rosenheim and Schidrowitz.
Jour. Chem. Soc., 73, 884.
Find that the specific rotatory power of quinine tannate in methyl alcohol solution at 15° is 40.1°.

1898 Schidrowitz.
See Rosenheim.

1900 Zeelt.
Pharm. Ztg., 45, 96; from Pharm. Wkblad. (1900).
Proc. Am. Pharm. Assn., 48, 813 (1900).
Describes a process for manufacturing quinine tannate.

1903 Christian.
Deutsch. Med. Woch., 29, 216.
Administered known quantities of quinine tannate to human beings and recovered the alkaloid excreted in the urine. In each of two experiments he recovered less than 25 per cent. of the total alkaloid given.

1906 Fränkel.
Die Arzneimittel-Synthese ed. 2, 140 (1906).
Calls attention to the possible undesirability of the large proportion of tannin in quinine tannate.

1906 Nierenstein.
Chem. Zentralhalle, 77, 11, 1417 (1906); from Collegium (1906).
Amorphous quinine tannate melts at 62-64° C.; it may be crystallized from ether by the addition of acetic anhydride; crystallized substance melts at 79-81°.

1909 Calliess.
Ap. Ztg., 24, 159.
Pharm. Zentralhalle, 50, 263, 807 (1909).
Describes a method of assay.

1910 Cohn.
Pharm. Zentralhalle, 51, 265.
Year Book Pharm., 12 (1910).
Method for manufacture.

1911 May.
Chem. Syn. Drugs, 84 (1911).
Mentions that quinine tannate is but slowly split up in the intestine and for this reason it is lacking in therapeutic promptitude and certainty.

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PROPOSED STANDARDS FOR CAMPHOR AND SPIRIT OF CAMPHOR.

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Spirit of Camphor and Camphor were made official in 1820. The Spirit has for many years been a very popular household remedy and in view of the fact that it has been reported as extremely variable in strength and quality by analysts in various parts of the country, it would seem desirable to introduce into the forthcoming Pharmacopoeia some special tests for determining its strength and purity. In the years that this preparation has been official, it, like many other official preparations, has been subjected several times to fancied improvements.

In general, changes of formula lead to confusion, and as these changes have many times been shown to have been ill advised, criticism has thus arisen to the effect that the committees of revision often do not give sufficient attention to them. The decennial revisions have sometimes seemed to be somewhat lacking in that definiteness of purpose which is conducive to confidence and healthy growth.

In tracing the evolution of Spirit of Camphor, several interesting changes are noted. It was official in 1820 as Tincture of Camphor, the title by which it is still known in the French Pharmacopœia. It was made by dissolving one Troy ounce of Camphor in one pint of Alcohol. This is the equivalent of about 6.14 gm. of Camphor dissolved in enough Alcohol (89.7%) to make 100 cc. There were two Pharmacopœias in 1830. That which resulted from the New York convention changed the title to Spirit of Camphor, the title by which it is known in the latest editions of the German, Swiss, British and Japanese Pharmacopœias. The Pharmacopœia which resulted from the Washington convention retained the title of Tincture. In both pharmacopœias the formula was changed to a strength of four Troy ounces of Camphor dissolved in two pints of Alcohol. This is the equivalent of about 11.54 gm. of Camphor dissolved in sufficient Alcohol (89.7%) to make 100 cc. In 1840 the Washington convention disregarded the timely change in the New York convention ten years before and continued the preparation without change until 1860. Then the title was changed to Spirit. No additional change was made in 1870 but in 1880 the formula was materially altered and the Spirit as then prepared consisted of Camphor, 10 parts, Alcohol (94%) 70 parts, and water 20 parts. This is the equivalent of about 8.72 gm. of camphor dissolved in sufficient Alcohol (80.56%) to make 100 cc.