(4) H. Thoms, Detection of Diethylphthalate in Ethereal Oils, *Apoth. Ztg.*, 40, 196 (1925); *Druggists Circ.*, 70, 145.

(5) E. E. Reid, Butyl Esters of Phthalic Acid, U. S. Patent 1,554,032 (Sept. 15, 1925); *C. A.*, 19, 3491.

THE ASSAY OF SALICYLATES AND BENZOATES, SECOND PAPER.

BY A. H. CLARK.

The United States Pharmacopœia (referred to hereafter as U. S. P. VIII, IX, or X as the case may be) has described a number of benzoates and salicylates. The U. S. P. X describes the benzoates of ammonium and sodium and the salicylates of ammonium, bismuth (basic), mercury (basic), sodium, strontium and physostigmine. Phenyl and methyl salicylates also are described. The U. S. P. IX described quinine salicylate and the U. S. P. VIII lithium benzoate and salicylate. This list is practically complete in so far as medicinally useful benzoates and salicylates are concerned.

The writer pointed out some time ago[1] that it is desirable to have a uniform or general method for the assay of these medicaments and suggested a method for the assay of sodium salicylate and sodium and ammonium benzoates[1] which he showed to be entirely satisfactory and very simple and time-saving. This method in principle consists in acidulating a solution of the salt in question and extracting the benzoic or salicylic acid with chloroform, evaporating the chloroform under stated conditions and weighing the acid obtained.

The present paper deals with the application of the above-mentioned method to the assay of the substances listed in the opening paragraph. In the previous paper the testing of the accuracy of the method on samples of undoubted purity was the prime object. In the present work this is considered proven and when the method gave concordant results on the commercial samples used the result was taken as final. A few observations which do not have a direct bearing on the question of assay but concern interesting points observed are appended in certain cases.

In any method of assay for a medicinal substance one always thinks of the therapeutically active radical or group as being the one that should be assayed. This may be a good principle to follow providing first of all that one knows which is the active part of a given substance. Obviously, convenience and accuracy should play a very important part in deciding on a method of analysis. If it is desirable to have a general method for a number of medicaments such a method should be sought regardless of any questions of therapeutic activity of the portion assayed. If it is more convenient, for example, to assay mercuric salicylate on the basis of its content of salicylic acid this should be done. Tests can be devised for the elimination of undue amounts of foreign metals and perhaps more readily than for undue amounts of foreign organic acids. If we carry the argument of relative therapeutic value very far we come to the point where we may consider all salicylates alike, or all sodium salts alike, or all mercury salts alike, and therefore why have official more than one salicylate, sodium compound, mercury compound, etc.? The absurdity of this argument should be apparent to any one, therefore why allow the question of therapeutics to enter into the matter?

[1] JOUR. A. PH. A., January 1926, p. 6.

AMMONIUM SALICYLATE.

Two samples were assayed. They were of different manufacture. Both samples were decidedly acid to litmus and when washed with anhydrous ether were found to yield considerable quantities of salicylic acid. The samples were not uniform in composition as shown by the assay. These features are being studied further.

Unmixed sample A gave the following percentages: 99.5; 97.9; 98.6. A well-mixed portion gave 98.12; 98.00, average 98.06 per cent pure.

Unmixed sample B gave the following: 99.33; 96.25; 95.00. A well-mixed portion gave 97.23 and 97.51, average 97.37 per cent pure.

The method is satisfactory but something was wrong with the samples. Is the U. S. P. X standard too high? Should there not be a test for free acid?

BISMUTH SALICYLATE, BASIC.

A weighed quantity of the salt, representing about 0.500 Gm. of salicylic acid, was transferred to a separator, about 50 cc. water added, followed by an excess of hydrochloric acid. The mixture was well shaken and the liberated salicylic acid extracted.

Sample A,1, contained 35.71 and 35.85, average 35.76 per cent of salicylic acid.

Sample A,2, a very old sample, contained 34.34 and 34.51, average 34.41 per cent salicylic acid.

Sample B,1, contained 33.95 and 34.28, average 34.12 per cent salicylic acid.

The U. S. P. X standard for this substance is 62 to 66 per cent bismuth oxide. The U. S. P. method of assay, particularly the evaporation of 5 cc. concentrated nitric acid, is objectionable, so why not fix a standard on the basis of the salicylic acid the determination of which is so readily and accurately accomplished? The acid is surely as important as the bismuth or why use the salt? On the basis of the above results a standard of 33 to 36 per cent salicylic acid would seem reasonable. Foreign or harmful metals could be excluded by proper tests and the purity of the salicylic acid fixed, if desirable, by a melting point determination.

MERCURY SALICYLATE, BASIC.

The method employed for this salt is as follows.—About 1.500 Gm., not more than this, is transferred to a 150-cc. Erlenmeyer flask. The flask is fitted with a good cork carrying a glass tube about one-half inch in diameter and about eighteen inches long. To the salt in the flask is added about 20 cc. of water and the flask rotated carefully until the salt is uniformly wetted. If this is not done troublesome clumping of the salt may occur. About 20 cc. of concentrated hydrochloric acid is added, the cork with its tube inserted, and heat applied with a Bunsen burner. The tube is held with the hand about ten inches above the flask and in this way overheating may be avoided. The heat is applied until the tube becomes warm to the hand, carefully rotating the flask and using the tube to support it. The heating is continued until the salt is in complete solution, which in but one case required more than about five minutes. The flask is then cooled and as much of its contents as possible transferred to a separator. The flask is then rinsed with several small quantities of chloroform, 25 to 30 cc. in all, each portion being trans-

ferred to the separator. The separator is well shaken, the chloroform drawn off and the complete extraction and collection of the acid accomplished as originally described.[1]

This may seem a rather tedious or complicated procedure, but the entire operation can be accomplished in a half hour or less.

The results obtained are as follows:

Sample A-1, gave 40.79 and 40.76, average 40.78 per cent salicylic acid.
Sample A-2, gave 42.88 and 42.40, average 42.64 per cent salicylic acid.
Sample B-1, gave 39.10 and 39.20, average 39.15 per cent salicylic acid.
Sample C-1, gave 40.70 and 41.00, average 40.85 per cent salicylic acid.

As a matter of interest and also to satisfy myself that the estimation of mercury could easily be accomplished by the standard sulphide method each of these samples was assayed for mercury. This is accomplished with surprising ease by dissolving 1.500 Gm. or less of the sample in a mixture of 20 cc. water and 20 cc. concentrated hydrochloric acid. Place the salt in an Erlenmeyer flask, add the acid and boil briskly for about five minutes, or until solution is complete; dilute to about 250 cc. with water, pass in hydrogen sulphide until saturated and proceed by the Gooch method. See U. S. P. X under the assay of mercuric chloride.

Sample A-1, gave 58.20 and 58.17, average 58.19 per cent mercury.
Sample A-2, gave 56.95 and 56.96, average 56.96 per cent mercury.
Sample B-1, gave 58.67 and 58.70, average 58.69 per cent mercury.
Sample C-1, gave 57.17 and 57.28, average 57.23 per cent mercury.

Since rather a wide variation must be allowed for in this salt no matter how it is assayed the writer can see no objection to fixing a standard on the basis of salicylic acid content. The results obtained on the four samples would indicate that from 40 to 43 per cent would be a fair standard. If the mercury must be assayed the sulphide method outlined above seems to the writer to be much less troublesome and far more time-saving than the U. S. P. X method, and it is certainly highly accurate.

STRONTIUM SALICYLATE.

One sample was assayed. It showed 97.00, 96.70, 96.77 and 97.03, average 96.88 per cent pure.

The assay is as readily carried out as that of sodium salicylate.

LITHIUM SALICYLATE.

Two very old samples were available and since the salt is no longer official it was not considered of sufficient interest to warrant the purchase of special samples. The assay is accurately and readily accomplished. Dissolve the weighed amount, about 0.600 Gm. in this case, in water, transfer to a separator, add excess of hydrochloric acid and proceed as usual. It is obvious that the U. S. P. X general method (ignition and titration of ash) is very unsatisfactory since the per cent of lithium is less than five and a correspondingly very large amount of salt would be required. Both samples were about 94 per cent pure in the condition in which they were found.

[1] JOUR. A. PH. A., January 1926, p. 6.

METHYL SALICYLATE.

Accurately weigh about 0.500 Gm., transfer it to a 500-cc. Erlenmeyer flask and add 25 cc. of alcohol and 25 cc. of about 10 per cent sodium hydroxide solution. Boil until the alcohol is expelled, cool and transfer to a separator and proceed as with sodium salicylate.

One commercial sample of methyl salicylate gave 98.99, 98.88, 98.91 and 98.69, average 98.87 per cent methyl salicylate.

PHENYL SALICYLATE.

An assay of this substance based upon its saponification with alcoholic potash is complicated by the fact that the phenol formed in the saponification is more difficult to remove than the methyl alcohol formed in the saponification of methyl salicylate. By applying the principle used by Puckner and Clark[1] in the estimation of phenol in pharmaceutical mixtures it seemed quite possible to accomplish this. After saponification of the salol, carbon dioxide is passed through the alkaline mixture until it no longer reddens phenolphthalein. This mixture is then extracted with chloroform to remove phenol, then made acid with hydrochloric acid and the liberated salicylic acid extracted with chloroform. Several trials gave results varying from 99 to 100.7 per cent on a commercial sample of salol. Because of a lack of time the technic of the method could not be developed to a point giving better results. Further work will be done on it.

Since the melting point is a good indication of the purity of salol a method of assay may not be required in the U. S. P. but any method is valuable which might be of service in estimating salol in pharmaceutical products such as tablets, pills, etc., and this method is being studied with a view to its possible use in this connection.

Acknowledgment is made to Prof. C. C. Glover for advice and encouragement during the progress of the work.

UNIVERSITY OF MICHIGAN,
COLLEGE OF PHARMACY,
ANN ARBOR, MICH.

THE STABILITY OF ATROPINE AND HYOSCYAMINE DURING PROCESS OF ANALYSIS.*

BY S. PALKIN AND H. R. WATKINS.

The problem of accurate quantitative determination of hyoscyamine and atropine has in spite of apparent simplicity remained a perplexing matter. No small part of the voluminous literature (1) on the solanaceous alkaloids is devoted to their extraction and determination, as well as to the study of the stability of the various members. Nevertheless, the reader is left with a vague impression as to the degree of their stability or instability. The exact conditions, for purposes of analysis, under which these alkaloids can be depended upon to remain stable throughout the process of evaluation are yet to be established.

* Contribution from Drug Control Laboratory, Bureau of Chemistry, U. S. Department of Agriculture.

[1] PROCEEDINGS OF THE A. PH. A., Vol. 56, p. 824 (1908).