In order to determine the absolute accuracy of the two methods a sample of powdered electrolytic iron was obtained through the courtesy of Dr. George D. Beal. This iron assayed between 99 and 100 per cent by direct titration with potassium permanganate after acid solution.

With the sample of pure iron both the U. S. P. and the modified British methods gave results between 99 and 100 per cent.

A sample of iron was prepared by thoroughly mixing 95 parts of powdered electrolytic iron with 4 parts of ferric oxide, 0.5 part of ferrous sulphide and 0.5 part of ferrous phosphide. This mixture containing 95 per cent of metallic iron was submitted to analysis by both methods.

The results obtained on this adulterated sample are set forth in Table II.

TABLE II.

No.	Modified B. P. Method.	U. S. P. XI Method.
1	98.11	95.10
2	97.57	94.71
3	96.85	96.56
4	98.09	95.17
5	97.28	94.60
6	94.75	94.20
7	97.95	...
8	94.18	...
9	98.00	...
10	98.40	...
11	98.20	...
12	98.20	...
13	98.72	...
14	98.42	...
Mean	97.48	95.06

It is obvious that in the presence of these impurities the modified method of the British Pharmacopœia fails to give results which correspond closely to the absolute content of elementary iron.

CONCLUSION.

1. The presence of ferric oxide, ferrous sulphide and ferrous phosphide in a sample of reduced iron vitiates the results obtained by the copper sulphate method. The mercuric chloride method gives absolute values in the presence of these impurities.

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(2) Frerichs, G., *Merck's Report*, July (1909), 165.

ASSAY METHODS FOR SALTS OF ORGANIC ACIDS.*

BY RICHARD M. HITCHENS.

The assay methods for alkali salts of organic acids have been for many years the subject of much discussion. A survey of the problems involved is given by Clark.[1]

* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] Clark, JOUR. A. PH. A., 15 (1926), 6.

The customary method of assay has been to ignite the salt to sodium carbonate which is determined by titration with standard acid. This method is subject to many sources of error; it is tedious and time-consuming. Ignition to sodium sulphate or to sodium chloride, which are determined gravimetrically, has been used by some investigators. Still others have isolated the acid by extraction and determined the acid gravimetrically or volumetrically. All of these methods require considerable time and are subject to many sources of error.

In 1927, Henville[1] described a new method of determining the cation in sodium salicylate and sodium benzoate. His method consists of direct titration of the aqueous solution of the salt with standard acid to a methyl orange end-point in the presence of diethyl ether to extract the organic acid as it is liberated. At a methyl orange end-point the solution is extracted with a fresh portion of ether and the titration continued to a second methyl orange end-point which is not affected by further extraction with ether.

Such a method is simple, direct, rapid and accurate. It furnishes the same information as does the conversion to sodium carbonate, sulphate or chloride but with a higher degree of accuracy and in a much shorter time.

The method was adopted by the 1932 British Pharmacopœia as an assay method for sodium benzoate and sodium salicylate except that bromphenol blue indicator was substituted for methyl orange.

In an attempt to simplify the method still further, Krantz and Schmidt,[2] working on the official monograph for United States Pharmacopœia XI, decreased the volume of the aqueous layer, increased the volume of diethyl ether and discarded the second extraction. As stated by Henville,[1] this procedure is valid for sodium benzoate, the end-point after the first extraction agreeing closely with that after the second. With sodium salicylate, however, the first end-point is somewhat indistinct and gives low results. Different analysts in this laboratory disagree as much as 0.5% on the first end-point, their results ranging from 99.0–99.5% on pure sodium salicylate. After the second ether extract the analysts agree well, obtaining values of from 99.8–100.0%.

By the proposed U. S. P. XI method, even pure sodium salicylate would assay only 99.5% as a maximum. It would seem advisable for the method of the U. S. Pharmacopœia to be revised, whereby two extractions are made, thus giving quantitative results. This should present no difficulties since the extra step is simple and rapid and requires no special equipment. The whole analysis may be completed in ten minutes.

The simplicity and accuracy attained by the Henville method for the assay of sodium benzoate and sodium salicylate suggests its adoption for other salts.

Although the method has been suggested only for these two salts it is in reality a general method of assay. Consider a salt MA. The reaction

$$MA + HCl \longrightarrow MCl + HA$$

can be carried to completion provided the following conditions are fulfilled:

(1) HA is sparingly soluble in water and readily soluble in some solvent immiscible with water.

[1] Henville, *Analyst*, 52 (1927), 149.

[2] Krantz and Schmidt, JOUR. A. PH. A., 52 (1933), 953.

(2) HA is not too strong an acid, Ka less than about 2.5×10^{-3}. If much stronger than this, complete liberation of the acid at a p_H value of 4, the methly orange end-point, can scarcely be effected without an excessive number of extractions.

(3) MOH is a base, the dissociation constant of which is greater that 10^{-6}. If lower, the end-point, where MCl alone is present in the aqueous layer, will occur in too acid a solution for accurate determination of the end-point.

(4) The salts MCl and MA are water-soluble and insoluble in the immiscible solvent.

Any such salt MA, therefore, can be assayed by this method if a suitable solvent can be found for the acid HA, if HA is fairly water-insoluble and not too strong, and if the base MOH is not too weak. The choice of solvent, the indicator and the number of extractions necessary will depend upon the salt in question.

Sodium benzoate conforms well with these specifications. With $Ka = 7 \times 10^{-5}$, at a p_H value of 4, about 30% of the benzoate remaining in the aqueous layer will be present as sodium benzoate, the rest as benzoic acid. Benzoic acid is readily ether-soluble and only slightly water-soluble. From solubility data one would expect about 500 parts of benzoic acid in the 75 cc. ether layer present in the U. S. P. XI analysis to one part in the 20-cc. aqueous layer, or that the first end-point would be about 0.2% low. Thus one ether extraction should be sufficient. This is verified by experiment.

Sodium salicylate is slightly different. The dissociation constant of salicylic acid is about 1×10^{-3}. Thus at a p_H value of 4, only 20% of the salicylate in the aqueous layer is present as salicylic acid; the remainder is sodium salicylate. From solubility data there should be about 600 parts of salicylic acid in the ether layer per one part in the aqueous layer. But there are four parts of sodium salicylate per one of salicylic acid so that the combined salicylates in the aqueous layer may amount to 0.8% of the original sample. The first end-point will be low by this amount. A second extraction is necessary to remove the last traces of salicylates. This is borne out by experiment.

Ammonium benzoate and salicylate may be assayed by this method; the same arguments hold as for the sodium salts. The correct indicator would be methyl red. Unfortunately this dissolves in the ether layer. Methyl orange, however, gives results only 0.05% high, well within the limits of accuracy of the method.

The method is applicable to other salicylates such as magnesium, zinc, strontium.

It is applicable also to sodium barbital. Barbital has an acid dissociation constant of about 10^{-7}. Thus at a p_H value of 4, practically complete liberation of barbital has occurred, only 0.1% of the barbital remaining in the aqueous layer being present as sodium barbital. Even though fairly water-soluble and only moderately ether-soluble, one ether extract should be ample to give quantitative results.

It is applicable also to sodium phenobarbital. Phenobarbital has an acid dissociation constant of about 4×10^{-7}. Thus at a p_H value of 4, 0.4% of the phenobarbital in the aqueous layer is present as the sodium salt. Since phenobarbital is only slightly water-soluble and readily ether-soluble, one extraction should give quantitative results.

The method was tested experimentally on the above salts.

Materials.—Sodium benzoate and salicylate, U. S. P. products dried to constant weight at 100° C. Ammonium benzoate and salicylate U. S. P. dried to constant weight over solid sodium hydroxide. Strontium salicylate U. S. P., magnesium salicylate, zinc salicylate, all hydrates and not dried before use. Sodium barbital U. S. P. dried to constant weight at 100° C. Sodium phenobarbital N. N. R. dried to constant weight at 140° C., according to the instructions of N. N. R.[1] and A. D. M. A.[2]

Reagents.—Diethyl ether U. S. P. was found to be sufficiently neutral without further treatment. *N*/2 hydrochloric acid was standardized gravimetrically by precipitation as silver chloride.

The procedure was essentially that of Krantz and Schmidt[3] except that after the first end-point had been reached the aqueous layer was drawn off through a separator into a second flask, 20 cc. of ether added and the titration continued until a second methyl orange end-point was reached.

The results are tabulated below. The first column states the salt titrated, the second the assay after one extraction, the third the assay after two extractions. Each analysis refers to a different sample of the salt.

Salt.	Assay after One Extraction.	Assay after Two Extractions.
Sodium benzoate	99.5%	99.7%
	99.6	99.8
	99.7	99.8
Sodium salicylate	99.5	100.0
	99.2	99.8
	99.2	99.9
Ammonium benzoate	99.0	99.2
	99.2	99.4
(by ammonia evolution)		99.1
		99.3
Ammonium salicylate	98.6	99.4
(by ammonia evolution)		99.4
Strontium salicylate,	98.9	99.5
dihydrate	99.3	99.9
Magnesium salicylate,	99.1	99.8
tetrahydrate	99.0	99.6
Zinc salicylate, trihydrate	101.0	102.2
Sodium barbital	99.9	99.9
	99.8	99.8
Sodium phenobarbital	98.5	98.5
	98.5	98.5

It is evident that sodium and ammonium benzoate give almost quantitative results with one extraction.

All of the salicylates show the same type of results, the first end-point being at least 0.5% low, the second quantitative.

The magnesium, strontium and zinc salicylates are all hydrates. No attempt was made to dry them to the proper water content since the object in view was to determine the difference between the end-point after one and after two ether extractions. The magnesium and strontium salts apparently contain the correct amount of water of hydration. The zinc salt is slightly over-dried.

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[1] "New & Nonofficial Remedies," American Medical Association.

[2] American Drug Manufacturers' Association, "Proceedings," 1933.

[3] Refers to footnote 2, page 12.

Sodium barbital gives quantitative results even with only one extraction. This would be expected on account of the weakly acidic nature of barbital.

The sodium phenobarbital gives low results even when dried at 140° C. This is in accord with the results of the A. D. M. A.[2] who found the salt to form a stable hydrate from which it was impossible to remove all the water even at 140° C. That this method does titrate quantitatively the cation in this salt is demonstrated in the following series of experiments.

As a further check on the method the following experiment was carried out on pure salicylic acid, benzoic acid, phenobarbital and barbital. A suitable weight was titrated directly with standard alkali to a phenolphthalein end-point. The water was removed by evaporating under reduced pressure. The resulting salt was titrated as above and the titration compared directly to that obtained by neutralizing exactly the same volume of sodium hydroxide with standard acid to a methyl orange end-point in the presence of ether. In this manner the effect of possible impurities in the commercial salts was eliminated, the problem being the quantitative recovery of the standard alkali added. Entirely analogous results to those in the above table were obtained. With phenobarbital and barbital quantitative recovery was obtained with one ether extraction; with benzoic acid within 0.2% on the first extraction and quantitative recovery on the second; with salicylic acid at least 0.5% low on the first extraction but quantitative recovery on the second. These experiments act as an independent check on the accuracy of the method.

CONCLUSION.

Henville's method for assay of sodium benzoate and sodium salicylate whereby the salt is titrated directly with standard acid in the presence of diethyl ether to a methyl orange end-point is a general method. It is applicable to water-soluble salts of the type MA where HA is an acid fairly insoluble in water and appreciably soluble in some solvent immiscible with water; where HA is not too strong an acid, apparent dissociation constant less than 2.5×10^{-3}; where MOH is not too weak, apparent dissociation constant greater than 10^{-6}.

The simplified assay method for sodium salicylate suggested by U. S. P. XI in which the end-point is taken after only one ether extraction, gives at least 0.5% low results, two extractions being necessary to give the correct assay.

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DIGITALIS ASSAY ON NORMAL AND EXSANGUINATED CATS.*

BY DAVID I. MACHT.

(WITH THE TECHNICAL ASSISTANCE OF M. B. MACHT.)

Pharmacologists in general recognize the cat method as the most useful means of assaying digitalis preparations. Variations crop up, however, even when this method is employed. To insure the most accurate and reliable data concerning

* From the Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc., Baltimore, Md.