

60 cc. solution No. 1
60 " " No. 2.
100 " 10 per cent. NaOH solution.
362 " aqua ammonia sp. gr. 0.90.
Dilute to 1 liter.

CHEMICAL LABORATORY,
MORRIS & COMPANY, CHICAGO.

METHYLSALICYLATE. THE ANALYTICAL SEPARATION AND DETERMINATION OF SALICYLIC ACID AND METHYLSALICYLATE, AND THE HYDROLYSIS OF THE ESTER.

By H. D. GIBBS.

Received July 3, 1908.

Since salicylic acid and salicylates have been prohibited in foods,¹ it becomes necessary in many cases to separate salicylic acid and its metal salts from its esters.

The methyl ester, either the synthetic preparation, or oil of gaultheria, or oil of betula, is often found to be a constituent of many non-alcoholic beverages, such as the so-called root beers and sarsaparillas, and soda water flavors. The United States Pharmacopœia and the National Formulary² authorize its use as a flavoring agent, and it is therefore often found in emulsions, the most common of which is cod-liver oil, and other pharmacopœial preparations.

Salicylic acid or its salts and its methyl ester may be, and often are, found together in the above preparations: *first*, through the incorporation of both in the original mixture; *second*, when methylsalicylate, either natural or synthetic, alone is used, the ester may contain varying amounts of free salicylic acid as an impurity; *third*, when a comparatively pure ester is employed, free salicylic acid may subsequently become a constituent of the compound through the hydrolysis of the ester.

An examination of all of the different samples of methylsalicylate available in this laboratory and in the city of Manila, eight in all, has revealed the presence of the free acid in every case. Two of these samples were represented to be genuine oil of gaultheria, and six were synthetic preparations. All were of European exportation and had been in stock in this city from a few days to over a year. The amounts of free salicylic acid varied from a trace in one laboratory sample to 0.025 per cent. by weight in a genuine oil of wintergreen. These small amounts do not wholly account for the larger quantities of salicylic acid or its salts which have been found in a number of different preparations upon the local markets and entering the Port of Manila.

¹ U. S. Dept. Agr., Food Inspection Decision 76 (1907).

² 3rd Ed. (1906), 46.

The hydrolysis of the ester will be shown¹ to account, in many cases, for the presence of free salicylic acid in preparations in which comparatively pure methylsalicylate has been employed as an ingredient. With alkalis the rate of hydrolysis is very rapid, and with acids and even with distilled water the hydrolysis is easily measurable. The temperature is an important factor of the rate. It is therefore not surprising that the formation of salicylic acid from methylsalicylate in this way is quite appreciable in foods or drugs which have been shipped by vessels to this port. The temperature of the holds of the vessels often rises above 30° in the tropics, the voyage by fastest steamers from Europe or the United States occupies about one month, and by sailing vessels a number of months, and during the entire voyage the rolling and pitching of the vessels produces a constant agitation of the contents of bottles, casks and other containers, maintaining, in all, favorable conditions for hydrolysis.

The Determination of Salicylic Acid in Methylsalicylate.—The free acid can be titrated directly. The indicators which have been found to be applicable are Congo red and erythrosine. Alfred J. Cohn² says: "Congo red may be used for estimating mineral acids in the presence of organic acids, as the latter do not affect it." This has been found to be an error, as salicylic acid can be accurately titrated, the end-point being very sharp when either standard sodium hydroxide, carbonate or bicarbonate solutions are used, the carboxyl group only being affected. Walker and Wood³ have used Congo red for titrating salicylic acid against barium hydroxide. Erythrosine has also been found to give fairly good results, although Congo red has been used almost entirely throughout this work.

In titrating the free acid in methylsalicylate, from 5 to 20 cc. of the ester are shaken with an equal quantity of neutral distilled water in a glass stoppered flask, and 0.02 *N* standard alkali added until the color indicating the end-point remains permanent on shaking. Standard solutions of sodium hydrogen carbonate⁴ are best used in this titration, for reasons explained further on, although sodium hydroxide solutions give accurate results. The titrations were carried out at the room temperature, which varied in this laboratory from 28° to 34°.

In order to show that the acidity of the samples was not due to acids other than salicylic, the following method was employed: Ten cc. of the ester or oil of gaultheria were extracted three times with 5 cc. por-

¹ While this phase of the question will be touched upon here, it will be further dealt with in a later paper.

² *Indicators and Test Papers*, J. Wiley & Sons, New York (1904), 56.

³ *THIS JOURNAL*, 73, 619 (1898)

⁴ Standard solutions were made from Kahlbaum's sodium acid carbonate, which was found to be very pure.

tions of 0.1 *N* sodium hydrogen carbonate. These solutions were united, extracted three times with chloroform to remove the ester which was in solution, made acid with sulphuric acid (1 to 3) and extracted three times with chloroform. The chloroform extracts were united, filtered into a weighed dish, and evaporated spontaneously in a vacuum desiccator. After weighing the residue it was dissolved in hot water and the salicylic acid determined colorimetrically.¹

Two of the samples analyzed gave the following results:

TABLE I.

| | Per cent. of salicylic acid. | | |
|--------------------------------------|------------------------------|---------------------------|-------------------|
| | By titration. | By weighing. ² | Colorimetrically. |
| Oil of gaultheria (genuine). | 0.025 | 0.046 | 0.028 |
| Synthetic methyl salicylate. | 0.0113 | 0.033 | 0.0113 |

Separation and Determination of Salicylic Acid and Methylsalicylate in Foods and Drugs.—The substance under investigation, containing salicylic acid and methylsalicylate, is made strongly alkaline to Congo red, with an approximately normal solution of pure sodium hydrogen carbonate,³ free from normal carbonate, and, if not homogeneous, the aqueous solution is separated and the process repeated with the residue until it is thoroughly extracted by the sodium hydrogen carbonate solution. All of the salicylic acid and small amounts of methylsalicylate have now passed into the sodium hydrogen carbonate solution, the former in the form of sodium salicylate. This solution is extracted repeatedly, not less than three times, with small amounts of chloroform⁴ until all traces of methylsalicylate have been removed. The sodium hydrogen carbonate solution is now made acid with sulphuric acid (1 to 3) and extracted in the usual way to remove and determine the salicylic acid.⁵

This method has been successfully applied to emulsions of cod liver oil, which are usually very difficult to separate. The sodium hydrogen carbonate layer, carrying the salicylic acid and small amounts of methyl-

¹ Methods of Analysis, U. S. Dept. Agric., Bull. 107, 180 (1907).

² The weights of salicylic acid are evidently too great for the reason that drying was imperfect. Small quantities of the acid are so easily volatilized that it was considered preferable to err in the opposite direction and rely upon the colorimetric method for accuracy.

³ Solutions of sodium hydrogen carbonate lose carbon dioxide and should be freshly prepared and kept in well stoppered bottles. The loss of carbon dioxide and consequent increase in the amount of sodium hydroxide in the sodium hydrogen carbonate solution is in most cases counterbalanced by the acidity of the substance under examination. When this substance is very acid it is best made alkaline by the addition of solid sodium hydrogen carbonate in order to avoid a great increase in the bulk of the solution.

⁴ Chloroform has been found to be better than ether, for removing the methylsalicylate from this solution for the reason that it is less soluble in aqueous solution.

⁵ Method of Analysis, *Loc. cit.*

salicylate, can be separated in a rapidly revolving centrifuge. With non-alcoholic beverages and soda water flavors, the method is especially easy of manipulation. During the process of extraction, while the methylsalicylate are still in the solution with the salicylic acid salts, the temperature should not be unduly raised for the reason that the decomposition of sodium hydrogen carbonate and the rate of hydrolysis of methylsalicylate are accelerated with increase in temperature. During the manipulation in this laboratory, where the temperature is always high, the solutions have been kept below 35° , which temperature has been found to be a fairly safe limit. Lower working temperatures are, of course, to be desired.

The ester, separated by chloroform extraction,¹ is saponified by heating, in a flask with reflux condenser attached, on a steam bath with a large excess of strong caustic alkali solution.

After saponification is complete, half an hour usually being sufficient, the condenser is detached and the heating is continued until all of the chloroform is expelled. The solution is then diluted to a known volume and the salicylic acid determined in aliquot portions. The following quantitative experiments serve to show the manipulation and the accuracy of the method.

1.0256 grams methylsalicylate were dissolved in 50 cc. of chloroform and 10 cc. portions saponified with 10 cc. of a 25 per cent. solution of caustic potash. After evaporation of the chloroform, the residue was diluted to 100 cc. and 2 cc. portions made acid (1 to 3) and extracted four times with small amounts of chloroform. The chloroform was evaporated in a vacuum desiccator, and the residue dissolved in 100 cc. hot water. The salicylic acid determined colorimetrically² in this solution gave 1.0640 grams methylsalicylate.

1.2277 grams treated as above gave 1.2667 grams.

0.1568 gram dissolved in 10 cc. of a 25 per cent. solution of sodium hydroxide gave I., 0.1499 g., II., 0.1565 g.

*The Hydrolysis of Methylsalicylate with Sodium Carbonate and Sodium Hydroxide.*³—Solutions of sodium hydroxide, approximately 0.2 and 0.1 *N*, were made by dissolving clean metallic sodium in distilled water from which the gases were expelled by boiling. 0.2 *N* sodium carbonate solutions were made from the pure salt and also from the carbonate formed by the ignition of sodium oxalate.

¹ In the case of oil emulsions and some other mixtures the ester is best separated, after the removal of the salicylic acid, by steam distillation from a sulphuric acid solution. Since methylsalicylate is partially hydrolyzed on heating in a sulphuric acid solution, it is necessary to carry on the distillation until all of the salicylic acid formed has passed over into the receiver.

² Color comparisons made with a wedge colorimeter.

³ A more extended investigation of the hydrolysis of methyl salicylate with acids, alkalies and water and the catalytic action of tropical sunlight is being carried on and will probably be presented in a later paper. The cases of sodium carbonate and hydroxide are here briefly taken up merely to show the basis of the analytical methods.

The solutions were agitated in bottles with an excess of methylsalicylate and 10 cc. portions removed and titrated at intervals.¹ The reactions were all carried on at 30° with variations not exceeding 1°. This is the prevailing temperature in this locality.

From the curves² shown in Fig. I it is noted that the hydrolysis of the ester with sodium hydroxide goes to completion, that is, to the point

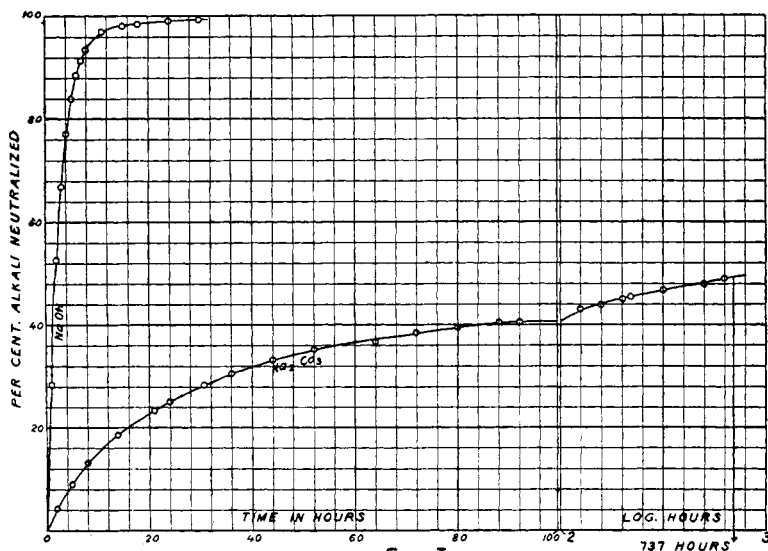
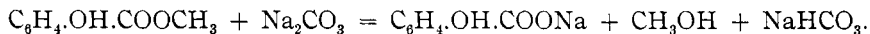


FIG. I.

HYDROLYSIS OF METHYLSALICYLATE

where all of the hydroxide has been used in the reaction, or at least very near completion in about 24 hours. With sodium carbonate, equilibrium, for all practical purposes, is reached in about one month, at the point where all of the normal carbonate has been converted into the hydrogen carbonate according to the equation:³

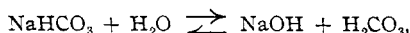


To prove that this is the end-point of the reaction, or at least the point where the rate is exceedingly slow, the ester was shaken for days with

¹ Ostwald-Luther, *Physico-Chemische Messungen*, Leipzig (1902), 447.

² The analytical data from which these curves are constructed, consisting of 83 determinations, can be found in the current number of the *Philippine Journal of Science*.

³ The hydrolytic dissociation of sodium hydrogen carbonate according to the equation



necessitates a gaseous pressure of carbon dioxide and a continuous loss of the gas with formation of normal sodium carbonate in the solution. A discussion of this question may be more fully entered into in a later paper. It is sufficient here to note that the effect due to this cause is very slight.

pure 0.1 N sodium hydrogen carbonate¹ solution in a number of sealed tubes. While a slight reaction was noted, it is believed that the substances are practically in equilibrium. Any reaction, taking place, is not sufficiently rapid to affect the accuracy of the analytical methods, previously described, which depend upon sodium hydrogen carbonate for the removal of salicylic acid as sodium salicylate from the presence of the methyl ester, without saponification of the latter.

Cahours² says that concentrated solutions of alkalis react with methylsalicylate in the cold to produce the salts of the ester. Freer³ has prepared sodium salicylic ethyl ester by the action of metallic sodium and by the reaction of sodium hydroxide upon the ester dissolved in ether. He speaks of the easy decomposition of this salt by moisture. The reactions with dilute solutions of sodium hydroxide and sodium carbonate, here described, are hydrolytic.⁴ Analyses of the solutions at the end-points of the reactions prove that the products of the saponifications are present in the amounts indicated by the theory.

TABLE II.

| Solution. | Per cent. methyl alcohol. | | Per cent. salicylic acid. | |
|--|---------------------------|--------|---------------------------|--------|
| | Theoretical. | Found. | Theoretical. | Found. |
| 0.203 Normal NaOH..... | 0.64 | 0.67 | 2.80 | 2.66 |
| 0.099 Normal NaOH..... | 0.32 | | 1.37 | 1.41 |
| 0.2 Normal Na ₂ CO ₃ | 0.32 | 0.314 | 1.38 | 1.33 |

Summary.

It is shown that methylsalicylate (synthetic), oil of gaultheria, or oil of betula, when used in foods and drugs, may give rise to the presence of salicylic acid, first, as an impurity in the ester, second, through its hydrolysis.

Methods for the detection and quantitative determination of salicylic acid and methylsalicylate in presence of each other are described.

The rate of saponification of methylsalicylate in solutions of sodium hydroxide and carbonate are studied.

The work in some of its other phases is being continued. The paper with more complete data is published in the current number of *Philippine Journal of Science*.

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MANILA, P. I., May, 1908.

¹ The amount of the hydroxide in this solution is very small. McCoy, *Am. Chem. J.*, 29, 453 (1903), has calculated the concentration to be 2.9×10^{-6} .

² *Ann. chim. phys.* [3], 10, 327 (1844).

³ *Am. Chem. J.*, 14, 411 (1892).

⁴ Secondary reactions may take place, to a small extent, not sufficient to affect the accuracy of the method. Some of these, probably due to light rays, are being studied.