AN ABSTRACT OF THE THESIS OF

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(Name) (Degree) (Major)

Date Thesis presented May, 1943

Title Microdetermination of Hydroxyl Content of Organic Compounds

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A simple method for the microdetermination of the hydroxyl content of organic compounds has been developed. The method is based upon the acetylation with an acetic anhydride-pyridine mixture. With the aid of this technique an extensive study has been made of the ease of acetylation and the conditions for acetylation of the hydroxyl groups in various compounds. It was found that the method gave good results with phenols and with primary and secondary alcohols, although there seemed to be a wide variation in the rapidity of acetylation. Tertiary alcohols did not acetylate to any great extent and consequently gave very low results. In addition to the variation in ease of acetylation of primary and secondary alcohols, it was found that the acetic anhydride employed must be acetate-free and that a 100 mole per cent excess must be employed to obtain a quantitative acetylation. It was also found that, while some materials acetylate very rapidly at 100° C., e.g., Borneol, other materials resinified at this temperature. The most general condition were found to be room temperature and an acetylation time of from 24 to 48 hours depending mainly upon the solubility of the compound in the acetylating mixture.

MICRODETERMINATION OF HYDROXYL CONTENT OF ORGANIC COMPOUNDS

by

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A THESIS

submitted to the

OREGON STATE COLLEGE

in partial fulfillment of
the requirements for the
degree of

MASTER OF ARTS

May 1943

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ACKNOWLEDGEMENTS

Acknowledgement is hereby given to Dr. B. E. Christensen for his many helpful suggestions and to Kenneth W. Hedberg who made some of the determinations herein recorded.

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Introduction

The simplest procedures for the determination of the hydroxyl content of organic compounds are those based on esterification. As yet little attention has been given to their application on a micro scale, a field in which they would be especially useful.

Several macro- and semimicromethods (1, 3, 5, 6, 8) employing both acetic anhydride and acetyl chloride have been described in the literature. Extensive esterification experiments with acetyl chloride have been reported recently from this laboratory (1). Since this reagent had proved quite satisfactory on a macro scale, experiments were conducted to adapt its use to a microdetermination.

In this connection, an apparatus similar to the modified methoxyl apparatus of Christensen, Friedman and Sato (2) was used. Due to the volatile nature of the acetyl chloride this procedure proved to be impractical. Acylations with stearyl chloride on the other hand were so erratic as to be unsatisfactory.

For these reasons the methoxyl apparatus was abandoned in favor of an hermetically sealed micro tube into which the reactants could be carefully weighed on a micro balance. Such a tube possessed the advantages of a Carius determination. In the initial experiments the alcohol was weighed into the tube which was then placed in dry ice. Acetyl chloride was then added, and the tube sealed. After an hour

the tube was opened under water and the aqueous solution was titrated for chloride and for acid. From this data it was possible to calculate the hydroxyl content of the compound. However the acetate content of the solution made it difficult to determine the chloride content with sufficient accuracy. This fact made it imperative that the amount of acetyl chloride be obtained by a weighing procedure. Therefore a series of tests were run in which the tube was carefully sealed after addition of the chloride and then weighed on a micro-balance. These results are tabulated in table I.

The low and somewhat erratic nature of the results could be plausible explained on the basis of an equilibrium mixture. Therefore efforts were made to remove one of the products thus allowing the reaction to go to completion. This was attempted by means of sealing a second micro tube filled with dimethyl aniline or pyridine inside the reaction tube. However this was not a practical solution in that the hydrochloride formed in each case covered and therefore closed the end of the small tube thus making further reaction impossible.

Attention was therefore directed to a study of the esterifications with acetic anhydride-pyridine mixture. Both Peterson and West (5) and Verley and Bölsing (8) have published methods based on the use of this reagent. Stodola (7) has reduced the procedure to a micro scale. Since extensive testing of this mixture has not been previously reported, the behavior of a large number of typical alcohols and phenols treated with acetic anhydride-pyridine solutions was studied. As a result of this work a simple microchemical technique based on the

TABLE I

ACETYLATION WITH ACETYL CHLORIDE

Alcohol (phenol)	Number of Determinations	% OH Theory	% OH Found	Average Deviation Parts per 1000
Borneol	10	11.1	10.6	33
n-Butyl	2	22.9	18.3	60
Isoamyl	2	19.3	18.0	36
n-Amyl	2	19.3	18.0	33
sec-Butyl	2	22.9	20.3	79
Catechol	2	30.9	27.0	33

use of a hermetically sealed tube has been developed in this laboratory which gives fairly satisfactory results for the microdetermination of the hydroxyl content of organic compounds.

Reagents

C. P. acetic anhydride, redistilled and acetate-free, kept in well-stoppered (screw cap) bottle; C.P. pyridine, redistilled and water-free; and 0.04 N sodium hydroxide, carbonate-free.

Apparatus

The reaction vessel consists of a melting point tube, 3 mm. in diameter and 6 cm. in length, made from a soft-glass test tube.

Three medicine droppers, for the delivery of alcohol, acetic anhydride, and pyridine, respectively, are made by drawing one end of a 6-mm. soft-glass tubing to a fine capillary and equipping the other end with a rubber policeman.

Glass plungers, 1.0 mm. x 0.5 cm., are made from soft-glass rod.

A microcentrifuge.

Analytical Procedure

Introduce 2 to 10 mg. of the compound into a weighed reaction tube by means of the dropper, or, in the case of solids, employ the

technique described by Niederl for filling Rast tubes (4).

Centrifuge and again reweigh the tube. Using the same technique, add approximately 20 to 25 mg. (4 to 5 drops) of pure acetic anhydride from the second dropper, recentrifuge, and weigh again. In order to ensure the quantitative conversion of the alcohol to the ester, a ratio of at least 2 moles of anhydride per equivalent of hydroxyl should be maintained.

Add 4 to 6 drops of pure pyridine and again centrifuge. The amount of pyridine does not appear to be critical except in a few cases involving solubility. Insert a small glass rod in the tube, seal, then shake well to ensure complete mixing, and set aside for 24 hours. At the same time run a blank to determine the volume of standard base required to neutralize the acid derived from 1 mg. of acetic anhydride.

Place the reaction tube in a 50-ml. Erlenmeyer flask, add 5 ml. of water, and then break the tube by means of a stout stirring rod. Titrate released acid with 0.04 N sodium hydroxide. The per cent hydroxyl can then be calculated by means of the formula:

$$\%(OH) = \frac{(\text{m. e. of anhydride used} - \text{m. e. of acid found}) \times 1700}{\text{mg. of sample}}$$

where m. e. of acid found = m. l x normality, m. e. of anhydride used = mg. of anhydride x ratio x normality, and ratio = ml. of base required to neutralize acid derived from 1 mg. of anhydride.

Results and Discussion

The results obtained with this procedure are given in Table II. In most cases they are the average of duplicate determinations.

This method is not applicable to the determination of tertiary alcohols. Ethyl citrate, t-amyl, and t-butyl alcohol gave very low results which confirm the observations of others.

Although all experiments were extended over a period of 24 hours at room temperature, these conditions are not to be considered as well-established optima. Since the reaction mixture is hermetically sealed, experiments can be conducted with equal ease at elevated temperatures. Several compounds have been reported to acetylate in 15 minutes at 100° C. in acetic anhydride and pyridine. In this laboratory borneol has been quantitatively acetylated in 35 minutes at 100° C. On the other hand a number of alcohols give poor results at higher temperatures, possible because of decomposition.

The author's experience indicates that the ease of acetylation varies with the individual compounds. The ratio of acetic anhydride to alcohol has been found to be somewhat critical and should not fall below 100 mole per cent excess per equivalent of hydroxyl. Since the hydroxyl is determined by difference, it is not a good policy to employ too large an excess for accurate work.

Care should be exercised in the selection of acetic anhydride. It is essential that pure redistilled anhydride (from a good fractionating column) be used to obtain the best results. In some of the

TABLE II

ACETYLATION WITH ACETIC ANHYDRIDE-PYRIDINE MIXTURES

Compound Determined	No. of Determinations	OH Theory %	OH Found (Average) %	Average Deviation Parts per 1000
Primary and Secondary Alcohols				
-Phenyl-n-propyl	2	12.4	12.3	0
Butyl	2	22.9	22.7	5
Isoamyl	2	19.3	19.25	8
Allyl	2	29.3	29.15	2
Cyclohexanol	2	17.0	16.90	6
Octanol-2	2	13.1	12.95	4
Hexanol	2	16.6	15.45	15
Benzyl	2	15.7	15.85	10
sec-Butyl	1	22.9	22.4	..
Cinnamyl	2	12.7	12.25	4
Diethycarbinol	2	19.3	18.4	5
2-Ethylbutanol	2	16.6	15.9	12

TABLE II
(Continued)

Compound Determined	No. of Determinations	OH Theory %	OH Found (Average) %	Average Deviation Parts per 1000
Polyhydric alcohols				
Ethylene glycol	4	54.6	54.0	20
Propylene glycol	6	44.7	41.0	29
Diethylene glycol	4	32.1	30.1	4
Mannitol	2	56.1	56.15	1
Sorbitol	2	56.1	54.7	0
Substituted alcohols				
Ethylene chlorohydrin	4	21.1	20.0	3
1,3-Dichloropropanol-2	2	13.1	12.8	0
Terpenes				
Borneol	2	11.0	11.1	0
Menthol	2	11.0	10.9	9
Geraniol	2	11.0	9.9	0
Eugenol	2	10.4	10.55	5
Isoeugenol	44	10.4	9.75	7
Citronellol	4	10.9	9.45	28

TABLE II
(Continued)

Compound Determined	No. of Determinations	OH Theory %	OH Found (Average) %	Average Deviation Parts per 1000
Miscellaneous				
Benzoin	..	8.0	8.11	0
Cholesterol (a)	2(a)	4.4	4.5	11
Phenols				
Phenol	2	18.1	17.65	3
o-Cresol	2	15.7	15.55	10
p-Cresol	2	15.7	15.7	22
m-Cresol	2	15.7	15.35	3
a-Naphthol	2	11.8	11.55	4
β-Naphthol	2	11.8	11.65	4
Resorcinol	2	30.9	30.8	6
Hydroquinone	2	30.9	30.7	3
Orcinol	2	27.4	26.9	4
Catechol	2	30.9	31.05	5
2-Hydroxy-1,4-dimethyl-benzene	2	13.9	13.8	8
Pyrogallol	3	40.5	40.0	17

(a) Hydrolyzed in usual way, then 10 ml. of 95% ethanol added to dissolve ester before titration.

TABLE II
(Continued)

Compound Determined	No. of Determinations	OH Theory %	OH Found (Average) %	Average Deviation Parts per 1000
Substituted phenols				
Vanillin		11.2	10.85	4
p-Hydroxy-benzaldehyde		13.9	13.65	4
Gallic acid		27.1	27.3	4
Thymol		11.0	11.15	4
Guaiacol		13.7	13.65	4
o-Chlorophenol		13.2	13.1	0
p-Chlorophenol		13.2	13.0	0
Methyl salicylate		11.2	11.35	4
Salicylic acid	2	12.3	12.35	4
m-Hydroxybenzoic	2	12.3	12.2	9
p-Hydroxybenzoic	2	12.2	12.25	4
4-Hydroxy-1,2-dimethyl benzene	2	13.9	14.15	4
m-Nitrophenol	2	12.2	12.1	9
p-Nitrophenol	2	12.2	11.35	4
o-Nitrophenol	2	12.2	11.45	2
p-Aminophenol	2	15.6	15.05	1
2-Hydroxy-1,4-dimethyl-benzene	2	13.9	13.8	7

TABLE II
(Continued)

Compound Determined	No. of Determinations	OH Theory %	OH Found (Average) %	Average Deviation Parts per 1000
Sugars				
Sucrose (b)	4	39.8	39.9	5
Xylose	2	45.5	45.55	3

(b) Ran 48 hours

initial work erratic results were traced to the presence of a considerable quantity of acetic acid in the acetic anhydride. As soon as this was remedied the results were nearer the theoretical values and were much more reproducible. In later experiments the acetic anhydride was redistilled in a 7-plate column. The titer of this anhydride agreed perfectly with the theoretical value.

The experiments with sugars were performed merely to ascertain the possibilities of a micromethod in this field. As indicated, the results are satisfactory and are in agreement with the data of Peterson and West (5).

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