THE ASSAY OF HYPOPHOSPHITES OFFICIAL IN THE NATIONAL FORMULARY.[*,1]

BY GLENN L. JENKINS[1] AND CHARLES F. BRUENING.[2]

The ammonium, calcium, iron, manganese, potassium and sodium hypophosphites are official in the National Formulary. The official methods of assay (1) for these salts are based, except in the case of iron hypophosphite, on the argentometric determination of the phosphate formed by the oxidation of the hypophosphite.

The official methods of assays for five of the hypophosphites, in addition to being indirect, are subject to other criticisms regarding accuracy (2), (3).

The results of a prescription survey (4) indicate that the official hypophosphite salts, as well as syrups containing hypophosphites, are extensively prescribed. It is desirable, therefore, because of their wide use and objections to the present official methods, to develop improved methods for the assay of these salts.

METHODS OF ASSAY.

Numerous methods have been proposed for the determination of hypophosphites. These methods may be divided into two main classes, namely: (*a*) Methods based on the determination of the phosphate formed by oxidation of the hypophosphite by acidimetric means or by variations of the molybdate method. These methods have been studied by Viebock and Fuchs (5), Mengdehl (6), Raunich (7), Fiest (8), Ferrey (9), Bond (3) and Barnard and McAbee (10). (*b*) Methods involving the oxidation of hypophosphite to phosphate and the subsequent determination of the quantity of oxidizing agent consumed in the reaction.

The work of Raquet and Pinte (11), Gall and Ditt (12), Hovorker (13), Wolf and Jung (14), Ionesco-Matiu and A. Popesco (15), Kolthoff (16), Bayer (17), Kosezegi (18), Boyce and Bauzil (19), Dickerson and Snyder (2), Ziry (20), National Formulary Bulletin (21), Brukl and Behr (22), Marchott and Steinhauser (23), Rupp and Kroll (24), Harrison (25), Marino and Pellegrini (26) and Cocking and Kettle (27) has showed that these methods of the second class are quite satisfactory. The oxidizing agents used in the above methods include potassium permanganate in alkaline and acid solution, potassium manganate, bromine, iodine, potassium iodate, iodic acid, potassium dichromate and mercuric chloride. The methods in this group appear to be satisfactory and several (21), (23), (24) have been selected for critical study.

EXPERIMENTAL PART.

The samples of the salts used were manufactured by a well-known and reputable chemical company. The sodium hypophosphite used was of the chemically pure (C.P.) grade, the only salt obtainable on the market in this grade. The other five salts were of the National Formulary (NF) grade. All the salts conformed strictly to the tests for purity of the National Formulary. The salts were dried over H_2SO_4 as directed in the National Formulary and these dried salts were used throughout this investigation.

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[1] From the Department of Pharmaceutical Chemistry, University of Maryland, School of Pharmacy.

[2] Abstracted from a thesis submitted to the Graduate School of the University of Maryland by Charles F. Bruening in partial fulfilment of the requirements for the degree of Master of Science.

NATIONAL FORMULARY METHODS.

All of the salts were assayed by the official methods (1) for the purpose of comparison with other methods and to see whether any justification exists for criticism to the methods (2), (3). The official methods of assay of five of the salts are essentially the same, differing from each other only in minor details. With the ammonium and manganese salts the positive ions are removed before proceeding with the assay, the ammonium ion being removed as ammonia from an alkaline solution and the manganese ion by precipitation as MnO_2 by means of hydrogen peroxide in an alkaline solution.

With the exceptions noted the basic method for five of the salts is: The hypophosphite salt is dissolved in water and oxidized by the addition of nitric acid, the solution being evaporated to dryness on the water-bath. More concentrated nitric acid is added and the evaporation repeated to obtain complete oxidation. After dissolving the residue in water and making alkaline to phenolphthalein, the phosphate is precipitated in an aliquot by the addition of an excess of $N/10$ $AgNO_3$; zinc oxide being used to keep the solution neutral. The reaction is represented by the equation $3AgNO_3 + Na_2HPO_4 \longrightarrow Ag_3PO_4 + HNO_3 + 2NaNO_3$. After making up to volume and filtering, an aliquot is titrated with $N/10$ NH_4CNS using ferric alum as indicator. To make the National Formulary methods more precise, one modification was adopted, namely, the oxidized residue was dissolved in distilled water and made up to a volume of 200 cc. instead of 100 cc. as specified, and aliquots of 20 cc. used in place of 10 cc. for the precipitation of the phosphate with standard silver nitrate. The results obtained are shown in Table I.

TABLE I.

Hypophosphite salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.	National Formulary Minimum Requirement Per Cent.
Sodium + H_2O	1.0008	0.9999	99.91	98
	1.0007	1.0013	100.06	
	1.0007	1.0020	100.13	
Potassium	0.9980	0.9687	97.06	98
	0.9982	0.9673	96.90	
	0.9985	0.9659	96.73	
Ammonium	1.0014	0.9606	95.93	98
	1.0013	0.9598	95.86	
	1.0008	0.9584	95.77	
Calcium	0.7503	0.7226	96.31	98
	0.7513	0.7266	96.71	
Manganese + H_2O	1.0009	0.8947	89.39	97
	1.0009	0.9103	90.95	
	1.0009	0.9029	90.21	
	1.0028	1.0007	99.79	98
Ferric	1.0031	1.0025	99.94	
	1.0008	0.9995	99.87	

The results for the iron salt have been included in this table although the official method of assay depends on a different process than that for the other salts. This method of assay determines the iron content by the usual iodometric method, after oxidation of the hypophosphite to phosphate, and results are expressed as ferric hypophosphite.

The results obtained for the first five salts, indicate that the official methods apparently give low results since only the sodium salt conforms to the minimum requirement of the National Formulary. The results for the manganese salt are very low although similar results were obtained using different samples of the salt.

NATIONAL FORMULARY METHODS, MODIFIED.

Silver phosphate, the yellow precipitate formed in the official methods, is soluble in dilute mineral acid and low results would necessarily follow if the zinc oxide failed to neutralize all the acid formed in the reaction; or it may be possible that even though all the acid is neutralized, as shown by neutrality to litmus, the solution is not at the optimum p_H to obtain complete precipitation.

To investigate the cause of low yields the National Formulary Methods were modified in that sodium acetate was used in the place of zinc oxide with the expectation of higher yields. The official methods of assays beginning with the precipitation were then repeated using aliquots from the same solutions as were used in the assays reported in Table I. The results are shown in Table II with the amounts of sodium acetate used.

TABLE II.

Hypophosphite Salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.	Sodium Acetate Used Gm.
Sodium + H_2O	1.0008	1.0317	103.09	0.4
	1.0007	1.0317	103.10	0.4
	1.0007	1.0338	103.31	0.4
Potassium	0.9980	0.9916	99.36	0.4
	0.9982	0.9930	99.48	0.4
	0.9985	0.9930	99.45	0.4
Ammonium	1.0014	0.9878	98.64	0.4
	1.0013	0.9872	98.59	0.4
	1.0008	0.9870	98.62	0.4
Calcium	0.7503	0.7385	98.43	0.4
	0.7503	0.7425	98.96	0.4
	0.7503	0.7419	98.88	1.0
	0.7503	0.7442	99.19	1.0

Although these results do not fully explain the reasons for low yields obtained by the official methods, they are considerably higher and indicate an improvement in the methods. They show, however, that complete oxidation is obtained by the National Formulary Methods. By this modification, the four salts used in this experiment all conform to the minimum requirement of the National Formulary, and the yield is not affected by the amount of sodium acetate used.

Calculating the sodium salt on the anhydrous basis the results are 85.59, 85.59 and 85.77 per cent; these results indicating that this salt has lost part of its water of hydration.

GRAVIMETRIC METHOD.

As a method for comparison with the National Formulary and Modified Methods, a method used for the determination of hypophosphorous acid given in Treadwell and Hall (28), involving the oxidation to phosphate and determination of the phosphate by precipitating as magnesium ammonium phosphate from a hot solution following the method of B. Schmitz (29), was selected.

Neubauer (30) and Gooch (31) have shown that precipitation in the cold makes it difficult to obtain a pure precipitate of magnesium ammonium phosphate; sometimes the precipitate is contaminated with $Mg_3(PO_4)_2$ and sometimes with $Mg(NH_4)_4(PO_4)_2$. If, however, the precipitation takes place in a hot solution, a very pure, coarsely crystalline precipitate of $Mg(NH_4)PO_4$ is obtained (29). This is ignited to $Mg_2P_2O_7$ and weighed.

Reagents: Nitric Acid, 36% HNO_3.
Dilute Hydrochloric Acid 10 Gm. HCl/100 cc.
Ammonia (Sp. Gr. 0.90).
Ammonia, 1.5 Normal (1 in 10).
Ammonium Acetate C.P. Crystals.
Magnesia Mixture: Dissolve 55 Gm. of crystallized $MgCl_2$ and 105 Gm. NH_4Cl in water adding a little HCl (3 cc. dilute used) and diluting to a volume of 1 liter. For 0.1 Gm. P_2O_5 use 6 cc. of solution.
Phenolphthalein Indicator, 1 Gm./100 cc.

Procedure: A weighed amount of the dried hypophosphite salt equivalent to about 5 millimols is dissolved in 5 cc. of distilled water, 5 cc. HNO_3 added and the solution evaporated to dryness on a water-bath. A 5-cc. portion of nitric acid is added to the residue and the evaporation to dryness repeated. The residue is dissolved in water, ammonia (sp. gr. 0.9) added until neutral to litmus and the solution finally diluted to 100 cc. Add a few drops of dilute HCl, an excess of magnesia mixture, 5 Gm. of ammonium acetate, and a few drops of phenolphthalein indicator. Heat nearly to boiling, run in 1.5*N* ammonia from a burette while constantly stirring until a turbidity forms. Stir till the precipitate is crystalline and then continue adding the ammonia until a red coloration is obtained. Allow the solution to cool completely, add one-fifth of its volume of ammonia (sp. gr. 0.9) and let stand at least four hours. Wash the precipitate three times by decantation with 1.5*N* ammonia, then transfer to a filter and wash free from chlorides with 1.5*N* ammonia. Finally moisten the precipitate with a small amount of 1.5*N* ammonia saturated with ammonium nitrate. Ignite very slowly, gradually increasing the heat until the precipitate is white. A muffle furnace is preferable, finally raising the temperature to 1000° C. and heating to constant weight.

A modified method is used for the calcium salt consisting in the addition of 3 Gm. of citric acid previous to precipitation. This modified method is also applicable to ferric hypophosphite.

To check the accuracy of this method the phosphate was determined on two pure samples of sodium phosphate. These samples were manufactured by different companies; sample "A" was Anhydrous Sodium Dibasic Phosphate C.P. and sample "B" the hydrated salt $Na_2HPO_4.12H_2O$ Analytical Grade. Sample "B" was recrystallized before using. Both samples were dried at 100° C. as recommended by Murray (32) and carefully assayed starting at the point "add a few drops of diluted HCl," etc. Table III shows the results obtained.

TABLE III.

Sample.	Weight of Sample Gm.	Amount Found Gm.	Deviation. Gm.	Deviation. Per Cent.
A	0.4466	0.4476	+0.0010	+0.22
B	0.4970	0.4972	+0.0002	+0.04
	0.5275	0.5282	+0.0007	+0.13
	0.5050	0.5059	+0.0009	+0.18

These results are satisfactory and although a trifle high, it is maintained that this method is as accurate as any of the phosphate methods. For this reason this method was used as a standard method of comparison, for those salts listed in Table IV. Throughout this investigation an electric muffle was used as results were found to be less accurate with a Fisher Burner probably due to incomplete conversion of the precipitate.

The results obtained by this method are shown in Table IV.

TABLE IV.

Hypophosphite Salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.
Sodium + H_2O	0.5004	0.5208	104.08
	0.5003	0.5216	104.26
	0.5003	0.5210	104.14
Potassium	0.4990	0.4984	99.88
	0.4991	0.4983	99.84
	0.4992	0.4988	99.92
Ammonium	0.5007	0.5006	99.98
	0.5006	0.5000	99.88
	0.5004	0.5008	100.08
Calcium	0.5370	0.5370	100.00
	0.5201	0.5203	100.04
	0.5205	0.5199	99.88

Calculating the sodium salt on an anhydrous basis the results are 86.40, 86.56 and 86.46 per cent. A moisture determination on this salt yielded residues representing 86.06 and 86.03 per cent agreeing with the results on analysis. The small difference may be due to decomposition of the salt at 110° C., the temperature used in drying.

The results show that the method as developed is applicable to the assay of the official hypophosphites. It gives accurate results, the only objection is that it is an indirect method. With the calcium salt it can be applied directly without first precipitating the phosphate as the molybdate compound, with the resultant saving of time. By this gravimetric method, more accurate results can be obtained by a double precipitation of the magnesium ammonium phosphate, and this procedure is recommended where large quantities of other salts are present.

BISMUTHATE METHOD.

In the selection of standard methods for comparison we have adopted the National Formulary Method for ferric hypophosphite. This rapid iodometric method yields excellent results and the iron content has been expressed as ferric hypophosphite.

In the same manner we have adopted the Bismuthate Method as our standard method for comparison for the Manganese salt. The manganese content of the salt was determined by this method as outlined in Treadwell-Hall (28), however, oxidizing the hypophosphite previously with nitric acid. This method yields consistent results as shown in Table V.

TABLE V.

Hypophosphite Salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.
Manganese + H_2O	1.5017	1.4752	98.24
	1.5017	1.4769	98.35
	1.5017	1.4756	98.26

PERMANGANATE METHOD.

Hypophosphites are oxidized by $KMnO_4$ in acid solution to phosphates and this reaction furnishes a basis for two methods as reported by Kolthoff (16) and the method given in the National Formulary Bulletin (21). Because these two methods are similar only the latter was selected for study. The National Formulary Bulletin Method was slightly modified and the following procedure adopted:

Accurately weigh about 0.7 Gm. of the salt and dissolve it in enough water to make a final volume of 500 cc. Place an aliquot of 50 cc. into a glass-stoppered flask, add 50 cc. of 0.1*N* $KMnO_4$ and 3 cc. of concentrated H_2SO_4; shake well and allow to stand over night in a dark place. Add 10 cc. of KI solution (20 Gm./100 cc.) and titrate the liberated iodine with 0.1*N* $Na_2S_2O_3$ until the solution becomes straw-color, then add 1 cc. of starch solution (0.5 Gm./100 cc.) and titrate until the solution becomes colorless. Carry out a blank determination at the same time. The difference between the two titrations with 0.1*N* $Na_2S_2O_3$ represents the equivalent amount of 0.1*N* $KMnO_4$ used in the oxidization.

The results are found in Table VI and the approximate time of standing is indicated.

TABLE VI.

Hypophosphite Salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.	Time Hours.
Ammonium	0.6159	0.6184	100.41	24
	0.6159	0.6188	100.47	24
	0.6159	0.6182	100.37	24
Sodium + H_2O	0.7893	0.8293	105.07	24
	0.7893	0.8287	104.99	24
	0.7893	0.8285	104.97	24
Potassium	0.7803	0.7757	99.41	12
	0.7803	0.7791	99.85	24
	0.7803	0.7864	100.78	36
	0.7803	0.7862	100.76	36

The yield by this method in most cases is in excess of 100 per cent and with the potassium salt the time was varied to note the relation of time to yield. Excessive yields are probably due to side reactions, impurities, etc., although a constant blank was obtained indicating that the oxidizing agent is stable in the solution used. It is important, however, to add the acid immediately after the permanganate to prevent the complete conversion to MnO_2 in the neutral solution. If this occurs, complete oxidation is difficult to attain even on long standing. Because of the high results obtained no further work was done on this method.

BROMINE METHOD.

Investigations have been made showing that bromine can be used to completely oxidize hypophosphites. This reaction takes place in acid solution as shown by the following equation.

$$H_3PO_2 + 2Br_2 + 2H_2O \longrightarrow H_3PO_4 + 4HBr.$$
$$1 \text{ equivalent weight } Br_2 = {}^1/_4 \text{ Mol. Wt. } H_3PO_2.$$

Rupp and Kroll in determining calcium hypophosphite (24) state that the oxidation is made exactly as in the determination of phenol, while Marchott and Steinhauser in assaying hypophosphorous acid (23) used a similar method, but state that the presence of a large excess of mineral acid retards the oxidation.

The method of Rupp and Kroll for calcium hypophosphite was slightly modified and applied to all the salts and the following method adopted to determine hypophosphites.

Reagents: 0.1*N* Bromide-Bromate Solution.
(Koppeschaar's Solution.) Dissolve 3 Gm. $KBrO_3$ and 50 Gm. KBr in water and dilute to 1 liter.
0.1*N* Sodium Thiosulphate.
Potassium Iodide (20 Gm./100 cc.).
Diluted Sulphuric Acid (10 Gm./100 cc.).
Sodium Hydroxide Solution (10 Gm./100 cc.).
Starch Solution (0.5 Gm./100 cc.).

Procedure: Accurately weigh about 0.7 Gm. of the salt and dissolve in enough water to make a final volume of 500 cc. Place an aliquot of 50 cc. in a glass-stoppered 250-cc. volumetric flask, add 50 cc. of 0.1*N* bromide-bromate solution and 20 cc. of diluted sulphuric acid; stopper, shake well and allow to stand for 2 hours. Add 10 cc. of the potassium iodide solution, shake the flask, and titrate the liberated iodine with 0.1*N* sodium thiosulphate until the solution becomes straw color, then add 2 cc. of the starch solution and titrate until the solution becomes colorless. Carry out a blank determination in the same way. The difference between the two titrations with the 0.1*N* sodium thiosulphate when multiplied by the appropriate factor gives the amount of hypophosphite salt present.

For iron hypophosphite the above procedure is not applicable due to the insolubility of the salt and to the interference of the ferric ion with the final titration. Therefore, the following procedure was used:

Accurately weigh about 0.15 Gm. of the ferric hypophosphite and transfer to a 200-cc. volumetric flask with a glass stopper. Add 100 cc. of 0.1*N* bromide-bromate solution, 20 cc. of diluted sulphuric acid, stopper and shake well; allow to stand shaking occasionally until the salt is completely dissolved. Standing over night will usually dissolve all the salt. Then add an excess (30 cc.) of sodium hydroxide solution, cool and make to volume. Filter off the precipitate (ferric phosphate and hydroxide) and to an aliquot of 100 cc. add 10 cc. of potassium iodide solution, an excess of diluted sulphuric acid and titrate the liberated iodine with 0.1*N* sodium thiosulphate.

The results obtained by this method and modification for the iron salt are shown in Table VII. With each of the first five-named salts, aliquots from the same solution were used, and the results expressed on the basis of amount of salt found in the entire solution.

TABLE VII.

Hypophosphite Salt.	Weight of Sample Gm.	Amount Found Gm.	Yield Per Cent.
Sodium + H_2O	0.7484	0.7786	104.04
	0.7484	0.7797	104.18
	0.7484	0.7789	104.08

Potassium	0.7282	0.7249	99.55
	0.7282	0.7254	99.62
	0.7282	0.7262	99.73
	0.7282	0.7252	99.59[*]
Ammonium	0.6670	0.6665	99.79
	0.6670	0.6650	99.70
	0.6670	0.6656	99.79
Calcium	0.6225	0.6177	99.23
	0.6225	0.6181	99.29
	0.6225	0.6181	99.29
Manganese + H_2O	0.6532	0.6421	98.30
	0.6532	0.6421	98.30
	0.6532	0.6424	98.35
Ferric	0.1528	0.1526	99.87
	0.1525	0.1525	100.00
	0.1513	0.1513	100.00

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[*] Time of standing 6 hours.

Calculating the sodium salt on the anhydrous basis the yields are 86.37, 86.49 and 86.41 per cent.

This method is simple and rapid and presents no difficulties. The bromide-bromate solution keeps very well, no appreciable change being detected after standing six months. It was also found that it is not necessary to run a blank each time as a constant blank was obtained. A factor was obtained by adding 10 cc. of the potassium iodide solution to 50 cc. of the bromide-bromate solution, acidifying with 20 cc. of dilute sulphuric acid and titrating with 0.1*N* sodium thiosulphate solution. As mentioned above this factor remained constant during the time of investigation of the salts although the sodium thiosulphate was standardized against potassium dichromate at frequent intervals.

COMPARISON AND DISCUSSION OF RESULTS.

For the purpose of comparison, the average yields from the different methods (Tables I to VII, except III) are listed in Table VIII.

TABLE VIII.

Hypophosphite Salt.	National Formulary Methods Table I Per Cent.	National Formulary Methods Modified Table II Per Cent.	Gravimetric Method Table IV Per Cent.	Bismuthate Method Table V Per Cent	Permanganate Method Table VI Per Cent.	Bromine Method Table VII Per Cent.
Sodium + H_2O	100.03	103.16	104.17	...	105.01	104.10
Potassium	96.90	99.43	99.88	...	100.46	99.63
Ammonium	95.85	98.62	99.98	...	100.42	99.76
Calcium	96.51	98.87	99.97	...	....	99.27
Manganese + H_2O	90.18	....	....	98.28	....	98.32
Ferric	99.87	....	....	...	....	99.96

As a basis of comparison for the first four salts we used the Gravimetric Method, for the manganese salt the Bismuthate Method, and for the iron salt the National Formulary Method. It is noted, however, that for the manganese and ferric salts we used the Law of Definite Proportions as a basis for our comparison.

With the acceptance of methods for comparison for all the salts, we are now in a position to discuss the methods of assay individually and find: The National Formulary Methods are unsatisfactory for the following reasons:

1. The methods are indirect ones, determining total phosphates rather than hypophosphites.

2. Although consistent results are obtained by the methods, all the results are low.

3. Some difficulty was encountered with the end-point in titrating the excess silver nitrate with $0.1N$ thiocyanate, a tendency for the end-point to fade being noted.

4. No provision is made for the volume occupied by the undissolved zinc oxide.

5. Although the actual determination of the phosphate is rapid, considerable time is involved in converting the salts to phosphates.

6. The method for ferric hypophosphite is not subject to these criticisms, since excellent results are obtained.

The National Formulary Methods, Modified, are an improvement on the National Formulary Methods for the following reasons:

1. Higher yields are obtained which approach the theoretical as determined by the Gravimetric Method. These yields indicate that sodium acetate is superior to zinc oxide as a buffer.

2. The methods are subject, however, to the criticisms listed in items 1, 3 and 5, under the National Formulary Method.

3. These methods may be used to replace the present official methods although the results are only partially satisfactory.

The Permanganate Method is considered unsatisfactory for the following reasons: 1. The length of the time of standing is objectionable. 2. High results are obtained in excess of the theoretical indicating side reactions, reactions with impurities, etc. 3. The method is apparently not applicable to all of the official salts.

The Bromine Method as developed is very satisfactory for the following reasons: 1. The method is simple and rapid. A complete assay can be run in about two and one-half hours for any of the salts with the exception of the iron salt which requires a longer time. 2. The method is a direct one. 3. The method yields excellent results. For the first four salts listed (Table VIII) close agreement is noted with the Gravimetric Method. With the manganese salt almost identical results are obtained by this method and the Bismuthate Method, and likewise with the iron salt, the results by this method agree remarkably well with those obtained by the National Formulary Method. 4. It can be made applicable to all the official salts. In the case of the iron salt, this method is about as rapid as the National Formulary Method and the results obtained may be of greater value. 5. It is suggested that this method replace the present National Formulary Methods for the official hypophosphites.

CONCLUSIONS.

1. The National Formulary Methods of Assay for Ammonium, Calcium, Potassium, Sodium and Manganese Hypophosphites give unsatisfactory results.

2. The National Formulary Method of Assay for Ferric Hypophosphite yields excellent results.

3. Modified National Formulary Methods of Assay for Ammonium, Calcium, Potassium and Sodium Hypophosphite give results nearer the theoretical than the National Formulary Methods of Assay.

4. The Permanganate Method is unsatisfactory due to its length and excessive yields.

5. The Gravimetric Method developed for the assay of the official hypophosphite salt, while not applicable to the manganese salt, is satisfactory. The method is simple and accurate.

6. The Bromine Method has been developed for assaying the official hypophosphites, and is applicable to all the official salts. The method is simple, rapid and accurate.

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EVALUATION OF A DETERIORATION FACTOR IN LIQUID PETROLATUM.*,[1]

BY P. L. BURRIN, A. G. WORTON AND F. E. BIBBINS.

INTRODUCTION.

The fact that some samples of liquid petrolatum develop peculiar odors when stored under optimum conditions, while other samples stored under the same con-

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* Scientific Section, A. PH. A., Portland meeting, 1936.

[1] From the Control Laboratories, Eli Lilly and Company.