SPIRIT OF NITROUS ETHER.*

BY H. ENGELHARDT AND O. E. WINTERS.

In a paper on Nitrous Ether presented at the City of Washington Branch of the American Pharmaceutical Association, Kebler, Palkin and Ewing state that in order to preserve the full amount of ethyl nitrite in Spirit of Nitrous Ether the latter must be bottled in small amber-colored containers stoppered with paraffined corks. If stored in large amber bottles kept in diffused light it is necessary to use absolute alcohol in the preparation of the Spirit.

While these recommendations possibly are of theoretical value they cannot well be carried out in practice. It would, for instance, be quite inconvenient for manufacturers to furnish one gallon of Spirit of Nitrous Ether in 128 1-oz. bottles.

Although the question in regard to the stability of Spirit of Nitrous Ether has been investigated numerous times, the following experiments which were undertaken a few years ago with the purpose in view to show at what rate the spirit deteriorates when bottled and kept under ordinary conditions may be of interest. They show that when the preparation is kept in flint, cork stoppered bottles in diffused light, conditions which are ordinarily met with in drug stores, a rather rapid deterioration takes place.

In connection with these experiments a few deficiencies in the test of the pharmacopœial assay process may be pointed out.

The U. S. P. directs that the percentage of ethyl nitrite in Spirit of Nitrous Ether be estimated gasometrically. On various occasions one of us has pointed out that this method might well be substituted by Dietze's Potassium Chlorate Method, as adopted by the Dutch Pharmacopœia, because by this method very accurate results, or at least just as accurate as those obtained by the U. S. P. process, are obtained. Another advantage in this method is that nitrometers and barometers, instruments which are not frequently found in drug stores, are not needed. It is further directed that 30 Gm. be shaken with 0.5 Gm. of potassium bicarbonate. Is this step necessary? The shaking with the alkali is done probably to remove any nitrous acid which has been formed in the spirit by hydrolysis on long standing. But is not nitrous acid just as effective as a stimulant and antispasmodic as its ethyl ester? Furthermore, the length of time during which the spirit is to be shaken with the bicarbonate should be given, because on prolonged standing the ester is saponified by the alkali. The U. S. P. then directs that 10 Cc. of the diluted neutralized spirit be introduced into a nitrometer and mixed with 10 Cc. potassium iodide solution, etc. Another source of error lies in this part of the process, especially when the concentrated salt solution recommended by the U. S. P. for filling the nitrometer is replaced by the mercury. When the two liquids are mixed and when the mercury columns are brought to the same level an accumulation of gas may be observed in the nitrometer amounting at times to 0.6 Cc. or more. This gas is air which was dissolved in the potassium iodide solution, for, when boiled and subsequently cooled potassium iodide solution is used, no separation of gas can be noticed. The U. S. P. should require either that the gas formed when mixing the spirit and potassium iodide solution be deducted from the final volume or that the air free potassium iodide

* Read before Scientific Section, A. Ph. A., Atlantic City meeting, 1916.

solution should be used. The U. S. P. further directs that the volume of gas should be noted when the volume has become constant (within 30 to 60 minutes). We have found that under ordinary conditions the volume becomes practically constant within a few minutes.

In the following tables the results obtained both gasometrically and volumetrically with a few samples of Spirit of Nitrous Ether are given. The volumetric method is carried out as follows:

To a mixture of 10 Cc. of distilled water and 5 Cc. of a cold aqueous solution of potassium chlorate 5 Gm. of the spirit and 5 Cc. of 10 percent nitric acid are added. The mixture is frequently shaken during one-half hour in a glass stoppered bottle, mixed with 15 Cc. of a $\frac{N}{10}$ silver nitrate solution and a few Cc. of ferric alum solution, and the excess of silver then titrated back with $\frac{N}{10}$ potassium sulphocyanide. The number of Cc. of silver nitrate solution multiplied by 0.022353 gives the amount of ethyl nitrite in 5 Gm. of the spirit.

NO. 1.

	Gasometric. *Percent.*	Volumetric. *Percent.*
Estimation direct, without treating with $KHCO_3$:		
Read at once	4.14	4.60
Read after ½ hour	4.13	4.58
Read after 1 hour	4.01	
Shaken with $KHCO_3$ for a few seconds:		
Read at once	3.56	4.01
Read after ½ hour	3.48	4.05
Allowed to stand with $KHCO_3$ for ½ hour, read at once	3.05	3.81
Read after ½ hour	3.00	

NO. 2.

Shaken with $KHCO_3$ for 5 min.	3.87	4.46
Read after ½ hour	3.85	4.39
Allowed to stand with $KHCO_3$ for 36 hours:		
Read after ½ hour	3.41	

NO. 3.

Estimation direct without treating with $KHCO_3$	6.95	7.21
Read at once	6.78	7.16
Shaken with $KHCO_3$ for 5 min.:		
Read at once	5.88	6.11
		6.17
Allowed to stand with $KHCO_3$ for 1 hour:		
Read at once	5.45	6.27
		6.21
Allowed to stand with $KHCO_3$ for 48 hours	5.05	5.97
Read at once	...	6.0

From these results it is plainly shown that by the volumetric method higher results are obtained than by the gasometric process. That spirit of nitrous ether is a rather unstable compound, even when kept under ordinary conditions, is shown by the following results covering analyses of spirits of different ages. The samples were kept in completely filled, one-ounce, cork-stoppered, flint bottles, protected from light, but under ordinary conditions as to temperature, etc.

Assayed on date of manufacture.	Assayed on reexamination after	Gasometric.	Volumetric.	Color on date of reexamination.
Percent.	*Months.*	*Percent.*	*Percent.*	
4.44	3	3.58	3.65	Colorless
4.29	7	3.51	3.42	Yellowish
4.25	10	3.67	3.75	Pale yellow
4.2	11	3.26	3.66	Colorless
4.4	13	3.22	3.46	Yellow
4.21	21	3.16	3.33	Yellow
4.4	26	1.34	1.47	Slightly
4.34	31	1.27	1.58	Deep yellow
4.27	38	1.17	1.66	Colorless

These results show that spirit of nitrous ether deteriorates shortly after being manufactured and also that the deterioration is a rapid one after about two years' standing. They further show that the color of the spirit gives no indication of the strength of the product, since samples with slight change of color showed as much deterioration as darker ones.

In conclusion we again wish to strongly recommend the adoption of the volumetric method for estimating the ethyl nitrite in spirit of nitrous ether and amyl nitrite, thus eliminating nitrometers and barometers from the utensils required for assaying pharmaceutical preparations altogether. Unfortunately, however, the new Pharmacopœia again gives the gasometric estimation of the ethyl nitrite.

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THE ASSAY METHODS AND PURITY REQUIREMENTS OF THE PHARMACOPŒIA AND THE NATIONAL FORMULARY.*

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The new Pharmacopœia of the United States, ninth decennial revision, and the National Formulary, fourth edition, impose additional responsibilities on the manufacturer as well as on the vendor or distributor of drugs and medicinal preparations. For the first time, in this country at least, fixed maximum as well as minimum requirements are made in the Pharmacopœia and in the National Formulary, and it is fair to assert that no books of standards now available come so near to theoretical perfection as do the new editions of our official standards which are now being distributed.

The purity rubrics introduced in the Pharmacopœia of the United States a decade or more ago have been considerably elaborated, and in the present edition the rubric for each article is generally accompanied by a specific method of assay.

This change in the nature of the official requirements is due to the fact that many critics of the previous edition of the Pharmacopœia of the United States have called attention to the desirability of having a clear, concise definition for each article or preparation, with a minimum and maximum limit for the active ingredients, to be accompanied by practical methods for their determination.

It has long since been asserted that it is impracticable, if not actually impossible, to comply absolutely with an unflexible fixed standard and it has also been pointed out that a fixed minimum requirement without a corresponding restriction of the maximum content of active constituent is unsatisfactory, in that it would not insure any degree of uniformity in the nature of the product. These

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